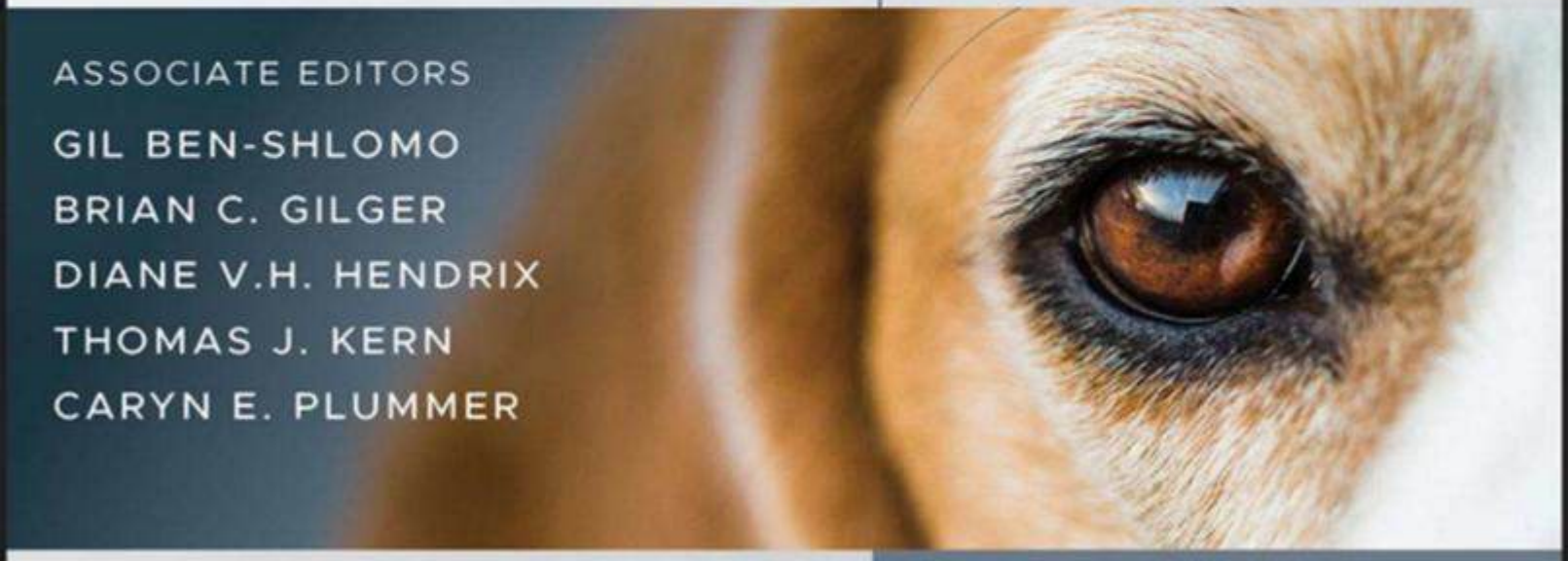



VETERINARY OPHTHALMOLOGY

EDITED BY **KIRK N. GELATT**

SIXTH EDITION



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Veterinary Ophthalmology

Volume I and Volume II

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This book is dedicated to the memory of Dr. Gil Ben-Shlomo, an exceptional scholar, teacher, father and friend. The veterinary ophthalmology community has lost a gentle doctor and a gentleman.

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Preface

In 1965 when I entered veterinary ophthalmology, it became very quickly apparent that there was a very limited information base or knowledge in veterinary ophthalmology. If this new clinical discipline was to grow and develop into a respected clinical specialty, we would need to develop our own scientific base, and compete with the other emerging clinical specialties in veterinary medicine. And we have! With our limited English-language books of *Veterinary Ophthalmology* by R.H. Smythe (1956), W.G. Magrane's first edition of *Canine Ophthalmology* (1965; Lea and Febiger), and *Diseases of the Canine Eye* by F.G. Startup (1969; Williams and Wilkins), and the chapter in *Advances in Veterinary Science* called 'Examination of the Eye' and 'Eye Operations in Animals' by Otto Überreiter (1959; Academic Press), we needed to "roll up our sleeves" and get to work big time!

We have available now (2021) a large number of veterinary ophthalmology books concentrating on the dog, cat, exotic animals, horses, ophthalmic pathology, and ophthalmic surgery. Two veterinary ophthalmology journals have proven invaluable to our success as a discipline. The first journal, *Veterinary and Comparative Ophthalmology*, was published by Fidia Research Foundation and Veterinary Practice Publishing (1991–1998), and our second journal was *Veterinary Ophthalmology* (published by Blackwell and Wiley-Blackwell, 1998 to present); they greatly assisted our development and proved critical for the distribution of new scientific information. In fact, the current journal provides more than 90% of animal ophthalmic literature annually worldwide.

In the late 1950s and extending into the 1970s, professional groups of budding veterinary ophthalmologists organized scientific societies to gather and exchange their knowledge and clinical experiences, which rapidly evolved to Colleges of Veterinary Ophthalmologists whose primary missions were to train new veterinary ophthalmologists (termed residents), and foster (and fund) research to "grow" the clinical discipline long term and worldwide. Nowadays these significant changes have greatly enriched veterinary ophthalmology, and markedly improved the quality of our ophthalmic animal patients.

The advances in this text, *Veterinary Ophthalmology*, have paralleled and documented the changes in veterinary ophthalmology, and has become our symbol of where we are today. In 1981, the first edition was released, consisting of 21 chapters (788 pages) by 22 authors, and was well received. As a result, subsequent editions followed: second edition (1991; 765 pages and 19 authors), and then in 1999 our last single-volume release (1544 pages, 37 chapters, and 44 authors). The third edition was markedly expanded and had color illustrations throughout the text.

The last two editions were two-volume sets: for 2007, volume one 535 pages, 9 chapters, and 45 authors, and for the second larger volume 1672 pages, 20 chapters, and 36 authors; and in 2012 for volume one 789 pages, 12 chapters, and 26 authors, and for the second volume 1479 pages, 22 chapters, and 39 authors. All editions were well referenced; in fact, a great value of this text is that it documents the advances in veterinary ophthalmology during the past half of the twentieth century, and the first two decades of the twenty-first century!

The sixth edition again consists of two volumes, 37 chapters, and 64 contributors. Like the last two editions, the first volume contains the basic science and foundations of clinical ophthalmology chapters and the first part of the third section on canine ophthalmology. Basic vision science courses in veterinary medical colleges are often an afterthought, and our veterinary ophthalmic basic sciences are frequently documented by veterinary ophthalmologists (rather than anatomists, physiologists, pharmacologists, etc.).

The first volume of the basic sciences and foundations of veterinary ophthalmology is designed to provide the base of those subjects that underpin the clinical sciences. They include embryology, anatomy, ophthalmology physiology, optics and physiology of vision, and fundamentals of vision in animals. In the foundations of clinical ophthalmology section, the chapters include immunity, microbiology, clinical pharmacology and therapeutics, ophthalmic pathology, ophthalmic examination and diagnostics, ophthalmic genetics and DNA testing, fundamentals of microsurgery, and photography. The third section starts with the chapters for

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the first part of the canine ophthalmology including orbit, eyelids, nasolacrimal system, lacrimal secretory system, conjunctiva and nictitating membrane, cornea and sclera, and glaucoma.

The second volume focuses on clinical ophthalmology in the different species, and starts with the second part of canine ophthalmology (chapters- anterior uvea, lens and cataract formation, surgery of the lens, vitreous, ocular fundus, surgery of the posterior segment, and optic nerve), and continues with feline, equine, food and fiber-producing animals, avian, New World camelids, laboratory animals, pocket pet animals, and exotics, and concludes with comparative neuro-ophthalmology, ophthalmic manifestations of systemic diseases, and the index. The sixth edition more or less has devoted space relative to the amount of time based on different animal species encountered in veterinary ophthalmology practice.

Now, in 2021, the sixth edition of *Veterinary Ophthalmology* continues to document this discipline's advances. The magnitude of this edition has now required five associate editors, who devoted their time and expertise to make it happen. Like for me, I'm certain it was a learning experience! They are Drs. Brian C. Gilger, Diane V.H. Hendrix, Thomas J. Kern, Caryn E. Plummer, and Gil Ben-Shlomo. Each editor chose their authors and respective chapters, based on their expertise and preferences. A book like this is a huge undertaking, and all of us have devoted hundreds of hours to make it a successful product for the profession. Our 64 authors contributed hundreds of hours to this edition, taking time away from family and practice, and we thank them.

When all the chapters had been submitted and production had started, the COVID-19 pandemic spread across the world like a massive hurricane. Terms like "face masks," "social distancing," "isolation," and "quarantine or shelter at home" became common terms, and our daily personal and professional routines were markedly disrupted. But progress in the production of the sixth edition continued uninterrupted.

We thank Erica Judisch, Executive Editor, Veterinary Medicine and Dentistry, and Purvi Patel, Project Editor, of Wiley-Blackwell for their expertise and assistance in making the sixth edition of *Veterinary Ophthalmology* a reality. Our copyeditors, Jane Grisdale and Sally Osborn, and project manager Mirjana Misina were superb. And lastly, we thank and appreciate the continued support and encouragement of our spouses and family members who bear with us as we struggle to meet our time schedules and other life priorities.

Distinguished Professor of Comparative Ophthalmology, Emeritus

Kirk N. Gelatt, VMD, Diplomate, American College of Veterinary Ophthalmologists

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This book is accompanied by a companion website:

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Section I

Basic Vision Sciences

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1

Ocular Embryology and Congenital Malformations

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An understanding of normal and abnormal ocular development is essential to the broader subjects of anatomy, physiology, and pathology. Embryology provides both insight into the development of structures such as the cornea, iridocorneal angle, and retina and their normal and pathologic functions, as well as a means of understanding how congenital malformations occur.

Investigations of ocular development have often used rodents as animal models. Comparison with studies of humans and other animals demonstrates that the sequence of developmental events is very similar across species (Cook, 1995; Cook & Sulik, 1986; Hilfer, 1983; O'Rahilly, 1983). Factors that must be considered when making interspecies comparisons include duration of gestation, differences in anatomic end point (e.g., presence of a tapetum, macula, or Schlemm's canal), and when eyelid fusion breaks (during the sixth month of gestation in the human versus 2 weeks postnatal in the dog; Table 1.1).

This chapter describes normal events and abnormalities in this developmental sequence that can lead to malformations. Bearing in mind the species differences alluded to earlier, the mouse is a valuable model in the study of normal and abnormal ocular morphogenesis. In particular, studying the effects of acute exposure to teratogens during development has provided valuable information about the specific timing of events that lead to malformations.

Gastrulation and Neurulation

Cellular mitosis following fertilization results in transformation of the single-cell zygote into a cluster of 12–16 cells. With continued cellular proliferation, this morula becomes a blastocyst, containing a fluid-filled cavity. The cells of the blastocyst will form both the embryo proper and the extraembryonic tissues (i.e., amnion and chorion). At this early stage, the embryo is a bilaminar disc, consisting of hypoblast and epiblast. This embryonic tissue divides the blastocyst space into the amniotic cavity (adjacent to epiblast) and the yolk sac (adjacent to hypoblast; Fig. 1.1).

Gastrulation (formation of the mesodermal germ layer) begins during day 10 of gestation in the dog (day 7 in the mouse; days 15–20 in the human). The primitive streak forms as a longitudinal groove within the epiblast (i.e., future ectoderm). Epiblast cells migrate toward the primitive streak, where they invaginate to form the mesoderm. This forms the three classic germ layers: ectoderm, mesoderm, and endoderm. Gastrulation proceeds in a cranial-to-caudal progression; simultaneously, the cranial surface ectoderm proliferates, forming bilateral elevations called the neural folds (i.e., the future brain). The columnar surface ectoderm in this area now becomes known as the neural ectoderm (Fig. 1.2).

As the neural folds elevate and approach each other, a specialized population of mesenchymal cells, the neural crest, emigrates from the neural ectoderm at its junction with the surface ectoderm (Fig. 1.3). Migration and differentiation of the neural crest cells are influenced by the hyaluronic acid-rich extracellular matrix. This acellular matrix is secreted by the surface epithelium as well as by the crest cells, and it forms a space through which the crest cells migrate. Fibronectin secreted by the noncrest cells forms the limits of this mesenchymal migration (LeDouarin & Teillet, 1974). Interactions between the migrating neural crest and the associated mesoderm appear to be essential for normal crest differentiation (LeDouarin & Teillet, 1974; Noden, 1993). The neural crest cells migrate peripherally beneath the surface ectoderm to spread throughout the embryo, populating the region around the optic vesicle and ultimately giving rise to nearly all the connective tissue structures of the eye (Table 1.2; Hilfer & Randolph, 1993; Johnston et al., 1979; Noden, 1993). The patterns of neural crest emergence and migration correlate with the segmental disposition of the developing brain.

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Table 1.1 Sequence of ocular development (Cook, 1995; O'Rahilly, 1983).

Human (Approximate Postfertilization Age)				Dog (Day Postfertilization)	
Month	**Week**	**Day**	**Mouse (Day Postfertilization)**	**Postnatal (P)**	**Developmental Events**
1	3	22	8	13	Optic sulci present in forebrain
	4	24	9	15	Optic sulci convert into optic vesicles
			10	17	Optic vesicle contacts surface ectoderm
					Lens placode begins to thicken
		26			Optic vesicle surrounded by neural crest mesenchyme
2	5	28	10.5		Optic vesicle begins to invaginate, forming optic cup
					Lens pit forms as lens placode invaginates
					Retinal primordium thickens, marginal zone present
		32	11	19	Optic vesicle invaginated to form optic cup
					Optic fissure delineated
					Retinal primordium consists of external limiting membrane, proliferative zone, primitive zone, marginal zone, and internal limiting membrane
					Oculomotor nerve present
		33	11.5	25	Pigment in outer layer of optic cup
					Hyaloid artery enters through the optic cup
					Lens vesicle separated from surface ectoderm
					Retina: inner marginal and outer nuclear zones
			11.5	29	Basement membrane of surface ectoderm intact
					Primary lens fibers form
					Trochlear and abducens nerves appear
					Lid folds present
	6	37	12		Edges of optic fissure in contact
			12	30	Tunica vasculosa lentis present
					Lens vesicle cavity obliterated
					Ciliary ganglion present
		41	12	32	Posterior retina consists of nerve fiber layer, inner neuroblastic layer, transient fiber layer of Chievitz, proliferative zone, outer neuroblastic layer, and external limiting membrane
			17	32	Eyelids fuse (dog)
	7				Anterior chamber beginning to form
			12.5	40	Secondary lens fibers present
		48	14	32	Corneal endothelium differentiated
	8	51			Optic nerve fibers reach the brain
					Optic stalk cavity is obliterated
					Lens sutures appear
					Acellular corneal stroma present
		54		30–35	Scleral condensation present
	9	57	17	40	First indication of ciliary processes and iris
					Extraocular muscles visible

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Table 1.1 (Continued)

Human (Approximate Postfertilization Age)			Mouse (Day Postfertilization)	Dog (Day Postfertilization)	
Month	**Week**	**Day**		**Postnatal (P)**	**Developmental Events**
				—	Eyelids fuse (occurs earlier in the dog)
	10			45	Pigment visible in iris stroma
					Ciliary processes touch lens equator
					Rudimentary rods and cones appear
				45–1 P	Hyaloid artery begins to atrophy to the disc
3	12			—	Branches of the central retinal artery form
4				51	Pupillary sphincter differentiates
					Retinal vessels present
				56	Ciliary muscle appears
				—	Eye axis forward (human)
—				56	Tapetum present (dog)
				2–14 P	Tunica vasculosa lentis atrophies
					Short eyelashes appear
5				40	Layers of the choroid are complete with pigmentation
6				—	Eyelids begin to open, light perception
				1 P	Pupillary dilator muscle present
7				1–14 P	Pupillary membrane atrophies
				1–16 P	Rod and cone inner and outer segments present in posterior retina
				10–13 P	Pars plana distinct
9				16–40 P	Retinal layers developed
				14 P	Regression of pupillary membrane, tunica vasculosa lentis, and hyaloid artery nearly complete
					Lacrimal duct canalized

Data from Aguirre et al. (1972), Akiya et al. (1986), Cook (1995), and van der Linde-Sipman et al. (2003).

It is important to note that mesenchyme is a general term for any embryonic connective tissue. Mesenchymal cells generally appear stellate and are actively migrating populations surrounded by extensive extracellular space. In contrast, the term *mesoderm* refers specifically to the middle embryonic germ layer. In other parts of the body (e.g., the axial skeletal system), mesenchyme develops primarily from mesoderm, with a lesser contribution from the neural crest. In the craniofacial region, however, mesoderm plays a relatively small role in the development of connective tissue structures. In the eye, mesoderm probably gives rise only to the striated myocytes of the extraocular muscles and vascular endothelium. Most of the craniofacial mesenchymal tissue comes from neural crest cells (Johnston et al., 1979).

The neural tube closes initially in the craniocervical region with closure proceeding cranially and caudally. Once closure is complete, the exterior of the embryo is fully covered by surface ectoderm, and the neural tube is lined by neural ectoderm. Neural segmentation then occurs to form the specific parts of the brain: forebrain (i.e., prosencephalon), midbrain (i.e., mesencephalon), and hindbrain (i.e., rhombencephalon; see Fig. 1.3 and Fig. 1.4). The optic vesicles develop from neural ectoderm within the forebrain, with the ocular connective tissue derivatives originating from the midbrain neural crest.

Formation of the Optic Vesicle and Optic Cup

The optic sulci are visible as paired evaginations of the forebrain neural ectoderm on day 13 of gestation in the dog (see Fig. 1.3, Fig. 1.4, Fig. 1.5, Fig. 1.6, and Fig. 1.7). The transformation from optic sulcus to optic vesicle occurs

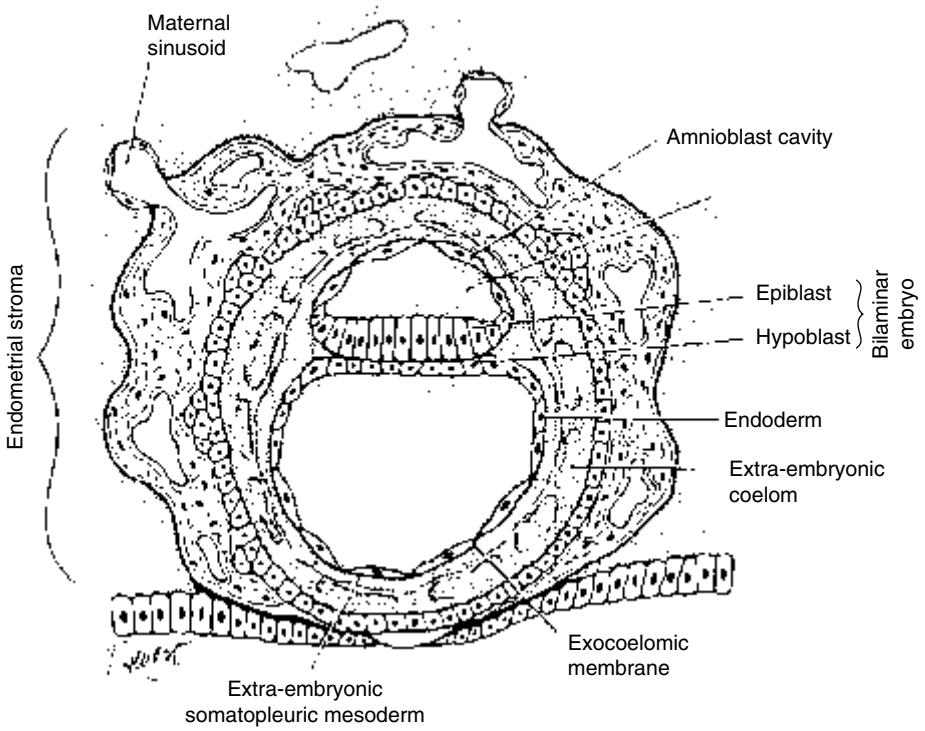


Figure 1.1 A blastocyst that has penetrated the maternal endometrium. An embryoblast has formed and consists of two cell layers: the epiblast above, and the hypoblast below. (Reprinted with permission from Cook, C., Sulik, K.K., & Wright, K.W. (2003) Embryology. In: *Pediatric Ophthalmology and Strabismus* (eds. Wright, K.W. & Spiegel, P.H.), pp. 3–38. New York: Springer.)

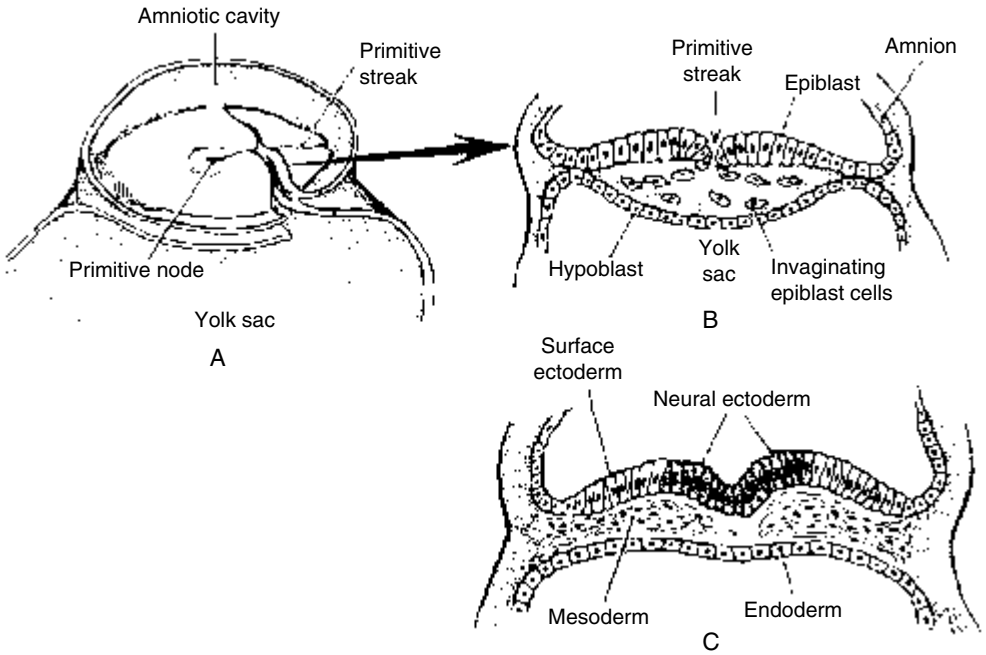


Figure 1.2 **A.** Dorsal view of an embryo in the gastrulation stage with the amnion removed. **B.** Cross-section through the primitive streak, representing invagination of epiblast cells between the epiblast and hypoblast layers. Note that the epiblast cells filling the middle area form the mesodermal layer. **C.** Cross-section through the neural plate. Note that the ectoderm in the area of the neural groove (shaded cells) has differentiated into neural ectoderm, whereas the ectoderm on each side of the neural groove is surface ectoderm (clear water cells). (Reprinted with permission from Cook, C., Sulik, K.K., & Wright, K.W. (2003) Embryology. In: *Pediatric Ophthalmology and Strabismus* (eds. Wright, K.W. & Spiegel, P.H.), pp. 3–38. New York: Springer.)

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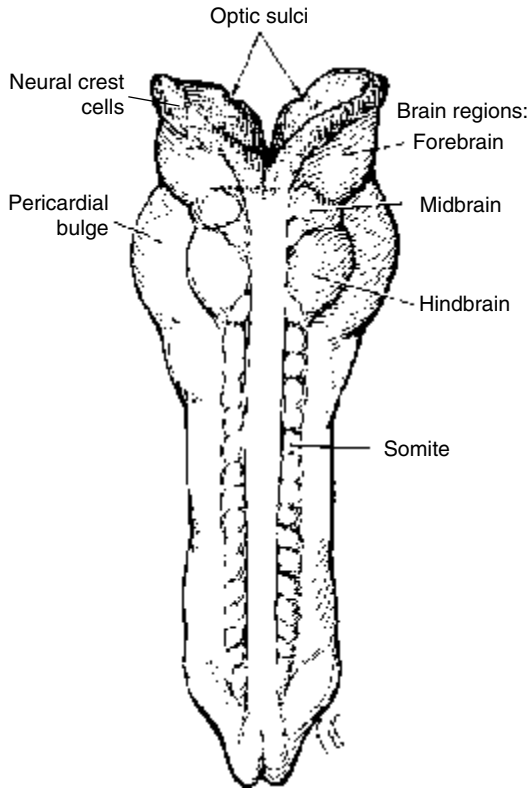


Figure 1.3 Dorsal view showing partial fusion of the neural folds to form the neural tube. Brain vesicles have divided into three regions: forebrain, midbrain, and hindbrain. The neural tube, groove, and facing surfaces of the large neural folds are lined with neural ectoderm (shaded cells), whereas surface ectoderm covers the rest of the embryo. Neural crest cells are found at the junction of the neural ectoderm and surface ectoderm. Neural crest cells migrate beneath the surface ectoderm, spreading throughout the embryo and specifically to the area of the optic sulci. Somites have formed along the lateral aspect of the closed cephalic neural tube. On the inside of both forebrain vesicles is the optic sulci. (Reprinted with permission from Cook, C., Sulik, K.K., & Wright, K.W. (2003) Embryology. In: *Pediatric Ophthalmology and Strabismus* (eds. Wright, K.W. & Spiegel, P.H.), pp. 3–38. New York: Springer.)

concurrent with the closure of the neural tube (day 15 in the dog). Intracellular filaments and microtubules within the cytoskeleton alter cell shape and allow for cell movement. In addition to the mechanical influences of the cytoskeleton and the extracellular matrix, localized proliferation and cell growth contribute to expansion of the optic vesicle (Fig. 1.5; Hilfer & Randolph, 1993; Hilfer et al., 1981).

The optic vesicle enlarges and, covered by its own basal lamina, approaches the basal lamina underlying the surface ectoderm (Fig. 1.5). The optic vesicle appears to play a significant role in the induction and size determination of the palpebral fissure and of the orbital and periocular structures (Jones et al., 1980). An external bulge indicating the presence of the enlarging optic vesicle can be seen at approximately day 17 in the dog.

Table 1.2 Embryonic origins of ocular tissues (Johnston et al., 1979; Noden, 1993; Yamashita & Sohal, 1987).

Neural Ectoderm	Neural Crest
Neural retina	Stroma of iris, ciliary body, choroid, and sclera
Retinal pigment epithelium	Ciliary muscles
Posterior iris epithelium	Corneal stroma and endothelium
Pupillary sphincter and dilator muscle (except in avian species)	Perivascular connective tissue and smooth muscle cells
	Striated muscles of iris (avian species only)
Bilayered ciliary epithelium	Meninges of optic nerve
	Orbital cartilage and bone
	Connective tissue of the extrinsic ocular muscles
	Endothelium of trabecular meshwork
Surface Ectoderm	**Mesoderm**
Lens	Extraocular myoblasts
Corneal and conjunctival epithelium	Vascular endothelium
Lacrimal gland	Schlemm's canal (human)
	Posterior sclera (?)

Data from Ashton (1966), Cook et al. (1991a), and Cook and Sulik (1986, 1988).

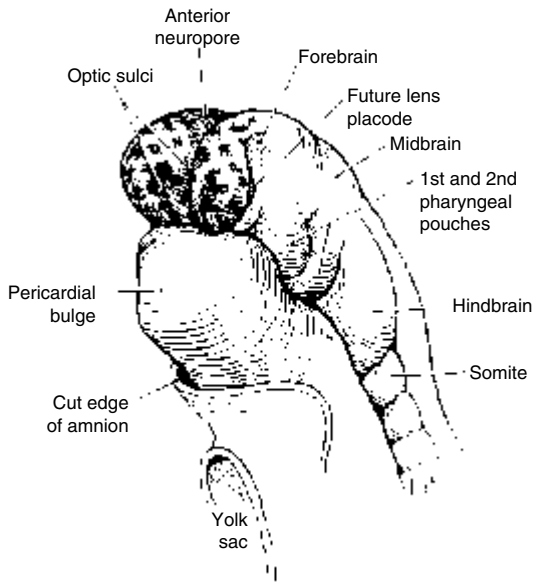


Figure 1.4 Development of the optic sulci, which are the first sign of eye development. Optic sulci on the inside of the forebrain vesicles consisting of neural ectoderm (shaded cells). The optic sulci evaginate toward the surface ectoderm as the forebrain vesicles simultaneously rotate inward to fuse. (Reprinted with permission from Cook, C., Sulik, K.K., & Wright, K.W. (2003) Embryology. In: *Pediatric Ophthalmology and Strabismus* (eds. Wright, K.W. & Spiegel, P.H.), pp. 3–38. New York: Springer.)

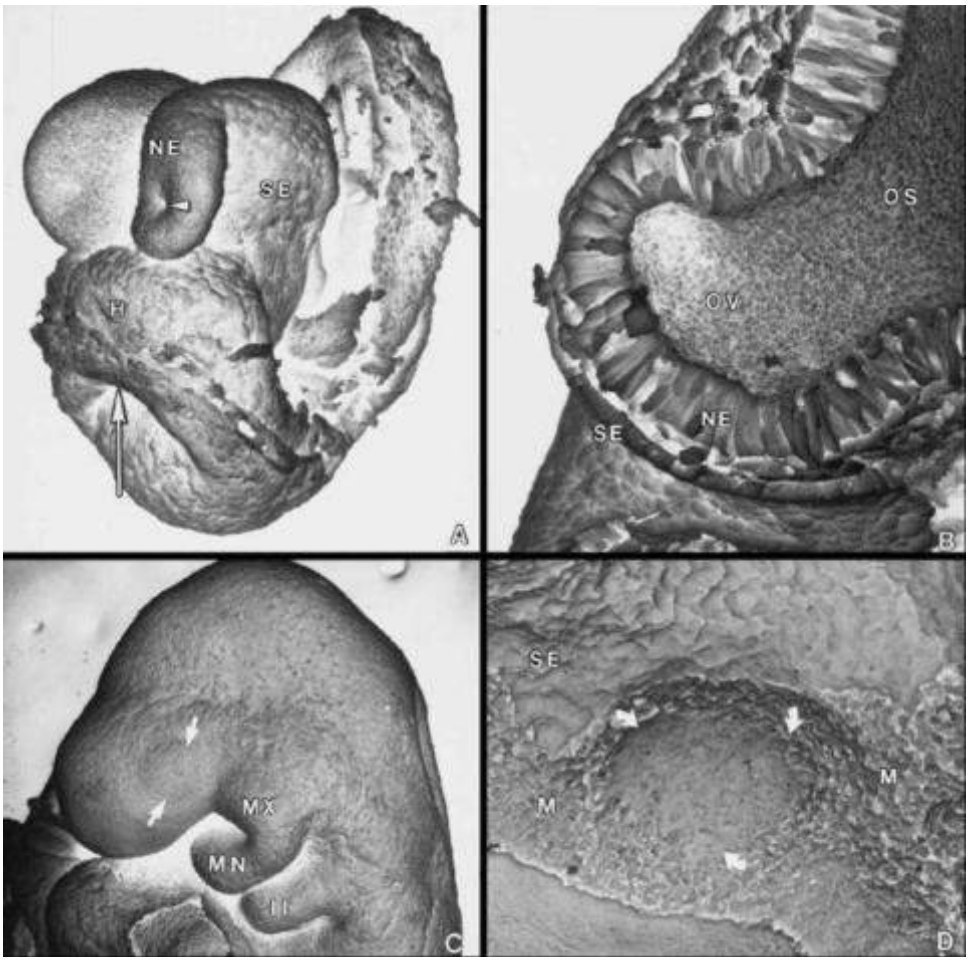


Figure 1.5 **A.** Scanning electron micrograph of a mouse embryo (six somite pairs) on day 8 of gestation, equivalent to day 13 of canine gestation. The amnion has been removed, and the neural folds have segmented into a forebrain region containing the optic sulci (arrowhead), which are evaginations of neural ectoderm (NE). The close proximity to the developing heart (H) can be seen. The area where the NE meets the surface ectoderm (SE) is where the neural fold will meet and fuse; this area also gives rise to the neural crest cells. The entrance to the foregut is indicated by the arrow. **B.** Scanning electron micrograph of the optic vesicle on day 9 of gestation in the mouse (day 15 in the dog). Expansion of the optic sulcus results in an optic vesicle (OV) that approaches the surface ectoderm (SE). A thin layer of mesenchyme is still present between the NE and the SE. The optic stalk (OS) is continuous with the ventricle of the forebrain. **C.** The bulge of the enlarging OV (arrows) can be seen externally. MN, mandibular prominence of the first visceral arch; MX, maxillary prominence of the first visceral arch; II, second visceral arch. **D.** Partial removal of the SE from an embryo of 25 somite pairs (day 17 in the dog; day 19 in the mouse) reveals the exposed basal lamina of the OV (arrows). Enlargement of the optic vesicle has displaced the adjacent mesenchyme (M) so that the basal lamina of the SE is in direct contact with that of the OV. (Reprinted with permission from Cook, C.S. & Sulik, K.K. (1986) Sequential scanning electron microscopic analyses of normal and spontaneously occurring abnormal ocular development in C57B1/6J mice. *Scanning Electron Microscopy*, **3**, 1215–1227.)

The optic vesicle and optic stalk invaginate through differential growth and infolding (Fig. 1.6 and Fig. 1.7). Local apical contraction (Wrenn & Wessells, 1969) and physiologic cell death (Schook, 1978) have been identified during invagination. The surface ectoderm in contact with the optic vesicle thickens to form the lens placode (Fig. 1.6, Fig. 1.7, and Fig. 1.8A, B), which then invaginates with the underlying neural ectoderm. The invaginating neural ectoderm folds onto itself as the space within the optic vesicle collapses, thus creating a double layer of neural ectoderm, the optic cup.

This process of optic vesicle/lens placode invagination progresses from inferior to superior, so the sides of the optic cup and stalk meet inferiorly in an area called the optic (choroid) fissure (Fig. 1.8F). Mesenchymal tissue (of primarily neural crest origin) surrounds and fills the optic cup, and by day 25 in the dog, the hyaloid artery develops from mesenchyme in the optic fissure. This artery courses from the optic stalk (i.e., the region of the future optic nerve) to the developing lens (Fig. 1.9 and Fig. 1.10). The two edges of the optic fissure meet and initially fuse anterior to the optic stalk, with fusion then progressing anteriorly and posteriorly.

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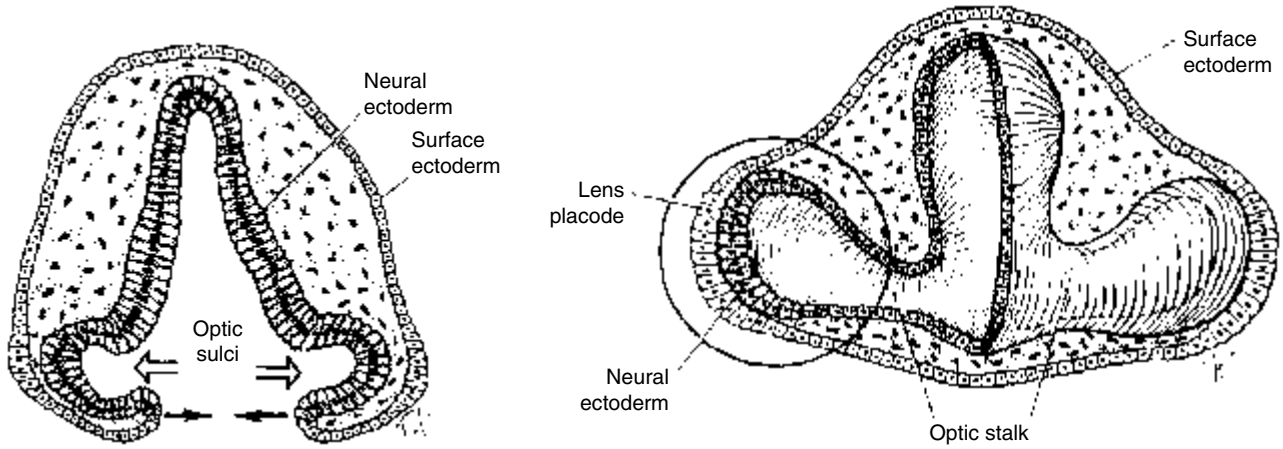


Figure 1.6 Cross-section at the level of the optic vesicle. Note that the neural tube is closed. The surface ectoderm now covers the surface of the forebrain, and the neural ectoderm is completely internalized. The surface ectoderm cells overlying the optic vesicles enlarge to form the early lens placode. (Reprinted with permission from Cook, C., Sulik, K.K., & Wright, K.W. (2003) Embryology. In: *Pediatric Ophthalmology and Strabismus* (eds. Wright, K.W. & Spiegel, P.H.), pp. 3–38. New York: Springer.)

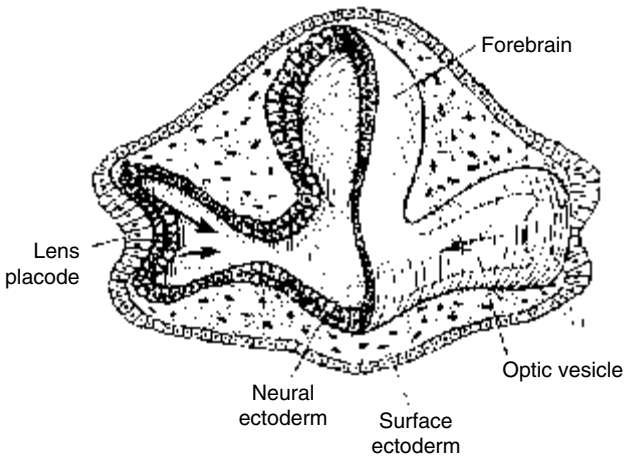


Figure 1.7 Transection showing invaginating lens placode and optic vesicle (arrows), thus creating the lens vesicle within the optic cup. Note the orientation of the eyes 180° from each other. (Reprinted with permission from Cook, C., Sulik, K.K., & Wright, K.W. (2003) Embryology. In: *Pediatric Ophthalmology and Strabismus* (eds. Wright, K.W. & Spiegel, P.H.), pp. 3–38. New York: Springer.)

This process is mediated by glycosaminoglycan-induced adhesion between the two edges of the fissure (Ikeda et al., 1995). Apoptosis has been identified in the inferior optic cup prior to formation of the optic fissure and, transiently, associated with its closure (Ozeki et al., 2000). Failure of this fissure to close normally may result in inferiorly located defects (i.e., colobomas) in the iris, choroid, or optic nerve. Colobomas other than those in the "typical" six o'clock location may occur through a different mechanism and are discussed later.

Closure of the optic cup through fusion of the optic fissure allows intraocular pressure (IOP) to be established. The protein in the embryonic vitreous humor (13% of plasma protein) is derived from plasma proteins entering the eye by diffusion out of permeable vessels in the anterior segment. After day 15, protein content in the vitreous decreases, possibly through dilution with aqueous humor produced by developing ciliary epithelium (Beebe et al., 1986).

Lens Formation

Before contact with the optic vesicle, the surface ectoderm first becomes competent to respond to lens inducers. Inductive signals from the anterior neural plate give this area of ectoderm a "lens-forming bias." Signals from the optic vesicle are required for complete lens differentiation, and inhibitory signals from the cranial neural crest may suppress any residual lens-forming bias in head ectoderm adjacent to the lens (Grainger et al., 1988, 1992). Adhesion between the optic vesicle and surface ectoderm exists, but there is no direct cell contact (Cohen, 1961; Hunt, 1961; Weiss & Jackson, 1961). The basement membranes of the optic vesicle and the surface ectoderm remain separate and intact throughout the contact period.

Thickening of the lens placode can be seen on day 17 in the dog. A tight, extracellular matrix-mediated adhesion between the optic vesicle and the surface ectoderm has been described (Aso et al., 1995; Cook & Sulik, 1988; Garcia-Porrero et al., 1979). This anchoring effect on the mitotically active ectoderm results in cell crowding and elongation and in formation of a thickened placode. This adhesion between the optic vesicle and lens placode also assures alignment of the lens and retina in the visual axis (Beebe, 1985). Abnormal orientation of the optic vesicle as it approaches the surface ectoderm may result in induction of a smaller lens vesicle,

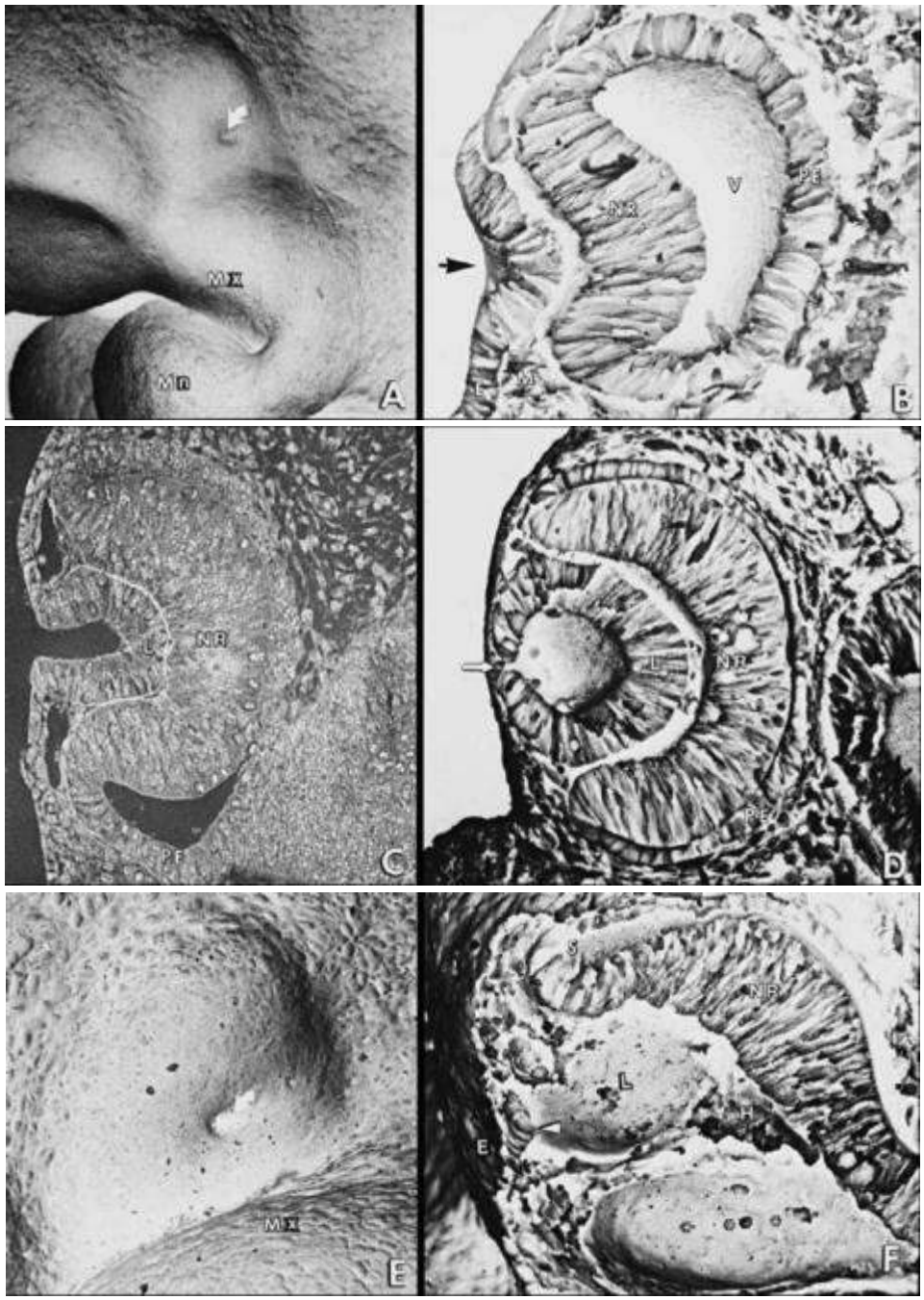


Figure 1.8 **A.** Mouse embryo on day 10 of gestation (29 somite pairs, equivalent to day 17 in the dog). On external examination, the invaginating lens placode can be seen (arrow). Note its position relative to the maxillary prominence (Mx) and mandibular (Mn) prominence of the first visceral arch. **B.** Frontal fracture through the lens placode (arrow) illustrates the associated thickening of the surface ectoderm (E). Mesenchyme (M) of neural crest origin is adjacent to the lens placode. As the precursor to the neural retina (NR), the distal portion of the optic vesicle concurrently thickens, whereas the proximal optic vesicle becomes a shorter, cuboidal layer that is the anlage of the retinal pigment epithelium (PE). The cavity of the optic vesicle (V) becomes progressively smaller. **C.** Light micrograph of the epithelium of the invagination lens placode (L). There is an abrupt transition between the thicker epithelium of the placode and the adjacent surface ectoderm, which is not unlike the transition between the future NR and PE. **D.** As the lens vesicle enlarges, the external opening of lens pore (arrow) becomes progressively smaller. The lens epithelial cells at the posterior pole of the lens elongate to form the primary lens fibers (L). NR, anlage of the neural retina; PE, anlage of the pigment epithelium (now a short cuboidal layer). **E.** External view of the lens pore (arrow) and its relationship to the Mx. **F.** Frontal fracture reveals the optic fissure (*) where the two sides of the invaginating optic cup meet. This forms an opening in the cup, allowing access to the hyaloid artery (H), which ramifies around the invaginating lens vesicle (L). The former cavity of the optic vesicle is obliterated except in the marginal sinus (S), at the transition between the NR and the PE. E, surface ectoderm. (Panels **B** and **F** reprinted with permission from Cook, C.S. & Sulik, K.K. (1986) Sequential scanning electron microscopic analyses of normal and spontaneously occurring abnormal ocular development in C57B1/6J mice. *Scanning Electron Microscopy,* **3**, 1215–1227; panels **C**, **D**, and **E** reprinted with permission from Cook, C. (1995) Embryogenesis of congenital eye malformations. *Veterinary and Comparative Ophthalmology*, **5**, 109–123.)

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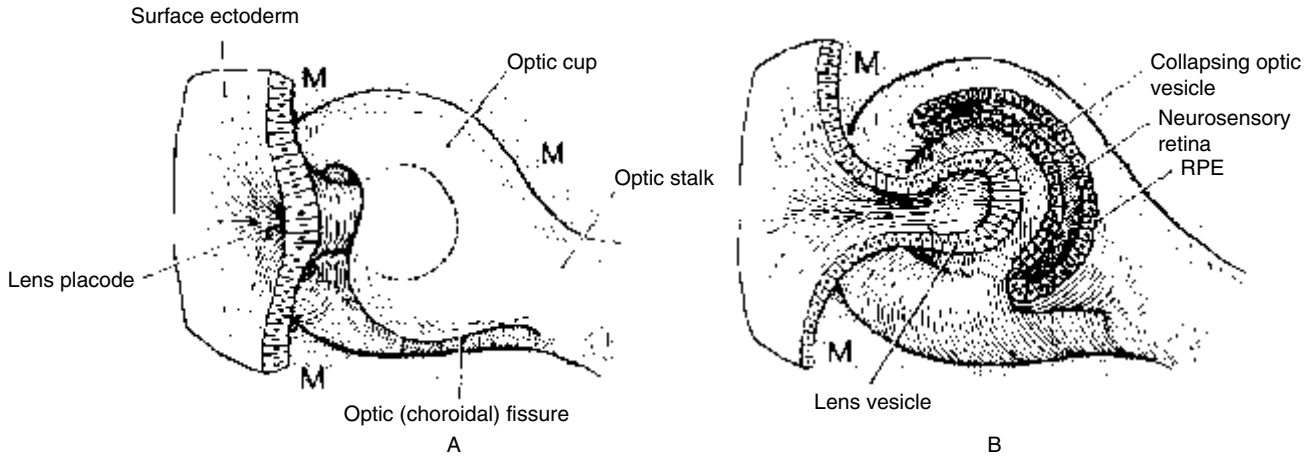
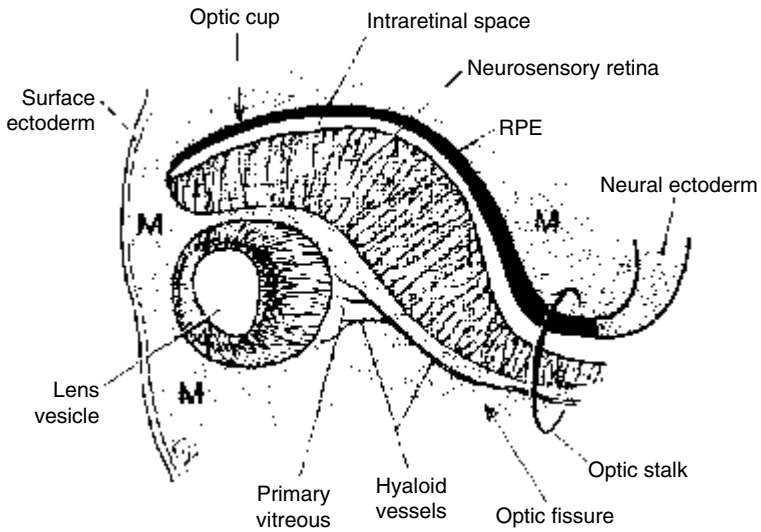


Figure 1.9 Formation of the lens vesicle and optic cup. Note that the optic fissure is present, because the optic cup is not yet fused inferiorly. **A.** Formation of lens vesicle and optic cup with inferior choroidal or optic fissure. Mesenchyme (M) surrounds the invaginating lens vesicle. **B.** Surface ectoderm forms the lens vesicle with a hollow interior. Note that the optic cup and optic stalk are of surface ectoderm origin. (Reprinted with permission from Cook, C., Sulik, K.K., & Wright, K.W. (2003) Embryology. In: *Pediatric Ophthalmology and Strabismus* (eds. Wright, K.W. & Spiegel, P.H.), pp. 3–38. New York: Springer.)

Figure 1.10 Cross-section through optic cup and optic fissure. The lens vesicle is separated from the surface ectoderm. Mesenchyme (M) surrounds the developing lens vesicle, and the hyaloid artery is seen within the optic fissure. (Reprinted with permission from Cook, C., Sulik, K.K., & Wright, K.W. (2003) Embryology. In: *Pediatric Ophthalmology and Strabismus* (eds. Wright, K.W. & Spiegel, P.H.), pp. 3–38. New York: Springer.)



which may assume an abnormal location within the optic cup (Cook & Sulik, 1988).

The lens placode invaginates, forming a hollow sphere, now referred to as a lens vesicle (Fig. 1.8C, D, Fig. 1.9, and Fig. 1.10). The size of the lens vesicle is determined by the contact area of the optic vesicle with the surface ectoderm and by the ability of the latter tissue to respond to induction. Aplasia may result from failure of lens induction or through later involutions of the lens vesicle, either before or after separation from the surface ectoderm (Aso et al., 1995).

Lens vesicle detachment is the initial event leading to formation of the chambers of the ocular anterior segment. This process is accompanied by active migration of epithelial cells out of the keratolenticular stalk, cellular necrosis, apoptosis, and basement membrane breakdown (Garcia-Porrero et al., 1979; Ozeki et al., 2001). Induction of a small lens vesicle that fails to undergo normal separation from the surface ectoderm is one of the characteristics of the teratogen-induced anterior segment dysgenesis described in animal models (Cook & Sulik, 1988). Anterior lenticonus and anterior capsular cataracts as well as anterior segment dysgenesis may result from faulty keratolenticular separation. Additional discussion of anterior segment dysgenesis occurs later in this chapter.

Following detachment from the surface ectoderm (day 25 in the dog), the lens vesicle is lined by a monolayer of cuboidal cells surrounded by a basal lamina, the future lens capsule. The primitive retina promotes primary lens fiber formation in the adjacent lens epithelial cells. Surgical rotation of the chick lens vesicle by 180° results in elongation of the lens epithelial

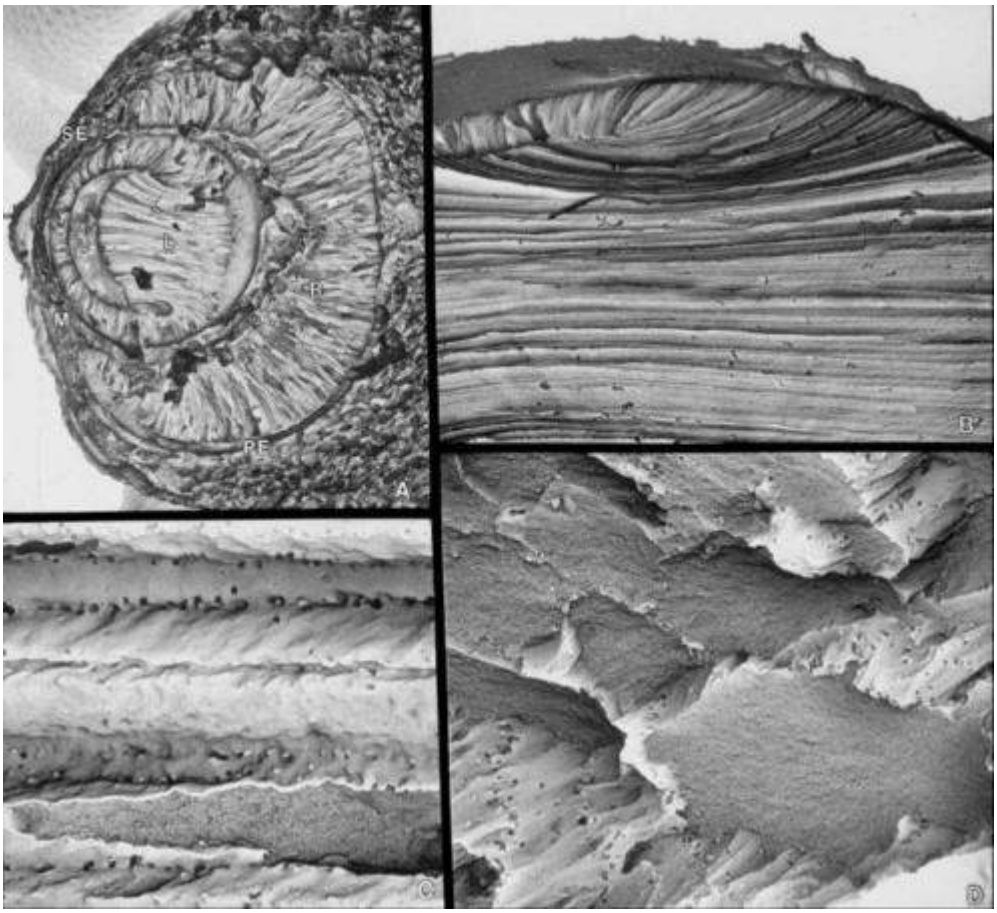


Figure 1.11 **A.** Following detachment of the lens vesicle from the surface ectoderm (SE), the posterior lens epithelial cells–primary lens fibers (L) elongate, obliterating the lens vesicle lumen (equivalent to day 29 of gestation in the dog). Invagination of the optic cup forms the inner neural retina (R) and the outer pigmented epithelium (PE). Mesenchyme of neural crest origin (M) surrounds the optic cup. **B.** Lens bow illustrating elongation of secondary lens fibers. **C** and **D.** Longitudinal view (**C**) and cross-section (**D**) of secondary lens fibers, illustrating the extensive interdigitations and the relative absence of extracellular space. (Reprinted with permission from Sulik, K.K. & Schoenwolf, G.C. (1985) Highlights of craniofacial morphogenesis in mammalian embryos, as revealed by scanning electron microscopy. *Scanning Electron Microscopy*, **4**, 1735–1752.)

cells nearest the presumptive retina, regardless of the orientation of the transplanted lens (Coulombre & Coulombre, 1969). Thus, while the retina develops independently of the lens, the lens appears to be dependent on the retinal primordium for its differentiation. The primitive lens filled with primary lens fibers is the embryonic lens nucleus. In the adult, the embryonic nucleus is the central sphere inside the "Y" sutures; there are no sutures within the embryonal nucleus (Fig. 1.11A, Fig. 1.12, and Fig. 1.13).

At birth, the lens consists almost entirely of lens nucleus, with minimal lens cortex. Lens cortex continues to develop from the anterior cuboidal epithelial cells, which remain mitotic throughout life. Differentiation of epithelial cells into secondary lens fibers occurs at the lens equator (i.e., lens bow; Fig. 1.11B). Lens fiber elongation is accompanied by a corresponding increase in cell volume and a decrease in intercellular space within the lens (Beebe et al., 1982). The lens fibers exhibit a hexagonal cross-sectional shape and extensive surface interdigitations (Fig. 1.11C, D). The secondary lens fibers course anteriorly and posteriorly around the embryonal nucleus to meet at the "Y" sutures (Fig. 1.13).

The zonule fibers are termed the *tertiary vitreous*, but their origin remains uncertain. The zonules may form from the developing ciliary epithelium or the endothelium of the posterior tunica vasculosa lentis (TVL). The embryonic TVL may produce fibrillin-2 and -3, providing a scaffold for zonule formation (Hubmacher et al., 2014). Abnormalities could result in congenital ectopia lentis. Congenitally displaced lenses are often small and are abnormally shaped (i.e., spherophakia), indicating a possible relationship between zonule traction and lens shape. Localized absence of zonules may result in a flattened lens equator; although not a true lens defect, this is often described inaccurately as a lens coloboma (see later Fig. 1.32).

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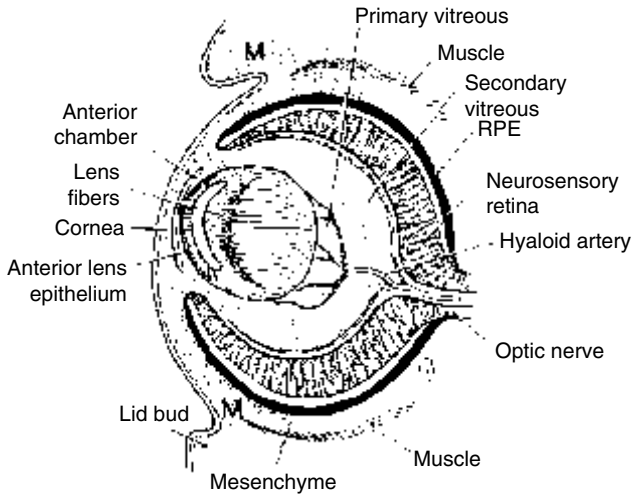


Figure 1.12 Overview of the developing eye surrounded by mesenchyme (M), which is mostly of neural crest origin. The hyaloid vasculature enters the optic cup through the optic fissure and surrounds the lens with capillaries that anastomose with the tunica vasculosa lentis. Axial migration of mesenchyme forms the corneal stroma and endothelium. RPE, retinal pigment epithelium. (Reprinted with permission from Cook, C., Sulik, K.K., & Wright, K.W. (2003) Embryology. In: *Pediatric Ophthalmology and Strabismus* (eds. Wright, K.W. & Spiegel, P.H.), pp. 3–38. New York: Springer.)

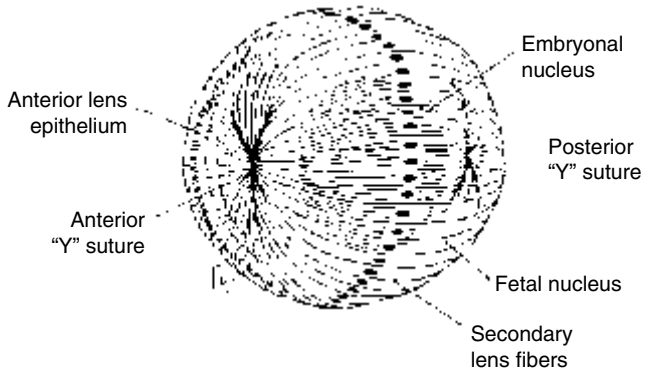


Figure 1.13 Secondary lens fibers and Y sutures. Secondary lens fibers elongate at the equator to span the entire lens, from the anterior to the posterior Y suture. The anterior Y suture is upright; the posterior Y suture is inverted. (Reprinted with permission from Cook, C., Sulik, K.K., & Wright, K.W. (2003) Embryology. In: *Pediatric Ophthalmology and Strabismus* (eds. Wright, K.W. & Spiegel, P.H.), pp. 3–38. New York: Springer.)

Vascular Development

The hyaloid artery is the termination of the primitive ophthalmic artery, a branch of the internal ophthalmic artery, and it remains within the optic cup following closure of the optic fissure. The hyaloid artery branches around the posterior lens capsule and continues anteriorly to anastomose with the network of vessels in the pupillary membrane (Fig. 1.14 and Fig. 1.15A, B; Schaepdrijver et al., 1989). The pupillary membrane consists of vessels and mesenchyme overlying the anterior lens capsule. This hyaloid vascular network that forms around the lens is called the anterior and posterior TVL. The hyaloid artery and associated TVL provide nutrition to the lens and anterior segment during its period of rapid differentiation. Venous drainage occurs via a network near the equatorial lens, in the area where the ciliary body will eventually develop. There is no discrete hyaloid vein (Schaepdrijver et al., 1989).

Once the ciliary body begins actively producing aqueous humor, which circulates and nourishes the lens, the hyaloid system is no longer needed. The hyaloid vasculature and

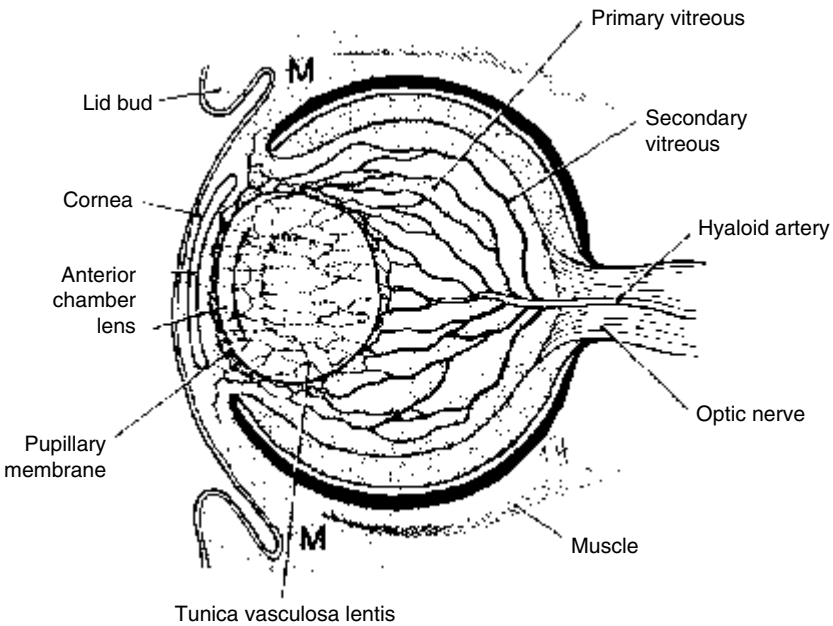


Figure 1.14 The hyaloid vascular system and tunica vasculosa lentis. (Reprinted with permission from Cook, C., Sulik, K.K., & Wright, K.W. (2003) Embryology. In: *Pediatric Ophthalmology and Strabismus* (eds. Wright, K.W. & Spiegel, P.H.), pp. 3–38. New York: Springer.)

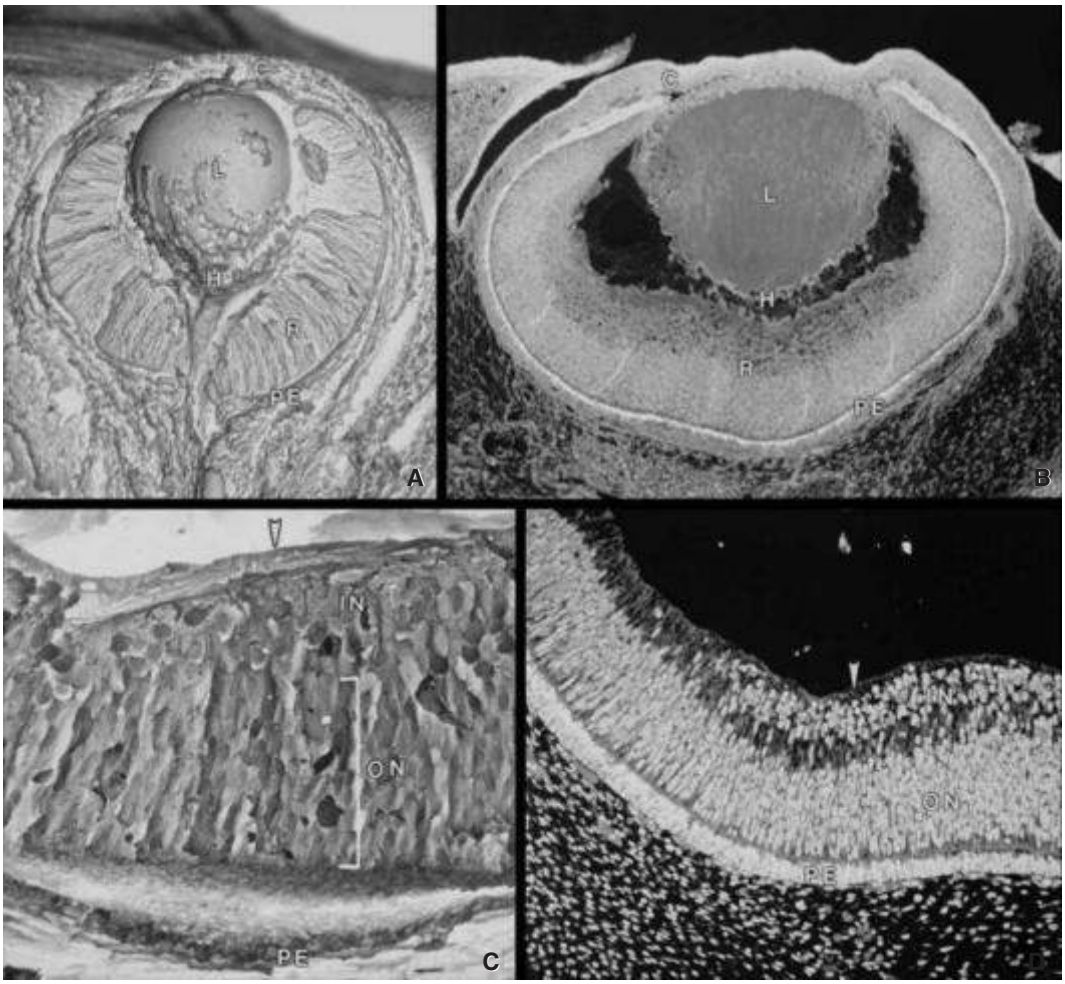


Figure 1.15 **A.** Scanning electron micrograph of a mouse embryo at 14 days of gestation (equivalent to day 32 in the dog). The hyaloid vasculature enters the optic cup through the optic stalk, and it surrounds the lens (L) with capillaries that anastomose with the tunica vasculosa lentis. Axial migration of mesenchyme forms the corneal stroma and endothelium (C). The retina (R) is becoming stratified, whereas the pigment epithelium (PE) remains cuboidal. **B.** The retina becomes stratified into an inner marginal zone and an outer nuclear zone. Note that the inner marginal zone is most prominent in the posterior pole. C, cornea; H, hyaloid artery; L, lens; R, retina. **C.** Segregation of the retina into inner (IN) and outer (ON) neuroblastic layers. The ganglion cells are the first to differentiate, giving rise to the nerve fiber layer (arrowhead). The PE has become artifactually separated in this specimen. **D.** Differentiation of the retina progresses from the central to the peripheral regions. Centrally, the inner (IN) and outer (ON) neuroblastic layers are apparent, with early formation of the nerve fiber layer (arrowhead). Peripherally, however, the retina consists of a single nuclear zone. Between the inner and outer neuroblastic layers is a clear zone, the transient fiber layer of Chievitz. This stage is equivalent to day 32 in the dog. (Panel **A** reprinted with permission from Sulik, K.K. & Schoenwold, G.C. (1985) Highlights of craniofacial morphogenesis in mammalian embryos, as revealed by scanning electron microscopy. *Scanning Electron Microscopy*, **4**, 1735–1752; panel **B** reprinted with permission from Cook, C.S. & Sulik K.K. (1986) Sequential scanning electron microscopic analyses of normal and spontaneously occurring abnormal ocular development in C57B1/6J mice. *Scanning Electron Microscopy*, **3**, 1215–1227; panels **C** and **D** reprinted with permission from Cook, C., Sulik, K.K., & Wright, K.W. (2003) Embryology. In: *Pediatric Ophthalmology and Strabismus* (eds. Wright, K.W. & Spiegel, P.H.), pp. 3–38. New York: Springer.)

TVL reach their maximal development by day 45 in the dog and then begin to regress.

As the peripheral hyaloid vasculature regresses, the retinal vessels develop. Vascular endothelial growth factor (VEGF)-A is a potent angiogenic peptide in the retina; antibody neutralization *in vivo* results in reduction in the hyaloid and retinal vasculature (Feeney et al., 2003). Spindle-shaped mesenchymal cells from the wall of the hyaloid artery at the optic disc form buds (*angiogenesis*) that invade the nerve fiber layer. In contrast, *vasculogenesis* refers to an assembly of dispersed angioblasts into solid cords of mesenchymal cells that later canalize (Fruttiger, 2002; Hughes et al., 2000). Controversy exists as to whether the process of retinal neovascularization occurs primarily through angiogenesis or vasculogenesis (Flower et al., 1985; Fruttiger, 2002; Hughes et al., 2000). Recent studies

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indicate that spindle-shaped cells dispersed within the retina, previously thought to be angioblasts, may be immature retinal astrocytes, with retinal vascularization occurring primarily through angiogenesis (Hughes et al., 2000). The primitive capillaries have laminated walls consisting of mitotically active cells secreting basement membrane. Those cells in direct contact with the bloodstream differentiate into endothelial cells; the outer cells become pericytes. Zonulae occludens and gap junctions initially join adjacent cells, but later the capillary endothelium is continuous (Ashton, 1966; Mutlu & Leipold, 1964). The primitive capillary endothelial cells are multipotent and can redifferentiate into fibroblastic, endothelial, or muscle cells, possibly illustrating a common origin for these different tissue types (Ashton, 1966).

Branches of the hyaloid artery become sporadically occluded by macrophages prior to their gradual atrophy (Jack, 1972). Placental growth factor (PlGF) and VEGF appear to be involved in hyaloid regression (Feeney et al., 2003; Martin et al., 2004). Proximal arteriolar vasoconstriction at birth precedes regression of the major hyaloid vasculature (Browning et al., 2001). Atrophy of the pupillary membrane, TVL, and hyaloid artery occurs initially through apoptosis (Ito & Yoshioka, 1999) and later through cellular necrosis (Zhu et al., 2000), and is usually complete by the time of eyelid opening 14 days postnatally.

The clinical lens anomaly known as Mittendorf's dot is a small (1 mm) area of fibrosis on the posterior lens capsule, and it is a manifestation of incomplete regression of the hyaloid artery where it was attached to the posterior lens capsule. Bergmeister's papilla represents a remnant of the hyaloid vasculature consisting of a small, fibrous glial tuft of tissue emanating from the center of the optic nerve. Both are frequently observed as incidental clinical findings.

Development of the Cornea and Anterior Chamber

The anterior margins of the optic cup advance beneath the surface ectoderm and adjacent neural crest mesenchyme after lens vesicle detachment (day 25 in the dog). The surface ectoderm overlying the optic cup (i.e., the presumptive corneal epithelium) secretes a thick matrix, the primary stroma (Hay, 1980; Hay & Revel, 1969). This acellular material consists of collagen fibrils and glycosaminoglycans. Mesenchymal neural crest cells migrate between the surface ectoderm and the optic cup, using the basal lamina of the lens vesicle as a substrate. Proteolysis of collagen IX triggers hydration of the hyaluronic acid, creating the space for cellular migration (Fitch et al., 1998). Initially, this loosely arranged mesenchyme fills the future anterior chamber, and it gives rise to the corneal endothelium and stroma, anterior iris stroma, ciliary muscle, and most structures of the iridocorneal angle (Fig. 1.16A). The presence of an adjacent lens vesicle is required for induction of corneal endothelium, identified by their production of the cell adhesion molecule, n-cadherin (Beebe & Coats, 2000). Type I collagen fibrils and fibronectin secreted by the developing keratocytes form the secondary corneal stroma. Subsequent dehydration results in much of the fibronectin being lost and in a 50% reduction in stromal thickness (Allen et al., 1955; LeDouarin & Teillet, 1974). The endothelium also is important to the dehydration of the stroma. Patches of endothelium become confluent and develop zonulae occludens during days 30–35 in the dog, and during this period Descemet's membrane also forms. The cornea achieves relative transparency at the end of gestation in the dog. Following eyelid opening at approximately 14 days postnatal in the dog, there is an initial decrease in corneal thickness over 4 weeks, presumably as the corneal endothelium become functional. Then, a gradual increase in thickness occurs over the next 6 months (Montiani-Ferreira et al., 2003).

Neural crest migration anterior to the lens to form the corneal stroma and iris stroma also results in formation of a solid sheet of mesenchymal tissue, which ultimately remodels to form the anterior chamber. The portion of this sheet that bridges the future pupil is called the pupillary membrane (Fig. 1.16B, C, and D). Vessels within the pupillary membrane form the TVL, which surrounds and nourishes the lens. These vessels are continuous with those of the primary vitreous (i.e., hyaloid). The vascular endothelium is the only intraocular tissue of mesodermal origin; even the vascular smooth muscle cells and pericytes that originate from mesoderm in the rest of the body are of neural crest origin in the eye (Johnston et al., 1979; Smelser & Ozanics, 1971). In humans, the endothelial lining of Schlemm's canal, like the vascular endothelium elsewhere, is of mesodermal origin. In the dog, atrophy of the pupillary membrane begins by day 45 of gestation and continues during the first two postnatal weeks (Aguirre et al., 1972). Separation of the corneal mesenchyme (neural crest-cell origin) from the lens (surface ectoderm origin) results in formation of the anterior chamber.

In a microphthalmic or nanophthalmic globe, the cornea is correspondingly reduced in diameter. The term *microcornea* is used to describe a cornea that is proportionally smaller than normal for the size of the globe. As with lens induction, determination of the corneal diameter occurs at the time of contact by the optic vesicle with the surface ectoderm. This induction is also sensitive to timing; if the optic vesicle–ectoderm contact occurs earlier or later than normal, the ectoderm may not be fully capable of responding appropriately, resulting in microcornea.

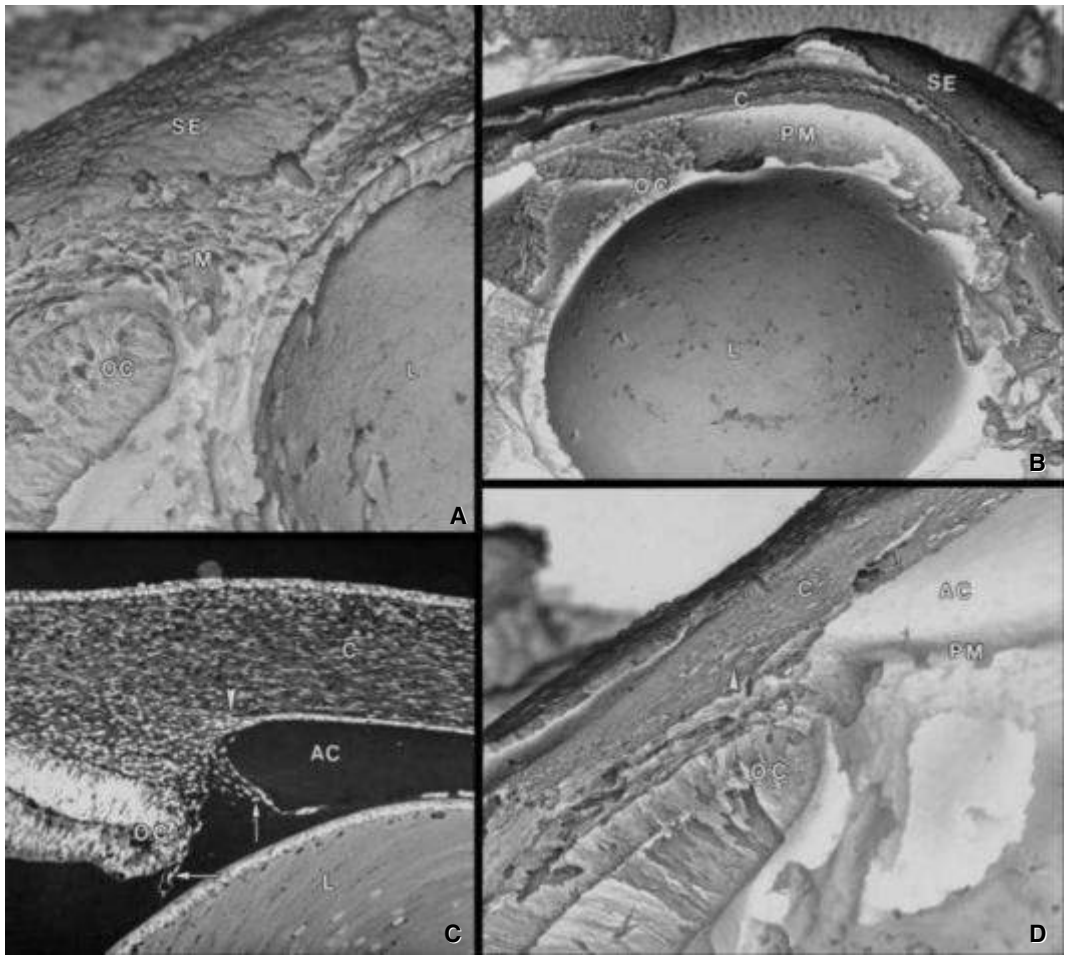


Figure 1.16 **A.** Scanning electron micrograph of a fetal human eye at approximately 42 days of gestation (equivalent to day 25 in the dog). The lens vesicle (L) has detached, and the neural crest–derived mesenchyme (M) is migrating axially between the optic cup (OC) and the surface ectoderm (SE). **B.** On day 54 in the human (day 32 in the dog), the pupillary membrane (PM) is seen within the anterior chamber. The corneal stroma (C) is apparent and is covered by the surface ectoderm (SE), which will become the corneal epithelium. OC, anterior margin of the optic cup, which will form the posterior epithelial layers of the iris, including the pupillary muscles. **C.** Light micrograph obtained at the same stage as in **B** illustrates the pupillary membrane and tunica vasculosa lentis (arrows) originating from the mesenchyme at the margin of the optic cup (OC). The limbal condensation that will become the scleral spur is indicated by the arrowhead. AC, anterior chamber; C, cornea; L, lens. **D.** Scanning electron micrograph of a fetal human eye at approximately 63 days of gestation. The AC is deeper and still bridged by the PM. Endothelialization of clefts within the neural crest–derived corneal stroma (C) by mesoderm will form Schlemm's canal (arrowhead) in the human eye. (Panels **A** and **D** reprinted with permission from Cook, C. (1989) Experimental models of anterior segment dysgenesis. *Ophthalmic Paediatrics and Genetics*, **10**, 33–46; panels **B** and **C** reprinted with permission from Cook, C., Sulik, K.K., & Wright, K.W. (2003) Embryology. In: *Pediatric Ophthalmology and Strabismus* (eds. Wright, K.W. & Spiegel, P.H.), pp. 3–38. New York: Springer.)

Development of the Iris, Ciliary Body, and Iridocorneal Angle

The two layers of the optic cup (neuroectoderm origin) consist of an inner, nonpigmented layer and an outer, pigmented layer. Both the pigmented and nonpigmented epithelium of the iris and the ciliary body develop from the anterior aspect of the optic cup; the retina develops from the posterior optic cup. The optic vesicle is organized with all cell apices directed to the center of the vesicle. During optic cup invagination, the apices of the inner and outer epithelial layers become adjacent. Thus, the cells of the optic cup are oriented apex to apex.

A thin, periodic acid–Schiff-positive basal lamina lines the inner aspect (i.e., vitreous side) of the nonpigmented epithelium and retina (i.e., inner limiting membrane). By approximately day 40 of gestation in the dog, both the pigmented and nonpigmented epithelial cells show apical cilia that project into the intercellular space. There also is increased prominence of Golgi complexes and associated vesicles within the ciliary epithelial cells. These changes, as well as the presence of "ciliary channels" between the

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apical surfaces, probably represent the first production of aqueous humor.

The iris stroma develops from the anterior segment mesenchymal tissue (neural-crest cell origin), and the iris pigmented and nonpigmented epithelium originate from the neural ectoderm of the optic cup. The smooth muscle of the pupillary sphincter and dilator muscles ultimately differentiate from these epithelial layers, and they represent the only mammalian muscles of neural ectodermal origin. In avian species, however, the skeletal muscle cells in the iris are of neural crest origin, with a possible small contribution of mesoderm to the ventral portion (Nakano & Nakamura, 1985; Yamashita & Sohal, 1986, 1987).

Differential growth of the optic cup epithelial layers results in folding of the inner layer, representing early anterior ciliary processes (Fig. 1.16B). The ciliary body epithelium develops from the neuroectoderm of the anterior optic cup, and the underlying mesenchyme differentiates into the ciliary muscles. Extracellular matrix secreted by the ciliary epithelium becomes the tertiary vitreous and, ultimately, is thought to develop into lens zonules.

Three phases of iridocorneal angle maturation have been described (Reme et al., 1983a, 1983b). First is separation of anterior mesenchyme into corneoscleral and iridociliary regions (i.e., trabecular primordium formation), followed by differentiation of ciliary muscle and folding of the neural ectoderm into ciliary processes. Second is enlargement of the corneal trabeculae and development of clefts in the area of the trabecular meshwork, which is accompanied by regression of the corneal endothelium covering the angle recess. Third is postnatal remodeling of the drainage angle, associated with cellular necrosis and phagocytosis by macrophages, resulting in opening of clefts in the trabecular meshwork and outflow pathways.

This change in the relationship of the trabecular meshwork to the ciliary body and iris root during the last trimester of human gestation occurs through differential growth, with posterior movement of the iris and the ciliary body relative to the trabecular meshwork exposing the outflow pathways. This results in progressive deepening of the chamber angle and normal conformation of the ciliary muscle and ciliary processes (Anderson, 1981). This is in contrast to previous theories of cleavage of the iris root from the cornea or atrophy of angle tissue (Barishak, 1978; Smelser & Ozanics, 1971; Wulle, 1972).

In species born with congenitally fused eyelids (i.e., dog and cat), development of the anterior chamber continues during this postnatal period before eyelid opening. At birth, the peripheral iris and cornea are in contact. Maturation of pectinate ligaments begins by 3 weeks postnatal and rarefaction of the uveal and corneoscleral trabecular meshworks to their adult state occurs during the first 8 weeks after birth. There is no evidence of mesenchymal splitting, cell death, or phagocytic activity (Samuelson & Gelatt, 1984a, 1984b).

Retina and Optic Nerve Development

Infolding of the neuroectodermal optic vesicle results in a bilayered optic cup with the apices of these two cell layers in direct contact. Primitive optic vesicle cells are columnar, but by 20 days of gestation in the dog, they form an outer cuboidal layer containing the first melanin granules in the developing embryo within the future retinal pigment epithelium (RPE). The neurosensory retina develops from the inner, nonpigmented layer of the optic cup, and the RPE originates from the outer, pigmented layer. Bruch's membrane (the basal lamina of the RPE) is first seen during this time, and becomes well developed over the next week, when the choriocapillaris is developing. By day 45 in the dog, the RPE cells take on a hexagonal cross-sectional shape and develop microvilli that interdigitate with projections from photoreceptors of the nonpigmented (inner) layer of the optic cup.

At the time of lens placode induction, the retinal primordium consists of an outer, nuclear zone and an inner, marginal (anuclear) zone. Cell proliferation occurs in the nuclear zone, with migration of cells into the marginal zone. This process forms the inner and outer neuroblastic layers, separated by their cell processes that make up the transient fiber layer of Chievitz (Fig. 1.15C, D). Cellular differentiation progresses from inner to outer layers and, regionally, from central to peripheral locations. Peripheral retinal differentiation may lag behind that occurring in the central retina by 3–8 days in the dog (Aguirre et al., 1972). Retinal histiogenesis beyond formation of the neuroblastic layers requires induction by a differentiated RPE. There are several rodent models of RPE dysplasia resulting in failure of later retinal differentiation and subsequent degeneration (Bumsted & Barnstable, 2000; Cook et al., 1991b). Retinal ganglion cells develop first within the inner neuroblastic layer, and axons of the ganglion cells collectively form the optic nerve. Cell bodies of the Müller and amacrine cells differentiate in the inner portion of the outer neuroblastic layer. Horizontal cells are found in the middle of this layer; the bipolar cells and photoreceptors mature last, in the outermost zone of the retina (Greiner & Weidman, 1980, 1981, 1982; Spira & Hollenberg, 1973).

Significant retinal differentiation continues postnatally, particularly in species born with fused eyelids. Expression of extracellular matrix elements, chondroitin sulfate, and heparin sulfate occurs in a spatiotemporally regulated manner, with a peak of chondroitin sulfate occurring at the time of eyelid opening, This corresponds to the period of photoreceptor differentiation (Erlich et al., 2003). At birth, the canine retina has reached a stage of development equivalent to the human at 3–4 months of gestation (Shively et al., 1971). In the kitten, all ganglion cells and central retinal cells are present at birth, with continued proliferation in the peripheral retina continuing during the first 2–3 postnatal weeks in dogs and cats (Johns et al., 1979; Shively et al., 1971).

Possible means of retinal regeneration have become reality with the discovery of neural stem cells in the mature eye of warm-blooded vertebrates (Engelhardt et al., 2004; Fischer, 2005). These include cells at the retinal margin, pigmented cells in the ciliary body and iris, nonpigmented cells in the ciliary body, and Müller glia within the retina. Under the influence of growth factors, these neuroectodermal cells in the avian are capable of undergoing differentiation into retinal cells (Fischer, 2005).

Sclera, Choroid, and Tapetum

These neural crest–derived tissues are all induced by the outer layer of the optic cup (future RPE). Normal RPE differentiation is a prerequisite for normal development of the sclera and choroid. The choroid and sclera are relatively differentiated at birth, but the tapetum in dogs and cats continues to develop and mature during the first 4 months postnatally. The initially mottled, blue appearance of the immature tapetum is replaced by the blue/green to yellow/orange color of the adult. These color variations seen in immature dogs can prove a challenge to accurate funduscopic assessment.

Posterior segment uveoscleral colobomas most often result from a primary RPE abnormality. Subalbinotic animals have a higher incidence of posterior segment colobomas, with reduced RPE pigmentation being a marker for abnormal RPE development (Bertram et al., 1984; Cook et al., 1991a; Gelatt & McGill, 1973; Gelatt & Veith, 1970; Munyard et al., 2007; Rubin et al., 1991). The most common example is the choroidal hypoplasia of Collie eye anomaly (Barnett, 1979).

Vitreous

The primary vitreous forms posteriorly, between the primitive lens and the inner layer of the optic cup (see Fig. 1.10 and Fig. 1.12). In addition to the vessels of the hyaloid system, the primary vitreous also contains mesenchymal cells, collagenous fibrillar material, and macrophages. The secondary vitreous forms as the fetal fissure closes, and contains a matrix of cellular and fibrillar material, including primitive hyalocytes, monocytes, and hyaluronic acid (Akiya et al., 1986; Bremer & Rasquin, 1998). Identification of microscopic vascular remnants throughout the vitreous of adult rabbits has led to speculation for interactive remodeling of the primary vitreous to form secondary vitreous (Los et al., 2000a, 2000b). Plasma proteins enter and leave the vitreous and, in the chick, there is a concentration of 13% of that found in plasma, until a decline to 4% of plasma levels occurs during the last week prior to hatching (Beebe et al., 1986). Primitive hyalocytes produce collagen fibrils that expand the volume of the secondary vitreous.

The tertiary vitreous forms as a thick accumulation of collagen fibers between the lens equator and the optic cup. These fibers are called the marginal bundle of Drualt or Drualt's bundle. Drualt's bundle has a strong attachment to the inner layer of the optic cup, and it is the precursor to the vitreous base and lens zonules. The early lens zonular fibers appear to be continuous with the inner, limiting membrane of the nonpigmented epithelial layer covering the ciliary muscle. Elastin and emulin (elastin microfibril interface located protein) have been identified in developing zonules and Descemet's membrane (Bressan et al., 1993; Horrigan et al., 1992). Experimental exposure of chick embryos to homocysteine results in deficient zonule development and congenital lens luxation (Maestro De Las Casas et al., 2003). Traction of the zonules contributes to expansion of the lens and localized absence of zonules can lead to a corresponding area of the lens that is flattened and inaccurately referred to as a lens coloboma (see later Fig. 1.32).

Atrophy of the primary vitreous and hyaloid leaves a clear, narrow central zone, which is called Cloquet's canal. In the mouse, Doppler ultrasound biomicroscopy has been used to document *in vivo* the decrease in blood velocity associated with hyaloid regression between birth and postnatal day 13 (Brown et al., 2005). Most of the posterior vitreous gel at birth is secondary vitreous, with the vitreous base and zonules representing tertiary vitreous.

Optic Nerve

Axons from the developing ganglion cells pass through vacuolated cells from the inner wall of the optic stalk. A glial sheath forms around the hyaloid artery. As the hyaloid artery regresses, the space between the hyaloid artery and the glial sheath enlarges. Bergmeister's papilla represents a remnant of these glial cells around the hyaloid artery. Glial cells migrate into the optic nerve and form the primitive optic disc. The glial cells around the optic nerve and the glial part of the lamina cribrosa come from the inner layer of the optic stalk, which is of neural ectoderm origin. Later, a mesenchymal (neural crest origin) portion of the lamina cribrosa develops. Myelinization of the optic nerve begins at the chiasm, progresses toward the eye, and reaches the optic disc after birth.

Eyelids

The eyelids develop from surface ectoderm, which gives rise to the epidermis, cilia, and conjunctival epithelium. Neural crest mesenchyme gives rise to deeper structures, including the dermis and tarsus. The eyelid muscles (i.e., orbicularis and levator) are derived from craniofacial condensations of mesoderm called somitomeres. In the craniofacial region, presumptive connective tissue–forming mesenchyme derived from the neural crest imparts spatial patterning information

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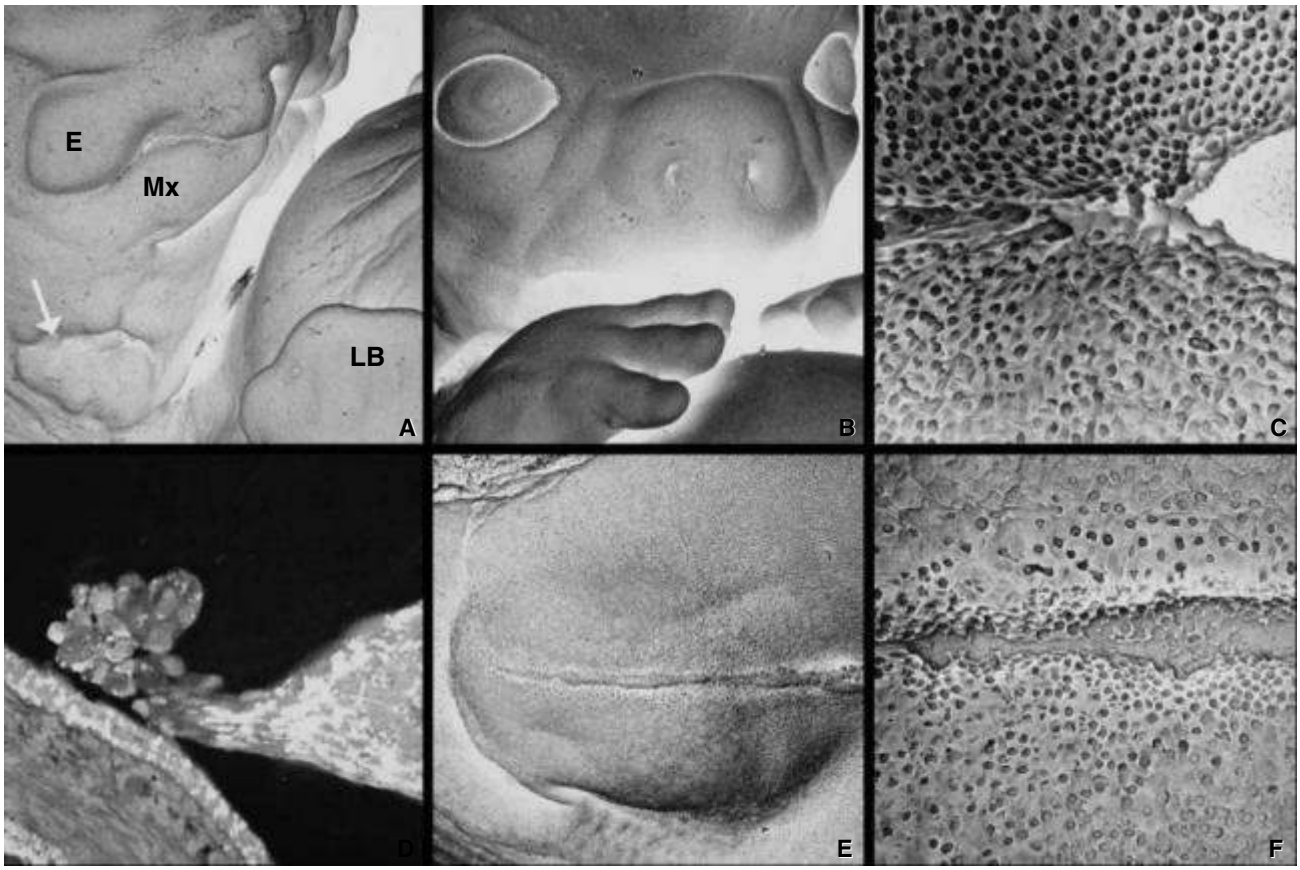


Figure 1.17 **A.** Lateral view of the head of a human embryo at 6 weeks of gestation. The individual hillocks that will form the external ear can be identified both cranial and caudal to the first visceral groove (arrow). The developing eye is adjacent to the maxillary prominence (Mx). LB, forelimb bud. **B.** Frontal view of the head of a human embryo at 8 weeks of gestation. Formation of the face is largely complete, and the eyelids are beginning to close. **C.** Eyelid closure begins at the medial and lateral canthi and progresses axially. **D.** Light micrograph of the eyelid marginal epithelium in a mouse at day 15 of gestation. The actively migrating epithelium forms a cluster of cells adjacent to the corneal epithelium. **E** and **F.** Surface view of the fused eyelids from a human embryo at 10 weeks of gestation. (Panels **A**, **B**, **E**, and **F** reprinted with permission from Sulik, K.K. & Schoenwolf G.C. (1985) Highlights of craniofacial morphogenesis in mammalian embryos, as revealed by scanning electron microscopy. *Scanning Electron Microscopy*, **4**, 1735–1752; panel **D** reprinted with permission from Cook, C.S. & Sulik, K.K. (1986) Sequential scanning electron microscopic analyses of normal and spontaneously occurring abnormal ocular development in C57B1/6J mice. *Scanning Electron Microscopy*, **3**, 1215–1227.)

upon myogenic cells that invade it (Noden, 1986). The upper eyelid develops from the frontonasal process; the lower eyelid develops from the maxillary process. The lid folds grow together and elongate to cover the developing eye (Fig. 1.17). The upper and lower lids fuse on day 32 of gestation in the dog. Separation occurs 2 weeks postnatally.

Extraocular Muscles

The extraocular muscles arise from mesoderm in somitomeres (i.e., preoptic mesodermal condensations; Jacobson, 1988; Meier, 1982; Meier & Tam, 1982; Packard & Meier, 1983; Tam, 1986; Tam et al., 1982; Tam & Trainor, 1994; Trainor & Tam, 1995). Spatial organization of developing eye muscles is initiated before they interact with the neural crest mesenchyme. Patterning of the segmental somitomeres follows that of the neural crest; that is, somitomere I (forebrain), somitomere III (caudal midbrain), and somitomeres IV and VI (hindbrain; Trainor & Tam, 1995). From studies of chick embryos, it has been shown that the oculomotor-innervated muscles originate from the first and second somitomeres, the superior oblique muscle from the third somitomere, and the lateral rectus muscle from the fourth somitomere (Wahl et al., 1994). The entire length of these muscles appears to develop spontaneously rather than from the orbital apex anteriorly, as had been previously postulated (Sevel, 1981, 1986). Congenital extraocular muscle abnormalities are rarely identified and reported in the dog (Martin, 1978). This may be a result of several factors, including the fact that the extraocular muscles are normally less well developed in domestic mammals compared with humans,

and the limited ability to assess minor abnormalities which would be manifest as impaired binocular vision.

Developmental Ocular Anomalies

Cyclopia and Synophthalmia

Formation of a single median globe (i.e., cyclopia) or two incompletely separated or fused globes (i.e., synophthalmia) may occur by two different mechanisms. The "fate maps," which have been produced for amphibian embryos, have revealed the original location of the neural ectodermal tissue that will form the globes as a single, bilobed area crossing the midline in the anterior third of the trilaminar embryonic disc. An early defect in separation of this single field could result in the formation of a single, or incompletely separated, median globe(s) (Fig 1.18A). After separation into bilateral optic vesicles, later loss of the midline territory in the embryo could result in fusion of the ocular fields. This loss of midline territory, prior to separation into two eye fields, is seen in holoprosencephaly, and the facial features characteristic of human fetal alcohol syndrome represent a mild end of the holoprosencephalic spectrum (Cohen & Sulik, 1992; Sulik & Johnston, 1982). Cases of cyclopia or synophthalmia are invariably associated with severe craniofacial malformations (Fig. 1.18A and B) and are usually nonviable.

Cyclopia is rarely identified in dogs (Njoku et al., 1978). However, in sheep, ingestion of the alkaloids (cyclopamine and jervine) from the weed *Veratrum californicum* by pregnant ewes on day 14 of gestation (total duration of gestation 150 days) is the best-documented example of teratogen-induced cyclopia and synophthalmia in domestic animals (Binns et al., 1959; Bryden et al., 1971; Cooper et al., 1998; Incardona et al., 1998; Keeler, 1990; Keeler & Binns, 1966; Saperstein, 1975). It has been shown that cyclopamine specifically blocks the Sonic hedgehog (Shh) signaling pathway (Cooper et al., 1998; Incardona et al., 1998, 2000). The specific timing for veratrum-induced cyclopia in sheep corresponds to the period of gastrulation and formation of the neural plate before separation of the optic fields. Exposure to the alkaloid earlier in gestation results in fetal death; later exposure causes skeletal malformation or has no effect, thus demonstrating the importance of narrow, sensitive periods in development.





Figure 1.18 **A.** Cyclopia in a Holstein calf, etiology unknown. Note the single median globe, palpebral fissure, cornea, and pupil. **B.** Cyclopia in a nonviable kitten. Note the narrow forebrain and midface regions. The limbs and axial skeleton are relatively normal, demonstrating limited effect on the forebrain region of the embryo. (Panel **A** courtesy of Brian Wilcock.)

Microphthalmia and Anophthalmia

Microphthalmia can occur early in development through a deficiency in the optic vesicle (Fig. 1.19A), or later through failure of normal growth and expansion of the optic cup (Fig. 1.19B). An early deficiency in the size of the globe as a



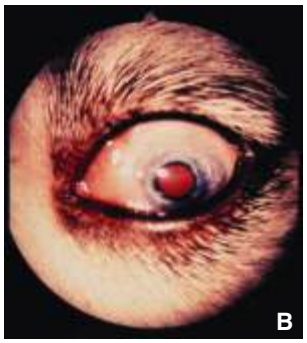


Figure 1.19 **A.** Microphthalmia and persistent pupillary membranes in a Chow Chow puppy. Note that the size of the palpebral fissure is proportional to the reduced size of the globe as a whole. This is consistent with microphthalmia induced at the optic vesicle stage. **B.** Microphthalmia induced at a later stage of gestation, possibly by delayed closure of the optic fissure, although this eye does not exhibit a coloboma. Note the larger size of the palpebral fissure relative to the small globe.

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whole is often associated with a correspondingly small, palpebral fissure. The fissure size is determined by the optic vesicle size during its contact with the surface ectoderm, so this supports a malformation sequence beginning at formation of the optic sulcus, optic vesicle, or earlier. Results from studies of teratogen-induced ocular malformations have been helpful in identifying sensitive developmental periods. Acute exposure to teratogens before optic sulcus formation results in an overall deficiency of the neural plate, with subsequent reduction in the optic vesicle size. When microphthalmia originates during development of the neural plate/optic sulcus, it is often associated with multiple ocular malformations, including anterior segment dysgenesis, cataract, retinal dysplasia, and persistence of the hyaloid (Table 1.3).

Later initiation of microphthalmia can occur through failure to establish early IOP (Berman & Pierro, 1969; Hero et al., 1991). Placement of a capillary tube into the vitreous cavity of the embryonic chick eye reduces the IOP and markedly slows growth of the eye (Coulombre, 1956). Histologic examination of the intubated eyes demonstrates a proportional reduction in the size of all ocular tissues except the neural retina and the lens, which are normal in size for the age of the eye. The retina in these eyes is highly convoluted, filling the small posterior segment. Thus, it has been concluded that growth of the neural retina occurs independent of the other ocular tissues. Experimental removal of the lens does not alter retinal growth (Coulombre & Coulombre, 1964). Growth of the choroid and sclera appears to depend on IOP, as does folding of the ciliary epithelium (Bard et al., 1975; Cook, 1989, 1995; Cook & Sulik, 1988). Thus, failure of fusion of the optic fissure can result in microphthalmia and associated malformations (i.e., colobomatous microphthalmia). A delay in closure of this fissure during a critical growth period may result in inadequate globe expansion as well. If the fissure eventually closes, however, it may be difficult to distinguish between colobomatous and noncolobomatous microphthalmia. If the optic vesicle develops normally before abnormal (delayed) closure of the optic fissure, the palpebral fissure may not be reduced in size as much as the globe as a whole is reduced (Fig. 1.19B). In most cases, microphthalmia occurs through a combination of cellular deficiency within the optic vesicle/cup compounded by failure of the optic fissure to close on schedule.

Table 1.3 Anomalies associated with microphthalmia in dogs.

Anomaly	Breed	References
Anterior segment dysgenesis	Saint Bernard, Doberman	Arnbjerg & Jensen (1982); Bergsjo et al. (1984); Boroffka et al. (1998); Lewis et al. (1986); Martin & Leipold (1974); Peiffer & Fischer (1983); Stades (1980, 1983); van der Linde-Sipman et al. (1983)
Cataract	Old English Sheepdog	Barrie et al. (1979)
	Akita	Laratta et al. (1985)
	Miniature Schnauzer	Gelatt et al. (1983); Samuelson et al. (1987); Zhang et al. (1991)
	Chow Chow	Collins et al. (1992)
	Cavalier King Charles Spaniel	Narfstrom & Dubielzig (1984)
	English Cocker Spaniel	Strande et al. (1988)
	Irish Wolfhound	Kern (1981)
Retinal dysplasia	Saint Bernard	Martin & Leipold (1974)
	Doberman	Arnbjerg & Jensen (1982); Bergsjo et al. (1984); Lewis et al. (1986); Peiffer & Fischer (1983)

Anophthalmia represents an extreme on the spectrum of microphthalmia. In most cases, careful examination of the orbital contents will reveal primitive ocular tissue (i.e., actual microphthalmia). True anophthalmia results from a severe developmental deficiency in the primitive forebrain, at a stage before optic sulcus formation. This usually results in a nonviable fetus.

Microphthalmia in domestic animals occurs sporadically and is associated with multiple malformations (Table 1.3), including anterior segment dysgenesis, cataract, persistent hyperplastic primary vitreous (Bayon et al., 2001; Boeve et al., 1992; van der Linde-Sipman et al., 1983), and retinal dysplasia (Bayon et al., 2001; Bertram et al., 1984). In the Doberman Pinscher, microphthalmia, anterior segment dysgenesis, and retinal dysplasia are thought to be inherited as autosomal recessive traits (Bergsjo et al., 1984). Inherited microphthalmia in Texel sheep has as its primary event abnormal development with involution of the lens vesicle followed by proliferation of dysplastic mesenchyme, which develops into cartilage, smooth muscle, fat, and lacrimal gland (van der Linde-Sipman et al., 2003).

A similar spectrum of multiple ocular malformations has been described as a presumably inherited condition associated with central nervous system malformations in Angus (Rupp & Knight, 1984), Shorthorn (Greene & Leipold, 1974), and Hereford cattle (Blackwell & Cobb, 1959; Kaswan et al., 1987), as well as in nondomestic species, including raptors (Buyukmihci et al., 1988), camel (Moore et al., 1999), and white-tailed deer (Wyand et al., 1972). Colobomatous microphthalmia is initiated later in gestation.

In swine, congenital microphthalmia has been historically reported to be associated with maternal vitamin A deficiency (Hale, 1935; Manoly, 1951; Roberts, 1948). Conversely, maternal excess of vitamin A and its analogue, retinoic acid, has been demonstrated (Bayon et al., 2001) to result

in teratogenic ocular and craniofacial malformations in humans and laboratory animals (Cook, 1989; Cook & Sulik, 1988, 1990; Mulder et al., 2000).

Colobomatous Malformations

A coloboma refers broadly to any congenital (present at birth) tissue defect. Ocular colobomas most frequently involve the vascular tunic of the eye, namely the iris and choroid. The spectrum encompasses minor defects (i.e., dyscoria) as well as major defects (i.e., aniridia). Aniridia occurs rarely in animals (Irby & Aguirre, 1985; Saunders & Fincher, 1951), but is seen as a malformation in humans associated with genetic syndromes including Rieger syndrome (*PITX2* gene; Perveen et al., 2000) and *PAX6* gene mutations (Sonoda et al., 2000). The iris stroma develops from neural crest mesenchyme induced by the bilayered epithelium of the anterior optic cup. Thus, a complete and full-thickness defect in the iris most likely results from incomplete axial expansion of the anterior optic cup. Iris hypoplasia represents the mild spectrum of this type of coloboma and is seen frequently in dogs (particularly those breeds characterized by subalbinism) and has been recognized as a genetic syndrome in horses (Ewart et al., 2000).

The classic explanation for localized colobomatous malformations involves failure of the optic fissure to close. Such failure may result in secondary "colobomatous" microphthalmia (Fig. 1.20) and, in experimental models, there may be deviation of the fissure by 90° or more. When defects are located in any inferior location (particularly in a small globe), this is the most likely explanation. This defect in closure of the optic fissure (future RPE and ciliary and iris epithelium) results in failure of induction of the adjacent choroid and sclera. Any or all of these layers may be affected. The clinically apparent sequella to abnormal fissure closure may be only a subtle degree of dyscoria (Matsuura et al., 2013).



Figure 1.20 Microphthalmia and an inferior coloboma of the scleral and uveal tissue allowing vitreous prolapse into the subconjunctival space. In colobomatous microphthalmia, globe expansion is impaired by the inability to establish intraocular pressure because of the optic fissure failing to close. Both mechanisms of microphthalmia may occur in a single eye.

Many colobomatous defects, however, occur in other locations (Briziarelli & Abrutyn, 1975; Gelatt et al., 1969; Gwin et al., 1981). Differentiation of the neural crest–derived stroma of the choroid and iris is determined by the adjacent structures of the outer layer of the optic cup: anteriorly the iris and ciliary epithelium, and posteriorly the RPE. In sequential analyses of animals exhibiting primary abnormalities in differentiation of the outer layer of the optic cup, anterior and posterior segment colobomas are associated with uveal epithelium/RPE defects (Cook et al., 1991a, 1991b; Zhao & Overbeek, 2001).

Prenatal studies of colobomas in the Australian Shepherd dog have demonstrated a primary defect in the RPE, resulting in hypoplasia of the adjacent choroid and sclera (Fig. 1.21 and Fig. 1.22; Cook et al., 1991a). This condition is referred to as merle ocular dysgenesis (MOD) because of the correlation with the merle coat coloration (Bertram et al., 1984). A similar spectrum has been identified in cattle (Gelatt et al., 1969), Great Dane dogs, and cats (Gwin et al., 1981) exhibiting incomplete albinism. It is likely that the subalbinism is associated with abnormal RPE that fails to induce the overlying neural crest.

Choroidal hypoplasia in the Collie dog (i.e., "Collie eye anomaly" or CEA; Barnett, 1979) may represent a malformation sequence similar to that of MOD (Fig. 1.23 and Fig. 1.24). Differences between CEA and MOD are illustrated in Table 1.4. CEA has been widely described in the Collie, Border Collie, Shetland Sheepdog, and Australian Shepherd (Barnett, 1979; Barnett & Stades, 1979; Bedford, 1982a; Rubin et al., 1991). Variations of this congenital malformation, including scleral ectasia, sporadically occur in other breeds as well (Bedford, 1998). It has been demonstrated that choroidal hypoplasia associated with CEA segregates as an autosomal recessive trait with nearly 100% penetrance (Lowe et al., 2003).

Optic nerve coloboma as an isolated finding is likely caused by localized failure of closure of the optic fissure that begins to close at the level of the disc with progression anterior and posterior. Optic nerve coloboma is seen unassociated with genetically identifiable CEA mutation NHEJ1 in the Nova Scotia Duck Tolling Retriever (Brown et al., 2018).

Dermoid

The presence of aberrant tissue (e.g., skin, cartilage, bone) within the orbit may originate early in development through abnormal differentiation of an isolated group of cells. Arrest or inclusions of epidermal and connective tissues (i.e., surface ectoderm and neural crest) may occur during closure of

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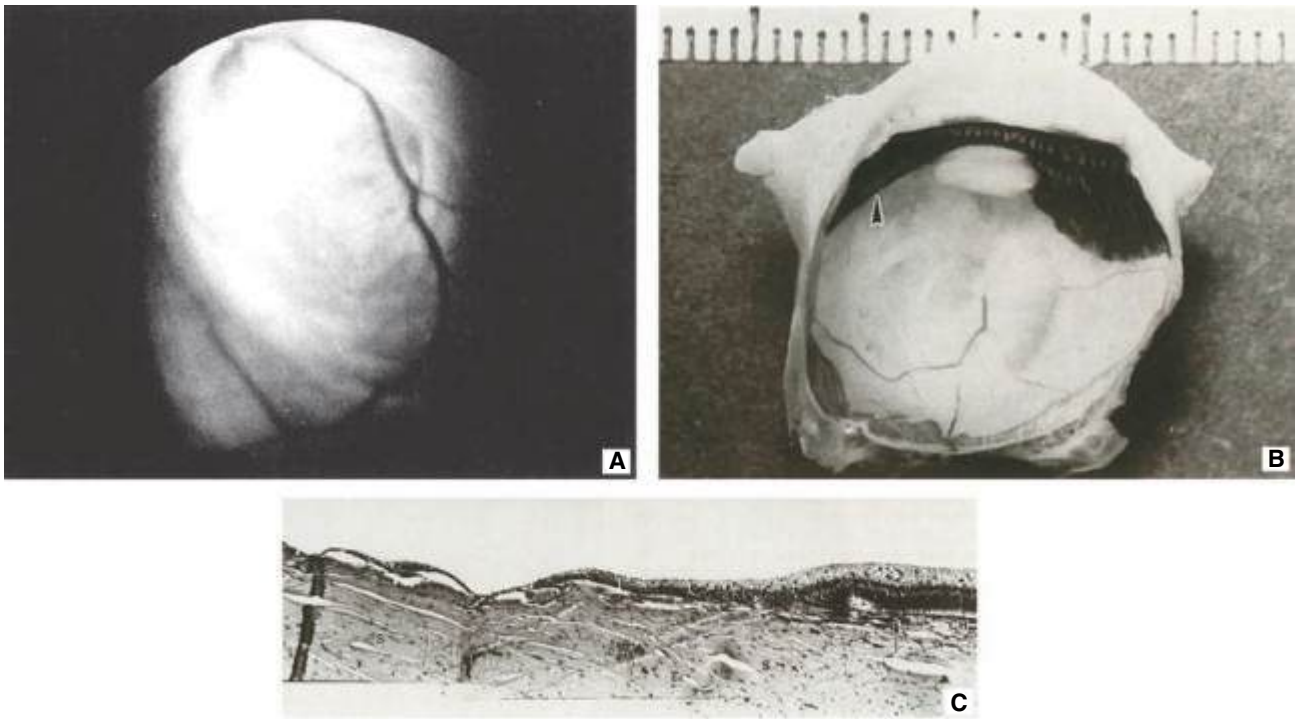


Figure 1.21 Clinical (**A**) and gross (**B**) photographs of the ocular fundus of an adult Australian Shepherd dog affected with merle ocular dysgenesis. Note the large excavation of the equatorial posterior segment. There is also a defect in the ciliary body (arrowhead), which was not apparent clinically. **C.** At the light microscopic level, defects such as this consist of a thin layer of sclera (S) lined by a glial membrane. Note the abrupt transition from normal retina, retinal pigment epithelium (RPE), and choroid seen on the right to the sudden loss of RPE and choroid at the level indicated by the arrow. (Reprinted with permission from Cook, C., Burling, K., & Nelson E. (1991) Embryogenesis of posterior segment colobomas in the Australian Shepherd dog. *Progress in Veterinary & Comparative Ophthalmology*, **1**, 163–170.)

the fetal clefts. Abnormal invagination of ectodermal tissue later in gestation may result in a pocket of well-differentiated dermal tissue. Eyelid dermoids may occur though isolation of an island of ectoderm later forming a nodule of tissue that is, strictly speaking, not abnormal in location, but in configuration, a nonneoplastic overgrowth of tissue disordered in structure (Fig. 1.25). These are termed *hamartomas* (i.e., benign tissue mass resulting from faulty development). Limbal dermoids represent *choristomas* (i.e., mass formed by tissue not normally found at this site; Fig. 1.26). Both eyelid epidermis and corneal epithelium originate from surface ectoderm, following induction by the optic vesicle, and there appears to be a narrow period during which the surface ectoderm can respond to inductive influences to produce a normal lens. The same may be true for induction of the cornea. Dermoids are seen in all species as an incidental finding, and they are seen as an inherited condition in cattle and some dog breeds (Adams et al., 1983; Barkyoumb & Leipold, 1984).

Anterior Segment Dysgenesis

The anterior segment dysgeneses identified in humans encompass a broad range of malformations, including Peters' anomaly, Axenfeld–Rieger syndrome, iridocorneal endothelium syndrome, posterior polymorphous dystrophy, and Sturge–Weber syndrome. Similar anomalies have been described in domestic animals, generally as sporadic occurrences (Irby & Aguirre, 1985; Peiffer, 1982; Rebhun, 1977; Swanson et al., 2001). Anterior segment dysgenesis is often associated with microphthalmia (Arnbjerg & Jensen, 1982; Bergsjo et al., 1984; Lewis et al., 1986; Martin & Leipold, 1974; Peiffer & Fischer, 1983).

In domestic animals, *persistent pupillary membranes* represent the most common manifestation of anterior segment dysgenesis. In the embryo, the pupillary membrane forms a solid sheet of tissue that is continuous with the iris at the level of the collarette (see Fig. 1.19). Regression occurs during the first two postnatal weeks, before eyelid opening in the dog. Persistence of some pupillary membrane strands was noted in 0.7% of 575 Beagles aged from 16 to 24 weeks (Bellhorn, 1974). Inherited persistent pupillary membranes occur in the Basenji dog (Bistner et al., 1971; Roberts & Bistner, 1968), and they may be associated with corneal or lens opacities (or both) at the site of membrane attachments. Complete persistence of a sheet of tissue bridging the pupil is rare and results in visual impairment. Persistent pupillary

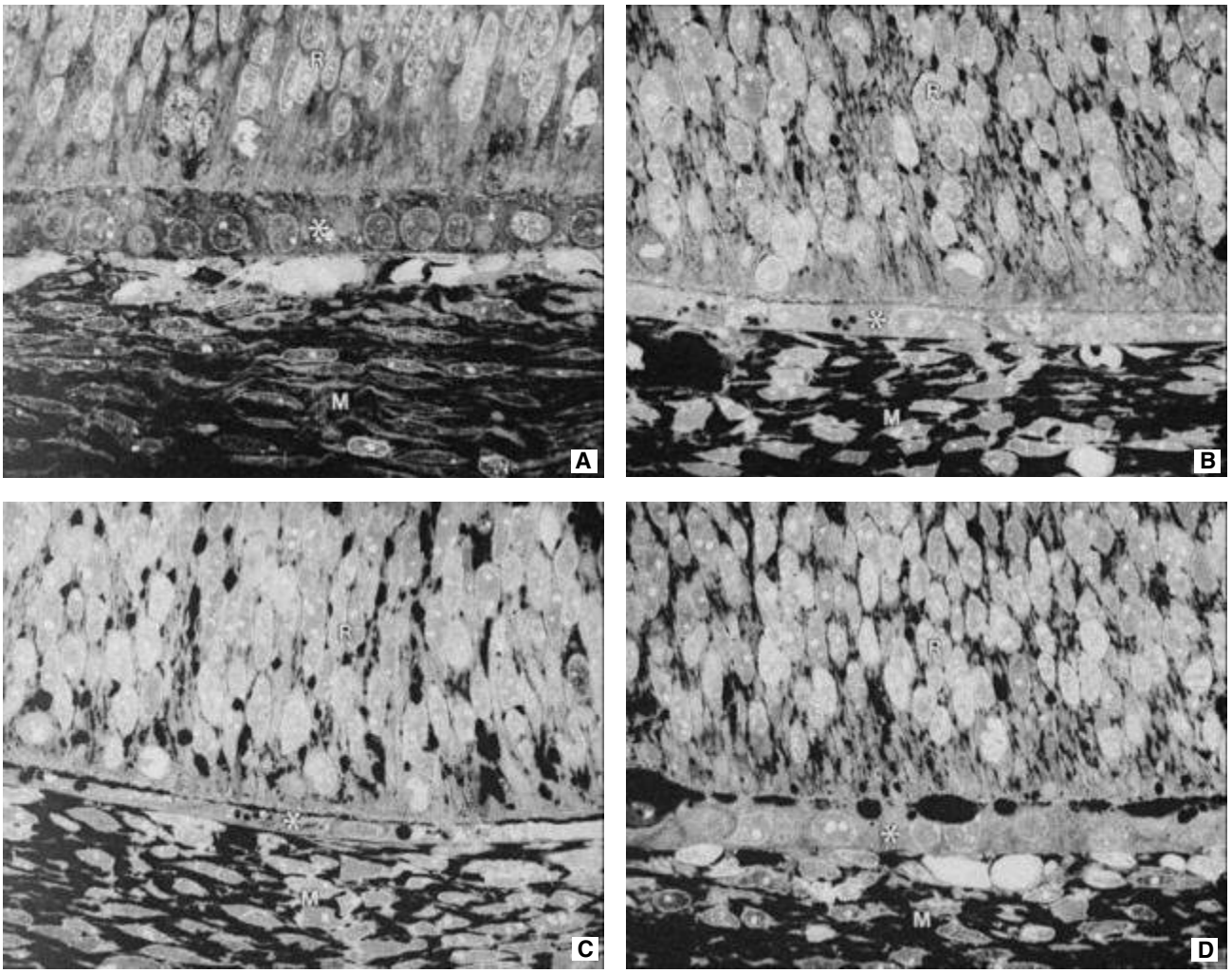


Figure 1.22 Sequential histology of merle ocular dysgenesis (MOD). **A.** Normal canine eye on day 30 of gestation. Note the cuboidal appearance of the nonpigmented retinal pigment epithelium (RPE; ·), which is closely apposed to the neural retina (R). The nuclei closest to the RPE are those of the outer neuroblastic layer. M, periocular mesenchyme—anlage of the choroid and sclera. **B.** MOD-affected eye on day 35 of gestation. The RPE (·) is shortened and contains a few intracytoplasmic vacuoles. **C** and **D.** MOD-affected eye on day 35 of gestation. The RPE (·) has become progressively thinner and exhibits a large number of vacuoles. Separation of the degenerating RPE from the neural retina also can be seen. (Reprinted with permission from Cook, C., Burling, K., & Nelson, E. (1991) Embryogenesis of posterior segment colobomas in the Australian shepherd dog. *Progress in Veterinary & Comparative Ophthalmology*, **1**, 163–170.)

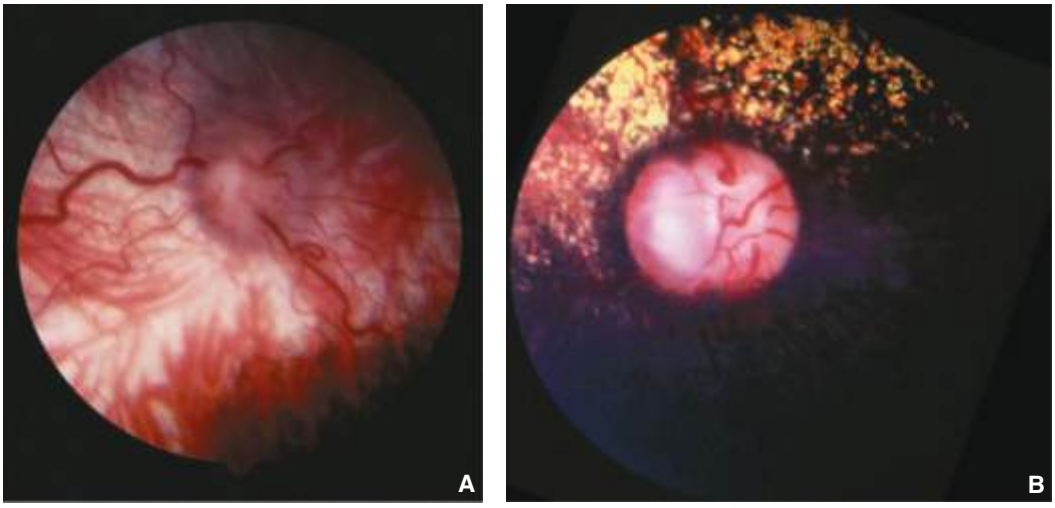


Figure 1.23 **A.** Fundus photograph of choroidal hypoplasia associated with Collie eye anomaly. Note the white sclera with superimposed choroidal and retinal vasculature. **B.** Optic nerve coloboma in a Collie affected with Collie eye anomaly. The coloboma is located temporally adjacent to an area of mild choroidal hypoplasia (identified by absence of tapetum and visible choroidal vasculature).

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Figure 1.24 Gross photograph of an optic nerve coloboma in a Collie. Note the excavation of thinned sclera lined by glial tissue (neuroectoderm) continuous with retina. (Reprinted with permission from Wilcock, B. (2007) *Pathologic Basis of the Veterinary Disease*, 4th ed. (eds. McGavin, M.D. & Zachary, J.F.). St. Louis, MO: Elsevier.)

Table 1.4 Comparative features of merle ocular dysgenesis and Collie eye anomaly.

	Merle Ocular Dysgenesis	Collie Eye Anomaly
Coat color	Homozygous merle	No correlation
Microphthalmia	Frequent	Rare/mild
Choroidal hypoplasia	Extensive scleral/ retinal defects	Common, localized
Optic nerve coloboma	Rare	Frequent
Cataract	Frequent	Rare
Iris coloboma	Frequent	Rare

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membranes also occur sporadically in other breeds (Strande et al., 1988).

Because most structures of the ocular anterior segment are of neural crest origin, it is tempting in cases of anterior segment anomalies to incriminate this cell population as being abnormal in differentiation, migration, or both. This



Figure 1.25 Eyelid dermoid in a Boxer dog. The tissue is histologically normal skin in a grossly normal location, but abnormal in configuration, representing a hamartoma. (Courtesy of Robert Peiffer.)



Figure 1.26 Limbal dermoid in a Lhasa Apso puppy. This is an example of a choristoma (histologically normal tissue in an abnormal location).

theory has resulted in labeling these conditions, when they occur in humans, as ocular neurocristopathies, particularly when other anomalies exist in tissues that are largely derived from the neural crest (e.g., craniofacial connective tissue, teeth; Bahn et al., 1984; Kupfer et al., 1975; Kupfer & Kaiser-Kupfer, 1978; Shields et al., 1985; Waring et al., 1975). When considering this theory, it is important to realize two concepts. First, the neural crest is the predominant cell population of the developing craniofacial region, particularly the eye. In fact, the list of ocular tissues *not* derived from neural crest is relatively small (see Table 1.2). Thus, the fact that most malformations of this region involve crest tissues may reflect their ubiquitous distribution rather than their common origin. The normal development of the choroid and sclera (also of neural crest origin) in most of these "neural crest syndromes" argues against a primary neural crest anomaly. Second, the neural crest is an actively migrating

population of cells and can be easily influenced by adjacent cell populations. Thus, the perceived anomaly of neural crest tissue may, in many cases, be a secondary effect.

Much of the maturation of the iridocorneal angle occurs late during gestation and during early postnatal life in the dog, but earlier events may influence development of the anterior segment. Anterior segment dysgenesis syndromes characterized primarily by axial defects in corneal stroma and endothelium, accompanied by corresponding malformations in the anterior lens capsule and epithelium (i.e., Peters' anomaly), most likely represent a manifestation of abnormal keratolenticular separation (Fig. 1.27 and Fig. 1.28). This spectrum of malformations that mimic Peters' anomaly can be induced by teratogen exposure in mice before optic sulcus invagination (Fig. 1.29 and Fig. 1.30; Cook, 1989; Cook & Sulik, 1988; Cook et al., 1987). Similar syndromes of anterior segment dysgenesis have been identified in humans following ethanol exposure (Miller et al., 1984; Stromland et al., 1991).



Figure 1.27 Clinical features of Peters' anomaly (anterior segment dysgenesis) resulting from abnormal separation of the lens vesicle from the surface ectoderm. **A.** Persistent pupillary membranes. **B.** Corneal opacity associated with defect in corneal endothelium, Descemet's membrane, and corneal stroma (neural crest). **C.** Iris hypoplasia. **D.** Anterior lenticonus and anterior polar cataract associated with partial defect in anterior lens capsule. (Drawing by Farid Mogannam.)

The size of the lens vesicle is determined by the area of contact between the optic vesicle and the surface ectoderm. Thus, factors influencing the size of the optic vesicle or the angle at which the optic vesicle approaches the surface ectoderm may affect the ultimate size of the lens vesicle. Microphakia resulting from optic vesicle deficiencies may be initiated very early in gestation (i.e., during formation of the neural plate). Microphakia associated with lens luxation has been described in two unrelated Siamese kittens (Molleda et al., 1995); as the globes were apparently otherwise normal, a primary abnormality in the lens placode ectoderm can be postulated. Aphakia is much more rare, and may occur through failure of contact between the optic vesicle and the surface ectoderm during the period when the surface ectoderm can respond to its inductive influences. As the anterior lens epithelium is required for induction of the corneal endothelium, this early initiation of aphakia would be associated with dysgenesis of the cornea and (likely) anterior uvea. Alternatively, normal induction of a lens vesicle followed by later involution would be expected to result in an eye with more normal anterior segment morphology. The lens aplasia (lap) mouse demonstrates faulty lens basement membrane formation associated with apoptosis and involution of the rudimentary lens vesicle (Aso et al., 1995, 1998). Sporadic cases of aphakia have been described in domestic animals, including a cat with associated retinal detachment but apparently normal iridocorneal structures (histopathology not available; Peiffer, 1982), and a litter of Saint Bernard puppies with multiple ocular malformations (Martin & Leipold, 1974). In humans, *in utero* exposure to rubella or parvovirus B can result in aphakia; anterior segment structures are variably affected (Hartwig et al., 1988). Abnormalities in lens shape (e.g., spherophakia, lens coloboma) may actually represent a primary abnormality in the ciliary processes, zonular fibers, or both, resulting in a lack of tension on the lens (Fig. 1.31 and Fig. 1.32). Thus, the term *coloboma* may be inaccurate when used in reference to a flattened equatorial portion of the lens that is not a true lens defect.

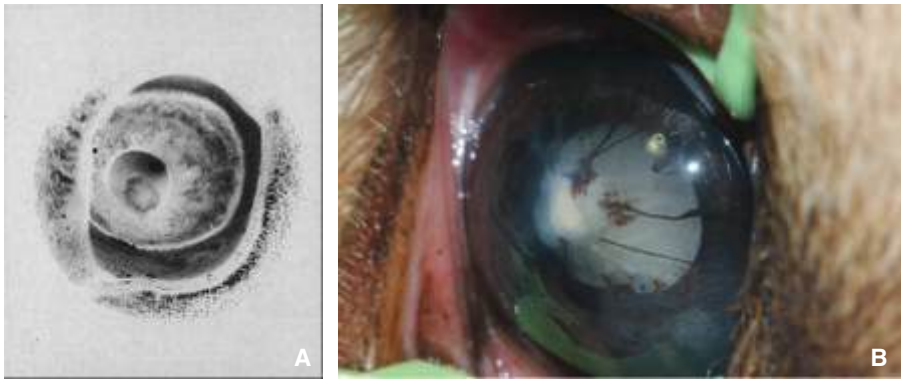


Figure 1.28 **A.** Clinical photograph of a puppy with Peters' anomaly exhibiting microphthalmia, a central corneal opacity, anterior axial cataract, and persistent pupillary membranes. **B.** A more severe form of anterior segment dysgenesis with visible lens material trapped within the axial cornea, accompanied by persistent pupillary membranes leading to the corneal defect.

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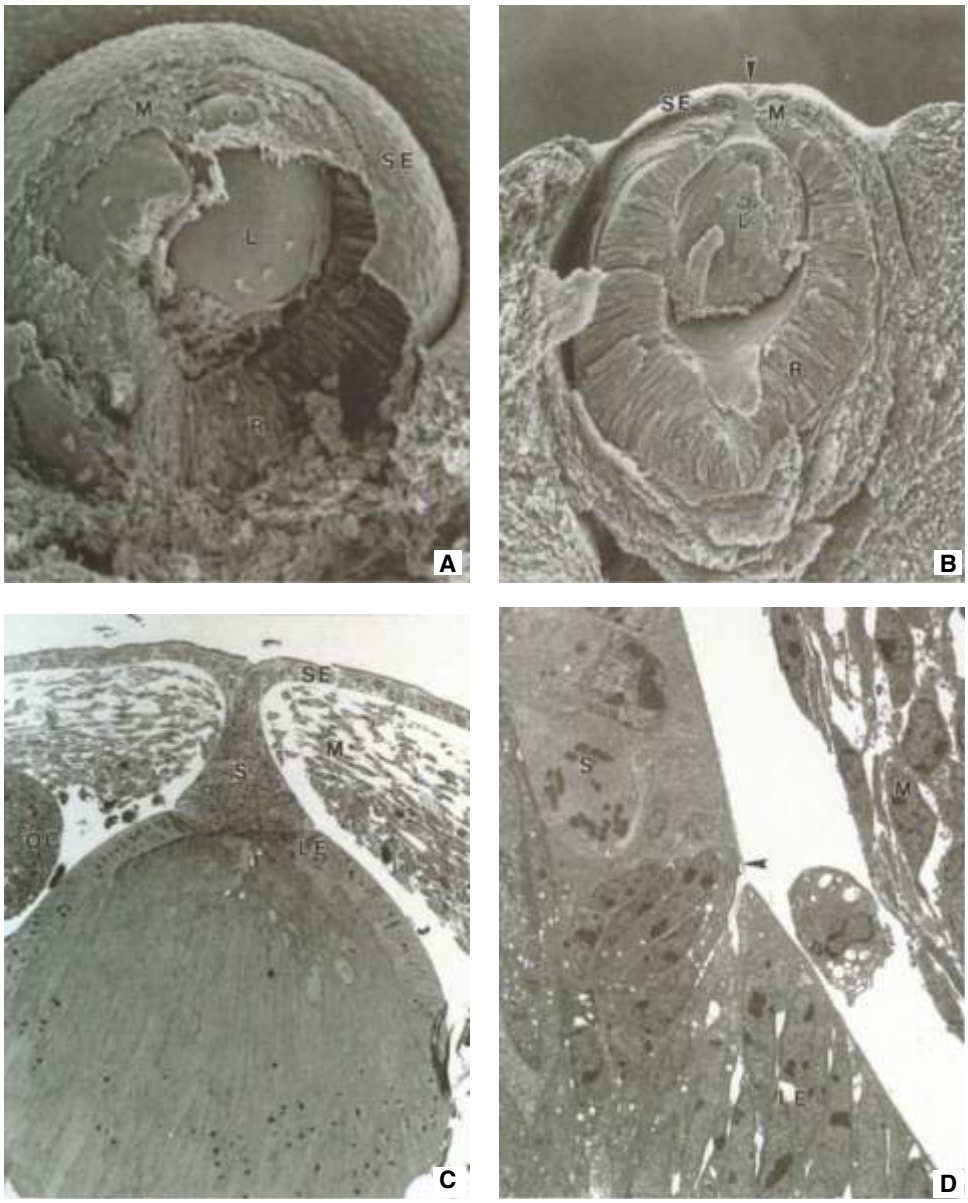


Figure 1.29 Keratolenticular dysgenesis induced by teratogen exposure in mice. **A.** Mouse embryo following acute exposure to ethanol during gastrulation. Delay in separation of the lens vesicle (L) from the surface ectoderm (SE) results in an anterior lenticonus (*) and failure of the mesenchyme (M) to complete its axial migration to form the corneal stroma, endothelium, and iris stroma. R, retinal primordium. Original magnification, 166×. **B**, **C**, and **D.** Mouse embryo following acute exposure to 13-*cis*-retinoic acid during gastrulation. A large keratolenticular stalk (S) persists and is continuous axially with the SE. The arrow in **B** indicates the incompletely closed lens pore. **D** is a transmission electron microscopic view of the stalk seen in **C.** There is discontinuity between the lens epithelium (LE) and the stalk epithelium (S). Adjacent neural crest mesenchyme (M) is visible, and two layers of basement membrane can be seen in **D**, bridging the lens–stalk junction as well as dividing the two zones. Mechanical interference with the axial migration of neural crest cells is responsible in this model for malformations, which mimics Peters' anomaly in the human. OC, optic cup. (Reprinted with permission from Cook, C. (1995) Embryogenesis of congenital eye malformations. *Veterinary and Comparative Ophthalmology*, **5**, 109–123.)

Uveal Cysts

Uveal cysts occur through failure of adhesion of the inner and outer layers of the optic cup. In the dog, they are most commonly identified as single or multiple spherical pigmented masses within the pupil or free-floating within the anterior chamber (Fig. 1.33 and Fig. 1.34). They appear to have a genetic predilection. In the cat, they are more often thick-walled and remain attached to the posterior iris surface, causing anterior displacement of the iris and shallowing of the anterior chamber, and may result in secondary glaucoma (Gemensky-Metzler et al., 2004). In cats they also

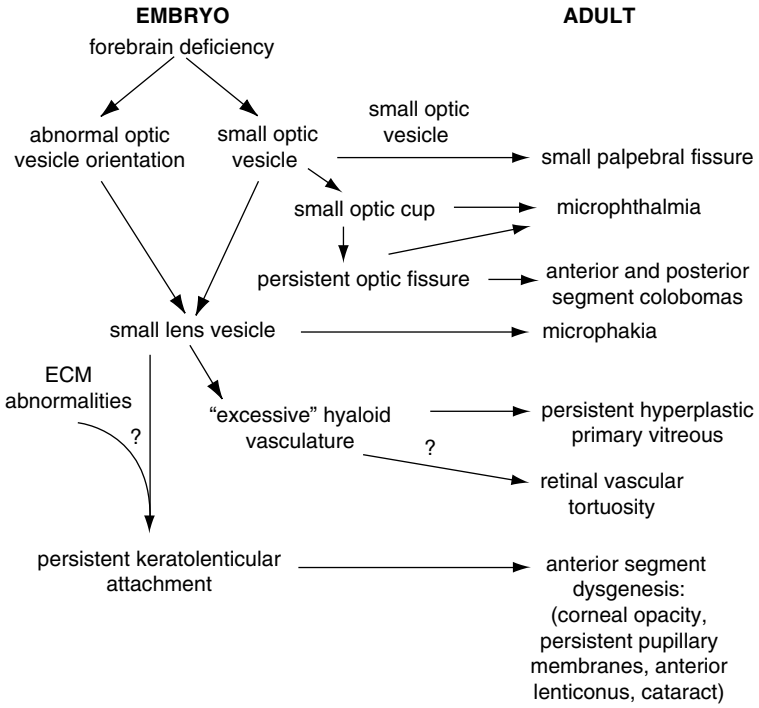


Figure 1.30 The relationship between microphthalmia and associated ocular malformations. An early embryonic insult (during gastrulation) leads to a deficiency in the forebrain and its derivatives, the optic sulci. The subsequently small optic vesicle often exhibits an abnormal relationship to the surface ectoderm, which is programmed (by the underlying neural crest) to form the lens. The result is a spectrum of malformations in the adult, including microphthalmia, microphakia, colobomas, persistent hyperplastic primary vitreous, and anterior segment dysgenesis. ECM, extracellular matrix. (Reprinted with permission from Cook, C. (1995) Embryogenesis of congenital eye malformations. *Veterinary and Comparative Ophthalmology*, **5**, 109–123.)

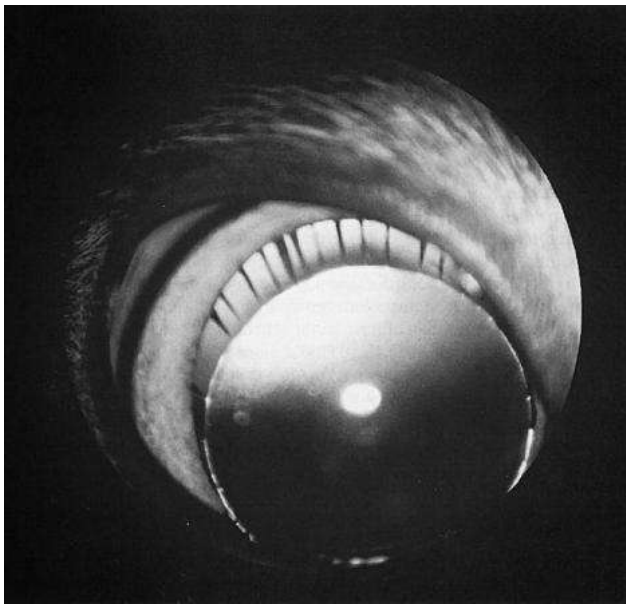


Figure 1.31 Microphakia and spherophakia in a cat. Note the elongated ciliary processes. The globe was not microphthalmic, and this most likely represented a primary abnormality in the surface ectoderm destined to become lens placode.

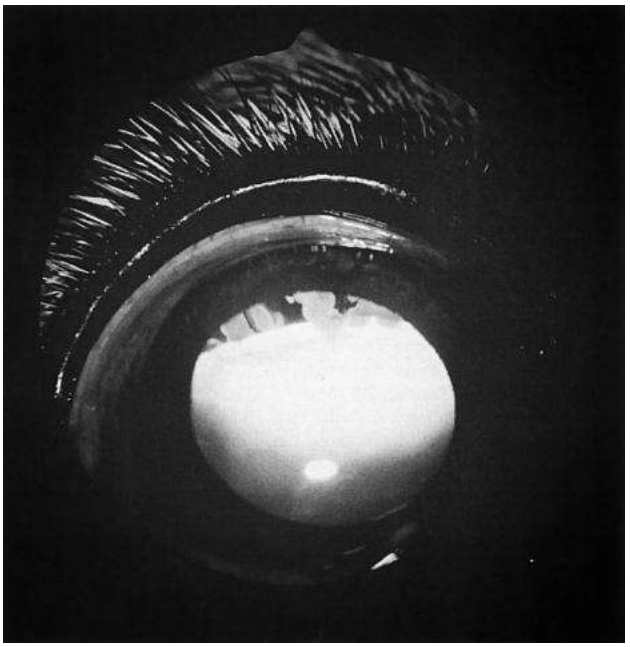


Figure 1.32 Nonpigmented ciliary body cysts in a cat. Note the flattened lens equator, which would incorrectly be called a lens coloboma. In this case, a medulloepithelioma of the ciliary body resulted both in the cysts and in the localized absence of zonules. Failure of normal traction by the zonule on the lens equator resulted in this flattened appearance. (Courtesy of Kristina Burling.)

appear to have a genetic predisposition, with Burmese cats overrepresented (Blacklock et al., 2016). When uveal cysts originate within the ciliary body, they can be nonpigmented (see Fig. 1.32).

Uveal cysts are often seen associated with pigmentary uveitis or pigmentary and cystic glaucoma in Golden Retriever dogs and other breeds. There has been a great deal of speculation about whether the cysts may play a causal role in the inflammatory disease process (Pumphrey et al., 2013; Townsend & Gornik, 2013). Uveal cysts seen in dogs affected

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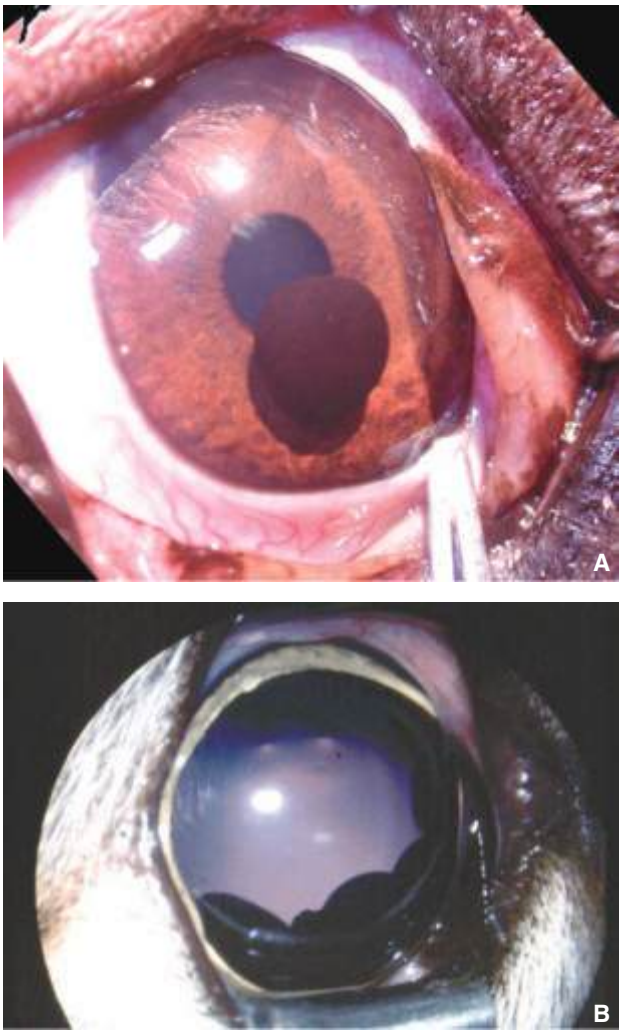


Figure 1.33 Iris cysts. **A.** Single iris cyst in a dog. **B.** Multiple iris cysts in a cat. In cats, these cysts are often thick-walled and remain attached to the posterior iris surface, causing anterior displacement of the iris and a shallow anterior chamber.

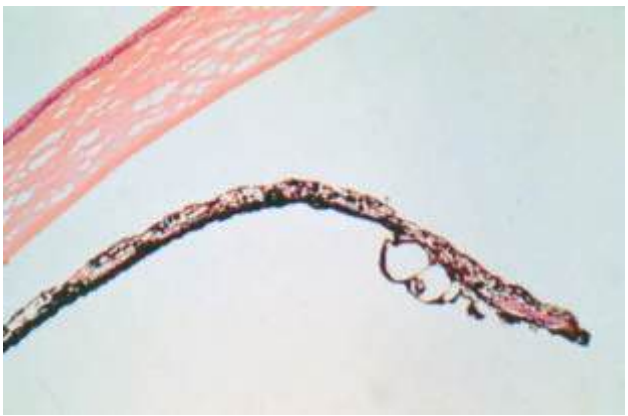


Figure 1.34 Histologic appearance of a uveal cyst on the posterior iris surface. These cysts form beneath the posterior pigmented epithelium and frequently separate to become free-floating spheres within the anterior chamber. (Courtesy of Robert Peiffer.)

with uveitis have a unique clinical appearance, being more translucent, irregularly shaped, and often adherent to the lens or cornea. This is in distinct contrast to the cysts commonly seen in other canine breeds with complete lack of inflammation.

Congenital Ocular Anomalies in Horses

A syndrome of multiple congenital ocular anomalies (MCOA) has been identified as a bilaterally symmetrical, inherited condition in several breeds of horses, most notably the Rocky Mountain breed, silver mutant ponies, and miniature horses (Andersson et al., 2011; Komaromy et al., 2011; Plummer & Ramsey, 2011; Ramsey et al., 1999a, 1999b; Fig. 1.35). Affected individuals most often have a silver coat color, and correlation with the Silver Dapple locus is suspected. The condition in the heterozygote is characterized by cysts of the posterior iris, ciliary body, and peripheral retina, indicating failure of adhesion of the inner and outer layers of the optic cup. These cysts are consistently located temporally, not associated with the optic fissure. Areas of current or previous retinal detachment were further manifestations of abnormal cup invagination and adhesion. The spectrum of anterior segment malformations seen in homozygous individuals included megalocornea, deep anterior chamber, iris hypoplasia, and cataract. Increased thickness of the central and peripheral corneas was noted and increased with age. Intraocular pressures were normal (Ramsey et al., 1999b). The syndrome in Rocky Mountain horses appears to exhibit codominant inheritance (Ewart et al., 2000). Cataracts have been identified in Exmoor ponies, with a suspected sex-linked mode of inheritance (Pinard & Basrur, 2011). Other congenital anomalies appear to occur rarely in horses, with occasional neonatal diagnosis of retinal and conjunctival hemorrhages thought to be due to injury during parturition (Barsotti et al., 2013).

Congenital Cataracts

Congenital cataracts resulting from abnormal formation of primary or secondary lens fibers would be expected to be localized to the nuclear region, and be nonprogressive. However, an early effect on the primary lens fibers may extend to involve the secondary fibers, resulting in a congenital cataract that progresses to involve the entire lens.

Abnormal lens vesicle invagination, separation, or defects in the lens epithelium or capsule would result in a cataract (with or without anterior or posterior lenticonus; Ori et al., 2000) that would remain associated with the peripheral portion of the lens, with the secondary lens fibers forming underneath (e.g., Old English Sheepdog, Barrie et al., 1979; Cavalier King Charles Spaniel, Narfstrom & Dubielzig, 1984). Congenital cataracts associated with mild microphthalmia (Miniature Schnauzer, Gelatt et al., 1983; Monaco

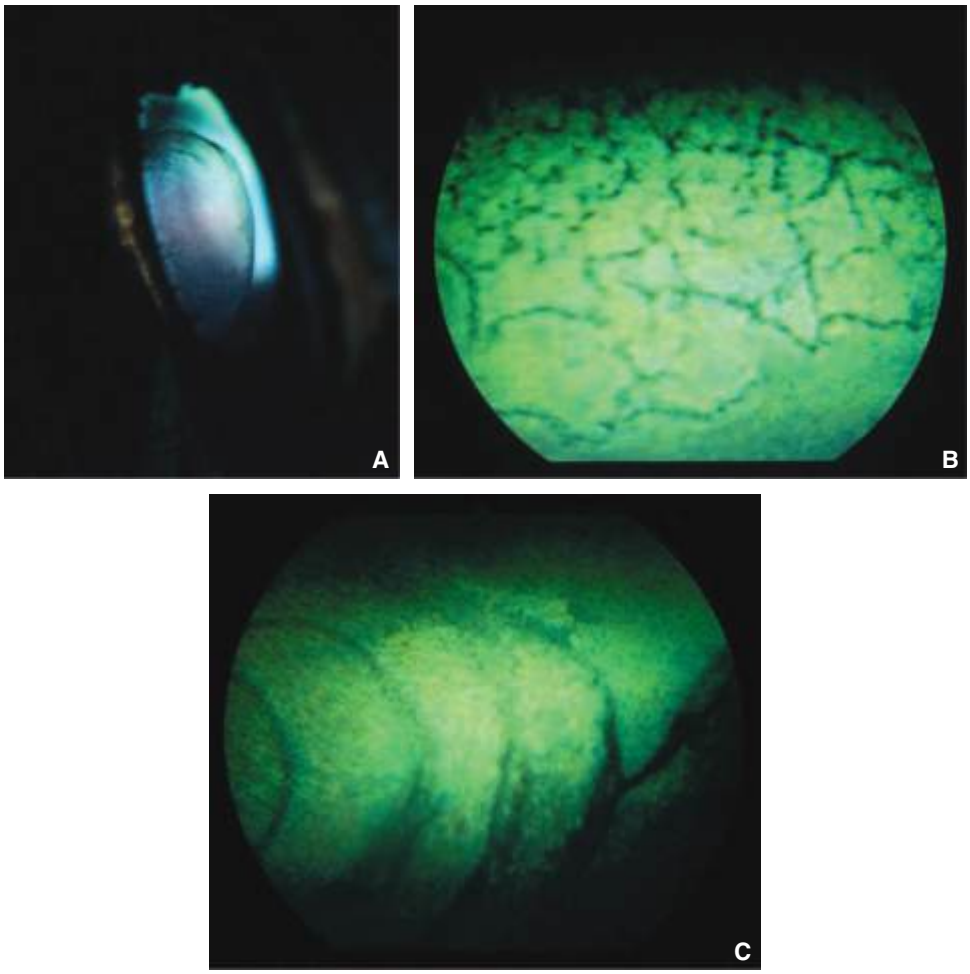


Figure 1.35 Spectrum of ocular lesions seen in Rocky Mountain horses. **A.** A large translucent cyst arising from the lateral part of the ciliary body extends into the vitreous cavity and occupies part of the temporal pupillary axis of the right eye. **B.** Retinal dysplasia is characterized by numerous pigmented folds located in the superior peripapillary neurosensory retina. **C.** Multiple, well-delineated, darkly pigmented curvilinear streaks of retinal pigment epithelium are present in the peripheral right tapetal fundus. These streaks originate and terminate at the ora ciliaris retinae and extend toward the optic papilla. They represent demarcation lines from previous retinal detachments and are referred to clinically as "high-water markers." (Reprinted with permission from Ramsey, D.T., Ewart, S.L., Render, J.A., et al. (1999) Congenital ocular abnormalities of Rocky Mountain horses. *Veterinary Ophthalmology*, **2**, 47–59.)

et al., 1985; Samuelson et al., 1987) may result from early abnormalities in the lens placode/epithelium, and they may involve the lens nucleus, cortex, or both. In the Miniature Schnauzer, these lesions are recessively inherited, typically bilateral, and initially involve the posterior subcapsular region with rapid progression (Gelatt et al., 1983; Zhang et al., 1991).

Congenital Glaucoma

Malformations of the iridocorneal angle (i.e., goniodysgenesis) have been described in several breeds, including the Basset Hound (Martin & Wyman, 1968; Wyman & Ketring, 1976) and the Bouvier des Flandres (van Rensburg et al., 1992). The iridocorneal angles of affected animals are malformed at birth, but the IOP often remains normal until middle age. Thus, the relationship between angle conformation and glaucoma is unclear. In English Springer Spaniels, a correlation was observed between pectinate ligament dysplasia and glaucoma (Bjerkas et al., 2002). Although pectinate ligament dysplasia is a congenital malformation, it may appear to clinically progress over time, as assessed by sequential gonioscopic evaluations in Flat-Coated Retrievers (Pearl et al., 2015).

Goniodysgenesis is characterized by abnormal tissue bridging the ciliary cleft. During normal development, this sheet undergoes rarefaction to form the pectinate ligament during the first three postnatal weeks (Martin, 1974; Samuelson & Gelatt, 1984a). Failure of this membrane to undergo normal atrophy is thought to result in goniodysgenesis. Congenital

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glaucoma associated with presumed primary iridoschisis (i.e., degeneration of the anterior iris) has been described in a cat (Brown et al., 1994).

Persistent Hyperplastic Primary Vitreous/ Persistent Hyperplastic Tunica Vasculosa Lentis

Variable persistence of the hyaloid occurs in association with many other types of malformations, including microphthalmia, microphakia, cataract, and retinal dysplasia (Fig. 1.36; Bayon et al., 2001; Boeve et al., 1992). Persistent hyperplastic primary vitreous/persistent hyperplastic tunica vasculosa lentis (PHPV/PHTVL) may occur secondary to other malformations or as a primary, spontaneous failure of vascular regression. This condition has been described as an inherited trait in the Doberman (Stades, 1980; van der Linde-Sipman et al., 1983) and the Bouvier des Flandres (van Rensburg et al., 1992), and has been identified in two cats (Allgoewer & Pfefferkorn, 2001). In the Doberman, the genetics appear to be something more than simple recessive (Stades, 1983).

The mechanism involved is failure of normal vascular regression and hyperplasia of the persistent tissue. Normal vitreous may have antiangiogenic properties, and it may be essential for initiating regression of the hyaloid. Expression of the Arf tumor suppressor gene in perivascular cells may repress VEGF expression, thus promoting hyaloid regression in mice (Martin et al. 2004). Thus, the primary abnormality in PHPV/PHTVL may rest with the product of the ciliary epithelium (i.e., secondary vitreous).

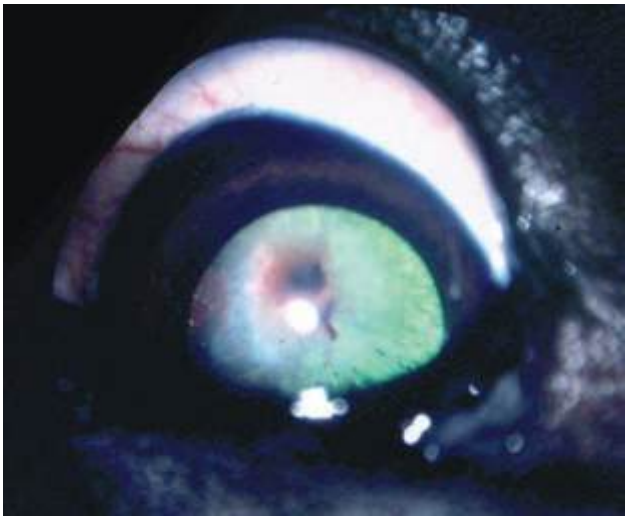


Figure 1.36 Persistent hyperplastic primary vitreous in a puppy associated with a posterior subcapsular cataract. This eye is also microphthalmic.

Retinal Dysplasia

Abnormal retinal differentiation results in rosettes and multifocal disorganization known as retinal dysplasia. Retinal folds without rosette formation may result from inequity in the relative growth rates of the inner (i.e., retinal) and outer (i.e., RPE) layers of the optic cup (Fig. 1.37 and Fig. 1.38). This is a particularly likely pathogenesis in cases in which the folds resolve as the animal matures; this is seen most commonly among Collies. These folds do not represent abnormal differentiation and thus are not

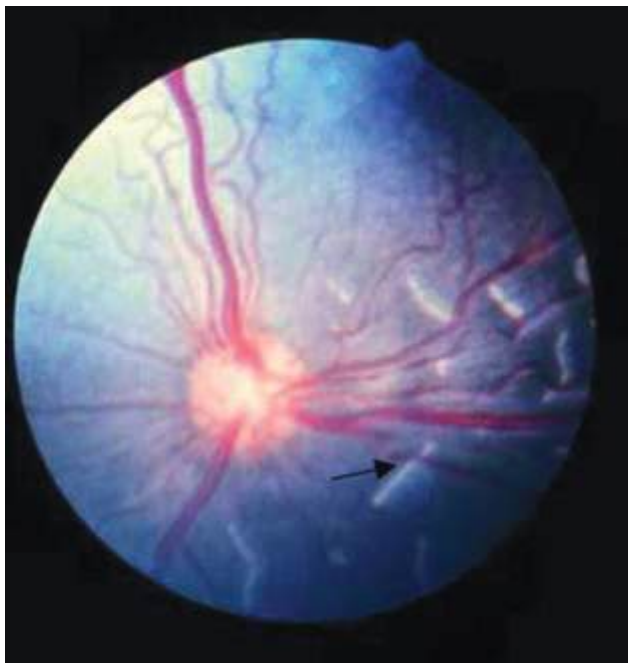


Figure 1.37 Fundus photograph of retinal folds in a young American Cocker Spaniel. These appear as single or multiple white curvilinear streaks. Elevation of a retinal vessel crossing a fold (arrow) can be seen.

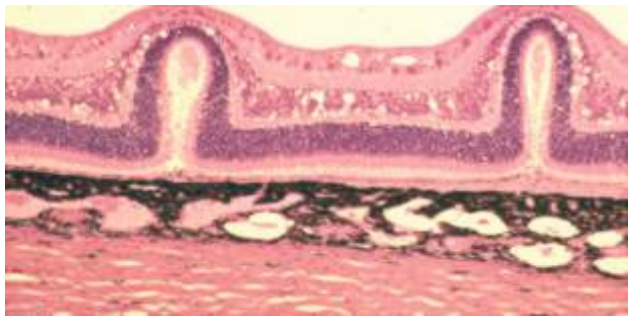


Figure 1.38 Histologic appearance of retinal folds. Note the normal stratification of the retinal layers and the mechanical distortion caused by disparate growth of the neural retina (inner optic cup) and the underlying RPE (outer optic cup). (Courtesy of Robert Peiffer.)

accurately referred to as dysplasia. Simple folding in the retina has been described in the American Cocker Spaniel (MacMillan & Lipton, 1978) and the Beagle (Heywood & Wells, 1970; Schiavo & Field, 1974). The genetic relationship between simple folds and true retinal dysplasia is undetermined.

True retinal dysplasia is characterized by disorganized development, the hallmark of which is the rosette. Abnormal or incomplete contact between the inner and outer layers of the optic cup during embryogenesis can result in dysplasia, with the most severe form associated with complete retinal nonattachment. This usually occurs in eyes that are microphthalmic with multiple ocular anomalies (e.g., Bedlington terrier, Rubin, 1963, 1968; Sealyham terrier, Ashton et al., 1968; and American Pit Bull terrier, Rodarte-Almeida et al., 2016). In the Labrador Retriever, retinal dysplasia genetically associated with skeletal anomalies is inherited as an autosomal dominant trait (Barnett et al., 1970; Carrig et al., 1988; Nelson & Macmillan, 1983). A similar form of inherited skeletal-ocular dysplasia is seen in the Samoyed dog (Aroch et al., 1996; Meyers et al., 1983).

Multifocal retinal rosettes in a retina that is partially attached to the underlying RPE represent the most common form of retinal dysplasia (Fig. 1.39 and Fig. 1.40). This condition has been described extensively in the English Springer Spaniel (Lavach et al., 1978; O'Toole et al., 1983). Retinal dysplasia occurs sporadically in other breeds (Bedford, 1982b) and species (Murphy et al., 1985). Multifocal, "geographic" retinal dysplasia most likely represents a later initiation of retinal disorganization. The dysplastic changes are first apparent at 45–50 days of gestation. Focal loss of cell junctions of the external limiting membrane is seen, with proliferation of neuroblasts in the retina forming rosettes (Whiteley, 1991). Retinal differentiation and maturation in the dog continue during the first 40 days postnatal. In addition, maturation of the tapetum during the first 6 months results in an inconsistent ability to detect mild forms of retinal dysplasia in puppies less than 10 weeks of age (Holle et al., 1999).

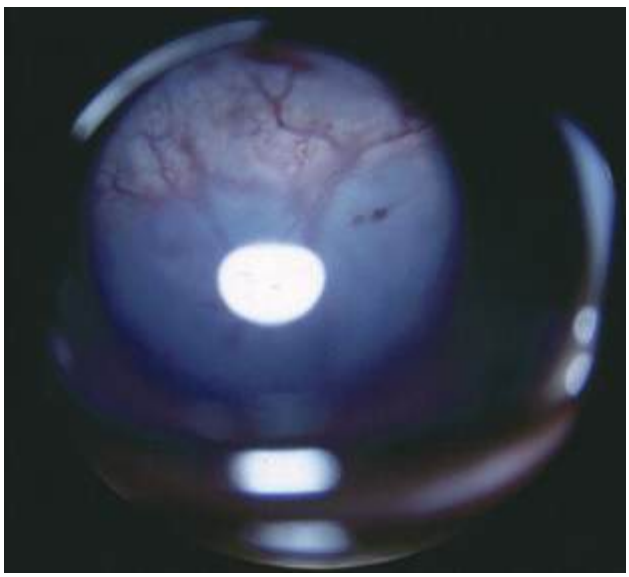


Figure 1.39 Geographic retinal dysplasia in an English Springer Spaniel. The retina is detached and lies just posterior to the lens; there are many folds visible.

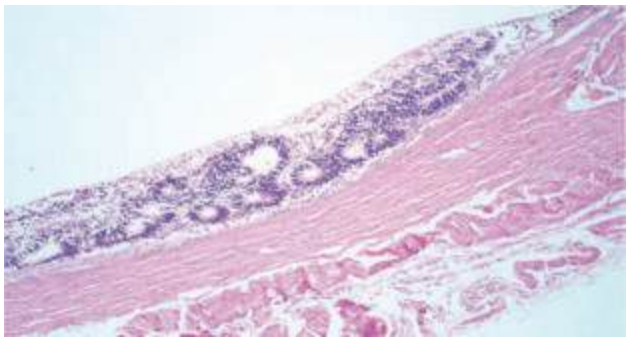


Figure 1.40 Histologic appearance of geographic retinal dysplasia. The retina exhibits disorganization and classic rosette formation. Note also the hypoplastic choroid. (Courtesy of Robert Peiffer.)

An unusual form of RPE dysplasia with duplication of neural retina in the outer layer of the optic cup has been described in several mutant mouse strains (Bumsted & Barnstable, 2000; Cook et al., 1991b). Large colobomas of the choroid and sclera in the areas adjacent to the dysplastic RPE illustrate the importance of this layer in coordinating differentiation of the neural crest.

Viral-induced "retinal dysplasia" has been associated with early postnatal exposure to canine herpesvirus and prenatal exposure to bovine viral diarrhea virus (Bistner et al., 1970; Brown et al., 1975; Kahrs et al., 1970), bluetongue virus in lambs (Silverstein & Al, 1971), and feline panleukopenia virus (Percy et al., 1975). Histopathologically, affected retinas are characterized by early inflammatory cell infiltrate and, later, by necrosis, gliosis, and diffuse disorganization of cell layers. Similar postnatal retinal disorganization can be induced in the dog by radiation exposure (Shively et al., 1970, 1972). These conditions are more accurately classified as teratogen-induced necrosis and degeneration rather than as dysplasia.

Optic Nerve Hypoplasia

Though difficult to document experimentally, optic nerve hypoplasia most likely results from a primary abnormality in the number or ultimate differentiation of the retinal ganglion cells (Fig. 1.41). Hypovitaminosis A in cattle can result

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Figure 1.41 Optic nerve hypoplasia in an 8-week-old Alsatian puppy. This was a unilateral lesion and the pup presented with anisocoria. (Courtesy of Robert Peiffer.)

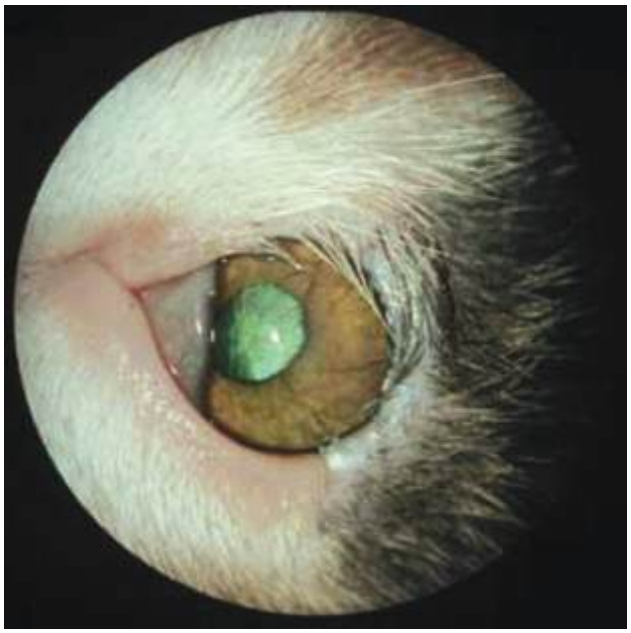


Figure 1.42 Eyelid coloboma in a kitten. The eyelid margin is absent from the temporal two-thirds of the upper lid. There is keratitis due to exposure and trichiasis. The eye also exhibits microphthalmia, dyscoria, and persistent pupillary membranes.

in stenosis of the optic foramen with secondary optic nerve degeneration, incorrectly labeled hypoplasia. Colobomas of the optic nerve result from failure of the optic fissure to close, as described for "typical" colobomas. Myelination of the optic nerve progresses from the brain to the eye during the first 3 weeks postnatal (Fox, 1963). Reduction in the amount of myelinization leads to a small optic disc that can mimic hypoplasia but is unassociated with vision deficits (termed micropapilla).

Eyelid Coloboma

The eyelids and palpebral fissure are initially induced at the time of contact of the optic vesicle with the surface ectoderm. This is also the time of induction of the lens placode. Eyelid agenesis (coloboma) occurs in domestic cats, often with concurrent persistent pupillary membranes, keratolenticular dysgenesis, and subtle to severe microphthalmia (Fig. 1.42; Glaze, 2005; Koch, 1979; Martin et al., 1997; Narfstrom, 1999). Eyelid colobomas occur less commonly in dogs (Fig. 1.43) and a case of upper eyelid agenesis has also been described in a Peregrine Falcon (Aguirre et al., 1972; Murphy et al., 1985) and in two sibling snow leopards (Hamoudi et al., 2013). The snow leopards also exhibited microphthalmia, typical anterior segment dysgenesis, and persistent hyaloid.

The receptivity of the surface ectoderm to the inductive influences of the optic vesicle is highly spatiotemporally



Figure 1.43 A Cavalier King Charles Spaniel with bilateral lower eyelid colobomas and dermoids. Note the notch defects in the central portion of the lower lids and the abnormal hair growth adjacent to the defects.

specific. The fairly consistent location of the defect in the temporal upper eyelid leads to suspicion of an abnormal orientation of the optic vesicle as it approaches the surface ectoderm, possibly eccentrically contacting the surface ectoderm in an area that is only partially receptive.

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2

Ophthalmic Anatomy

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Introduction

A thorough understanding of normal ophthalmic anatomy is an integral part of the foundational knowledge of a veterinary ophthalmologist. It is important to be able to differentiate normal anatomic structures from abnormal structures during ophthalmic examinations, histopathologic examinations, or during surgical procedures. The veterinary ophthalmologist examines eyes from a wide variety of animal species. During vertebrate evolution, the eye has largely retained the same basic components, but important and clinically relevant differences do exist. This chapter will primarily present the normal ophthalmic anatomy of dogs, cats, horses, livestock species, and birds. The anatomy of selected exotic species is covered in Section IV, but there is also a tremendous amount of literature elsewhere for reference.

Orbit

The orbit is the bony fossa that surrounds and protects the eye while separating it from the cranial cavity. Through numerous foramina, the orbit also provides pathways for various blood vessels and nerves involved in the function of the eye. The size, shape, and position of the orbit are closely associated with time of visual activity and feeding behavior (Table 2.1). In domestic carnivores such as the cat and dog, the orbital axes are set rostrolaterally, approximately 10° and 20° from midline, respectively (Prince et al., 1960). As a result, these animals possess enhanced binocular vision, which serves to improve predatory feeding behavior. In horses and ruminants, the orbits are positioned more laterally than carnivores, being approximately 40° (i.e., horses) and 50° (i.e., cattle) from midline. Monocular vision in these and other ungulate species is enhanced, providing a strong panoramic line of vision that allows for scanning the horizon to search for potential predators. In the rabbit, the axis of each eye extends as much as 85° from the midline; this orbit placement also occurs among the majority of lizards, some snakes, and in certain fish. In these latter instances where binocular vision has become greatly reduced, there is a tendency for the eyes to protrude so that the visual axis of the eye can expand what the optic axis of the skull has provided (Prince et al., 1960).

In addition to size, shape, and position, all vertebrate orbits are one of two kinds: the enclosed orbit, which is completely encompassed by bone; or the open or incomplete orbit, which is only partially surrounded by bone (Fig. 2.1, Fig. 2.2, and Fig. 2.3). Among domestic animals, horses, sheep, cattle, and goats have enclosed orbits. Pigs and carnivores (i.e., dogs and cats) have open orbits. The enclosed orbit of large herbivorous prey species is theorized to be essential for protection, whereas the open orbit gives animals such as carnivores the ability to open their jaws widely during consumption of prey (Prince, 1956).

The bony orbit typically consists of five to seven bones, depending on the species (Table 2.2). The canine orbit is composed of five, and sometimes six, bones, the supraorbital ligament that extends from the frontal to the zygomatic bone, and the periosteum (Fig. 2.1). The orbital rim is formed by the frontal, lacrimal, and zygomatic bones. Laterally, the orbit is formed by the supraorbital ligament which is contiguous with a fibroelastic connective tissue sheath for much of the floor of the orbit. The orbital floor is incomplete, being partially formed by the sphenoid and palatine bones. In the feline orbit, the processes of the frontal and zygomatic bones extend a great deal more toward one another, resulting in a shortened supraorbital ligament (Fig. 2.1). In animals with enclosed orbits, closure of the temporal side of the orbit is accomplished by union of the zygomatic process of the frontal bone with the frontal process of the zygomatic bone

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(see Fig. 2.2 and Fig. 2.3). In the horse, the zygomatic process of the temporal bone intervenes between these two and completes the orbital rim (see Fig. 2.3).

Within the orbit, various foramina and fissures provide osseous pathways for blood vessels and nerves to pass from the cranial cavity and alar canal into the orbital region. Those foramina of rather constant position in domestic animals are the rostral alar, ethmoidal, lacrimal, orbital, ovale, optic, rotundum, and supraorbital. Other foramina closely related to the orbital structures are within the pterygopalatine region, and these are the maxillary, caudal palatine, and sphenopalatine (Table 2.3). The orbital foramen is elongated in most domestic animals except the horse; therefore, it is referred to as the orbital fissure. In cattle, the orbital fissure and foramen rotundum are typically fused to form the foramen orbitorotundum (see Fig. 2.2).

Orbital Fascia

The orbital fascia consists of a thin, tough connective tissue lining that envelops all the structures within the orbit, including the bony fossa itself. This fascia consists of three anatomic components: the periorbita, Tenon's capsule or fascia bulbi, and the extraocular muscle (EOM) fascial sheaths (Fig. 2.4).

The periorbita is a conically shaped, fibrous membrane that lines the orbit and encloses the globe, EOMs, blood vessels, and nerves. The apex of the periorbita is located where the optic nerve exits the orbit. At this point, it is continuous with the dural sheath of the optic nerve. In the orbit, it is thin, attaches firmly to the orbital bones, and forms their periosteum. In the dog, the periorbita does not always fuse with the periosteum of the frontal and the sphenoid bones (Constantinescu & McClure, 1990). Instead, the periosteum and periorbita often remain distinct and separate in these orbital regions. In animals with an incomplete lateral orbital

Table 2.1 Orbital dimensions.

Dimension	Feline (mm)	Canine (mm)	Bovine (mm)	Equine (mm)
Width	24	29	65	62
Height	26	28	64	59
Depth	—	49	120	98
Distance between orbits	23	36	151	173

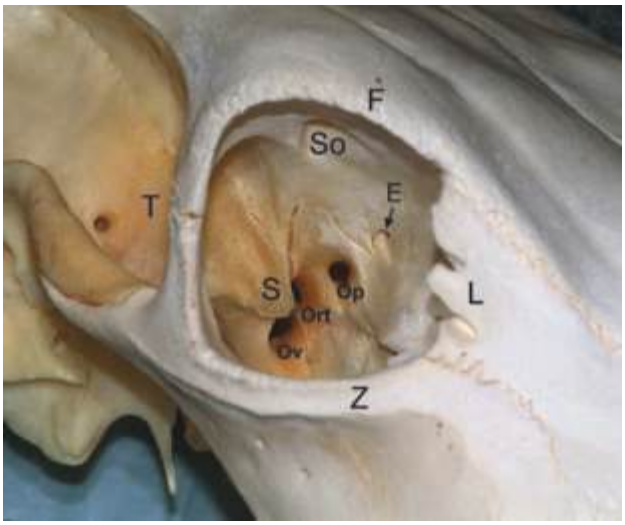


Figure 2.2 Bovine orbit. Bones of the orbit: frontal (F), lacrimal (L), sphenoid (S), temporal (T), zygomatic (Z). Orbital foramina: ethmoidal (E), optic (Op), orbitorotundum (Ort), ovale (Ov), supraorbital (So).

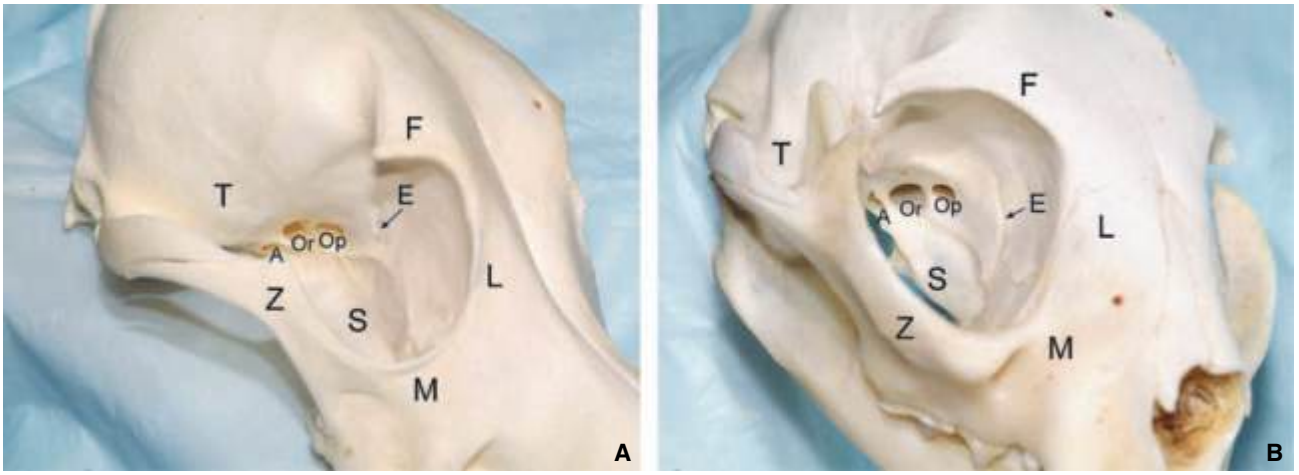


Figure 2.1 **A.** Canine orbit. **B.** Feline orbit. Bones of the orbit: frontal (F), lacrimal (L), maxilla (M), sphenoid (S), temporal (T), zygomatic (Z). Orbital foramina: rostral alar (A), ethmoidal (E), optic (Op), orbital fissure (Or).

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wall, the periorbita is thicker laterally next to the orbital ligament. Anteriorly, in the dorsolateral part of the orbit, the periorbita separates and surrounds the lacrimal gland. At the orbital rim, it divides again, one part becoming continuous with the periosteum of the facial bones and the other, that is, the septum orbitale, merging with the eyelids and becoming continuous with the tarsal plates (the fibrous sheet in the eyelids). Within the periorbital tissue of carnivores (dogs and cats), smooth muscle has been observed along the lateral wall of the orbit, portions of the roof and floor of the orbit, and next to the periosteal lining of orbital bones (Brunton, 1938). The smooth muscle is oriented circularly so that when observed in the coronal plane, the muscle fibers are seen longitudinally. Contraction of the muscle has been produced by stimulation of the cervical sympathetic nerve trunk and results in forward movement of the globe. Although the function of this fibromuscular tissue remains unknown, it may facilitate repositioning the eye within the orbit during relaxation of the retractor oculi muscle.

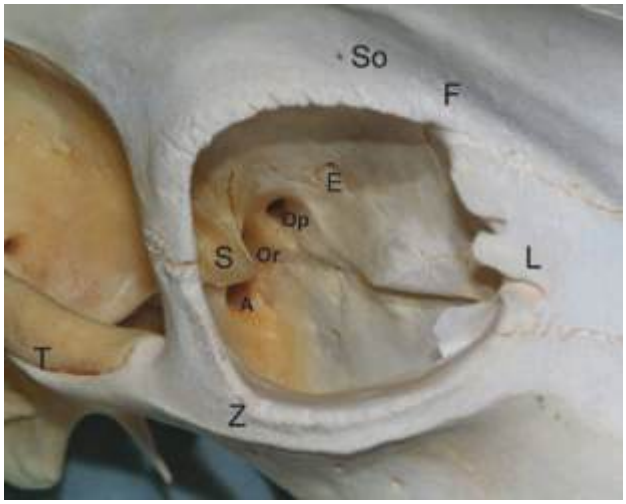


Figure 2.3 Equine orbit. Bones of the orbit: frontal (F), lacrimal (L), sphenoid (S), temporal (T), zygomatic (Z). Orbital foramina: rostral alar (A), ethmoidal (E), optic (Op), orbital fissure (Or), supraorbital (So).

Tenon's capsule (fascia bulbi) is connective tissue on the outer aspect of the sclera. Tenon's capsule is separated from the sclera by a narrow, cleft-like space filled with loose connective tissue, Tenon's space. Tenon's capsule is attached to the sclera near the corneoscleral junction (i.e., limbus), and it becomes continuous with the fascia surrounding the EOMs.

The fascial sheaths of the EOMs are dense, fibrous membranes loosely attached to the muscles with fine trabeculae of connective tissue. These sheaths are continuous with, or reflections of, Tenon's capsule, but they are not always considered part of it.

In the dog, the muscular fasciae consist of three layers. A superficial, thick layer extends caudally from the orbital septum and is penetrated by blood vessels and nerves. A middle layer consists of superficial and deep sheets that anteriorly attach to the outer junction of the sclera and cornea. A deep layer next to the surface of the EOMs separates the recti muscles from the retractor oculi muscles (Constantinescu & McClure, 1990).

Extraocular Muscles and Orbital Fat

The three sheets of orbital fascia are separated by orbital fat. Orbital fat fills the dead space in the orbit and acts as a protective cushion for the eye. The amount of orbital fat varies between individuals and to a greater extent between species. The color of orbital fat ranges from white to yellow. The yellow coloration is attributed to higher levels of lutein, beta-carotene, retinol, and other unidentified carotenoids (Sires et al., 2001). Some animals, including birds and many reptiles, have very little orbital fat (Duke-Elder, 1958). When the retractor oculi muscle contracts, orbital fat can displace the glandular tissue associated with the nictitating membrane, resulting in its passive movement over the cornea. In the dog, orbital fat surrounds the optic nerve and forms a

Table 2.2 Orbital bones.

Animal	Lacrimal	Zygomatic	Frontal	Sphenoid	Palatine	Maxillary	Ethmoid	Temporal
Dog	X	X	X	X	X	X		
Cat	X	X	X	X	X	X		
Horse	X	X	X	X	X			X
Ox	X	X	X	X	X	X		
Sheep	X	X	X	X	X	X		
Goat	X	X	X	X	X			
Pig	X	X	X	X	X		X	
Rabbit	X	X	X	X	X			X
Human	X	X	X	X	X	X	X	

Table 2.3 Foramina and associated nerves and vessels.

Foramen or fissure	Species	Associated nerves and vessels
Alar, rostral	Canine, equine, feline	Maxillary artery and nerve
Ethmoidal (one or more)	All species	Ethmoidal vessels and nerve
Orbital	Canine, equine, feline	Abducens, oculomotor, ophthalmic, and trochlear nerves
Orbitorotundum	Bovine	Cranial nerves III–IV, retinal, and internal maxillary arteries
Optic	All species	Optic nerve, internal ophthalmic artery
Rotundum	Canine, equine, feline	Maxillary nerve
Supraorbital	Bovine, canine, equine (feline variable)	Supraorbital vessels and nerve
Caudal palatine	All species	Major palatine vessels and nerve
Maxillary	All species	Infraorbital vessels and nerve
Sphenopalatine	All species	Sphenopalatine vessels and pterygopalatine nerve

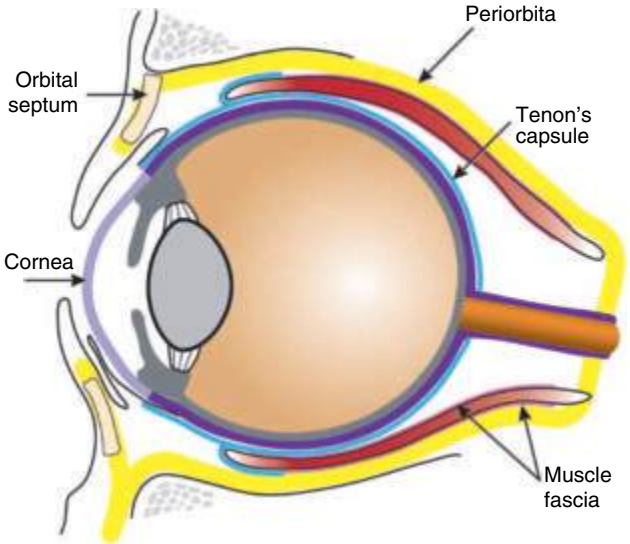


Figure 2.4 Divisions of orbital fascia.

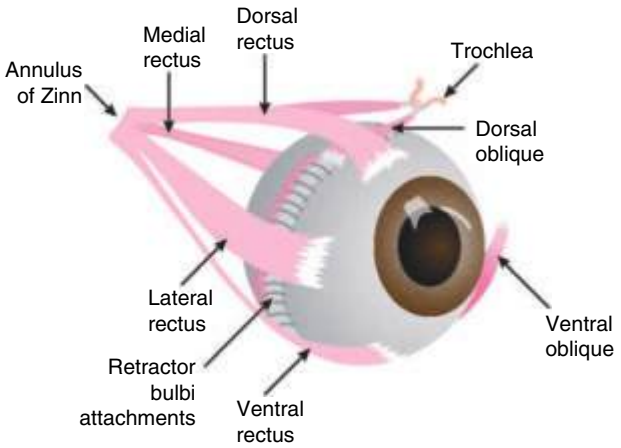


Figure 2.5 Arrangement of the orbital muscles of domestic animals.

cone that separates the optic nerve from the retractor oculi muscle (Murphy et al., 2012).

The EOMs suspend the globe in the orbit and provide ocular motility. There are four rectus muscles: the dorsal, ventral, medial, and lateral recti (Fig. 2.5 and Fig. 2.6). They originate from the orbital apex (i.e., annulus of Zinn) and insert, in the dog, approximately 5 mm posterior to the limbus medially, 6 mm ventrally, 7 mm dorsally, and 9 mm laterally (see Fig. 2.5, Fig. 2.6, and Fig. 2.7). They move the eye in the direction of their names (Table 2.4). The dorsal (superior) oblique originates from the medial orbital apex, continuing forward dorsomedially to pass through a trochlea located near the medial canthus. It then turns acutely, passing dorsolaterally to the globe. It pulls the dorsal aspect of the globe medially and ventrally (intorsion). The ventral (inferior) oblique originates from the anterolateral margin of the palatine bone on the medial orbital wall and passes beneath the eye, crossing the ventral rectus tendon. The muscle divides as it reaches the lateral rectus, with the anterior portion covering the insertion of the lateral rectus and the posterior portion inserting beneath the rectus. The ventral oblique moves the globe medially and dorsally (extorsion) (Prince et al., 1960).

The EOM of birds vary among species. For example, the superior oblique in hawks can produce forces greater than those of owls allowing for greater globe torsion which corresponds with globe shape. Hawks have more globular-shaped eyes and keep their heads facing forwards when tracking prey in contrast with owls that have tubular eyes and utilize head movement to direct field of view (Plochocki et al., 2018).

The retractor oculi (retractor bulbi) muscle originates at the orbital apex and continues forward to form a cone surrounding the optic nerve and inserting posterior and deep to the recti muscles (see Fig. 2.5, Fig. 2.6, and Fig. 2.7). The retractor oculi muscle retracts the globe into the orbit.

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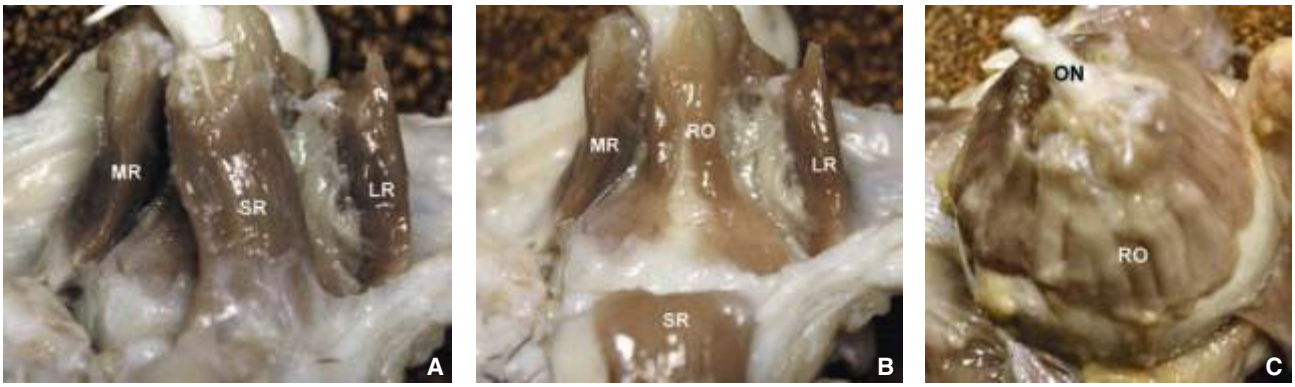


Figure 2.6 Superior lateral view of the canine extraocular musculature. **A.** Lateral rectus muscle (LR), medial rectus muscle (MR), superior rectus muscle (SR). **B.** Same view as seen in **A** but with the superior rectus muscle retracted. RO, retractor oculi muscle. **C.** Posterior view of the equine extraocular musculature. RO, retractor oculi muscle; ON, optic nerve.

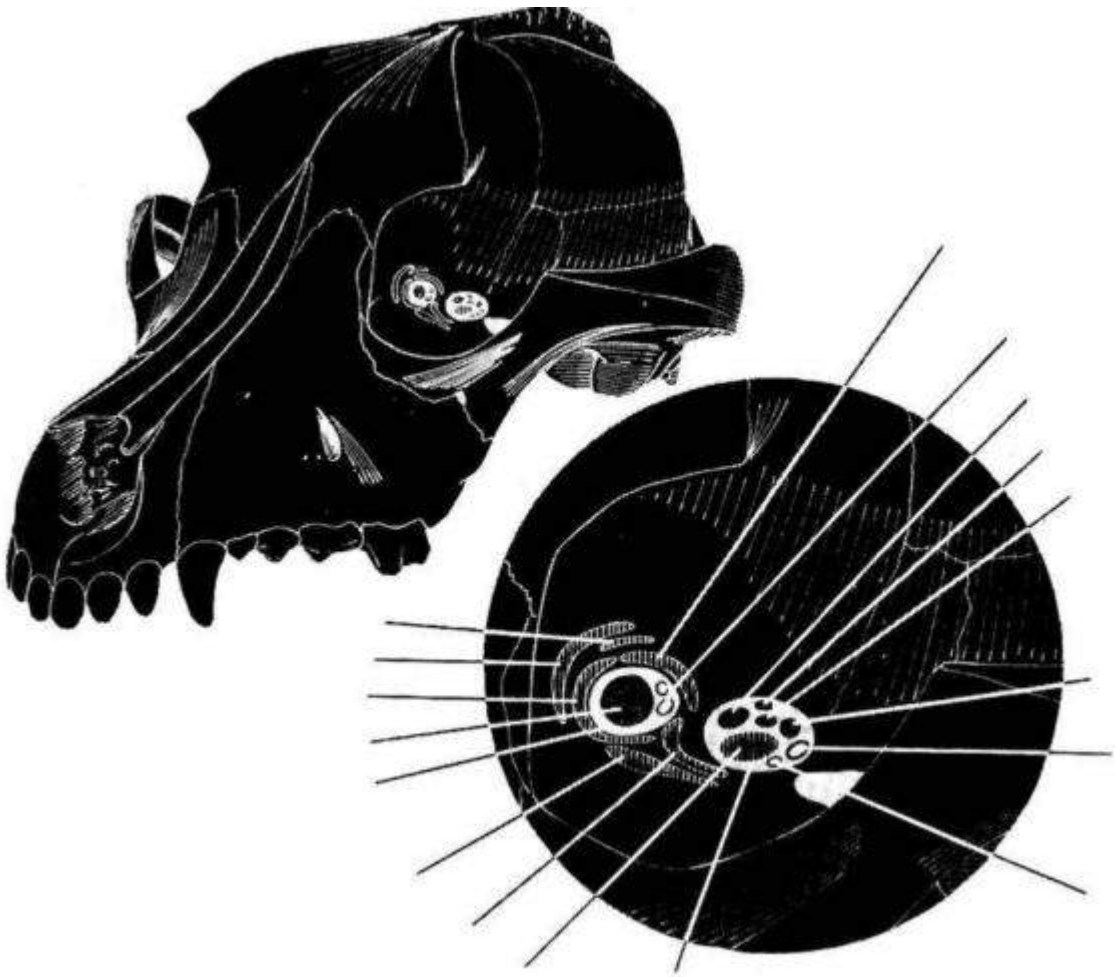


Figure 2.7 Orbital apex of the dog, illustrating structures passing through the optic foramen and orbital fissure as well as the extraocular muscle attachments. (*Source:* Modified from Evans, H. & Christensen, G. (1979) *Miller's Anatomy of the Dog.*, 2nd ed. Philadelphia, PA: W.B. Saunders. Reproduced with permission of Elsevier.)

Table 2.4 Muscles of the eye and eyelids.

Muscle	Function	Nerve supply
Dorsal (superior) rectus	Rotates globe upward	Oculomotor
Ventral (inferior) rectus	Rotates globe downward	Oculomotor
Medial rectus	Rotates globe medially	Oculomotor
Lateral rectus	Rotates globe laterally	Abducens
Dorsal (superior) oblique	Rotates dorsal part of globe medially and ventrally	Trochlear
Ventral (inferior) oblique	Rotates ventral part of globe medially and dorsally	Oculomotor
Retractor oculi (bulbi)	Retracts globe	Abducens
Levator palpebrae superioris	Raises upper eyelid	Oculomotor
Orbicularis oculi	Closes palpebral fissure	Facial
Retractor anguli oculi	Lengthens lateral palpebral fissure	Facial

The retractor oculi muscle is ubiquitous among mammals, but it is absent in various nonmammalian groups, including birds and snakes. The dorsal, ventral, and medial recti as well as the ventral oblique muscles are innervated by the oculomotor nerve (cranial nerve [CN] III), whereas the lateral rectus and retractor oculi muscles are innervated by the abducens nerve (CN VI), and the dorsal oblique muscle is innervated by the trochlear nerve (CN IV) (see Table 2.4).

Eyelids

The eyelids, or palpebrae, are thin folds of skin continuous with the facial skin. The upper (superior) and lower (inferior) eyelids meet to form the lateral and medial canthi (singular canthus). The opening formed by the upper and lower eyelids is the palpebral fissure. This fissure is prevented from assuming a circular shape by the medial (nasal) and lateral (temporal) palpebral ligaments that attach each canthus to the orbital wall. The medial ligament inserts into the periosteum of the nasal bones, whereas the lateral ligament inserts into the temporal fascia and bones associated with the lateral orbit. In the dog, the lateral ligament is essentially replaced by the retractor anguli oculi muscle and its tendon. Closure of the eyelids is achieved by contraction of the orbicularis oculi muscle located deep in the eyelids. Opening the eyelids is accomplished by relaxation of the orbicularis oculi muscle and contraction of the levator palpebrae superioris muscle, which inserts into the upper tarsus.

In the dog the upper eyelid has two to four rows of eyelashes (i.e., cilia) that usually begin near the medial quarter or third



Figure 2.8 Canine eye: medial canthus (A), lateral canthus (B), cilia (C), nictitating membrane (D), ciliary zone of iris (E), pupillary zone of iris (F), collarette (G). *Insert:* Arrows indicate meibomian gland openings.

and either extend across to the lateral canthus or end shortly before the canthus (Fig. 2.8). The lower eyelid has no cilia and has a hairless region approximately 2 mm wide adjacent to the eyelid margin extending the length of the lower eyelid and around the lateral canthus. The medial canthus, unlike the lateral canthus, has variable amounts of facial hair.

In the cat neither lid has cilia, but the leading row of hair from the medial third laterally on the upper eyelid is distinct enough in most cats to be considered cilia (accessory cilia or eyelashes).

In the horse a protuberance of variable size and pigmentation (i.e., the lacrimal caruncle) is present at the medial canthus (Fig. 2.9). The lateral canthus is more rounded than that of the dog, and small amounts of bulbar conjunctiva and sclera are visible both medially and laterally. The exposed lateral conjunctiva is often pigmented. The cilia are well developed on the upper eyelid but absent on the lower eyelid. The cilia begin near the junction of the medial third and the middle third of the eyelid, and they extend almost to the lateral canthus. The facial hair is sparse adjacent to the lower eyelid margins at both the medial and lateral canthi and often at the medial upper eyelid. Horizontal folds are present in both the upper and lower eyelids. Vibrissae (long, specialized tactile hairs) are present on the base of the lower eyelid and on the medial aspect of the upper eyelid.

The eyelids protect the eyes from light, produce part of the tear film, spread the tear film across the cornea, and remove debris from the cornea and conjunctival surfaces. Through closure in a 'zipper-like' fashion from lateral to medial, the eyelids also direct the preocular tear film into the nasolacrimal drainage system.

Histologically, the eyelids consist of four parts: the outermost layer contiguous with adjacent skin, the subjacent orbicularis oculi muscle layer, followed internally by a tarsus and stromal layer, and the innermost layer, the palpebral conjunctiva (Fig. 2.10).

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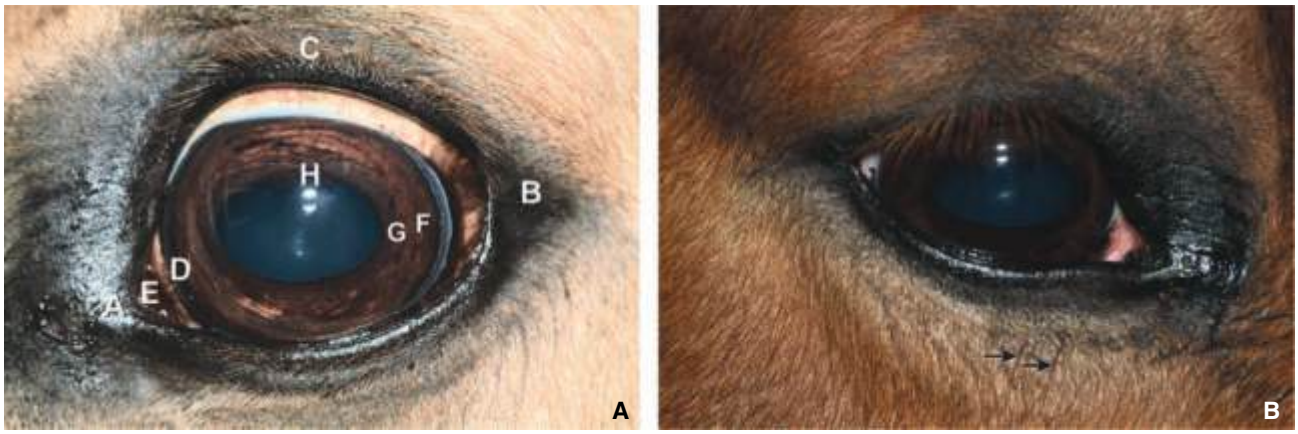


Figure 2.9 Equine eye. **A**. Medial canthus (A), lateral canthus (B), cilia (C), nictitating membrane (D), lacrimal caruncle (E), ciliary zone of iris (F), pupillary zone of iris (G), granula iridica (H). **B**. Arrows indicate vibrissae.

The outer layer of the eyelid is skin covered by a dense coat of hairs with associated sebaceous and tubular glands. In dogs and cats, the hair follicles might be compound. Tactile hairs (pili supraorbitales), similar to the eyebrows of humans, may be present on or near the upper eyelids. Bundles of smooth muscle fibers, arrectores ciliorum, extend from the follicles of the eyelashes toward the tarsus. These muscle bundles are absent in carnivores and humans, but they are common in ruminants (Prince, 1956). The roots of the large cilia are in close association with prominent sebaceous glands (glands of Zeis) and modified apocrine sweat glands (glands of Moll, ciliary glands). The epithelium near the terminus of the gland consists of an outer myoepithelial layer and an inner layer of flattened glandular cells. The structure and location of the glands of Moll are similar in all domestic species (Adam et al., 1970). In primates, including humans, these glands contain a variety of antimicrobial proteins (Stoeckelhuber et al., 2004). These apocrine glands may provide host defense at the margin of the eyelids and possibly in the tears.

Deep to the eyelid skin, there is dense collagenous stroma and bundles of striated muscle fibers that comprise the orbicularis oculi muscle. The orbicularis oculi muscle is arranged in parallel rows that extend nearly the full length of each eyelid. In humans, nearly 90% of the orbicularis oculi muscle fibers consist of the fast type (Hwang et al., 2011).

In the upper eyelid, the levator palpebrae superioris muscle, which originates from the orbital apex, fans out along the dorsal half of the midstroma. The muscle extends toward the inner connective tissue boundary of the orbicularis oculi muscle ending in individual small tendons. The eyelid muscles are separated from the posterior epithelial lining of the eyelids (i.e., the palpebral conjunctiva) by a narrow layer of dense connective tissue. This tissue is well developed in humans and is referred to as the cartilaginous tarsal plate; in most veterinary species, it is less developed (fibrous tissue) and referred to as the tarsus.

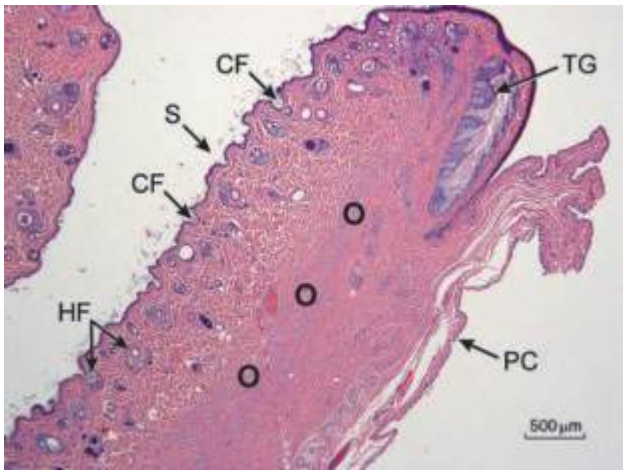


Figure 2.10 Photomicrograph of the eyelid of a dog: hair follicle (HF), cilia follicle (CF), palpebral conjunctiva (PC), tarsal gland (TG), skin (S), orbicularis oculi muscle fibers (O).

The meibomian (tarsal) glands (see Fig. 2.8 and Fig. 2.10) are located in the distal portion of the tarsus near the eyelid margins and contribute to the outer, oily component of the preocular tear film. There are typically 20–40 glands present in each eyelid in the dog (Pollock, 1979), and they are usually more developed in the upper eyelid, especially in cats. These holocrine, modified sebaceous glands form parallel rows of lobules, which have their duct openings on the eyelid margins. The meibomian gland ducts are lined by a keratinized stratified squamous epithelium (Jester et al., 1981). Each gland is made of a number of holocrine acini, which are arranged in vertical columns and open into a central duct. Individual acini have an associated plexi of nerve fibers, which are believed to stimulate their secretion (Chung et al., 1996; Seifert & Spitznas, 1996). The nerve fibers, which are largely parasympathetic in origin, closely appose the basement membrane of each acinus. The eyelids of the

Asian elephant, rock hyrax, and birds are devoid of meibomian glands.

In addition to the meibomian glands, there are accessory lacrimal glands associated with the eyelids. In humans they are referred to as the glands of Krause and Wolfring. The glands of Wolfring are found along the posterior lining of the eyelids whereas the glands of Krause are located at the conjunctival fornix. In domestic species, these accessory glands are most commonly located in the conjunctiva and have been referred to as conjunctival glands. Their contribution to the volume of tear film in cats is negligible (McLaughlin et al., 1988).

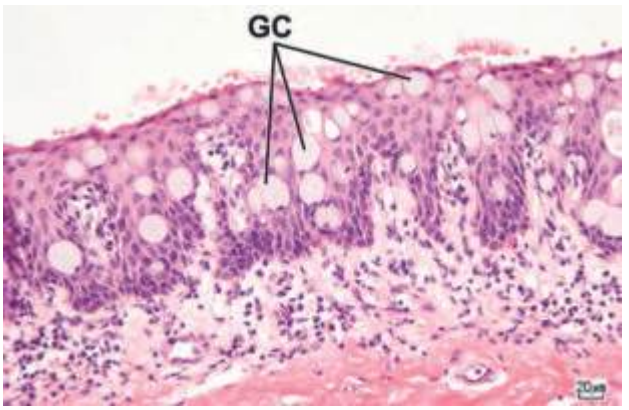


Figure 2.11 Palpebral conjunctiva of a porcine eyelid is externally lined by a stratified to pseudostratified columnar epithelium possessing numerous goblet cells (GC) near the fornix.

Conjunctiva

The conjunctiva is a mucous membrane that lines the inner aspect of the eyelids, the anterior and posterior surfaces of the nictitating membrane (NM), and the exposed sclera. The conjunctiva consists of a thin layer of loose connective tissue beneath a simple to stratified squamous epithelium that becomes consistently stratified toward the eyelid margin. The palpebral conjunctiva lines the inner aspect of the eyelids. As the conjunctiva reflects onto the globe, it is called the bulbar conjunctiva and becomes continuous with the limbal and corneal epithelium. The conjunctiva on the anterior and posterior surfaces of the nictitating membrane is contiguous with the palpebral and bulbar conjunctiva mucosa, respectively. The junction between the palpebral and bulbar conjunctiva is the conjunctival fornix, and the epithelial lining in this region varies according to species, ranging from pseudostratified columnar to stratified cuboidal (Goller & Weyrauch, 1993).

Ventrally, an additional fold is formed by reflection of the conjunctiva over the NM. The reflections at the conjunctival fornix and NM form the conjunctival sac. All parts of the conjunctiva are continuous, but for descriptive purposes, it is divided into the palpebral, bulbar, and fornix conjunctiva and further referenced to specific eyelids. The distribution of goblet cells in the conjunctiva is heterogeneous in the dog (Moore et al., 1987). The highest densities occur along the lower nasal and middle fornix and the lower tarsal portion of the palpebral conjunctiva (Fig. 2.11). In cats the conjunctival goblet cell density varies widely by region but is highest in the anterior surface of the NM and the conjunctival fornices (Sebbag et al., 2016). Additionally, in most domestic species, the bulbar conjunctiva has been reported to either essentially lack goblet cells or has a much lower population of these mucus-forming cells (Bourges-Abella et al., 2007; Doughty, 2002; Grahn et al., 2005). At the fornix, the conjunctiva is arranged into small folds that contain protruding goblet cells and, dorsolaterally, the openings of the lacrimal gland's ducts (Goller & Weyrauch, 1993).

The substantia propria of the conjunctiva is composed of two layers: a superficial adenoid layer, which in the dog and cat contains a variable presence of lymphatic follicles and glands; and a deep, fibrous layer that contains the conjunctival nerves and vessels. The arteries of the conjunctiva arise from the anterior ciliary arteries, which are branches of the external ophthalmic artery, and from branches of the superior and inferior palpebral and malar arteries (Murphy et al., 2012).

The lymphatics of the conjunctiva, called the conjunctiva-associated lymphatic tissue (CALT), are arranged in two plexuses: a superficial and a deep system. CALT is generally diffuse with intermittent nodules or follicles. Often the diffuse component of CALT infiltrates and is adjacent to tear-secreting glands, especially those associated with the NM. Variations in the size and distribution of nodules occur between the upper and lower eyelids and are influenced by exposure to various foreign substances including potentially infectious microorganisms (Fix & Arp, 1991). Cells such as CD8-positive suppressor/cytotoxic effector cells are generally more prevalent (Knop & Knop, 2005). CALT of domestic and wildlife species can have follicle-associated conjunctival epithelium where goblet cells are characteristically absent, being replaced by antigen-absorptive cells called M (i.e., microfold) cells (Samuelson et al., 2011). The ultrastructural appearance of these cells is not identical to those described in mucosa-associated lymphoid tissues throughout the body (Chodosh et al., 1998). The lymphatic drainage of the conjunctiva is toward both commissures, where the drainage joins the lymphatics of the eyelids. Drainage from the lateral commissure is to the parotid lymph nodes, whereas the medial regions drain to the mandibular lymph nodes.

The conjunctiva at the fornix is very thin and translucent, and it lies loosely on the underlying connective tissue. In the domestic carnivore, approximately 3 mm from the limbus, the bulbar conjunctiva, Tenon's capsule, and sclera become closely united. The connective tissue is much more abundant in this location in the dog than in humans and other species.

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The primary functions of the conjunctiva are to prevent desiccation of the cornea, to allow mobility of the eyelids and the globe, and to provide a physical and physiological barrier against microorganisms and foreign bodies. This latter role is most important considering that conjunctival sacs house considerable microbial flora, including many potential pathogens (Samuelson et al., 1984a).

Nictitating Membrane

The NM (membrana nictitans, third eyelid, or *plica semilunaris*) protrudes from the medial canthus in the ventromedial anterior orbit (see Fig. 2.8). It contains a cartilaginous, T-shaped plate, the horizontal part of which is parallel with the free or leading edge of the membrane (Fig. 2.12). In many animal species, the free edge is pigmented. The stroma consists of loose to dense connective tissue that supports glandular and lymphoid tissue (Fig. 2.13). The distal portion of the anterior (i.e., palpebral) and posterior (i.e., bulbar) surfaces is usually covered with nonkeratinized stratified squamous epithelium. The NM possesses a prominent accessory lacrimal gland often referred to as the NM gland (nictitans gland) or gland of the NM (Murphy et al., 2012). In many species, the gland surrounds much of the vertical base of the cartilaginous plate. This gland is serous in horses and cats, mixed (seromucous) in cattle and dogs, and mostly mucous in pigs (Aughey & Frye, 2001; Murphy et al., 2012).

The cartilage of the NM is predominately elastic in horses, cats, and pigs and hyaline in ruminants and dogs (Banks, 1993). The three-dimensional shape of the cartilage varies considerably among domestic species (Schlegel et al., 2001). The horizontal portion of the T cartilage appears as a reverse S-shape in the cat, a crescent-shape in the dog, and a hook-shape in the horse.

The Harderian gland (Harder's gland) when present, is usually located posterior to the NM, and appears grossly and histologically to be an extension of the NM gland. This glandular tissue in some animals can be considerably larger than the NM gland. The anatomical presence of the Harderian gland among mammals has been found mostly in rodents (mouse, rat, Guinea-pig, Mongolian gerbil, golden hamster, wood mouse, Plains mouse, various squirrel species, chipmunk, and deer mouse), with only the Mongolian gerbil having the nictitans gland as well. Other mammals that possess the Harderian gland exclusively include members of Insectivora (hedgehog and shrews), species of deer (red deer, fallow deer), nine-banded armadillo, cottontail rabbit, and

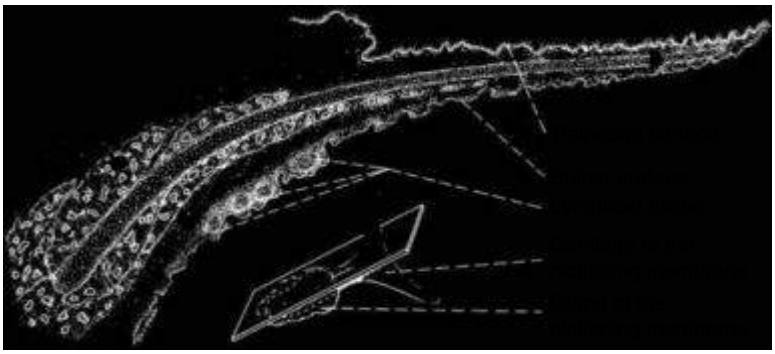


Figure 2.12 Drawing of a histologic section of the mammalian nictitating membrane. (*Source:* Modified from Evans, H. & Christensen, G. (1979) *Miller's Anatomy of the Dog*, 2nd ed. Philadelphia, PA: W.B. Saunders. Reproduced with permission of Elsevier.)

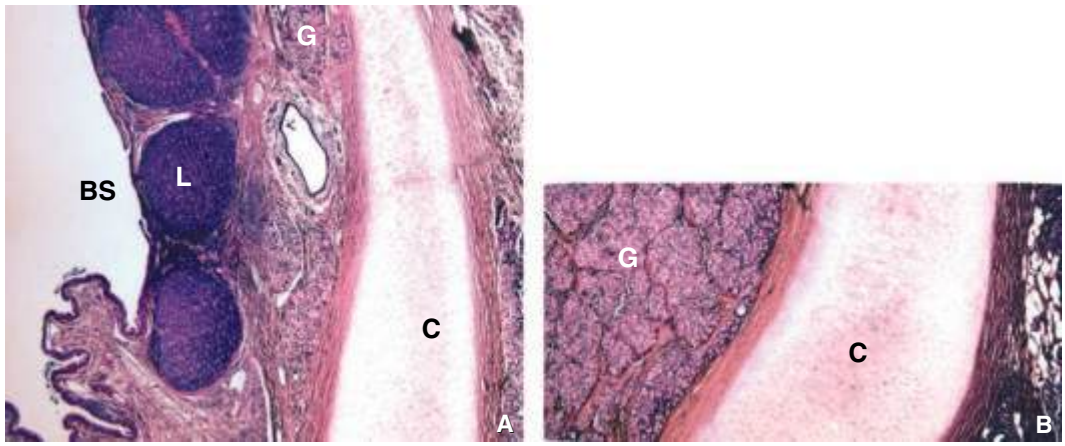


Figure 2.13 **A**, **B**. Nictitating membrane of the horse contains both glandular (G) and lymphoid (L) tissues, with the latter being superficially located within the stroma next to the bulbar surface (BS). C, cartilage. (Original magnification, 10×.)

Afghan pika. Besides the Mongolian gerbil, mammals with both nictitans and Harderian glands are the pig and rabbit (Sakai, 1992).

In mammals, the secretory cells of the Harderian glands are columnar and lined by myoepithelium. The adenomeres are generally tubular or tubuloalveolar and secrete lipid materials in addition to seromucous products. In rodents, the lipids are released uniquely in an exocytotic (merocrine) manner (Payne, 1994). Most importantly, their secretions contain unusual compounds including porphyrins and melatonin (Menendez-Pelaez & Buzzel, 1992; Spike et al., 1992).

Harderian glands contain autonomically controlled nerves and are also under the control of gonadal, thyroid, and pituitary hormones. The functions of this gland remain speculative, but they may include immunologic defense, photoprotection, provision for thermoregulatory lipids, osmoregulation, reproductive influences, and pheromone production.

In most domestic animals, the movement of the NM is indirect, resulting from contraction of the retractor oculi muscle, which retracts the globe into the orbital space and causes passive elevation of the NM. However, in the domestic cat, the retractor oculi muscle is less well developed, and small bundles of smooth muscle have been found in the NM that most likely contribute to its more rapid movements. Specifically, there are nine strands of smooth muscle fibers that extend into the feline's NM and are believed to be involved with its protrusion and retraction (Nuyttens & Simoens, 1995). Each strand is discrete, much like the erector pili muscle associated with hair follicles of skin, but more developed. These smooth muscle bundles or strands contribute to forward movement of the NM, quite possibly in response to an endocrine signal (fight or flight). In birds and other nonmammalian species that lack a retractor oculi muscle, movement of the NM is controlled by the pyramidalis and quadratus muscles, attached to the posterior surface of the sclera (Duke-Elder, 1958). The pyramidalis and the quadratus muscles are skeletal muscles controlled by the oculomotor nucleus that moves the NM anteriorly (Bravo & Inzunza, 1985; Maier et al., 1972).

Lacrimal and Nasolacrimal System

An adequate precorneal tear film (PTF) is necessary for optical integrity, maintenance of the cornea, and normal ocular function. The PTF serves several functions, including the following

1) maintenance of an optically uniform corneal surface
2) removal of foreign material and debris from the cornea and conjunctival sac
3) delivery of an oxygen source to the avascular cornea, and
4) provision of antimicrobial substances.

The PTF is trilaminar, although all three layers are intricately mingled. The outer, thin, oily layer is produced by the meibomian glands and sebaceous glands of Zeis. This layer reduces evaporation of the underlying aqueous layer and forms a barrier along the lid margins that prevents tear overflow.

The middle layer is the aqueous layer and is secreted by the orbital lacrimal gland (61.7%), the accessory glands (3.1%), and the gland of the NM (35.2%) (Gelatt et al., 1975). This layer delivers oxygen and other nutrients to the avascular cornea and provides a volume of fluid to 'flush' the ocular surface and remove debris.

The innermost layer is the mucin layer and is produced predominately by the conjunctival goblet cells. The glycocalyx, produced by the corneal epithelial cells, also contributes to the mucin layer. The mucin produced by lacrimal and lacrimal-accessory glands that have mucus-secreting cells, contributes to the mucin layer as well. The mucin is adsorbed to the corneal epithelial surface and is distributed evenly during normal blinking. This layer provides a hydrophilic surface over which the aqueous tear fluid spreads evenly and lubricates the corneal and conjunctival surfaces.

Excess lacrimal fluid collects by gravity in the lower conjunctival sac and is mechanically 'pumped' through the upper and lower lacrimal puncta located approximately 1–2 mm inside the margin of the medial eyelid. Each punctum is surrounded by smooth muscle that works in coordination with eyelid blinking to remove excess lacrimal fluid and prevent its backflow. The puncta continue as the upper and lower canaliculi, which pass slightly vertically away from the eyelid margins and turn toward the medial canthus, pass through the periorbita, and meet at a dilation, the lacrimal sac, located in the lacrimal fossa of the lacrimal bone (Fig. 2.14). This sac empties into the nasolacrimal duct, which passes through a short, bony canal and opens into the nasal cavity, where it continues as a duct until it reaches an opening at the floor of the nostril approximately 1 cm from the end of the nares. Approximately 40% of dogs have an

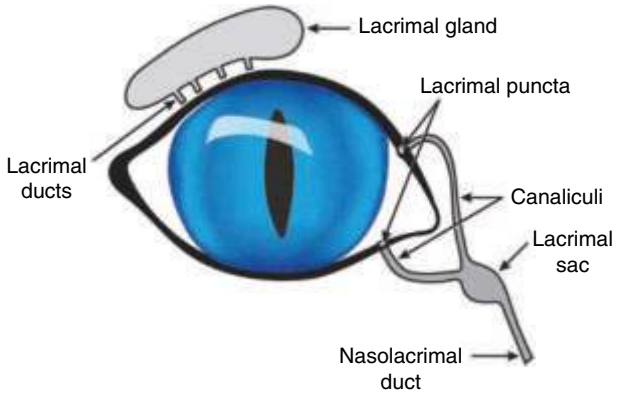


Figure 2.14 The nasolacrimal system.

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accessory opening in the canal as it passes by the root of the upper canine tooth (Michel, 1955). For a comprehensive review of the nasolacrimal system anatomy and disorders, the reader is referred to Ali et al. (2019).

The lacrimal gland is a diamond-shaped structure in the dorsolateral aspect of the orbit underneath the orbital ligament (Park et al., 2016). The mean length, width, thickness, and weight of the lacrimal gland in three different breeds of dogs were ~17 ± 0.7 mm, ~13 ± 0.4 mm, ~3 ± 0.1 mm, and ~316 ± 21 mg, respectively (Park et al., 2016). Fifteen to 20 small ductules drain into the superior conjunctival fornix. Histologically, the gland is a tubuloalveolar type. The lacrimal gland produces the majority of the aqueous portion of the preocular tear film. In rats and rabbits, mucous components are also secreted from the lacrimal gland (Ding et al., 2011; Draper et al., 1998). The innervation to the lacrimal gland is not fully understood, but the lacrimal branch of CN V, sympathetic, and parasympathetic nerves are all involved in its function. Clinically, certain cholinergic drugs (e.g., pilocarpine) stimulate tear secretion, whereas other drugs (i.e., anticholinergics) decrease tear secretion.

Globe

Components

The globe is composed of three basic layers or coats (Fig. 2.15). The outer layer is the fibrous tunic which is further divided into the cornea and sclera. The fibrous tunic provides shape to the eye. In addition, the anterior portion of the fibrous tunic (i.e., the cornea) is transparent, thus enabling light to pass through, and is shaped in a manner that makes it a powerful lens that refracts light rays centrally, toward the visual axis of the eye. The middle layer is the vascular tunic, called the uvea (meaning "grape"). The uvea is further divided into the iris, ciliary body, and choroid and is heavily pigmented and vascularized. It functions to restrict the amount of light entering the eye and to provide nourishment and remove waste products. The innermost layer is the nervous tunic, which consists of the retina and optic nerve. The three tunics embrace the large, inner, transparent media of the eye: the aqueous humor, lens, and vitreous humor, which collectively function to transmit and refract light to the retina and provide an internal pressure that keeps the globe firmly distended.

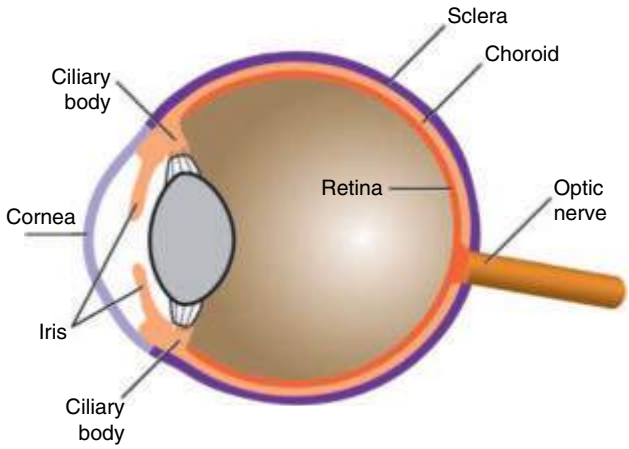


Figure 2.15 The three tunics that comprise the mammalian globe. Outermost fibrous tunic (light and dark purple), consisting of the cornea and sclera; the middle tunic called the uvea (light orange), consisting of the iris, ciliary body and choroid; and the nervous tunic (dark orange) consisting of the retina and optic nerve.

Size, Shape, and Topography

The eyes in domestic animals are quite variable in size, but their shapes are comparatively uniform, being spherical in most instances, in which the three axes of the globe (anteroposterior, horizontal or transverse, and vertical) are nearly identical in dimensions (see Table 2.5 and Table 2.6). Some of the larger ungulates, including the cow and horse, possess globes that are relatively flattened in the anteroposterior axis (Fig. 2.16). The geometric axis of the eye is positioned from the center of the cornea (i.e., anterior pole) to the posterior center of the sclera (i.e., posterior pole). Two principal planes, the equatorial and meridional, are traditionally used

Table 2.5 External globe dimensions.

Animal	Meridional A–P axis of the eye, A (mm)	Equatorial axis, V (mm)	Horizontal, T (mm)	Ratio of A/V/T	Ratio of V/T
Horse	43.68	47.63	48.45	1:1.09:1.10	1:1.10
Cow	35.34	40.82	41.90	1:1.15:1.18	1:1.02
Sheep	26.85	30.02	30.86	1:1.11:1.15	1:1.02
Pig	24.60	26.53	26.23	1:1.08:1.06	1:0.99
Dog	21.73	21.34	21.17	1:0.98:0.97	1:0.99
Cat	21.30	20.60	20.55	1:0.97:0.96	1:0.99

Source: Translated from Bayer, J. (1914) *Angenheilkunde*. Vienna: Braumueller.

Table 2.6 Globe dimensions.

Animal	Axial globe length (mm)	Anterior chamber depth (mm)	Axial lens thickness (mm)	Vitreous chamber depth (mm)	Reference
Horse	39.23 ± 1.26	5.63 ± 0.86	11.75 ± 0.80		McMullen & Gilger, 2006
	40.4 ± 1.8	6.8 ± 0.5	11.7 ± 0.6	21.8 ± 1.3	Mouney et al., 2012
Dog	20 ± 1.6	3.8 ± 0.1	6.7 ± 1.0		Williams, 2004
Cat	19.75 ± 1.59	4.66 ± 0.86		7.92 ± 0.86	Konrade et al., 2012
	20.91 ± 0.53	5.07 ± 0.36	7.77 ± 0.23		Gilger et al., 1998

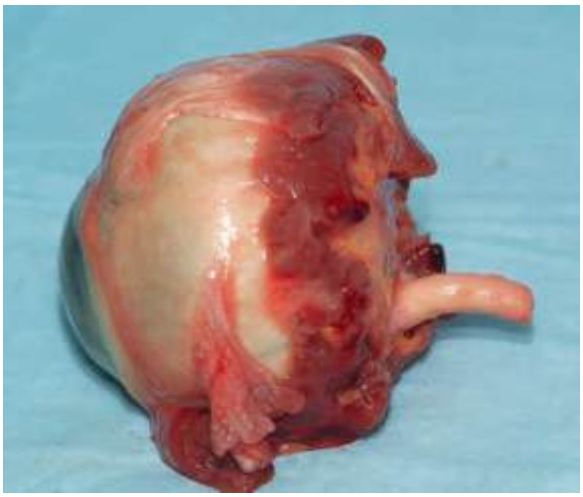


Figure 2.16 Lateral view of an equine globe. Note the marked flattening in the anteroposterior axis and the marked ventral exit of the optic nerve from the posterior pole.

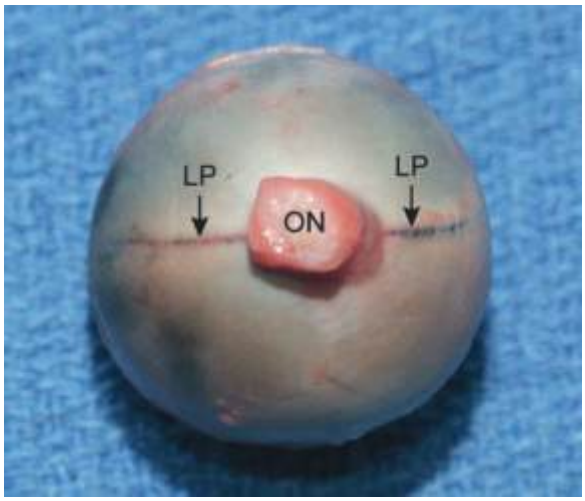


Figure 2.18 Posterior view of a canine globe. LP, long posterior ciliary artery; ON, optic nerve.

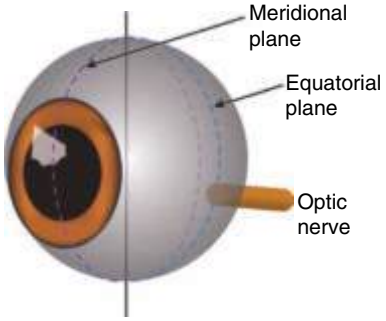


Figure 2.17 The equatorial and meridional planes of the eye.

in references to the three axes (Fig. 2.17). The equatorial plane bisects the anterior and posterior poles and is perpendicular to the meridional plane. Any plane that runs parallel to the equatorial plane is called the frontal, coronal, radial, or transverse plane. The meridional plane moves along the anteroposterior axis of the eye, vertically dividing it into medial and lateral halves, even though meridional planes can be horizontal or oblique. Planes that run parallel to the meridional plane are described as sagittal planes.

The optic nerve in most domestic animals lies inferior and lateral to the posterior pole. Surrounding the optic nerve are many ciliary nerves and short posterior ciliary arteries. In normal dogs, the mean number of short posterior ciliary arteries is 12 (~7 dorsally and ~5 ventrally) (Frick & Dubielzig, 2016). The posterior ciliary nerves pursue a long intrascleral course (up to 12 mm) before entering the suprachoroidal space to reach the iris, ciliary body, and limbus. In the dog, the long posterior ciliary arteries enter the sclera approximately 3–5 mm from the optic nerve in the horizontal meridian (Fig. 2.18). In the cat, these arteries can enter the sclera immediately adjacent to the optic nerve. These vessels are visible on the nasal and temporal sides of the eye within the sclera at least as far as the equator before entering the choroidal space. At this point, each artery accompanies the long ciliary nerve to the iris and ciliary body. Recurrent vascular branches enter the choroid, but the main vessel trunk continues to be the major supply to the iris. A variable number of vortex veins (usually four) emerge from the sclera posterior to the equator; typically, two vortex veins are present dorsally and two ventrally.

Several topographic features help establish the proper anatomic positions of an enucleated globe. For example,

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observation of the long posterior arteries and the longer horizontal dimension of the cornea determines the horizontal meridian. Location of the ventral exit of the optic nerve and the dorsal oblique muscle tendon establish the dorsoventral aspect of the globe. Remnants of the NM and the lateral placement of the optic nerve to the posterior pole determine the medial and lateral aspects.

Cornea

The cornea is the transparent, anterior portion of the fibrous tunic of the globe. Like the lens, the cornea is normally clear and transmits and refracts light (40–42 diopters in dogs). The avascular cornea relies on both the aqueous humor and tear film for nourishment and on the eyelids and NM for protection from the external environment.

The cornea is elliptical in shape, with a horizontal diameter greater than the vertical. In the dog and the cat, the difference between these diameters is small, thus making their corneas appear almost circular (see Fig. 2.8). In most ungulates, this difference is much more pronounced, allowing for a remarkable horizontal field of view (Fig. 2.19) that is further complemented by the lateral positioning of the orbits. The combination of the exaggerated corneal dimensions and orbital positions in these grazing animals appears to be the adaptive result of their feeding behavior, affording them greater protection from predators.

Corneal thickness varies between species, breeds, individuals, and location (i.e., central vs. peripheral cornea). In most domestic animals, it is less than 1 mm thick. Table 2.7 lists the central corneal thickness in dogs, cats, and horses using selected noninvasive diagnostic imaging modalities. One study using ultrasonic pachymetry in cats found there is no significant difference in mean corneal thickness between the central and peripheral cornea (Gilger et al., 1993). However, another study using the same modality found that the feline cornea is not uniform in thickness; when compared with the axial cornea, the superior nasal area is thinner, and the temporal area is thicker (Schoster et al., 1995). In dogs, the superior peripheral and temporal peripheral cornea are significantly thicker than the central cornea (Gilger et al., 1991).

Corneal thickness is also influenced by age and time of day. Corneal thickness increases significantly with age in the dog, cat, and horse (Gilger et al., 1991, 1993; Herbig & Eule, 2015). Additionally, central corneal thickness and intraocular pressure (IOP) in healthy Beagles are significantly lower

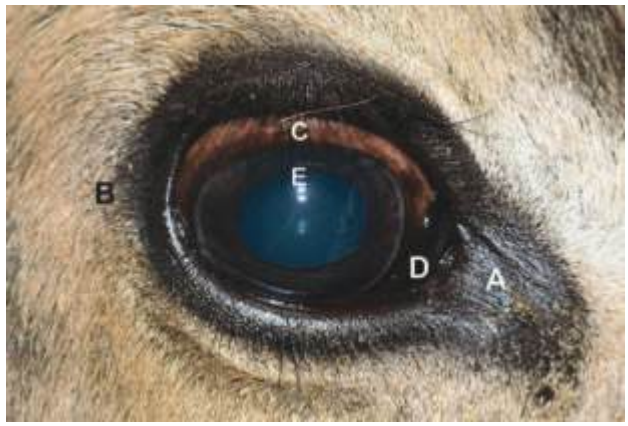


Figure 2.19 The globe of the cow viewed anteriorly. Note the horizontally elongated ellipse of the cornea. A, medial canthus; B, lateral canthus; C, cilia; D, nictitating membrane; E, granula iridica.

Table 2.7 Corneal thickness.*

	SD-OCT (μm)	Scheimpflug (μm)	Confocal (μm)	Ultrasound pachymetry (μm)	High resolution ultrasound biomicroscopy (μm)
Dog	610.56 ± 57.48[d] 587.72 ± 32.44[f] 611.2 ± 40.3[j] 497.54 ± 29.76[n] 606.83 ± 39.5[s]	629.73 ± 64.57[d] 606.83 ± 39.45[h]	585 ± 79[k]	560 ± 5.2[a] 554.95 ± 72.41[c] 598.54 ± 32.28[f] 555.49 ± 17.19[n] 545.6 ± 21.7[q]	689.77+55.93[d]
Cat	584.93 ± 39.05[e] 629.08 ± 47.05[g]	606.41 ± 44.18[e]	592 ± 80[k]	578 ± 64[b] 546 ± 48[r]	
Horse	812.0 ± 44.1[i] 800 ± 50[l]		835[m]	770.0 ± 7.5[o] 785.6 ± 2.98[p] (Miniature Horse)	

* Most data is from the central cornea, but not all papers stated measurement location.
SD-OCT, spectral-domain optical coherence tomography.
[a] Gilger et al., 1991; [b] Gilger et al., 1993; [c] Garzon-Ariza et al., 2017; [d] Wolfel et al., 2017; [e] Cleymaet et al., 2016; [f] Alario & Pirie, 2014b; [g] Alario & Pirie, 2013a; [h] Alario & Pirie, 2013b; [i] Pirie et al., 2014; [j] Alario & Pirie, 2014a; [k] Kafarnik et al., 2007; [l] Pinto & Gilger, 2014; [m] Ledbetter & Scarlett, 2009; [n] Strom et al., 2016a; [o] Ramsey et al., 1999; [p] Plummer et al., 2003; [q] Martin-Suarez et al., 2014; [r] Schoster et al., 1995; [s] Alario & Pirie, 2013b

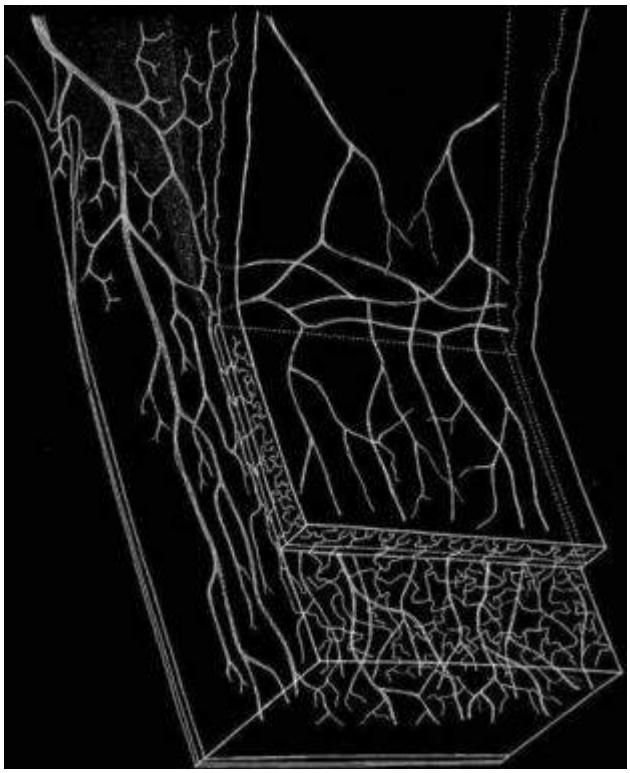


Figure 2.20 Innervation of the limbus and cornea. The long ciliary nerve (A) supplies the limbal region, then sends branches into the cornea. Nerves also supply the trabecular meshwork (B) and the region of the canal of Schlemm (i.e., angular aqueous plexus in nonprimates). Note the paucity of nerves in the deep cornea (C) and their absence in the region of Descemet's membrane as compared with a multitude of branched endings of nerves within the anterior stroma (D) and epithelium. (*Source:* Modified from Hogan, M.J., Alvarado, J.A. & Weddell, J.E. (1971) *Histology of the Human Eye*. Philadelphia, PA: W.B. Saunders. Reproduced with permission of Elsevier.)

in the afternoon/evening than in the morning (Garzon-Ariza et al., 2017; Martin-Suarez et al., 2014).

The cornea is richly supplied with sensory nerves, particularly pain receptors, and this sensitivity provides protection to the cornea and helps maintain transparency (Fig. 2.20). The cornea is innervated by the long ciliary nerves, which are derived from the ophthalmic branch of the trigeminal nerve (Mawas, 1951). The epithelial cell layers are richly innervated, and these nerve endings are unsheathed among the epitheliae. Use of immunohistochemical localization of neuropeptides associated with the ciliary ganglion in the dog has revealed the presence of a well-developed pattern of epithelial innervation consisting of numerous horizontally oriented leash formations at the level of the epithelial basal cells (Marfurt et al., 2001). These formations comprise anastomotic networks of variously sized nerve fascicles that course circumferentially along the limbus, becoming oblique to eventually radial in orientation centrally. By comparison, stromal innervations, which exist superficially, consist of main bundles that repetitively branch in a dichotomous manner to create elaborate axonal arborizations. In general, the most superficial layers are primarily innervated with pain receptors, whereas more pressure receptors are found in the stroma. This explains why a superficial corneal injury is often more painful than a deeper wound.

The following anatomic factors contribute to the transparency of the cornea

1) lack of blood vessels
2) nonkeratinized surface epithelium maintained by a PTF
3) lack of pigmentation
4) relative dehydration (deturgescence), and
5) size and organization of stromal collagen fibrils.

The cornea comprises four (sometimes five) layers. From superficial to deep, the layers are the epithelium, Bowman's layer (in some species), stroma, Descemet's membrane, and endothelium (Fig. 2.21).

Corneal Epithelium

The corneal epithelium is a nonkeratinized, stratified squamous epithelium that covers the anterior corneal surface. The epithelium is approximately 25–40 μm thick in the domestic carnivore and two to four times thicker in the ungulate. In the dog, cat, and bird, the anterior epithelium consists of a single layer of basal cells that lie on a thin basement membrane; two or three layers of polyhedral (i.e., wing) cells and two or three layers of nonkeratinized squamous cells (Fig. 2.21 and Fig. 2.22). In larger animals, the layers of polyhedral and squamous cells are more numerous. The cells are arranged to provide orderly replacement of the surface cells during desquamation. In normal Beagles, the superficial epithelial cell diameter is 43.3 ± 6.6 μm

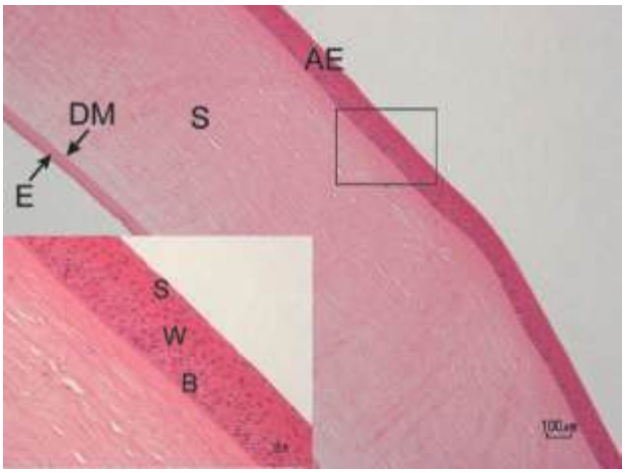


Figure 2.21 Histologic view of the four layers in the equine cornea: anterior epithelium (AE), stroma (S), Descemet's membrane (DM), and endothelium (E). *Insert*: Basal cells (B), wing cells (W), squamous cells (S).

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and the basal cell diameter is 4.4 ± 0.7 µm as examined via *in vivo* confocal microscopy (Strom et. al., 2016b).

The basal cells are tall, columnar cells with a flattened base and domed apex. They are crowded together, and as a result, the nuclei, which are located in the apical region, are often forced into two or alternating layers. Mitosis is confined to the basal cells or those cells immediately superficial to the basal cells (i.e., stratum germinativum). Adjacent cell surfaces have small infoldings with numerous desmosomal attachments (Hogan et al., 1971; Shively & Epling, 1970). Occasional lymphocytes are present in the basal epithelium and more superficial layers.

Wing cells are polygonal-shaped cells superficial to the basal cells. Wing cells vary from two or three layers in thickness to several layers, depending on the species and the location in the cornea. These layers form a transition zone between the columnar basal cells and the more superficial squamous cells.

There are several layers of flattened superficial squamous cells. The cells appear to be flat and polygonal with straight borders on scanning electron microscopy (SEM) (Fig. 2.23 and Fig. 2.24). Both light and dark cell types can be identified. The light cells contain more microvillae and microplicae. These numerous projections scatter electrons and, as a result, produce a lighter appearance of the cell. The darker cells are older and are occasionally seen to be desquamating

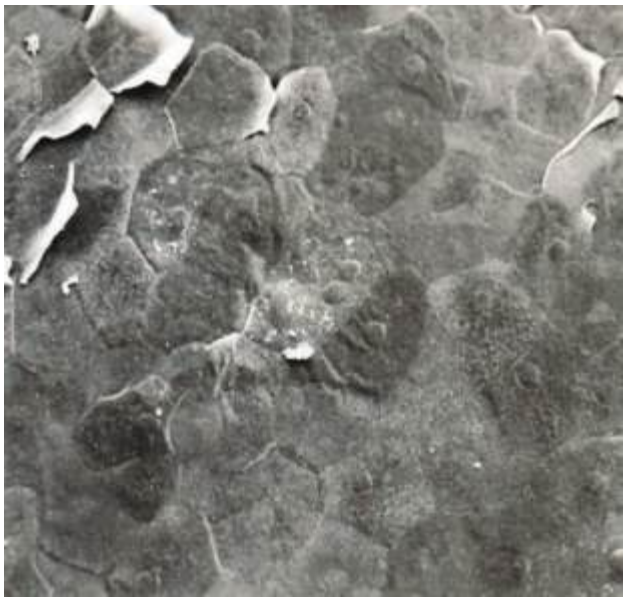


Figure 2.23 SEM shows the surface of the anterior epithelium of a bovine cornea. The surface cells can be light or dark. Note the round bulges, where the nuclei lie within each cell. Note also that some cells appear to be desquamating. (Original magnification, 400×.)

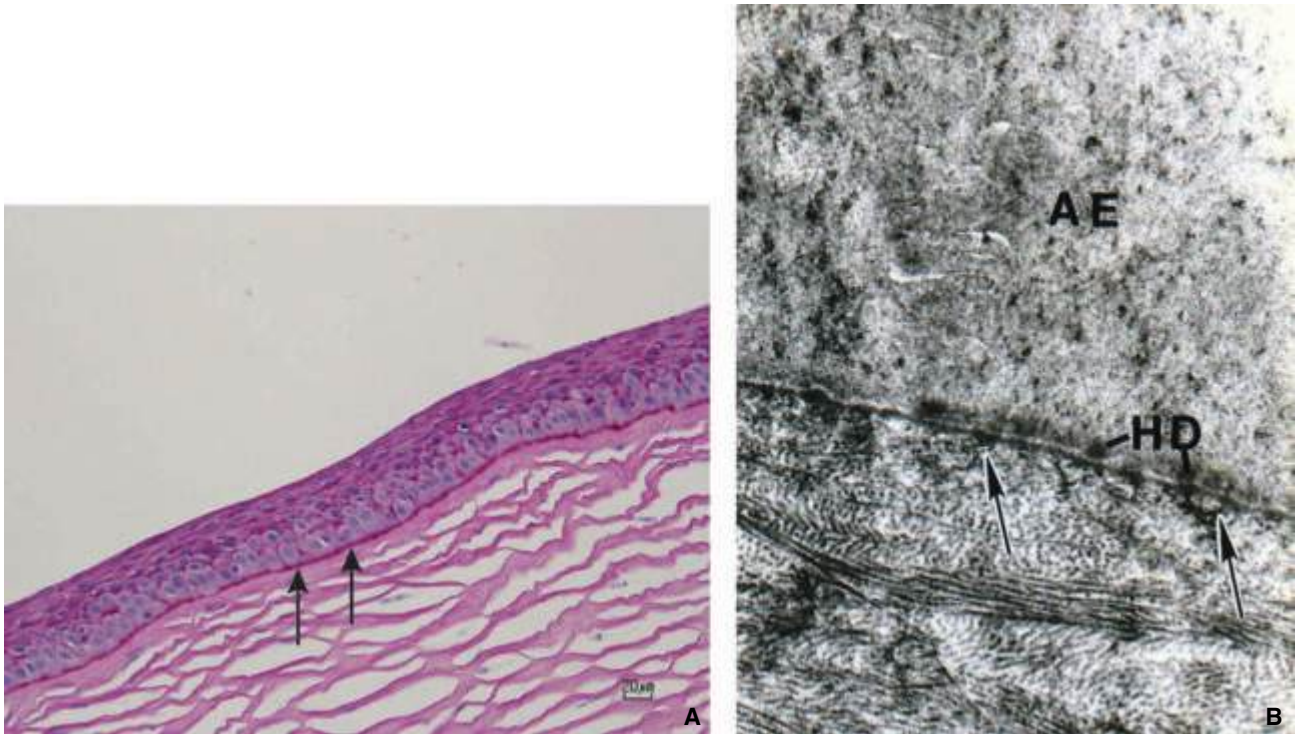


Figure 2.22 Basement membrane (arrows) of the anterior epithelium of the canine cornea viewed light microscopically with the aid of PAS stain (**A**) and ultrastructurally (**B**). AE, anterior epithelium; HD, hemidesmosomes. (Original magnification, 18,000×.)

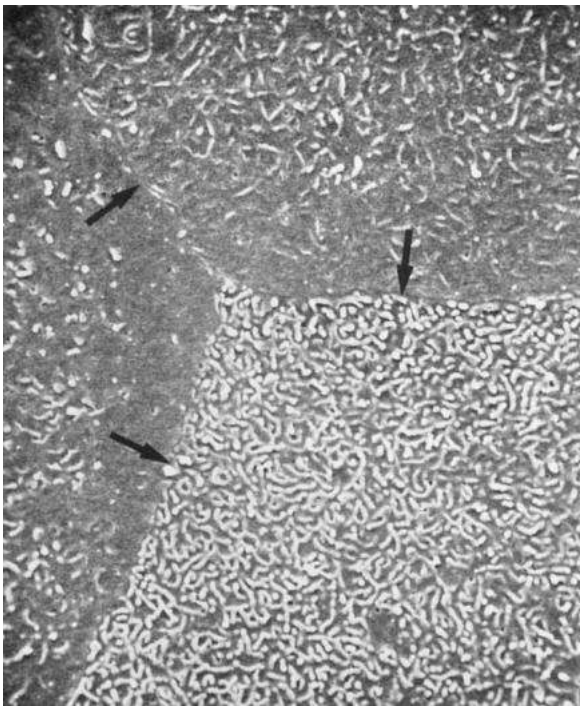


Figure 2.24 SEM shows the corneal epithelial surface of a horse. Junction of a light cell with two dark cells (arrows) illustrates the increased numbers of microplicae and microvillae in the light cell. (Original magnification, 3888×.)

(see Fig. 2.23). Cells in the central cornea have more projections (i.e., microplicae and microvillae) than those in the periphery. It has been proposed that the fine microplicae and microvillae that considerably expand the cells' surface area enable movement of oxygen, potential nutrients, and various metabolic products across the exposed cell membranes of the outermost squamous epithelial cells (Collin & Collin, 2006). However, it is unlikely that the surface expansion would facilitate that process significantly among terrestrial mammals. More than likely, the microprojections of the squamous epithelial cells, which can be sometimes intricate in their patterns, allow mucin of the PTF to adhere firmly to the anterior epithelium which aids in stabilizing the tear film on the corneal surface (Blumcke & Morgenroth, 1976; Harding et al., 1974).

The cytoplasm of the superficial cells contains numerous tonofilaments and vesicles but generally lacks the mitochondria, rough endoplasmic reticulum, and ribosomes that are present in the basal and wing cells. Cytokeratins have been demonstrated in the corneal epithelium of several species (Nautscher et al., 2016). Numerous desmosomal attachments are present, and the surface cells have a zonula occludentes on their lateral membranes.

The corneal epithelium is thicker at the periphery of the cornea than in the center. With the junction of the bulbar conjunctiva, however, it abruptly thins, and pigmented cells

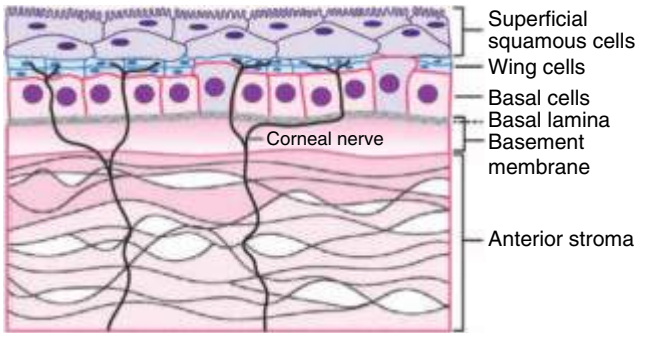


Figure 2.25 The corneal epithelium and anterior stroma. Nonkeratinized squamous cells (2–3 layers), wing cells (2–3 layers) basal cells (single layer), basal lamina, and corneal nerves.

are observed. At the limbus, pigment is scattered in all layers except the superficial squamous cells. Nerves enter the epithelium and terminate among the wing cells (Fig. 2.25; Hogan et al., 1971).

Beneath the epithelium is a basement membrane, which stains positively with periodic acid–Schiff (PAS) (see Fig. 2.22A). The basal cells are firmly attached to the basal lamina of the basement membrane (i.e., anterior limiting lamina) by hemidesmosomes, anchoring collagen fibrils, and the glycoprotein laminin. Various types of collagen are found within the different layers of the cornea (Table 2.8). Interestingly, evidence of type IV collagen, which is ubiquitous throughout basement membranes of the body, is weak (Nakamura et al., 1994a, 1994b). Hyaluronan and fibronectin also have been associated with corneal epithelial attachment (Nakamura et al.,1994a). Ultrastructurally, the basement membrane consists of a 30–55 nm thick osmiophilic layer that is separated from the basal cell plasma membrane by a 25 nm wide, electron-lucent zone (see Fig. 2.22B). Hemidesmosomes attach the basal cells to the basement membrane, which in turn anchors the epithelium to the stroma. The arrangement of hemidesmosomes varies among different animals, being linear among mammals and amphibians, in rosettes among birds and reptiles, and punctate without arrangement, or completely absent, among fish (Buck, 1983). The epithelial cells have strong regenerative abilities (basal cell turnover time is approximately 7 days), but after removal of the basal lamina, weeks to months may be necessary for it to completely reestablish; until the basement membrane is completely reformed, the epithelium can be easily removed from the stroma (Gelatt & Samuelson, 1982; Khodadoust et al., 1968).

Stroma

The corneal stroma (i.e., the substantia propria) constitutes 90% of the corneal thickness. It consists of transparent lamellae of collagenous tissue, and these lamellae lie in sheets and separate easily into planes (Fig. 2.26A).

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Table 2.8 Location of glycans and collagen types in the cornea.

Location	Types of collagen	Glycans[a]	References
Anterior epithelium/ basement membrane	IV, VI, and VII	Laminin, fibronectin, hyaluronans	Nakamura et al., 1994b; Smolek & Klyce, 1993
Bowman's layer/ anterior stroma	I, III, V, and VI	Heparan sulfate	Gordon et al., 1994
Stroma	I, III, V, VI, and XII	Chondroitin 6- and 4-sulfates, dermatan sulfate	Cintron & Covington, 1990; Doane et al., 1992; Linsenmayer et al., 1993; Nakamura et al., 1994b; Takahashi et al., 1993
Descemet's membrane	I, III, IV, V, VI, and VIII	Laminin, fibronectin tenascin, P component, heparan sulfate	Tamura et al., 1991

[a] Includes glycoproteins and glycosaminoglycans.

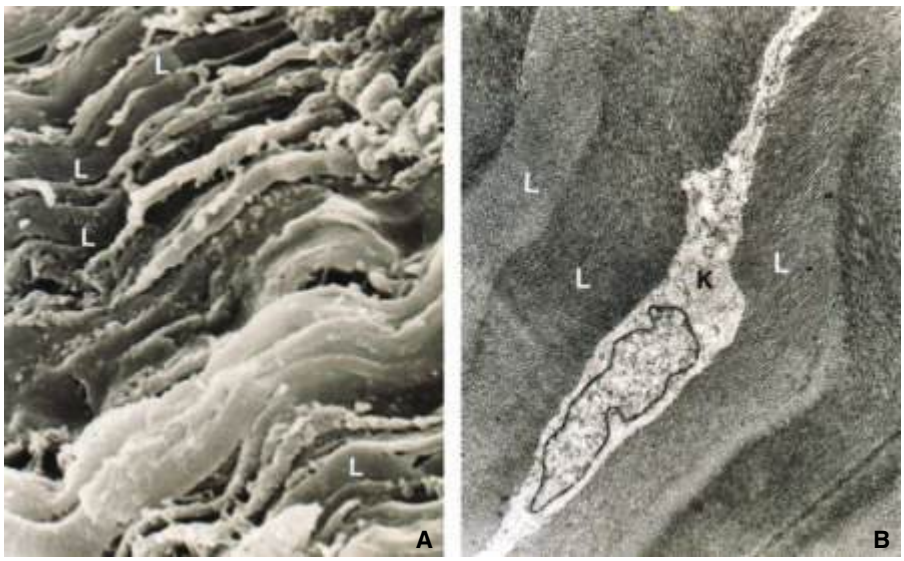


Figure 2.26 **A.** SEM of corneal stroma in the dog. (Original magnification, 7,400×.) **B.** TEM of corneal stroma in the horse consists of layers or lamellae (L) of collagen, which are sparsely interspersed with keratocytes (K). (Original magnification, 10,000×.)

Between the lamella are fixed cells and infrequent wandering cells. The fixed cells are fibrocytes, which are called keratocytes, and their extensions contribute to the formation and maintenance of the stromal lamellae. The keratocytes have thin nuclei, ill-defined borders, and delicate cell membranes (Fig. 2.26B). Similar to lens fibers, these cells possess crystallins, which are believed to facilitate tissue transparency (Jester, 2008). Keratocytes can transform into myofibroblasts when deep corneal injury occurs, and they can form scar tissue that is not transparent. In normal Beagles the keratocyte density in the anterior and posterior stroma is ~993 ± 134 cells/mm^2 and ~789 ± 87 cells/mm^2, respectively. Cell density is significantly greater and nuclei size is significantly smaller in the anterior stroma in comparison with the posterior stroma (Strom et al., 2016b).

The lamellae are parallel bundles of collagen fibrils, with each lamella running the entire diameter of the cornea. All the collagen fibrils within a lamella are parallel, but between lamellae, they vary greatly in direction (Fig. 2.26). The lamellae of the posterior stroma are more regular in arrangement than those of the anterior third of the stroma. The anterior lamellae are more oblique to the surface, and they have more branching and interweaving.

The precise organization of the corneal stroma is the most important factor in maintaining corneal clarity, which involves the select integration of collagen and amorphous ground matrix, consisting of select proteoglycans such as lumican, keratocan, osteoglycin, and decorin (Hassell & Birk, 2010). The collagen in the human cornea has a periodicity of 100 nm (Dawson et al., 2011). This special arrangement of the collagen in the stroma is believed to permit 99%

of the light entering the cornea to pass without scatter (Hogan et al., 1971). The stroma is comprised of at least five types of collagen (see Table 2.8). Of these five, collagen type I is by far the most prevalent, forming the small, evenly sized, striated fibrils. Type VI is associated only with the interfibrillar matrix that forms a network around the fibrils. Evidence from adult mice suggests that type VI is connected with type I through chondroitin/dermatan sulfate glycosaminoglycans (GAGs). Type VI, which is associated with the fibrils and keratocytes, appears to play a role in cell–matrix interactions, which would be especially important during development and repair (Doane et al., 1992). In comparison, type V is combined or coassembled with type I, and it is believed to be responsible for the formation of the small, uniform diameter of the striated fibril, which is approximately 25 nm in most species (Linsenmayer et al., 1993). Types III and XII are both suspected to be developmental forms, with type III being the more common; their importance during wound repair is unknown.

Collagen fibrils, along with the proteoglycans and their associated GAGs and glycoproteins, constitute 15%–25% of the stroma, and they are the principal support structure of the cornea. These collagen fibrils form the matrix for a specialized population of proteoglycans within the corneal stroma (Borcherding et al., 1978; Hassell & Birk, 2010). The cornea is 75%–85% water, and it is relatively dehydrated compared with other tissues. This state of dehydration is termed deturgescence and is, in part, a function of the endothelium and epithelium. These cells move water out of the stroma via energy-dependent Na^+/K^+ adenosine triphosphatase (ATPase) pumps, being most active in the endothelium. Other "pumps" for deturgescence might also exist, including carbonic anhydrase. These cells pump Na^+ and HCO^{3-} ions outward, into the aqueous humor and tears. An osmotic gradient is established, and water flows down the gradient from the corneal stroma into the aqueous humor. Experimentally, removal of the epithelium produces an increase of 200% in corneal thickness after 24 hours because of the influx of water. Removal of the endothelium produces an increase of 500% or more in thickness as the permeability increases sixfold, so the endothelium appears to be more important in maintenance of corneal deturgescence (Watsky et al., 1995). Figure 2.27 illustrates the primary roles the endothelium plays, both as a pump and as a barrier. The barrier component is provided by the tight junctions occurring apically along the lateral faces of adjoining cells next to the anterior chamber. These tight junctions are sensitive to calcium exposure, and they break down when excess free Ca^{++} exists in the aqueous humor. The Na^+/K^+ ATPase pump is located along the lateral membranes of neighboring cells (see Fig. 2.27). A breakdown of the pump, the barrier, or both will result in rapid movement of water into the highly hydrophilic stroma, causing corneal edema to develop.

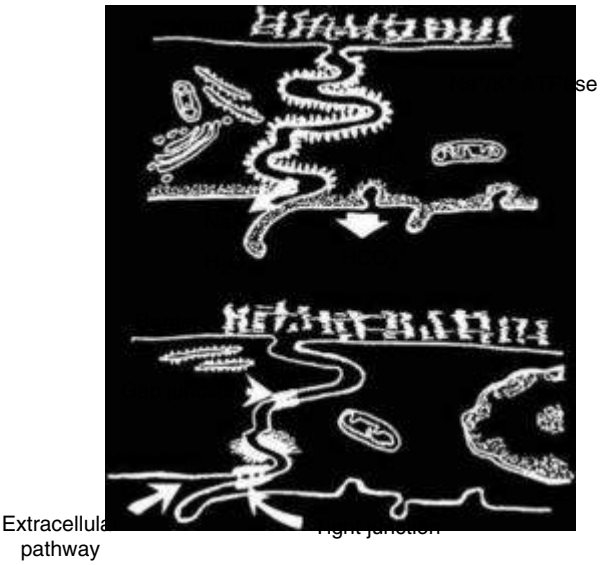


Figure 2.27 Location of the corneal endothelial metabolic pump (Na^+/K^+ ATPase along the lateral membranes and carbonic anhydrase along the apical margins) and barrier (apical tight junctions along the lateral membranes). (*Source:* Redrawn from Watsky, M.A., Olsen, T.W. & Edelhauser, H.F. (1995) Cornea and sclera. In: *Duane's Foundation of Clinical Ophthalmology* (eds Tasman, W. & Jaeger, E.A.), Vol. 2. Philadelphia, PA: J.B. Lippincott.)

The presence of GAGs in the cornea allows the pumps to be effective. Thus, any change in the population of the GAGs, any significant damage to the epithelium or endothelium, or any pressure exerted on the cornea causes a physical rearrangement of the precise collagen organization, which in turn results in opacification of the cornea. GAGs in the cornea consist of heparan sulfates, hyaluronic acid, undersulfated chondroitin sulfates, chondroitin 6-sulfate, chondroitin 4-sulfate, keratan sulfates, and dermatan sulfates (see Table 2.8). The most abundant of these is keratan sulfate, followed by dermatan sulfate (Cintron & Covington, 1990). Nearly all keratan sulfates are derived from stromal fibroblasts (i.e., keratocytes), whereas heparan sulfates are largely derived from the corneal epithelium, particularly as individuals mature. Hyaluronic acids, however, are formed to a fair degree by the corneal endothelium. Each corneal cell type contributes its own specific array of distinct GAG classes as well as other glycoconjugates to the extracellular matrix of the cornea. Corneal keratan sulfate, which differs from that in cartilage by length, branching, and cross-linkage within the polymer, will absorb two to three times more water than chondroitin sulfates, but the latter will retain water eight to nine times more effectively than keratan sulfate. Because of the different water-binding ability of GAGs, keratan sulfate is concentrated within the posterior bovine cornea, where it facilitates movement of water from the aqueous humor into the cornea (Castoro et al., 1988). Dermatan sulfate is concentrated within the anterior stroma.

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In addition to the differential concentration of GAGs within the corneal stroma, the relative amount of keratan sulfate is lower toward the limbus, whereas the level of dermatan sulfate increases (Borcherding et al., 1978). As the amount of keratan sulfate decreases towards the limbus, a corresponding increase in collagen fiber size and lack of organization, as seen in the sclera, occurs.

The anterior-most stroma has a thin, cell-free zone corresponding in location with the anterior-limiting membrane, also known as Bowman's layer (anterior lamina), in humans and nonhuman primates. Bowman's layer is also present in birds, giraffes, dolphins, some whales, and large herbivores (Fig. 2.28; Hayashi et al., 2002; Murphy et al., 1991; Samuelson et al., 2005). In avian and human corneas, Bowman's layer is 10–15 µm thick, relatively acellular, and composed of collagen fibrils of various types (see Fig. 2.28; Table 2.8). Bowman's layer fibrils are smaller in diameter and less uniform than those of the stroma (Gordon et al., 1994). The anterior epithelium produces the majority of the collagen associated with this modified, acellular zone of the cornea. Bowman's layer is not elastic, and when damaged it is replaced with scar tissue. Bowman's layers of the land-based species share similarities in size, morphology, and histochemistry, differing substantially from that of marine mammals, which may reflect a variation of roles that this structure plays. Among whales, Bowman's layer is not thought to exist in deep-diving species, suggesting that its presence may be more closely associated with ocular function near or at the surface of the water.

Descemet's Membrane

Descemet's membrane is a PAS-positive, homogenous, acellular membrane that is the basement membrane of the posterior endothelium. Descemet's membrane is produced throughout life, thus becoming thicker as individuals age. Clinically, the membrane shows elasticity, but it contains only fine collagen fibrils (Jakus, 1956). Descemet's membrane is normally under some tension and when ruptured it tends to curl like a scroll. Descemet's membrane ends at the

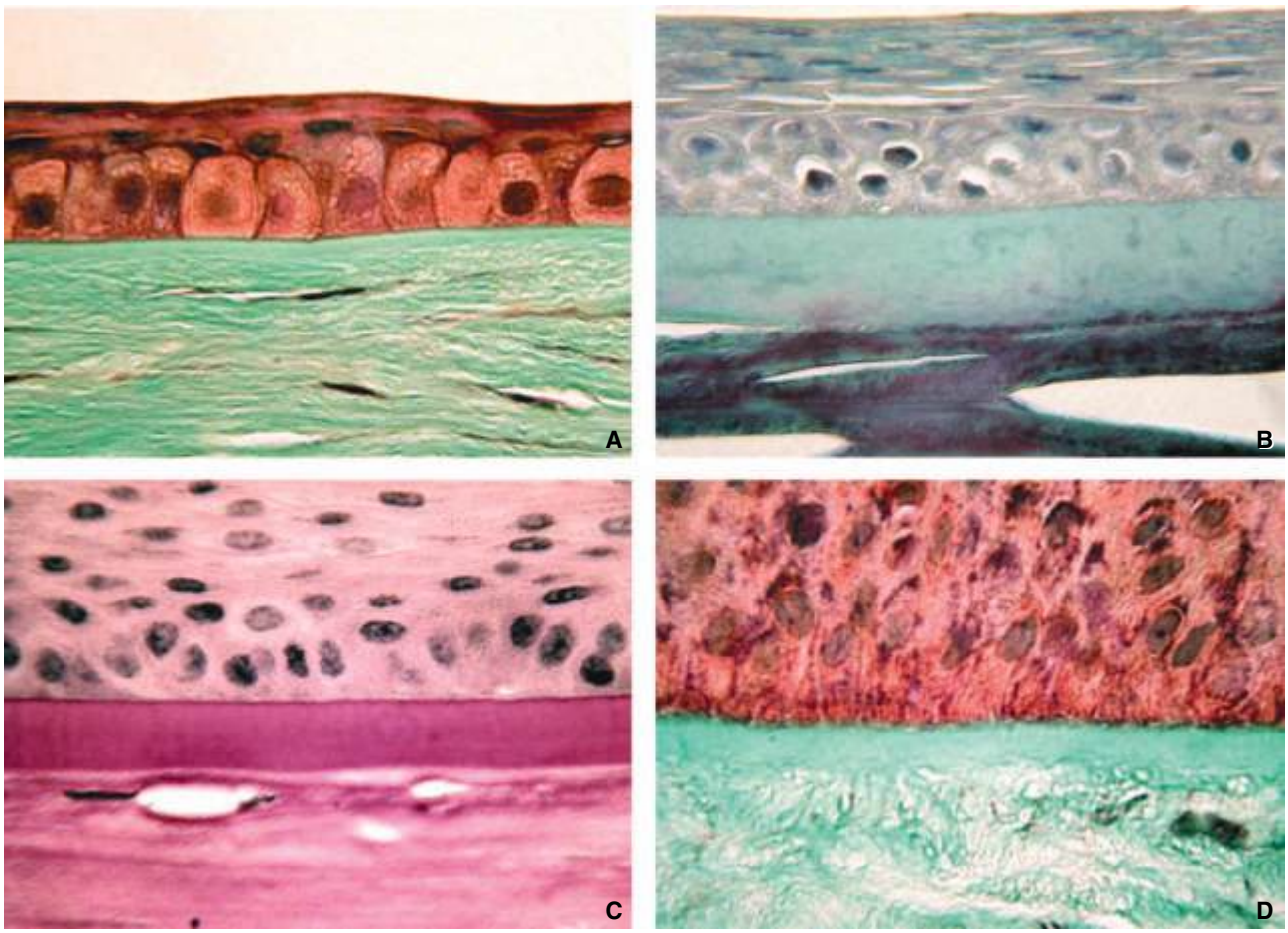


Figure 2.28 Bowman's layer among mammalian species. **A.** Rhesus monkey. (Original magnification, 400×; Masson trichrome stain.). **B.** Bottle-nosed dolphin. (Original magnification, 400×; Masson trichrome stain.). **C.** Pilot whale. (Original magnification, 400×; PAS stain.). **D.** Giraffe (Original magnification, 400×; Masson trichrome stain.). (Courtesy of AZ Zivotofsky and D Zivotofsky.)

apex of the trabecular meshwork in the limbal region. To some degree, its composition is similar to that of the trabeculae of the iridocorneal angle (ICA). Descemet's membrane is comprised of a number of collagen types, including type VIII, which is found in the ICA but not elsewhere in the cornea (see Table 2.8) (Tamura et al., 1991). Ultrastructurally, Descemet's membrane is distinctly layered in most animals, usually having a relatively thin anterior, unbanded zone next to the stroma, followed by a broad-banded zone and then by another broad, posterior unbanded zone located next to the endothelium. Collagen types III and IV comprise the posterior unbanded zone, types IV and VIII the anterior banded zone, and types V and VI the anterior unbanded zone (Smolek & Klyce, 1993).

Corneal Endothelium

The corneal endothelium is a single layer of flattened cells lining the inner cornea (Fig. 2.21). The regenerative ability of the endothelium varies with species and age. In most species active mitosis of the endothelium occurs primarily in the immature animal (Chi et al., 1960; Laing et al., 1976; MacCallum et al., 1983; Oh, 1963; von Sallman et al., 1961). Specular microscopy and SEM of adult eyes reveal that the cells are usually hexagonally shaped (Fig. 2.29). Closer inspection by SEM reveals that the surface is spotted with small microvillae and pores, and that the lateral edges of one cell interdigitate with another (Fig. 2.29B). In young canines (i.e., 1–4 weeks of age), many of the cells do not have the typical hexagonal shape. Pronounced pleomorphism has also been observed in kittens and rabbits (MacCallum et al., 1983).

Transmission electron microscopy (TEM) reveals the extensive, lateral, convoluted interdigitations between adjacent cells in the dog (Fig. 2.30). The cell junctions, including zonulae occludentes and maculae adherentes, are located at the lateral cell margins. The abundance of mitochondria, smooth and rough endoplasmic reticulum, and a variety of vesicles, indicates these cells are metabolically active. There is gradual loss of the hexagonal shape in older animals caused by a gradual decrease in the overall cell density of the

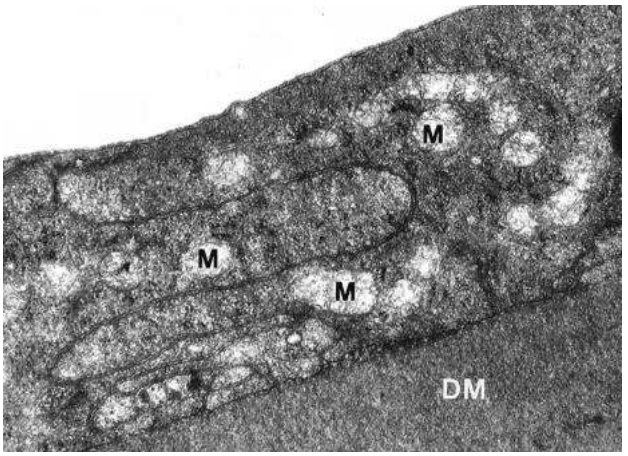


Figure 2.30 The lateral interdigitations observed between endothelial cells along the surface continue throughout the entire thickness of adjacent cells in the canine cornea. Numerous mitochondria (M) are associated with these interdigitations. DM, Descemet's membrane. (Original magnification, 16,000×.)

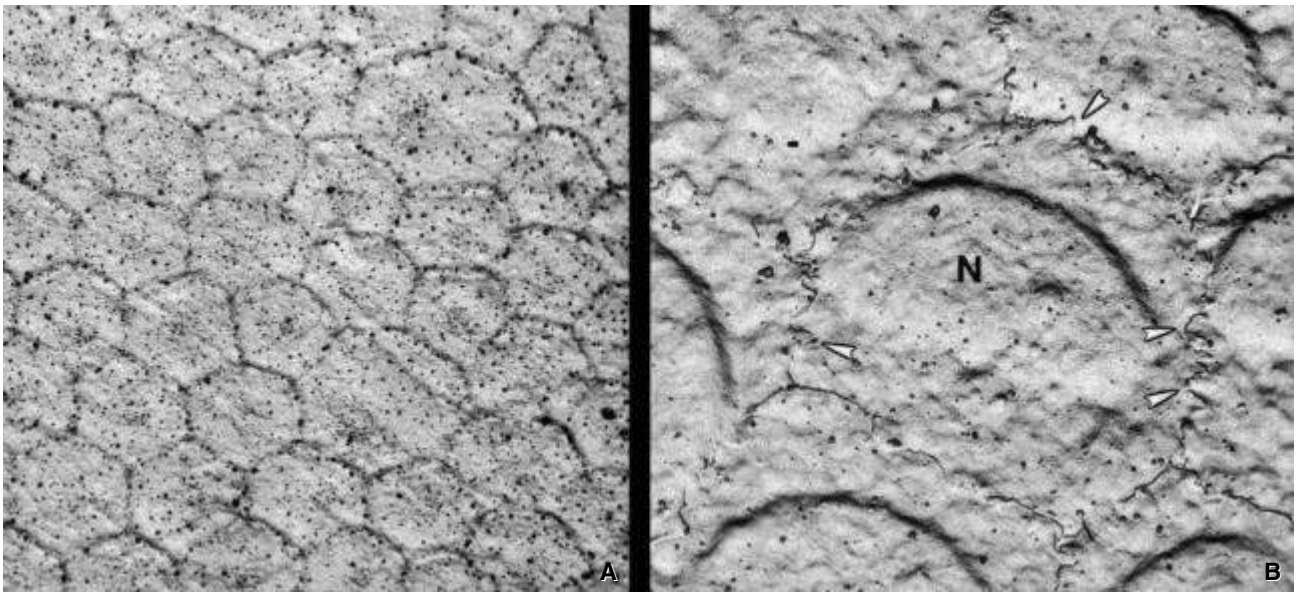


Figure 2.29 SEM of a 4-year-old canine corneal endothelium reveals occasional variability in cell size (**A**) and the lateral surface interdigitations (arrows) between cells (**B**). The most prominent feature of the endothelial cell is the nucleus (N), which bulges slightly into the anterior chamber. (Original magnification: **A**, 960×; **B**, 3500×.)

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endothelium. In young dogs, endothelial density is greater than 3000 cells/mm^2 with approximately 3600 cells/mm^2 in dogs younger than 1 year (Kafarnik et al., 2007). As animals age, endothelial density can gradually decrease to 50% or less of that number.

With a smaller population of cells, the endothelial cells spread out and produce more pump sites to compensate for increasing leakage. An age-related decrease in the density of corneal endothelial cells results in little change in overall corneal thickness (Andrew et al., 2001). If the cell density continues to decrease, however, the cells become too attenuated, resulting in the pumps being unable to withstand the increasing leakage with concomitant corneal thickening and loss of optical clarity. This point is known as corneal decompensation, and it usually occurs when the endothelial cell density decreases to between 500 and 800 cells/mm^2.

Sclera

The sclera comprises the remainder of the fibrous tunic of the globe. Anteriorly, it merges with the peripheral cornea and the bulbar conjunctiva to form a transition zone, the limbus (Fig. 2.31). At the limbus, the sclera is variably pigmented, and the overlying epithelium is thicker, with pigmented epithelial cells. The stroma loses the regular arrangement characteristic of the cornea and takes on a less organized appearance of irregular, dense connective tissue. Numerous blood vessels (i.e., the anastomosing branches of the anterior ciliary arteries) terminate in the loops of the marginal plexus, then drain back into the conjunctival venules.

Along the outer portion of the scleral stroma is an interconnecting network of veins, the intrascleral plexus, which receives aqueous humor from the veins that drain the angular aqueous plexus (AAP) (Fig. 2.32). In domestic animals the intrascleral plexus is variably connected with the choroidal venous system, the vortex system (Fig. 2.33; Smith et al., 1988; Van Buskirk, 1979). The intrascleral plexus is variable in size and depth within the sclera (Natiello et al., 2005; Sharpnack et al., 1984; Troncoso, 1942b; Ujiie & Bill, 1984). For example, in rabbits and primates, the plexus is formed on the outer side of circumferentially coursing canals, and it is composed of small vessels deep in the sclera. In carnivores, the intrascleral plexus is prominent and composed of

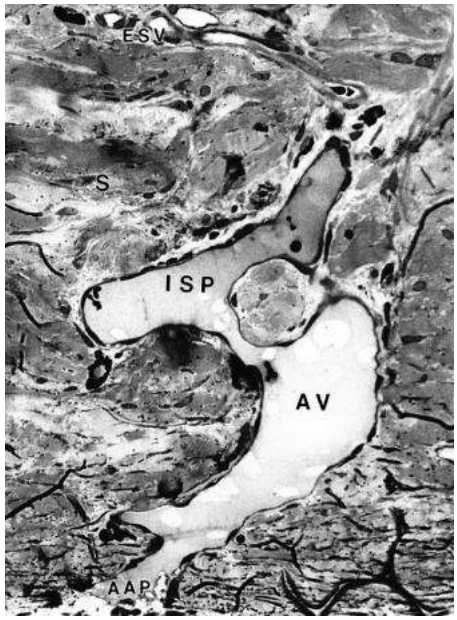


Figure 2.32 The intrascleral plexus (ISP) of a dog is located within the midsclera (S), and is interconnected to the angular aqueous plexus (AAP) by aqueous veins (AV). ESV, episcleral veins. (Original magnification, 125×.)

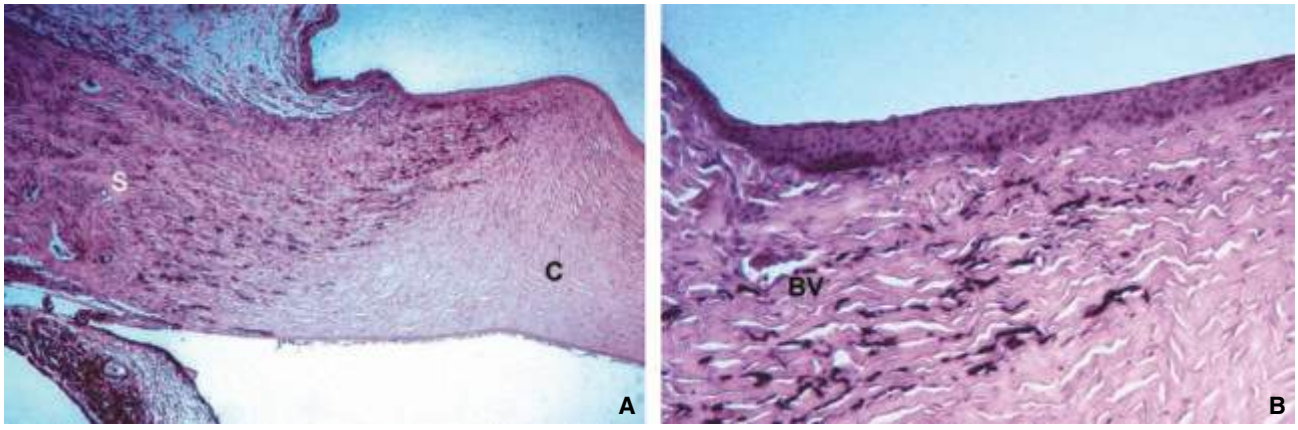


Figure 2.31 Photomicrographs of canine limbus. **A.** The irregular connective tissue of the sclera (S) merges with the highly organized connective tissue of the cornea (C). **B.** Close-up of the outer limbus reveals an anterior epithelium that is markedly thickened, and contains small blood vessels (BV), and melanocytes. (Original magnification, 250×.)

two to four large, anastomosing vessels in the midsclera. The intrascleral plexus also receives afferent channels superficially via the episcleral network at the limbus. In the horse, the plexus, which is less prominent, collateralizes entirely with the anterior vortex system, because it is oriented radially to facilitate unidirectional flow outward from the angle region toward the vortex veins; in carnivores and primates, the reservoirs receiving aqueous humor are circumferentially oriented.

The color of the sclera depends on the thickness of its stroma, appearing blue when thin (less than 0.2 mm) or yellow with increased fat content (carotenoids). The inner surface, which is referred to as the lamina fusca, is brown because of the adherent suprachoroidal pigment. The sclera contains elastic fibers that are interlaced among the collagen fibers, as are melanocytes (anteriorly) and fibrocytes. The collagen fibers, fibrocytes, and occasional melanocytes are arranged meridionally, obliquely, and radially in an irregular fashion. Its rigidity provides resistance to intraocular fluid pressure, and several channels, or emissaria, are present for the passage of blood vessels and nerves. The most notable emissaria accommodate the optic nerve, long and short ciliary nerves, long posterior ciliary arteries, vortex veins, and anterior ciliary vessels.

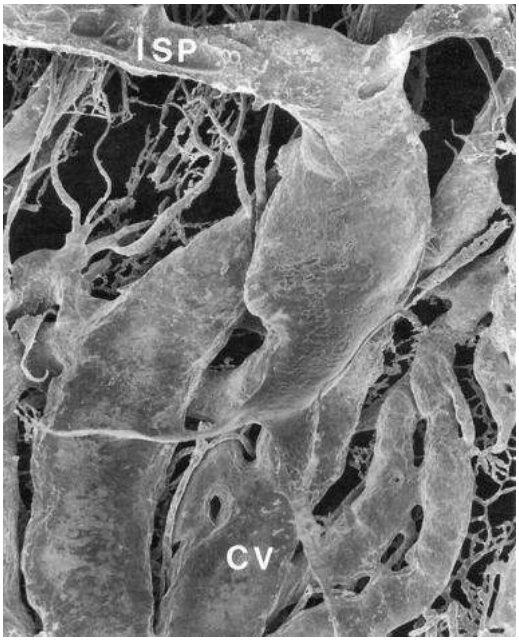


Figure 2.33 Corrosion cast of the canine ocular microvasculature demonstrates collateralization of the intrascleral plexus (ISP) with choroidal veins (CV) of the vortex system. (Original magnification, 410×.)

Scleral thickness varies considerably among species and in different areas of the globe. The sclera is thinnest near the equator, posterior to the insertions of the EOMs, and in the dog is only 0.12 mm thick (Table 2.9). By comparison, in the pig it thins to 0.43 mm, then nearly doubles its thickness for much of the posterior portion of the eye, being comparable to that of the human eye (Olsen et al., 2002). The region of the intrascleral venous plexus is the thickest area in animals with a well-developed plexus (e.g., the dog and cat), whereas in ungulates, the region of the optic nerve entrance or posterior pole is the thickest. At the point where the optic nerve passes through the sclera, it becomes sieve-like in the area known as the lamina cribrosa.

In most cetaceans the sclera increases to thicknesses not found elsewhere among vertebrate species. The posteriorly broadened sclera likely maintains the widened and flattened shape of the retina and choroid, which is observed in the large eyes of most cetaceans and of many terrestrial species (Murphy et al., 1991; Walls, 1942).

The episclera is a collagenous, vascular, and elastic tissue that is between the sclera and the conjunctiva and attaches to Tenon's capsule. Tenon's capsule consists of small, compact bundles of collagen that lie parallel to the surface of the episclera.

Besides dense connective tissue, the sclera can be largely composed of cartilage, as in fish, lizards, chelonians, some

Table 2.9 Thickness of the sclera.

Animal	Center of fundus (mm)	Optic nerve entry point (mm)	Globe equator (mm)	Limbus (mm)
Horse	1.5–2.2	1.35	0.5–0.3	1.1
	1.9		0.4	
Cow	1.9	2.20	1.0	1.2–1.5
Sheep	1.0–1.2	No increase in thickness	0.25–0.30	0.4–0.5
Pig	1.0–1.2	Thicker	0.5–0.8	
Cat	0.09–0.20	0.13–0.60	0.09–0.20	1.1, in the form of a ring 5–7 mm wide
Dog	Similar to the cat, only thinner	0.3–0.4	0.12–0.20	0.6

Source: Translated from Bayer, J. (1914) *Angenheilkunde*. Vienna: Braumueller; and from Donovan, R.H., et al. (1974) Histology of the normal collie eye. *Annals of Ophthalmology*, **6**, 257.

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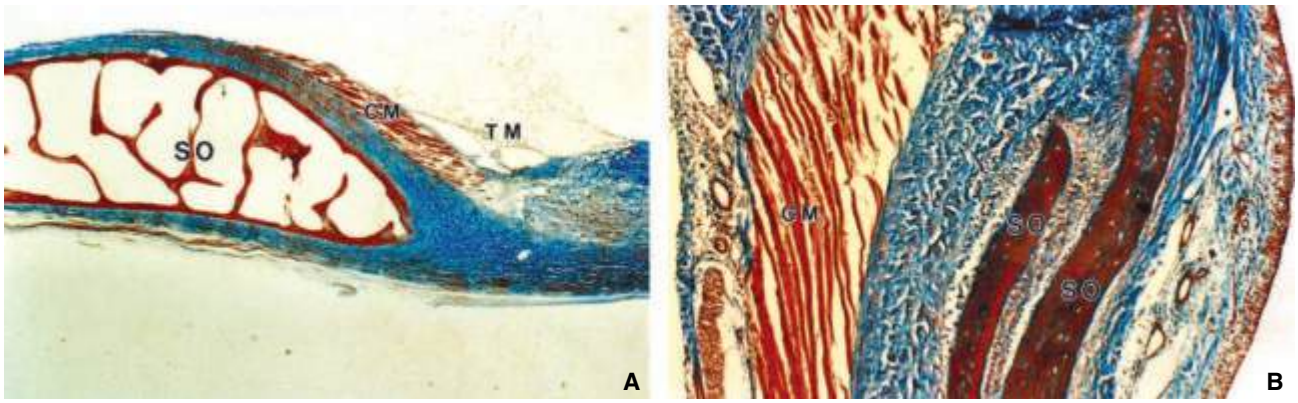


Figure 2.34 Scleral ossicles (SO) in birds vary in size and shape. **A.** Screech owl with large intraosseous spaces. (Original magnification, 40×.) **B.** Chicken with smaller scleral ossicles and considerable overlap between adjacent ossicles (Original magnification, 100×). CM, ciliary body musculature (Crampton's muscle); TM, trabecular meshwork.

amphibians, and birds. When cartilage is found in the sclera, it usually forms a complete cup that extends to the margin of the cornea or, in birds and lizards, to a ring of bony plates or ossicles. Scleral ossicles are located external to the ciliary body (Fig. 2.34). Though birds and reptiles possess this structure, the ossicle is believed to have originated from fish and was eventually passed on to amphibians. Birds with the greatest range of accommodation, such as the kingfisher and other diving birds, have larger ossicles than those species tending to be more confined to land (Curtis & Miller, 1938). Ossicles are believed to have evolved for retaining ocular rigidity. The number of ossicles that comprise a ring can vary within the same species; in individual eyes with fewer ossicles the single ossicle area increases, resulting in a constant scleral ring area (Canavese et al., 1994).

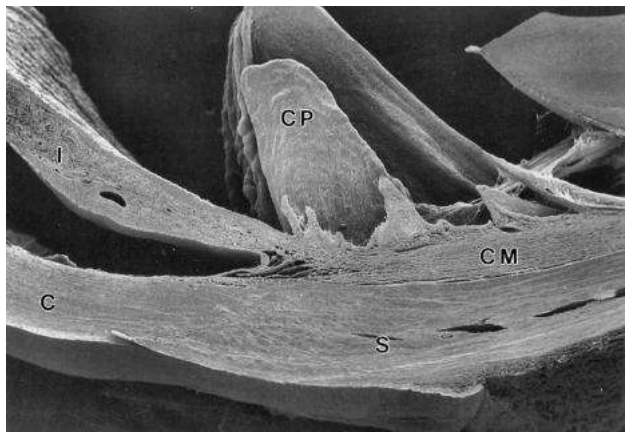


Figure 2.35 SEM of the canine anterior uvea: cornea (C), ciliary processes (CP), ciliary body musculature (CM), iris (I), sclera (S). (Original magnification, 25×.)

Uvea

The iris, ciliary body, and choroid form the uvea. Unlike the fibrous coat, the uveal coat is highly vascular and usually pigmented. The ciliary body and choroid are attached to the internal surface of the sclera (Fig. 2.35). The iris originates from the anterior portion of the ciliary body, and it extends centrally to form a diaphragm anterior to the lens. The iris and ciliary body are the anterior uvea, and the choroid is the posterior uvea.

Iris

The iris is a diaphragm that extends centrally from the ciliary body to cover the anterior surface of the lens, except for a central opening, the pupil. It divides the anterior ocular compartment into anterior and posterior chambers, which communicate through the pupil. The shape of the pupil varies among species. Among mammals, it is round in primates, canines, most large felines (cougar, leopard, lion, and tiger) and pigs; it is vertical when constricted in the smaller felines (bobcat, lynx, and domestic cat); and it is oval in a horizontal plane in herbivores (horses, cattle, sheep, and goats) (Fig. 2.8, Fig. 2.9, and Fig. 2.19). In herbivores, along the upper and lower margin of the pupil are several round dark brown 'masses' referred to as granula iridica (corpora nigra) (see Fig. 2.9 and Fig. 2.36). Camelids have a pupillary ruff along the dorsal and ventral pupillary margins. These pigmented masses are extensions of the posterior pigmented epithelium that augment the effectiveness of pupillary constriction. Occasional myocytes of the sphincter muscle are present in the basal portion of the granula iridica of goats and horses. The presence of these cells indicates that the granula iridica probably plays more than a passive role during changes of pupillary size and shape. Eyes of animals with pupils that constrict to a slit are believed, in most instances, to be more sensitive to light than those with circular pupils (Prince, 1956).



Figure 2.36 Equine iris (I) and anterior ciliary body (CB). The arrow points to the granula iridica, which continues posteriorly as the posterior pigment epithelium (PE).

The iris has a central pupillary zone and a peripheral ciliary zone. The demarcation between these two zones is the collarette, which is best demonstrated with moderate pupillary constriction. The portion of the pupillary zone adjacent to the pupil is sometimes more pigmented than the rest of the iris.

The function of the iris is to control the quantity of light entering the posterior segment through a central pupil. Constriction of the pupil reduces the amount of light entering the eye. Narrowing the pupil also eliminates the peripheral portion of the refractive system, which diminishes lenticular spherical and chromatic aberrations. During periods of reduced light, the pupil dilates allowing maximal stimulation of photoreceptor cells.

The iris is composed of an anterior border layer, stroma and sphincter muscle, and posterior epithelial layers (see Fig. 2.36). The anterior border layer consists of two cell types: fibroblasts and melanocytes. Results of electron microscopic studies indicate these cells are fibrocytic in nature rather than forming an epithelial sheet (Donovan et al., 1974a; Rohen, 1961; Tousimis & Fine, 1959). The anterior cells, which lack a basement membrane, form an almost continuous layer with their cellular processes, but frequent small openings with large intercellular spaces and extension of underlying melanocyte processes break the continuity. This anterior fibrocytic layer can be exquisitely thin and easily overlooked histologically. Particles measuring up to 200 µm in diameter can diffuse into the iris stroma through the anterior portion of the iris (Rodriques et al., 1988; Smith et al., 1986). One or more layers of melanocytes are deep to the single layer of fibroblasts and compose the remainder of the anterior border layer. For the most part, the melanocytes are oriented parallel to the iris surface, and their processes intermingle with other melanocytes and anterior fibroblasts with no intercellular junctions. The shape of the melanin granules in the stroma varies between species and with the maturity of the granules. The pigment granules in the cat and dog are lanceolate to ovoid in shape, whereas they are round to ovoid in the horse (Sharpnack et al., 1984; Tousimis, 1963). In addition to the scattered melanocytes in the anterior stroma of many dog irides, a dense band of melanocytes can be present in the ciliary zone anterior to the dilator muscle, extending centrally to the sphincter muscle. The granules are generally smaller and more rod-like than the pigmented granules of the posterior epithelium. Particularly in the horse and the dog, large cells containing pigment are associated with capillaries and venules near the sphincter muscle (Tousimis & Fine, 1959; Woberman & Fine, 1972). These are thought to be macrophages of hematogenous origin. In humans, these cells are known as the clump cells of Koganei (Woberman & Fine, 1972).

The iris stroma is composed of fine collagenous fibers, chromatophores, and fibroblasts. The stroma is loosely arranged except around blood vessels and nerves, where it can form dense sheaths. The collagen fibrils are organized to some extent in overlapping, wide arcades running from the pupil to the ciliary body (Shively & Epling, 1969). Despite the dense histologic appearance, considerable extracellular space is evident ultrastructurally.

Iridal color varies considerably among individuals, breeds, and species. The variation of iridal color results from the amount and type of pigmentation present. The coloration of irides in most domestic animals is dark brown, golden brown, gold, blue, or blue–green. Several avian species have brightly colored irides. Historically, these bright colors were thought to result from the presence of carotenoids, an idea based on a single study of the yellow iris of chickens performed over 50 years ago. Carotenoid-bearing cells are referred to as xanthophores, and their presence certainly has been demonstrated to produce brightly colored irides. However, purines and pteridines are also major iridal pigments in a variety of avian species, including doves and great-horned owls (Oliphant, 1988). Combinations of purines, pteridines, and carotenoids probably occur. Development of these pigments within an individual has been known to take a considerable amount of time, even as long as several years (Oliphant, 1988).

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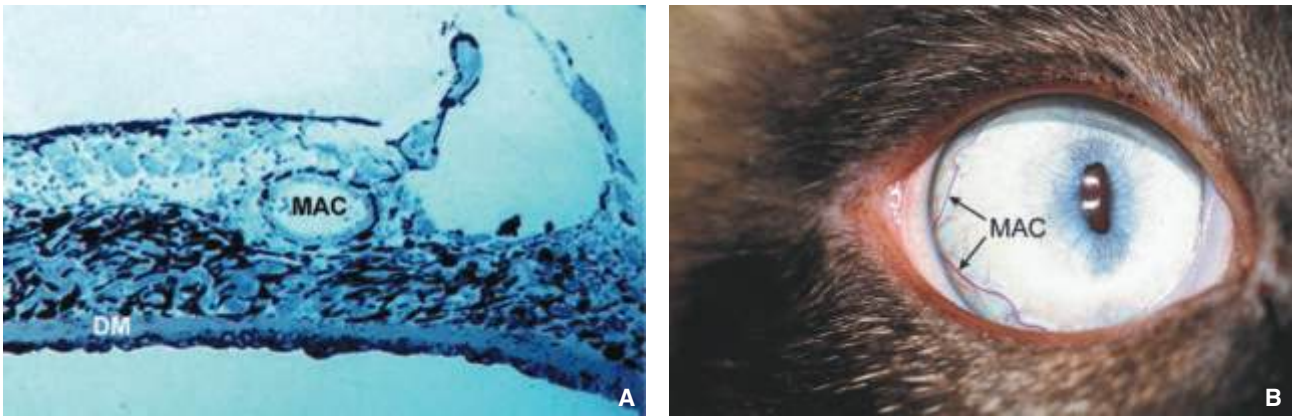


Figure 2.37 **A.** In many canine irides, melanocytes are concentrated in a wide band anterior to the dilator muscle (DM), as seen in the lower half of this iris. MAC, major arterial circle. (Original magnification, 100×.) **B**. The major arterial circle (MAC) in the peripheral iris of a cat.

The major arterial circle is located at the peripheral iris root or the anterior ciliary body (Fig. 2.37). The arteries enter at the nine- and three-o'clock positions as terminations of the medial and lateral branches of the long posterior ciliary arteries. Each artery branches dorsally and ventrally to pass circumferentially toward the opposite artery and forms an incomplete arterial circle in most species. In primates, the major arterial circle forms a completely enclosed ring. The major arterial circle gives rise to numerous radial arteries that end either in a capillary bed near the pupillary margin (i.e., in the dog and cat) or in a minor arterial circle of the iris (i.e., in primates and pigs). There is some debate over the presence of secondary arterial circles in the equine iris (Anderson & Anderson, 1977; Smith et al., 1988).

The arteries radial to the pupil are tortuous in most animals. The degree of tortuosity might reflect differences in pupil mobility between species. The radial arteries lose the internal elastic membrane that is present in the major arterial circle artery, and they have only one layer of smooth muscle cells, compared with two to four in the arteries of the major arterial circle. A thick basement membrane is present externally, which also surrounds the smooth muscle cells, but this membrane is interrupted by frequent myoepithelial junctions.

A capillary network near the pupillary margin connects the terminal arterioles with the venules, which pass to the base of the iris behind the arterioles in the posterior stroma. The capillary endothelium is not fenestrated, but the type of intercellular junctions varies with species. Mice, monkeys, and humans have tight junctions (zonula occludens), but rats, cats, and pigs have 4 nm gap junctions between desmosomes (maculae occludentes) (Szalay et al., 1975).

Venous drainage of the iris occurs through tortuous, radial vessels that empty directly into the anterior choroidal veins and out the vortex veins (Fig. 2.38). These vessels typically

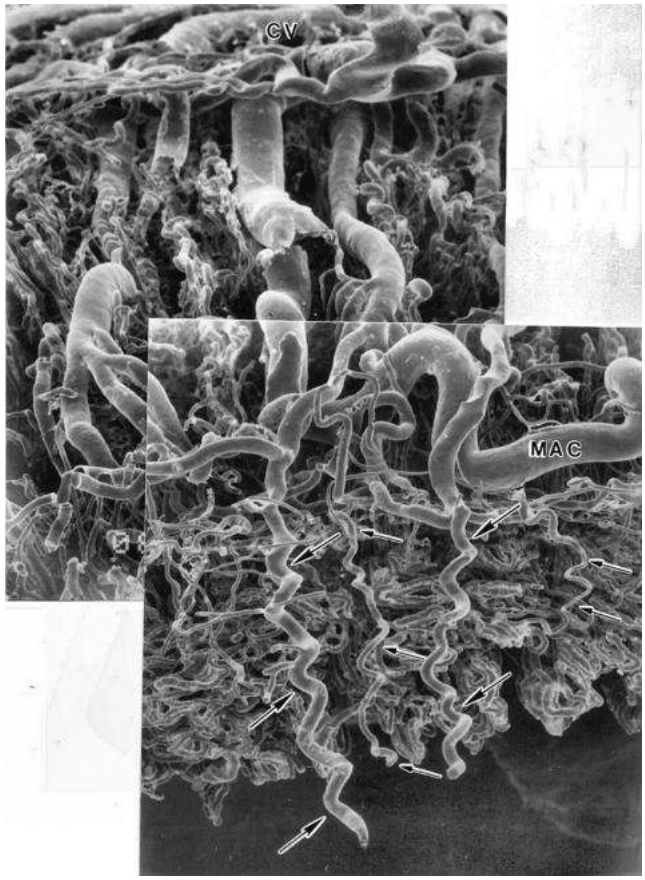


Figure 2.38 SEM corrosion cast of the anterior microvasculature of the equine eye. The iridal arteries (small arrows) and veins (large arrows) have a tortuous appearance as they progress toward the pupil. Note the iridal veins eventually empty posteriorly, into the anterior choroidal venous system (CV). MAC, major arterial circle. (Original magnification, 40×.)

number four in humans, pigs, and cats, but may vary in other species (Anderson & Anderson, 1977; Risco & Nopanitaya, 1980; Van Buskirk, 1979). In horses, a unique variation of iridal venous drainage exists where branches of the intrascleral venous plexus empty into the bases of the iridal veins, which in turn empty into the anterior choroidal venous circulation (Smith et al., 1988).

The iridal sphincter muscle, which is a flat band of thin, circular bundles of smooth muscle fibers in mammals and striated muscle fibers in nonmammalian species, is located in the iris stroma near the pupil. In the dog and cat, it lies in the posterior stroma, separated from the pigmented epithelium and subjacent dilator muscle by a thin layer of connective tissue (Fig. 2.39A). In the horse, the sphincter occupies the main portion of the central stroma and is capped by the granula iridica when present (Fig. 2.39B). The shape of the sphincter muscle varies among species according to the pupillary shape (Fig. 2.40; Prince, 1956). The sphincter muscle is innervated primarily by parasympathetic nerve fibers.

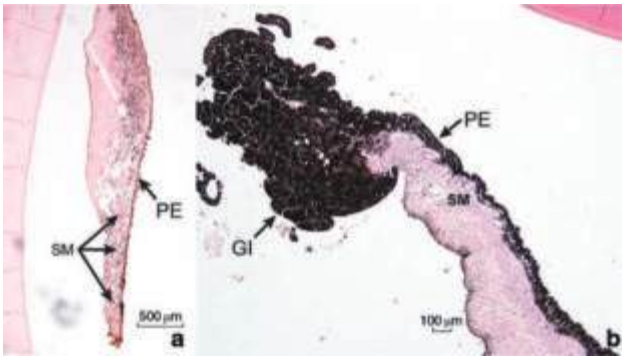


Figure 2.39 Sphincter muscle (SM) location in the dog (**A**) and in the horse (**B**). The sphincter muscle in the horse is capped by the granula iridica (GI), which is a proliferation of the posterior epithelium (PE). (Original magnification, 200×.)

The iridal dilator muscle is a single layer of smooth muscle fibers in the posterior iridal stroma extending from the iris sphincter to the iris periphery. These muscle fibers apically (i.e., posteriorly) contain pigment around their nuclei and are innervated by sympathetic nerve fibers. The basal regions of each cell, which contain the myofilaments, overlap one another in a shingle-like fashion. This cell layer could be considered as a highly developed, pigmented myoepithelium. The size of the dilator muscle varies between species, being well developed in the dog and involving the full circumference of the iris. In the horse, it is less developed, and in species with elongated pupils, it is poorly developed adjacent to the long axis of the pupil (Prince et al., 1960).

The posterior iridal surface is covered by two layers of epithelium. The anterior layer, which forms the dilator muscle, is continuous with the pigmented epithelium of the ciliary body, whereas the posterior layer, which is densely pigmented, is continuous with the nonpigmented epithelium of the ciliary body.

The basal aspect of the posterior epithelium of the iris faces the posterior chamber and has numerous surface projections (Fig. 2.41). The posterior surface of the iris contains folds that extend to the base of the ciliary processes. These folds are radially oriented, but the pigmented epithelial cells are oriented with their long axis running circumferentially in the iris, thus giving rise to two patterns on the posterior surface (Donovan et al., 1974a). A basement membrane separates the cells from the posterior chamber but does not follow all the invaginations of the cell surface. The lateral cell surfaces of the posterior epithelium have numerous slender cell processes with scattered desmosomes. In general, large spaces occur between the lateral cell membranes, which allow free access to the posterior chamber. The nuclei of the iridal posterior epithelium in the dog are oval and moderately indented, whereas the nuclei in the horse are often bizarre-shaped, being indented by adjacent pigment granules.

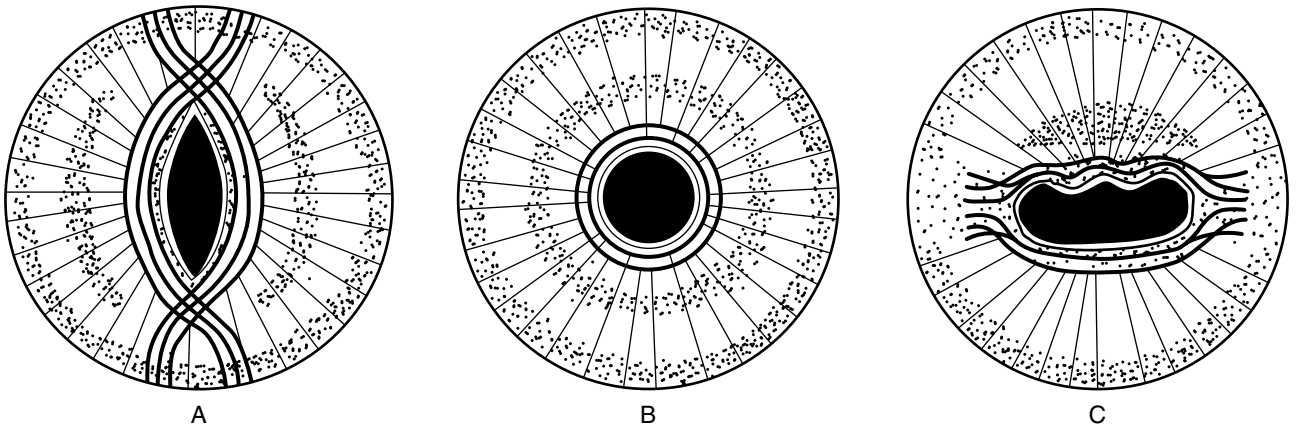


Figure 2.40 **A.** Iris sphincter muscles that create a slit pupil when the pupil is constricted found in domestic cats, bobcats, and lynx. **B.** The circular iris sphincter muscle as found in primates, birds, dogs, and pigs. **C.** Iris sphincter muscle in an ungulate with a horizontal pupil. (*Source:* Redrawn from Prince, J.H. (1956) *Comparative Anatomy of the Eye*. Springfield, IL: Charles C. Thomas.)

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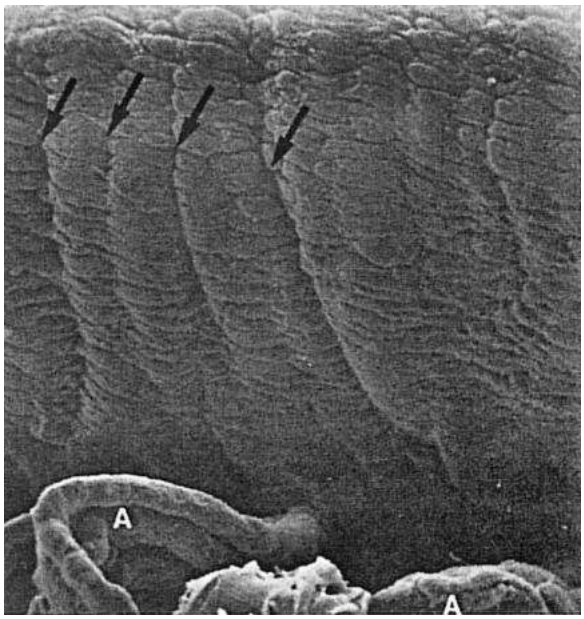


Figure 2.41 SEM of the posterior iris surface of a cat. Arrows point to radial folds. Tips of ciliary processes (A). Note circumferential orientation of clumps of posterior epithelium with small bumps from melanin granules. (Original magnification, 81×.)

The apical portion of the cells of the anterior epithelium (iris dilator muscle) contains the nucleus and is located adjacent to the apical portion of the posterior epithelium. Melanin granules are predominately present in the apical portion of the cell. The myoepithelial (basal) portion has scattered melanin granules, forms irregular projections into the stroma, and is covered by a basement membrane. In the horse, basement membrane material fills much of the intercellular space between projections of the myoepithelium.

In avian species and other lower vertebrates, the iris muscles are striated. In addition to controlling the amount of light that enters the back of the eye, the iris of birds is thought to contribute to lenticular accommodation. Changes in the pupil diameters of chickens and pigeons result in changes in the positioning of their lenses (Glasser & Howland, 1995). In some birds and other animals, for example, American alligators, the sphincter and dilator muscles are both striated and smooth. Specifically, in great-horned owls, pupillary constriction occurs mostly by skeletal muscle and pupillary dilation mostly by the radial myoepithelium, which contains smooth muscle myofilaments (Oliphant, 1983).

The iris contains numerous myelinated and nonmyelinated nerves for autonomic innervation. The myelinated fibers do not specifically follow the iris vessels, but they have a similar pattern as they follow the collagen fibers of the stroma. Upon entering the iris, each long ciliary nerve forms a dorsal and a ventral branch, to form a circular nerve in the ciliary zone and also to meet their counterparts from the opposite side dorsally and ventrally. Radial nerve bundles from the circular nerve pass centrally to the pupil with a corkscrew shape, presumably to accommodate pupillary constriction. A circular plexus is formed near the collarette, from which branches continue toward the pupil, then divide, and intersect to form a rhomboid-shaped mesh (Saari, 1971).

The belief that reflex constriction of the mammalian pupil in response to light depends exclusively on neural pathways between the eye and central nervous system may not be true (Lau et al., 1992). In both golden hamsters and hooded rats, effective constriction of the pupil in response to light occurred after a variety of interventions, including bilateral intraorbital optic nerve transection and unilateral intracranial optic nerve transection with enucleation of the contralateral eye, combined in some cases with bilateral removal of the superior cervical ganglia, pinealectomy, or both. The constrictions that occurred after these different interventions were considerably slower than the usual, neuronally driven reflex but present. Interestingly, the slow, nonneural pupillary reflex was not observed in albino animals, which suggests a possible melanin-mediated component to the slow pupillary light reflex.

Ciliary Body

The ciliary body is a heavily pigmented structure that provides nourishment for and removes wastes from the cornea and lens and participates in lens accommodation. The ciliary body is divided into the anterior pars plicata (corona ciliaris) and the posterior pars plana. The pars plicata consists of a ring of 70–100 ciliary processes, depending on the species, with intervening valleys (Fig. 2.42; Prince et al., 1960). The

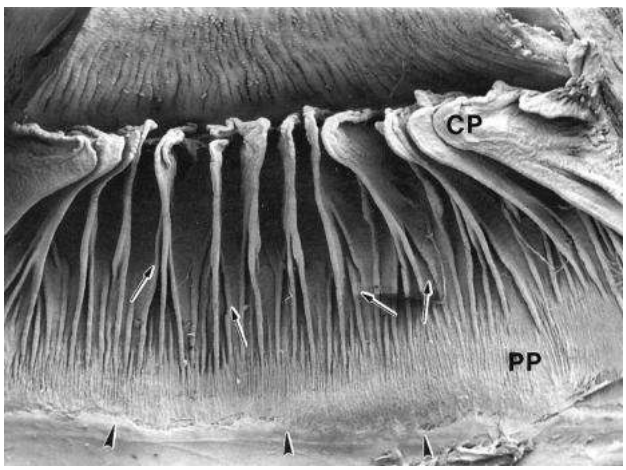


Figure 2.42 Inner surface of the ciliary body of a dog treated with α-chymotrypsin to remove the lenticular zonules. Note the thin ciliary processes (CP), which posteriorly give rise to smaller secondary folds (small arrows). These folds flatten and disappear in the region called the pars plana (PP), which ends posteriorly at the adjoining retina, forming a line known as the ora ciliaris retinae (arrowheads). (Original magnification, 18×.)

processes are generally more prominent and numerous in animals with larger anterior chambers (the cow and horse have 100 and 102 processes, respectively) than in animals with smaller anterior chambers (carnivores and primates have 74–76 processes) (Prince et al., 1960). Ciliary body processes are often absent in lower vertebrates (most fish, lizards, and snakes) (Duke-Elder, 1958; Prince, 1956; Prince et al., 1960). In anurans, birds, and some reptiles, the ciliary body processes are attached to the lens and participate directly in accommodation. In mammals, the ciliary body processes are attached to the lenticular zonules, which connect to the lens equator.

The appearance of individual ciliary body processes varies among species. In carnivores, the processes are thin and bladelike, with rounded tips that are invested with zonular fibers. Between the major ciliary processes, wide valleys with smaller, secondary folds are present. Many of the smaller secondary folds originating near the pars plana merge with the major processes at their base. The surface of each process has numerous convolutions, but most of it is obscured by the attachments of the zonular fibers (Fig. 2.43; Troncoso, 1942a).

In some ungulates, the ridge of the ciliary processes is capped by a broad, convoluted surface that overhangs the main body of the processes (Troncoso, 1942a). Numerous zonular fibers extend from a firm attachment on the sides of the processes to the lens. These fibers also run circumferentially, connecting the broad ridges together (Fig. 2.44). The cap of broad convolutions stops before the anterior tips of the ciliary processes, which are free of fibers.

Each ciliary process consists of a central core of stroma and blood vessels covered by a double layer of epithelium: an inner, nonpigmented, cuboidal epithelium, and an outer, pigmented, cuboidal epithelium (Fig. 2.45). In ungulates, the double-layered epithelium is more columnar than cuboidal. The nonpigmented ciliary body epithelium is confluent posteriorly with the neurosensory retina at the ora ciliaris retinae and anteriorly with the posterior pigmented epithelium of the iris. The basal surfaces of these cells face the posterior chamber and can be irregular. The basement membrane of this epithelial layer follows the general contour, but it does not pass down into the small irregularities or into the intercellular spaces. The basement membrane helps to anchor the lenticular zonular fibers and vitreous base.

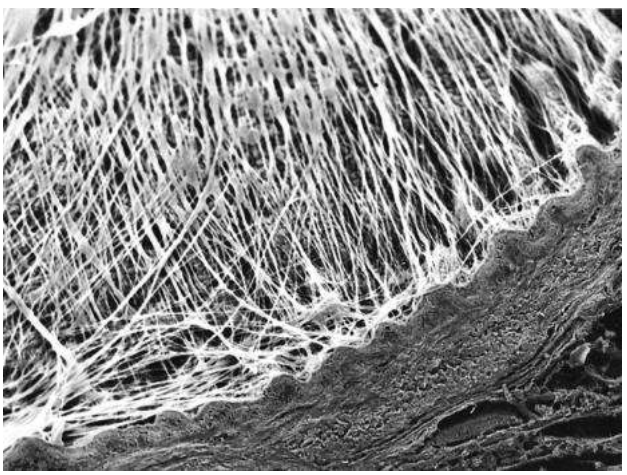


Figure 2.43 SEM (sagittal view) of the inner ciliary body of a dog reveals numerous zonular fibers attached along the epithelial surface. (Original magnification, 130×.)

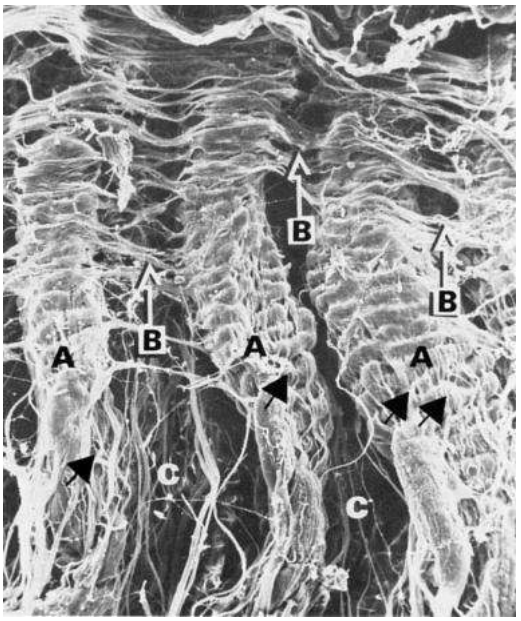


Figure 2.44 SEM of the ciliary processes and zonular fibers in a horse. Ciliary process (A). White arrows point in the direction of the lens equator as well as to the horizontal fiber network joining adjacent process (B). Zonular fibers in valleys between processes (C). Note also the zonular fiber ensheathment of the ciliary processes (black arrows). (Original magnification, 41×.)

The lateral cell surfaces of the nonpigmented epithelium have numerous villous processes along the bottom one-half to two-thirds. Cystic intercellular spaces in this region and in the pars plana are filled with material that has the staining characteristics of GAGs. The base of the cells also reacts positively for the same material. The nonpigmented epithelium most likely produces the GAGs of the vitreous humor. These cells secrete the GAGs, which consist mostly of hyaluronans, laterally into the cystic intercellular spaces, which then communicate with the vitreous base (Fine & Yanoff, 1979). The enzyme carbonic anhydrase has been cytochemically localized at or in the nonpigmented epithelium (Streeten, 1988).

The types of cellular junctions between the nonpigmented and pigmented epithelium of the ciliary processes consist of many gap junctions interspersed with desmosomes and

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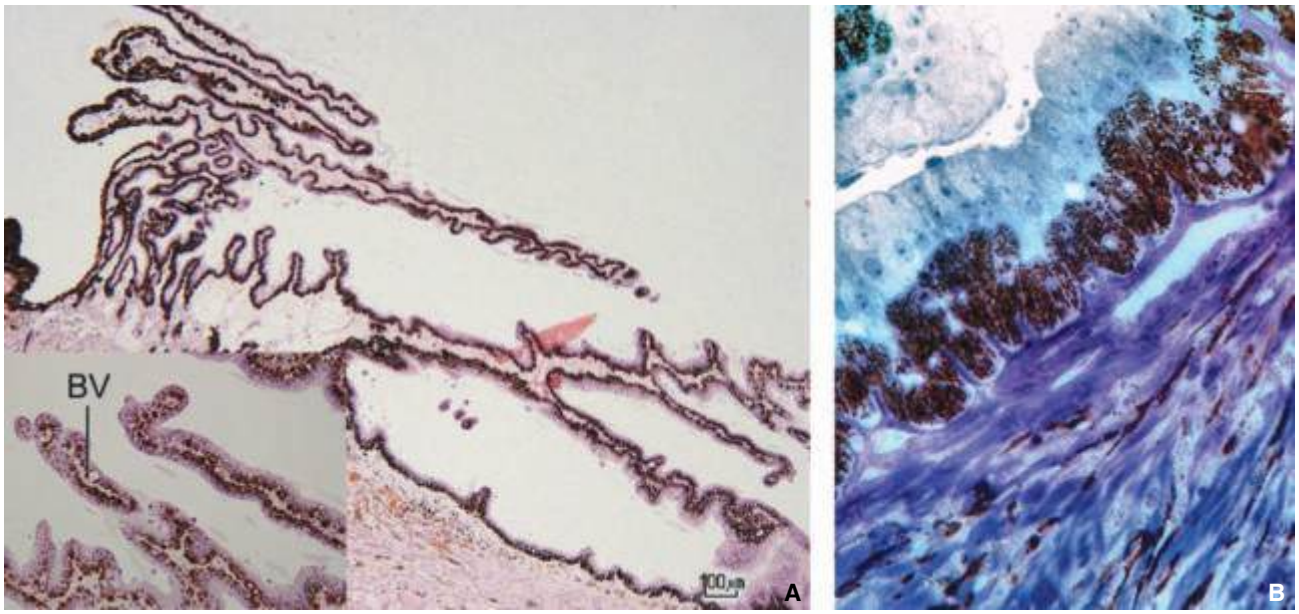


Figure 2.45 The bilayered ciliary epithelium that lines the ciliary processes and intervening valleys. The outer layer is pigmented; the inner layer is nonpigmented. **A.** Feline ciliary processes. *Insert:* Cross-section of ciliary processes. The bilayered epithelium, which is cuboidal, lines blood vessels (BV), which together form a blood–aqueous barrier. **B.** Longitudinal section of an equine ciliary epithelium at the base of a process. Both layers are considerably more columnar than those in the dog and cat. (Original magnification, 400×.)

unusual junctions termed puncta adherentes, which resemble desmosomes but lack the larger tonofilaments and associated intercellular central band (Streeten, 1988). The lateral intercellular junctions of the nonpigmented epithelium consist of desmosomes, except at the apical end (Fig. 2.46). The apical ends possess gap junctions, zonula adherens, and zonula occludens, which represent the anatomic site of the blood–aqueous barrier (Fig. 2.46; Shabo et al., 1976; Smith, 1971; Smith & Raviola, 1983; Smith & Rudt, 1973; Streeten, 1988). There are also dilated portions of the apical intercellular spaces with villous cytoplasmic processes protruding into them. These dilations are termed ciliary channels, and they are usually near the apical termination of two adjacent cells.

The ciliary process pigmented epithelium is confluent with the retinal pigment epithelium. Anteriorly, it continues as the anterior pigmented epithelial layer of the iris, which forms the dilator muscle. The pigmented epithelium is generally cuboidal and heavily laden with round-to-oval melanin granules. The basal aspect of the pigmented epithelium faces the ciliary body stroma and is covered by a basement membrane. In some instances, the basement membrane of adjacent capillaries in the ciliary processes comes into contact with the basement membrane of the pigmented epithelium to form a thickened, irregular, common basement membrane. The lateral cell surfaces of the pigmented epithelium are joined by desmosomes, and the basal cell surfaces have no specialized junctions. The nuclei of both pigmented and nonpigmented epithelia are located apically. The cytoplasm

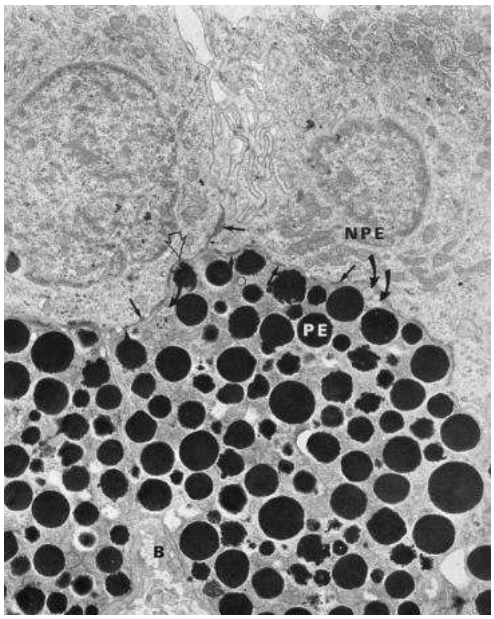


Figure 2.46 Apical junctions of nonpigmented (NPE) and pigmented (PE) ciliary epithelium in a cat. The nonpigmented epithelial nuclei are located apically; the wide intercellular spaces and villi can be seen in the basilar aspect of the intercellular spaces of the nonpigmented epithelium. The apical aspect of the nonpigmented intercellular space is the anatomic site of the blood–aqueous barrier and contains a fascia occludens (small arrow) and fascia adherentes (large arrow). The apical cell surfaces contain a fascia adherentes, gap junctions (open arrows), and arch-shaped gap junctions (curved arrows). The basement membrane (B) of the pigmented epithelium. (Original magnification, 9800×.)

of the pigmented epithelium contains melanin granules, rough endoplasmic reticulum, smooth endoplasmic reticulum, free ribosomes (polysomes), and mitochondria.

A thin layer of loose connective tissue with blood vessels and nerves lies under the ciliary epithelium, separating the ciliary body epithelium from the underlying ciliary body musculature. The vascular plexus within the stroma of the ciliary process is leaky, being lined with a fenestrated endothelium. Fibrocytes and melanocytes are sparsely populated within the stroma, being more concentrated near the ciliary body muscle (CBM).

The pars plana is the flat, posterior portion of the ciliary body that extends from the posterior termination of the processes to the retina (ora ciliaris retinae) (see Fig. 2.42). The width of the pars plana varies because the retina extends more anteriorly in the inferior and medial quadrant in most species, enhancing peripheral vision. Therefore, the pars plana is usually widest superiorly and laterally. In the dog, the ora ciliaris retinae is 8 mm behind the limbus dorsally and laterally but only 4 mm ventrally and medially (Donovan et al., 1974a).

Ciliary Body Musculature

The CBM is comprised of smooth muscle fibers in mammals. Contraction of the CBM draws the ciliary processes and body both forward and inward, thus relaxing the lenticular zonules (suspensory ligament of the lens) and altering the shape and refraction of the lens. This muscle is often weakly developed in many nonprimate species and as a result, offers poor accommodative ability.

On the basis of ciliary body musculature development, the placental mammalian ICA has been categorized into three main groups: the herbivorous, the carnivorous, and the anthropoid (Henderson, 1926; Tripathi, 1974). The categorization depicted in Fig. 2.47 was originally inspired from observations of the ciliary regions of the dog, pig, and ape (Duke-Elder, 1958).

The herbivorous type has been characterized as the most common and primitive in orders of mammals up to and including ungulates. This type of angle consists of an inner layer of connective tissue that forms a baseplate of the ciliary body and extends from the root of the iris to the ora ciliaris retinae. It also consists of an outer layer of smooth muscle that presses against the sclera externally and runs meridionally from the corneoscleral junction toward the ora ciliaris retinae (Fig. 2.47A and Fig. 2.48A). The two layers are often referred to as "leaves" that separate anteriorly and form the ciliary cleft. The ciliary cleft is then a triangular area that varies both in depth (i.e., length) and height, and functionally may be considered a posterolateral extension of the anterior chamber into the ciliary body. Historically, this region was called the ciliioscleral sinus, but because it neither separates the ciliary body from the sclera nor is a part of the ciliary venous sinus,

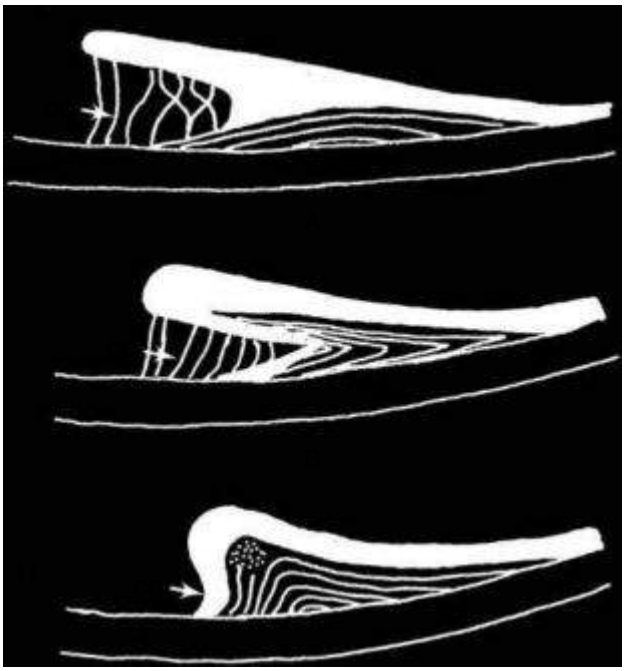


Figure 2.47 Degree of development of the ciliary body musculature among mammalian iridocorneal angles in the ungulate (**A**), carnivore (**B**), and ape (**C**). The ciliary body musculature is most pronounced in primates and least developed in ungulates. The size of the iridocorneal angle and its cilioscleral cleft or sinus (CC) is inversely large or most pronounced in the ungulate. (*Source:* Redrawn from Duke-Elder, S. (1958) *System of Ophthalmology. Vol. I. The Eye in Evolution*. London: Henry Kimpton.)

the term ciliioscleral sinus has been replaced with ciliary cleft (Duke-Elder, 1958; Tripathi, 1974; Troncoso, 1938).

The ciliary cleft is an area containing wide spaces filled with aqueous humor and interspersed with cell-lined cords of connective tissue. The spaces between the fibrous cords were initially described in cattle and horses, and they have been often referred to as Fontana's spaces (Samuelson, 1996).

The carnivorous type possesses a bi-leaflet configuration as well, but the fibrous inner leaf or layer is usually replaced by meridionally oriented smooth muscle and some radially oriented muscle fibers (see Fig. 2.47 and Fig. 2.48B) (Duke-Elder, 1958). Similar to the herbivorous type, the two leaves separate anteriorly and hold a wide, deep ciliary cleft. In both the herbivorous and carnivorous types, the ciliary cleft offers little support to properly anchor the iris. Compensation for wide and deep ciliary clefts is provided by a series of pectinate ligaments attaching the anterior iridal root and inner ciliary baseplate to the limbal cornea.

The anthropoid type differs sharply in its configuration compared with the other types (see Fig. 2.47C and Fig. 2.48C). The ciliary body musculature of primates is believed to be the most highly developed among mammals. The muscle, which has three components (i.e., radial, meridional, and circular),

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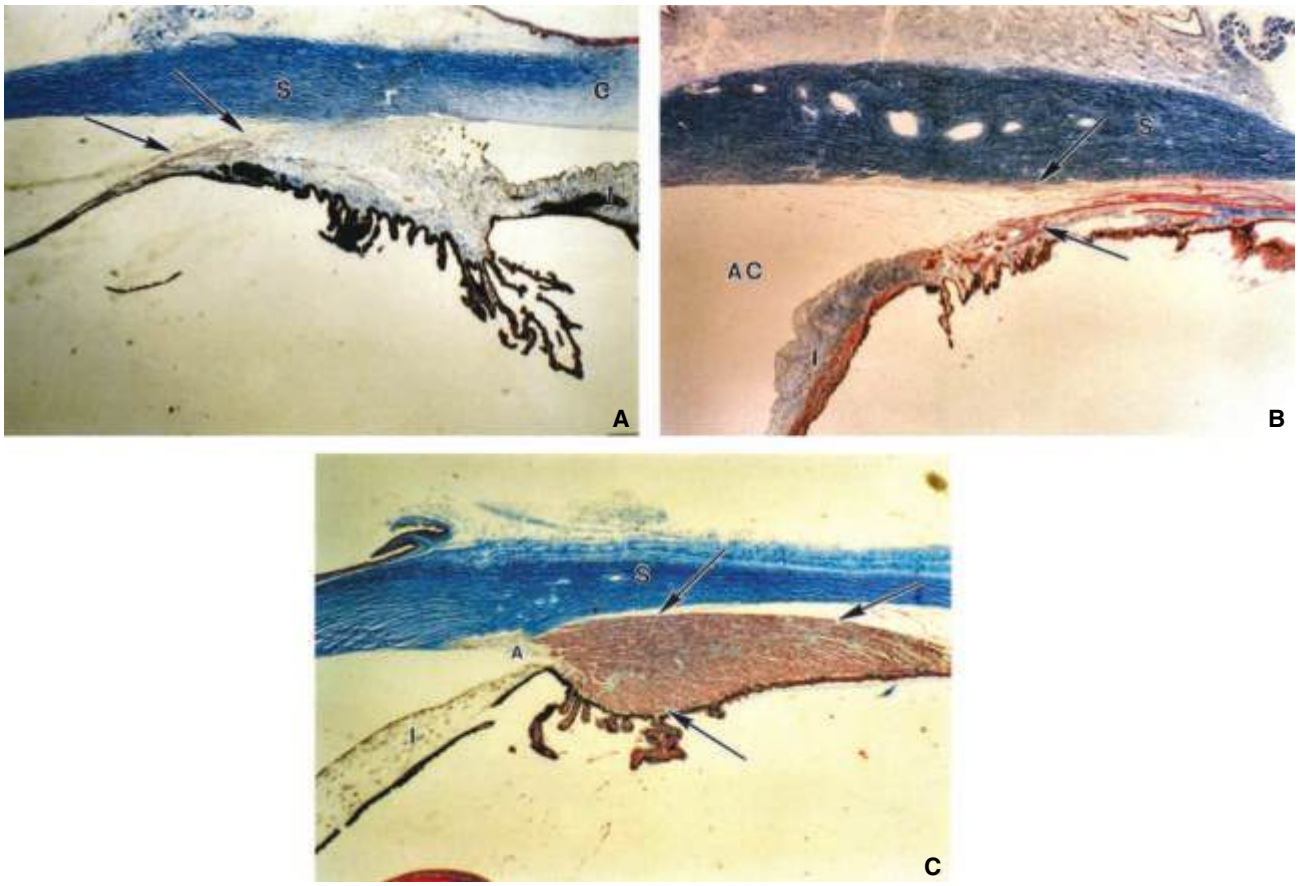


Figure 2.48 **A.** The deer has the traditional herbivorous type of iridocorneal angle and associated ciliary body musculature, which forms a single outer "leaf" (arrows) as it lines the outer, posterior portion of the iridocorneal angle. C, cornea; I, iris; S, sclera. (Original magnification, 20×.) **B.** The cat possesses the traditional carnivorous type of iridocorneal angle, which forms a "bileaflet" anteriorly (arrows). I, iris; S, sclera; AC, anterior chamber. (Original magnification, 25×.) **C.** The Rhesus monkey has the anthropoid type, which consists of small iridocorneal angle and a well-developed ciliary body musculature (*arrows*). I, iris; S, sclera; A, iridocorneal angle. (Original magnification, 20×.)

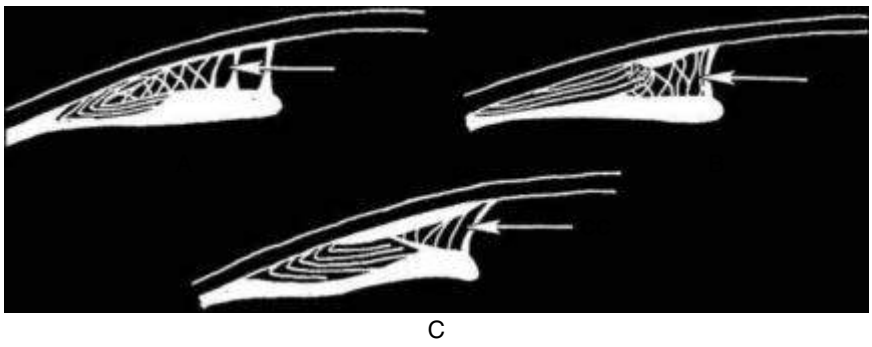


Figure 2.49 Three additional configurations of the eutherian nonprimate iridocorneal angle. Ciliary body musculature is indicated by linear shading. Ciliary cleft (CC). **A.** Small diurnal herbivore. **B.** Large diurnal herbivore. **C.** "High" accommodative carnivore. (Samuelson, D.A. (1996) A reevaluation of the comparative anatomy of the Eutherian iridocorneal angle and associated ciliary body musculature. *Veterinary & Comparative Ophthalmology*, **6**, 153–172.)

forms a large, anterior pyramidal structure that provides a strong baseplate for iridal attachment. The anterior portion of the CBM has replaced both the ciliary cleft, which barely exists in the anthropoid angle, and the pectinate ligaments, which vestigially consist of scattered iridal processes.

In addition to the three basic forms of CBM and ICA, three more configurations have been described among nonprimate mammals (Fig. 2.49; Samuelson, 1996). Among herbivores, two other types have been identified: the small diurnal herbivore and the large diurnal herbivore. In the

small diurnal herbivore, such as the squirrel, a deep ciliary cleft is lined by inner and outer leaves of fibrous tissue and smooth muscle of the ciliary body. In the large diurnal herbivore, such as the pig, there is a well-developed ciliary cleft and outer leaf of ciliary muscle, which anteriorly includes circularly oriented muscle embedded within a scleral spur. The scleral spur is a small ridge of dense connective tissue that separates the muscle fibers from the posterior ICA. TEM of different ungulates has revealed that many of the muscle fibers, especially those located anteriorly, course more circumferentially than meridionally (Samuelson & Lewis, 1995). This difference in orientation of the musculature is most evident in the pig and water buffalo. In these animals, circular muscle fibers are located near the innermost portion of the posterior end of the ciliary cleft.

A third type occurs in "high" accommodative carnivores, such as raccoons and ferrets. In this configuration, the anterior CBM is highly developed but not as an outer leaflet. Instead, the anterior musculature extends as a single leaflet either internally (i.e., raccoons) or intermediately (i.e., ferrets) (Fig. 2.49C and Fig. 2.50).

In birds and other nonmammalian species, the CBM consists of skeletal muscle cells that are primarily meridional. At least two distinct muscle bundles are located in this region of the avian eye: an anterior bundle, which is known as the muscle of Crampton, arises near the corneal margin; and a posterior bundle, which is known as Brücke's muscle. In birds such as the hawk, Brücke's muscle is well developed and sometimes is referred to as two muscles: Müller's (anterior) and Brücke's (Duke-Elder, 1958). Contraction of Brücke's muscle causes the ciliary body to push against or compress the lens, thus deforming it, whereas contraction of Crampton's muscle alters the shape of the cornea by shortening its radius of curvature.

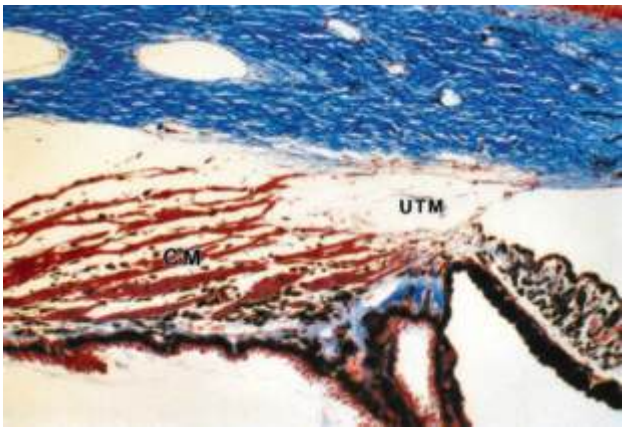


Figure 2.50 The mongoose has the "high" accommodative type of iridocorneal angle. CM, ciliary body musculature; UTM, trabecular meshwork. (Original magnification, 100×.)

Ciliary Body Vasculature

The blood supply of the ciliary body derives from the two long posterior ciliary arteries and the anterior ciliary arteries. As the long posterior arteries pass into the suprachoroidal space equatorially along the lateromedial horizontal plane, they undergo several divisions. These divisions anastomose anteriorly with branches of the anterior ciliary arteries to form the major arterial circle, which is located either in the base of the iris or the anterior ciliary body (see Fig. 2.37 and Fig. 2.38). The anterior ciliary arteries, which arise from branches of the ophthalmic artery, typically enter the globe at the attachment sites for the recti muscles and help to supply the ciliary muscles (Streeten, 1988). The major arterial circle is the primary vasculature supply of the ciliary processes.

Numerous anatomic variations of this vasculature have been found among mammals (Funk & Rohen, 1990; Matsuo, 1973; Morrison & Van Buskirk, 1983; Morrison et al., 1987a, 1987b; Natiello & Samuelson, 2005). In primates and rabbits, two types of arterioles supply the major and minor processes, whereas in other species, a single type of arteriole originates from the major arterial circle and supplies the ciliary process vasculature (Morrison & Van Buskirk, 1983; Morrison et al., 1987a, 1987b; Natiello & Samuelson, 2005). Discrete interspecies variations occur in the angioarchitecture of the ciliary processes (Fig. 2.51). Rodents, rats and Guinea pigs have extensive interprocess connections and concentrically parallel capillaries that are irregularly dilated and travel posteriorly, emptying into the anteriormost choroidal veins. Carnivores such as dogs and cats have processes supplied by one arteriole that is directed posteriorly throughout its length, with capillary arcades that extend to each process margin, from which they empty into venous sinuses.

The mammalian CBM is supplied by parasympathetic fibers from the oculomotor nerve and by sympathetic nerve fibers. The parasympathetic fibers leave the oculomotor nerve, penetrate the ventral oblique muscle, and synapse in the ciliary ganglion. From the ciliary ganglion, short ciliary nerves penetrate the sclera around the optic nerve to pass into the sclera and suprachoroidal space innervating the ciliary muscle and iris muscles. The sympathetic fibers arrive via the long ciliary nerves from the dorsal or superior cervical ganglia in a similar manner (Gum et al., 2007).

Iridocorneal Angle

Aqueous humor is produced by the ciliary body epithelium and enters the posterior chamber before flowing through the pupil into the anterior chamber. In the conventional outflow pathway, aqueous humor exits the eye through the corneoscleral trabecular meshwork.

The anatomy of the aqueous humor outflow system has been extensively studied in humans, nonhuman primates,

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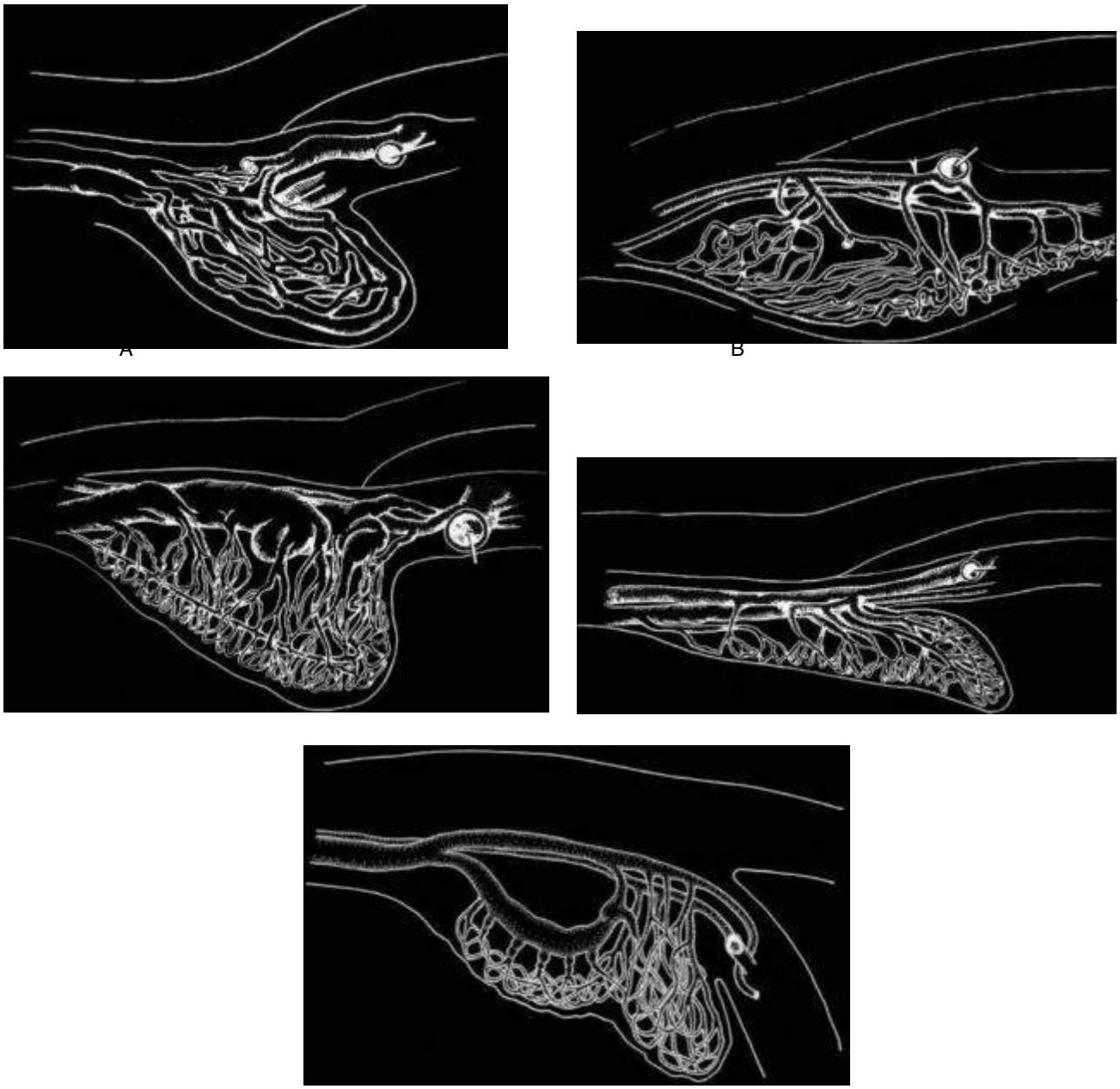


Figure 2.51 Comparative angioarchitecture of the ciliary processes. **A.** Rodents, **B.** Rabbit, **C.** Carnivores, **D.** Ungulates, **E.** Manatee. C, cornea; CV, choroidal vein; I, iris; MAC, major arterial circle. (*Source:* Modified from Morrison, J.C., DeFrank, M.P. & Van Buskirk, E.M. (1987) Comparative microvascular anatomy of mammalian ciliary processes. *Investigative Ophthalmology Visual Science*, **28**, 1325–1340; Morrison, J.C., DeFrank, M.P. & Van Buskirk, E.M. (1987) Regional microvascular anatomy of the rabbit ciliary body. *Investigative Ophthalmology Visual Science*, **28**, 1314–1324; Natiello, N. & Samuelson, D. (2005) Three-dimensional reconstruction of the angioarchitecture of the ciliary body of the West Indian Manatee (*Trichechus manatus*). *Veterinary Ophthalmology*, **8**, 367–373.)

dogs, cats, rabbits, horses, and other ungulate species (Bedford & Grierson, 1986; Bill, 1975b; Inomata et al., 1972; Martin, 1975; McMaster & Macri, 1968; Samuelson & Gelatt, 1984a, 1984b; Samuelson & Lewis, 1995; Samuelson et al., 1989; Sharpnack et al., 1984; Smith & Rudt, 1973; Smith et al., 1986, 1988; Tripathi, 1971a, 1974; Troncoso, 1938, 1942a). This system primarily consists of the ICA, which is bounded anteriorly by the peripheral cornea and perilimbal sclera, and posteriorly by the peripheral iris and anterior CBM. From amphibians to higher mammals, the ICA consists of an irregular, reticular network of connective tissue beams called trabeculae that are lined partially or entirely by a single layer of cells (Samuelson, 1996; Tripathi, 1971a, 1974). The size of the ICA varies among species. In dogs of

different ages and breeds that had undergone cataract surgery, the size of the ICA as determined by the angle opening distance (the distance between the internal limbus and the base of the iris) using ultrasound biomicroscopy was found to vary considerably (Crumley et al., 2009). At the expense of the CBM, a proportionally larger sinus is found in most domestic animals than in humans.

The pectinate ligaments consist of long strands anchoring the anterior base of the iris to the inner peripheral cornea (Fig. 2.52 and Fig. 2.53). In the dog and cat, these strands are usually slender and widely separated from each other, thus making it difficult to visualize histologically an intact pectinate ligament fiber for its entire length. In the rabbit and pig, the strands are somewhat shorter and thicker than those of domestic carnivores (Simones et al., 1996). In contrast, most ungulates possess moderately broad to very stout pectinate ligaments (Fig. 2.54). The pectinate ligaments are entirely lined by cells that are confluent with the anterior surface of the iris. In ICAs with stout pectinate ligaments, the anterior chamber freely communicates with the ICA through pores that lead into a collection of small channels surrounded by cords of densely packed collagen. Posteriorly, the pectinate ligament anastomoses with anterior beams of the trabecular meshwork. In mammals, the network of

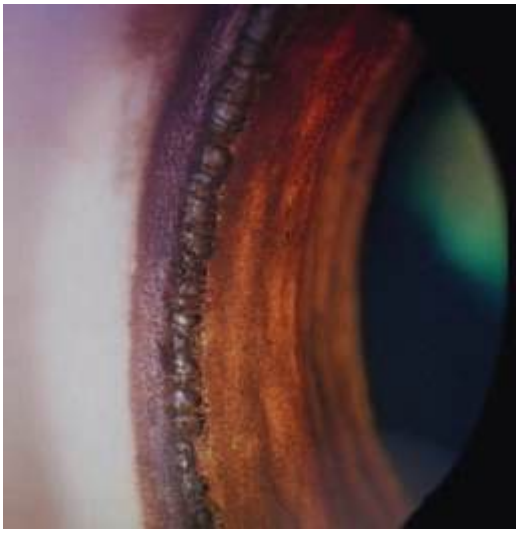


Figure 2.52 Gonioscopic view of the anterior ciliary body shows the fibrous strands, known as the pectinate ligaments, that attach the anterior base of the iris to the limbus.

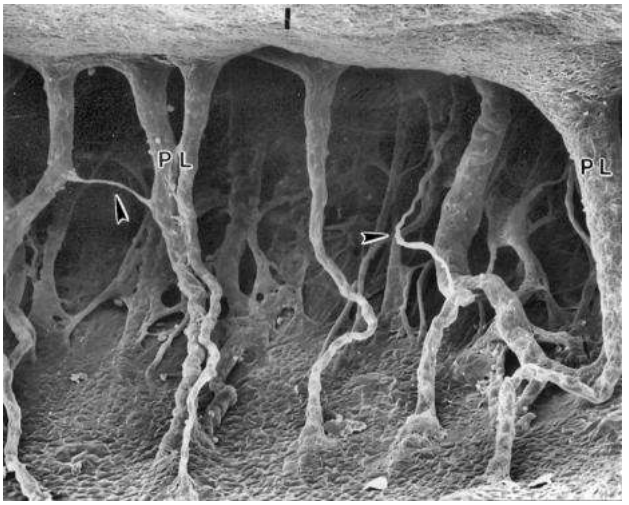


Figure 2.53 Frontal view SEM of the canine iridocorneal angle. Fibrous pillars that attach the iris (I) to the limbus form the pectinate ligaments (PL). Arrows indicate smaller fibrous connections between these pillars and uveal trabeculae located behind the pectinate ligament. (Original magnification, 160×.)

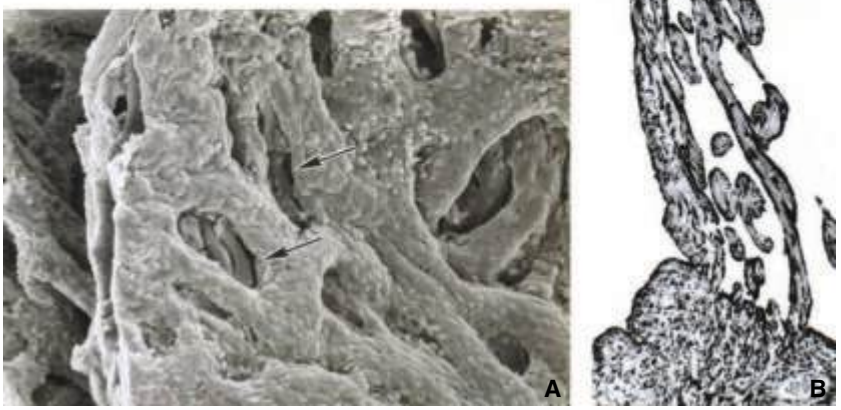


Figure 2.54 Frontal view SEM (**A**) and sagittal view light micrograph (**B**) of the equine pectinate ligament. Anteriorly pores (arrows) form openings that permit the aqueous humor to move from the anterior chamber into the iridocorneal angle. (Original magnification: **A**, 200×; **B**, 100×.)

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trabeculae is usually subdivided into two regions. The uveal trabecular meshwork, which in most animals comprises most of the inner ICA area, thus forming the ciliary cleft, and the corneoscleral trabecular meshwork, which is similar in construction to the uveal meshwork but smaller both in size of the trabecular beams and the channels or spaces between the cell-lined beams.

The uveal meshwork interconnects the inner, anterior CBM with the pectinate ligament. For the most part, the uveal trabeculae are oriented meridionally. In most animals, these beams are completely encased by an endothelium referred to as trabecular cells. The beams branch increasingly toward the CBM in radial and circular directions. As a result, the posterior uveal trabeculae are smaller, with smaller intertrabecular spaces separating them. The posterior uveal meshwork often merges imperceptibly with the posterior, innermost regions of the corneoscleral trabecular meshwork.

The corneoscleral trabecular meshworks of domestic animals are characterized mainly by small trabeculae separated by small intertrabecular spaces. In carnivores, these trabeculae are incompletely lined by trabecular cells (Fig. 2.55). By comparison, in certain ungulates, including horses, bison, and water buffalo, each trabecula is completely lined by trabecular cells. In ruminants and pigs, individual trabeculae can be completely lined, whereas others are incompletely lined.

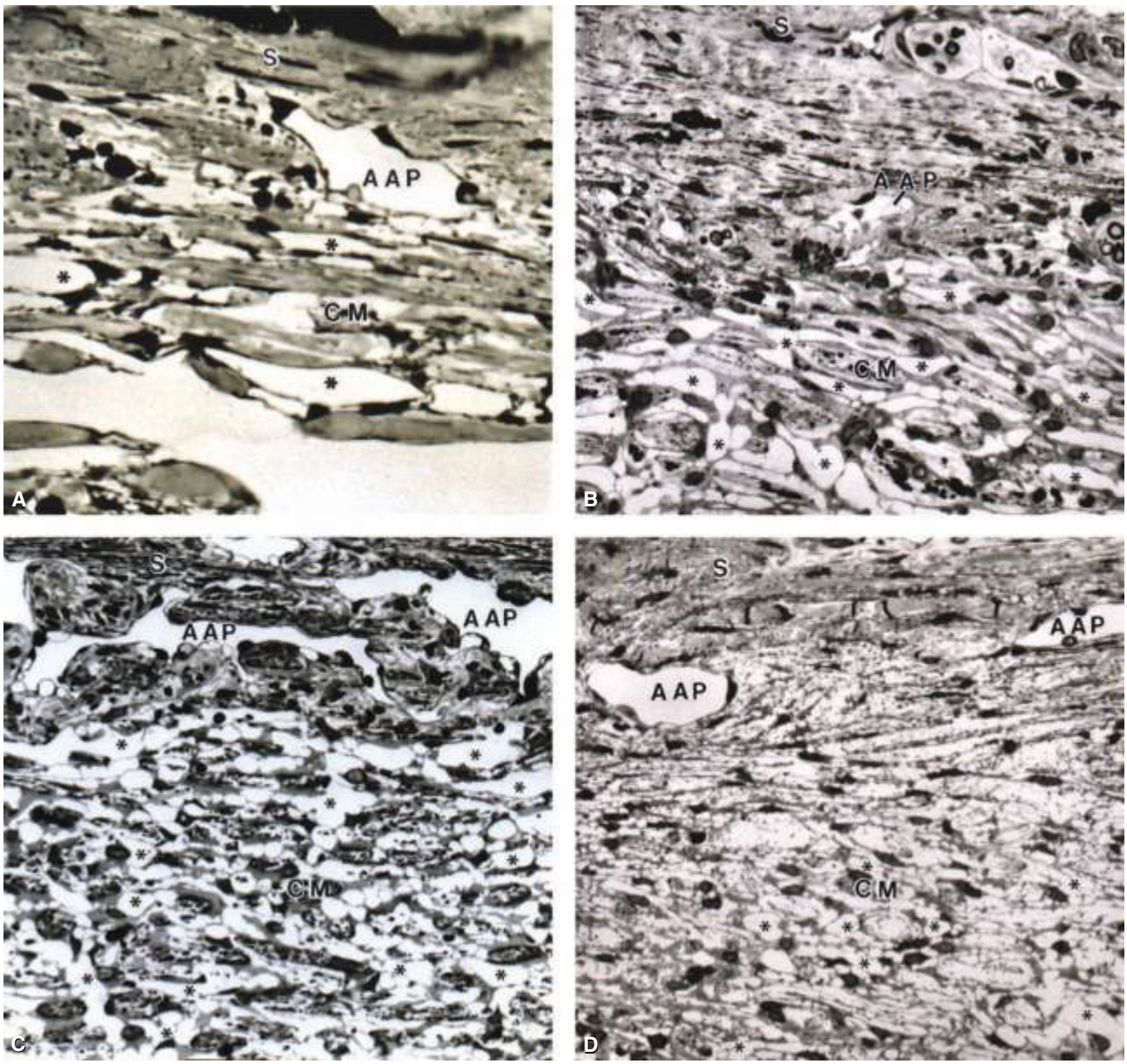


Figure 2.55 **A–D.** The corneoscleral trabecular meshwork (CM), sclera (S) and adjacent angular aqueous plexus (AAP) in the dog (asterisks indicate intertrabecular spaces). (Original magnification: All, 400×.) **B.** Bison, **C.** Horse, **D.** Pig.

Composition of the trabeculae varies very little among species (Bedford & Grierson, 1986; Samuelson, 1996; Samuelson & Gelatt, 1984a, 1984b; Samuelson et al., 1989; Tripathi, 1971a). The core, or center, of each beam is made up of circularly and meridionally oriented collagen fibers interspersed with a modified elastin (Gong et al., 1989). The core is usually enveloped by a cortical zone consisting of amorphous, granular material surrounded by basement membrane-like material. In cats, horses, and water buffalo, the larger corneoscleral trabeculae and smaller uveal trabeculae have multiple layers of basement membrane-like material within the cortical zone (Samuelson et al., 1989; Tripathi, 1974). In horses, a narrow zone of thickened, rounded, corneoscleral trabeculae is present between the outflow veins of the ICA and the pectinate ligament. These trabeculae possess no basement membrane-like material; instead, they have long-spacing collagen.

Trabecular cells are similar across species, being fibroblast-like with slender cell processes that attach to adjacent cells and their processes. These processes allow the corneoscleral trabecular meshwork to act as a sieve, thus reducing the size of the particles that can move into the meshwork (Garcia et al., 1986; Johnson et al., 1990; Samuelson et al., 1985; Smith et al., 1986). The degree of meshwork porosity varies between species, with the dog having a more porous meshwork when compared with the horse. The trabecular cell also has the ability to ingest a wide variety of particles, which can range greatly in size (Samuelson et al., 1984b). The phagocytic-like quality of the trabecular cell provides the ICA with an indigenous clearance mechanism for debris, thus reducing possibilities for an inflammatory response (Grierson & Lee, 1973; Sherwood & Richardson, 1981).

An operculum is located within the canine corneoscleral trabecular meshwork (Samuelson et al., 2001). The operculum comprises much of the nonfiltering portion of the trabecular meshwork in the anterior portion of the ICA (Rohen & Lutjen-Drecoll, 1989). It consists of the peripheral extension of the corneal endothelium (and its subjacent basement membrane, i.e., Descemet's membrane) and the underlying, anteriormost portion of the corneoscleral trabecular meshwork. The operculum is especially well developed in dogs, rabbits, and nonhuman primates (Fig. 2.56; Samuelson, 1996). The peripheral termination of the corneal endothelium and its basement membrane leads to what is referred to as the cribriform ligament because it branches both posteroexternally, into the corneoscleral trabecular meshwork, and posterointernally, joining with the anterior uveal trabeculae. The function of the operculum is unknown; however, cells intimately associated with the operculum (i.e., Schwalbe's line cells) are secretory in nature, able to form and release certain enzymes, including enolase and hyaluronans synthase, and phospholipid surfactant-like material (Fig. 2.57; Allen et al., 1955; Lutjen-Decoll & Rohen, 1992; Raviola,

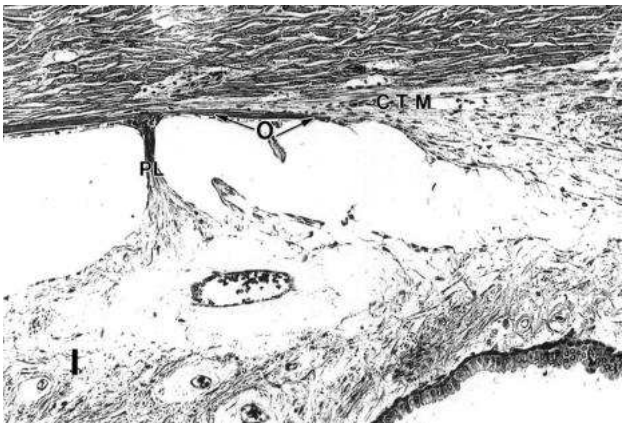


Figure 2.56 In the rabbit, as in most carnivores and monkeys, the peripheral corneal endothelium and its basement membrane extend posteriorly at variable lengths beyond the pectinate ligaments (PL) and form the operculum (O). In turn, the operculum forms a lid-like cover over the anteriormost corneoscleral trabecular meshwork (CTM). I, iris. (Original magnification, 100×.)

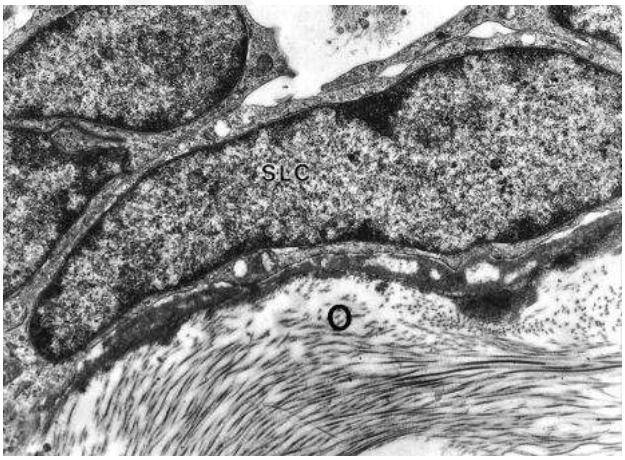


Figure 2.57 Cells associated with the operculum in the dog form clusters and can be linearly arranged (SLC, Schwalbe's line cells) within the anteriormost regions of the corneoscleral trabecular meshwork. O, operculum. (Original magnification, 9800×.)

1982; Samuelson et al., 2001; Stone et al., 1984). Although the role these cells play in the mature ICA has yet to be determined, Schwalbe's line cells represent a distinct subpopulation within most mammalian ICAs.

The external boundary of the corneoscleral trabecular meshwork is formed by the sclera and a plexus of aqueous humor collector vessels. In mammals and most lower vertebrates, the aqueous humor chiefly exits the eye through the trabecular meshworks into these vessels (see Fig. 2.55). In most mammals, these vessels consist of a small network of veins collectively termed the AAP (Tripathi, 1971a, 1974). These vessels have radially oriented lumens, differing from the circumferentially coursing canal of Schlemm in primates (Grierson et al., 1977; Kayes, 1967; Tripathi,

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1971b). The plexiform nature of the drainage vessels in most mammals allows removal of a substantial amount of aqueous humor. The single canal in primates most likely represents an evolutionary adaptation for removal of aqueous humor from a relatively small anterior chamber through a small, compact ICA bordered by a large and highly developed CBM essential for accommodation. Adjacent to the meshwork are aqueous collecting channels, which in turn empty into the intrascleral venous plexus and then the vortex veins.

The size of the individual collector vessels (i.e., trabecular veins) and the tissue immediately adjacent to the AAP varies considerably among mammals. The trabecular veins in cattle, sheep, and water buffalo are large and extensive. Those associated with dogs, cats, pigs, and horses are less prominent but are still extensive.

The manner by which aqueous humor flows into the trabecular veins of the AAP or canal of Schlemm is not completely understood (Allingham et al., 1989; Grierson et al., 1977; Kayes, 1967; Lee & Grierson, 1975; Samuelson, 1996; Tripathi, 1971b). Most of the aqueous humor is thought to move through large, vacuole-like structures of the inner endothelial cells (see Fig. 2.55).

The area adjacent to the trabecular veins typically consists of a zone of cellular elements intermixed with irregularly arranged elastin, collagen, and basement membrane-like material. These elements are much more compact in the horse than in other mammals, except for humans. They constitute a separate zone, called the juxtacanalicular zone that is readily distinguished from the rest of the outer corneoscleral trabecular meshwork. The function of this zone has yet to be determined, but it may contribute substantially to aqueous humor outflow resistance.

In some species, including dogs, rats, rabbits, and humans, smooth muscle-like cells (myofibroblastic cells) have been observed in the trabecular meshwork, especially adjacent to the aqueous humor outflow channels and along the distal or outer walls of the AAP and Schlemm's canal (de Kater et al., 1990; Ryland et al., 2003). In the dog, the presence of myofibroblastic cells within the ICA suggests that these cells and the smooth muscle cells of the ciliary body along the same plane of orientation function to facilitate the removal of aqueous humor and are likely to be influenced by vascular mediators. Whether all myofibroblastic cells play a significant role in regulation of aqueous humor outflow is unknown.

GAGs form an integral component of trabeculae within the ICA and the area adjacent to the AAP (and canal of Schlemm). Treatment with hyaluronidase results in lowering of the IOP. GAGs appear to regulate IOP via their state of polymerization, which controls hydration capacity and swelling or shrinking (Grierson & Lee, 1975; Gum et al., 1992; Knepper et al., 1996; Samuelson & Gelatt, 1998; Samuelson et al., 1987b).

Uveoscleral Outflow

Aqueous humor is not entirely removed by a plexus of collector vessels via the ICA. Some aqueous humor drains either posteriorly into the vitreous humor, anteriorly within the iridal stroma and across the cornea, or exteroposteriorly along a supraciliary–suprachoroidal space into the adjacent sclera (Fig. 2.58; Bill, 1985; Bill & Phillips, 1971; McMaster & Macri, 1968; Smith et al., 1988). The lattermost pathway is called the uveoscleral, or unconventional, outflow pathway. The degree of uveoscleral outflow varies remarkably between species, with cats experiencing the least drainage (3%), followed by humans (4%–14%), rabbits (13%), dogs (15%), and nonhuman primates (30%–65%) (Barrie et al., 1985; Bill & Phillips, 1971). In the horse, the uveoscleral pathway may be just as important as the conventional route for aqueous humor removal. Large spaces of the outer uveal meshwork become confluent posteriorly, with a uniquely wide and well-defined meshwork between the CBM and the sclera (i.e., the supraciliary space). This region, which has been found only in the horse, is called the supraciliary meshwork, and most likely represents a major pathway for aqueous humor removal (Fig. 2.59; Samuelson et al., 1989).

In pigs, cattle, dogs, cats, and horses, the outer anterior CBM forms longitudinal and circumferential attachments to trabeculae of the ICA (Samuelson & Birkin-Streit, 2011; Sedacca et al., 2011). Spaces between the endings of the CBM form avenues for the beginning of the uveoscleral pathway (Fig. 2.60). In pigs, the corneoscleral trabecular meshwork is anchored by a scleral spur, which in turn anchors much of the outer CBM. As a result, the uveoscleral pathway is limited to small intertrabecular spaces of the

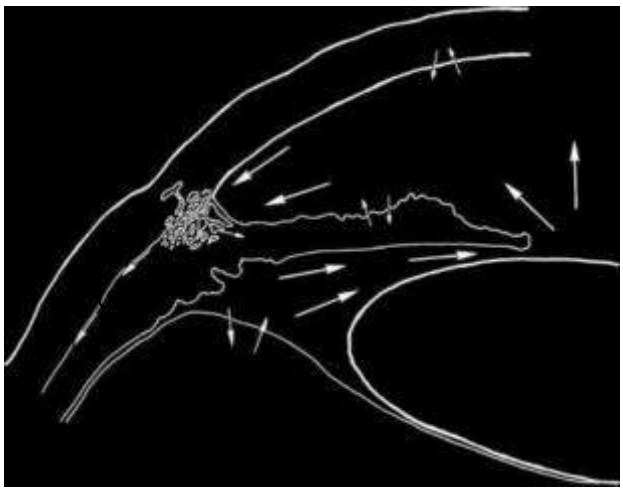


Figure 2.58 The majority of aqueous humor flows from the posterior chamber (PC) into the anterior chamber (AC), where it is removed via the iridocorneal angle by the trabecular meshwork and angular aqueous plexus (AAP). Other drainage routes include exchange across the vitreous face (V), iris vessels (I), and corneal endothelium (C), and via the uveoscleral (US) pathway.

posterior ICA that interface with the anterior CBM. Within the outer ciliary body, there are blood vessels in close proximity to the sclera. More posteriorly, the supraciliary space contains occasional collagenous trabeculae (Sedacca et al., 2011).

In cattle and domestic carnivores, outer anterior muscle bundles attach the CBM to the sclera with an anterior elastic sheath, which is especially well developed in dogs. Initially, the uveoscleral pathway consists of small intercellular spaces lying between the attachments of the anterior smooth muscle bundles of the ciliary body and the posterior uveal trabecular meshwork. Within the supraciliary space, slender trabeculae are most numerous anteriorly extending from the ciliary body obliquely and radially.

In horses, the outer anterior muscle bundles of the ciliary body are connected to branching connective tissue trabeculae within the uveoscleral pathway that are attached radially to the sclera (Samuelson et al., 1989; Sedacca et al., 2011). An elastic sheath lines this portion of the uveoscleral pathway. Trabeculae within the supraciliary space are extensive, consisting of either collagen or muscle. Both types of trabeculae are often branched and lined by melanocytes, becoming less numerous, narrower, and less branched posteriorly.

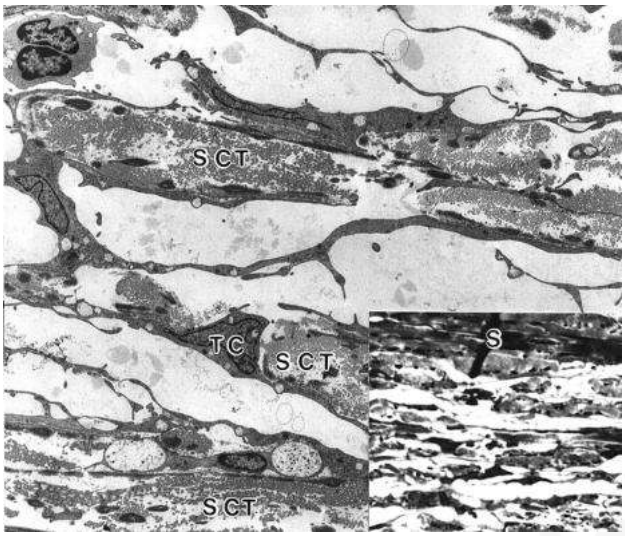


Figure 2.59 Located between the ciliary body meshwork and the sclera (i.e., supraciliary space), the supraciliary meshwork likely represents a major pathway for aqueous humor drainage in the horse via uveoscleral outflow. SCT, supraciliary trabecula; TC, trabecular cell. (Original magnification, 3500×.) *Insert*: Light micrograph of the meshwork. S, sclera. (Original magnification, 200×.)

Aging

A number of age-related changes occur in the ciliary body. As the nonpigmented epithelium grows older, its basement membrane thickens greatly, becoming multilaminar (Streeten, 1988). The pigmented epithelial basement membrane similarly thickens with age, producing a nearly identical multilaminar appearance. The nonpigmented epithelium thins irregularly. The stroma of the ciliary body concomitantly thickens because of increased amounts of collagen and other extracellular materials. The degree of pigmentation in the ciliary body lessens with age, particularly in the pigmented epithelium along the crests of the ciliary processes (Streeten, 1988).

Age-related changes associated with the ICA are well documented in humans and dogs (Bedford & Grierson, 1986; Hogan et al., 1971; Samuelson & Gelatt, 1984a, 1984b, 1998). The cortical zone within the trabecula broadens in older individuals. This thickening is caused by the presence of additional basement membrane-like material and additional amorphous material. The thickened cortical zone could contribute to increased thickening of the corneoscleral

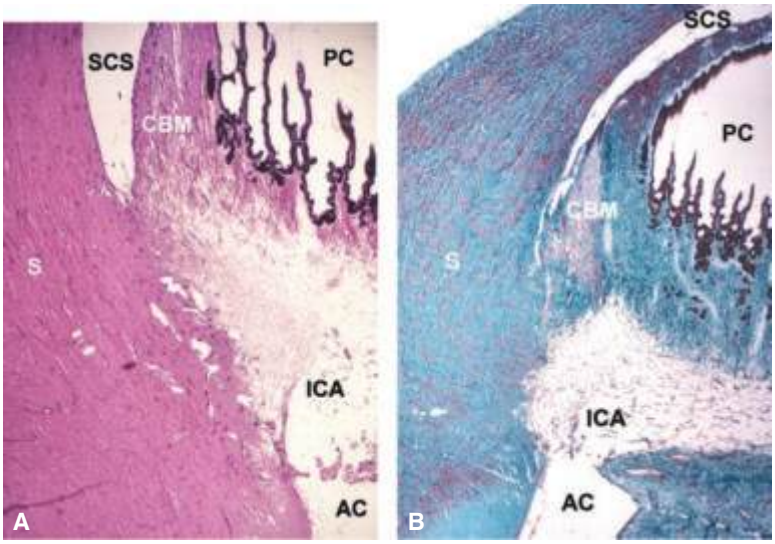


Figure 2.60 Anterior uveoscleral outflow pathway viewed tangentially. **A.** Bovine anterior uvea. (Original magnification, 20×.) **B.** Porcine anterior uvea. (Original magnification, 20×.) AC, anterior chamber; CBM, ciliary body musculature; ICA, iridocorneal angle; PC, posterior chamber; S, sclera; SCS, supraciliary space; UTM, uveal trabecular meshwork.

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trabeculae within the canine ICA. Use of PAS stain, which reacts strongly with basement membrane material, on normal laboratory-quality Beagle ICAs of different ages (from 3 months to 8 years) demonstrates positive reactions within the corneoscleral trabecular meshwork, especially along the posterior extension of Descemet's membrane. The apparent increase in PAS staining with age occurs mostly within the anteriormost portion of the corneoscleral trabecular meshwork. No age-related changes have been observed or reported within the uveal trabeculae of the canine ICA (Bedford & Grierson, 1986).

Perhaps the most discernable alterations of the canine ICA with regard to age are those associated with the extracellular fibers comprising the bulk of each trabecula. When comparing the average diameter of the collagen fibril as well as the distribution of diameter size within the inner and outer regions of the corneoscleral trabecular meshwork and subjacent sclera next to the aqueous plexus at different ages, several changes are recognized (Gelatt & Samuelson, 1986). The average diameter of collagen fibrils within the outer corneoscleral trabecular meshwork increases by approximately 25% during the second and third years of life compared with the latter half of the first year (Samuelson & Gelatt, 1998). On the other hand, collagen fibrils within the inner corneoscleral trabecular meshwork and adjacent outer uveal trabecular meshwork become progressively thinner during the first 3 years of life. Early age-related changes in collagen fibrillar size are most remarkable within the sclera forming the outermost lining of the ICA, increasing nearly 100% in average diameter over a 2.5-year period. The increase of collagen fibrillar size within the inner scleral wall of the limbal region occurs unevenly, with some fibrils remaining small and others attaining considerable widths.

The appearance of the trabecular (i.e., endothelial) cells in both the uveal and corneoscleral meshworks changes mostly during the first year of life. As the cells become more separated spatially, they elongate and possess less clustered cytoplasmic processes. In older animals (>4 years of age), fewer cells are observed in both meshworks compared with those in younger animals (<1 year of age). By the end of the first year, the average cellular density of both meshworks has dropped by nearly 30% (Samuelson & Gelatt, 1998). The lowering of cellular density during this period undoubtedly results from the overall increase in ICA size during the first year of life in dogs (Samuelson & Gelatt, 1984a, 1984b). A further substantial decrease in cellular density is not observed for another 5 years, until the seventh and eighth years of age. The size of the ICAs in older dogs (7–8 years of age) is, in fact, slightly smaller than that in the younger mature dogs (1–6 years of age), which may be attributed to the age-related increase in lens size. These changes appear to reduce the area available for aqueous humor outflow.

Innervation

As mentioned previously, the ciliary musculature is innervated both sympathetically and parasympathetically (Gum et al., 2007; Murphy et al., 2012). Cholinergic and adrenergic nerve endings have been observed in the various components of the ciliary body, including the trabecular meshwork and within the ICA. In the dog, cholinergic activity is most intense in the musculature, ciliary processes, and epithelium. Dense adrenergic innervation, however, is located in the subepithelial portions of the ciliary body (Gwin et al., 1979). Species differences in the distribution of these nerves among many lower mammals have been demonstrated (Ehinger, 1966a), but the function of the cholinergic and adrenergic nerves within the ciliary body remains speculative (Ehinger, 1966b; Nomura & Smelser, 1974).

Choroid

The choroid is the posterior portion of the uveal coat. It is composed primarily of blood vessels (mainly thin-walled veins) and pigmented support tissues. It is the main source of nutrition for the outer layers of the retina. In most domestic animals, the anterior margin of the choroid joins the ciliary body along a regular, nonserrated junction called the ora ciliaris retinae. In primates, the junction is irregular and serrated and termed the ora serrata. The choroid tends to thicken along the posterior pole, becoming thinner toward the globe equator.

For morphologic discussions, the choroid is divided externally to internally, as shown in Fig. 2.61, into

1) the suprachoroidea
2) the large-vessel layer
3) the medium-sized vessel and tapetum layer, and
4) the choriocapillaris.

The tapetal layer varies among species, and it is absent in pigs, squirrels, rodents, rabbits, kangaroos, llamas, alpacas, and many nonhuman primates.

Suprachoroidea

The suprachoroidea consists of elastic, heavily pigmented connective tissue that forms a transition between the sclera and the choroid. Branching collagen lamellae traverse the potential suprachoroidal space to fasten the choroid to the lamina fusca of the inner sclera (see Fig. 2.61). During processing for histologic examination, the choroid frequently separates from the sclera. The suprachoroidea also functions as the posterior component for uveoscleral outflow. Aqueous humor that has moved along this narrow junction of the sclera and choroid diffuses into the sclera and, subsequently, the systemic circulation. The layers of melanocytes and fibrocytes and the interspersing collagen and elastic fibers may produce resistance to uveoscleral drainage, even though

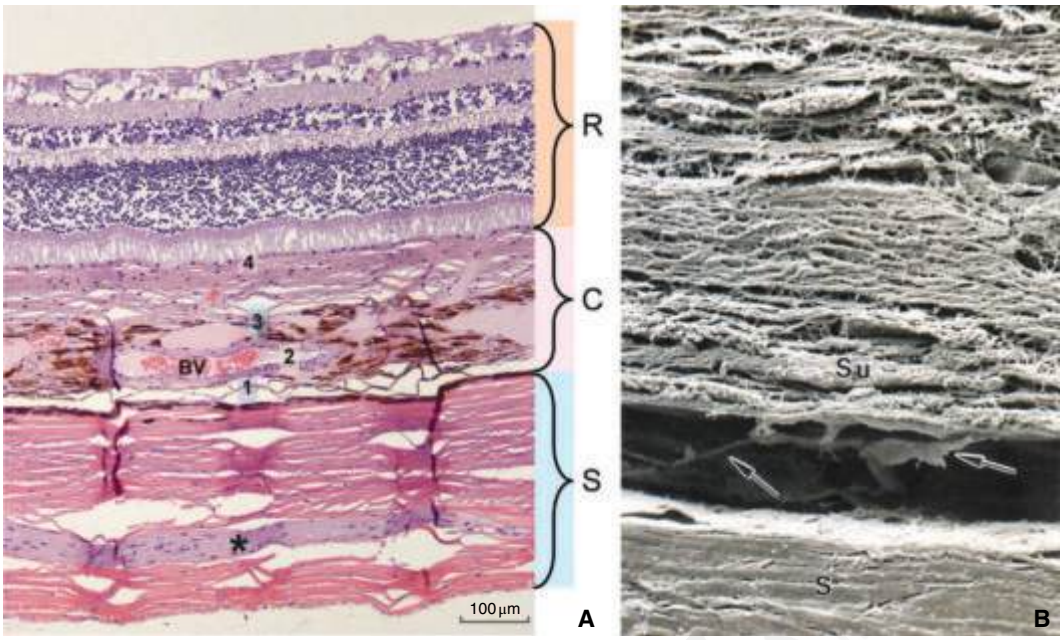


Figure 2.61 **A.** The canine choroid (C) consists of the suprachoroidea (1), large-vessel layer (2), medium-sized vessel and tapetum layer (3), and choriocapillaris (4). R, retina; BV, blood vessel. * denotes a nerve within the sclera (S). **B.** SEM shows a close-up view of the outer choroid, where the suprachoroidea (Su) forms fine collagenous attachments (arrows) with lamina fusca of the sclera (S). (Original magnification, 850×.)

a cellular barrier has not been found (Koseki, 1992). The long posterior ciliary nerves and arteries course their way anteriorly in the suprachoroidea along the horizontal meridian (Castro-Correia, 1967).

In birds, this region also contains a layer of nonvascular smooth muscle cells (DeStefano & Mugnaini, 1997). This layer is believed to be innervated by somatostatin-expressing neurons located within the avian choroid. The function of this band or layer of smooth muscle within the suprachoroidea is unknown, but its location suggests that it could play a significant role in uveoscleral outflow and IOP regulation.

Large-Vessel Layer

Immediately internal to the suprachoroidea is a vascular plexus embedded in loose connective tissue containing melanocytes and fibrocytes. This plexus is composed mostly of large veins and scattered arteries (Fig. 2.62). These veins merge centripetally into four or more prominent vortex veins located obliquely near the globe equator between the horizontal and vertical meridians. In cross section, the veins are cavern-like, occupying 50% or more of the total volume of the choroid (see Fig. 2.61 and Fig. 2.63). They frequently collateralize with each other and communicate anteriorly with anterior ciliary veins, the intrascleral venous plexus, and the iridal veins (Natiello et al., 2005; Wong & Macri, 1964). The large arteries, which are much fewer in number, are mostly branches of the short posterior ciliary arteries,



Figure 2.62 SEM corrosion cast of the choroidal vasculature in the dog. Large arrows indicate collateralization of the intrascleral plexus (ISP) with the large choroidal veins (V). Small arrows indicate choroidal arteries. (Original magnification, 10×.)

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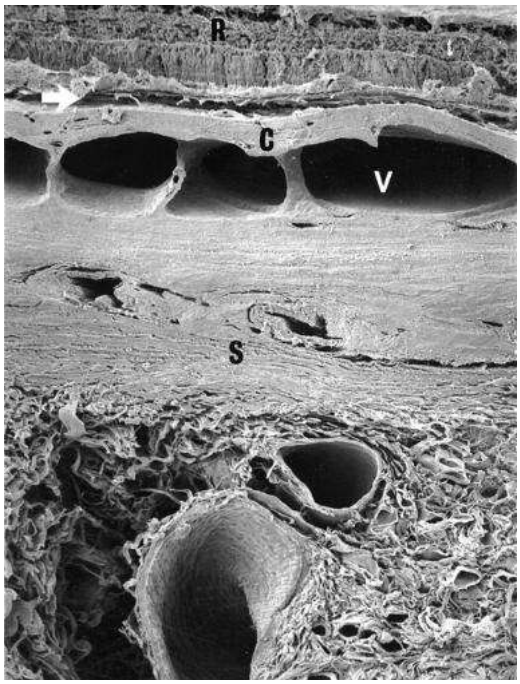


Figure 2.63 SEM of the posterior canine eye shows the choroid (C) is composed mostly of large, cavernous veins (V) that drain the choriocapillaris (arrow), which nourishes the outer retina (R). S, sclera. (Original magnification, 25×.)

which enter the globe in the vicinity of the optic nerve and supply the retina, optic nerve, and choroid. To a lesser extent, the choroid also receives blood from the long posterior ciliary arteries and the anterior ciliary arteries (Torczynski, 1988).

In addition to providing the major source of oxygen and nutrients for the retina, the large vessels may act as a "cooling system," dissipating the heat produced from light absorption (Auker et al., 1982; Parver et al., 1982). The osmotic pressure created by high levels of plasma proteins in the choroidal tissue fluid might also assist in keeping the retina attached to the retinal pigment epithelium (RPE), by allowing retinal fluids to pass into the choroid, then subsequently into the suprachoroidea, sclera, and episcleral tissues (Bill, 1968, 1975a, 1985).

In the avian eye, the large veins are directly associated with another bed of vessels, which have been referred to as sinusoids, lacunae, or most recently, lymphatic vessels (DeStefano & Mugnaini, 1997; Meriney & Pilar, 1987; Walls, 1942). These vessels comprise a major portion of the choroidal volume, and they serve as a large reservoir that may assist in IOP regulation by removal of fluid from the blood vessels (DeStefano & Mugnaini, 1997; Meriney & Pilar, 1987). Morphologically, the vessels are similar to lymphatic vessels, with a fenestrated endothelium but no innervation or defined, basal lamina-associated smooth muscle. These vessels are mostly located next to the suprachoroidea, and a

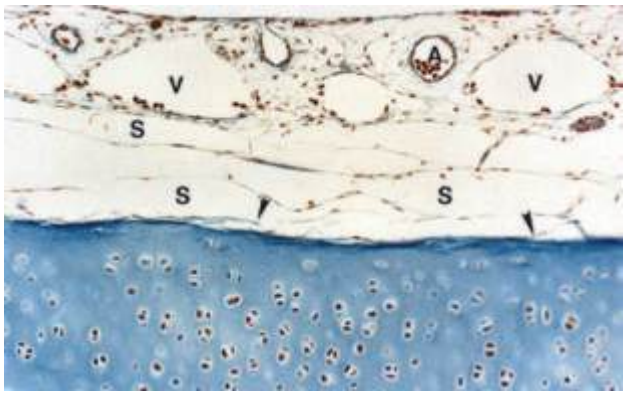


Figure 2.64 The outer choroid in the avian (i.e., chicken) eye consists of sinusoids (S) that extend to the suprachoroidea (arrows) and adjacent "cup" of hyaline cartilage. A, arteries; V, veins. (Original magnification, 200×.)

portion of them extends into adjacent large veins as the latter exit the choroid (Fig. 2.64). The combination of these accessory vessels in the outer choroid and the previously discussed thin band of smooth muscle within the suprachoroidea distinguishes the avian from the mammalian choroid.

Medium-Sized Vessel and Tapetum Layer

A small layer of medium-sized vessels and pigmented reticular connective tissue lies internal to the large-vessel layer. These vessels are emissaries between a single sheet of capillaries and the layer of large blood vessels. The medium-sized vessels, especially the arteries, dichotomously branch, radiating slightly inward in a fanlike manner from the larger vessels. The cells surrounding these vessels consist of melanocytes and fibrocytes. In heavily pigmented individuals, the melanocyte is the predominant cell type. In most domestic animals, the melanocyte possesses characteristically oval-to-round melanin granules ranging from 0.1 to 4.0 μm in diameter. The extracellular space consists of loosely arranged bundles of collagen interspaced with numerous elastic fibers.

Nonmyelinated nerve fibers in the choroid are predominantly associated with the vascular system, and most of the nerves are associated with the arterial system. They arrive in the choroid as short ciliary nerves around the optic nerve and provide numerous collaterals in the posteroanterior route. They follow the short posterior ciliary artery branches, and they give off anastomotic branches. Most of the nerve endings provide motor input to the smooth muscles of the arteries.

In most domestic animals, the dorsal portion of the choroid at the medium-sized vessel layer contains a layer of reflective tissue called the tapetum lucidum. The tapetum is roughly triangular in shape when viewed funduscopically, and it varies in color (Fig. 2.65). It reflects light that has

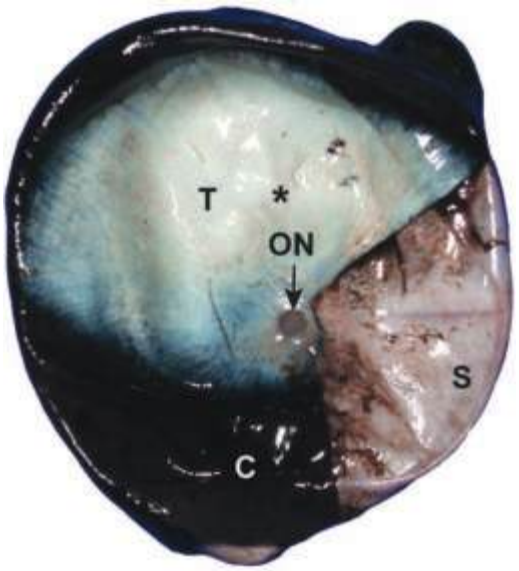


Figure 2.65 The tapetum lucidum (T), which is always located dorsally, usually ends along the horizontal plane next to or including the optic nerve head (ON). In this specimen, a portion of the retina and choroid (*) have been removed to demonstrate the posterior eyewall, the sclera (S). Feline globe.

passed through the retina and thus restimulates the photoreceptor cells. The tapetum lucidum is responsible both for the "eyeshine" seen at night when the eye is illuminated and for the variable background color of the ocular fundus when viewed ophthalmoscopically during fundic examination. Animals without a tapetum lucidum have diurnal habits and red or orange to pale gray (depending on the amount of choroidal pigmentation) fundic reflections (Young & Braekevelt, 1993). The red-to-orange backgrounds result from reflection of light from choroidal blood vessels in less pigmented individuals.

The tapetal layer is composed of regularly arranged collagenous fibers in herbivores (i.e., the tapetum fibrosum in horses, cattle, sheep, and goats) and of specific polyhedral cells, or iridocytes, containing reflecting crystals in carnivores (i.e., the tapetum cellulosum in the dog and cat). Animals with a tapetum show great color variation depending on species, breed, age, and amount of pigmentation. Microscopically, the tapetum is interposed between the branching vessels in the choroid and the single layer of the choriocapillaris beneath the retina. The thickness of the tapetum varies, being multilayered at its center and thinning to a single cell (or lamella) at its periphery and adjacent to the optic nerve. The tapetum develops late in animals born with immature eyes (e.g., dogs and cats); it is usually completely developed by 4 months of age. Animals born with mature eyes (e.g., ungulates and equines) have a well-developed tapetum at birth.

Histologically, the tapetum cellulosum is composed of rectangular-shaped cells, iridocytes, with a species-dependent

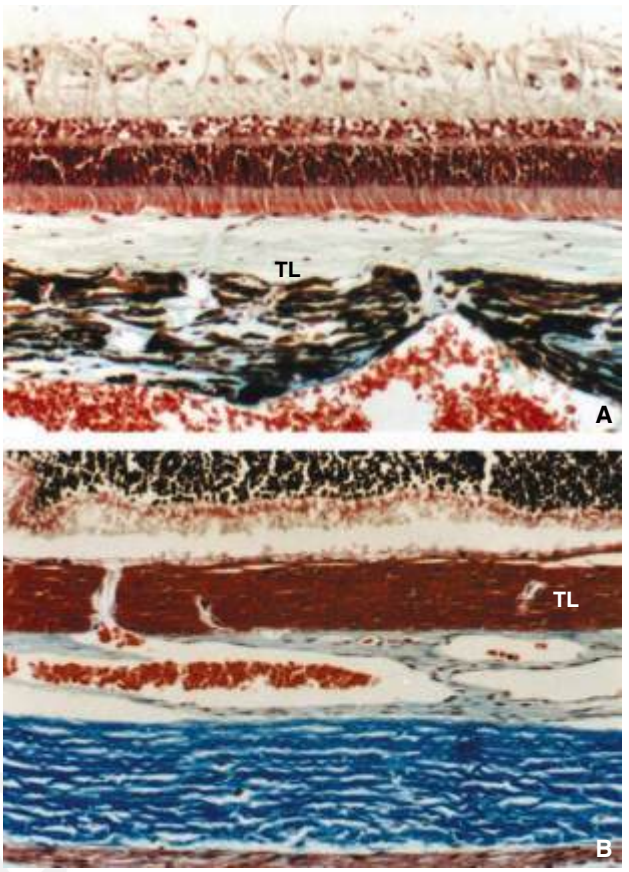


Figure 2.66 The carnivorous tapetum lucidum (TL) consists of layers of cells, called iridocytes, which vary in number, size, and composition. **A.** The dog. **B.** The cat. (Original magnification: 200×.)

variability in number of cell layers (Fig. 2.66; Table 2.10). The tapetal layer is thickest centrally and thins toward the periphery until the tapetum cellulosum is replaced by regular choroidal stroma. From the underlying choroidal stroma, numerous small vessels penetrate the tapetal layer to form a single-layered capillary bed, known as the choriocapillaris network, on the inner surface of the tapetum. Iridocytes have a round nucleus with a prominent nucleolus; in tangential sections, the tapetal cells are polygonal.

The most striking ultrastructural feature of tapetal cells in the dog and cat is the presence of numerous slender, electron-dense rods in the cytoplasm. These rods in the cat are densely packed, uniform in size, circular in cross section, and circumferentially arranged into highly organized groups (Fig. 2.67). The sides of adjacent tapetal cells have a wider intercellular space, separated by collagen and elastic fibrils, than the ends of the cells, which are in closer apposition to each other. Within each cell, there may be several groups of rods, often oriented at right angles to each other but still maintaining their long axis parallel to the retinal surface. The rods are membrane-bound and pack the cytoplasm so that the remaining organelles are limited to the perinuclear

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Table 2.10 Choroidal tapeta among selected vertebrates.

Classification	Type of tapetum	Reflective material	Thickness	Size of fibrils or rodlet dimensions
Fish (Elasmobranchs)	Occlusible	Guanine	60–80 μm	12–20 superposed crystals
Dog	Cellulosum	Zinc cysteine	9–20 layers	Length: 4 μm Diameter: 0.14–0.18 μm Spacing: 0.20 μm
Cat	Cellulosum	Riboflavin, zinc	10–30 layers	Length: 0.10–6 μm Diameter: 0.10–10 μm Spacing: 0.08–0.20 μm
Cow	Fibrosum			Diameter: 0.15–0.20 μm Spacing: 0.20 μm
Sheep	Fibrosum	Collagen	9-16 layers	Diameter: 0.15 μm Spacing: 0.08–0.2 μm

Source: From Ollivier, F.J., et al. (2004) Comparative morphology of the tapetum lucidum (among selected species). *Veterinary Ophthalmology*, **1**, 11–23. Reproduced with permission of John Wiley & Sons.

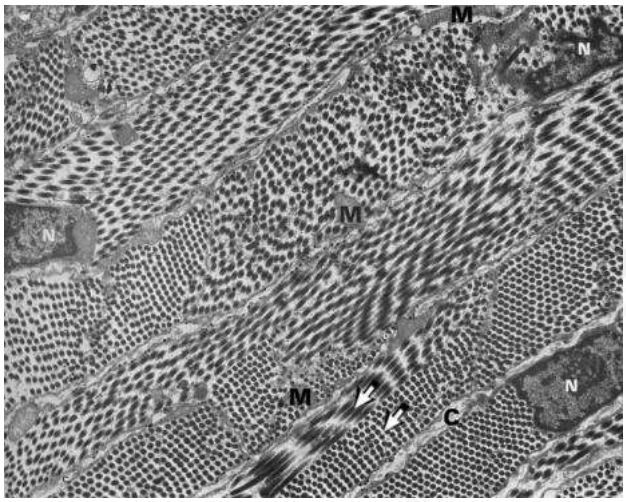


Figure 2.67 Tapetal cells of a cat. The main cytoplasmic components are the rods; mitochondria (M) are infrequent. The rods are uniform in a group concerning spatial orientation, but more than one group is often present within a cell (arrows). The sides of adjacent cells have wide intercellular spaces with scattered collagen fibrils (C), whereas the ends of the cells are in close apposition. N, nucleus of tapetal cell. (Original magnification, 7750×.)

region and the cell periphery. Melanin granules are present in small numbers in the tapetal cells on the scleral side of the tapetum (Chijiiwa et al., 1990; Pedler, 1963), and tapetal rods have the ability to bind calcium at a similar level to melanin; this suggests that, in all likelihood, the iridocyte is a modified melanocyte. The chemical composition of the tapetal layer varies among species. A high level of zinc (zinc cysteine) is present in canine iridocytes, whereas feline iridocytes contain abundant riboflavin and zinc (Braekevelt, 1993a). The tapetal rods are believed to contain high concentrations of these substances (Pirie, 1966).

In ungulates, closely and regularly arranged collagen fibers comprise the tapetum, which is often referred to as a fibrous tapetum. The fibrous tapetum is basically acellular, except for an occasional fibrocyte. The collagen fibrils are organized into well-ordered lamellae that branch and interconnect with adjacent lamellae at the same level, parallel with the retinal surface. The collagen fibrils within each layer vary little in diameter (approximately 80 nm) and have a regular spatial arrangement similar to that seen in the corneal stroma (see Fig. 2.26).

Small blood vessels, typically capillaries, penetrate the tapetum at right angles to the long axis of the iridocytes in carnivores, and to the collagen lamellae in herbivores, directly interconnecting the medium-sized blood vessels with the choriocapillaris (Fig. 2.68). When observed ophthalmoscopically, these end-on vessels are sometimes called the "stars of Winslow." In the dog and cat, these vessels are separated from the iridocytes by a small amount of loose connective tissue and a lining of fibrocytes (see Fig. 2.68).

In nonmammalian species, the tapetum lucidum is either located within the retina (teleosts and some reptiles) or within the choroid (elasmobranches). The tapetum lucidum is consistently absent in birds (Pirie, 1966). With a retinal tapetum lucidum, either lipid- or guanine-laden material lies within the cytoplasm of the RPE (Ollivier et al., 2004; Schwab et al., 2002). Among teleosts, movement of melanin granules within the RPE occurs depending on the environmental illumination, with the melanin granules migrating toward the vitreous humor (forward) during illumination or toward the sclera (backward) during dim light or darkness. The movement of melanin granules causes the reflective material within the RPE to become masked or occluded. Consequently, these retinal tapeta lucida are referred to as occlusible. In elasmobranchs, the tapetum lucidum is also occlusible, but not because of melanin movement. In a

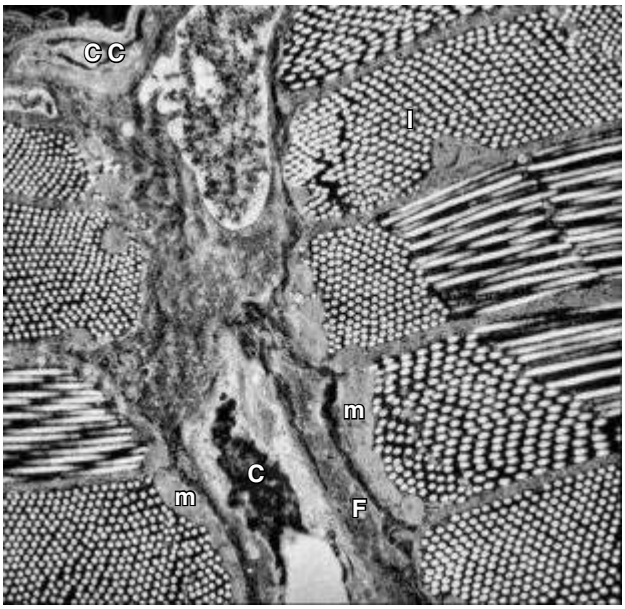


Figure 2.68 Capillaries (C) vertically interconnect medium-sized blood vessels with the choriocapillaris (CC) in the cat. The iridocytes (I), or tapetal cells, line up evenly next to these capillaries. The end of each iridocyte is bordered by mitochondria (m). F, fibrocyte. (Original magnification, 7200×.)

phenomenon termed retinomotor movement, RPE cell processes and the photoreceptors experience positional rearrangements based on changes in ambient lighting. The RPE processes move between and over the reflective cells within the tapetum during illumination, masking the reflective material. Then in low light conditions, this movement is reversed, exposing the reflective material and enhancing the ability of the photoreceptors to process light.

Choriocapillaris

The choriocapillaris is the innermost layer of choroidal vessels, forming a thin layer of capillaries separated from the RPE by a basement membrane complex known as Bruch's membrane (Fig. 2.69). The lumen of the choriocapillaris is fairly wide, allowing red blood cells to pass through two to three abreast. The endothelial lining of the choriocapillaris possesses numerous circular fenestrations, which are often arranged in rows. External to the endothelium is a basement membrane forming the external layer of Bruch's membrane. Bruch's membrane is poorly developed in many domestic animals when compared to primates. In most diurnal species that lack a tapetum lucidum, including pigs and primates, Bruch's membrane is pentalaminated, consisting of basal laminae of the RPE and choriocapillaris endothelia, two adjacent layers of collagen, and an intervening band of elastic fibers. In animals with tapeta, and especially with

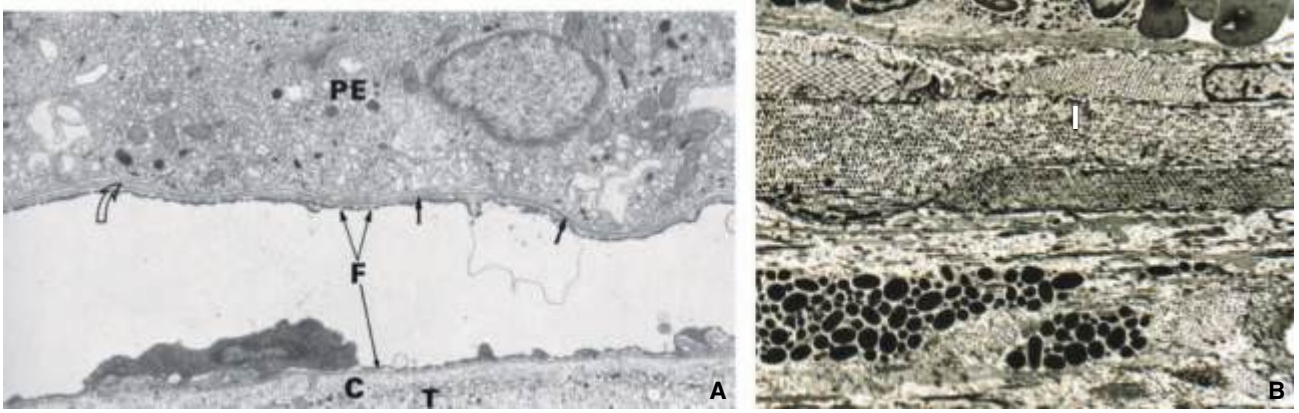


Figure 2.69 Choriocapillaris in the dog. **A.** Note the numerous fenestrations (F) in the endothelium. Bruch's membrane in most places consists of only the fusion of the pigment epithelium (PE) and the endothelial basal lamina (dark arrows), but small amounts of the collagenous zone are visible when they separate (open arrow). Note how the tapetum (T) is buffered from the capillary by a layer of collagenous tissue (C). Note also the lack of pigment in the PE over the area of the tapetum. (Original magnification, 12,400×.) **B.** The choriocapillaris (CC) forms the innermost layer of the choroid, being a wide capillary bed intimately associated with the RPE. I, iridocyte. (Original magnification, 3000×.)

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cellular tapeta, Bruch's membrane is reduced to a trilaminated structure consisting of two basal laminae and a layer of collagen.

Lens

The crystalline lens is a transparent, avascular structure that focuses light onto the retina. It is suspended within the eye by zonules arising from the ciliary body epithelium (i.e., pars plicata) and attaching circumferentially to the lens capsule at the lens equator. The lens is also held in place posteriorly within a shallow depression in the anterior vitreous (i.e., the patella fossa), and the iris rests against it anteriorly. In many mammals, birds, and reptiles, the lens is biconvex; the degree of convexity (i.e., shape) is able to change during accommodation because of the elasticity of the capsule and the pliability of the lens fibers. In young mammals, the lens is quite soft, with only a small, central, denser nucleus. The lens grows throughout life, with newly formed fibers added continuously to the outermost cortex, causing compression of the central, older zone of lens fibers. This results in a hardening of the central nucleus (i.e., nuclear sclerosis), which reduces accommodation ability as the lens ages.

The refractive power of the lens is less than the cornea because the change of refractive index is much greater at the air–cornea interface than at the aqueous–lens and lens–vitreous interfaces. Contraction of the CBM reduces tension on the lenticular zonules, thereby changing the shape of the lens resulting in an alteration of the dioptric power. Of the roughly 60 diopters of total refractive power of the eye, the lens contributes approximately 13–16 diopters in humans. In dogs, the dioptric power of the lens contributes approximately 40 diopters. The remaining refraction is provided by the cornea. Some mammals, including monotremes, marsupials, some herbivores, aquatic (primarily marine), placentals, and many nocturnal types such as mice and rats, have no known accommodative mechanism (Prince, 1956). Others, such as ungulates, accommodate weakly, having poor near vision; as a result, they rely more on other senses to detect near objects.

The lens is proportionately larger in domestic animals than in humans. The dog lens has a volume of approximately 0.5 mL and averages 7 mm in thickness at the anteroposterior axis, with a 10-mm equatorial diameter. The proportion of lens volume to entire globe volume ranges from 1 : 8 to 1 : 10. The equine lens, on the other hand, has a volume of approximately 3 mL, 12–15 mm average anteroposterior axis thickness, an approximately 21-mm equatorial diameter, and a lens–globe ratio of 1 : 20. Lens volumes of sheep, cattle, and pigs fall between these volumes, thicknesses, and diameters (Table 2.11). The lens consists of an enveloping basement membrane called the lens capsule, an anterior epithelium, and lens fibers occupying two main zones: the nucleus and the cortex (Fig. 2.70).

Table 2.11 Lens measurements in domestic animals.

Animal	Volume (mL)	Anteroposterior axis (mm)	Diameter (mm)
Dog	0.5	7	10
Cat	0.5	7.5–7.8	9–10.4
Horse	3.0	12–15	18–22
Cow	2–2.3	12–14.9	17.2–19.5
Sheep	0.9–1.2	8–12	12–15
Pig	0.5–0.8	7.5–8.1	9.5–11

Source: Translated from Bayer, J. (1914) *Angenheilkunde*. Vienna: Braumueller.

Table 2.12 Lens capsule measurements in the dog.

Age	Anterior pole (μm)	Equator (μm)	Posterior pole (μm)
Neonatal	1.9	3.8	1.9
1 week	2.9	4.8	1.9
4 weeks	6.7	7.6	3.8
8 weeks	10.5	7.6	3.8
12 weeks	20.9	7.6	3.8
16 weeks	21.9	7.6	3.8
1 year	48.5	7.6	3.8

Source: Monaco, M.A., Samuelson, D.A. & Gelatt, K.N. (1985) Morphology and postnatal development of the normal lens in the dog and congenital cataract in the Miniature Schnauzer. *Lens Research*, **2**, 393–433.

Lens Capsule

The lens fibers are completely enclosed within a thick, PAS-positive capsule, which is the exaggerated basement membrane of the lens epithelium. It has elastic properties but no elastic fibers (Hogan et al., 1971). The thickness of the capsule varies by region, with the thinnest being the posterior pole. The canine lens capsule thickness is 8–12 μm at the equator, 50–70 μm anteriorly, and only 2–4 μm posteriorly. Most of the capsule thickening occurs during the first year of life (Table 2.12; Monaco et al., 1985). As in most basement membranes, the main component of the lens capsule is type IV collagen.

Anterior Epithelium

Lining the anterior capsule is a monolayer of lens epithelial cells that continuously produce new basement membrane (i.e., capsule material). The cells are cuboidal to squamous axially at the anterior pole of the lens, become columnar near the equator, then elongate into slender hexagonal lens fibers. Nuclei are lost as lens fibers mature and move centrally. The lens epithelium lines only the interior aspect of the anterior surface of the capsule postnatally. The cell apices face the outer lens fibers, being attached to the underlying

cortical fibers by tight junctions (zonula occludens) and macula adherens (Benedetti et al., 1976; Hogan et al., 1971; Monaco et al., 1985; Rafferty & Esson, 1974; Samuelson et al., 1987a). The posterior lens epithelium forms the embryonic primary lens fibers and, thus, is absent under the posterior lens capsule later in life.

Mature lens fibers become dependent on the anterior epithelium for maintaining a critical level of dehydration, which allows the soluble proteins to be functionally effective, and for providing a healthy level of reduced glutathione. The lens epithelium is highly susceptible to damage caused by factors such as changes in local oxygen concentration, exposure to toxins, X-ray irradiation, and ultraviolet (UV) light damage. Nocturnal (and arrhythmic) animals might be less able to compensate for exposure to bright light, as free-radical scavenging and other defense mechanisms might differ between species.

Lens Fibers

Immediately anterior to the lens equator is a proliferative zone within the epithelium, referred to as the lens bow (Fig. 2.70 and Fig. 2.71). The cells within this zone begin to mitose at approximately the same time the primary lens fibers form during early fetal development. This zone of mitosis continues throughout life. The most recently formed cells elongate, with the apical portion of the cell extending forward beneath the epithelium and the basal portion posteriorly along the capsule (Fig. 2.72). As these cells transform into lens fibers, small ball-and-socket interdigitations begin to develop (Fig. 2.73) and the lens fibers become roughly hexagonal in shape. The ball-and-socket junctions, which are present along the length of the fibers, are formed only at the six angular regions; in this way, any particular lens fiber is tightly coupled to six other lens fibers, including two older fibers, two of the same generation, and two younger fibers. In addition to these cytoplasmic interdigitations are many gap junctions, or nexi (Philipson et al., 1975). The nucleus of each developing lens fiber retains its central location, and the difference in the degree of elongation between younger and older developing lens fibers creates the lens bow configuration of nuclei at the equator (see Fig. 2.70, Fig. 2.72, and Fig. 2.74).

The lens fibers elongate toward the anterior and posterior poles, forming a U-shaped cell. The fibers do not reach the full distance from one pole to the next, much less the entire circumference of the lens; rather, they meet fibers from the opposite side to form the anterior and posterior lens sutures. The sutures are simply the junctions from opposite fibers at

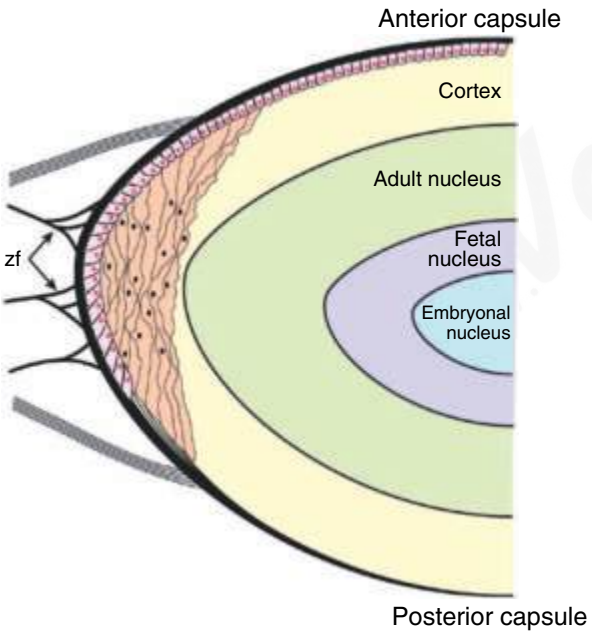


Figure 2.70 Composite drawing of the lens, capsule, attachments, and nuclear zones. The lens epithelial cells line the anterior capsule. At the equator, these dividing cells elongate to form lens cortical cells (fibers). As they elongate anteriorly and posteriorly toward the sutures, their nuclei migrate somewhat anterior to the equator and form the lens bow. Zonular fibers (zf) attach to the anterior and posterior lens capsule and to the equatorial capsule, forming pericapsular or zonular lamellae of the lens. (*Source:* Modified from Hogan, M.J., Alvarado, J.A. & Weddell, J.E. (1971) *Histology of the Human Eye*. Philadelphia, PA: W.B. Saunders. Reproduced with permission of Elsevier.)

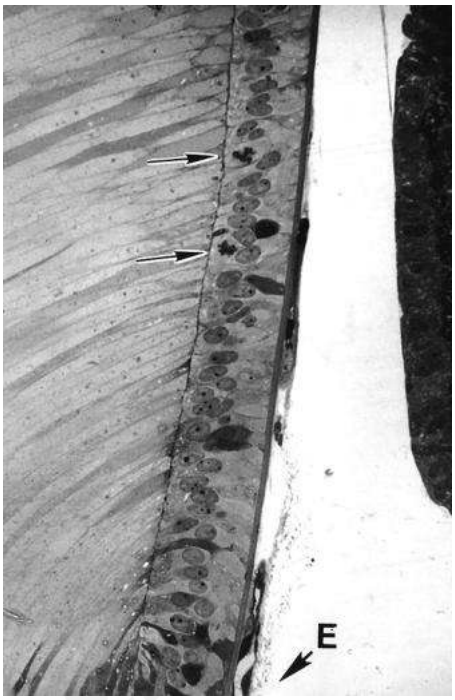


Figure 2.71 The anterior epithelium of a neonatal canine lens near the equator (E) has a proliferative zone at which cells undergo mitosis (arrows) and, subsequently, are pushed toward the equator. (Original magnification, 400×.)

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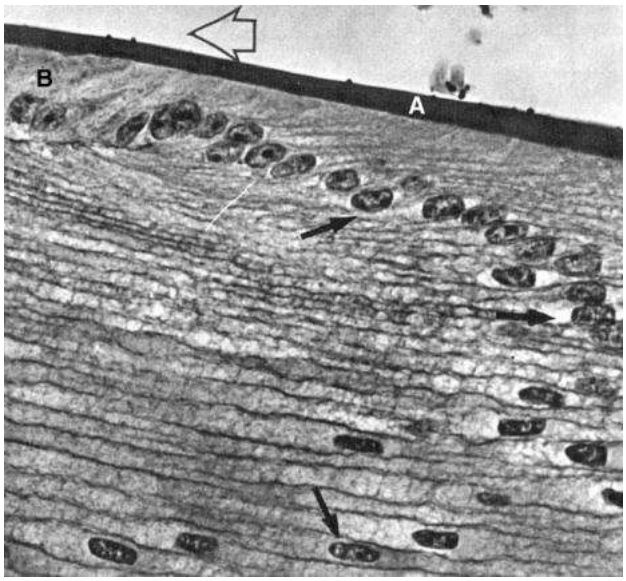


Figure 2.72 Young horse lens near the equator. Lens capsule (A) and columnar lens epithelium (B) at equator. Arrows delineate the formation of the lens bow by the nuclei of the newly formed fibers. Open arrow points rostrally. (Original magnification, 500×.)

a given level in the lens. They vary in configuration among species and at different levels within the lens.

The sutures usually form a Y-shaped pattern near the center of the lens, but in older eyes, they become more complex, with branching arms in the more superficial layers (Fig. 2.75). The suture patterns extend throughout the depth of the lens, but they are apparent *in vivo* only at optical interfaces. The sutures in the anterior half are typically in an upright Y-shaped pattern, whereas those on the posterior half are an inverted Y-shaped pattern. Figure 2.76 illustrates how inversion of the suture pattern develops and how a fiber attaches to opposite sites on a suture arm at its anterior and posterior limits (Hogan et al., 1971). At the lens sutures, the fibers markedly interdigitate with each other (Fig. 2.77). The interdigitations can affect optical quality to some degree by varying the focal length of light in this region of the lens, especially in the presence of nuclear sclerosis, lens pathology, or both (Kuszak et al., 1991). Overall, the combination of these well-developed regions for cell attachment, including the ball-and-socket and gap junctions, make the lens a remarkably unified structure. Lens fibers that become attached at the suture have fully matured; these cells lie in the deep bow zone and eventually lose their nuclei and organelles (Kuwabara & Imaizumi, 1974).

The mammalian adult lens consists of lens fibers formed chronologically throughout life. The oldest portion, formed during embryonic development, is in the center of the lens and known as the embryonic nucleus. It is a small, dark, lucent zone. Extending outwardly, the fetal nucleus, adult nucleus, and cortex are respectively encountered. These portions are frequently subdivided clinically into anterior and posterior divisions to further localize lesions (Daniel et al., 1984; Martin, 1969).

The surface of lens fibers varies according to the location within the lens. In newly mature fibers (i.e., the outer cortex), the ball-and-socket junctions are the dominant feature along each hexagonal edge (see Fig. 2.73). This feature is notably reduced in the lens fibers in the inner cortex next to the adult nucleus. The reduction in size of these interdigitations and the undulating appearance of the fibers undoubtedly result from the increasing compression this region undergoes. This change is even more remarkable in the nucleus, in which lens fibers have lost their ball-and-socket

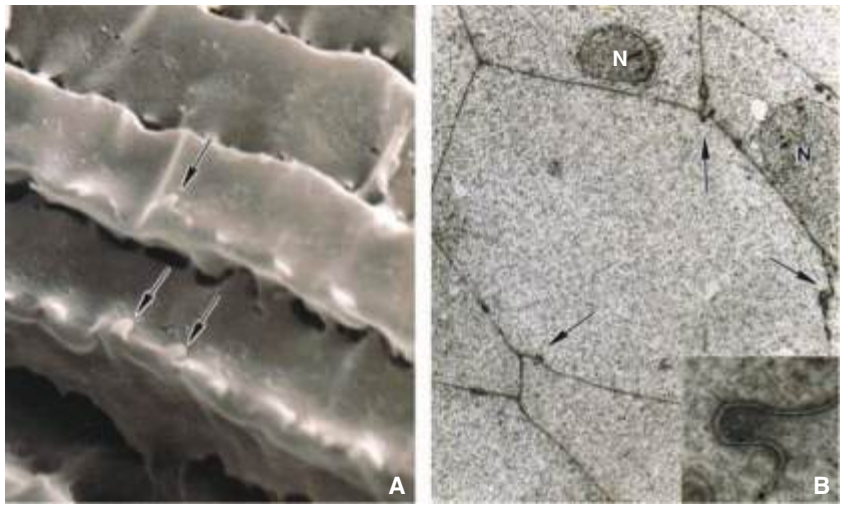


Figure 2.73 Newly formed canine secondary lens fibers are evenly hexagonal in cross-section. They form small ball-and-socket junctions (arrows) along their six angular edges. **A.** SEM. (Original magnification, 6,600×.) **B.** TEM. (Original magnification, 8,000×.) *Insert*: Close-up of one of the ball-and-socket junctions. N, nucleus. (Original magnification, 30,000×.)

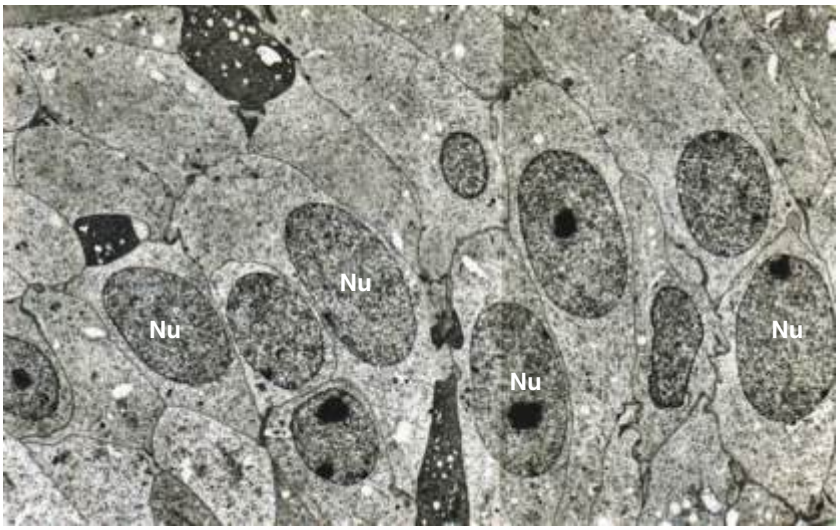


Figure 2.74 At the equator of a dog lens, the nuclei (Nu) of the newly forming secondary lens fibers are arranged linearly, taking up a central location within each cell. As these fibers mature, their nuclei are more rostrally or anteriorly located, achieving a bow-like configuration. These cells possess a great deal of free ribosomes and rough endoplasmic reticulum. (Original magnification, 3000×.)



Figure 2.75 Stereoscopic view of the posterior pole in an adult bovine lens demonstrates the distinct, Y-shaped suture pattern where lens fibers attach to each other. Branching arms (arrowheads) of the Y-shaped sutures occur more superficially, representing the attachment of younger cells. (Original magnification, 40×.)

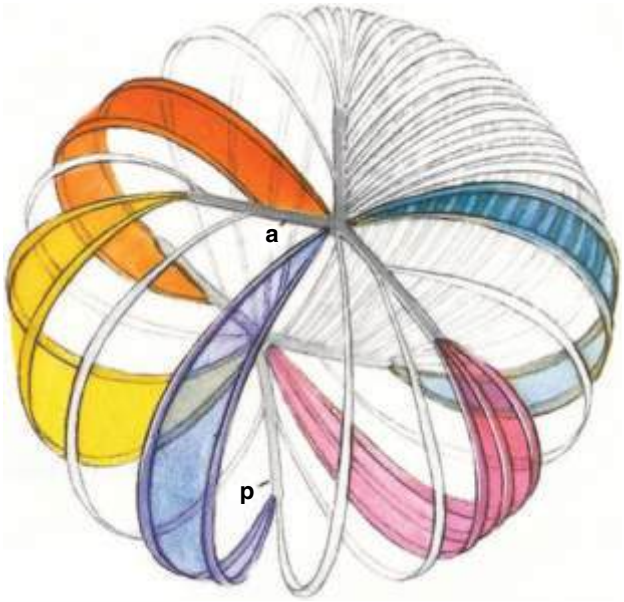


Figure 2.76 Drawing of the embryonal lens (i.e., nucleus) shows the anterior (a) Y suture, posterior (p) Y suture, and arrangement of the lens cells. The lens cells are depicted as wide, shaded bands. Those that attach to the tips of the Y sutures at one pole of the lens (a) attach to the fork of the Y at the opposite pole (p). (*Source:* Revised from Hogan, M.J., Alvarado, J.A. & Weddell, J.E. (1971) *Histology of the Human Eye*. Philadelphia: WB Saunders. Reproduced with permission of Elsevier.)

junctions entirely and instead possess tongue-and-groove junctions.

To a greater extent than in mammals, lenticular accommodation in birds depends on the ability of the lens to change shape. The avian lens is generally softer and more flexible than the mammalian lens, and consequently is more readily deformed during contraction of the ciliary body and peripheral iris musculature (Glasser et al., 1995). As the anterior uveal muscles contract, it is theorized that the ciliary body pushes against the mid-equatorial region of the lens while the peripheral edge of the iris presses against the anterior equatorial surface (Fig. 2.78). As an evolutionary adaptation to this activity, the avian lens has an annular pad (i.e., 'ringwulst'), which consists of lens fibers that are relatively enlarged and arranged radially instead of

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concentrically (Fig. 2.79). The size of the annular pad appears to relate directly to the degree of accommodative ability. In both birds and reptiles, the ciliary processes directly contact the lens equator, and zonules are not present.

Between the annular pad and the main lens body exists a space called the cavum lenticuli, which separates these two distinct zones of the avian lens (Willekens & Vrensen, 1985). Annular pad fibers have a hexagonal circumference and are similar to young developing mammalian lens fibers. The annular pad fibers are smooth-surfaced, lacking any anchoring cellular processes (as in the chicken, song thrush, and kestrel), or they may be studded with edge protrusions, including ball-and-socket junctions (Willekens & Vrensen, 1985). At the transition between the annular pad and the main lens body, the cells become considerably elongated, and their nuclei appear to be oval before they disappear. The germinative epithelial cells differentiate in two phases: first

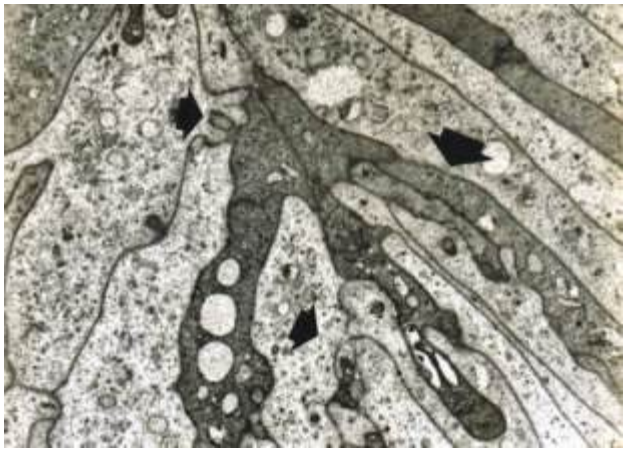


Figure 2.77 Close-up of a suture line in a dog lens reveals the great amount of cellular interdigitation (arrows) between adjacent lens fibers. (Original magnification, 5,000×.)

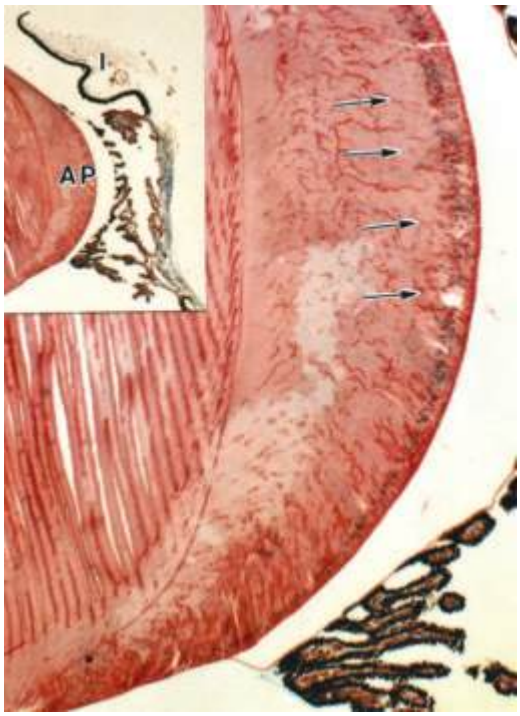


Figure 2.79 The "ringwulst," or annular pad (AP), of a screech owl's lens consists of radially arranged cells (arrows) that can withstand direct pressure. (Original magnification, 200×.) *Insert*: Overview of the annular pad. I, iris. (Original magnification, 20×.)

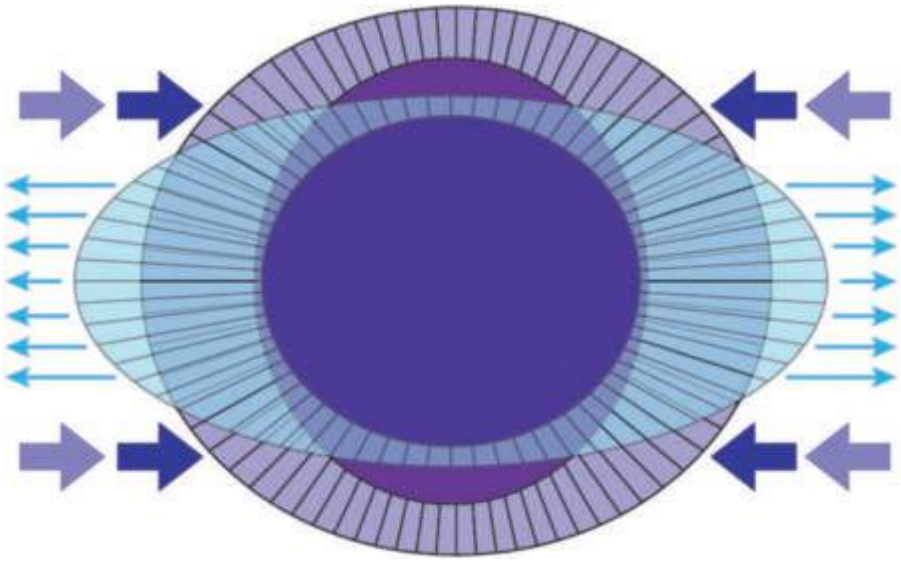


Figure 2.78 The avian lens is capable of dramatic changes in shape during accommodation, because it can be physically compressed (broad arrows) into a more rounded shape by the adjacent ciliary processes. By comparison, the lens "at rest" is stretched by zonules (small arrows) into a biconvex form.

into annular pad fibers that are elongated horizontal to the anteroposterior axis of the lens, and then into main lens body fibers, which continue to elongate further and eventually lose their organelles.

Zonular Attachment

The mammalian lens is circumferentially suspended from the ciliary body by fibers called zonules. Zonular attachment is achieved by a complex arrangement of fibers that insert onto the lens capsule in a zone encompassing the equator and a short distance both anterior and posterior to the equator (Fig. 2.80A, B; Farnsworth et al., 1976). Each zonular fiber is made of numerous small fibrils, which are visible under SEM as they attach to the lens capsule (Fig. 2.80C). The zonular fibers spread out near the equator and terminate into smaller bundles. Each of these bundles also fan out and form a network that ramifies over the surface of the lens capsule, approximately 1.5–2.0 mm away from the lens equator. As each smaller bundle of fibrils blends into the outer capsule, it is interwoven with an adjacent bundle, thus providing added strength for its insertion.

It was once believed that the zonular fibrils consisted of collagen and were perhaps a condensation of vitreous; zonules are therefore referred to as the tertiary vitreous. However, the fibrils are composed in part of a noncollagenous glycoprotein, fibrillin-1, that is also found in elastin (Cain et al., 2006; Dische & Murty, 1974; Streeten & Licari, 1981). Zonular fibers are believed to originate from the ciliary body, specifically the nonpigmented epithelium (Gloor, 1974). At the level of the ciliary body nonpigmented epithelium, the fibrils do not penetrate the basement membrane entirely, but rather intermix with the inner folds of the basement membrane. At the level of the lens, the zonules insert

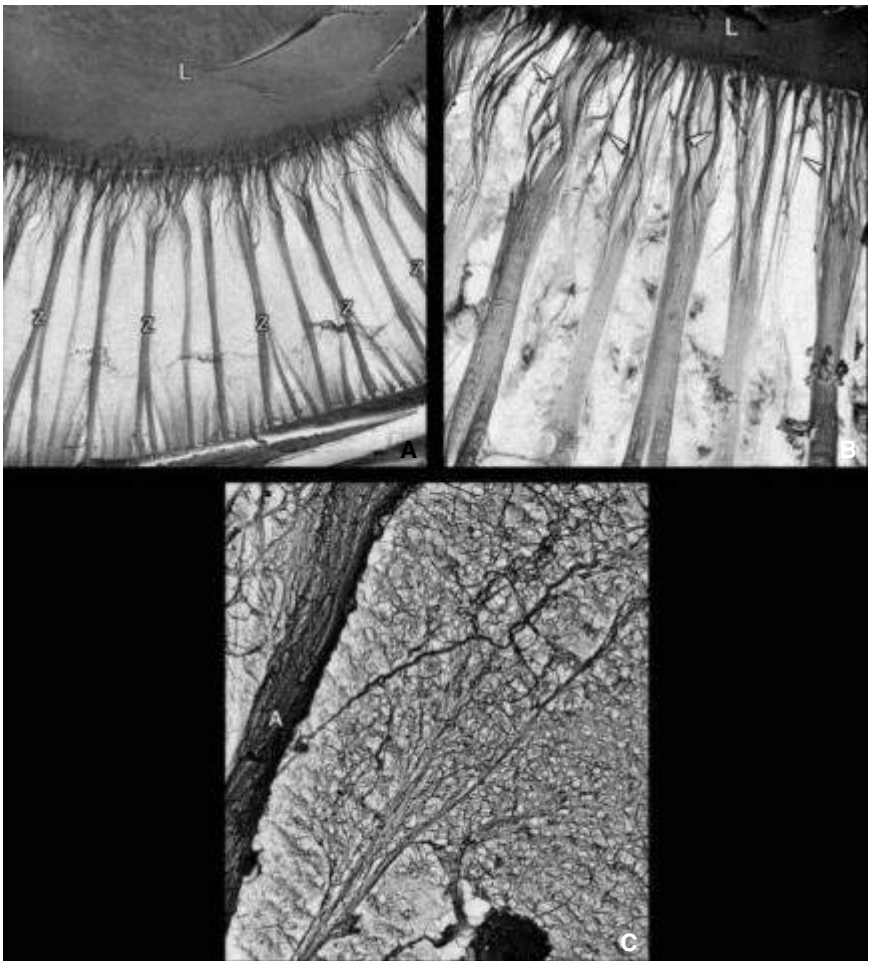


Figure 2.80 Zonular attachments to the lens in a dog. **A.** SEM shows zonules (Z) extend from the ciliary body onto the equator of the lens (L) in a ring-like manner, covering each ciliary process. (Original magnification, 30×.) **B.** SEM shows that each zonule consists of bundles (arrowheads) of fibrils, which are most apparent next to the lens (L). (Original magnification, 78×.) **C.** SEM shows termination of zonular fibrils, which unravel to form a dense meshwork over the capsule that greatly increases the surface area of attachment. A, zonular fiber. (Original magnification, 1600×.)

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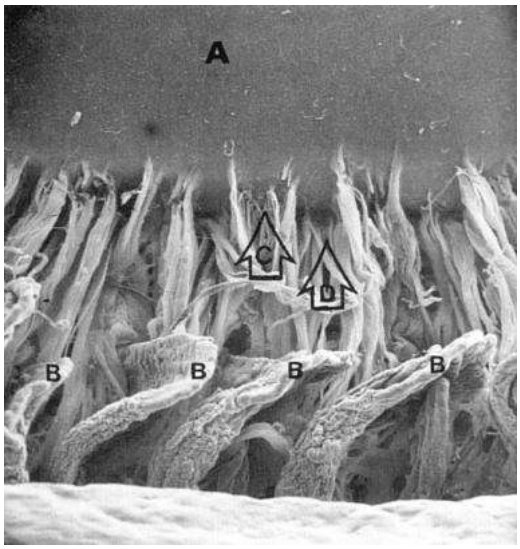


Figure 2.81 Caudal-view SEM of ciliary processes and zonular attachments to the lens in a cat. A, Posterior lens. B, Ciliary processes. C, Posterior zonular fibers. D, Anterior zonular fibers. Note the zonular fibers extending from the valleys and producing a cluster of fibers at their lenticular insertion with gaps between bundles. (Original magnification, 40×.)

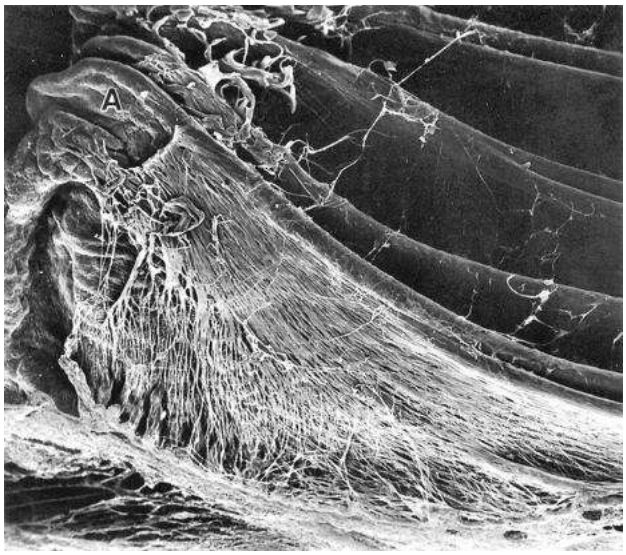


Figure 2.82 SEM shows that the apical portion (A) of each ciliary process in the dog is not intimately associated with zonular fibers. (Original magnification, 50×.)

intracapsularly, mixing with the type IV collagen of the lens capsule (Hiraoka et al., 2010).

The relationship of the zonules to ciliary processes varies to some extent among species. In primates, the zonular fibers originate largely from the pars plana, within 1 mm anterior to the ora serrata (Raviola, 1971; Rohen, 1979; Streeten, 1992). As the zonules course anteriorly, almost all have a close attachment to ciliary processes, adhering strongly to the valleys between the folds and along the sides of the processes.

In the cat, the zonular fibers largely appear to bypass the ciliary processes and insert in the valleys (Fig. 2.81). In the dog, tips of the ciliary processes are free of zonular fibers, but the remaining process is ensheathed very intimately with the zonules (see Fig. 2.43 and Fig. 2.82; Gelatt & Samuelson, 1998). The fibers as a group can be followed to the base of the ciliary process. As the fibers insert into the lens capsule, they can fan out over a breadth of 300 µm, and as a result overlap considerably with fibers arising from adjacent processes. The horse (see Fig. 2.44) has numerous fibers both ensheathing the processes and in the valleys, and both types continue down to the pars plana. In addition, an extensive network of fibers runs horizontally, joining the ridges of the processes.

Vitreous

The vitreous humor is a transparent hydrogel that comprises a portion of the clear ocular media and accounts for up to two-thirds of globe volume. Vitreous volumes in selected species are listed in Table 2.13. Anteriorly, the vitreous provides support for the lens as it rests in a shallow concavity (i.e., the patella fossa), whereas posteriorly, the vitreous abuts the neurosensory retina. As a result, the vitreous functions to transmit light, to maintain the shape of the eye, and to help maintain the normal position of the lens and retina (Jaffe, 1969).

Table 2.13 Vitreous humor volume in selected species.

Animal	Vitreous volume (mL)
Dog[a]	1.7
Horse[a]	26.15
Calf	10
Pig	3.5
Rabbit	1
Human	4

Source: Modified from Jaffe, N. (1969) *The Vitreous in Clinical Ophthalmology*. St Louis.
[a] Gilger et al., 2005.

Embryologically, the vitreous is composed of three components

1) the primary vitreous (containing the hyaloid artery system)
2) the secondary (definitive, or adult) vitreous, and
3) the tertiary vitreous (lens zonules, discussed earlier).

The primary, or primitive, vitreous develops first, as the hyaloid artery system courses through it to provide a blood supply to the avascular developing lens. The secondary

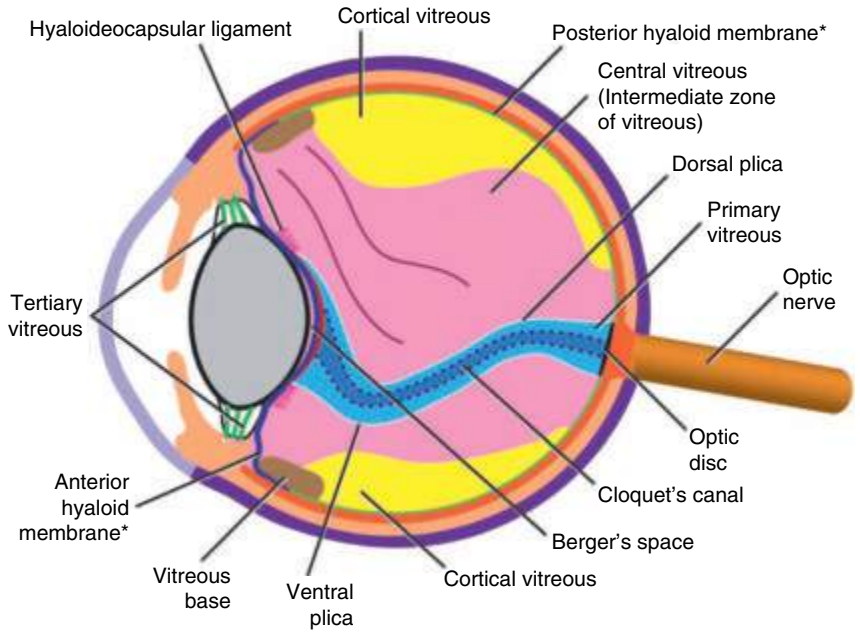


Figure 2.83 The various components of and spaces within the vitreous. The secondary, or adult, vitreous is composed of the cortical and central (intermediate zone) components. (*Not a true 'membrane'.)

vitreous then forms around the primary vitreous, leaving the primary vitreous at the central core of the vitreal compartment. The secondary vitreous becomes the definitive, or adult, vitreous.

Within the adult vitreous exist several anatomic structures, potential spaces, and connection points between the vitreous and adjacent tissues (Fig. 2.83). The core of the primary vitreous around which the adult vitreous develops is occupied by Cloquet's canal (i.e., the hyaloid canal), a potential space that contained the hyaloid artery in the embryonic eye. The remnant of the anterior insertion of the hyaloid artery appears as a dense, white, small dot (i.e., Mittendorf's dot) with a variable "corkscrew" tail extending from the posterior pole of the lens. The anterior and posterior surfaces of the vitreous are lined by the anterior and posterior hyaloid membranes, respectively; though, no true 'membrane' exists in an ultrastructural sense at either location. The peripheral portion of the vitreous next to the retina is referred to as the cortex. Here, the collagen fibrils of the cortex join the basement membranes of Müller and glial retinal cells.

A potential space, sometimes referred to as Berger's space, exists between the posterior lens capsule and the anterior hyaloid membrane. The anterior hyaloid membrane curves forward from the region of the ora ciliaris retinae (i.e., vitreous base) to blend in with the peripheral posterior lens capsule, where a strong circumferential attachment forms (i.e., the hyaloideocapsular ligament). The adult vitreous attaches firmly to the area around the optic disc, the region of the ora ciliaris retinae (i.e., vitreous base), and at the hyaloideocapsular ligament.

The central portion of the vitreous consists of tracts, which are layers of funnel-shaped sheets or plicae fitted one into another (see Fig. 2.83). Between the cortex and central vitreous exists a border layer composed of many compacted lamella, with each lamella consisting of a meshwork of collagen fibrils (Faulborn & Bowald, 1982).

The vitreous is 99% water; the remaining 1% is a network of polygonal, hydrated fibrils consisting of type II collagen and hyaluronic acid (McLaughlin & McLaughlin, 1986; Snowden & Swann, 1980). The collagen fibrils interconnect with the hyaluronic acid by associated GAGs, consisting principally of chondroitin sulfate IV and VI and heparan sulfate (Goes et al., 2005; Noulas et al., 2002). A number of proteins are also part of the vitreal extracellular matrix; these proteins are produced primarily by the posterior half of the nonpigmented ciliary epithelium and appear to be in a continuous state of turnover (Bishop et al., 2002).

The vitreous has a relatively low cell density, with most cells found in the cortex near the vitreous base. The main cell type is the hyalocyte, which is a histiocyte with a poorly developed lysosomal system. Hyalocytes can produce hyaluronic acid *in vitro* and are thought to contribute to formation of the vitreous humor, along with the nonpigmented ciliary body epithelium and the non-neuronal cells of the retina (Jacobson, 1976). However, the possibility that these cells play a role in remodeling events in the vitreous, rather than in hyaluronic acid production, is plausible. In addition to the hyalocyte, fibrocytes and glial cells, found next to the ciliary body and the optic disc, comprise roughly one-tenth of the total population of vitreal cells (Balazs et al., 1964).

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The consistency of the vitreous is quite variable, because of the different proportions of gel to liquid that occur among species and at different ages. In the cat and dog, the cortex is fluid, and the center is dense. In cattle, pigs, and sheep, the entire vitreous is nearly homogenous in structure and of high density. Like ruminants, the pig and the horse do not show a separation into cortical and central zones, but the vitreous is of comparatively low optical density. The rabbit vitreous is of such low optical density that it could hardly be examined (Eisner, 1975, 1988; Eisner & Bachmann, 1974a, 1974b, 1974c, 1974d). The consistency of the vitreous is also influenced by aging. In most species, holes and liquefaction (i.e., syneresis) occur in older individuals, particularly in the central region.

Retina

The retina and optic nerve are derivatives of the forebrain; consequently, their morphology and physiology are similar to that of the brain. The neurosensory retina is connected to the brain by the optic nerve and the optic tracts. The rods and cones, the primary retinal photoreceptors, comprise a complex layer of specialized cells, which contain photopigments that convert light energy into a series of biochemical events. The RPE furnishes important metabolites to the photoreceptors; it also actively phagocytizes the outermost photoreceptor segments as they are shed during normal outer-segment renewal. The retina has one of the highest rates of metabolism of any tissue in the body and receives almost all its nutrition from the retinal and choroidal capillaries.

The function of the retina is to turn light stimuli from the external environment into nervous impulses and transmit this information accurately to the brain, where it is then interpreted as vision. Stimulation of the photoreceptors by light alters the release of a neurotransmitter; this response is received and modified by cells with nuclei located in the inner nuclear layer (i.e., amacrine, bioplar, and horizontal cells) (Fig. 2.84). The modified message is then relayed to ganglion cells, with axons that form the nerve fiber layer and extend through the optic nerve to targets in the brain (including the lateral geniculate nucleus and occipital cortex) (see Chapter 4).

Classically, 10 layers are described in retinal histology. The neurosensory retina contains nine, and the supportive pigmented epithelium is the tenth layer (Fig. 2.85). The

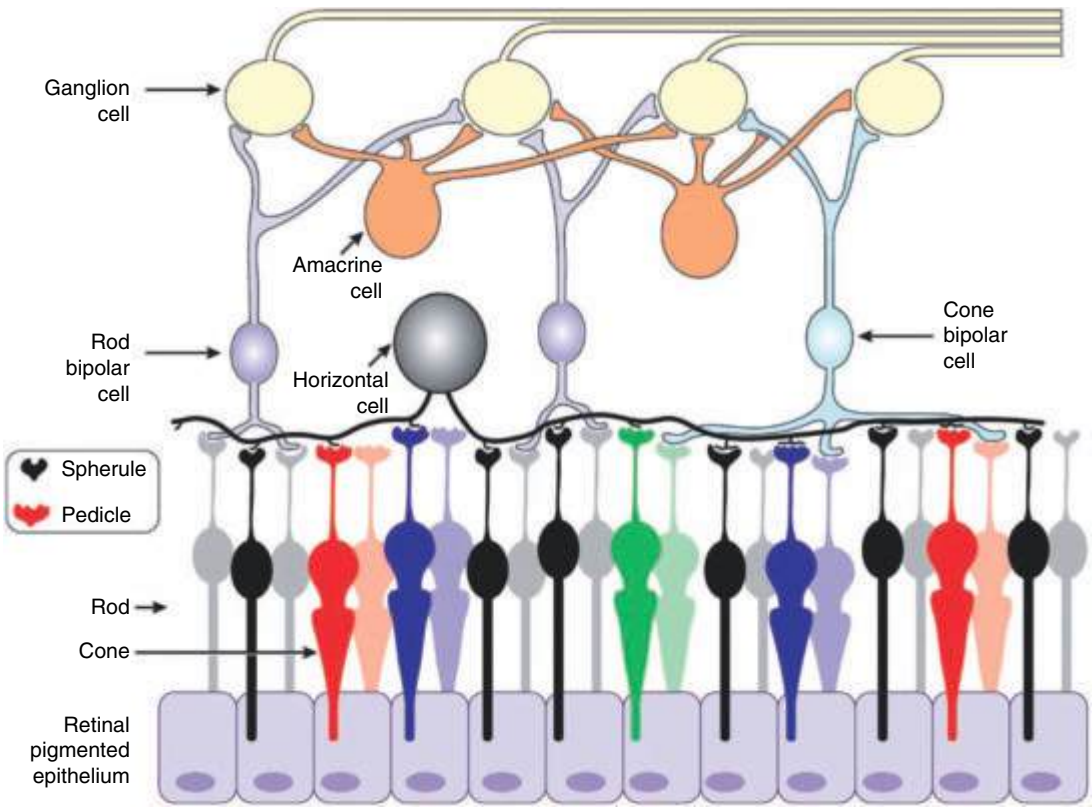


Figure 2.84 Relationship between different neuronal cells within the retina. The amacrine cell has a reciprocal inhibitory response onto the bipolar cell from which the information originated and acts to adjust the sensitivity of the ganglion cell synapse after receiving a signal. Horizontal cells interconnect laterally to integrate and regulate input from multiple photoreceptors.

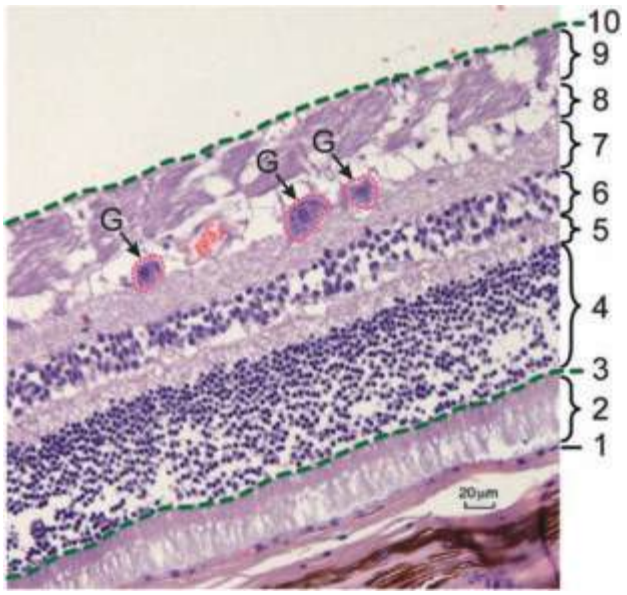


Figure 2.85 The retina consists of nine discrete layers and a supportive pigmented epithelium that forms an outer, tenth layer, as demonstrated by light microscopy in the dog. G, ganglion cell; 1, retinal pigment epithelium; 2, photoreceptor layer; 3, outer limiting membrane; 4, outer nuclear layer; 5, outer plexiform layer; 6, inner nuclear layer; 7, inner plexiform layer; 8, ganglion cell layer; 9, nerve fiber layer; 10, inner limiting membrane. The outer and inner limiting membranes are denoted by dashed lines.

10 identifiable layers are considered, sclerad to vitread, in the following order:

1) RPE
2) photoreceptor layer (rod and cone layer)
3) outer limiting membrane
4) outer nuclear layer
5) outer plexiform layer
6) inner nuclear layer
7) inner plexiform layer
8) ganglion cell layer
9) nerve fiber layer, and
10) inner limiting membrane.

Retinal Pigment Epithelium

The RPE is a monolayer of flat, polygonal cells that forms the outermost layer of the retina. It is the continuation of the outer pigmented epithelial layer of the ciliary body. The RPE is more adherent to the choroid than to the rest of the retinal tissue, and it serves an important role in nutrient transport from the choriocapillaris to the outer layers of the retina. Each cell sends cytoplasmic processes inward to surround the photoreceptor outer segments, which help to filter out excessive amounts of light and increase the photoreceptors' individual sensitivity. The cells also phagocytize the outer segments of photoreceptors as they are continuously shed.

The RPE cells are usually densely pigmented, but there is some variability in the intensity of pigmentation amongst individual animals. This variability is largely based on hair color and the relative amount of pigmentation in other areas of the eye; for instance, RPE cells might contain light, rust-colored pigment in a tan or red colored animal, or pigment could be virtually absent in an animal with a blue iris (i.e., subalbinotic). Additionally, RPE cells overlying the tapetum lucidum, when present, are devoid of pigment. The absence of melanin permits light to pass through the RPE to the tapetum and then reflect back to the light-sensitive photoreceptors.

On flat preparations, the RPE of most species forms a mosaic of hexagonal cells, which is most uniform in the posterior pole and in young animals. In most species, except the rat and rabbit, these cells are generally mononucleate. In general, the cells are larger and have more binucleate forms near the ora ciliaris retinae (Tso & Friedman, 1967).

The morphology and location of RPE melanosomes varies to some degree among different animals. The shape of melanosomes is typically oval, but they can be more elliptical in diurnal species such as birds and various reptiles (Kuwabara, 1979). The elliptical to nearly lanceolate melanosomes are frequently positioned within apical microvilli, which are cytoplasmic projections of the RPE cells that lie between and surround the photoreceptors. These microvilli offer substantial shielding for the photoreceptors against scattered light. Melanosomes within the RPE of arrhythmic and nocturnal species, such as the rat, hamster, mouse, and bat, tend to be rounder, fewer in number, and less frequently located within the microvilli.

In addition to providing protection against light scatter, the apical microvilli surround the outermost and oldest portion of the photoreceptor outer segments. No cell membrane attachments exist between the RPE and the photoreceptors, but a viscous ground substance of GAGs surrounds the photoreceptor outer segments (Fine & Yanoff, 1979; Spitznas & Hogan, 1970; Weale, 1963). On SEM examination, the apical microvilli are quite numerous, being clustered next to outer segments that have fractured and adhered to the RPE during routine cryopreparation, as shown in Fig. 2.86. Microvilli are especially large and long in the RPE of many nonmammalian animals (Kuwabara, 1979). The lateral RPE cell surfaces near the apical end have a well-defined junctional complex, including zonular occludens and zonular adherens.

The basal aspect of the RPE rests on Bruch's membrane, a basal complex in the capillary zone over the choriocapillaris. Marked basal infoldings of the cell membrane contrast sharply with the basement membrane, which is relatively smooth (Fig. 2.87). The size and organization of the basal infoldings vary to some degree among mammals (Braekevelt, 1986, 1990a, 1990b). In birds, the basal infoldings are especially developed and tightly packed as opposed to those in mammals, which tend to be smaller and irregularly

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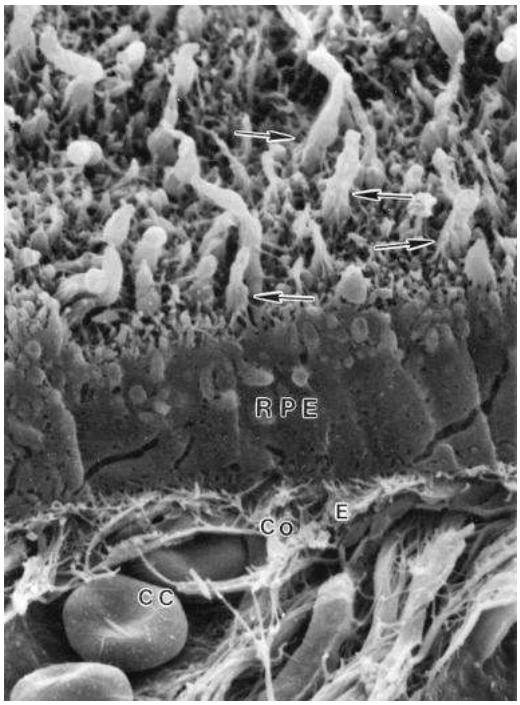


Figure 2.86 SEM shows cryofractured RPE and the underlying choriocapillaris (CC) of a sheep. Arrows indicate photoreceptor outer segments that remain fastened to apical villi. Note the strands of collagen (Co) and elastic fibers (E) that make up much of Bruch's membrane. (Original magnification, 6,000×.)

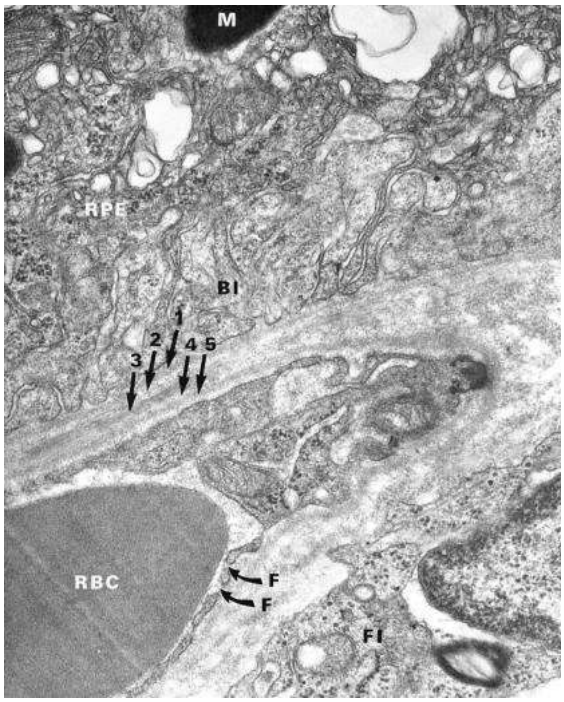


Figure 2.87 TEM shows the basal complex (i.e., Bruch's membrane) in the capillary zone over the non-tapetal region of a dog. Note the RPE with melanin (M) granules and basal infoldings (BI) of the RPE. The basal complex consists of: 1, basal lamina of RPE; 2, inner collagenous zone; 3, elastic layer; 4, outer collagenous zone; 5, basal lamina of choriocapillaris. F, fenestrations in choriocapillary endothelium; FI, fibroblast in anterior choroid; RBC, erythrocyte in choriocapillaris. (Original magnification, 43,600×.)

positioned (Braekevelt, 1990b, 1998a; Braekevelt & Thorlakson, 1993). In animals with a cellular tapetum, the basement membrane of the pigment epithelium and the basement membrane of the choriocapillaris occasionally fuse, thus reducing the pentalaminated structure to a single layer. More often, however, the basement membrane of both epithelia remains, with a shared collagenous zone of variable thickness.

Neurosensory Retina

The neurosensory retina varies in thickness (Table 2.14), being thickest near the optic disc and tapering toward the ora ciliaris retinae. The width of all layers decreases, but the nerve fiber layer contributes the most to the variation in thickness. Most domestic animals have a central retina of approximately 200–240 µm and a peripheral retina of 100–190 µm (Brown, 1968; Donovan et al., 1974b; Prince et al., 1960). In animals with poorly vascularized or avascular retinas, retinal thickness rarely exceeds 140 µm, which is the proposed oxygen diffusion maximum for retinal tissue (Buttery et al., 1991; Chase, 1982; Dollery et al., 1969).

The retinal photoreceptors are the primary visual cells of the eye and are the first-order neurons (see Fig. 2.84). Rods function in dim or reduced illumination, and cones function

Table 2.14 Retinal thickness measured by optical coherence tomography.

Animal	Retinal thickness (µm)	Retinal location	Reference
Dog[a]	198.7	Dorsal/superior	Hernandez-Merino et al., 2011
	164.4	Ventral/inferior	
Cat	245	Peripapillary	Gekeler et al., 2007
	204	Peripheral	
	182	Area centralis	
Horse[b]	239	Dorsal	Pinto & Gilger, 2014
	133	Ventral	
	276	Nasal	
	263	Temporal	
Cow[c]	235	Tapetal (dorsal)	Chauhan & Marshall, 1999
	120	Non-tapetal (ventral)	
Human	160	Foveola[d]	Chauhan & Marshall, 1999
	258	Clivus[e]	

[a] Female Beagle dogs.
[b] Measurements taken 1.0 mm from optic disc.
[c] Cadaveric globes.
[d] Central depression within fovea.
[e] Sloping wall of fovea.

in bright light. The rods allow detection of shapes and motion, while the cones provide sharp visual acuity and color sensitivity. Primates and many avian and reptilian species possess cone-rich regions completely free of rods. These regions are called foveae (i.e., fovea centralis) and are responsible for the perception of different hues of color, high resolution, binocular fixation, and depth perception. Domestic animals do not have foveal pits, but dogs have been shown to have a small fovea-like structure, a fovea plana (Beltran et al., 2014). Other domestic animals instead possess an area of high cone density called the area centralis. The area centralis, which surrounds the fovea plana, frequently occurs in a location 1.5 mm temporal and 0.6 mm superior to the optic disc in the dog, which corresponds to a location 1.2 disc diameters temporal and 0.6 disc diameters superior to the optic disc for purposes of clinical ophthalmoscopy (Mowat et al., 2008). The visual streak is a region of the retina with increased ganglion cell density that occurs in a horizontal band, dorsal to the optic disc. The area centralis resides within the visual streak, and these terms are sometimes used synonymously. Often, the two regions are nearly identical, or even topographically identical. Instances do occur, however, in which peak ganglion-cell densities do not topographically match peak cone densities (Rapaport & Stone, 1984). Instead, a specific subpopulation of ganglion cells might be associated with the area centralis (Enroth-Cugell & Robson, 1966; Provis, 1979).

Photoreceptor cell densities have been measured in a variety of species, including the dog and cat (Table 2.15; Beltran et al., 2014; Koch & Rubin, 1972; Mowat et al., 2008; Østerberg, 1935; Steinberg et al., 1973). In the cat, the cones in the area centralis are approximately six to seven times more numerous than in the periphery (26,000–27,000 cells/mm^2 vs. 4,000 cells/mm^2). By comparison, the rods of the cat are similar in density when comparing the peripheral retina (250,000 cells/mm^2) to the area centralis (275,000 cells/mm^2); however, the density of the rods nearly doubles (460,000 cells/mm^2) along a zone surrounding the area centralis (Steinberg et al., 1973).

In general, animals with foveae and well-developed areas centrales or visual streaks, including fish, reptiles, birds, squirrels, ungulates, carnivores, and primates, are essentially diurnal or arrhythmic (Duke-Elder, 1958). True nocturnal species possess rod-dominant retinas lacking cone-rich centers. Diurnal predaceous birds can have two foveae, a principal "deep" central fovea and a shallower temporal fovea. The central fovea provides enhanced lateral viewing for these animals, whereas the temporal fovea provides straight-ahead projection, enhancing the binocular field (Fig. 2.88; Meyer, 1977; Tucker, 2000). The bi-foveate condition in diurnal raptors is closely associated with orbit orientation and amount of eye movement (O'Rourke et al., 2010). There appear to be strong relationships between depth of field, optimal range of stereopsis and motion parallax, and selective prey detection.

Photoreceptor Layer (Rod and Cone Layer)

The photoreceptor layer contains only the outer parts of the photoreceptor cells known as the inner and outer segments; the photoreceptor nuclei are contained in the outer nuclear layer. These segments are cylindrically to conically shaped and closely packed together, with a radial orientation parallel to incoming light as it passes through the pupil (Fig. 2.89). The segments are stimulated by incoming light to initiate the conversion of light to a nerve signal (i.e., phototransduction) that will ultimately be relayed to the brain, which eventually forms a visual image.

Table 2.15 Photoreceptor densities and ratios.

Animal	Photoreceptor density (cells/mm^2)	Location	Rod-cone ratio	Reference
Dog	23,000 cones/mm^2	Area centralis	23:1	Mowat et al., 2008
	501,000 rods/mm^2			Mowat et al., 2008
	127,000 cones/mm^2	Fovea-like area		Beltran et al., 2014
	7,500 cones/mm^2	Inferior periphery	41:1	Mowat et al., 2008
	305,000 rods/mm^2			Mowat et al., 2008
	200,000 rods/mm^2	Ora ciliaris retinae		Yamaue et al., 2015
Cat	487,000	Area centralis	11:1	Steinberg et al., 1973
	279,000	Periphery	65:1	
	253,000	Ora ciliaris retinae	100:1	
Sheep	120,000–298,000	Dorsotemporal	20:1	Shinozaki et al., 2010
	203,000	Area centralis	6:1	
Pig	138,500	Entire retina	8:1	Chandler et al., 1999
Human	5,000 cones/mm^2	Ora serrata	50:1	Østerberg, 1935
	40,000 rods/mm^2	Ora serrata		

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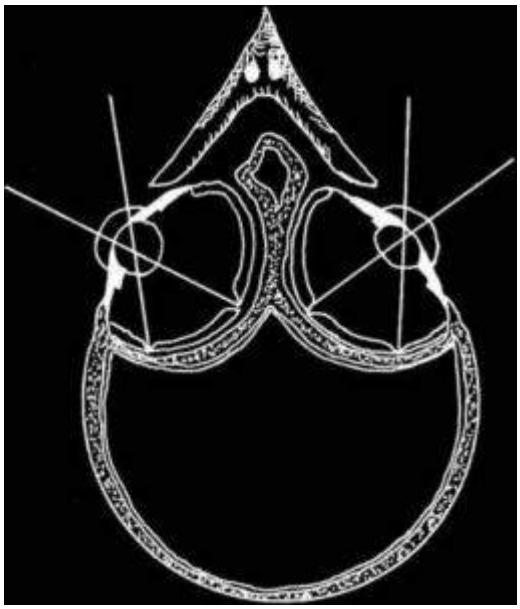


Figure 2.88 The foveal arrangement in the swallow, which possesses two foveae within each eye: one located temporally (T) for binocular vision, and one located centrally (C) for panoramic vision. (*Source:* Redrawn from Duke-Elder, S. (1958) *System of Ophthalmology. Vol I. The Eye in Evolution*. London: Henry Kimpton.)

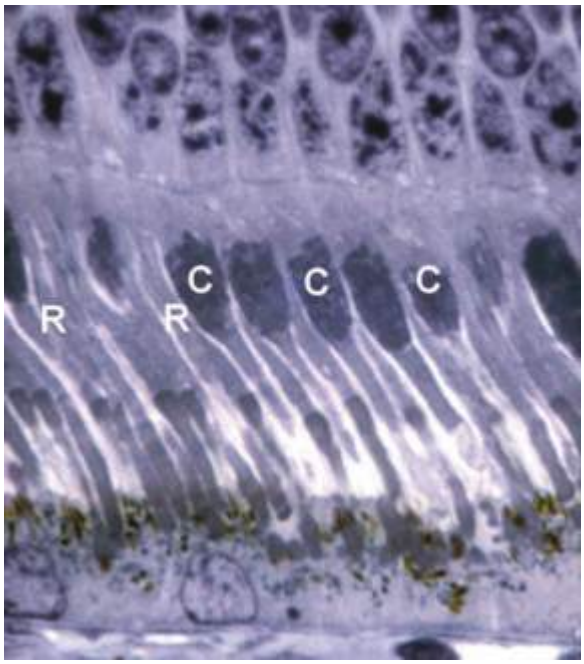


Figure 2.89 The photoreceptor layer of the pig contains many cones (C) among the rods (R) within the area centralis, making this animal well suited for day vision. Note that the rods are uniform in width throughout their length, while the cones are conically shaped due to variation in disc width at one end.. (Original magnification, 400×.)

The outer segments of the rods and cones are composed of stacks of membranous discs surrounded by the cell membrane. The rods form stacks of discs of uniform width throughout their length and are longer than the cone outer segments (Fig. 2.89 and Fig. 2.90; see Fig. 4.26). The cones form stacks of discs wider at one end, producing a conical shape (Fig. 2.89; see Fig. 4.26). In the area centralis, the cones are longer and more slender; nevertheless, they remain easily distinguished from the rods (see Fig. 2.89). The invaginations of the photoreceptor cell membrane, which form the disc lamellae, constitute the major morphologic difference between cones and rods (Cohen, 1969). In cones, which are the most ancestral photoreceptors, the discs remain connected to the cell membrane, whereas with rods, the discs are detached and fill the outer segment like a 'stack of coins' (Fig. 2.90) (Hogan et al., 1971; Rodieck, 1973).

The discs contain visual photopigments that are sensitive to different wavelengths of light. Cones contain a more diverse array of photopigments compared with rods, as cones are traditionally responsible for color vision. Retinal physiology is covered in detail in Chapter 4 and fundamentals of animal vision is covered in Chapter 5.

The photoreceptor outer segments are connected to the inner segments by a nonmotile cilium (Fig. 2.91A). The inner segments carry the cellular machinery necessary to meet the high metabolic demands of each photoreceptor cell. The outer portion of the inner segment is called the ellipsoid, and it is filled with long, tubular mitochondria that produce ATP (see Fig. 2.91B and Fig. 2.92). The cone ellipsoid

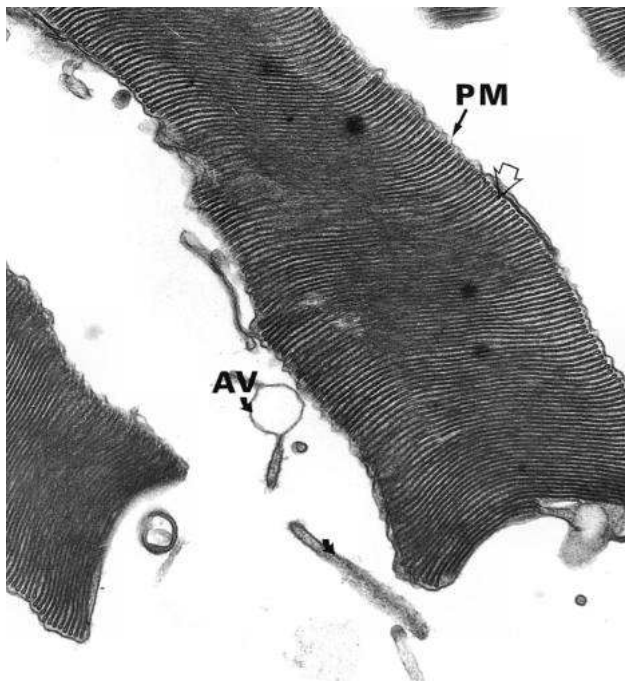


Figure 2.90 Tip of the outer segment discs in a rod of a young dog. Note that the discs or lamellae are separated from each other as well from as the plasma membrane (PM). The intralamellar space is slightly dilated at their periphery (arrow). Apical villi (AV) of pigmented epithelium are found between outer segments. (Original magnification, 54,000×.)

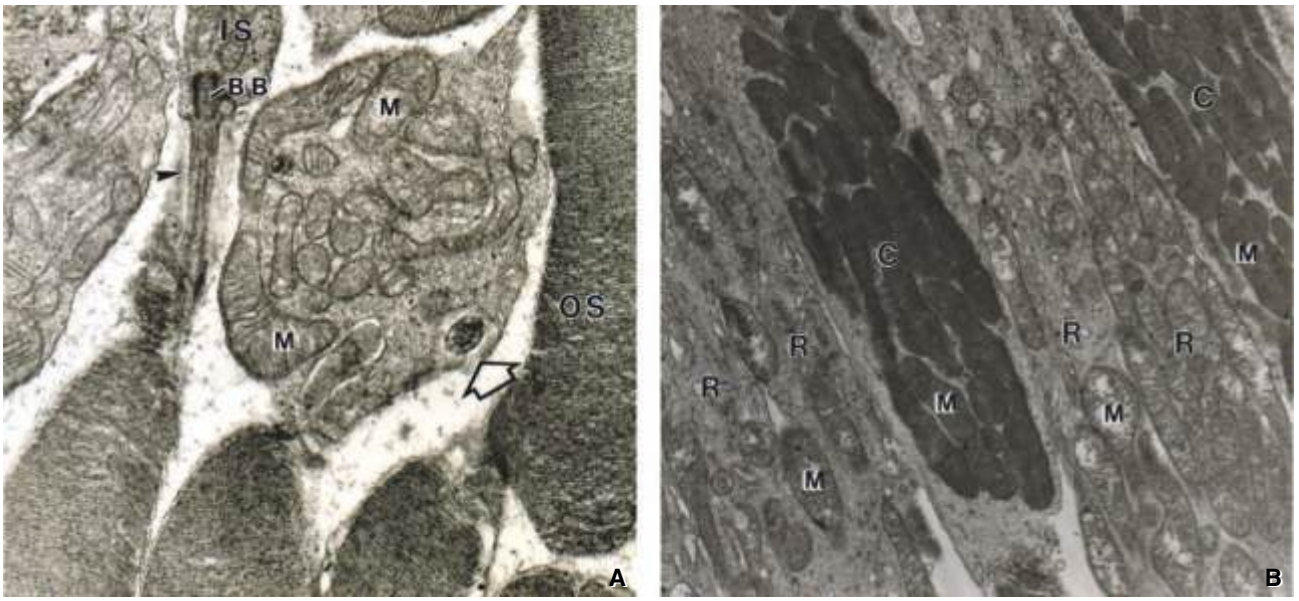


Figure 2.91 **A.** The outer portion of a rod inner segment (IS) of a dog contains a basal body (BB) that gives rise to the connecting cilium (arrowhead). Note the oblique plane of an adjacent inner segment reveals the peripheral placement (open arrow) of these basal bodies and confluent cilia. M, mitochondria; OS, outer segment. (Original magnification, 18,000×.) **B.** The ellipsoids of rods (R) and cones (C) in the central retina of a sheep. The cone ellipsoids possess more mitochondria (M) than the rod ellipsoids. (Original magnification, 11,000×.)

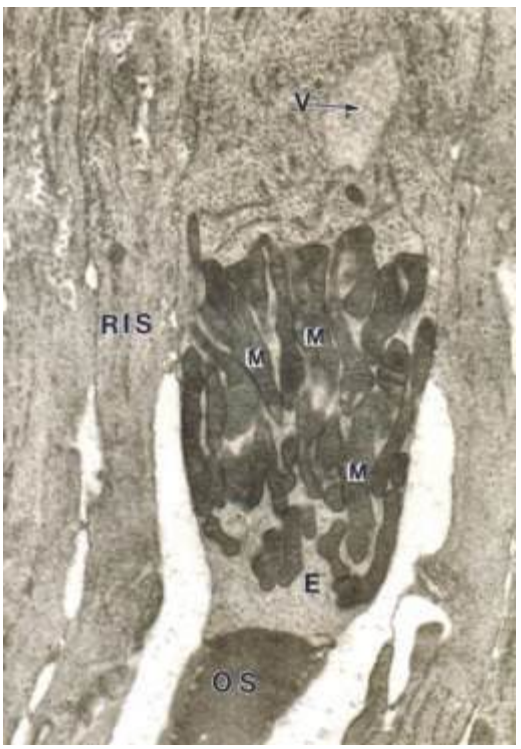


Figure 2.92 Inner portion of the outer segment (OS) and adjacent inner segment of a porcine cone. E, ellipsoid; M, mitochondria; RIS, rod inner segment; V, vesicle. (Original magnification, 10,000×.)

is more broad and conical, and contains more mitochondria, than the rod ellipsoid. In a number of vertebrates, including birds, reptiles, amphibians, and nonplacental mammals, the cone ellipsoid contains an oil droplet that separates the numerous mitochondria from the connecting cilium (Prince et al., 1960). The appearance of this droplet varies according to the species and type of cone (Braekevelt, 1993b, 1993c). The function of the oil droplet has undergone considerable speculation, and since the 19th century, it has been thought to serve as a light filter, allowing only specific wavelengths to be transmitted to the outer segments (King-Smith, 1969; Schultze, 1866).

The vitread or inner portion of the inner segment is called the myoid, and it is the principal site of protein synthesis. The myoid contains ribosomes, rough and smooth endoplasmic reticulum, Golgi bodies, and rare mitochondria. In the pig, the cone myoid may also contain a fairly prominent vesicle (see Fig. 2.91). In the avian myoid, there is an area filled with glycogen, called the paraboloid, that is best recognized with light microscopy through use of histochemical localization.

Rod and cone inner segments are separated from each other by long, villous extensions of Müller cells called fiber baskets (Fig. 2.93). The fiber baskets are virtually identical morphologically among the vertebrate species, but they are less numerous in retinas with intraretinal vasculature (Uga & Smelser, 1973). It is hypothesized that these cell

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Figure 2.93 Long, villous extensions of Müller cells, known as fiber baskets (FB), occur ubiquitously in the vertebrate eye, as shown here in the dog. OLM, outer limiting membrane. (Original magnification, 35,000×.)

processes serve to keep the extracellular portion of the photoreceptor layer dehydrated and thus help to maintain proper alignment of the outer segments (Sigelman & Ozanics, 1988). These processes are also likely involved in the exchange of metabolites with the RPE, thereby helping to provide a homeostatic environment for the outer segments (Magalhaes, 1976).

In addition to the rod and cone photoreceptors, there is a third class of primary photoreceptors known as the double-cone photoreceptor, which is found in all vertebrate groups except placental mammals. The double-cone consists of two closely associated, but separated, cone photoreceptors that differ in size, shape, and structure (Fig. 2.94). The significance of the double-cone has yet to be determined, but it is the dominant photoreceptor in diurnal animals, occupying up to 82% of the retina at the inner segment level (Meyer, 1977; Walls, 1942). The chief cone of the double-cone pair is the longer of the two, and it possesses an oil droplet. The accessory cone, on the other hand, lacks an oil droplet, having instead a conspicuous paraboloid (i.e., barrel-shaped body of glycogen).

Outer Limiting Membrane

An extremely thin limiting membrane composed of the junctional complexes between Müller cells, as well as between Müller and photoreceptor cells, forms a lateral intercellular border between the inner segments of the photoreceptor layer and their nuclei (Fig. 2.93). The function of the outer limiting membrane is somewhat speculative.



Figure 2.94 An avian double-cone photoreceptor. Nu, nucleus; OD, oil droplet; P, paraboloid. (*Source:* Modified from Duke-Elder, S. (1958) *System of Ophthalmology. Vol I. The Eye in Evolution*. London: Henry Kimpton. Reproduced with permission of Elsevier.)

In addition to holding the outer retina together, the outer limiting membrane most likely forms a barrier between the photoreceptor layer extracellular spaces and the rest of the neurosensory retina. It might also help to maintain the location of the photoreceptor nuclei away from the highly metabolic inner segments, thus reducing the potential for oxidative injury.

Outer Nuclear Layer

The soma, or cell bodies, of the photoreceptors are contained within this layer. The number of rows of nuclei varies greatly according to species and location within the retina. In the central retina, the dog and cat possess the greatest depth of rows (10–15 and 12–18, respectively), whereas ungulates have fewer rows (five in the horse and pig, 10 in the cow) (Table 2.16). The outer nuclear layer gradually thins as it approaches the peripheral retina where the density of rods and cones decreases. Cone nuclei are universally situated next to the outer limiting membrane. In mammals, they are usually larger, oval, and more histologically euchromatic (i.e., more lightly staining) than the rod nuclei (Fig. 2.95). Rod nuclei are smaller, round to oval, darker, and more heterochromatic (i.e., more darkly staining).

Additional structures in the outer nuclear layer include rod and cone connecting fibers, rod and cone axons, and Müller cell processes. The rod and cone connecting fibers link the photoreceptor nuclei to their respective inner

Table 2.16 Rows of nuclei in the outer nuclear layer.

		Peripheral retina	
Animal	**Central retina**	**Dorsal**	**Ventral**
Dog	10–15	8–9[a]	8–10[a]
Cat	12–18	8–10[a]	8–10[a]
Horse	4–6	3–4[b]	3[b]
Cow	8–10	3–4[b]	3–4[b]
Pig	5–6	3–4[a]	3–4[a]

[a] Measurements taken 1.0 mm from ora ciliaris retinae.
[b] Measurements taken 2.0 mm from ora ciliaris retinae.

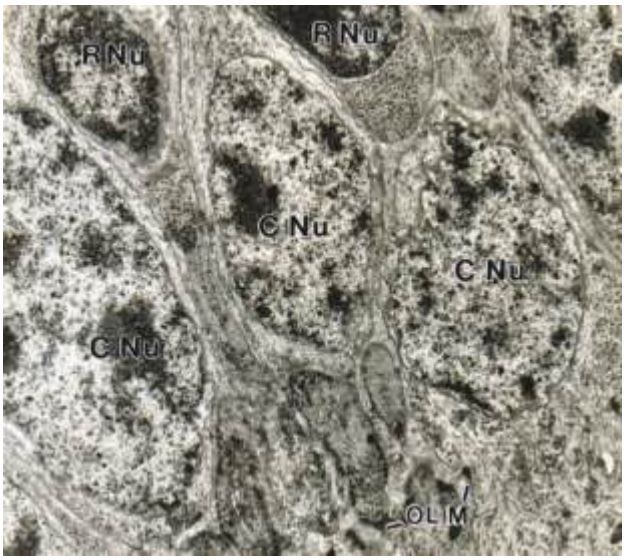


Figure 2.95 Within the outer nuclear layer of a sheep, cone nuclei (CNu) form a single layer next to the outer (i.e., external) limiting membrane (OLM). The rod nuclei (RNu) are typically smaller and more heterochromatic. (Original magnification, 6,500×.)

segments, while the axons of the rod and cone nuclei extend into the outer plexiform layer to synapse with horizontal and bipolar cells.

Outer Plexiform Layer

The axons of the photoreceptors and their synaptic connections are the two components of the outer plexiform layer. The photoreceptors of the outer nuclear layer form connections with the horizontal and bipolar cells of the inner nuclear layer (see Fig. 2.84 and Fig. 2.85). The rod axons typically terminate in pear-shaped spherules, whereas cone axons end in larger, broader pedicles (see Fig. 2.84). The rod spherule has one or more invaginations at which ribbon synapses occur, whereas the cone pedicle has numerous, more shallow invaginations of ribbon synapses (see Fig. 2.84). The cone pedicles usually extend further vitread into the outer plexiform layer (Hogan et al., 1971; Kaas et al., 1972; Rodieck, 1973; Shively et al., 1970).

Two distinct types of synapses occur in the outer plexiform layer, and each is specific to the rod spherule or the cone pedicle. The invagination of each rod spherule synaptic expansion contains two deeply inserted, horizontal cell processes laterally and one or more bipolar cell process centrally (see Fig. 2.84; Fig. 4.22B). Within the presynaptic spherule at the site of synaptic expansion is a dense lamellar structure, the synaptic ribbon, which is oriented perpendicularly and close to the cytoplasmic invaginations (Fig. 2.96). A specific horizontal cell will contact a spherule only once, but each spherule may be contacted by several horizontal cells as well as by the dendritic processes from one to four bipolar cells.

The shallow, broad invaginations of each cone pedicle synaptic expansion contain flat bipolar cell processes. Horizontal cell processes may have conventional synaptic contacts between bipolar cell processes, and they can have both pre- and postsynaptic sites along their length. In the cat, the horizontal cell processes synapse only to cones, and the axon terminal connects exclusively to rods (Kolb, 1974; Kolb & Famiglietti, 1974). Thus, rods and cones are interconnected primarily by horizontal cells. Direct contact through gap junctions (connexin channels) also exists between adjacent cones and between rods and cones (Bloomfield & Völgyi, 2009; Park et al., 1994; Witkovsky, 1992).

Inner Nuclear Layer

The inner nuclear layer is composed of the soma of horizontal, bipolar, amacrine, interplexiform (in some retinas), and Müller cells. The neurons in this layer maintain connections

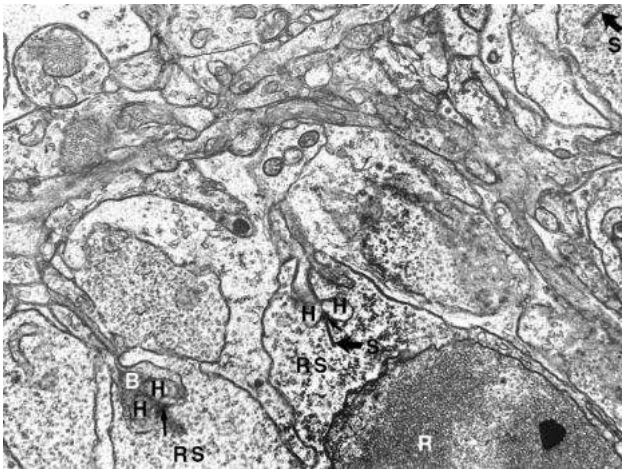


Figure 2.96 Outer plexiform layer of the cat. Synaptic vesicles fill spherules, and the small arrows point to an arciform density. B, bipolar cell process; H, horizontal cell process; R, rod nuclei; RS, rod spherules; S, ribbon synapse in rod spherule with synaptic ribbon. (Original magnification, 22,500×.)

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between the photoreceptor layer and the ganglion cell layer and are involved in modification and integration of the neural responses elicited by the stimuli. Specifically, horizontal and bipolar cells are second-order neurons that connect with photoreceptors (first-order neurons) and ganglion cells (third-order neurons). Amacrine cells are inhibitory cells that interact with bipolar cells and ganglion cells, and Müller cells are the main glial cell of the retina. Little is known about the function of interplexiform cells, but they increase the gain in the photoreceptor-to-bipolar synapses, at least in some species (Jiang et al., 2014).

The horizontal cell nuclei are positioned along the outermost margin of the inner nuclear layer (near the outer plexiform layer), whereas the amacrine cells are positioned along the innermost margin (near the inner plexiform layer) (Fig. 2.97). These two cell types have ramifying branches in their respective plexiform layers and act as integrating units. The bipolar cell nuclei and Müller cell nuclei comprise the intermediate zone of the inner nuclear layer (Hogan et al., 1971; Shively et al., 1970; Sigelman & Ozanics, 1988).

The nuclei of horizontal cells are large, with a single, prominent nucleolus. The cells are also characterized by their wide, horizontally oriented cell processes. There are different kinds of horizontal cells: axonless and those with axons (Boycott et al., 1987; Gallego, 1986; Kolb, 1974; Kolb et al., 1992). They have been studied in several species, including cats, horses (Guo & Sugita, 2002; Macneil et al., 2009; Sandmann et al., 1996b), some even-toed ungulates (Sandmann et al., 1996a), rabbits (Mills & Massey, 1992; Strettoi & Masland, 1995), and tree shrews (Müller & Peichl, 1993).

In horses and related species, type B horizontal cells outnumber type A from 5:1 to 10:1. The type A horizontal cells are unusual among mammals in that they have very large dendritic fields. These dendrites, which are fine and sparsely branched, appear to contact cones selectively, specifically blue cones, which comprise 10%–25% of the cone population. Type B cell densities range between 500 and 900 cells/mm^2 within the visual streak, being greater than 1000 cells/mm^2 in the area centralis at the temporal end of the visual streak. The density of type B cells drops sharply away from the visual streak to between 100 and 300 cells/mm^2. By comparison, type A cell density is between 50 and 100 cells/mm^2 within the visual streak and from 15 to 45 cells/mm^2 peripherally (Sandmann et al., 1996b).

The bipolar cell is the second most numerous neuron in the retina of most domestic animals, and it constitutes the radial connection between the photoreceptors and the ganglion cells. In cone-rich retinas, the numbers of bipolar cells increase remarkably, as do those of amacrine cells. Bipolar cell dendritic processes in the outer plexiform layer synapse with photoreceptors and horizontal cells. Axonal processes then terminate in the inner plexiform layer, synapsing with amacrine and ganglion cells. Among mammalian retinas, the inner nuclear layer houses the somata of a single type of rod bipolar cell and a variety of cone bipolar cell types.

Cone bipolar cells can be divided into many types, consisting of 11 in the cat (Cohen & Sterling, 1990; Kolb & Nelson, 1996). Flat, diffuse bipolar cells synapse with several cones, whereas midget bipolar cells synapse with single cones. All cone bipolar cells can synapse with ganglion cells and amacrine cells in the internal plexiform layer. For the most part, cone bipolar cells have narrow dendritic and

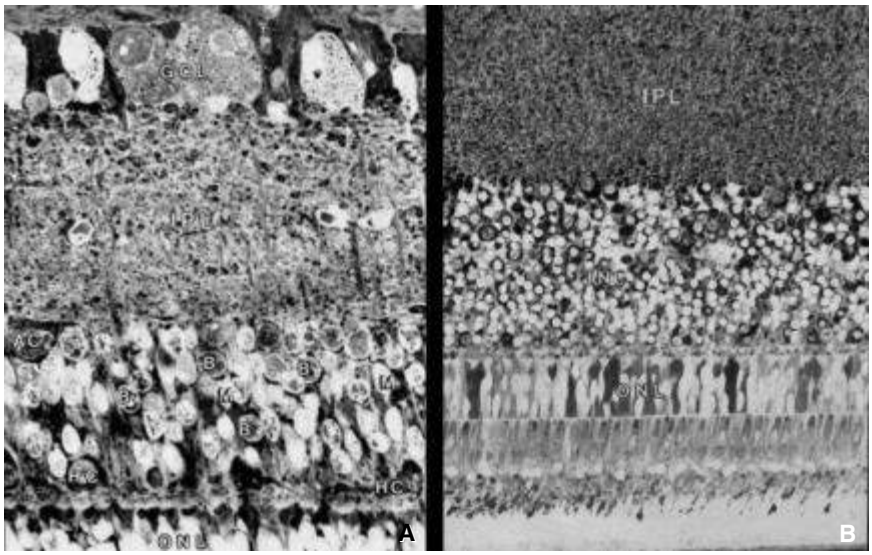


Figure 2.97 Inner nuclear layer (INL) and inner plexiform layer (IPL) of a pig (**A**) and a chicken (**B**). AC, amacrine cell; B, bipolar cell; GCL, ganglion cell layer; HC, horizontal cell; M, Müller cell; ONL, outer nuclear layer. (Original magnification: **A**, 100×; **B**, 200×.)

axonal fields, which would be expected in radial transmission of information for high-spatial resolution.

Amacrine cells do not have recognizable axons, and their processes terminate in the region of the inner plexiform layer (Rodieck, 1973). Ultrastructural studies have demonstrated that these neurons are of the pseudounipolar type, having axons with the characteristic synaptic vesicles but also having features in common with dendrites (Sigelman & Ozanics, 1988). Amacrine cells are located vitread in the inner nuclear layer, and they often have indented euchromatic nuclei. Their cytoplasm is more copious than that of bipolar cells, being filled with polysomes and rough endoplasm reticulum, mitochondria, neurofilaments, and tubules. Collectively, amacrine cells provide horizontal integration in the inner plexiform layer between bipolar cell terminals, ganglion cell dendrites, and other amacrine cells.

Another type of amacrine cell is located in the ganglion cell layer and appropriately named the displaced amacrine cell (Chang & Straznicky, 1992; Vaney et al., 1991). Most amacrine cells of the peripheral cat retina consist of this type (White & Chalupa, 1991).

In addition to the horizontal cell, bipolar cell, and amacrine cell, there is a fourth neuron of the inner nuclear layer, called the interplexiform cell, that is not found in all retinas (Iuvone, 1986; Linberg et al., 1996; Park et al., 1994). This neuron, which is observed in the innermost zone of the inner nuclear layer, has both pre- and postsynaptic processes in the inner plexiform layer and presynaptic connections with horizontal and bipolar cells via a long horizontal process extending to the outer plexiform layer. As a result, it provides a feedback mechanism from the inner retina to the outer synaptic layer (Jiang et al., 2014).

Müller cells (radial glial cells) are the principal nonneuronal cell of the vertebrate retina and serve as support cells for most neurons in the retina. In teleost fish, Müller cells can obtain stem cell characteristics after retinal damage and play an important role in the regeneration of the retina, whereas they can both be protective and harmful to the damaged retina in mammals (Goldman, 2014). They tend to have more cytoplasm and to lie in the outer portion of the inner nuclear layer. Müller cells are elongated, branching cells that extend from the internal limiting membrane to beyond the external limiting membrane. They are important for internal structural support as well as for retinal nutrition. Müller cell fibers fill almost all the extracellular space between neural cells. In both the outer nuclear and ganglion cell layers, Müller cells form close contacts to the neuronal somata, entirely encasing them, compared with the neuronal somata of the inner nuclear layer, which are only partially wrapped (Distler & Dreher, 1996; Robinson et al., 1989). Their nuclei are angular and have denser chromatin than other nuclei in the inner nuclear layer. The vitread ends of the Müller cells possess end feet, which have the ability to phagocytize foreign substances and consequently may play an important role in normal retinal function (Nishizono et al., 1993). The lateral sides of the end feet contain gap junctions, thus allowing these cells to transmit information throughout the retina.

As a cell type within the vertebrate retina, the Müller cell is unique in that it consists of a single morphologic class or type. These cells do vary in length according to the overall thickness of the retina, being shortest peripherally and longest centrally. Müller cells have a neuronal-like distribution with densities highest parafoveally and in the visual streak (Distler & Dreher, 1996; Robinson et al., 1989).

Inner Plexiform Layer

The inner plexiform layer comprises the cell processes of the inner nuclear and ganglion cell layers, at which synapses between bipolar, amacrine, and ganglion cells occur. The bipolar cells synapse in ribbon synapses with two postsynaptic elements, and hence are termed a dyad. The postsynaptic elements of the dyad consist of: (1) a ganglion cell dendrite and an amacrine cell process, or (2) two amacrine cell processes (see Fig. 2.84 and Fig. 2.98).

In addition to the ribbon synapses, abundant conventional synapses are present on amacrine cells. These synapses involve bipolar cells, ganglion cells, and other amacrine cells. Some act as reciprocal synapses back onto a bipolar cell after participating in a dyad synapse (see Fig. 2.98); thus, a single amacrine cell might connect presynaptically and

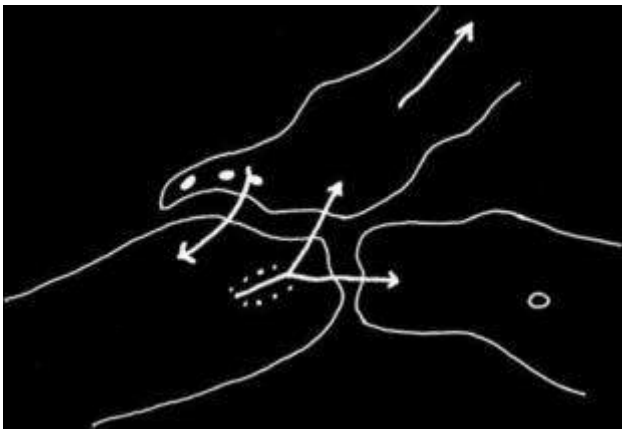


Figure 2.98 The bipolar–amacrine–ganglion cell interaction. The bipolar cell (B) projects onto both the ganglion (G) and the amacrine (A) cells. The amacrine cell controls or adjusts the bipolar cell in a negative feedback arrangement. 1, further interactions; 2, reciprocal inhibition. (*Source:* Redrawn from Records, R.E., et al. (1988) Electrical signals of the retinal microcircuitry and the visual cortex. In: *Biomedical Foundations of Ophthalmology* (eds Duane, T.D. & Jaeger, E.A.), Vol. 2. Philadelphia, PA: J.B. Lippincott.)

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postsynaptically to different areas of the same bipolar cell. In addition, serial synapses between two or more adjacent amacrine cell processes have been observed (Dowling & Werblin, 1971; Kolb, 1997; Masland, 2012).

The bipolar cell axons contain numerous synaptic vesicles and mitochondria. The ganglion cell axons are the only processes in the inner plexiform layer without synaptic vesicles. They are pale, with smooth and rough endoplasmic reticulum, small mitochondria, and microtubules. The amacrine cell processes, which also are pale and possess large mitochondria and synaptic vesicles, are the most numerous because of the extensive arborization of their axons.

Functionally, the outer plexiform layer is organized to enhance static or spatial aspects so as to accentuate contrast in the retinal image. The inner plexiform layer appears to be involved in temporal or dynamic activities, enhancing motion and direction responses (Dowling & Werblin, 1971).

Ganglion Cell Layer

This layer contains different types of ganglion cells, neuroglial cells, and retinal blood vessels. It is the innermost cell layer of the retina and consists of a single layer of cells, except in the area centralis and visual streak, where it can be two or three cell layers thick (see Fig. 2.85 and Fig. 2.97). In primates and various nonmammalian species, the ganglion cell layer can be six to nine cell layers thick.

With measurement of retinal ganglion cell isodensity lines, the location of the visual streak and associated area centralis has been determined in many vertebrate species. The ganglion cell density of those species of greatest veterinary importance are in Table 2.17 (Henderson, 1985; Peichl, 1992; Silveira et al., 1989; Wong, 1989). In most instances, isodensity measurements of the ganglion cells reveal a streak along the horizontal axis that often extends more temporally than nasally. Some variations of the shape and location of the visual streak do occur. In the dog and cat, the visual streak is more concentric than elongated (Gonzalez-Soriano et al., 1995). In the horse, which has a narrow, elongated visual streak, the highest ganglion cell density occurs within its temporal portion, at which optimal resolution is believed to be restricted (Timney & Keil, 1992). In the elephant, in addition to a concentration of ganglion cells along the horizontal plane inferior to the optic disc, is another concentration of ganglion cells in the dorsal temporal retina, which may be an evolutionary adaptation enabling the animal to monitor its trunk (Stone & Halasz, 1989). In sloths, the visual streak is oriented vertically in the ventral temporal retina. The location of the visual streak may be an adaptation allowing the three-toed sloth to rotate uniquely its head 180° while climbing upside down along horizontal branches (Costa et al., 1987). Giraffes, like other artiodactyls, have both a horizontal streak and a temporal area which improve resolution along the horizon and in the frontal visual field, respectively. Giraffes also have a dorsal arch related to their head height that affords enhanced resolution in the inferior visual field. Additionally, the alpha ganglion cell distribution pattern is unique to the giraffe, and it enhances acquisition of motion information for the control of tongue movement during foraging and the detection of predators (Coimbra et al., 2013).

Three basic forms of ganglion cells have been described in the cat, and extensive research has related the morphology of these cells to their neurophysiology (see Chapter 4; Henderson, 1985). Boycott and Wassle described α-, β-, and

Table 2.17 Ganglion cell densities in various species.

Animal	Ganglion cell density (per mm^2)	Total ganglion cells	Reference
Dog	5,300–14,400 (area centralis)	109,000	Gonzalez-Soriano et al., 1995
		115,000	Peichl, 1992
	1,500 (area centralis)	75,000[a]	McGreevy et al., 2004
Cat	9,000–10,000		Hughes, 1975
Horse	6,500 (area centralis)		Hebel, 1976
	3,000 (area centralis)		Evans & McGreevy, 2007
		440,000	Guo & Sugita 2000
Cow	5,000 (area centralis)		Hebel, 1976
	600–2,400 (peripherally)		Hebel & Holländer, 1979
Rabbit	4,700–5,400		Robinson et al., 1989
			Vaney, 1980;
Human	32,000–38,000		Curcio et al., 1990

[a] Only large and medium size cells were counted in this study.

γ-ganglion cells in the retina on the basis of dendritic fields, and these morphologic types correspond with the three physiologic types of ganglion cells (Y, X, and W) (Boycott & Wassle, 1974; Levick, 1975). The size of the dendritic fields for each of the three morphologic types varies with location in the retinal field. All three are represented throughout the retina, including the visual streak and area centralis, but the proportions vary.

Alpha- or Y-cells have rather sparsely branching dendrites and a large perikaryon and are found primarily within the peripheral retina. In the canine retina, the density of the α-cell varies by location, and they comprise between 3% and 14% of the total ganglion cell population in the dog (Peichl, 1992).

Beta or X ganglion cells are smaller than α-cells and have more branches. They are also more numerous than α-cells, being more concentrated within the area centralis and visual streak than peripherally.

Gamma- or W-cells, which have a small perikaryon with a few thin, infrequently branching dendrites, are also numerous and mostly concentrated in the central retina. They are most often directly connected with midget bipolar cells, which synapse solely with cones. These ganglion cells are involved in high-resolution vision and project mostly to the superior colliculus (Stone & Keens, 1980). In the cat, the γ-cells comprise nearly one-half the ganglion cells in most of the nasal retina but only one-third of those in the temporal retina and area centralis (Stein & Berson, 1995).

Ultrastructurally, the types of ganglion cells have not been differentiated. In general, they have abundant cytoplasm containing rough endoplasmic reticulum, ribosomes, a smooth-surfaced endoplasmic reticulum, dense membrane-bound bodies, and mitochondria (Beauchemin, 1974; Hogan et al., 1971; Shively et al., 1970).

Nerve Fiber Layer

Axons of ganglion cells gather in the nerve fiber layer, converging to turn at right angles and course to the posterior pole at which the optic nerve exits the globe. To maintain transparency of the retina, the axons lack myelin sheaths. Some neuroglial cells and the cellular processes of Müller cells are also present among the axons. Large retinal vessels occur in the nerve fiber layer as well as in the ganglion cell and inner plexiform layers.

The nerve fiber layer increases in thickness as it approaches the optic disc. The axons, which do not branch, pass radially to the optic nerve, except in the area centralis, where the concentration of axons arising from this region causes the more peripheral axons to take an altered course around this area to reach the optic disc. Axonal diameters within the optic nerve may be as much as 30% greater than those within the nerve fiber layer (Fitzgibbon & Funke, 1994).

The neurons of the nerve fiber layer are mainly centripetal (i.e., afferent) fibers carrying impulses from the retina to the brain. The axons are of various sizes, and the large axons originate from the large ganglion cells (Y- or a-cells). In some species, centrifugal (i.e., efferent) fibers carrying impulses from the brain to the retina have been described. In birds, the presence of centrifugal fibers is well established, but in other animals, the existence of these fibers is controversial (Brooks et al, 1999; Matsuyama, 1973; Rodieck, 1973).

In addition to Müller cells, glial cells are present in the inner retina, being found in the inner plexiform, ganglion cell, and nerve fiber layers. Astrocytes have long, branching processes found along the retinal blood vessels in vascular retinas, but these cells are not present in avascular retinas. Astrocytes play a supportive role structurally, and perhaps nutritionally, around blood vessels and nerve axons and are the main producers of vascular endothelial growth factor (VEGF) under both normal conditions and in disease (Ozaki et al, 2000; Rodieck, 1973). Furthermore, they are an essential part of the blood–retinal barrier.

Inner Limiting Membrane

The inner limiting membrane is a true basement membrane formed by the fused terminations of Müller cells. Vitreal fibrils insert into the membrane, effectively establishing a 'fusion' between the neurosensory retina and the vitreous body.

Retinal Vasculature

Classically, variations in the retinal vasculature have been categorized into four basic patterns: holangiotic, merangiotic, paurangiotic, and anangiotic. Most mammals possess the holangiotic pattern, in which the majority of the neurosensory retina receives a direct blood supply. The merangiotic pattern consists of blood vessels localized to a region of the retina medial and lateral to the optic disc. Examples of animals with this retinal vascular pattern are lagomorphs (rabbits and pika). In the paurangiotic pattern, blood vessels within the retina occur only circumferentially near the optic disc (peripapillarily). This pattern can be found in certain ungulates, such as horses, elephants, and rhinoceroses, and in some marsupials such as kangaroos. The anangiotic pattern is characterized by an absence of any vasculature within the neurosensory retina, and it occurs in sugar gliders, Guinea pigs, chinchillas, and nonmammalian species such as birds. In general, the retinal arterial supply in domestic animals comes from the short posterior ciliary arteries, which are termed cilioretinal arteries, rather than via a central retinal artery origin as in higher primates, rats, and mice (Henkind, 1966; Matlu & Leopold, 1964; Michaelson, 1954; Prince et al., 1960).

In the holangiotic pattern of the cat, three major pairs of cilioretinal arterioles and venules are present, originating

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around the optic disc margin. They consist of a dorsomedial pair that curves laterally, a ventromedial pair, and a ventrolateral pair. These vessels arc around the area centralis, leaving what appears clinically as a vessel-free zone; however, a capillary network exists in intercommunicating nets within the nerve fiber and inner nuclear layers. Adjacent to arterioles is a 100–200-µm capillary-free zone (Matlu & Leopold, 1964). In the dog, approximately 20 cilioretinal arterioles and three to four major venules radiate from the optic disc. Additional smaller venules join the larger venules on the optic disc and form a very short central retinal vein. The capillary network is extensive and similar to that of the cat in its depth, having a capillary-free zone around arterioles and a capillary network over the area centralis.

Histologically, the larger vessels of holangiotic retinas lie within the nerve fiber, ganglion cell, and inner plexiform layers. Capillaries, however, lie mostly within the inner nuclear layer and, to a lesser extent, within the ganglion cell and nerve fiber layers. Ultrastructurally, one to four endothelial cells line a capillary lumen. A basement membrane covers the endothelium as well as divides the surrounding mural cells (i.e., pericytes) and their processes (Shively et al., 1970). Adjacent endothelial cells are attached by desmosomes and tight junctions (Sigelman & Ozanics, 1988).

Around the optic disc, the paurangiotic retina of the horse contains approximately 30 fine arterioles and 30 venules of approximately 25 and 35 µm diameter, respectively (Michaelson, 1954). Ophthalmoscopically, they cannot be distinguished from each other, and they radiate 360 degrees outward from the disc for 6 mm horizontally and 3–4 mm vertically. The arterioles do not form a capillary network at their terminations; rather, they pass directly into the venules, which have arteriolar annuli at the point of side-arm branching (Michaelson, 1954; Prince et al., 1960).

In the merangiotic rabbit retina, there is a horizontal band of vessels confluent with medullated nerve fibers, emanating medially and laterally from each side of the optic disc. The vessels branch in a side-branch manner rather than dichotomously, which is usually the case in most mammals (Hyvarinen, 1967). Four capillary areas are located within the horizontal band, including superficial net capillaries, deep capillaries of the nerve fiber layer, peripheral capillaries, and peripapillary capillaries.

In the anangiotic avian retina, vasculature is restricted to a structure called the pecten (pecten oculi), which lies vitread to the optic nerve. The pecten is a highly pigmented, pleated structure reminiscent of ciliary processes, and it contains a rich plexus of small blood vessels (Fig. 2.99). The plexus is supplied by tributaries of the ophthalmotemporal artery and lacks any direct connections with the neighboring choroidal circulation (Iskandar et al., 1988). The main function of the pecten is to provide nourishment for the inner retina (Duke-Elder, 1958; Meyer, 1977). When viewed grossly, the pecten can be divided into three types: the pleated type seen in most birds; the conical type found in kiwi; and the vaned type reported in the ostrich (Meyer, 1977; Sillman, 1973). Among the pleated pecten, the number of pleats and the size vary considerably within avian species. The variations appear to be associated with the general activity of the species, including its visual capability. The size of the pecten and

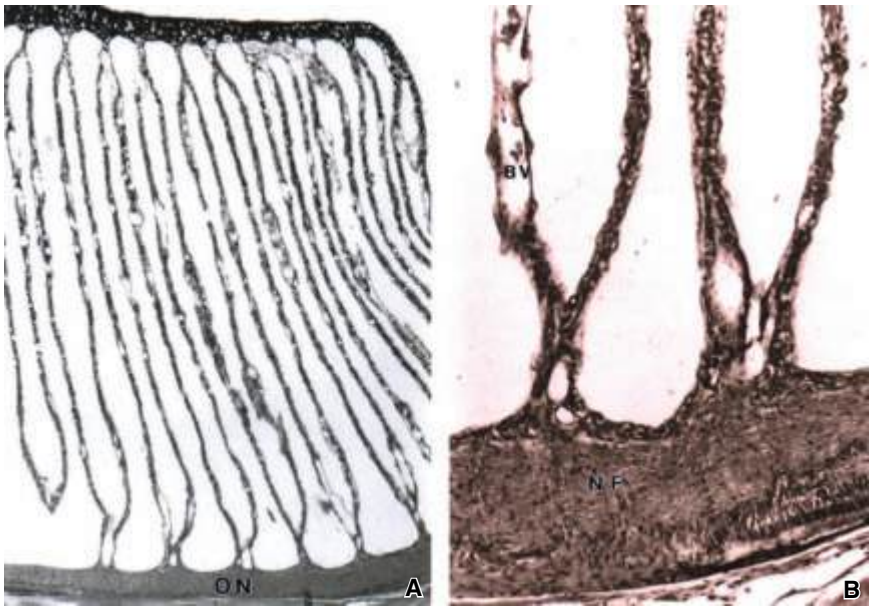


Figure 2.99 **A.** The avian pecten, as seen here in the chicken, consists of a pleated vascular plexus that lies vitread atop the optic nerve head (ON). (Original magnification, 50×.) **B.** Close-up of the base of the pecten as it internally lines the nerve fibers (NF) that form the optic nerve head. BV, blood vessels of the pecten. (Original magnification, 250×.)

its number of folds are indicative of its role in transport of substances to the avascular retina (Braekevelt, 1991, 1994, 1998b).

The amount of pigmentation varies among pecten of different birds, but melanin is especially located along the apical portion, which may protect the blood vessels against exposure to UV light (Kiama et al., 1994). The amount of UV light the retina and pecten receive has not been determined in birds; however, evidence indicates that at least some avian retinas use UV light for visual detection (Bennett & Cuthill, 1994). In addition to providing protection against the damaging influence of UV light, the extensive population of melanocytes may also offer structural support to the pecten (Braekevelt, 1991, 1993d; Smith et al., 1996).

Aging

In aging eyes, the inner limiting membrane becomes thickened and increasingly vacuolated. The inner and outer plexiform layers can have cystoid spaces. The layers of the sensory retina, especially the outer nuclear layer of the peripheral retina, progressively thin (Gao & Hollyfield, 1992). A displacement or migration of photoreceptor nuclei into the photoreceptor layer also occurs with age in humans and rats (Gartner & Henkind, 1981; Lai, 1980). RPE cells decrease in number and, concomitantly, fill with residual bodies, including aging pigment (lipofuscin) (Feeney-Burns et al., 1984; Fite & Bengston, 1989; Gao & Hollyfield, 1992).

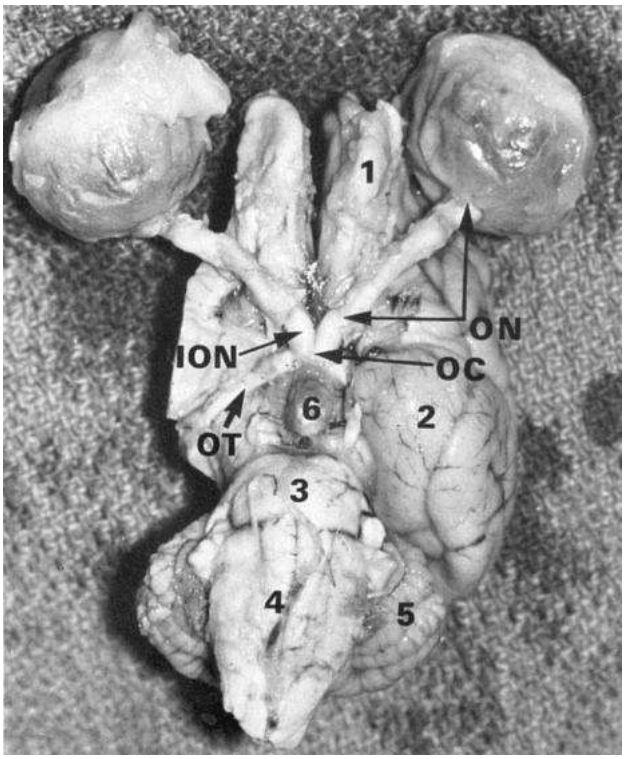


Figure 2.100 Ventral view of the dog brain–eye relationship. The right cerebral hemisphere has been removed; note how physically close the eyes are to the brain. ION, intracranial optic nerve; OC, optic chiasm; ON, orbital optic nerve; OT, optic tracts; 1, olfactory tract; 2, piriform lobe; 3, pons; 4, medulla; 5, cerebellum; 6, pituitary.

Optic Nerve

Retinal ganglion cell axons leave the nerve fiber layer and form the optic disc. From this area, they pass through the choroid and sclera and into the orbit as the optic nerve. In addition to ganglion cell axons, the optic nerve is composed of glial cells and septae, which arise from the pia mater. The visual axons synapse in the lateral geniculate nucleus, whereas the pupillomotor fibers synapse in the nucleus of CN III.

The optic nerve extends from the globe to the optic chiasm, and it consists of four regions: intraocular, intraorbital, intracanalicular, and intracranial (Fig. 2.100; Brooks et al., 1999). Because of similar anatomic properties, the optic nerve is considered to be more of a nerve fiber tract of the brain than a peripheral nerve (Hogan et al., 1971). The intraocular optic nerve consists of retinal, choroidal, and scleral portions.

The terms optic disc, papilla, and optic nerve head are interchangeable and include the retinal and choroidal portions of the optic nerve. Optic papilla refers to an elevation of the nerve head, and its presence and development vary among and within species (Hogan et al., 1971). Within the optic papilla is a central depression called the physiologic cup. The cup is lined by a plaque of astrocytes known as the central supporting tissue meniscus of Kuhnt (Fig. 2.101). An exaggeration of this tissue is Bergmeister's papilla, which is the remnant of the hyaloid artery on the disc's surface.

Converging nerve fibers of the retina cluster into fascicles or bundles as they become lined by glial (fibrous astrocytes) and collagenous (lamina cribrosa) elements. The astrocytes are oriented perpendicularly to the length of the bundle, thus separating the nerve fibers from all non-neuronal components, that is, extracellular fibers of connective tissue, blood vessels, and microglia. Vitread, the astrocytes and associated loose connective tissue form capillary-bearing trabeculae that support the nerve bundles as they turn 90° into the scleral canal from the nerve fiber layer (Fig. 2.102; Hayreh, 1974). This region is referred to as the choroidal or the anterior lamina cribrosa portion of the optic nerve.

Two morphologic types of fibrous astrocytes are present throughout the optic nerve: thin-bodied and thick-bodied (Trivino et al., 1996). Thin-bodied astrocytes are located more anteriorly, both accompanying and contacting axons. Thick-bodied astrocytes are located throughout the optic nerve head and the prelaminar, laminar, and postlaminar regions. Within the posterior prelaminar region, these cells

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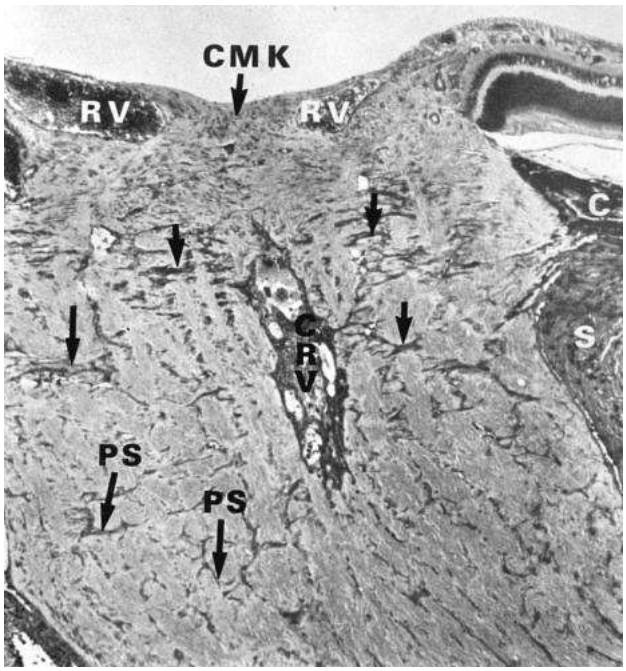


Figure 2.101 The optic nerve head and bulbar optic nerve of a dog. Arrows indicate lamina cribrosa; note the number of astrocytes anterior to it. C, choroid; CMK, central meniscus of Kuhnt (accumulation of astrocytes in physiologic cup); CRV, central retinal vein; RV, retinal veins; S, sclera; PS, pial septa. (Original magnification, 720×.)



Figure 2.102 Trypsin digest of a canine optic nerve shows the network of collagen beams that make up the lamina cribrosa (LC). These beams, which are largely a continuation of the fibrous tunic, are interconnected externally to pial septa (PS). (Original magnification, 25×.) (Courtesy of D.E. Brooks.)

form glial tubes, which guide axons into the lamina cribrosa (Trivino et al., 1996).

Sclerad, the posterior region of the lamina cribrosa consists of meridional extensions of the sclera. In turn, these extensions consist of successive laminar sheets with radially aligned perforations (see Fig. 2.102). Each lamina possesses a capillary in its center. As in the retina, the optic nerve capillaries are nonfenestrated, having tight junctions (i.e., zonula adherens) (Anderson & Baverman, 1976; Brooks et al., 1989). The lamina cribrosa of cats, dogs, horses, squirrels, and monkeys is well developed, having prominent collagenous laminae (Brooks et al., 1989; Tansley, 1956). By comparison, the lamina cribrosa of mice, rats, and rabbits is poorly developed, lacking substantial amounts of collagen within the lamina. Among rodents, the lamina cribrosa in the rat optic nerve is least developed, consisting of only one or two beams of sparse connective tissue (Johanssen, 1987); however, the lamina cribrosa of guinea pigs is considerably more developed, consisting of three or more beams of abundant connective tissue. Of the different types of collagen within the lamina cribrosa, type VI predominates.

The axons within the optic nerve are easily distinguished by their tubular processes, which contain evenly dispersed neurofilaments and neurotubules, and occasional vesicles and mitochondria. The vesicles, mitochondria, lipids, proteins, and other cytoplasmic materials are continuously transported within the axon either toward the synaptic ending (orthograde) or toward the cell body (retrograde), in a movement called axonal flow. Axonal flow within the optic nerve is normally unimpeded throughout the life of the ganglion cell; however, at the lamina cribrosa axonal flow is susceptible to blockage, which usually results from elevated IOP (Samuelson et al., 1983; Williams et al., 1983a). As the IOP rises, the laminar perforations lose their proper alignment, and axonal flow is interrupted (Brooks et al., 1989, 1994; Quigley & Addicks, 1981; Samuelson et al., 1983). Partial constriction of axoplasmic flow, however, has been found at the lamina cribrosa of normotensive eyes among a wide range of mammals, including humans, cats, rabbits, rats, Guinea pigs, sheep, cattle, and pigs (Hollander et al., 1995). This constriction may result from the pressure gradient across the lamina cribrosa and could play a role in normotensive glaucoma. In dogs, each axon is myelinated by oligodendrocytes throughout the entire optic nerve, including the optic disc. In cats, horses, cattle, and humans, myelination begins posterior to the lamina cribrosa and is responsible for the marked increase in optic nerve diameter after exiting the lamina cribrosa (Prince et al., 1960).

The number of optic nerve fibers, their density and size, vary considerably among species (Fig. 2.103; Table 2.18; Ashton, 1960; Beazley & Dunlop, 1983; Brooks et al., 1995a, 1995b; Bruesch & Arey, 1942; Do Nascimento et al., 1991; Fischer & Kirby, 1991; Fitch et al., 1991; Flocks, 1956; Flugel et al., 1991; Fritz, 1906; Fukuda et al., 1982; Geri et al., 1982; Henderson, 1985; Jonas et al., 1990, 1992; Kirby et al., 1982; Krinkle et al., 1985; Levy et al., 1996; Novokhatshii & Reshetniak, 1987; Qijiu et al., 1981; Sanchez et al., 1986; Shen et al., 1985; Silveira et al., 1989; Vaney & Hughes, 1976; Virchow, 1910; Wakakuwa et al., 1987; Williams et al., 1983a). Animals with poorly developed eyes, such as mole

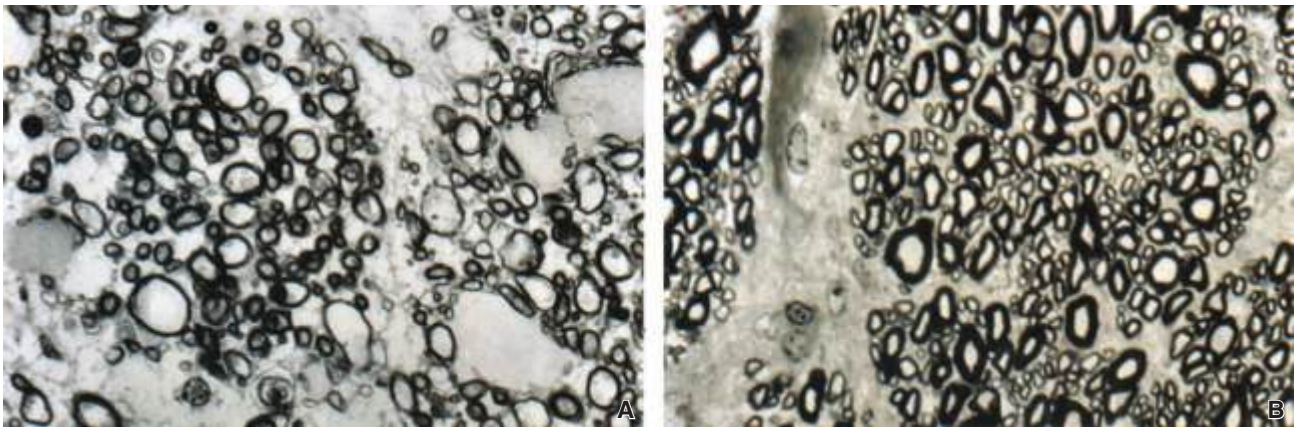


Figure 2.103 Cross-section of the optic nerve in a dog (**A**) and a horse (**B**) posterior to the laminar cribrosa. In both species, the widths of individual nerve fibers vary a great deal within a nerve fiber bundle. The myelin sheaths of the nerve fibers in the horse are generally thicker than those in the dog, reflecting the longer distances they extend in that species. (Original magnification, 1,000×.)

Table 2.18 Axon count and density of the optic nerve.

Animal	Total axon count	Axon density (per mm^2)	Mean fiber diameter (μm)	Reference
Dog	145,000–165,000	~50,000	1.5	Brooks et al., 1995a; Bruesch & Arey, 1942; Krinkle et al., 1985; Novokhatshii & Reshetniak, 1987; Williams et al., 1983b
Cat	193,000	78,000	1.6	Williams et al., 1983b
Horse	1.08 million	62,800	1.9	Brooks et al., 1995b
Rat	102,085	568,000	0.6–0.83	Fukuda et al., 1982
Rabbit	394,000	354, 395	1.0	Vaney & Hughes, 1976
Human	1.1–1.2 million	150,000	~100	Jonas et al., 1990, 1992

rats, contain approximately 900–1800 nerve fibers, whereas those with highly developed eyes, such as various primates, have 100–150 times that number. Interestingly, the size of the eye often does not correlate with the total number of nerve fibers within the optic nerve.

The orbital portion of the optic nerve is covered by the three meningeal sheaths of the central nervous system: the dura mater, the arachnoid sheath, and the pia mater. The outermost sheath is the thick dura mater, which fuses with the sclera anteriorly. Posteriorly, at the optic foramen, it divides into two layers. The outermost of these layers reflects onto orbital periosteum, and the innermost is continuous with the dura of the cranial vault (Fig. 2.104). The collagenous fibers of the dura run longitudinally on the external surface and circumferentially internally. The principal cell type is the fibroblast (Donovan et al., 1974b; Prince et al., 1960). The arachnoid sheath is internal to the dural sheath, and it is composed of collagen trabeculae covered by fibroblastic meningothelial cells. The pia mater is closely apposed to the nerve and sends septa radially into the nerve, thus dividing it into columns (Fig. 2.105). Small blood vessels accompany the pial septae into the optic nerve.

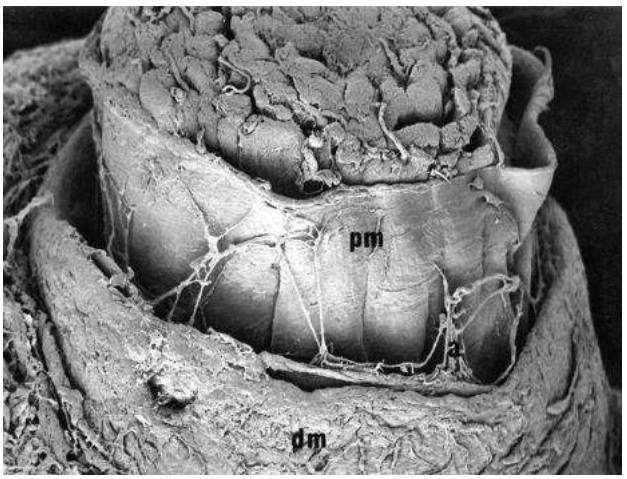


Figure 2.104 SEM shows how the orbital optic nerve is protected by the three meningeal layers, or sheaths, of the central nervous system; the thick dura mater (dm), which is internally lined by the arachnoid and its trabeculae; and the pia mater (pm). (Original magnification, 33×.)

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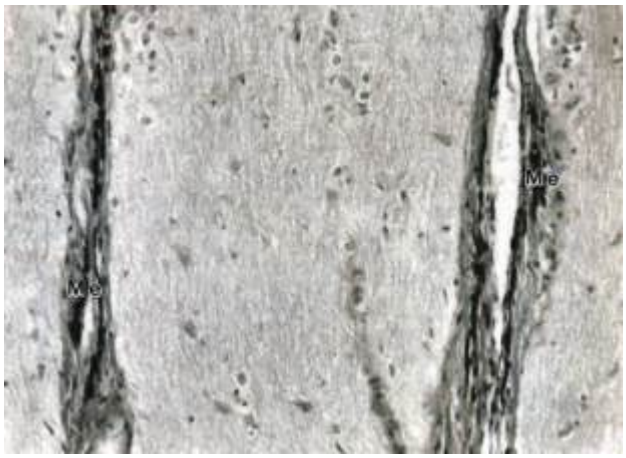


Figure 2.105 Pial septae within the pig orbital optic nerve can contain melanocytes (Me) and separate the nerve fiber bundles into long columns. (Original magnification, 200×.)

Vasculature of the Eye and Orbit

Among domestic animals, the main supply of blood to the eye and orbit is via the internal maxillary artery (a branch of the external carotid artery), which after passing through the alar canal, branches to give rise to the external ophthalmic artery. By comparison, in primates, the entire microcirculation of the eye and most of the orbital circulation is supplied via the internal carotid artery, which gives rise to the internal ophthalmic artery (Prince et al., 1960).

Domestic animals possess both internal and external ophthalmic arteries, but the external ophthalmic artery provides most of the circulation to the eye. Both the long and short posterior ciliary arteries as well as the lacrimal, muscular, and supraorbital arteries derive from the external ophthalmic artery. The internal ophthalmic artery, which is relatively small, provides the blood supply for the optic nerve and anastomoses with the external ophthalmic artery or one of its branches (Fig. 2.106); this anastomosis is especially prominent in the dog.

The blood vessels of the retina and choroid arise from both the long and short posterior ciliary arteries. Domestic animals generally have a number of small arteries entering the retinal layers from around the optic disc; a single central retinal artery does not exist.

In the horse, the choroidal vasculature is fed by short posterior ciliary arteries, which originate from the four posterior ciliary arteries, including the lateral and medial posterior arteries that continue anteriorly. Additionally, choroidoretinal

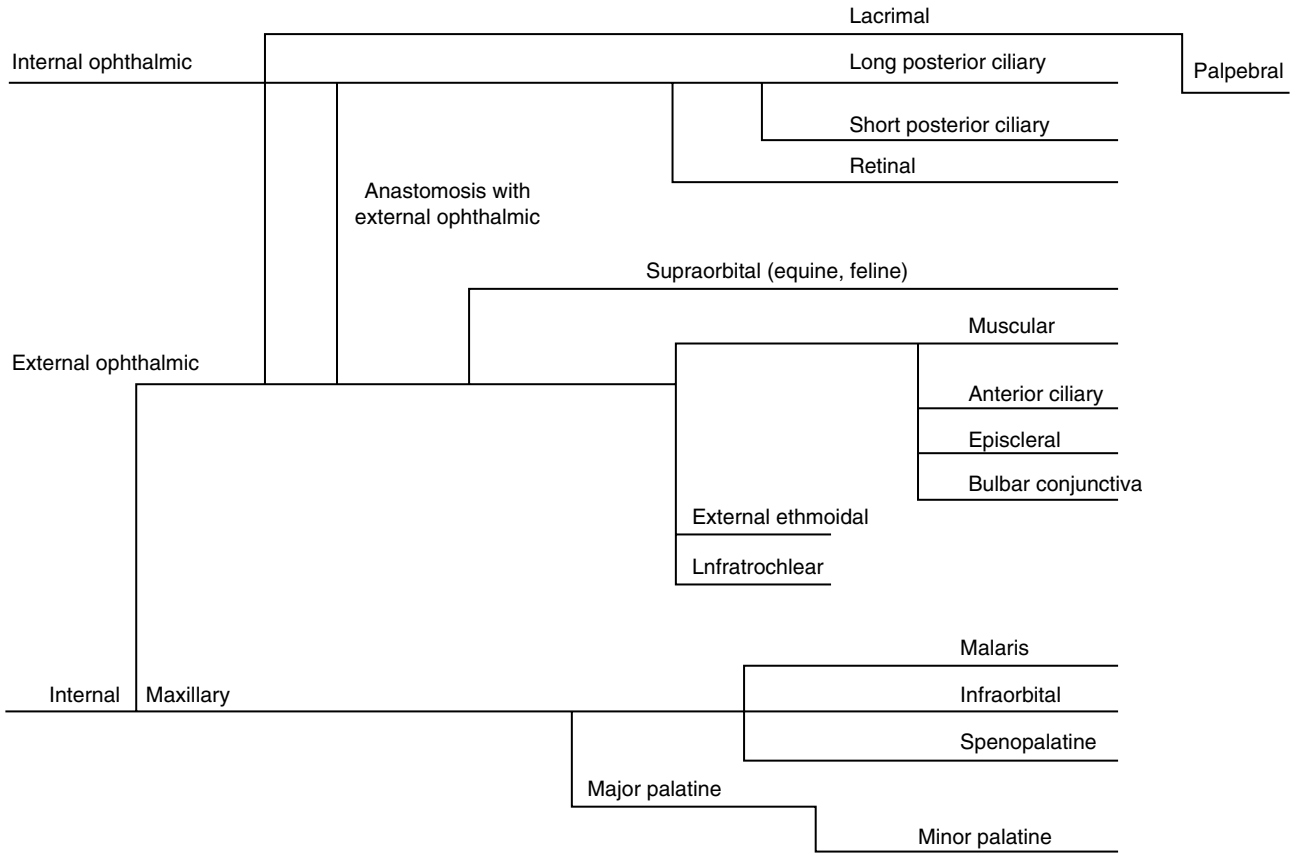


Figure 2.106 Arterial system of the mammalian orbit. Note that variations exist in different animals.

arteries form a network around the optic nerve, giving rise to small retinal arterioles that characterize the paurangiotic fundus of this species as well as giving rise to peridiscal choroidal branches (Simoens et al., 1996).

In small mammals, the arterial supply to the eye is comparable but can be understandably reduced. In the hamster, the primary blood supply for the eye is derived from the long posterior ciliary artery, which initially enters the optic nerve head region and separates into three branches, consisting of the medial and lateral long posterior ciliary arteries and the central retinal artery (Ninomiya & Inomata, 2005). The central retinal artery, in turn, branches into six radiating arterioles, which characterize the holangiotic fundus of this animal.

Venous drainage of the eye varies considerably among domestic animals (Fig. 2.107; Prince et al., 1960). In the dog, the two main venous channels within the orbit are the supraorbital and the inferior orbital veins. The lacrimal, superior vortex, ethmoidal, and several muscular veins empty into a large dilation of the supraorbital vein. The inferior vortex and malaris veins empty into the inferior orbital veins, which anastomose anteriorly and join the supraorbital dilation at the apex of the orbit posteriorly. Two prominent veins drain the supraorbital dilation: the orbital vein, which enters the intracranial system; and an internal maxillary vein, which connects to the external jugular vein (Prince et al., 1960).

The cat has an external rete or vascular network that is more venous than arterial (Prince et al., 1960). The anterior ciliary veins, four vortex veins, and a pair of fine long posterior veins empty into the rete (Tousimis, 1963). The inferior vortex vein and anterior ciliary veins initially join the inferior orbital veins, and the superior vortex vein drains initially into the superior orbital veins. The rete is drained by a large ophthalmic vein, which passes into the external jugular. The supraorbital vein also empties anteriorly into the facial vein via the angular and inferior orbital veins, which eventually empty into the internal jugular vein (Prince et al., 1960).

In the horse, the principal venous channels of the eye consist of the ophthalmic, orbital, supraorbital, and reflex veins. The dorsal ophthalmic vein receives blood from the superior vortex, palpebral, and lacrimal veins (Fig. 2.108). The dorsal ophthalmic vein is joined posteriorly by the anterior ciliary,

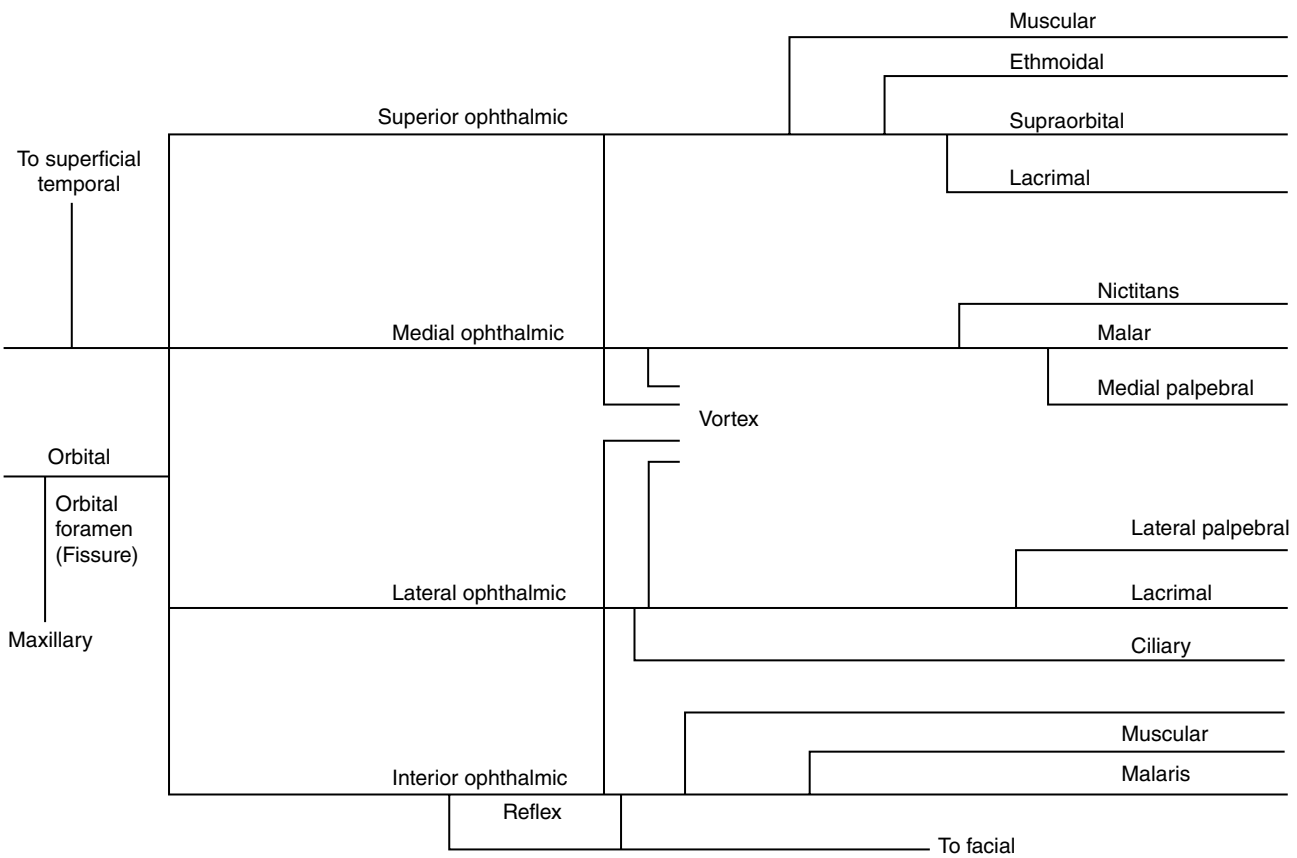


Figure 2.107 Venous system of the mammalian orbit. (*Source:* Modified from Prince, J.H., Diesen, C.D., Eglitis, I. & Ruskell, G.L. (1960) *Anatomy and Histology of the Eye and Orbit in Domestic Animals*. Springfield, IL: Charles C. Thomas. Reproduced with permission of Charles C. Thomas Publisher.)

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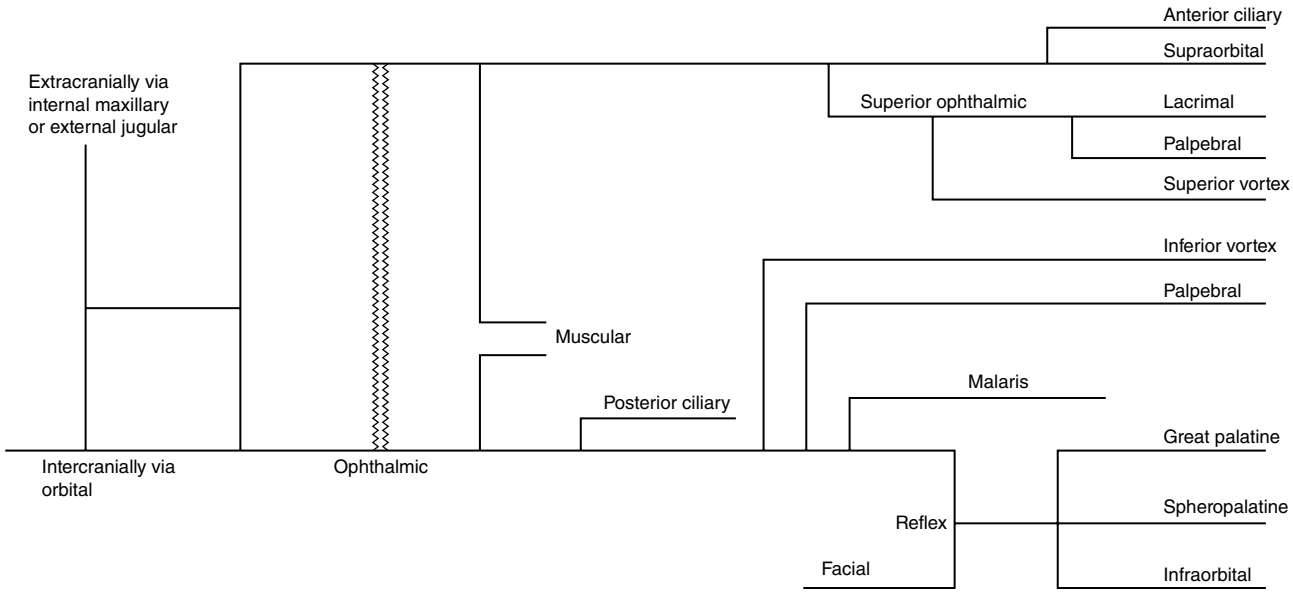


Figure 2.108 Venous system of the equine orbit. (*Source:* Modified from Prince, J.H., Diesen, C.D., Eglitis, I. & Ruskell, G.L. (1960) *Anatomy and Histology of the Eye and Orbit in Domestic Animals*. Springfield, IL: Charles C. Thomas. Reproduced with permission of Charles C. Thomas Publisher.)

supraorbital, muscularis, infratrochlear veins, and ultimately, the ophthalmic vein at the apex of the orbit, at which point blood is then drained intracranially by the orbital vein and extracranially by the internal maxillary vein. The ophthalmic vein also passes anteriorly to become the reflex vein after first receiving the inferior vortex veins via muscular veins, posterior ciliary veins, inferior vortex veins, and palpebral veins (Prince et al., 1960). The reflex vein receives the great palatine, sphenopalatine, and infraorbital veins before joining the facial vein.

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3

Physiology of the Eye

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Functional knowledge of ocular physiology in animal species provides a critical foundation for clinicians practicing comparative and veterinary ophthalmology. Diagnostic procedures, interactions of ocular tissues and drugs, ophthalmic diseases, and surgical procedures require a thorough understanding of the normal physiology as well as the pathophysiology of the eye and its associated structures. This chapter presents the physiology of the eye, especially regarding the adnexa, anterior segment, ocular circulation, aqueous humor dynamics, lens, and vitreous. The optics and physiology of vision are presented in Chapter 4.

The rate at which both relatively simple and complex ocular physiological mechanisms are being studied is incredible. This chapter presents the fundamental physiological phenomena of the eye required by the clinical veterinary ophthalmologist. Other resources should be referenced for the newest and most detailed information and that associated with less commonly seen species.

Anterior Eye Structures

Eyelids

The eyelids of domestic animals are designed to protect the eye, particularly the cornea. All domestic animal species have a superior (upper) and inferior (lower) eyelid; most have a nictitating membrane (NM, third eyelid). The eyelids contain the meibomian glands; these are large sebaceous glands that secrete the outer, oily layer of the precorneal tear film (PTF). The conjunctiva which lines the inside of the eyelids and reflects onto the globe contains goblet cells that contribute the mucin to the PTF; accessory lacrimal glands are also present in some species. The normal blinking of the eyelids maintains the physiologic thickness of the preocular tear film, aids movement of the tears both to and within the nasolacrimal system, and helps eliminate small particles from the corneal and conjunctival surfaces. Reflex closure of the eyelids protects the anterior segment from external trauma.

The eyelids determine the shape and width of the palpebral fissure, along with the associated medial and lateral canthal ligamentous and muscle attachments. For example, a wide, round palpebral fissure is normal among brachycephalic breeds, and a narrow, almond-shaped palpebral fissure is normal among dolichocephalic breeds. The shape of the palpebral fissure also depends on the relationship of the globe to the orbit. A small globe in a deep orbit allows a narrow palpebral fissure; the opposite occurs with a large globe in a shallow orbit. The NM aids in protection of the conjunctiva and cornea by moving, either passively or actively, over the cornea when the globe is retracted. The NM contains one or more important accessory, tear-producing glands that contribute to the aqueous portion of the PTF. The NM also helps to support the position of the lower eyelid through its mass in the ventromedial cul-de-sac, and it forms part of the lacrimal lake in the medial canthus. In all animals, if the globe is retracted by the retractor bulbi muscles or decreases in size, the membrane passively begins to cover the eye.

Eyelid closure is mediated by the efferent fibers of the facial nerve (CN VII) and their effects on the orbicularis oculi muscles. The oculomotor (CN III) innervates the *levator palpebral superioris*, which is responsible for opening the upper eyelid.

Eyelid closure is the end result of three eyelid reflexes, the corneal, palpebral, and dazzle reflexes, and the menace response (Table 3.1). The corneal and palpebral reflexes are primitive reflexes with a purely subcortical course. Both are

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elicited by touch, with the afferent pathway being the ophthalmic branch of the trigeminal nerve (corneal) or the ophthalmic and maxillary branches of the trigeminal nerve (palpebral). The efferent pathway of these two reflexes as well as the menace response is the facial nerve stimulating the orbicularis oculi muscles, resulting in a blink. These reflexes are present immediately following birth or eyelid opening. By contrast, the menace response is cortically mediated and is initiated by a threatening gesture. The visual input results in a blink closure via the facial nerve or globe retraction via the abducens nerve. This response requires integration and interpretation and is a learned response (see Chapter 36).

Blinking and blink rates have been studied in many species under varying circumstances and methodologies, making comparisons and generalized statements difficult (Table 3.2). However, a few generalizations can be made. Blinking does not occur randomly, and blinks are often associated with gaze shifts and saccades. One of the theories for this timing is that blinking temporarily blocks visual information, and blinking during gaze shifts and saccades takes advantage of blocking vision when the images are already degraded from movement (Yorzinski, 2016). Diurnal primates and birds have higher blink rates than nocturnal primates and birds (Kirsten & Kirsten, 1983; Tada et al., 2013). A large comparative study showed that in general, larger mammals and primates blink more often than smaller mammals (Blount, 1927).

Eyelids in the Dog

In dogs, the upper eyelid, which contains the cilia or eyelashes, is more mobile than the lower eyelid. When the eyelids are closed, most of the ambient light is prevented from entering the eyes. Restrained dogs blink 10–20 times/min in comparison to unrestrained dogs (Table 3.2; Gum & MacKay, 2013). Some 50% of dogs' blinks are incomplete (Harmer & Williams, 2003). Puppies normally open their eyelids between 10 and 15 days of age (Glaze, 2011).

Eyelids in the Cat

In cats, both eyelids lack cilia. The eyelids of pigmented cats allow no more than 5% of light at longer wavelengths to be transmitted (Crawford & Marc, 1976). Kittens normally open their eyelids between 10 and 15 days of age; however, both eyes do not always open on the same day (Blakemore & Cummings, 1975).

The NM of the feline species is large and active and may passively or actively cover part of the cornea or be drawn into the medial canthus. It can extend at least two-thirds of the way across the cornea and contains nine smooth muscles which lead to active retraction or protrusion (Nuyttens & Simoens, 1995). The smooth muscle that draws the membrane into the medial canthus is innervated exclusively by postganglionic adrenergic sympathetic nerve fibers, with cell bodies located in the anterior cervical ganglion. Their axons follow the oculomotor nerve. Normally, the NM shows no spontaneous activity, because the smooth muscle lacks tight junctions like that of the visceral smooth muscle. Each muscle cell is innervated by one or more axons, thus confirming that activation of the smooth muscle in the NM is neurogenic and that the myogenic conduction normally found in visceral smooth muscles does not occur (Marshall, 1974). Cats are the only common domestic animal in which sympathetic stimulation will cause the NM to move slightly. The NM permits ~10% of applied light to pass in this species (Crawford & Marc, 1976).

Other Species

Horse

In horses, the cilia are long and numerous on the upper eyelid, except near the medial canthus. While horses blink at 19 blinks/minute, approximately 33% each of the blinks are minimal incomplete, moderate incomplete, or complete, with only 6% of the blinks having a complete squeeze. Lid

Table 3.1 Reflexes involving the blink response.

	Cornea Reflex	Palpebral Reflex	Menace Response[a]	Dazzle Reflex
Stimulus	Corneal touch	Eyelid touch	Menacing gesture	Bright light
Receptors	Somesthetic	Somesthetic	Photoreceptors	Photoreceptors
Afferent pathway	Trigeminal nerve (ophthalmic)	Trigeminal nerve (ophthalmic & maxillary)	Optic nerve	Optic nerve
Interneuron	Subcortical	Subcortical	Cortical, cerebellum	Subcortical
Efferent pathway	Facial nerve	Facial nerve	Facial nerve, VI, IX	Facial nerve
Effectors	Orbicularis oculi muscle	Orbicularis oculi muscle	Orbicularis oculi muscle, retractor bulbi muscle	Orbicularis oculi muscle
Response	Blink	Blink	Blink, retract globe[b]	Blink

[a] If sufficient cortex of one cerebral hemisphere is damaged, the menace reaction cannot be elicited in the contralateral eye of the dog. Pathology of the cerebellar cortex can also affect the menace reaction.
[b] The menace response can also involve turning the head or moving away from the stimulus.

Table 3.2 Blinking rates of domestic animals.

Species	Blinks/Minute	Interblink Period	Concurrent Blinks
Dog	3–5[a]	20–30 seconds[b,c]	85%[a]
Cat	1–5 per 5 min[a]	18.5 seconds[b]	70%[a]
Horse	19[d]		77%[d]
Cattle	5[e]		60%[e]
Pigs	10 [e]		90%[e]

[a] Gum & MacKay (2013).
[b] Blount (1927).
[c] Dogs have partial blinks every few seconds between complete blinks.
[d] Best et al. (2018).
[e] Gum (1991).

closure is approximately twice as rapid as lid opening (Best et al., 2018). Eyelids are open at birth.

Long tactile hairs, or vibrissae, are present on both the dorsal brow and lower eyelid. The vibrissae are long, stout, single shafts of hair that are usually thicker than adjacent skin hair; they may provide additional sensation for the eyelids.

Cattle, Sheep, and Pigs

In cattle, sheep, and pigs, the upper eyelid is the most mobile, and the majority of cilia are present on the upper eyelid. Pigs, rabbits, rodents, and some ruminants have a deeper structure, the Harder's gland or harderian gland, in addition to the superficial gland of the NM. This gland secretes lipids, porphyrins, indoles, and growth factors and is thus also important for lubrication of the eye.

In the pig, the meibomian glands are poorly developed, and the primary eyelid glands are sweat glands. Eyelids are open at birth.

Birds and Reptiles

In birds and certain reptiles, the lower eyelid is larger and more mobile than the upper eyelid. There are no feathers corresponding to eyelashes on the lids. The superciliary line refers to feathers that correspond to the eyebrow and are often different colors than surrounding feathers. The superciliary or supraorbital ridge refers to the unfeathered bony protuberance just dorsal to the orbital rim that is seen in many raptors, such as eagles and hawks. This ridge is thought to provide shade to the eye. Birds blink with both eyelids or the NM alone. In contrast to mammals, the nearly transparent NM of birds is under direct skeletal muscular control. Two muscles extraneous to the lid pull the NM over the entire cornea as many as 15–20 times per minute, even with the other eyelids closed (Gum & MacKay, 2013). Blinks in peacocks are strongly associated with gaze shifts (Yorzinski, 2016). The NM also contains a superficial tear gland, and some species have a deeper harderian gland. Chicks hatch with their eyes open.

Tear Production and Drainage

Both the optical and normal functions of the cornea depend on the integrity of the lacrimal system. The PTF maintains an optically uniform corneal surface by smoothing out minor irregularities, removing foreign matter from the cornea and conjunctiva, lubricating the conjunctiva and cornea, providing nutrients to the avascular cornea, and controlling the local bacterial flora. The PTF also undergoes constant evaporation and formation of transient "dry spots." Hence, the rate of tear evaporation appears to be directly related to the rate of blinking, since the rate of blinking is faster than the development of these dry spots (Milder & Weil, 1983). Actual tear flow rates are difficult to measure in most species; however, in the horse, the tear flow rate was estimated to be 34 µL/min with a tear volume of 234 µL, which indicates a tear volume turnover rate of approximately 7 minutes (Chen & Ward, 2010). By comparison, tear turnover and tear evaporation rates in humans are ~1 ± 0.4 µL/min and 0.14 ± 0.07 µL/min, respectively (Tomlinson et al., 2009).

In all species studied, the PTF can be loosely divided into three layers that intermix (Fig. 3.1). The outer layer (~0.1 µm) is a very thin, oily layer that forms a reversible, noncollapsible, multilayer film with the primary purpose of stabilizing the air–tear interface (Eftimov et al., 2017). The primary constituent of this lipid layer is the meibomian gland secretions (MGS), or meibum, a composite lipid-rich mixture. Up to 22 wt% comprises nonlipid components (proteins, salts, and polysaccharides; McMahon et al., 2013). The main lipid classes found in canine MGS (cMGS) are very long-chain cholesteryl esters, wax esters, (O-acyl)-omega-hydroxy fatty acids (OAHFA), and cholesteryl esters of OAHFA (Butovich et al., 2011). The lipidomes of cMGS and human MGS are

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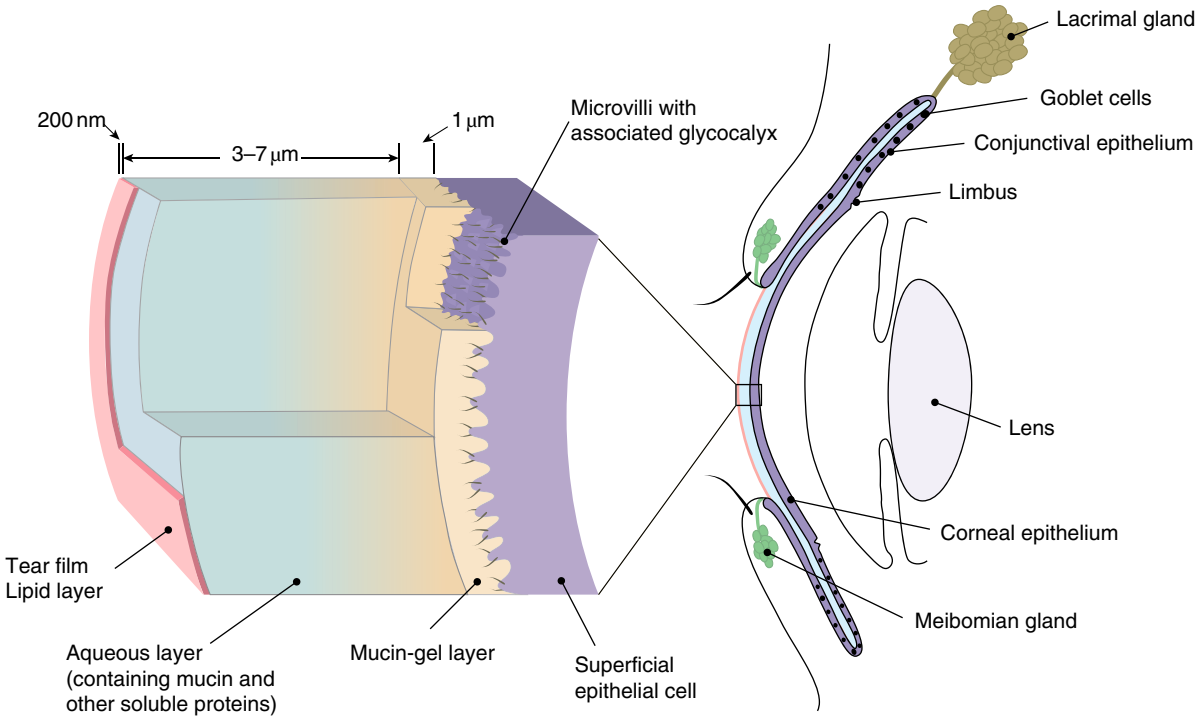


Figure 3.1 The tear film is a complex multilayered fluid phase. This figure represents the classic three-layered model, composed of a mucin-gel layer adjacent to the epithelial surface, an aqueous layer containing mucin, and other soluble proteins and a thin lipid film on the outermost surface. (Reproduced with permission from Yanez-Soto, B., Mannis, M.J., Schwab, I.R., et al. (2014) Interfacial phenomena and the ocular surface. *Ocular Surface*, **12**, 178–201.)

similar, implying similar biosynthetic and biodegradation pathways. However, dogs have a relatively larger proportion of OAHFA than humans, which could be related to a higher tear film stability and lower blink rate in dogs versus humans (Butovich et al., 2011). The same types of molecules are found in the MGS of cattle, rodents, and marsupials (Butovich et al., 2011; Nicolaides & Santos, 1985). This outer lipid layer prevents evaporation of the underlying layers and overflow of tear film onto the eyelids, spreads over the aqueous subphase, imparts stability to the tear film, thickens the aqueous subphase, provides a smooth optical surface for the cornea, constitutes a barrier against foreign particles, provides some antimicrobial activity, and seals the lid margins during prolonged closure. Additionally, it prevents maceration of the lid skin by the tears (Bron et al., 2004).

The lipid layer is produced by sebaceous glands (i.e., tarsal or meibomian glands) of the eyelids. These glands undergo holocrine secretion (release of the entire cell and its contents). Androgens as well as neurotransmitters are likely involved in the regulation of MGS. Androgen receptor mRNA and protein have been isolated from rat, rabbit, and human meibomian acinar epithelial cells. Additionally, the neuropeptides, calcitonin gene-related peptide, substance P, neuropeptide Y, and vasoactive intestinal peptide have been identified in association with meibomian glands in humans and guinea pigs (Davidson & Kuonen, 2004). A lipid layer may not be present in all species, as one was not detected in sea lions (Kelleher Davis et al., 2013).

The middle aqueous layer (~7 µm) is the thickest (>60% of the total tear film thickness) and performs the primary functions of the tear film. This layer is composed of ~98% water and ~2% solids, comprising predominantly proteins. The aqueous layer contains inorganic salts, glucose, urea, proteins, glycoproteins, and soluble mucins (Butovich et al., 2008; Hicks & Carrington, 1997; Hicks et al., 1998). The lacrimal gland, gland of the NM, harderian gland, and accessory lacrimal glands in the conjunctiva all contribute to its formation. Destruction or excision of the lacrimal gland or NM gland results in a variable reduction in aqueous tear production (Gelatt et al., 1975; Helper et al., 1974; McLaughlin et al., 1988; Saito et al., 2001). These studies indicate that approximately two-thirds of the aqueous tear production is produced by the lacrimal gland, approximately one-third by the gland of the third eyelid, and a very minor amount by the accessory lacrimal glands in the conjunctiva; however, there is variability between dogs. The aqueous portion is evaluated clinically primarily through use of the Schirmer tear test (STT), but the phenol red thread test can be used in very small animals.

The deep, or mucin, layer (~1 µm) is composed of tear mucins produced by the apocrine conjunctival goblet cells, as well as an underlying glycocalyx which is associated with the corneal and conjunctival microvilli. The distribution of goblet cells varies among species. The fornix is rich in goblet cells in dogs, cats, and horses (Bourges-Abella et al., 2007; Eördögh et al., 2017; Moore et al., 1987; Sebbag et al., 2016), whereas the highest density in chinchillas and guinea pigs is in the palpebral conjunctiva (Gasser et al., 2011; Voigt et al., 2012). All species have lower concentrations of goblet cells in the bulbar conjunctiva. In rats and mice, the goblet cells occur in clusters, while in rabbits, cats, dogs, and humans, they appear as single cells (Huang et al, 1988). Mucin is produced by goblet cells in response to mechanical, immune, histamine, antigenic, or (direct or indirect) neural stimulation (Davidson & Kuonen, 2004). The gel-forming mucin layer contains glycoproteins (20–40 million daltons and classified as MUC1-21), which are carbohydrate–protein complexes characterized by the presence of hexosamines, hexoses, and sialic acid.

The glycocalyx comprises polysaccharides that are produced by the stratified squamous epithelial cells of the cornea and conjunctiva and project from the surface microvilli of those cells. They are considered membrane-spanning mucins versus secreted mucins that are described above (Dartt, 2011). In dogs, MUC16 is expressed at a higher level than MUC1 and MUC4, whereas rabbits have relatively equal expression of all three mucins. Additionally, the peripheral corneal epithelium has higher MUC1, MUC4, and MUC16 mRNA expression when compared with the central corneal epithelium (Leonard et al., 2016). Roles specific to these membrane-associated mucins include promotion of water retention, provision of a dense barrier to pathogens and debris, participation in signal transduction, and direct interaction with the actin cytoskeleton (Gipson & Argueso, 2003). Mucins from the goblet cells and the corneal epithelial cells both play a critical role in lubricating the corneal surface, thus making its hydrophobic surface more hydrophilic (to permit spreading), and in stabilizing the PTF (Van Haeringen, 1981). The mucin layer as well as the integrity of the outermost layer of corneal epithelium are necessary for retention of the tear film on the cornea (Mishima, 1965).

Tears are a clear and slightly alkaline solution, with a mean pH of 8.3, 8.1, and 7.8 in cattle, dogs, and horses, respectively (Beckwith-Cohen et al., 2014). In humans, horses, cattle, and rabbits, tear electrolyte concentration is similar to that of plasma, except for potassium, which is three to six times more abundant in tears, thus indicating an active transport mechanism (Best et al., 2015; Maidment et al., 1985; Mircheff, 1989). Tear film osmolarity/osmolality is influenced by the rate of tear secretion, evaporation, and composition. It is similar in cats (329 mOsm/L), dogs (356 mOsmol/L), and rabbits (376 mmol/kg; Davis & Townsend, 2011; Korth et al., 2010; Wei et al., 2012), whereas humans (283 mmol/kg) and horses (284 mmol/kg) have a lower osmolarity (Best et al., 2015; Wei et al., 2012). Even though the units are different, osmolarity and osmolality are interchangeable parameters in aqueous solutions such as the tear film.

In human patients, increased osmolarity is correlated with a faster tear film break-up time and greater surface tension. Additionally, hyperosmolarity induces expression and production of inflammatory cytokines and activates several signaling pathways that activate inflammatory cells (Davis & Townsend, 2011). Mean total solids concentration in the PTF of horses, cattle, and dogs is ~2 ± 1.3 g/dL, ~1 ± 0.6 g/dL, and ~0.3 ± 0.2 g/dL, respectively (Beckwith-Cohen et al., 2014). The glucose concentration is lower in human tears than in plasma, but its concentration parallels that in plasma. However, in human patients with diabetes, the elevated glucose concentrations in tears appear to be related to the tissue fluids and are not from the lacrimal gland secretions (Zhang et al., 2011). Normal horses have measurable cortisol in their tears that approximates serum cortisol following adrenocorticotropic hormone (ACTH) stimulation. The results of this study raise the question of whether this cortisol could hinder corneal healing in this species (Monk et al., 2014).

The PTF contains both nonspecific and specific antimicrobial substances. Nonspecific substances include lysozyme, lactoferrin, α-lysine, and complement. Specific antimicrobial substances include secretory immunoglobulins A, G, and M. Toll-like receptors that play a role in the defense against many types of microbial infections are expressed by the corneal and conjunctival epithelial cells in humans and horses (Gornik et al., 2011; Kumar & Yu, 2006). Protein concentrations in canine tears average 0.35 g/dL, with 93% globulin, 4% albumin, and 3% lysozyme, which is a ubiquitous antibacterial enzyme that hydrolyzes bacterial cell walls (Roberts & Erickson, 1962). Lysozyme is produced by the conjunctival goblet cells and has antibacterial and antifungal properties; its concentration increases with conjunctivitis (Roberts & Erickson, 1962). Relative to humans and nonhuman primates, domestic animals have very low amounts of lysozyme (e.g., the horse has one-half to one-fourth that of human tears) and the cat has none (Bonavida et al., 1968; Erickson et al., 1956; Luchter & Gurisatti, 1974; Marts et al., 1977). Lysozyme activity has not been detected in cattle, but it has been detected in sheep and goats (Daubs, 1976). Lactoferrin has been identified in the PTF of humans, dogs, cats, cattle, and other mammals, and reversibly binds the iron that would be available for bacterial metabolism and growth (Holmberg et al., 2004). Immunoglobulin A (IgA) contributes to ocular defenses by coating bacterial and viral microorganisms leading to agglutination, neutralization, and lysis. IgA is present in greater concentrations in the PTF than immunoglobulins G and M (Davidson & Kuonen, 2004). Cat tears have a 6.6 mg/mL total protein concentration with 9.7% IgA (Petznick et al., 2012).

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The lacrimal nerve, a branch of the trigeminal nerve, is primarily sensory but also provides the lacrimal gland with its parasympathetic (release ACh and VIP neurotransmitters) and sympathetic (release norepinephrine and neuropeptide Y neurotransmitters) fibers (Elsby & Wilson, 1967; Powell & Martin, 1989). Both adrenergic and cholinergic distribution patterns around the acini and blood vessels of the canine lacrimal gland are similar; however, the cholinergic fibers appear to be greater in number than the adrenergic fibers (Powell & Martin, 1989). The acinar cells are primarily responsible for secretion of proteins in lacrimal gland fluid. These proteins are synthesized in the endoplasmic reticulum, modified in the Golgi apparatus, and stored in secretory granules. Stimulation of the cholinergic and adrenergic fibers in the lacrimal gland initiates release of these proteins into the lacrimal fluid. This process requires a series of separate cellular pathways that use secondary messengers and is controlled by signal transduction (Dartt, 1989).

Lacrimation is stimulated by painful irritants, eye diseases, mechanical or olfactory stimuli of the nasal mucous membranes, and sinus diseases. Tear production as assessed with the external ocular surfaces anesthetized and the lower conjunctival fornix dried by Dacron swabs (STT II) measures ~50% of that measured without manipulation (STT I) in the cat and dog. Larger dogs also have greater wetting per minute than smaller dogs as measured with the STT I (Berger & King, 1998; Gelatt et al., 1975). Additionally, canine neonates have lower tear production than adults (da Silva et al., 2013; Verboven et al., 2014). In one litter of puppies, both the STT I and STT II increased significantly until 9 and 10 weeks of age, respectively (Verboven et al., 2014). Clinical estimation of the rate of evaporation (and, indirectly, of the mucus component of the PTF) is performed through determining the time (in seconds) for the tear film to break up (Carrington et al., 1987a, 1987b, 1987c). While somewhat subjective, this has been studied in dogs and cats and is covered in Chapter 10.

The nasolacrimal drainage system eliminates used tear film and any excessive tears. The PTF accumulates along the palpebral margin of each eyelid and is forced by blinking to move medially into the lacrimal puncta. When the tears are in the lacrimal pool and the facial muscles relax, the tears flow into the canaliculi by capillary action. Normal breathing movements also facilitate this flow into the canaliculi. Reflex blinking of the eyelids closes the lacrimal sac, which acts as a passive pump. Pseudoperistaltic motion of the nasolacrimal duct allows movement of the tears into the nasal cavity (François & Neetens, 1973). Autoregulation of the lacrimal system with receptors in the excretory portion has been suggested in studies of human tear flow (François & Neetens, 1973). Evaluation of canalicular function in humans suggests that destruction of either canaliculus alone does not affect excretion of tears; in domestic animals, the lower canaliculus is considered to be the more important for tear drainage (Jones et al., 1972).

Cornea

The clear cornea serves as a window for the eye with two critical optical properties, transparency and refractive power, both of which are essential for vision. The cornea, with the sclera, protects the inner components of the eye from injury through its exquisite structure, biomechanics, and sensitivity.

Transparency

The cornea serves as the most powerful refractive structure of the eye. To fulfill this role, it must remain transparent. Corneal clarity is a result of the lattice-like organization of the stromal collagen fibrils as well as the transparency of the cells within the cornea. The state of relative dehydration, hypocellularity, unmyelinated nerve fibers, a nonkeratinized epithelium, and absence of blood vessels and pigment also contribute to corneal transparency. For further details on how the cornea refracts light, see Chapter 4.

The corneal stroma comprises the bulk of the cornea and is responsible for 90% of its thickness. It is predominantly composed of water that is stabilized by an organized network of collagens, glycosaminoglycans (GAGs), and glycoproteins. Cellular and nerve components are also present. Type 1 collagen is the most abundant form in the cornea; it aggregates into structural, banded fibrils with a uniform diameter of 25 nm in the central cornea that gradually increase to 50 nm at the limbus (Meek, 2008; White et al., 1997). Correspondingly, interfibrillar spacing is relatively constant in the central cornea at 20 nm and gradually increases in the paraxial cornea, before rapidly increasing at the limbus (Meek, 2008). The GAGs are important for maintaining this regular spacing between fibrils. The uniform-thickness, small collagen fibrils arrange into parallel lamellae running at oblique angles to each other, and are separated by less than a wavelength of light (Fig. 3.2; Maurice, 1960). This formation results in a highly ordered lattice-like arrangement whereby short-range order results in corneal transparency via destructive interference. However, it lacks the precise arrangement of a true crystalline lattice. The parallel arrangement of the corneal collagen fibers extends from the center of the cornea to its periphery, where the fibrils develop a concentric configuration to form a "weave" at the limbus, which in turn provides strength and helps to maintain its curvature. For further details on the constituents and structure of the cornea, see Chapter 2.

Quiescent keratocytes lie between collagenous lamellae to form a closed, exquisitely structured syncytium (Nishida et al., 1988). These three-dimensional, stellate-shaped cells comprise a cell body with multiple, extensive dendritic processes that interact with other keratocytes. Abundant corneal crystallins (~25–30% of the intracellular soluble protein), such as aldehyde dehydrogenase and transketolase,

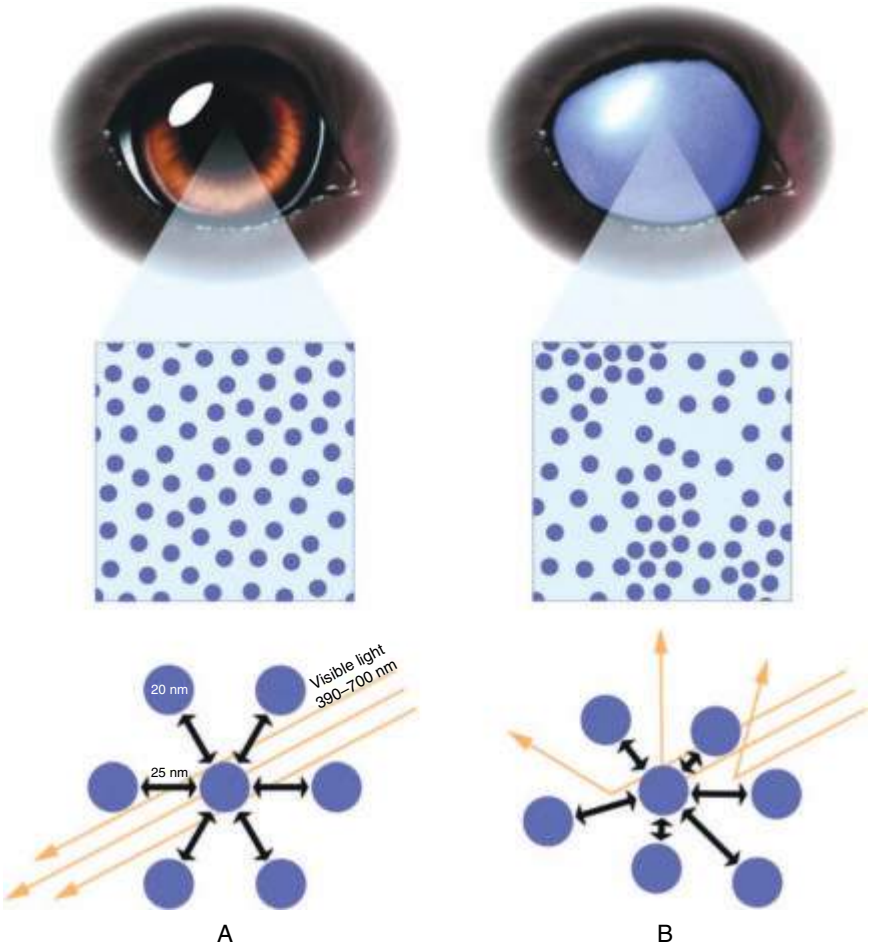


Figure 3.2 In the normal cornea (**A**), a cross-section of the corneal fibrils demonstrates a nearly perfect lattice arrangement, with equidistant collagen fibrils permitting light transmission and concomitant transparency. By contrast, swelling of the cornea with edema (**B**) disrupts this highly ordered arrangement, resulting in light diffraction and an opaque, blue cornea.

minimize refractive differences in the keratocyte cytoplasm, thus ensuring transparency of these cells. Furthermore, the dendritic cellular processes of normal keratocytes demonstrate negligible backscatter of light (Jester et al., 1999). The thinness and even spacing of keratocytes in a clockwise circular arrangement throughout the stroma also minimize light scatter. Upon corneal wounding, transformation of keratocytes to activated fibroblasts and myofibroblasts results in a dramatic increase in cell volume and subsequent dilution of corneal crystallins with a concomitant increase in light scatter (Jester et al., 2012). Corneal scarring is now thought to be due to alterations in the light-scattering properties of keratocytes, in addition to changes to the extracellular matrix (Jester, 2008).

The epithelium and endothelium are responsible for maintaining the cornea in a relatively dehydrated state. Specifically, loss of the corneal epithelium or endothelium results in a 200% or 500% increase in corneal thickness, respectively, due to stromal edema (Maurice & Giardini, 1951). Anatomic integrity of the epithelium and endothelium provides two-way, physical barriers against the influx of tears and aqueous humor (AH), respectively. However, the multiple-layered epithelium provides a relatively impermeable barrier versus the leaky, single-layered endothelium. The endothelium primarily maintains stromal deturgescence via active transport that is energetically maintained by sodium potassium–activated adenosine triphosphatases (Na^+-K^+-ATPases; Dikstein & Maurice, 1972). A summary of the molecular mechanisms that contribute to the corneal endothelial pump was provided by Bonanno (2012).

Metabolism

Steady-state hydration in the cornea occurs when the endothelial leak and pump rates are equivalent; this process is termed the "pump-leak" mechanism (Maurice, 1960). The leaky barrier function of the endothelium may at first seem counterintuitive, but most nutrients for the cornea, except

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oxygen, come from the AH. Thus, leakiness of the endothelium is essential to providing bulk fluid flow through a tissue that lacks blood and lymphatic vessels. Glucose transporters are found on both the apical and basolateral endothelial cell membranes that face the AH and stroma, respectively, to ensure transcellular glucose flux (Kumagai et al., 1994). The corneal epithelium converts glucose to glucose-6-phosphate, where it is subsequently metabolized to pyruvate via glycolysis. Most of this pyruvate is then metabolized into lactate, but some is diverted into the tricarboxylic acid cycle to produce ATP. Glucose is also stored in the epithelium as glycogen, which can be used for energy under stressful conditions such as corneal injury.

The corneal epithelium and keratocytes in the anterior stroma obtain oxygen for aerobic glycolysis from the precorneal tear film, while the endothelium and keratocytes in the posterior stroma receive their oxygen from the AH. Upon eyelid closure, oxygenation of the anterior cornea is achieved by exposure to the palpebral conjunctiva and its vasculature. However, the palpebral conjunctiva has approximately one-third the atmospheric oxygen concentration, resulting in reduced corneal oxygenation (Chhabra et al., 2009). Consequently, the corneal epithelium will rely on anaerobic glycolysis for energetic needs in the absence of oxygen. If excessive lactate is produced by this process, corneal hydration occurs (Forrester et al., 1996; Maurice, 1960). Glucose is also metabolized by the corneal epithelium via the pentose phosphate shunt, which produces nicotinamide-adenine dinucleotide phosphate (NADPH), an important free radical scavenger. Other metabolites from this pathway are ribose-5-phosphate (ribose-P) and reduced triphosphatepyridine nucleotide. Ribose-P is used in nucleic acid synthesis of DNA or RNA, whereas triphosphate-pyridine nucleotide is used by the corneal epithelium for lipid synthesis. Keratocytes primarily metabolize glucose via the pentose phosphate shunt as their metabolic needs are limited, and primarily relate to maintenance of the collagen fibrils and GAGs within the stroma. By contrast, the corneal endothelium has immense glucose needs (~5 times that of the epithelium) to sustain its pump mechanism. It uses similar glycolytic pathways as the epithelium: mainly anaerobic glycolysis, with the pentose phosphate and tricarboxylic acid pathways also making substantial contributions.

Biomechanics

The cornea is a thick-walled, pressurized, partially intertwined, unidirectionally fibril-reinforced laminate biocomposite, which imparts stiffness, strength, and extensibility to withstand both inner and outer forces that may alter its shape or integrity (Dawson et al., 2011; US Department of Defense, 1997; Hayes et al., 2007; Thomasy et al., 2014). A soft, fibrous connective tissue, like the cornea, usually is much stronger in the parallel versus perpendicular direction to the collagen fibrils (Fung, 1981). Consequently, the collagen fibrils are arranged into complex hierarchic structures, which give the cornea its anisotropic mechanical properties (Silver et al., 1992). The collagen lamellar architecture of the cornea varies dramatically between vertebrate species, with nonmammalian vertebrates exhibiting an orthogonal-rotational arrangement with a marked increase in lamellar branching in species such that birds >> reptiles > amphibians > fish; by contrast, the mammalian species exhibit a random pattern (Winkler et al., 2015). In mammals without a Bowman's membrane, the biomechanical behaviors of the cornea from the macro- to nanoscale are primarily due to the collagen architecture in three composite-like regions: anterior stroma, posterior stroma, and Descemet's membrane (Fig 3.3; Boyce et al., 2007; Bron, 2001; Elsheikh et al., 2008; Jue & Maurice, 1986; Meek & Newton, 1999; Winkler et al., 2015).

Tissues are biomechanically characterized by measuring the elastic modulus, a property that defines a material's ability to resist deformation under an applied stress, which approximates its stiffness. The elastic moduli of the layers of the cornea have been reported and the values can differ markedly depending on methods of measurement and/or sample preparation (McKee et al., 2011). In thin, heterogenous tissues such as the cornea, atomic force microscopy (AFM) is optimal for determining the micron-scale deformations that cells and their adjacent matrix experience. The elastic moduli of the corneal layers as measured by AFM have been reported in the human and the rabbit (Table 3.3); all layers of the human cornea were stiffer than those of the rabbit (Last et al., 2009, 2012; Thomasy et al., 2014). The variability in corneal collagen fiber organization and matrix properties observed between species likely contributes to their diverse mechanical properties (Thomasy et al., 2014; Worthington et al., 2014). For more information on corneal biomechanics, we direct the reader to these excellent summaries: Dawson et al. (2011), Kling and Hafezi (2017), Pinero and Alcon (2015), and Ruberti et al. (2011).

Sensitivity and Innervation

The cornea is an exquisitely sensitive tissue, and this sensitivity provides a critical protective function. Upon stimulation of the cornea, involuntary blinking occurs via intermediate relays from the ophthalmic branch of the trigeminal nerve to orbicularis oculi innervation from the facial nerve – a fundamental reaction termed the corneal or blink reflex. Concomitant with the blink reflex is reflex tearing from parasympathetic innervation to the lacrimal gland. During extreme pain, the corneal reflex is exaggerated, and blepharospasm sometimes occurs such that the eyelids cannot be opened voluntarily. Corneal sensitivity varies by species, region of the cornea, and, in the dog and cat, skull conformation (Barrett et al., 1991; Blocker & van der Woerdt,

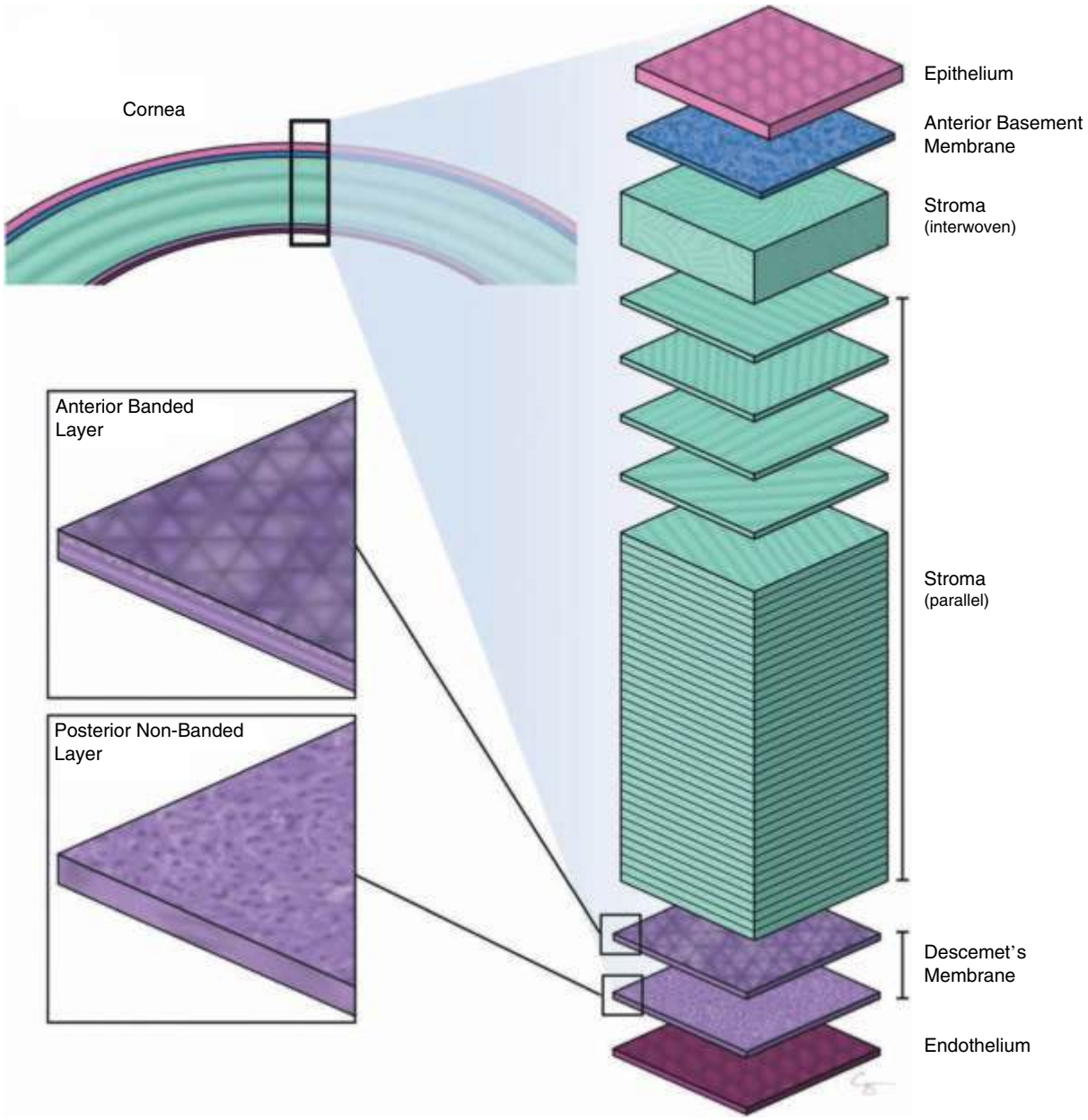


Figure 3.3 Schematic of collagen fiber organization in the canine cornea. The epithelium produces an anterior basement membrane with a complex surface topography consisting of a meshwork of fibers and holes. The anterior 10% of the cornea comprises unidirectional, interwoven collagen lamellae, while the posterior 90% consists of unidirectional, nonwoven collagen lamellae with a random orientation. Descemet's membrane, the specialized basement membrane of the endothelium, can be divided into the anterior banded and posterior non-banded layers. The anterior banded layer is dominated by collagen VIII, which appears as a hexagonal network en face and parallel bands in transverse section. The surface topography posterior non-banded layer has a rich network of intertwined fibers, but with a smaller pore size in comparison to the anterior basement membrane.

2001; Good et al., 2003). For example, corneal sensitivity in dogs, as measured by the Cochet–Bonnet esthesiometer and histology of the corneal nerves, was highest, intermediate, and lowest in the dolichocephalic, mesatocephalic, and brachycephalic skull types, respectively (Barrett et al., 1991). Similarly, the central cornea is less sensitive in brachycephalic cats than Domestic Shorthair (DSH) cats (Blocker & van der Woerdt, 2001). Corneal sensitivity is greatest in the central cornea and lower in the peripheral cornea (Barrett et al., 1991; Good et al., 2003). For more detailed information on corneal esthesiometry, see Chapter 10.

The cornea is one of the most richly innervated tissues in the body. Most corneal nerve fibers are sensory in origin and respond to mechanical, chemical, and thermal stimuli via

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Table 3.3 Elastic moduli of layers of the cornea as determined by atomic force microscopy in rabbits and humans.

	Elastic Modulus (kPa)	
Corneal Layer	**Rabbit (Thomasy et al., 2014)**	**Human (Last et al., 2009, 2012)**
Epithelium	0.6 ± 0.3	Not assessed
Anterior basement membrane	4.5 ± 1.2	7.5 ± 4.2
Bowman's layer	Absent	110 ± 13
Stroma	1.1 ± 0.6 (anterior) 0.4 ± 0.2 (posterior)	33 ± 6 (anterior)
Descemet's membrane	12 ± 7.4	50 ± 18
Endothelium	4.1 ± 1.7	Not assessed

the ophthalmic branch of the trigeminal nerve. However, a small proportion of nerves are sympathetic or parasympathetic in origin and derive from the superior cervical ganglion or ciliary ganglion, respectively. Corneal nerve organization is similar across mammalian species, with only minor interspecies differences. All mammalian corneas contain a dense limbal plexus, multiple radially directed stromal nerve bundles, a dense highly anastomotic subepithelial plexus, and a richly innervated epithelium (Fig. 3.4; Marfurt et al., 2001).

In the dog, corneal innervation arises from the corneal limbal plexus, which comprises a 0.8–1 mm wide, ring-like band, surrounding the peripheral cornea. Morphologically, this plexus can be further subdivided into a predominantly perivascular, outer, periscleral zone and a denser and more highly branched inner, pericorneal zone. From the limbal plexus, nerve fibers enter into the stroma as 14–18 prominent, radially directed, superficial stromal bundles that are

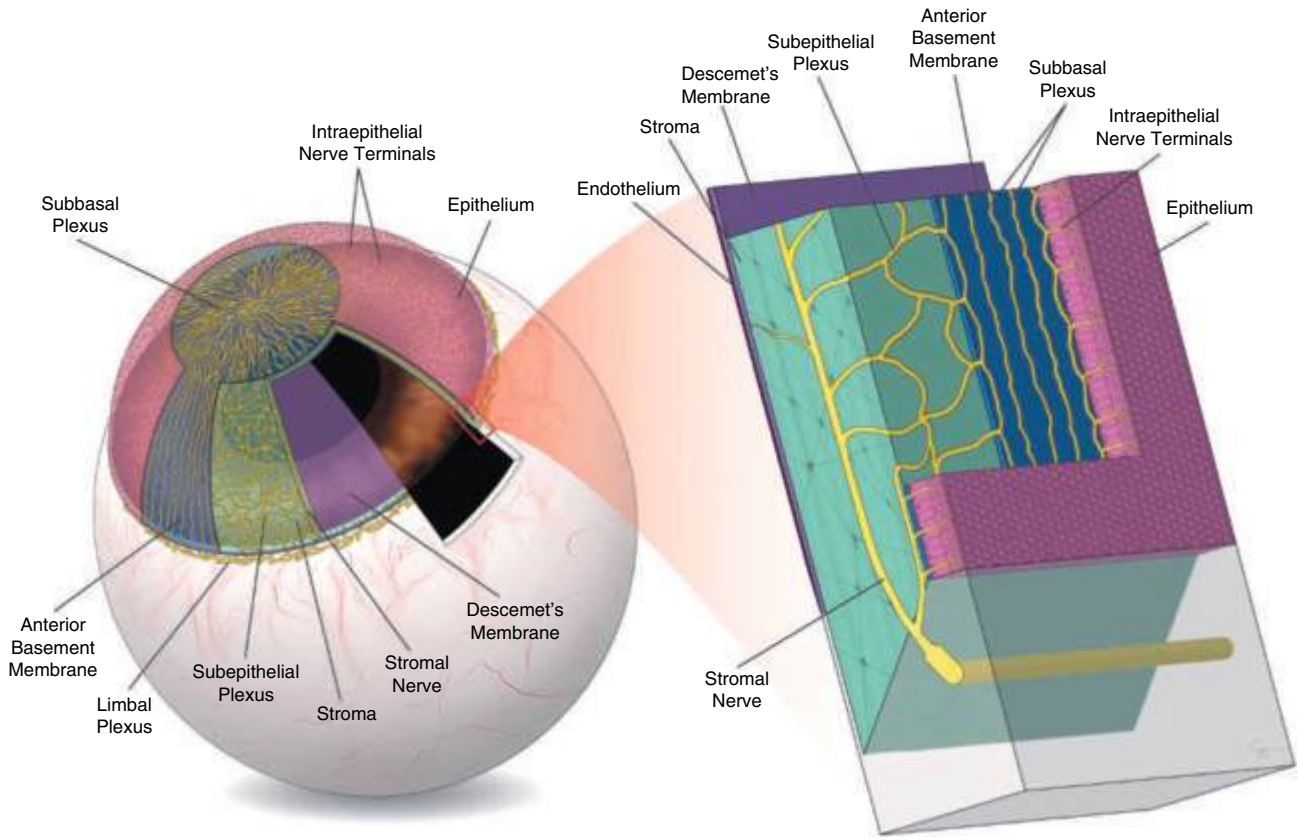


Figure 3.4 Schematic of corneal innervation. The limbal plexus is a ring-like band of predominantly myelinated fibers in the sclera adjacent to the cornea. From the limbal plexus, nerve fibers enter into the corneal stroma as nerve bundles and lose their myelin as they traverse to the central cornea. The subepithelial plexus is a dense, anastomosing network of thin axons immediately underlying the anterior basement membrane. The subepithelial plexus gives rise to the subbasal plexus, a whorl-shaped network of axons between the anterior basement membrane and basal epithelium where nerve fibers run horizontally as long parallel nerves, termed leashes. The axons of the subbasal plexus then vertically ascend to terminate in various layers of the epithelium.

evenly distributed around the limbus (Marfurt et al., 2001). The number of stromal bundles varies among mammals, with 6–8 and ~60 bundles in the rat and human, respectively (Muller et al., 1996; Sasaoka et al., 1984). Any myelinated axons included in stromal nerve bundle will lose their myelin as they traverse toward the central cornea. Each bundle in the canine cornea contains approximately 30 to 40 axons which undergo repetitive dichotomous branching to form complex axonal trees that innervate the anterior cornea (Marfurt et al., 2001). Immediately beneath the anterior basement membrane is a dense, anastomosing network of exceptionally thin, preterminal axons that comprise the subepithelial nerve plexus. The subbasal plexus arises from subepithelial nerve fibers entering the basal epithelium to form unique, preterminal arborizations termed epithelial leashes which exhibit a highly ordered distribution and give rise to a profusion of smaller, ascending branches (Marfurt et al., 2001). The subbasal nerve plexus of dogs, cats, and humans has a centripetal whorl-like pattern, whereas cattle and rabbits exhibit a horizontal pattern that is directed nasally (He et al.,2019; Marfurt et al., 2019). The innervation of the epithelium is denser than any other surface epithelium such that injury to a single epithelial cell may be sufficient to stimulate nociception (Marfurt, 2000). While the anterior cornea is densely innervated, only sparse nerve fibers are present in the posterior cornea and are typically adjacent to the corneal endothelium (Marfurt et al., 2001). Thus, superficial corneal ulcers are typically more painful than deep stromal ulcers.

The majority of sensory fibers that innervate the cornea are activated by a variety of exogenous mechanical, chemical, and thermal stimuli, as well as endogenous factors released by tissue injury, and are thus termed polymodal nociceptors (Belmonte & Giraldez, 1981; Belmonte et al., 1991; Gallar et al., 1993). The remainder of the sensory fibers innervating the cornea comprise mechano-nocireceptors and cold thermal receptors, which are only activated in response to mechanical forces or changes in temperature, respectively (Gallar et al., 1993; Tanelian & Beuerman, 1984). Furthermore, electrophysiologic recordings of impulses from corneal nerve fibers of anesthetized cats demonstrated that different types of stimuli evoked variable responses from the three aforementioned sensory receptors (Acosta et al., 2001).

In addition to their contributions to corneal protection via the blink reflex and reflex tearing, corneal nerves maintain corneal epithelial health through the secretion of trophic factors and maintenance of basal tear secretions (Lawrenson, 1997; Muller et al., 2003). Specifically, corneal nerves secrete a variety of neurotransmitters, including acetylcholine, vasoactive intestinal peptide (VIP), and neurotensin, as well as neuropeptides such as substance P and calcitonin gene-related protein (CGRP), which are critical to corneal epithelial proliferation and function (Belmonte et al., 2004; Muller et al., 2003). Thus, impairment of corneal sensory innervation, termed neurotrophic keratitis, causes decreased corneal healing, increased epithelial permeability, and recurrent corneal ulcers (Beuerman & Schimmelpfennig, 1980; Bonini et al., 2003; Muller et al., 2003; Scott & Bistner, 1973). The neuropeptides CGRP and substance P also act as neurogenic mediators of inflammatory responses by inducing vasodilatation, plasma extravasation, and cytokine release following their release from depolarized nociceptor endings (Bynke et al., 1984; Keen et al., 1982). This neurogenic inflammation impacts both the injured cornea and the noninjured conjunctiva, iris, and ciliary body, as nerve impulses from stimulated nociceptors travel not only centripetally through the axon to the central nervous system, but also to nonstimulated peripheral axon branches of the trigeminal nerve. This reflex is likely responsible for the clinical signs of conjunctival hyperemia and anterior uveitis, including miosis, ocular hypotension, and aqueous flare associated with an isolated corneal lesion (Belmonte et al., 2004).

Iris and Pupil

Pupillary functions include regulating light entering the posterior segment of the eye, increasing the depth of focus for near vision, and minimizing optical aberrations by the lens. The iris muscles consist of both a constrictor (sphincter) that encircles the pupil and radial dilator muscle. The sphincter muscle is an annular band of smooth muscles near the pupillary margin of the iris and is derived from neural ectoderm. The dilator muscle, also derived from neural ectoderm, consists of a series of myoepithelial cells that extend from near the pupillary margin to the base of the iris and are contiguous posteriorly with the pigmented epithelium of the ciliary body. Pupil size varies on the basis of the balance between these two muscle groups. The constrictor muscle, which is the stronger of the two, is innervated by the oculomotor nerve (CN III) which provides primarily parasympathetic control; by contrast, the dilator muscle is innervated primarily by sympathetic nerves. The constrictor muscle causes miosis, and the dilator muscle is responsible for mydriasis. Bright light decreases pupil size. The sympathetic activity in the iridal dilator muscle and ciliary body musculature (discussed later) is mediated by a combination of β-receptors (β_1 and β_2) and α-receptors (α_1 and α_2; Yoshitomi & Ito, 1986). Components of the pupillary light reflex (PLR) are listed in Table 3.4.

Species differences of the α- and β-receptors have been demonstrated among humans, rabbits, nonhuman primates, cats, and dogs, and they are summarized in Table 3.5 (Bartlett & Jaanus, 1989; Colasabti & Trotter, 1981; Jones & Studdert, 1975; Lee & Wang, 1975; Loewy et al., 1973; Macri & Cevario, 1974; Murphy & Howland, 1986; Neufeld & Sears, 1974; Ogidigben & Potter, 1993; Piccone et al., 1988; Potter & Rowland,

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1978; Shields, 1992; Toyoshima et al., 1980; van Alphen et al., 1965; Vareilles et al., 1977b; Wallenstein & Wang, 1979; Yoshitomi & Ito, 1986, 1988; Zimmerman, 1993). These receptors alter the effects of drugs on the eye. For example, feline pupils constrict with the use of timolol, a nonselective β-adrenergic antagonist, because the feline iris sphincter muscle has primarily β-adrenergic nerve fibers (van Alphen et al., 1965). Because β-adrenergic nerve fibers are inhibitory to the sphincter muscle, the miosis in response to topically applied timolol is suspected to be the result of its antagonism of inhibitory input to the sphincter muscle (Kiland et al., 2016). Most synapses in the ciliary ganglion are involved in relaying impulses that result in accommodation; the remainder are concerned with constriction of the pupil. Pure mu opioid agonists such as morphine act on subcortical cells (i.e., oculomotor nuclear complex) to cause constriction of the canine pupil and dilation of the feline pupil because of the release of catecholamines from the adrenal glands (Lee & Wang, 1975; Wallenstein & Wang, 1979). Endogenous prostaglandin F2α appears to be involved in maintaining muscle tone in the sphincter muscle of the iris. Prostaglandins most likely act directly on these muscles, and they appear to act to a lesser extent on the dilator muscles of the canine iris (Yoshitomi & Ito, 1988). Exogenous prostaglandin analogues cause miosis in cats, dogs, and horses, and the receptors have been detected in the iris and ciliary body of several mammals (Bhattacherjee & Paterson, 1994; Bhattacherjee et al., 1997; Gum et al., 1991; Willis et al., 2001). Additionally, biologically active peptides have been isolated in the nerve supply of the intraocular muscles. For example, neuropeptide Y has a modulatory role on the iris dilator muscles that enhances adrenergic-induced contractions. By itself, however, neuropeptide Y does not have any potent contractile qualities (Piccone et al., 1988).

Iridal color and pupil size vary widely among species, and the irides of the young are often a different color than those of the adult. Iris color, or the amount of melanin, influences the effects of many drugs, as melanin can bind drugs, increasing their time to onset and duration (Ogidigben & Potter, 1993).

Pupil shape also varies among species. Vertical pupils are most commonly seen in terrestrial mammals and reptiles that are ambush predators and are diurnal. Prey species tend to have horizontally elongated pupils. These respective variations are thought to keep images on the vertical and horizontal contours sharp. In domesticated cats, the constricted pupil is a vertical slit, whereas in the larger, wild felidae, it is circular. On dilation, the vertical sides of the domestic feline pupil expand to produce a circular pupil. The constrictor muscle fibers are vertically oriented, and therefore contraction leads to a vertically oriented slit pupil. Additionally, in prey with horizontal pupils, changing head pitch causes torsional movement of the eye, such that the pupil's long axis maintains rough alignment with the horizon (Banks et al., 2015).

In young horses, the pupil is more circular than in adults. Under illumination, the ends of the oval pupil of mature horses do not constrict, but the dorsal and ventral borders do. In bright daylight, the superior granula iridica occludes the central papillary opening, resulting in two apertures and assisting with focusing through the creation of Scheiner's disc phenomenon (Murphy & Howland, 1986). With very low illumination or administration of a mydriatic, the dorsal and ventral borders of the pupil dilate, thereby forming a circular pupil. The equine pupil responds relatively slowly to a light stimulus in comparison to that of cats and dogs.

Table 3.4 Components of the pupillary light reflex.

Stimulus	Illumination of the Retina
Receptors	Photoreceptors (rods and cones)
Afferent pathway	Optic nerve–optic tract to pretectal area (ipsi- and contralateral via posterior commissure)
Efferent pathway	Pretectal area to the parasympathetic nucleus of CN III (ipsi- and contralateral), and then parasympathetic fibers to ciliary ganglion (via CN III)
	Postganglionic fibers to the iris
Effector	Sphincter muscle of the iris
Response	Miosis (constriction of the pupil both direct and consensual reflex)

Table 3.5 Adrenergic receptors in the iris and ciliary body.

Species	Iris Sphincter	Iris Dilator	Ciliary Muscles
Human	α and β equally	Mainly α, very few or no β	Mainly β, very few α
Rabbit	Mainly β, few α	Mainly α, few β	Mainly α, few β
Monkey	Mainly α, perhaps β	Mainly α, few β	Only β, no α
Cat	Mainly β, some α	Mainly α, some β	Mainly β, some α
Dog	α and β	α And β	?

The avian pupil is circular and highly motile. The consensual pupillary reflex is usually absent (because of total decussation of nerve fibers at the optic chiasm), but occasionally a strong beam of light may traverse the posterior ocular layers and the thin medial orbital bones to stimulate the opposite retina. As the constrictor and dilator muscles are mainly striated with varying amounts of nonstriated fibers, the pupil is not affected by traditional mydriatic agents, but it can be dilated by various neuromuscular-blocking drugs.

When dogs are under combined injectable and inhalation anesthesia, the pupil reaches a steady baseline size. In this state, light stimulation causes a rapid pupil constriction, an initial redilation phase, and a slower secondary recovery to baseline. As light intensity increases, the amplitude of pupil constriction increases, and the latency decreases. Average constriction velocity and initial redilation velocity increase with increasing stimulus intensities, but then gradually decline with intensities greater than 11 log photons/cm^2/s. Similar to humans, dogs demonstrate intrinsically photosensitive retinal ganglion cells (ipRGC) that contribute to the PLR. Melanopsin, the ipRGC photopigment, has peak sensitivity at 480 nm. The ipRGCs are slow to activate and have a high threshold. Below the ipRGC threshold, PLRs to blue and red stimuli are similar. However, when the ipRGCs are strongly activated with a blue stimulus at 14.5 log photons/cm^2/s intensity, pupil constriction persists for at least 60 seconds after the stimulus is removed. Additionally in dogs, the stimulus intensity required to elicit a threshold PLR is approximately 10-fold lower than that required to elicit a scotopic threshold ERG response in the dark-adapted state (Whiting et al., 2013).

Nutrition of Intraocular Tissues

While allowing light transmission through the eye, nutrients are provided and waste is removed by two systems of blood vessels (i.e., retinal vessels, uveal vessels), the formation and egress of AH, and the vitreous body. Intraocular tissues lack a typical lymphatic system, and the uveal tract (i.e., iris, ciliary body, and choroid) provides this function.

Ocular Circulation

The choroid, ciliary body, and iris are supplied by the uveal vessels. The outer retina in some animals (e.g., dogs, cats, ruminants, and pigs) and almost all or the entire retina in others (e.g., horses, guinea pigs) is nourished by diffusion from the uveal vessels in the choroid. The inner retina is supplied by retinal vessels in many species. Blood vessels supplying the cornea and lens in the embryo regress before birth or shortly thereafter, leaving the AH as the primary source of nutrients for the cornea and lens.

Birds have a unique structure, the *pecten oculi*, which is a heavily pigmented, highly vascularized, and usually fanlike structure projecting from the surface of the optic nerve into the vitreous. A similar structure occurs in reptiles, termed the *conus papillaris*. The avian pecten likely functions as an important source of nutrients for the inner retina (Bellhorn & Bellhorn, 1975; Wingstrand & Munk, 1965). This assumption is based on the observations that the avian retina is thicker than oxygen could perfuse from the choroid and that the pectinate artery resistive and pulsatility indices are low (Chase, 1982; de Moraes et al., 2017; Ferreira et al., 2016). The pecten may also control the intraocular pH, which is affected by acidic retinal waste products (Brach, 1975). Several marine mammals, the bottlenose dolphin (*Tursiops truncatus*), spotted seal (*Phoca largha*), and California sea lion (*Zalophus californianus*), have an ophthalmic rete from which the retinal and choroidal arteries are derived. A higher degree of thermal emission in this area than adjacent areas of the skin suggests that the rete might conserve ocular heat so that photoreceptor and ocular muscle function can be maintained in a cold ambient temperature. Additionally, the rete may have a flow-damping effect by maintaining resistance to blood flow in the orbit (Ninomiya, 2017; Ninomiya et al., 2014).

Ocular Blood Flow

The vascular pressure promoting flow, the resistance of blood vessels, and the viscosity of the blood all influence the blood flow through all tissues, including the eye. The pressure head for blood flow (i.e., perfusion pressure) is the difference in pressure between the arteries and the veins. In the eye, the intraocular pressure (IOP) approximates the venous pressure, so the perfusion pressure is the difference in pressure between the small arteries entering the eye and the IOP (Bill, 1963). Of clinical importance is that the perfusion pressure to the eye is reduced by lowering the blood pressure or raising the IOP, as occurs in glaucoma. Studies of hemodynamics in the rabbit ophthalmic artery demonstrate that autoregulation maintains normal blood velocity and resistance when the IOP is below 40 mmHg. However, at higher pressures the autoregulatory capacity is limited (Yang et al., 2011)

Anterior Uveal Blood Flow

In most species, the major arterial circle of the iris is formed by the nasal and temporal long posterior ciliary arteries. The iris and ciliary body receive approximately 1% and 10%, respectively, of the ocular blood flow (Bill, 1975). In humans and rabbits, additional iridal blood flow occurs from the anterior ciliary arteries via the extraocular muscles (EOM). Blood flow to the ciliary body in most species that have been studied is provided by the iridal major arterial circle,

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branches of the anterior ciliary arteries, and branches of the long posterior ciliary arteries. The cat and monkey iris and ciliary body have autoregulation of their blood flow. Carbon dioxide dilates the anterior uveal vessels, and sympathetic α-adrenergic receptors cause vasoconstriction in the anterior uvea. Parasympathetic muscarinic receptors and prostaglandins, however, cause vasodilation (Alm & Bill, 1972). Prostaglandins E_1 and $F_{2\alpha}$ appear to cause a two- to threefold increase in blood flow to the anterior uvea when applied topically (Green et al., 1985).

Choroidal Blood Flow

The outer retina (and the entire retina in some species) depends on choroidal blood flow for nutrients and waste removal. In the animal species studied, most of the blood supply to the choroid is supplied by the short posterior ciliary arteries, but some of the peripheral choroid receives blood from the major arterial circle of the iris. The choroidal capillaries are fenestrated and large (diameter 15–50 μm). These vessels are highly permeable and permit glucose, proteins, and other substances in the blood to enter the choroid.

Within the choroid, these proteins create a high osmotic pressure gradient that assists in removal of fluids from the retina. The short posterior ciliary arteries appear to supply well-defined territories within the choroid. As a result, these "watershed zones" can develop with marked elevations of IOP, and appear in the dog as pyramidal-shaped areas of choroidal and retinal degeneration extending from the optic nerve head.

The rate of uveal blood flow is rapid (1.2 mL/min in the cat), with a mean combined retinal and choroidal circulation time of 3–4 seconds (Bill, 1962; Freidman & Smith, 1965). In monkeys, 95% of the ocular blood flows through the uveal tract, of which 85% is through the choroid. With this high rate of blood flow, oxygen extraction from each millimeter of blood is low (~5%–10%). The oxygen content of choroidal venous blood is 95% of that in arterial blood. Reduced flow rates result in higher oxygen extraction, so that total extraction is reached. This protects the oxygen supply to the retina, and it also protects the eye from light-generated thermal damage (Bill, 1975). Choroidal vessels have little to no autoregulatory mechanism, but carbon dioxide is a potent vasodilator of choroidal vessels (Kiel & Shepherd, 1992; Mann et al., 1995; Yu et al., 1988). Choroidal vessels are under the strong influence of sympathetic stimulation, which can result in a 60% reduction of choroidal blood flow. Parasympathetic fibers have been found in the choroid of monkeys, but no studies concerning the relationship of these fibers to blood flow have been conducted. The α-adrenergic drugs cause vasoconstriction of choroidal vessels, but β-adrenergic drugs have no effect (Bill, 1975). In rabbits, α- and β-adrenergic blockade causes choroidal vasodilation and vasoconstriction, respectively (Kiel & Shepherd, 1992).

Retinal Blood Flow

The retina receives 4% of the ocular blood flow in the monkey (Bill, 1975). In cats, 20% of the oxygen consumed by the retina is delivered through the retinal circulation and the remaining 80% is via the choroidal circulation (Alm & Bill, 1972). Similar data are not available for other domestic animals.

Blood flow in the innermost retina is practically unaffected by moderate changes in perfusion pressure. Autoregulation of retinal blood flow is extensive in the cat, monkey, and pig, and protects the retinal circulation from large variations in perfusion pressure (Alm & Bill, 1972; Attariwala et al., 1994). Both metabolic and myogenous autoregulation are present in the eye. Metabolic control of retinal blood flow is similar to that of blood flow to the brain. In the brain, increased PO_2 and decreased PCO_2 cause vasoconstriction, and decreased PO_2 and increased PCO_2 cause vasodilation. In the cat, maximum retinal vasodilation occurs with an increased PCO_2 of 75–80 mmHg, so as to increase flow from 15 to 50 mL/min (Alm & Bill, 1972). Interestingly, retinopathy of prematurity occurs when immature eyes with developing blood vessels are exposed to higher oxygen concentrations than the normal physiologic *in utero* hypoxia. The increased oxygen causes vasoconstriction and inhibition of vascular development, with obliteration of vessels. With the hypoxic injury is a concomitant, rebound release of angiogenic factors that lead to pathologic angiogenesis. Signs include vasoproliferation, retinal edema, hemorrhages, and possible retinal detachment (Dogra et al., 2017).

Neural control of retinal blood flow is limited to those vessels indirectly affecting retinal blood flow. Retinal vessels have α-adrenergic-binding sites that, when stimulated, cause vasoconstriction, thus increasing retinal vascular resistance (Forster et al., 1987; Hoste et al., 1989). Retinal arteries most likely autoregulate through a myogenic mechanism, which is activated based on stretch. During sympathetic stimulation, myogenic autoregulatory responses appear to increase (Hoste et al., 1989). Opening and closing of capillary beds in many tissues occur with varying metabolic needs. Spontaneous contractions and dilations of small retinal arterioles have been observed in kittens, but are rare in adult cats (Bill, 1975). In general, it is believed that choroidal blood flow is constant through all capillary beds; however, regional blood flow in the retina decreases from the optic disc to the periphery (Laatikairen, 1976).

The vascular endothelial cells may produce nitric oxide, endothelins, prostaglandins, and renin-angiotensin products in response to chemical stimuli (e.g., acetylcholine, brachykinin), changes in blood pressure and blood vessel wall stress, changes in local oxygen levels, and other stimuli (Brown & Jampol, 1996). As the mechanisms of local autoregulation become better understood, pharmacologic modulation of these processes may become possible.

The theoretical oxygen diffusion maximum of 143 µm plays a significant role in animal species with avascular retinas; as a result, avascular retinas are usually very thin and have short photoreceptors, no tapeta, high glycogen levels in the Müller cells, and no retinal taper (Chase 1982).

Blood Flow of the Optic Nerve Head

Blood flow of the optic nerve head is usually provided primarily by branches from the short posterior ciliary arteries. In humans, cats, and rabbits, optic nerve head blood flow possesses autoregulation over a wide range of IOPs (~30–75 mmHg), but in humans, this autoregulation is most efficient when IOP is 6–30 mmHg (Shonat et al., 1992; Weinstein et al., 1983). Ocular perfusion pressure, the relationship between systemic blood pressure and IOP, determines blood flow in the optic nerve head. The autoregulatory capacity of optic nerve head blood flow is more susceptible to an ocular perfusion pressure decrease induced by lowering the blood pressure, compared with that induced by increasing the intraocular pressure (Wang et al., 2015).

Studies of blood flow in the optic nerve head have been limited by the small tissue mass involved. The optic nerve head is subjected to several different pressures as well as to the tissue stress at the level of the scleral lamina cribrosa. Axons from the retinal ganglion cells exit the eye under the effect of IOP, passing through the lamina scleral cribrosa at progressively decreasing tissue pressures to become the optic nerve. The retrolaminar pressure for these axons in the dog is approximately 7 mmHg and relates directly to the cerebrospinal pressure (Morgan et al., 1995). Both short- and long-term elevations in IOP also produce tissue changes within the lamina cribrosa that influence blood flow and axon vitality.

Ocular Barriers

The blood–ocular barriers contain endothelial and epithelial tight junctions with varying degrees of "leakiness." These barriers prevent nearly all protein movement and are effective against low-molecular-weight solutes such as fluorescein and sucrose. The complexities of these structures differ between the various vascular beds, which allow movement of some substances from one compartment to the other. The two primary barriers within the eye are the blood–aqueous barrier (BAB) and the blood–retinal barrier (BRB). Other lesser barriers of the eye exist as well. The zonula occludens of the corneal epithelium prevents the movement of ions and therefore fluid from the tears into the stroma, prevents some evaporation, and protects the cornea from pathogens. The partial obliteration of the intercellular spaces provided by the macula occludens of the corneal endothelial cells prevents bulk flow of AH into the corneal stroma but allows moderate diffusion of small nutrients and water.

Blood–Aqueous Barrier

The BAB depends primarily on the tight junctions in the nonpigmented ciliary body epithelium, the nonfenestrated iris capillaries, and the posterior iris epithelium. The anterior BAB in the iris allows transcellular transport by means of vesicles. Paracellular transport is controlled by tight junction extensions (Riva et al., 2011). The anterior surface of the iris does not serve as a barrier as it does not have a continuous cellular layer. The epithelial portion of the BAB is the inner, nonpigmented ciliary epithelium, and it controls the flow of fluid into the posterior chamber. The BAB is less effective than the retinal epithelial barrier, because protein can pass into the AH through leakage in other parts of the anterior uvea. Both the ciliary body and choroidal blood vessels are highly fenestrated and thus leak most of their plasma components, including protein, into the stroma.

No barrier is present between the AH and the vitreous humor, which allows the diffusion of solutes from the posterior aqueous into the vitreous humor, or between the anterior uvea and the sclera (Elgin, 1964). Breakdown of the BAB is seen clinically as an aqueous flare in anterior uveitis or secondary to loss of AH, as in anterior chamber paracentesis.

Blood–Retinal Barrier

The tight junctions between the retinal pigmented epithelial cells comprise the epithelial portion of the BRB. The nonfenestrated retinal capillary endothelium with tight junctions between the cells comprises the endothelial portion of the BRB. The most permeable point of the BRB is the optic nerve head, at which substances from the choroid can pass into the nerve (Rodriquez-Peralta, 1975). The choroidal capillaries are highly permeable to permit passage of all low-molecular-weight compounds and proteins. Thus, nutrients from the choroidal blood supply pass readily into the retinal pigment epithelium, where numerous transport systems account for the selectivity of the barrier and elaborate transcellular pathways exist to pass them on into the retina (Mann et al., 2003). This high protein permeability of the choroidal vessels also elevates osmotic pressure, which helps fluid to pass out of the retina. The transport of water from the retina to the choroid is driven by the active transport of chloride to prevent water accumulation in the subretinal space. No significant barrier exists between the vitreous body and the retina.

Aqueous Humor and Intraocular Pressure

In the normal eye, IOP is generated by flow of AH against resistance, and is necessary to maintain the appropriate shape and optical properties of the globe. AH is a clear, colorless liquid that fills the anterior and posterior chambers as well as the pupil. It has a refractive index of 1.335, which

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is slightly denser than water, and is a critical constituent of the eye's optical system. As AH is formed by the ciliary body processes, it enters the posterior chamber and flows through the pupil into the anterior chamber, where it leaves the eye through the corneoscleral trabecular and uveoscleral outflow pathways. The rate of AH formation equals the outflow, so the IOP is maintained relatively constant, and the refractive surfaces of the eye are kept in a normal position.

This continuous flow of AH supplies the avascular cornea and lens with nutrients and also removes their waste products. A convection current exists within the anterior chamber whereby AH circulates downward adjacent to the air-cooled cornea and upward near the lens where the temperature is warmer. This thermal circulation is responsible for the deposition of cellular material – termed keratic precipitates – on the inferior aspect of the corneal endothelium.

Aqueous Humor Formation

The ciliary body has several critical functions, including production of AH by active secretion, ultrafiltration, and diffusion; generation of IOP through the aqueous dynamic process; influencing through its musculature the conventional (i.e., corneoscleral trabecular meshwork or pressure-sensitive) AH outflow; provision of blood and nerve supplies for the anterior segment; control of accommodation via its musculature; formation of the BAB; and provision of the entry for nonconventional (i.e., uveoscleral or pressure-insensitive) AH outflow. Furthermore, the ciliary body is also rich in antioxidant systems, with significant concentrations of catalase, superoxide dismutase, and glutathione peroxidase types I and II. In addition, the ciliary body is the major drug detoxification center in the eye, with its microsomes containing the cytochrome P_{450} proteins, which catalyze many drugs. In avian species, the ciliary body musculature is composed of distinct anterior and posterior components that alter the corneal curvature for corneal accommodation and move the ciliary body anteriorly for lenticular accommodation (Glasser & Howland 1996; Murphy et al., 1995).

The bilayered ciliary epithelium, consisting of the outer pigmented epithelium (PE) and inner nonpigmented epithelium (NPE), is the site for AH secretion. At their apical borders, the PE and NPE connect via gap junctions to form an intricate network (Fig. 3.5). Adjacent NPE cells are joined by tight junctions to form a barrier that inhibits paracellular diffusion. AH is formed by three basic mechanisms: diffusion, ultrafiltration, and active secretion by the NPE. The processes of diffusion and ultrafiltration form the "reservoir" of the plasma ultrafiltrate in the stroma of the ciliary body, from which the AH is derived via active secretion by the ciliary epithelium. Diffusion of solutes, such as carbohydrates, occurs from a region of higher concentration to that of lower concentration. By contrast, ultrafiltration occurs when movement of a compound across a cell membrane is increased by a hydrostatic force; in this case, from differences between ciliary body capillary pressure and IOP. Energy-dependent active transport is required to secrete solutes against a concentration gradient across the basolateral membrane of the NPE; it is the most important factor in AH formation (Cole, 1977; Pederson & Green, 1973). Two enzymes critical in this process, Na^+-K^+-ATPase and carbonic anhydrase (CA), are abundantly present in the NPE. The Na^+-K^+-ATPase is membrane-bound and is found in the highest concentrations along the basolateral interdigitation of these cells (Flugel & Lutjen-Drecoll, 1988). Inhibition of the Na^+-K^+-ATPase with cardiac glycosides (e.g., oubain) or vanadate causes a marked decrease in aqueous formation (Bonting & Becker, 1964; Cole, 1977; Garg & Oppelt, 1970) as differences in osmolarity between plasma and AH are small, thereby making the rate of aqueous production dependent on the rate of solute transfer (Maren, 1995).

Due to the primary active secretion of sodium, other molecules and ions cross over the epithelium by secondary active transport. As a consequence, increased concentrations of ascorbate, amino acids, and chloride are observed in AH relative to plasma in most mammalian species (Bito et al., 1965; Blogg & Coles, 1970; Cole, 1974; Gabelt & Kaufman, 2011; Graymore, 1970; McLaughlin & McLaughlin, 1988; Tulamo et al., 1990). Electroneutrality is maintained by anions accompanying the actively transported sodium; channels allow passage of chloride on the basolateral NPE membrane and a passive transporter exchanges bicarbonate for chloride. As a result, high osmolarity is produced on the basolateral aspect of the NPE, thus initiating diffusion of water out of the cells by aquaporins (Frigeri et al., 1995; Verkman, 2003). To continue the process, sodium and chloride constantly enter the PE via Na^+/H^+ and Cl^-/HCO_3^- antiports and a Na-K-2Cl cotransporter. Chloride is just as critical as sodium in driving AH formation, such that A3 adenosine receptor agonists, which enhance chloride release, increase IOP in mice.

CA is abundant in the cytoplasm and on the basal and lateral membranes of the NPE and PE and catalyzes the following reaction:

$$CO_2 + H_2O \leftrightarrow HCO_3^- + H^+.$$

Formation of bicarbonate by CA is essential for secretion of AH, such that inhibition of CA results in decreased active transport of sodium by the NPE; it is unclear how this process occurs, although several hypotheses exist (Gabelt & Kaufman, 2011). Topical and systemic CA inhibitors substantially decrease AH production, therefore reducing IOP, and are thus useful in the management of glaucoma (Higginbotham, 1989; Maslanka, 2015).

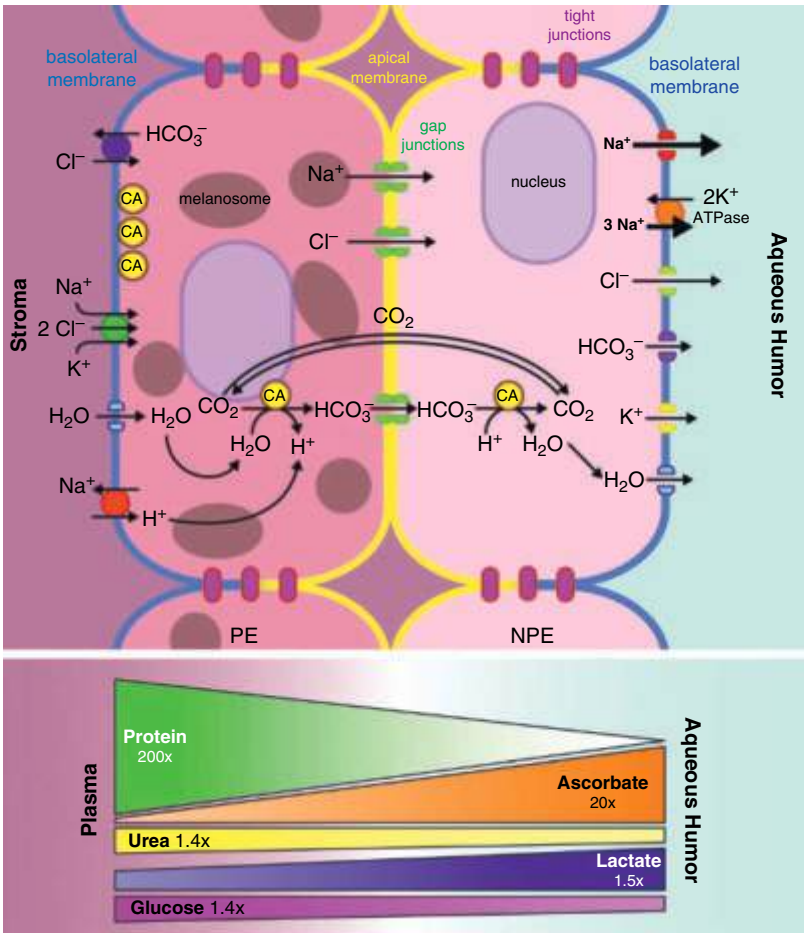


Figure 3.5 Schematic of aqueous humor (AH) production across the pigmented epithelium (PE) and nonpigmented epithelium (NPE) of the ciliary body. Note the position of the critical enzyme, sodium-potassium-activated adenosine triphosphatase (Na^+-K^+-ATPase) on the basolateral enzyme of the NPE. Carbonic anhydrase (CA), also critical to AH formation, is abundant in the cytoplasm of both the NPE and PE. Ion transporters and channels facilitate transfer of Na^+, K^+, chloride (Cl^-) and bicarbonate ($HCO3^-$) into, between, and out of the NPE and PE, while aquaporins enable water movement. Relative solute concentrations that most markedly differ between aqueous humor and plasma can be found at the bottom.

Aqueous Humor Composition

As an ultrafiltrate of plasma, the compositions of AH and plasma are similar, with a few notable exceptions: a low protein concentration, high ascorbate and lactate concentrations, and reduced amounts of urea, glucose, and nonprotein nitrogen occur within AH versus plasma (Fig. 3.5; Blogg & Coles, 1970; Caprioli, 1987; Cole, 1974; Graymore, 1970). Thus, breakdown of the BAB modifies the composition of the AH, primarily by the addition of proteins and prostaglandins, and increases light scattering. The resultant Tyndall effects makes a slit-lamp beam evident within the anterior chamber, an observation clinically known as aqueous flare. With the addition of proteins, the aqueous composition closely approximates that of plasma and is termed *plasmoid aqueous*. Plasmoid aqueous in domestic animals forms fibrin clots easily due to high concentrations of the glycoprotein fibrinogen. Unless treated pharmacologically, these fibrin clots can cause numerous complications, including anterior and/or posterior synechiae or adhesions between the iris and the cornea and/or lens.

Ascorbate concentration in the AH exceeds that in plasma due to an active transport mechanism (Chu & Candia, 1988). This high concentration of ascorbate might assist in protecting the anterior segment structures from oxidative damage induced by ultraviolet radiation. For example, AH ascorbate concentrations are ~35 times greater in diurnal versus nocturnal mammals, suggesting the importance of its role as an antioxidant to prevent photic damage (Koskela et al., 1989). Furthermore, ascorbate is a cofactor in electron transfer reactions, is a reducing agent in hydroxylation reactions, helps regulate production of GAGs in the trabecular meshwork, and might play a role in the storage of iridal catecholamines (Chu & Candia, 1988; DiMattio, 1989).

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In addition to protein and ascorbate, other organic compounds constitute the AH, and their concentrations vary relative to plasma. In most mammalian species, the concentration of amino acids in the AH is higher than that in the plasma, suggesting active transport of amino acids is occurring across the ciliary epithelium (Dickinson et al., 1968; Reddy et al., 1977). In the dog, however, amino acid concentrations are less in AH than in plasma (Bito et al., 1965). In this species, the vitreous may act as a "sink" for some of the amino acids, thus causing the deficiency (Dickinson et al., 1968; Reddy et al., 1977). Carbohydrate concentrations in the AH are ~80% of plasma since they enter by diffusion and are subsequently metabolized by the lens and cornea. Thus, the concentration of diffusible substances in blood can impact its amount in the AH. For example, the concentration of glucose in AH is markedly increased in diabetic patients due to elevated plasma concentrations. Urea concentration in the AH is also ~80% that of plasma. Results of previous studies in the dog have indicated that urea penetrates the BAB very slowly; therefore, a steady concentration as compared to that in plasma is never reached, thus resulting in a lower amount of urea in the AH (Davson & Weld, 1941). By contrast, immunoglobulins, enzymes, and lipids are present in much lower concentrations in AH versus plasma due to the BAB.

The major cations in the AH are sodium, potassium, calcium, and magnesium, with sodium comprising 95% of the total cation concentration. Sodium enters the AH via active transport, with a net flow of water into the posterior chamber. The major anions in AH are chloride, bicarbonate, phosphate, ascorbate, and lactate. The chloride and bicarbonate ions enter with sodium, but their concentrations vary among species. For example, in the horse, the aqueous chloride concentration exceeds that of plasma, whereas the amount of bicarbonate in aqueous is less than that of plasma. By contrast, the bicarbonate concentration is higher and the chloride concentration is lower in the AH of the guinea pig (Davson & Weld, 1941; Davson, 1969). Because the total anion and cation concentrations must equal each other, the combined chloride and bicarbonate concentrations equal the sodium concentration. Lactate is found in much higher concentrations in the AH versus plasma likely due to glycolysis by the lens, cornea, ciliary body, and retina, since it does not appear to accumulate in the posterior chamber (Riley, 1972).

The viscosity, or resistance of fluid to flow, of normal AH varies markedly between species, with raptors, particularly barred owls, having a much more viscous AH than dogs, cats, and horses (Davis et al., 2015). Similarly, teleosts, specifically rainbow trout, are reported to have an AH viscosity that is 10 times greater than that of dogs; this difference is due to a high concentration of hyaluronic acid in rainbow trout versus canine AH (Hoffert & Fromm, 1969).

Aqueous Humor Regulation

The rate of aqueous formation by the ciliary epithelium is influenced by sympathetic and parasympathetic innervation as well as humoral mechanisms to maintain a steady-state IOP. Adrenergic regulation of AH formation is complex and the role of some receptor subtypes remains unclear. The β-adrenergic antagonists, such as timolol, lower IOP by decreasing AH production (Coakes & Brubaker, 1978; Schenker et al., 1981; Yablonski et al., 1978); more information on this important drug class for glaucoma management can be found in Chapters 8 and 20. During sleep, AH formation decreases ~50% via modulation of the β-arrestin/cAMP signaling pathway by β-adrenergic receptors in humans (Brubaker, 1991; Reiss et al., 1984; Sit et al., 2008). Thus, IOP exhibits a circadian rhythm, which varies depending on whether animals are nocturnal or diurnal. For example, diurnal species such as dogs and primates (Gelatt et al., 1981; Komaromy et al., 1998) exhibit the greatest IOP during the day, while in nocturnal species such as cats and rats IOP peaks at night (Del Sole et al., 2007; Moore et al., 1996). Consequently, β-antagonists provide little additional reduction in AH production during sleep and may be less effective at controlling IOP during this time period in glaucomatous patients (Sit et al., 2008). The α-2-adrenergic agonists, including brimonidine, markedly lower IOP in humans by decreasing AH formation, but no change in IOP was observed following topical brimonidine administration to glaucomatous Beagles (Gelatt & MacKay, 2001) or normal horses (Von Zup et al., 2017), suggesting that the effects of this drug class vary by species.

Cholinergic regulation of AH formation and composition are similarly ambiguous. For example, parasympathomimetic nerve stimulation or drugs have been demonstrated to increase, decrease, or not change the rate of AH production; these differences are likely due to species and technique-related effects (Berggren, 1970; Bill, 1967a; Chiou et al., 1980; Green & Padgett, 1979; Macri & Cevario, 1974; Stjernschantz, 1976; Uusitalo, 1972). Cholinergic agents may regulate amino acid transport from the blood to the AH as well as modulate inorganic ion concentrations within the AH (Bito et al., 1965; Walinder, 1966; Walinder & Bill, 1969). In aggregate, these studies suggest that the influence of parasympathetic drugs such as pilocarpine is relatively minor in AH formation, and that their efficacy in decreasing IOP is likely due to increased AH outflow.

Other pharmacologic agents as well as local, systemic, and surgical factors can influence AH formation, as reviewed by Gabelt and Kaufman (2011). Importantly, an increase in IOP causes a reduction in AH inflow due to an alteration in the hydrostatic pressure gradient. However, IOP depends on systemic blood pressure to a small degree. For example, marked hypotension reduces blood flow to the eye and concomitantly lowers IOP (Green, 1984; Macri & Cevario, 1975).

In summary, the regulation of AH formation is complex and is influenced by a multitude of factors.

Aqueous Humor Outflow

AH dynamics involve the balance between production (i.e., active secretion) and outflow via the conventional and nonconventional routes (Fig. 3.6). Conventional outflow consists of AH flow through the corneoscleral trabecular meshwork (TM), while the nonconventional route involves uveoscleral outflow (Cruise & McClure, 1981; Samuelson et al., 1985). Depending on the species, ~50–95% of AH drains through the TM via conventional outflow (Table 3.6).

Structural and Biomechanical Attributes

The TM is a complex, three-dimensional structure comprising cells supported by an intricate extracellular matrix (ECM). The TM can be divided into three portions: uveal, the innermost portion; corneoscleral, the middle region; and the juxtacanalicular zone, the outermost section nearest the sclera. The pore size of each TM zone decreases from inward to outward, with the juxtacanalicular zone consisting of several endothelial cell layers that produce a matrix comprising GAGs, collagen, fibronectin, and other glycoproteins in which these cells are embedded. Thus, the juxtacanalicular zone, which is immediately adjacent to Schlemm's canal in primates or the angular aqueous plexus (AAP) in most

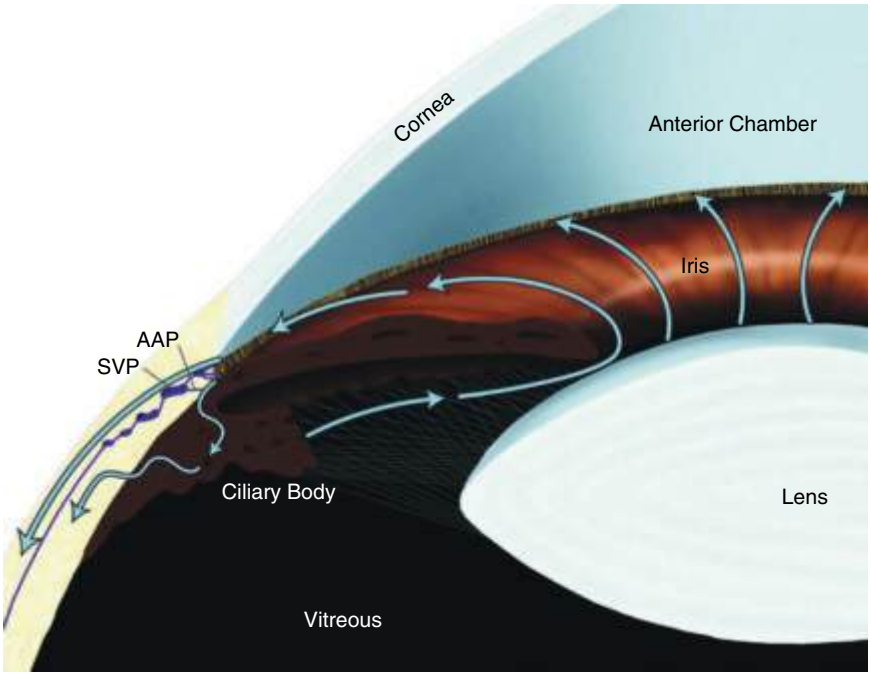


Figure 3.6 Aqueous humor (AH) drainage occurs via the traditional and uveoscleral outflow pathways in the iridocorneal angle of the dog. The ciliary body epithelium produces AH, which flows from the posterior chamber, through the pupil, and into the anterior chamber. Then, AH drains through the pectinate ligament to enter the trabecular meshwork. In the traditional outflow pathway, AH enters the angular aqueous plexus (AAP) to drain anteriorly to the episcleral and conjunctival veins or posteriorly into the scleral venous plexus (SVP) and vortex veins. With uveoscleral outflow, AH flows through the ciliary muscle interstitium to the supraciliary and suprachoroidal spaces to diffuse out the sclera.

Table 3.6 Estimates of aqueous humor dynamics in selected species.

	Dog	Cat	Rabbit	Cow	Horse	Nonhuman Primate
Estimated normal IOP (mmHg)	15–18	17–19	15–20	20–30	17–28	13–15
"C" outflow (μL/mmHg/min by tonography)	0.24–0.30	0.27–0.32	0.22–0.28	—	0.90	0.24–0.28
Uveoscleral outflow (μL/min)	15%	3%	13%	—	—	30%–65%
Episcleral venous pressure (mmHg)	10–12	8	9	—	—	10–11
Aqueous formation (μL/min)	5.22	6.00–7.00	1.84	—	—	2.75

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domestic animals, is thought to be the major site of aqueous outflow resistance.

Other studies suggest that the main site of resistance to outflow is the endothelial lining of the AAP and its ECM (Samuelson & Gelatt, 1984a, 1984b; Tripathi & Tripathi, 1972). However, the site of filtration may be different from the site of flow resistance (Johnson et al., 1990). AH transport through the endothelium of the AAP (or Schlemm's canal in nonhuman primates and domestic chickens) is thought to occur via transcellular pores, large vacuoles, or pinocytotic vesicles. However, paracellular routes between the endothelial cells of Schlemm's canal have also been proposed and may be pressure sensitive, particularly at higher IOPs (Epstein & Rohen, 1991; Sabanay et al., 2000; Ye et al., 1997). Nevertheless, disputes regarding juxtacanalicular versus inner wall resistance and transcellular versus paracellular transport are unlikely to translate to major differences in therapeutic approaches from a clinical perspective.

Excessive deposition of ECM and concomitant stiffening of the TM are critical to the pathogenesis of primary open angle glaucoma (POAG) in humans (Chatterjee et al., 2014; Last et al., 2011) and likely dogs with the *ADAMTS10* mutation (Ahonen et al., 2014; Boote et al., 2016; Kuchtey et al., 2011, 2013; Palko et al., 2013, 2016). Thus, phagocytic activity of TM cells and macrophages is important in ECM remodeling and removal of large particulate material (Gasiorowski & Russell, 2009). A malfunction of endothelial phagocytosis and reduced numbers of trabecular endothelial cells may also contribute to the pathogenesis of POAG (Samuelson et al., 1984). The nonfiltering portion of the canine iridocorneal angle (ICA) has been shown to contain Schwalbe's line cells, which have both secretory and epithelial characteristics. Recently, a stem cell niche was identified in Schwalbe's line of cynomolgus macaques, which may serve to repopulate cells in the TM and/or corneal endothelium (Braunger et al., 2014). Changes in the morphology and number of Schwalbe's line cells correlate with disease progression in Beagles with POAG (Samuelson et al., 2001), suggesting that loss of this cell population is important in the pathogenesis of glaucoma.

Fluid Dynamics

As the CB produces AH, the tissues comprising the ICA resist AH outflow, thus generating IOP. Steady-state IOP occurs when the rates of AH inflow and outflow are equivalent. The AH exits the eye by passive bulk flow via two routes in the ICA:

1) The traditional or conventional pathway, which involves passage through the TM, AAP, scleral venous plexus, veins of the episclera and conjunctiva (anterior) or vortex veins (posterior), and systemic venous circulation.
2) The uveoscleral or nonconventional pathway, which involves passage through the iris root, anterior face of the ciliary body muscle, supraciliary or suprachoroidal space, and out through the sclera.

The traditional pathway is dependent on IOP, while the uveoscleral pathway is not, as long as IOP is greater than 7–10 mmHg (Bill, 1966a, 1967b, 1975). At very low IOP, the net pressure gradient across the nonconventional pathway declines, so that uveoscleral outflow subsequently decreases. It is unknown why uveoscleral outflow is largely independent of IOP, but it may relate to complex relationships between pressure and resistance between the fluid compartments and the soft tissues that comprise this route (Bill, 1975). For example, the pressure gradient between the anterior chamber and suprachoroid is independent of IOP, thus fluid flow between these compartments is also IOP independent. Uveoscleral outflow is primarily impacted by the state of the ciliary body and by the hydrostatic pressure difference between the anterior chamber and the suprachoroidal space (Barrie et al., 1985; Bill, 1966a; Emi et al., 1989; Gelatt et al., 1979). Contraction of the ciliary body musculature decreases unconventional outflow, possibly by reducing the extracellular spaces; in turn, relaxation increases outflow via this route. Thus, pilocarpine, a parasympathomimetic, and atropine, a parasympatholytic, will decrease and increase uveoscleral outflow by contracting and relaxing the ciliary body muscle, respectively (Bill, 1967a; Lutjen-Drecoll & Kaufman, 1993; Rohen et al., 1967).

Formulae can be used to describe the formation and drainage of AH (Table 3.7).

Table 3.7 Aqueous humor dynamics formulae.

I	$F_{in} = F_{at} + F_{uf}$ **F = flow (µl/min)** F_{in} = total AH inflow F_{at} = inflow from active transport F_{uf} = inflow from ultrafiltration
II	$F_{out} = F_{trab} + F_{uveo}$ F_{out} = total AH outflow F_{trab} = outflow via the trabecular meshwork F_{uveo} = outflow via uveoscleral pathway
III	$C_{total} = C_{trab} + C_{uv} + C_{pseudo}$ C = facility or conductance of flow (µl/min/mmHg) C_{total} = total AH outflow facility C_{trab} = facility of outflow via the trabecular meshwork C_{uv} = facility of outflow via the uveoscleral pathway C_{pseudo} = pseudofacility
III	At steady state, $F = F_{in} = F_{out}$
IV	$F = C_{trab} (P_i - P_e)$ *Goldmann equation* **P = Pressure (mmHg)** P_i = IOP P_e = episcleral venous pressure
V	$F_{in} = C_{trab}(P_i - P_e) + F_{uveo}$
VI	$P_i = P_e + (F_{in} - F_{uveo)/} C_{trab}$

Episcleral venous pressure or the "backpressure" created by the venous portion of the conventional pathway in the AAP or Schlemm's canal constitutes approximately 50%–75% of the resistance that determines IOP. While minor anatomic variations in the venous system exist between species, results of pressure studies in humans, nonhuman primates, rabbits, and dogs reveal episcleral venous pressure to be between 8 and 12 mmHg (Bill, 1966b; Gelatt et al., 1982b; Maepea & Bill, 1989; Talusan & Schwartz, 1981; Tripathi & Tripathi, 1973). Arteriovenous anastomoses within the episcleral vasculature have been demonstrated in the rabbit, dog, owl monkey, and cynomolgus monkey. These vascular shunts may function in rabbits and dogs, where the episcleral vasculature appears to lack a capillary system, and in the monkey species as an emergency system to elevate IOP after globe perforation or to retrogradely flush the outflow channels (Funk & Rohen, 1996; Rohen & Funk, 1994). Episcleral venous pressure can be measured by direct cannulation (using very fine glass pipettes) or indirect partial to complete compression schemes (using a string-gauge system or a fluid-filled chamber; Gelatt et al., 1982b). The term *pseudofacility* refers to pressure-dependent ultrafiltration formation of AH. It was assumed that any measurement procedure for AH dynamics that temporarily elevated IOP (e.g., perfusion of the anterior chamber, tonography, perilimbal suction cup) would temporarily decrease the rate of humor formation. This slight decrease in the rate of formation would alter the pressure-sensitive outflow measurements obtained by tonography and was termed *false facility*, or *pseudofacility*. Results of studies that involved compressing the episcleral venous pressure of the AH outflow systems in humans and nonhuman primates suggest the pseudofacility to be as high as a 20% error (Brubaker & Kupfer, 1966; Kupfer & Sanderson, 1968). However, fluorophotometric measurements of AH formation rates indicate that these sudden (but limited) increases in IOP do not suppress the rate of AH formation. Indeed, fluorophotometry measurements in both normal and glaucomatous human eyes indicate that rates of AH formation are essentially the same (Beneyto Martin et al., 1995). Thus, the temporary increase in IOP observed in the original experiments by Brubaker and colleagues may be due to immediate dilation of the intraocular blood vessels followed by slow accumulation of AH (Brubaker & Kupfer 1966; Moses et al., 1985).

Results of earlier studies indicated that the volume of the anterior chamber directly relates to the rate of aqueous outflow, so that animals with large eyes have faster outflow rates (Tripathi, 1974; Tripathi & Tripathi, 1972, 1973). The resistance to aqueous outflow is inversely proportional to the facility of outflow (C_{total}).

Regulation of Outflow

Cholinergic agonists such as pilocarpine decrease outflow resistance by contraction of the ciliary muscle and subsequent spreading of the TM. This effect is rapid, such that intravenous administration of pilocarpine to vervet monkeys results in a near-instantaneous decrease in outflow resistance, suggesting that the effect may be mediated by a structure perfused by arteries (Bárány, 1967). Ciliary muscle disinsertion and removal of the iris obliterate this acute response to pilocarpine, suggesting that it is mediated completely by ciliary muscle contraction rather than a direct effect on the TM (Kaufman & Bárány, 1976). The M3 subtype of the muscarinic receptor is strongly expressed in the ciliary muscle and thought to mediate the changes in outflow facility in response to cholinergic agonists (Gabelt, 1994; Gabelt & Kaufman, 1992; Zhang et al., 1995). Because the effect of cholinergic agonists on trabecular outflow (increase) is greater than that on uveoscleral outflow (decrease), the net effect is an increase in AH outflow and concomitant decrease in IOP. As expected, cholinergic antagonists such as atropine decrease traditional outflow and increase nontraditional outflow by similar mechanisms.

Stimulation of adrenergic receptors by nonspecific agonists such as epinephrine increases outflow, but the precise mechanism remains elusive despite extensive study (Ballintine & Garner, 1961; Bárány, 1968; Bill, 1969, 1970; Krill et al., 1965; Sears, 1966). However, it is likely to involve stimulation of β_2 receptors on TM cells and subsequent increased cyclic adenosine monophosphate (AMP) production (Kaufman, 1987; Neufeld et al., 1972, 1975; Neufeld & Sears, 1975; Sears & Neufeld, 1975). Downstream effects may include disruption of actin filaments within TM cells, changes in cell shape, cell–cell and cell–ECM interactions, altered TM structure, and increased hydraulic conductivity within the TM (Kaufman, 1981; Kaufman & Rentzhog, 1981). Epinephrine also increases uveoscleral outflow, likely by stimulation of β-receptors in the ciliary muscle and subsequent relaxation (Bill, 1969; Casey, 1966; Schenker et al., 1981; Tornqvist, 1966; Townsend & Brubaker, 1980; van Alphen et al., 1962, 1965).

Many other influences on the rate of AH formation and regulation of IOP have been proposed. For example, a center in the feline diencephalon has been found that, when stimulated, causes alterations in the IOP (Gloster, 1960). Central nervous system (CNS) regulation of IOP is poorly understood, however, and hormonal control of AH production may be involved (Niederer et al., 1975). The influence of the CNS on AH dynamics was reviewed by Denis and colleagues (1994).

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Methods to Measure Aqueous Dynamics

Both invasive and noninvasive methods are used to investigate AH dynamics (Table 3.8), and normative values have been described in domestic and laboratory animal species.

AH formation has been measured using both invasive and noninvasive techniques. As one may anticipate, early methods were invasive and essentially measured the dilution of intracamerally injected substances over short time periods. With the AH volume within the anterior and posterior chambers measured and the amount of dilution of the tracer estimated, the total amount of AH produced per unit of time could be determined. Knowledge of anterior and posterior chamber volumes is critical to determining the rate of AH production (Table 3.9; McLaren et al., 1990; Toris et al., 1995). Unfortunately, a major limitation of these studies is variability in the determination of the anterior and posterior chamber volumes. In glaucomatous animals, these chambers may be altered considerably, and their volumes are subsequently difficult to determine. In response to these invasive experiments, fluorophotometry was developed as both an experimental and a clinical procedure to noninvasively determine the rate of AH formation in many species, including humans.

Table 3.8 Methods to investigate aqueous humor dynamics.

I	Techniques to investigate the formation of aqueous humor Cannulation of anterior chamber: constant rate/constant pressure perfusion Direct view/measurement of newly formed aqueous humor Use of markers in aqueous humor (radioactive, fluorescein, paraminophippuric acid). Measure the decay rate of intracamerally injected isotopes. Fluorophotometry, a noninvasive method, is primarily used today
II	Procedures to investigate the exit of aqueous humor Ocular perfusion to lower IOP Perilimbic suction cup Tonography (conventional outflow/pressure sensitive) Use of markers (fluorescein, nitrotetrazolin, latex spheres, radioactive tracers). Both conventional and uveoscleral outflow routes are measured
III	Methods to measure the episcleral venous pressure Partial to complete collapse of the episcleral veins to affect alteration in the blood flow Torsion balance Pressure chamber (filled with air or saline) Air jet Ocular compression Direct cannulation and measurement by transducer

Fluorophotometry is a noninvasive method for studying AH flow dynamics, for evaluating ocular pharmaceutical agents used to treat glaucoma, and for determining iris permeability in both normal and disease states (Bartels, 1988; Brubaker, 1991; Kurnik et al., 1989; McLaren & Brubaker, 1988). Fluorophotometry of the anterior chamber and vitreous can assess the permeability of the BRB in the normal and diseased eye. Fluorophotometry has been used extensively in humans (Brubaker, 1991), nonhuman primates (Toris et al., 2010), rabbits (Reitsamer et al., 2009; Zhao et al., 2010), cats (Crumley et al., 2012; Lee et al., 1984), dogs (Cawrse et al., 2001; Skorobohach et al., 2003; Ward et al., 2001), and, most recently, the red-tailed hawk (Jones & Ward, 2012). This tool can also be used to assess permeability coefficients of the BAB involved in health and disease, and determine the effects of selected drugs on the BAB.

To determine AH outflow, perfusion of the anterior chamber (AC) of *in vivo* and *ex vivo* eyes has been performed in numerous species. The constant pressure perfusion technique is the most frequently used. It involves maintaining a constant level of IOP with periodic, intermittent, or continuous volumes of perfusate. In the perfusion decay test, either a preselected volume of perfusate is injected or a preselected IOP is achieved. Once the perfusate has been injected, the time for the IOP to regain the baseline or preexisting measurement is obtained. In many ways, the perfusion techniques are similar to the noninvasive tonography methods. The two-step constant perfusion of the anterior chamber, as

Table 3.9 Comparative volumes of the chambers and select structures of the eye.

Species	Anterior Chamber (mL)	Posterior Chamber (mL)	Lens Volume (mL)	Vitreous Volume (mL)
Human	0.2	0.06	0.2	3.9
Rabbit	0.3	0.06	0.2	1.5
Pig	0.3	—	—	3.0
Dog	0.8	0.2	0.5	3.2
Cat	0.8	0.3	0.3	2.8
Cow	1.7	1.5	2.2	20.9
Horse	2.4	1.6	3.1	28.2

reported by Bárány and Scotchbrook (1954), has become the most frequently reported procedure. Briefly, the technique includes constant perfusion of the anterior chamber at two different IOPs (~2–3 and 8–10 mmHg above baseline) for several minutes. The total (i.e., perfusion) facility is determined by dividing the difference in perfusion rates between the two IOPs by the pressure difference between them. Pseudofacility may account for approximately 0.02 μL/min/mmHg with this procedure in humans.

Ample literature is available on anterior chamber perfusion in several species. The type of perfusate, duration of perfusion (i.e., the "washout effect"), eye preparation, IOP during perfusion, addition of certain enzymes, and drugs (including anesthesia and other substances) may directly influence the perfusion rate. If perfusion of the anterior chamber is planned, the literature should be consulted and carefully evaluated. In general, the rates of perfusion obtained in the animals investigated have correlated closely with the values obtained by the noninvasive tonographic and fluorophotometric methods. For more information on tonography to noninvasively measure conventional outflow, see Chapter 10. Several methods have been used to demonstrate anatomic routes and quantity of uveoscleral outflow, as well as of conventional (i.e., corneoscleral) outflow.

The percentages accounted for by uveoscleral outflow range from 30% to 65% in nonhuman primates, 15% in dogs, 13% in rabbits, 4% to 14% in humans, and 3% in cats (Table 3.6; Barrie et al., 1985; Bill, 1966a, 1966b; Bill & Phillips, 1971; Zhan et al., 1998). The horse appears to have an extensive uveoscleral outflow system (Smith et al., 1986), but the volume and percentage of the total outflow system have not been reported. For additional information on unconventional outflow in a variety of species under numerous conditions, the reader is referred to the thorough review by Johnson and colleagues (2017).

Uveoscleral outflow can be demonstrated using observable tracers measuring from 10.0 nm to 1.0 μm in diameter. As one would anticipate, the smaller-diameter (i.e., pore) tracers penetrate the different tissues to greater extents. After perfusion at different IOPs and for different time intervals, the eyes (especially the root of the iris, entire ciliary body, suprachoroidal space, and choroid, even as far posterior as the optic nerve) are examined by light microscopy, scanning electron microscopy, and transmission electron microscopy for these markers. These same methods have also demonstrated the ability of the trabecular endothelium and wandering macrophages to phagocytize particulate material within the outflow pathways. An alternative method to estimate the amount of uveoscleral outflow (either as μL or %) is by using radioactive isotopes injected into the anterior chamber; the time, amount of the isotope, or both is standardized. At the conclusion of perfusion, the ocular tissues are either dissected into the different sections, analyzed for radioactivity, or the entire globe is sectioned, and the radioactivity of each area is measured by scintillation counter. Measurements of tracers in the fluids within the intrascleral veins, episcleral veins, and vortex veins are alternate methods of determining the different routes of AH outflow, but these methods require the anatomy of these venous systems to be determined. There may be mixing between the systems, and the tracer concentrations in the anterior chamber and blood must be established at the same time. Atraumatic entry to the intrascleral or episcleral venous system (or both) must be available.

Ocular Rigidity

Another key concept in the measurement of IOP is ocular rigidity (k), or the resistance offered by the fibrous tunics of the eye (i.e., sclera and cornea) to a change in intraocular volume. Ocular rigidity may also be defined as the change in IOP per incremental change in the intraocular volume; this resistance manifests as a change in IOP. Ocular rigidity is determined by Schiotz tonometry, and it estimates the change in volume (open manometer system) when the instrument is placed on the cornea as well as after injections of exact volumes or preselected elevations in IOP. This logarithmic relationship between IOP and volume of the globe is:

$$\log P_2/P_1 = k\left(V_2 - V_1\right).$$

Ocular rigidity is a constant characteristic of each eye, but it also depends on IOP. Hence, the distensibility of each globe varies among individuals as well as with the IOP. Dogs and cats have greater scleral elasticity than humans, so less resistance is offered with indentation tonometry, and buphthalmia occurs more readily with prolonged, increased IOP (Peiffer et al., 1978; Wyman, 1973). Manometric studies to develop Schiotz tonometer calibration tables for the dog, rabbit, and cat have not been successful clinically and may, perhaps, be associated with different individual rigidities for the cornea and sclera (Miller & Pickett, 1992). Consequently, Schiotz tonometry is rarely performed in animals.

Intraocular Pressure

In many species, IOPs as measured with tonometry in normal animals have been reported (Table 3.10). In humans and animals, fluctuations in IOP occur for a variety of reasons (Table 3.11), and a review of considerations for conducting IOP studies in animals was recently performed (Millar & Pang, 2015). Diurnal IOP variations generally occur in most species; in humans and dogs, the highest pressure occurs in the morning and the lowest in the afternoon (Gelatt et al., 1981). By contrast, the greatest IOPs occur during the day and the lowest IOPs are documented at night in the rabbit, cat, horse, and nonhuman primate (Bertolucci et al., 2009). In glaucomatous canine patients, diurnal IOP fluctuations

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Table 3.10 Intraocular pressures in select animal species.

	IOP Results		
Species	**Mean ± SD**	**Tonometer**	**Investigator**
Alligator	23.7 ± 2.1	TonoPen	Whittaker et al. (1995)
Cat	22.6 ± 4.0 19.7 ± 5.6	Mackay-Marg TonoPen	Miller et al. (1991b)
Cow	28.2 ± 4.6 26.9 ± 6.7	Mackay-Marg TonoPen XL	Gum (1990)
Chinchilla	3.0 ± 1.8 9.7 ± 2.5	TonoVet-D TonoVet-D	Müller et al. (2010) Snyder et al. (2018)
Dog	15.7 ± 4.2 16.7 ± 4.0 17.8 ± 0.9 (pm) 21.5 ± 0.8 (am)	Mackay-Marg TonoPen Mackay-Marg	Miller et al. (1991a) Gelatt et al. (1981)
Ferret	22.8 ± 5.5 15.4 ± 1.1 14.1 ± 0.4	TonoPen TonoPen Vet TonoVet	Sapienza et al. (1991) Di Girolamo et al. (2013)
Frog			
White's tree frogs	16.8 ± 3.9 14.7 ± 1.6	TonoLab-R TonoVet-D	Hausmann et al. (2017)
Goat (pygmy)	11.8 ± 1.5 10.8 ± 1.7	TonoVet-D TonoPen XL	Broadwater et al. (2007)
Guinea pig	18.3 ± 4.6 6.1 ± 2.2	TonoPen Vet TonoVet	Coster et al. (2008)
Horse	25.5 ± 4.0 23.5 ± 6.1 23.3 ± 6.9	Mackay-Marg Mackay-Marg TonoPen	Cohen & Reinke (1970) Miller et al. (1990)
Mouse (no anesthetic)	14.6 ± 0.5	TonoLab	Ding et al. (2011)
Nonhuman primate			
Rhesus (ketamine)	14.9 ± 2.1 15.4 ± 2.6	Pneumatonograph TonoPen XL	Bito et al. (1979) Komaromy et al. (1998)
Tibetan monkey	29.3 ± 0.9	TonoVet-P	Liu et al. (2011)
Rabbit	19.5 ± 1.8 17.9 ± 2.1 9.5 ± 2.6 15.4 ± 2.2	Pneumatonograph TonoVet TonoPen Avia	Vareilles et al. (1977a, 1977b) Smith & Gregory (1989) Pereira et al. (2011)
Raptor			
Red-tailed hawk	20.6 ± 3.4	TonoPen	Stiles et al. (1994)
Golden eagle	21.5 ± 3.0		
Great horned owl	10.8 ± 3.6		
White-tailed sea eagle	26.9 ± 5.8	TonoVet	Reuter et al. (2011)
Northern goshawk	18.3 ± 3.8		
Red kite	13.0 ± 5.5		
Eurasian sparrowhawk	15.5 ± 2.5		
Common buzzard	26.9 ± 7.0		
Common kestrel	9.8 ± 2.5		
Peregrine falcon	12.7 ± 5.8		
Tawny owl	9.4 ± 4.1		
Long-eared owl	7.8 ± 3.2		
Barn owl	10.8 ± 3.8		
Rat	17.3 ± 5.3	TonoPen	Mermoud et al. (1994)
	21.4 ± 1.0	TonoPen	Sappington et al. (2010)
Sheep	10.6 ± 1.4	Perkins	Gerometta et al. (2009)

Table 3.11 Factors that cause short- and long-term fluctuations in intraocular pressure.

Short-Term	Long-Term
Diurnal changes	Aging
Forced eyelid closure	Race/breed
Contraction of retactor bulbi muscles	Hormones
Coughing/valsalva maneuver	Glucocorticoids
Abrupt changes in blood pressure	Growth hormone
Pulse	Estrogen
Struggling/electroshock	Progesterone
Changes in body/head position	Obesity
Succinylcholine	Myopia
Acidosis	Gender
	Season

are typically much greater in comparison to normal dogs (Gelatt et al., 1981). Consequently, antiglaucoma medications administered once daily to dogs should be given in the evening to mitigate IOP spikes in the morning, when pressures are typically the greatest (Gelatt & MacKay, 2001).

Lens

The second most powerful refracting structure in the eye is the lens. Like the cornea, the lens is a transparent tissue without a direct blood supply. The lens depends primarily on AH for its metabolic needs. Most of the lens proteins are soluble, with a small amount of glycoproteins, whereas the cornea consists mostly of insoluble collagen and a relatively large amount of glycoproteins.

Lens epithelial cells (LECs) are the progenitors of the lens fibers and transition into lens fiber cells of the cortex at the equator. This process is characterized by distinct biochemical and morphologic changes, such as the synthesis of crystallin proteins, cell elongation, loss of cellular organelles, and disintegration of the nucleus (Ochiai et al., 2014).

Transparency of the lens depends primarily on the highly ordered lens cell arrangement, as well as on the solubility and physical arrangements of its proteins. The lens behaves as a cell syncytium both biochemically and electrically. The lens consists of approximately 68% water, 38% protein, and small amounts of lipids, inorganic ions, carbohydrates, ascorbic acid, glutathione, and amino acids (Viteri et al., 2004). Both the anterior and posterior lens capsules are the lens's extracellular matrix and, like a typical epithelial basement membrane, consist of Type IV collagen and heparan sulfate proteoglycan. The thickness of the anterior lens capsule increases with age because of the anterior location of the lens epithelial cells (Bernays & Peiffer, 2000).

The protein content of the lens is very high in comparison to other organs. Protein synthesis ceases with formation of the lens fiber cells, and all the protein changes that occur after this stage are posttranslational modifications. Lens proteins are divided into water-soluble proteins and water-insoluble proteins. Crystallins comprise 80–90% of the water-soluble lens proteins (Andley, 2007; Piatigorsky, 2003). Most of the insoluble proteins occur in the lens nucleus, whereas the soluble proteins are concentrated in the lens cortex (Harding & Dilley, 1976). The insoluble proteins are associated primarily with membranes of the lens fibers; the soluble proteins comprise the bulk of the refractive fibers of the lens and are considered the structural proteins of the lens. The percentages of soluble and insoluble proteins vary among species and with the pathophysiologic state of the lens. With aging, water-soluble proteins coalesce to make high-molecular-weight aggregates and their hydrophilicity diminishes (Ortwerth & Olesen, 1989). Additionally, when the lens becomes cataractous, the level of water-insoluble proteins increases.

The crystallin proteins are classified as classical or taxon-specific. Crystallins evolved from stress proteins and enzymes (Andley, 2007). Classical crystallins comprise α-crystallins and the β/γ-crystallin superfamily. Crystallins form very stable and durable structures. All vertebrate lenses accumulate large amounts of classical crystallins in their fiber cells. Alpha-crystallins are not only refractive, but as members of the family of small heat shock proteins, they also serve as molecular chaperones that function to protect against physiologic stress. Alpha-crystallins account for almost 50% of the protein mass of the human lens and are thought to bind to partially unfolded β/γ-crystallins and

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interact with cytoskeletal proteins, preventing further aggregation, interaction, and precipitation, which would lead to lens opacification (Andley, 2007).

The β/γ-crystallin superfamily is more diverse than the α-crystallins, but its functional role is less evident. Previously the β/γ-crystallins were thought to be two distinct protein families, but protein sequencing has shown that they are closely related. The major difference is that β-crystallins tend to form multimers and γ-crystallins exist as monomers (Driessen et al., 1981).

Taxon-specific crystallins vary between species and provide the lens with transparency and enzymatic capacity. This ability to serve in both capacities is referred to as gene sharing. One example is δ-crystallin, which is a soluble protein that also has argininosuccinate lyase activity and accumulates only in the lenses of birds and reptiles. Delta-crystallin is the first and major crystallin (70%) in the lens of the developing chicken (Das & Piatigorsky, 1988; Piatigorsky & Wistow, 1989). Additionally, these crystallins may have been recruited as lens proteins because of their thermodynamic stability, which is required for the long life of fiber cells (Wistow & Piatigorsky, 1987).

The long prismatic lens fiber cells are organized in tightly packed units with interdigitations that appear as a three-dimensional jigsaw puzzle. The interdigitations stabilize the lateral membranes of the lens fibers, and they are specialized gap junctions that join all the lens cells, thus permitting them to act as a syncytium. Gap junctions mediate cell-to-cell transport of molecules, which is critical since most fibers are distant from their nutrient sources, the aqueous and vitreous humors. Lens fiber cells have a higher concentration of gap junctions than any other cells in the body. The lens fiber cytoskeleton contains micro-filaments and intermediate filaments that are composed of vimentin, filensin, and phakinin. These filaments have a knobby structure leading to the name, beaded filaments, which are only found in lens fiber cells, suggesting a very specialized role. The functions of the beaded filaments probably relate to crystallin packing and density distribution, as well as their being attachment sites for the crystallin molecules (Ireland & Maisel, 1984).

Aquaporins comprise a family of intrinsic membrane proteins involved in water transport in many tissues. Specifically, AQP0 has been localized to the canine lens fibers as well as the lens of other mammals (Karasawa et al., 2011). In rats and most likely other animals, the AQP0 are located on the lens equatorial fiber plasma membranes, both in a diffuse arrangement and in clusters that correspond to specialized junctions between fibers and interact with gap junctions in the apical surface of the fiber. These adaptations are thought to assist the circulating fluxes of ions and water needed to move nutrients into and waste products out of the nucleus. The fluxes are directed from the poles of the lens toward the equator. These adaptations allow the lens to avoid being dependent on the diffusion–consumption equation or capillaries used by other tissues (Zampighi et al., 2002). Homeostasis, especially that associated with solute exchange from the aqueous and vitreous humors to the lens fibers, has been extensively studied. A review by Dahm and colleagues (2011) summarizes current information into four main forms of transport:

1) Paracellular transport via the intercellular spaces between the LECs and the underlying lens fibers is driven by Na^+ leak conductance. This mechanism accounts for the influx of ions, water, and small molecules such as glucose, amino acids, and ascorbic acid.
2) Plasma membrane-based transport of small molecules from the lens's extracellular space into the lens fiber's cytoplasm is via ion and water channels and specific transporters for small molecules.
3) Gap-junctional transport accounts for the flux of ions, water, and small molecules from superficial fibers toward the deep fibers, and also accounts for the efflux of waste products at the epithelial cell lens fiber interface in the equatorial regions.
4) Vesicle-mediated active transport by caveoli accounts for the uptake of macromolecules such as growth factors and other regulatory factors necessary for the normal development and maintenance of lens fibers. Coated vesicles are involved in the uptake of lipoproteins and cholesterol by superficial fibers needed for the biogenesis of new membranes, as lens fiber cells increase their length by up to 1,000-fold (Dahm et al., 2011).

The lens epithelium is the major site of energy production in the lens. Energy is used for active transport of inorganic ions and amino acids and for protein synthesis. Osmoregulation occurs through active transport and involves the action of Na^+-K^+- ATPase to maintain high K^+ and amino acid concentrations and low Na^+, Cl^-, and water concentrations within the lens. The movement of water is passive and occurs with the active cation transport. As the Na^+ ion is transported from the lens, K^+ is transported into the lens (Fig. 3.7) in a manner similar to that in red blood cells. A deficiency of lens Na^+-K^+-ATPase results in cataracts in mice because of the breakdown of this critical pump mechanism (Kinoshita, 1974).

The lens undergoes major oxidative stress due to constant exposure to light and oxidants. Oxidative stress is reduced by radical scavenging antioxidants such as glutathione, carnitine, and ascorbic acid, which are present at high concentrations in the lens. However, some species such as dogs, rabbits, and guinea pigs have lower concentrations of ascorbic acid in the lens than in the AH (Kuck, 1970). The function of lenticular ascorbic acid most likely relates to oxidation–reduction reactions or is coupled to glutathione metabolism (Berger et al., 1988). In humans, the lens epithelium contains transporter molecules for ascorbate, which

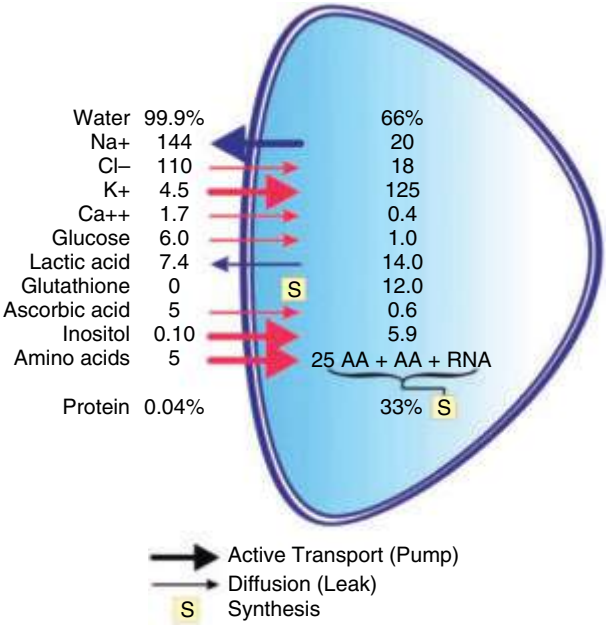


Figure 3.7 Chemical composition of the aqueous humor and lens. Water and protein are expressed as percentages of lens weight. Na+, Cl–, K+, and Ca++ ions are expressed in microequivalent per milliliter of lens water. Other compounds are expressed in micromole per gram of lens weight or micromole per milliliter of aqueous humor. AA, amino acid; RNA, ribonucleic acid.

ensure adequate metabolism and help to protect against damage by free radicals. A deficiency in these protective mechanisms can result in cataractogenic changes (Andley & Clark, 1989). Glutathione is a tripeptide of glutamine, cysteine, and glycine. It is synthesized in the lens epithelial cells and superficial fiber cells and provides most of the protection against oxidative damage in the lens. Glutathione furnishes sulfhydryl groups for the lens proteins, thereby preserving their solubility, and for Na^+-K^+-ATPases, thereby maintaining these transport "pumps." Other biologic functions include participation in amino acid transport with γ-glutamyl transpeptidase and as a substrate for glutathione peroxidase, which destroys cytotoxic lipid hydroperoxides. In a normal lens, glutathione is predominantly in the reduced form (GSH), with the concentration of the oxidized form of glutathione at only 2.1%–2.6% that of the reduced form. Concentrations of both the reduced and the oxidized forms of glutathione are decreased in cataract formation, except in advanced cataract patients, where the amount of the oxidized form is 9% that of the reduced form (Gelatt et al., 1982a). Carnitine is known to have an antioxidative and antiradical role on the ocular surface. The same is suspected to be true in the lens. Recently, the carnitine transporter SLC22A5 was identified in canine lens epithelium and is thought to be responsible for the transport of carnitine to the lens from AH (Ochiai et al., 2014). A major factor involved in cataract formation is oxidative damage caused by O_2 radicals, peroxide (H_2O_2), OH^-, and ultraviolet radiation.

Telomerase is a ribonucleoprotein responsible for maintaining telomere length, preventing chromosomal degradation and recombination, and repairing DNA strand breaks, thereby preventing cell senescence. Telomerase activity has been found in normal canine, feline, and murine lens epithelial cells in the central, germinative, and equatorial regions at equivalent concentrations. Telomerase activity may be in the germinative epithelium to maintain its proliferative potential and prevent cell senescence, whereas it may function in the quiescent, central lens to maintain telomeres damaged by oxidative stress and ultraviolet light exposure, thereby preventing accelerated loss of these elements, which can trigger cell senescence (Colitz et al., 1999).

The lens capsule functions as a semipermeable membrane. It prevents direct contact between the lens and the surrounding ocular environment and protects the lens from the invasion of pathogens. However, the capsule allows water, small solutes, many proteins, and waste to pass, thereby enabling the lens to grow and perform metabolic functions (Danysh & Duncan, 2009). Its mechanical functions include maintaining the shape of the lens in association with accommodating and providing for the attachment of the zonules. Additionally, a contractile system appears to exist in the lens epithelial and cortical cells, and though its physiologic function is not completely understood, it seems to stabilize the shape of the lens (Rafferty et al., 1990).

The primary source of energy for the lens is glucose, which diffuses from the AH. Energy is derived from anaerobic glycolysis and is used for active cation transport and protein synthesis. Oxygen is not necessary for normal lens metabolism, though a small percentage of glucose is metabolized through the Krebs cycle. The hexose monophosphate (i.e., pentose) shunt and the sorbitol pathway are other pathways of glucose metabolism in the lens. The major end product of glucose metabolism in the lens is lactic acid, which diffuses into the AH. The rate of glycolysis is controlled by the amount of hexokinase and the rate of entrance of glucose into the lens. With high concentrations of glucose (>175 mg/dL), the level of glucose-6-phosphate increases, which inhibits hexokinase and limits the rate of glycolysis. This process prevents excessive buildup of lactic acid in the lens, which would lower the pH and activate the lens proteases (Kuck, 1970). With very high blood and AH glucose concentrations, as occur in diabetes mellitus, the enzyme aldose reductase is activated as an alternative route of glucose metabolism in the lens (Sato & Kador, 1989). The result is an accumulation of sorbitol in the lens cells, which causes swelling associated with the increased osmotic pressure. The outcome is a diabetic cataract.

Aging changes in the lens include an increase in insoluble proteins and changes in the cytoskeleton. Normal proteolysis

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truncates many of the soluble crystallins and contributes to aging changes. The increase in water-insoluble proteins most likely occurs because of crystallin binding and interactions with the cytoskeletal/membrane components. The chaperone role of α-crystallin, whereby the α-crystallin binds to partially unfolded β/γ-crystallins and interacts with cytoskeletal proteins to prevent uncontrolled aggregation, ultimately increases the amount of insoluble proteins. The increase in insoluble proteins is also secondary to covalent interactions between crystallin fragments (Su et al., 2011). Additionally, with age, the flow of antioxidants from the metabolically active cortex to the lens nucleus decreases, predisposing the lens to cataract development. Iron is also implicated in cataract development, due to its ability to catalyze the formation of free radicals, and aging cataractous lenses have higher concentrations of iron. Normally excess iron is safely stored in ferritin, a ubiquitous protein. One study found that modified fiber cell ferritin L chains are present at the highest amount in the outermost layers of both cataractous and noncataractous canine lenses. They decrease gradually in the inner layers of the fiber mass and are undetectable in the inner two layers of cataractous lenses. By contrast, modified ferritin H chains are ubiquitous throughout noncataractous lens cortex, but are found in decreasing amounts toward the interior of the lens. However, in cataractous lenses, normal-sized ferritin H chains are present in smaller quantities in the outer fiber layers, and increase in quantity and size in the inner layers. These different amounts and types of ferritin may reflect a response of the lens to increased oxidative stress during cataractogenesis (Goralska et al., 2009).

The Vitreous

Vitreal Structure and Aging

Physically, the vitreous is a hydrogel that consists of >98% water and fills the posterior cavity of the eye. Collagen comprises the framework of the vitreous and provides its plasticity. Despite the low protein content, a diverse array of >1,200 soluble proteins have been identified in the vitreous (Murthy et al., 2014). Spaces between the collagen fibers are filled with hyaluronic acid (HA), which provides viscoelasticity to the vitreous (Fig. 3.8). An increase in the collagen content of the vitreous makes it more solid, or gel-like, while a decrease in the collagen content makes its consistency more fluid. Species differ in the collagen content of their vitreous, which accounts for variability in its consistency. Generally, the cortical areas of the vitreous contain more collagen, so they are more rigid than other portions. The vitreous contains few cells, termed hyalocytes. Hyalocytes belong to the monocyte/macrophage lineage and derive from bone marrow. Their origin is not from glial cells or retinal pigment epithelial cells, as previously thought. Hyalocytes are important for extracellular matrix synthesis, vitreous cavity immunology regulation, and modulation of inflammation (Sakamoto & Ishibashi, 2011).

The embryonic vitreous is very dense and therefore translucent. As an individual matures, however, important structural changes occur in the vitreous. The axial length of the vitreous increases, which is critical for growth of the eye (discussed later). The overall collagen content remains unchanged in the adult, but the HA concentration undergoes a fourfold increase in both cattle and humans (Balazs, 1982; Balazs et al., 1959). This change in the HA-to-collagen ratio contributes to greater dispersal of the collagen fibrils, because the newly synthesized HA molecules push the collagen fibril bundles further apart, thus increasing the optical clarity of the vitreous. These changes in HA–collagen interactions as well as in the GAG contents of the vitreous do not cease upon reaching adulthood. Rather, these alterations continue throughout life, and they are believed to be responsible for the vitreal liquefaction observed as part of the aging process in some species (Sebag, 1989). In humans, rheologic (i.e., the gel-liquid state of the vitreous) changes begin in the central vitreous at 5 years of age and continue throughout life, so that in the geriatric patient, more than 50% of the vitreous is eventually liquefied (Balazs, 1982). As liquefaction progresses, the collagen bundles are packed into the remaining gel fraction, whereas HA molecules are redistributed to the liquid fraction. A common complication of this progressive liquefaction is separation of the posterior vitreous cortex from the retinal inner limiting membrane. This detachment, which predisposes to retinal tears, has been implicated as a risk factor in rhegmatogenous retinal detachment in dogs (Hendrix et al., 1993).

Vitreous Functions

The vitreous is the largest structure in the eye, occupying approximately 80% of the globe (Sebag, 1989). It contributes to the development, optics, structure, physiology, and metabolism of the eye. The vitreous plays an important role in the growth of the eye by contributing to the increase in globe size. Inserting a drainage tube into the vitreous cavity of chicken embryos lowers intravitreal pressure and effectively stops the growth of the eye, and vitrectomy of rabbit eyes has a similar inhibitory effect (Arciniegas et al., 1980; Coulombre, 1956). By contrast, vitreal elongation will cause an increase in the axial length of the globe. This lengthens the path of the incoming light, thus providing for greater light refraction. In some aquatic species, such as goldfish, this increased vitreal refractivity is a physiologic mechanism that compensates for the loss of refractive power when the cornea is submerged in water (Seltner et al., 1989). In terrestrial species, the increased refraction by the vitreous leads to myopia. Vitreal elongation resulting in axial myopia has been induced through visual deprivation in a number of species, including

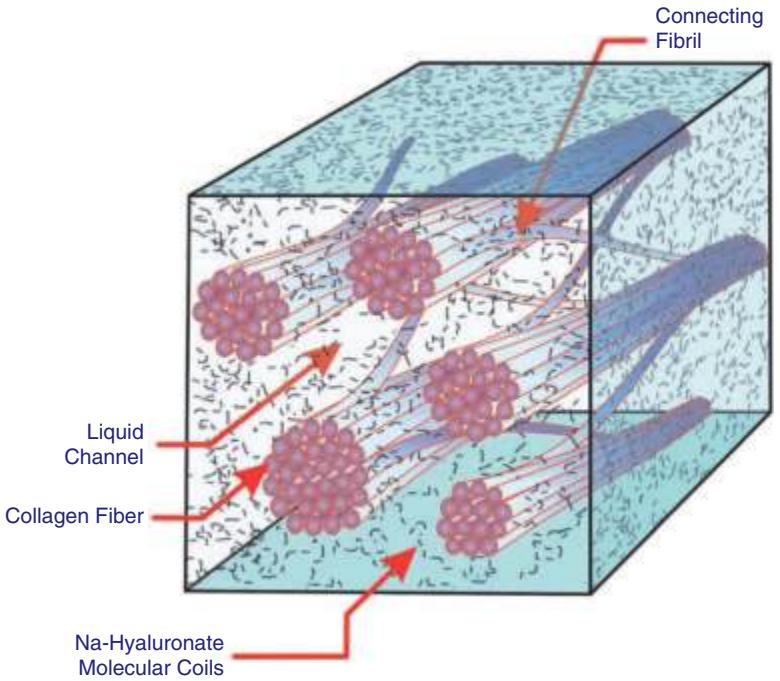


Figure 3.8 Schematic of the vitreal ultrastructure. Parallel collagen fibrils are packed into bundles that aggregate and, ultimately, form visible fibers. Hyaluronic acid and water molecules fill the interfibrillar spaces. (Modified with permission from Sebag, J. & Balazs, E.A. (1989) Morphology and ultrastructure of human vitreous fibers. *Investigative Ophthalmology & Visual Science*, 30, 1867–1873.)

nonhuman primates, chickens, and cats (Belkin et al., 1967; Hodos et al., 1985; Raviola & Wiesel, 1985). This elongation of the vitreous is affected by the synthesis of collagen. Synthesis, molecular reconfiguration, and hydration of HA molecules likewise change the volume of the vitreous and, hence, of the eye (Sebag, 1989).

Diffusion is slow and bulk flow is limited in a gel such as the vitreous. Therefore, topically administered substances are prevented from reaching the retina and optic nerve and systemically administered antimicrobials are unable to reach the center of the vitreous (Lund-Andersen & Sander, 2011). This slow change of substance concentrations has been used in humans to determine time of death and aid in postmortem diagnosis in manatees (Swain et al., 2015; Varela & Bossart, 2005).

The optical transparency of the vitreous is primarily due to a low concentration of structural macromolecules (0.2% w/v) and soluble proteins (Lund-Andersen & Sander, 2011). Additionally, the configuration of highly hydrated glycosaminoglycan chains separating small-diameter collagen fibers aids in the passage of light with minimal scattering (Bettelheim & Balazs, 1968). Another important factor in optical clarity is the blood–vitreous barrier; HA is thought to act as a barrier that prevents diffusion of macromolecules and cells into the vitreous, except in cases of trauma or cortex disruption (Hultsch, 1977). Inflammatory responses, neovascularization, and collagenase activity are likewise suppressed in the vitreous (Hultsch, 1977; Jacobson et al., 1985; Lutty et al., 1983). As a result of these anatomic and physiologic properties, the vitreous transmits 90% of light at wavelengths between 300 and 1400 nm (Boettner & Wolter, 1962).

In addition to its refractive role, the vitreous appears to have additional functions in the process of accommodation. In both humans and monkeys, imaging has revealed that the vitreous bows posteriorly as the ciliary body contracts (Croft et al., 2013). This movement is in proportion to the accommodative amplitude. The vitreous also plays an important role in ocular metabolism. It serves as a storage site for retinal metabolites, including glycogen, amino acids, and potassium (Newman, 1984; Reddy, 1979; Weiss, 1972). Retinal and lenticular waste products, including lactic acid and free radicals, are absorbed by the vitreous, which thus serves to protect the lens and retina from toxic compounds (Sebag, 1989; Ueno et al., 1987). In cattle, these molecules (and water) can diffuse across the vitreous through pores that are 400 nm in diameter (Fatt, 1977). HA serves as a barrier to this diffusion process (Foulds et al., 1985); therefore, molecule size and HA concentration are two of the primary factors affecting the diffusion of molecules through the vitreous. A decrease in HA concentration, which results in vitreous liquefaction, will thus lead to an increase in particle diffusion through the vitreous. Therefore, pathologic or aging processes leading to a decreased HA concentration and vitreal liquefaction will affect the nutrient supply, waste removal, and drug delivery in the posterior segment of the eye (Balazs & Denlinger, 1982).

The vitreous also provides some mechanical and structural support to the lens and retina (Schmidt & Coulter, 1981). Furthermore, its viscoelastic properties protect the internal eye structures from trauma and stress, especially

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during rapid eye movement (REM). Concentrations of collagen and HA, as well as the nature of their cross-links, contribute to this viscoelasticity. For example, in humans, the concentration of vitreal HA and collagen is twice as high as in the pig, and this corresponds to a 60% increase in the spring constant of human versus porcine vitreous (Weber et al., 1982). Woodpecker vitreous differs from human vitreous in that it does not have vitreo-retinal attachments. This lack of coupling of the vitreous to the posterior pole, as well as the orientation of the eye with respect to the axis of striking, is thought to reduce relative shearing motions that would be expected to result in ocular trauma from the woodpecker's rapid acceleration–deceleration movements (Wygnanski-Jaffe et al., 2007).

Ocular Mobility

As Chapter 5 discusses, higher-resolution vision is subserved by a small section of the retina termed the *area centralis*. Visual acuity as well as other parameters of vision (e.g., color perception) decrease rapidly in the more peripheral retina outside the area centralis. To keep an object of interest in the center of the visual field, so that its image will stimulate the area centralis (or fovea in birds and primates), vertebrates rely on the actions of six or seven EOM.

Domestic species have four rectus EOM – dorsal (or superior), ventral (inferior), nasal (medial), and temporal (lateral) – all of which move the eye in those respective directions (see Chapter 2). The oculomotor nerve (CN III) innervates the dorsal, ventral, and medial rectus muscles, and the abducens nerve (CN VI) innervates the lateral rectus muscle. Two oblique muscles that work in conjunction with the rectus muscles are also present. The ventral oblique, which is innervated by the oculomotor nerve, rotates the ventral aspect of the eyeball both nasally and dorsally; the dorsal oblique, which is innervated by the trochlear nerve (CN IV), rotates the dorsal aspect of the eyeball both nasally and ventrally. These muscles keep vision horizontally level irrespective of eye position in the orbit. The retractor bulbi, which is present in most species other than primates and birds, is innervated by CN VI and pulls the globe deeper within the orbit. The EOM contain both fast (~85%) and slow (~15%) fibers; however, in contrast to noncranial skeletal muscles, they exhibit both very fast contractility and extreme fatigue resistance. Even among the EOM there is great variation in the composition of each muscle in regard to the myosin heavy chain isoforms that assist with the dynamic physiologic properties and CNS control of eye movements (McLoon, 2011). The EOM are highly aerobic as well as resistant to injury and oxidative stress, with only cardiac muscle having a higher blood flow rate (Wooten & Reis, 1972). Additionally, normal EOM undergo myonuclear addition and subtraction throughout life while maintaining overall size and function, which is not observed in any noncranial muscles (McLoon et al., 2004). A motor axon innervates five to ten muscle fibers in the extrinsic eye muscles, whereas thousands may be innervated by a single axon in skeletal muscles, thus allowing for finer control of eye muscles by the CNS (Gum & MacKay, 2013).

The EOM of the eyes of birds are generally similar to those of mammals, other than the lack of a retractor bulbi muscle. In addition, the rectus muscles are much less robust than in mammals. Globe shape varies considerably among avian species, but the globes are relatively large, such that the two eyes weigh nearly as much as the brain (Martin, 1982). The globe shape and tight fit within the orbit impede globe movement, thus leading to the less robust rectus muscles. Birds compensate for this restricted globe mobility through movement of upper body and neck muscles to obtain a spatial perspective on objects.

Simplistically, two fundamental laws govern eye movements. The first, formulated by Sherrington, states that antagonistic muscles (in the same eye) have reciprocal innervation. In other words, stimulation of an agonistic muscle (e.g., medial rectus) occurs concurrently with inhibition of the antagonistic muscle (e.g., lateral rectus) in the same eye (Sherrington, 1947). The second governs innervation of yoked muscle pairs (i.e., the two muscles responsible for moving both eyes in the same direction). In the 19th century, Hering, (1977) discovered that in mammals, yoked muscle pairs are always equally innervated; therefore, a lateral movement of the left eye will be accompanied by an identical, medial movement of the right eye. Additionally, several EOM pulley systems have been hypothesized but not proven (Miller, 2019).

The seven EOM are responsible for numerous types of eye movements. Saccadic eye movements are very rapid (up to 1000°/s) and very brief (<0.1 second). They are intended for fast correction of eye position to rapidly bring the image of interest onto the area centralis. Thus, saccadic movements are used mostly when tracking a fast-moving object or to begin pursuit of a formerly stationary object.

Once the image of the object has been "captured" by the area centralis, smooth pursuit eye movements are used to match the speed of the object and to maintain its image in the area centralis. Required minor corrections and adjustments are, again, executed by saccadic movements. This combination of alternating rapid and slow eye movements is called optokinetic nystagmus (discussed later), which can be used to track objects moving at speeds <100°/s (Feldon & Burde, 1992). Saccades and smooth pursuit constitute the two types of conjugate (or version) eye movements, in which the two eyes move together without changing the angle between them.

Vergence eye movements, in contrast, change the angle of intersection between the two eyes. These can be either

convergent (i.e., increasing the angle between the visual axes to focus on a near target) or divergent (i.e., decreasing the angle between the visual axes to focus on a far target). Vergence movements are usually slow (<21°/s) and they have two roles. The first is to aid in visualizing nearby objects, which is a process that combines convergent eye movement, accommodation, and miosis. The second is to resolve any small misalignments between the two visual axes that otherwise might result in a disparity between the retinal images of the two eyes.

The afferent stimulus for all these eye movements is the visualized object. If the head is moving, however, eye movement is controlled by a different afferent limb, which allows for a faster tracking response. In this case, the stimulus is the acceleration of the head. Linear acceleration stimulates the otoliths of the vestibular apparatus, and angular acceleration stimulates the hair cells of the semicircular canals. These organs provide the afferent input for the vestibulo-ocular reflex (VOR), the neuronal pathways of which are discussed in detail in Chapter 36. The reflex produces immediate, but slow, eye movements, which compensate for movement of the head and help stabilize the image on the area centralis. Thus, if the head moves up, the VOR moves the eyes down, and if the head moves to the left, the VOR moves the eyes to the right. It appears that the cat makes greater use of the VOR arc than the dog to follow moving objects. Comparison of the dog and cat when visually following a bouncing ball is most dramatic.

Nystagmus is usually characterized by a rapid eye movement in one direction and a slow movement in the opposite direction. Nystagmus can be either horizontal or vertical. The types of nystagmus are categorized on the basis of their causes, and they include optokinetic, rotatory, postrotatory, ocular, caloric, galvanic, anesthetic, brain stem, cerebellar, and vestibular. In optokinetic nystagmus, the eyelids must be open, and the fast phase is opposite in direction to the movement of the visual stimuli. However, the visual stimuli can be moving with the head stationary, or the head and body can be moving with the visual stimuli stationary. In the latter case, the fast phase is in the same direction as the movement of the head. This can be used as an objective means of detecting vision in animals. Optokinetic nystagmus usually occurs in the horizontal plane and is less well substantiated in the vertical plane. In rotatory nystagmus, the fast phase is in the same direction as the rotation of the head. In postrotatory nystagmus, which is seen after rotation stops, the fast phase is opposite to the direction of the rotation of the head. Postrotatory nystagmus lasts approximately 10 seconds after rotation stops. In rotatory and postrotatory nystagmus, the stimuli are acceleration and deceleration, respectively. At a constant rate of rotation, nystagmus does not occur if the lids are closed. Optokinetic nystagmus occurs if the eyelids are open. Ocular nystagmus is associated with congenital blindness and has a wandering or searching movement of the eyes rather than the distinct fast and slow phases (see Chapter 36 for more details).

There are several other types of eye movements. During certain stages of sleep, REM occurs, usually in bursts lasting from 5 to 60 minutes. Numerous REM bursts, which are traditionally associated with dreaming, may occur during a single sleep. Sleep patterns vary with age, however. Discrete eye movement bursts during certain stages of sleep are infrequent in newborn kittens, but after 3 weeks of age adult patterns of sleep develop (Hoppenbrouwers & Sterman, 1975).

Another important class of movements, microsaccades or micronystagmus, are those that maintain eye position while gazing at a stationary target (Alpern, 1982). These movements are required to maintain fixation on the object even when both the observer and the target are immobile. Though slow drifts are also used for this purpose, position maintenance movements are usually characterized by their low magnitude (several minutes/arc) and high frequency (1–50 per second).

Kittens are born with a divergent strabismus that is evident following eyelid opening at approximately 12–14 days postnatally. Normal interocular alignment, which depends on visual stimuli, develops during the second postnatal month (Sherman, 1972). Crossed eyes (i.e., convergent strabismus), which are commonly seen in adult Siamese cats and certain albino mammals, result from a genetic neuroanatomic defect in the primary visual pathway that involves the retinogeniculate and geniculocortical projections (Robertson et al., 1980; Shatz & Levay, 1979).

Oculocardiac Reflex

The oculocardiac reflex can cause reflexive slowing of the heart and can be stimulated by pressure on the globe, tension on the extraocular muscles or iris, or increased intraorbital pressure caused by injection, hemorrhage, or a foreign body. The most common effect of the reflex is bradycardia, but other clinically significant effects are cardiac arrest and ventricular fibrillation. The oculocardiac reflex has been reported in humans, dogs, cats, horses, rabbits, mice, and a cockatiel (Clutton et al., 1988; Panneton & Burton, 1985; Pipo et al., 1996; Rhode et al., 1958; Short & Rebhun, 1980; Walsh & Hoyt, 1969). The afferent arc of the oculocardiac reflex begins with the long and short ciliary nerves to the ciliary ganglion. The ophthalmic division of the trigeminal nerve (CN V) continues to the trigeminal ganglion to its sensory nucleus. The afferent arc continues along short internuncial fibers in the reticular formation to connect with the efferent pathway in the motor nucleus of the vagus nerve (CN X) to the myocardium. Sensory stimulation of the eye and orbital areas results in stimulation of the vagal nucleus

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in the brain stem, thus causing a reflexive slowing of the heart. Conscious, healthy rabbits and dogs do not show clinically significant decreases in heart rate with globe compression of 1 minute (Turner-Giannico et al., 2014). Endotracheal intubation can cause vagal stimulation as well, resulting in similar reflexive cardiac alterations (Brunson, 1980). In the dog, as the IOP increases, the heart rate may also increase, thus indicating the possibility of an intraocular-sympathetic-cardiac reflex as well as a trigeminovagal reflex (Howard & Sawyer, 1975).

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4

Optics and Physiology of Vision

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The aim of this chapter is to describe the physical, anatomic, and physiologic aspects of the process of vision. With this aim in mind, the chapter has been divided into two parts. The first part is devoted to visual optics. It covers the physical changes that light undergoes during its passage from the cornea, through the various structures and tissues of the eye, until it reaches the retina. One may question the amount of text that has been devoted to optical aberrations in the eye and to species not normally seen as patients, such as aquatic animals, chickens, and fish; however, understanding how various species cope with these aberrations, or with their unique habitat, is fundamental to the understanding of visual optics.

The second part of this chapter is devoted to visual processing and describes what happens once light reaches the retina. This part is dedicated to the neuronal processes of vision and describes the generation, processing, and propagation of the visual signal in the retina, the visual pathways, and the cortex. Both these parts lay the foundations for understanding how optical and neuronal processes enable the detection of stimulus movement, details, and color that create the rich experience of vision described in Chapter 5.

Visual Optics

Physical Optics

Light

The nature of light has long been a subject of controversy. Light has alternately been described as a wave (first proposed by Huygens in 1678) or as photon particles (first proposed by Newton in 1672). However, these descriptions are not mutually exclusive. Quantum optics (first proposed by Planck in 1900) integrates both models to explain the dual nature of light and its interaction with matter. Both models also are applicable in the eye: the wave theory explains the physical changes light undergoes during its passage through the eye, and the particle theory explains the energy transformation that occurs when light is absorbed in the outer segments of the photoreceptors. Therefore, the first part of this chapter discusses light as a wave, while the second part discusses it as a particle.

Light behaves like a wave as it passes through transparent media such as air, vacuum, or the visual axis of the eye. Much like a wave of water, a wave of light has two principal characteristics (Fig. 4.1). Its amplitude, A, is the maximum value of the field generated by the propagating wave; it determines the wave's intensity. The wavelength, λ, is the distance between adjacent wave crests; it determines the wave's location in the electromagnetic spectrum. As Fig. 4.2 shows, light, which is the visible portion of the electromagnetic spectrum, occupies a small fraction of that spectrum, which ranges from cosmic and gamma rays ($\lambda < 10^{-10}$ m) to radio transmission ($\lambda > 10^{3}$ m). In humans, visible light ranges in wavelength from approximately 380 (i.e., deep blue) to 780 (i.e., deep red) nm (Wang et al., 2014). However, additional wavelengths, outside the 380–780 nm spectrum, can be seen by other species. For example, many nonmammalian species, and some mammals, possess ultraviolet (UV) vision that allows them to detect light with a wavelength shorter than 380 nm, enabling them to see hues that are not perceived by humans (Odeen et al., 2011). This capability is used in both foraging and courting behavior (Hogg et al., 2011). At the other end of the spectrum, fish living in blackwater rivers, in which the maximally transmitted light is longer than 600 nm, have evolved near-infrared (IR) vision, enabling them to detect light with a wavelength longer than 780 nm that is prevalent in their environment (Shcherbakov et al., 2013). The cat retina has also been shown to respond to IR light (826–875 nm), though the functional and behavioral implications of this capability are not clear (Gekeler et al., 2006). This is not to be confused with the IR "vision"

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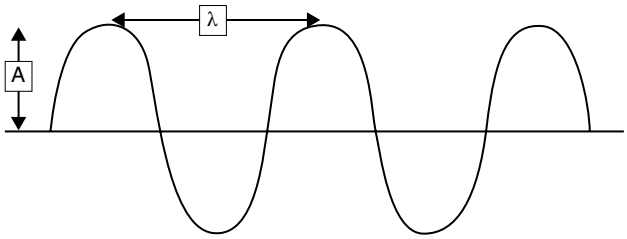


Figure 4.1 Representation of light as a wave, which is characterized by two parameters. Its amplitude (A) is the maximum value the wave obtains as it propagates. Its wavelength (λ) is the distance between two consecutive peaks.

of snakes, which relies on the heat-detection properties of the pit organs (Bolívar-G et al., 2014).

At the same time, light also possesses the properties of particles, termed *photons*, which represent quanta of energy that can be emitted (at the light source) or absorbed (e.g., by retinal photoreceptors). The amount of energy in a given photon is inversely proportional to its wavelength; therefore, blue light possesses more energy than red light, which has a longer wavelength (see Fig. 4.2). An example of the particle nature of light is seen in the use of cobalt blue light to highlight fluorescein staining of corneal ulcers. Fluorescein sodium molecules absorb photons of blue light and reemit photons with a lower energy content, in the yellow-green portion of the spectrum, in a process known as fluorescence (Glasgow, 2016).

As light strikes the photoreceptor outer segments, it is absorbed by a visual photopigment. The function of this two-part molecule reflects the principles of quantum physics, as it utilizes both the wave properties and the particle properties of light. The first part of the molecule, the *opsin*, determines the wavelength of the light that the photopigment will absorb, thus determining color vision. The second part of the molecule, the visual chromophore or *retinal*, uses the energy of the photon particle to undergo isomerization (from 11-*cis*-retinal into all-*trans*-retinal in the case of rhodopsin), thereby initiating conversion of a light stimulus into an electric signal. This process, the *phototransduction process*, which is discussed in detail later in this chapter, is the first step in the initiation and propagation of a visual signal.

Photometry

Photometry is the quantitative measurement of visible light. Photometry measures a number of interrelated properties of light, using a basic unit called a *candela*. Two important characteristics of light are its *luminous intensity*, which describes the intensity of a light source (as measured in candela), and its *luminance*, which describes its brightness reflected from a surface (as measured in foot-Lamberts or *candela/m*^{2}). These two properties are related, but they are not necessarily proportional. A handheld transilluminator is a bright source of light, but it possesses low intensity and therefore cannot be used to illuminate a football stadium. On the other hand, a streetlight provides high-intensity light, which illuminates a large area, but it is not bright and does not provide enough illumination to conduct cataract surgery. Table 4.1 provides the luminances of several common sources of light.

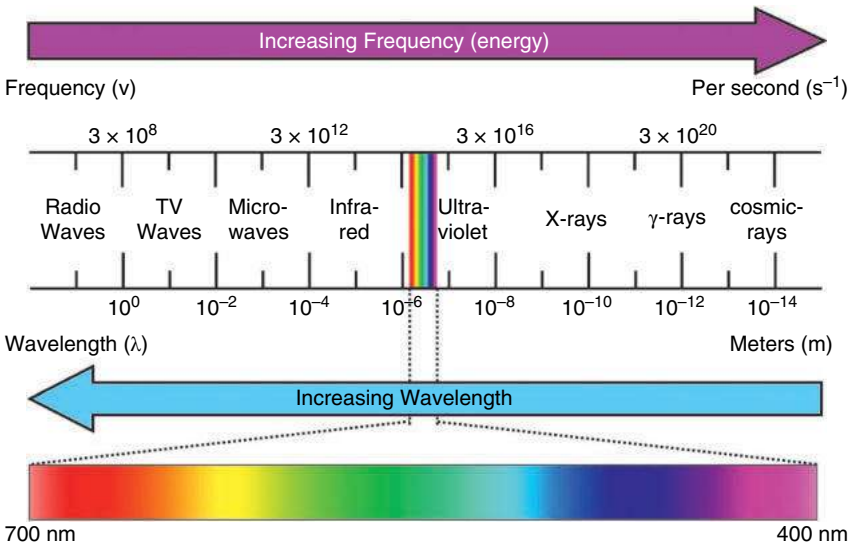


Figure 4.2 Spectrum of electromagnetic radiation. Visible light occupies only a small portion of the spectrum. Most humans can see radiation with a wavelength of approximately between 380 and 780 nm. Some animal species see a more limited part of the spectrum, while others can discern larger portions of the spectrum, as they are also able to perceive shorter (ultraviolet) or longer (infrared) light. Note that the wavelength (blue arrow) of a light wave are inversely related to its energy and frequency (purple arrow). (Reproduced from www.chemicalconnection.org.uk with permission of Dr. Paul Murray.)

Table 4.1 Luminances of natural and artificial light sources[a].

Source	Luminance (cd/m^2)
Sun	10^9
Car light	10^7
Incandescent tungsten lamp	10^6–10^7
Fluorescent lamp	10^4–10^5
Clear sky at noon	10^4
Full moon	10^3
Street lamp	0.1–1.0
Moonless night sky	10^{-3}–10^{-6}

Source: Adapted from Millodot, M. (2018) *Dictionary of Optometry and Visual Science*, 8th ed. St. Louis, MO: Elsevier.
[a] In general, only the *photopic* system is active at a luminance > 3 cd/m^2; at a luminance < 0.03 cd/m^2, the *scotopic* system functions alone. Both systems are active at intermediate luminance values, which are defined as *mesopic* vision.

Luminance is measured using photometers, which are divided into two major classes. Visual photometers provide a subjective reading, because the observer compares the illumination of the measured light with that of a standard light. Photoelectric photometers convert the measured light into an electric current, which is displayed by the instrument. Photometry measurements are extremely important in electroretinographic (ERG) recordings because they are used to describe such variables as threshold, ambient and adapting lights, and stimulus luminance.

Transmission and Reflection

As noted, human vision is limited to a wavelength range of 380–780 nm. This limitation is a result of two factors. The first is the absorption spectrum of the opsin component of the visual photopigment, mentioned previously. The second limiting factor is the transmission, reflection, and attenuation of the various wavelengths by the ocular media, which depend on several properties, the most significant being the wavelength of the light, the angle of incidence, and the clarity of the media.

In humans, radiation wavelengths of 300–2500 nm are transmitted through the cornea (Boettner & Wolter, 1962). Not all wavelengths, however, are transmitted through the cornea equally, as transmission is directly related to wavelength. For example, the human cornea transmits 95% of light with wavelengths of 650 nm or longer, but only 80% of light with a wavelength of 425 nm (Calhoun et al., 2015). In the rabbit, the cornea transmits 89%–93% of the light at 370–500 nm, falling to 50% transmittance at 310 nm and a mere 2% at wavelengths below 290 nm (McLaren & Brubaker, 1996).

Additional attenuation of transmission occurs inside the eye (Fig. 4.3). Even though light with wavelengths of up to 2500 nm passes the cornea, there is barely any transmission of wavelengths greater than 1950 nm through the aqueous humor, and in humans the lens only transmits wavelengths between 390 and 1400 nm (Boettner & Wolter, 1962). A similar range of wavelengths is transmitted through the pig eye (Lei & Yao, 2006). The implication of these numbers is that the aqueous and lens act as color filters, preventing UV and IR light with very short and very long wavelengths (which has passed the cornea) from reaching the retina. The UV filtering by the lens is of particular importance, as UV light is a risk factor in a number of retinal diseases, particularly age-related macular degeneration (Schick et al., 2016). Therefore, intraocular lenses (IOLs) contain chemically-bound UV filters to restore this protection in pseudophakic patients. Consequently, aphakic humans can detect UV radiation following lens extraction, having lost the UV-filtering lens (Li et al., 2017b). In other words, human opsin is capable of absorbing UV light, but these wavelengths do not reach the retina of phakic subjects (Griswold & Stark, 1992). Conversely, transmittance of light by the eye does not automatically result in vision, because transmitted radiation must be absorbed by a photopigment sensitive to that wavelength before the light can be perceived. This is why humans cannot perceive infrared light, even though it reaches the retina (Fig. 4.3).

Additional ocular structures, such as tear film (Choy et al., 2011) and eyelids (Bierman et al., 2011), also act as color filters, causing significant attenuation of short-wavelength

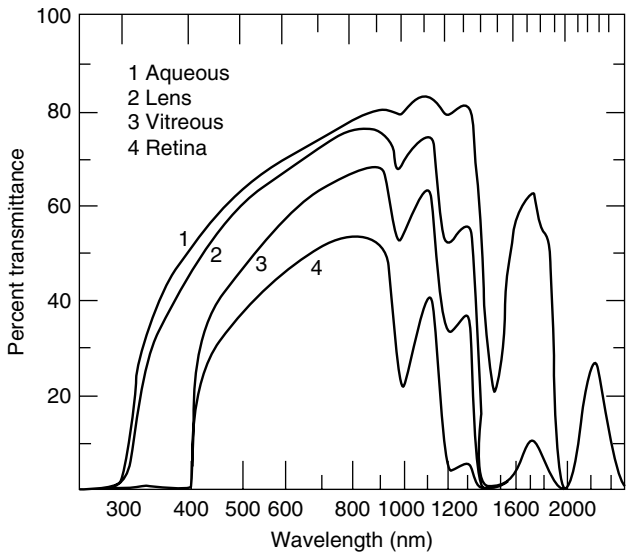


Figure 4.3 Transmittance rates of light through various structures of the human eye, not including light lost due to reflection or scatter, at each wavelength. (Reprinted with permission from Boettner, E.A. & Wolter, J.R. (1962) Transmission of the ocular media. *Investigative Ophthalmology*, **1**, 776–783.)

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light. Thus, when cumulative transmittances are calculated for the successive components of the eye, a maximal transmittance rate in humans of 84% is obtained for light between 650 and 850 nm (Boettner & Wolter, 1962), while in rabbits the transmittance rate for light between 370 and 500 nm is 90% (McLaren & Brubaker, 1996). Obviously, transmission will be further reduced by ocular opacities. Grade II nuclear cataracts in rats cause a 50% reduction in transmission of light compared with grade I cataracts (Nishimoto & Sasaki, 1995), and in humans the light scatter index for nuclear cataracts is twice that of cortical cataracts (Siik et al., 1999). Age is another factor affecting transmittance. Transmission of light at 480 nm through the human lens decreases by 72% from the age of 10 years to the age of 80 years (Kessel et al., 2010), thus affecting the color perception of the elderly. Surprisingly, however, studies have failed to demonstrate age-related decline in transmittance in the human cornea (van den Berg & Tan, 1994).

Ocular surfaces can also reflect back incoming light, depending on the angle of incidence. Light that strikes a surface at an oblique angle is reflected back; it is not transmitted into the new medium. The critical angle for reflection is determined by the difference in the indices of refraction between the two media (discussed in the next section). Most of the reflection that takes place in the eye occurs as incoming light strikes the cornea because of the large difference in refraction indices between the cornea and air. Reflection that occurs at the cornea–air interface affects not only incoming light, but also outgoing light. Thus, internal reflection of outgoing light back into the eye prevents the ophthalmologist from examining the iridocorneal angle. Goniolenses filled with fluid are used to decrease the difference in refractive indices between the cornea and air, thus increasing the critical angle and permitting rays emanating from the iridocorneal angle to pass through the cornea (Wilson, 2006).

Light that is not transmitted and not reflected can be either scattered in the eye or absorbed by pigments. Foremost among these pigments are the photopigments of the photoreceptor outer segments, which absorb photons and thus initiate the visual process. Additional absorption processes in the eye may have clinical implications. Cyclophotocoagulation in glaucoma patients is based on the preferential absorbance of 810 and 1064 nm radiation of the diode and Nd : YAG lasers, respectively, by melanin-containing tissue (Bras & Maggio, 2015). In addition, absorption of UV solar radiation has been implicated in diseases such as canine chronic superficial keratitis (Chandler et al., 2008), squamous cell carcinoma in cattle (Pausch et al., 2012), and pterygium (Zhou et al., 2016), cataract, and macular degeneration in humans (Delcourt et al., 2014). The interaction of the cornea with UV light may also hold implications for corneal cross-linking treatment (Lombardo et al., 2015).

Geometric Optics

Refraction

In vacuum, light travels at a constant speed (c) of approximately 3×10^8 m/s. As it strikes denser media, light undergoes three changes:

1) Its velocity is reduced.
2) Its wavelength shortens.
3) It is bent (unless it struck the surface of the medium at a 90° angle).

The first two changes are expressed in the equation

$$n = c/v = \lambda/\lambda_m,$$

where n is the *index of refraction* (or bending) of the new, dense medium; c and λ are the speed and wavelength, respectively, in vacuum; and ν and λ_m are the velocity and wavelength, respectively, in the new, dense medium.

Since the index of refraction of any medium other than vacuum is greater than one ($n > 1$), it follows that $c > \nu$; that is, the speed of light in the new medium (ν) is less than it was in vacuum (c). For the same reason ($n > 1$), it follows that $\lambda > \lambda_m$; that is, the wavelength of light in the new medium (λ_m) is shorter than it was in vacuum (λ).

The third change that occurs when light passes into a dense medium is bending, or refraction. The amount of refraction that occurs as light passes from one medium to another is described by Snell's law (Fig. 4.4) and is determined by the angle of incidence and by the refractive indices

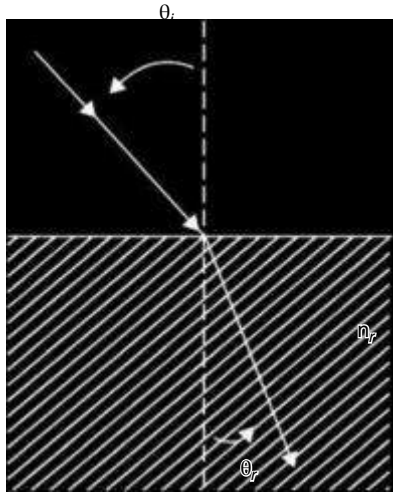


Figure 4.4 Refraction of light as it passes from one medium to another is governed by Snell's law, summarized in the formula below the diagram. The angle of refraction (θ_r) is a function of the angle of incidence (θ_i) and the refractive indices of the two mediums. In this representation, $n_i < n_r$; therefore, $\theta_i > \theta_r$.

of both media. Because various structures of the eye differ in their refraction indices, light is successively refracted (bent) as it passes from air through the precorneal tear film (PTF), cornea, aqueous humor, lens, and vitreous on its way to the retina (see the next section, "Visual Optics").

Vergence

An object that bends (or refracts) light is called a lens. When a single ray of light strikes a lens, the ray undergoes simple refraction, as depicted in Fig. 4.4. Most objects or images, however, generate a pencil of light rays rather than a single ray. When a pencil of rays strikes a lens, they spread apart (i.e., diverge) or come together (i.e., converge). Convergence, or positive vergence, occurs when light strikes a convex lens (Fig. 4.5A, B). Such a lens has a positive power, indicating that it forms a *real image*, which means that incoming rays from the object are converged and focused on the other side of the lens (see Fig. 4.5A, B). On the other hand, divergence, or negative vergence, occurs when light strikes a concave lens (Fig. 4.5C). The negative power of the concave lens indicates that it forms a *virtual* or *aerial* image, which means that the diverging rays are traced, using imaginary extensions, backward to a "focused" virtual image "located" on the same side of the lens as the object (dashed, "imaginary" lines in Fig. 4.5C).

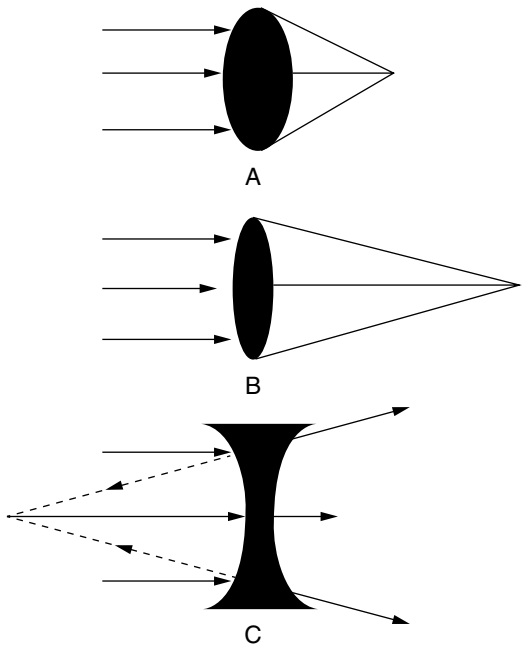


Figure 4.5 Refraction of light through various lenses. **A.** A spherical convex lens with a power of 10 D focuses parallel light rays at a distance of 0.1 m. **B.** A flatter, less spherical convex lens with a power of 5 D focuses parallel rays at a distance of 0.2 m. **C.** Parallel rays passing through a concave spherical lens diverge. A virtual image is formed by tracing back (dashed lines) the diverging rays.

The vergence power (i.e., amount of bending) of a lens is measured in units called *diopters*. One diopter (D) is the vergence power of a lens with a focal length (f) of 1 m when in air. In broader terms,

$$D = 1/f.$$

The focal length of a lens is the distance between the center of the lens and the point at which parallel rays of light are brought into focus by that lens. The focal length of a lens is directly proportional to its curvature radius. Therefore, the vergence power (or the diopter power) of the lens increases as its curvature increases (or its radius of curvature decreases). For example, a convex lens with a focal length of 0.1 m will have a power of +10 D ($D = 1/f = 1/0.1\,m = 10\,D$), while a flatter convex lens with a focal length of 0.2 m will be "weaker," with a power of +5 D ($D = 1/f = 1/0.2\,m = 5\,D$; compare Fig. 4.5A and Fig. 4.5B). On the other hand, a concave lens with a focal length of 0.2 m will have a power of −5 D (Fig. 4.5C).

The vergence powers of lenses in an optical system are additive. Thus, if the lenses in Fig. 4.5A and Fig. 4.5B were placed next to each other, the resulting optical system would have a theoretical power of +15 D. If all three lenses in Fig. 4.5 were combined into one system, it would have a power of +10 D. This principle also holds in the eye, as the refractive contributions of the successive ocular surfaces are added to form a focused or blurred image on the outer segments of the photoreceptors.

As noted, the former formula describes the refractive powers of lenses in air. When placed in a medium with a refractive index n, the refractive power of the lens is described by the formula

$$D = n/f.$$

Since $n > 1$ for any medium other than vacuum, it follows that the refractive power of the lens is reduced in other media. This is what happens to lenses in the eye, an effect that is described in detail in the following section.

Visual Optics

Refractive Structures of the Eye

Precorneal Tear Film and Cornea

As mentioned, light is successively refracted by the various ocular structures as it passes through the eye on its way to the retina. Table 4.2 lists the refractive indices and powers of various ocular surfaces in humans. The most anterior optical surface of the eye is the PTF. By strict definition, it could be argued that the tear film is the most refractive layer of the eye. This is due to the large difference in refractive indices as light passes from air, which has a refractive index of almost 1, into the tear film, which has a refractive index of 1.337 (Barbero, 2006). Factoring the refractive indices of air and the tear film into Snell's law reveals that the human PTF has

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Table 4.2 Refraction constants in the human eye.

Structure	Refractive Index	Refractive Power (D)	Reference
Tear film	1.336	43.0[a]	Montes-Mico et al. (2004)
Cornea	1.376	42.3[a]	Duke-Elder (1970); Naeser et al. (2016)
Anterior surface	1.401	48.2	Patel et al. (1995)
Posterior surface	1.373	−5.9	Patel et al. (1995)
Lens	1.41	21.9	Chang et al. (2017); Duke-Elder (1970)
Anterior surface		8.4	Millodot (1982)
Posterior surface		14.0	Millodot (1982)
Vitreous/aqueous	1.336		Duke-Elder (1970)
Retina	1.363		Millodot (1982)

[a] The refractive power of the cornea and tears is not additive. Rather, that of the former arises from the latter, and from its interface with air. The net power of the tears and the anterior and posterior cornea is 43 D.

a refractive power of 43 D (Montes-Mico et al., 2004). Alterations in the composition (Fish et al., 2004) or breakup time (Montes-Mico et al., 2004) of the PTF may change the refractive power of the eye by as much as 1.3 D and may contribute to the blurry vision complaints commonly encountered in (human) dry eye patients (Koh, 2016). Conversely, successful treatment of dry eye can cause a significant improvement in blurred vision (Toshida et al., 2017). The effect of PTF deficiencies on the quality of vision in animal patients has yet to be studied.

The cornea is the next organ through which incoming light passes. As can be seen in Table 4.2, the human corneal stroma has a refractive index of 1.376. Because this value is slightly higher than the refractive index of the tear film, passage of light from the PTF into the anterior layers of the cornea results in an additional 5 D of refractive power (Courville et al., 2004). However, these 5 D are "lost" when light passes from the posterior cornea into the aqueous humor, which has a refractive index nearly identical to that of the PTF. When combined, the PTF and the cornea of humans contribute a net refractive power of 43 D. Strictly speaking, these 43 D are contributed by the tear film, as they are due to the large difference between the refractive indices of air and the PTF. Still, by convention, this power is usually attributed to the cornea (see Table 4.2). Therefore, in humans, for example, the cornea contributes approximately 70% of the total 60 D power of the eye, thus making it our largest refractive organ (Courville et al., 2004).

Another factor affecting the refractive power of the cornea, besides the refractive index, is its curvature. Because the cornea converges light, it acts as a convex lens. As stated earlier, the refractive power of such a lens depends to a large extent on its curvature radius. Therefore, in large eyes, which are characterized by relatively flat corneas, the refractive power of the cornea is reduced. Conversely, in small eyes with more spherical corneas, its power is increased. Table 4.3 shows that the inverse relationship between globe axial length and the refractive power of the cornea is maintained across a large range of species. Furthermore, the central and peripheral corneas have different curvatures and consequently differ in their refractive powers (see "Spherical and Chromatic Aberrations" later in this chapter). It is suggested that evolutionary changes in corneal curvature and shape, especially between mammalian and nonmammalian species, are reflected in collagen lamellar organization in the stroma (Winkler et al., 2015).

Lens

As noted, because of the similar refractive indices of the cornea and aqueous humor, the refraction that occurs as light passes from the former into the latter and during its passage through the aqueous has little overall optical significance. Therefore, the next significant refractive structure through which light passes after the cornea is the lens (see Table 4.2 and Table 4.4). As in the case of the cornea, the refractive power of the lens is determined by both its refractive index and its curvature. In humans and in many nonaquatic species, the refractive index of the lens nucleus is about 1.41; it decreases gradually toward the cortex, forming a bell-shaped refractive index curve known as the *gradient index* (GRIN). In humans, the refractive index in the subcapsular regions is about 1.38 (Piersckionek & Regini, 2012). Since these values are relatively similar to that of the aqueous humor (range, in most species, 1.334–1.338), the lens in these species has a rather low refractive power (Hughes, 1977). In humans, the calculated refractive power of the lens is approximately 22 D (Chang et al., 2017). The implication of this value is that contrary to the popular belief of the general public, the lens is not the main refractive organ of the eye, as its refractive power is less than half of that of the human cornea. The refractive index of the lens increases in aquatic species, where it can be as high as 1.66, resulting in significantly higher refractive power (Sivak, 1978).

Table 4.3 Eye size (ascending order) and corneal power (descending order) in selected animal species.

Species	Axial Length (mm)	Corneal Power (D)	References
Goldfish	4.2	129 (in air)	Hughes (1977)
Rat	6.3	112.7	Hughes (1977)
Chicken	8.9	108	Cohen et al. (2008)
Guinea pig	8.9	83.9	Howlett & McFadden (2007)
Sea otter	14.0	59.2	Murphy et al. (1990)
Rhesus monkey (4 months)	16.3	56	Qiao-Grider et al. (2010)
Rabbit	18.0	44.6	Hughes (1977); Wang et al. (2014)
Cat	21.3	43.0	Habib et al. (1995)
Dog	19.5–21.9	37.8–43.2[a]	Gaiddon et al. (1991); Nelms et al. (1994); Rosolen et al. (1995)
Ostrich	38.0	25.3	Martin et al. (2001)
Elephant	38.8	21.3	Murphy et al. (1992a)
Horse	39.2	16.5 D	McMullen & Gilger (2006)
Horse	43.7	15.7–19.5	Farrall & Handscombe (1990); Miller & Murphy (2017)

[a] The range of values in the dog probably reflects a breed difference, because larger breeds have flatter corneas (Gaiddon et al., 1991).

Table 4.4 Lens power and refractive indices (both in descending order) in selected animal species.

Species	Lens Power (D)	Refractive Index	References
Rat	243.9	1.683	Hughes (1977)
Guinea pig	160.0	1.649	Howlett & McFadden (2007)
Rabbit	75.0	1.6	Hughes (1977)
	58[a]		Sanchez et al. (2017)
Cat	52.9	1.554	Hughes (1977)
Cynomolgus monkey	52.0	1.42	Borja et al. (2010)
Chicken (90 days)	48.1	1.44	Iribarren et al. (2014)
Dog	41.5[b]		Davidson et al. (1993)
Horse	14.9–15.4	1.42	Farrall & Handscombe (1990); Mouney et al. (2012)
Horse	14[b]		Harrington et al. (2013); Townsend et al. (2012)

[a] Calculated value;
[b] Value is based on dioptric strength of intraocular lens needed to regain emmetropia in pseudophakic patients.

The second factor determining lenticular refractivity, the lens curvature, also differs between aquatic and nonaquatic species. Generally, it can be said that the lens is spherical in fish and aquatic mammals, while it is more discoid (i.e., less spherical) in terrestrial species (see Fig. 4.5A and Fig. 4.5B, respectively). Therefore, the lens will have a higher refractive power in the former compared to the latter. The reason for the increased refractive index and lens curvature in aquatic species is the loss of corneal refractive power under water and is discussed later in this chapter. Of course, the curvature (and hence the refractive power) of the lens can also be changed actively through a process termed *accommodation* (see the next section).

Vitreous

The next refractive organ is the vitreous. Though there is little refraction as light passes from the lens into the vitreous (due to their similar refractive indices), the vitreous plays an important role in the refractive development of the eye. Vitreous elongation increases the axial length of the eye, thereby increasing the refractive path of light and inducing myopia, or nearsightedness (Fig. 4.6). In certain fish, this mechanism serves to increase ocular refraction and compensate for loss of corneal refractive power. In different goldfish strains, for example, the vitreous body can contribute anywhere from 37% to 70% of the total axial length of the eye (Seltner et al., 1989). In visual deprivation studies conducted

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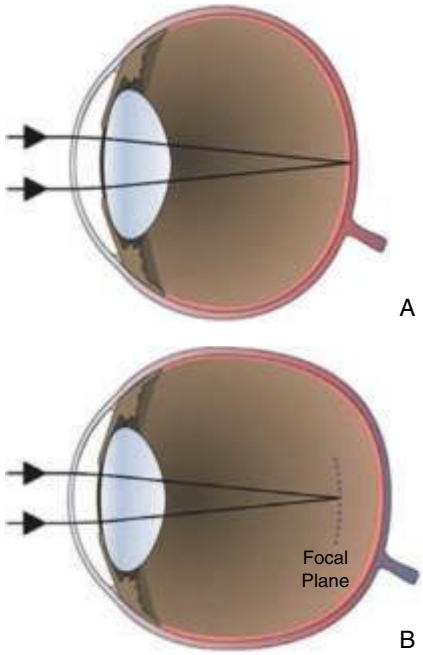


Figure 4.6 The effect of vitreous elongation on ocular refraction. **A.** A focused, emmetropic eye. **B.** The refractive power of the eye has not changed, and the light is focused on the same spot as in panel **A.** However, due to vitreous elongation, the retina has moved posteriorly, and therefore the light is now focused in front of the retina. As a result, the eye is now nearsighted, or myopic.

during critical developmental periods in species as diverse as chickens (Stone et al., 2016), fish (Sivak, 2008), tree shrews (Gawne et al., 2017), and nonhuman primates (Smith et al., 2015), the deprivation-induced myopia was a result of elongation of the vitreous body.

Accommodation

Accommodation is a rapid change in the refractive power of the eye, which is intended to bring the images of objects at different distances into focus on the retina. The stimulus for the accommodative response is a blurred, or defocused, retinal image (Buehren & Collins, 2006). In vertebrates, eyes accommodate by one or more of the following mechanisms (Glasser, 2011):

1) Changing the curvature or position of the lens.
2) Changing the corneal curvature.
3) Changing the distance between the cornea and retina.
4) Having two or more separate optical pathways of different refractive powers (discussed under "Static Accommodation" later in this chapter).

Accommodation is most commonly measured using *infrared photoretinoscopy*, which uses reflection of IR light from the fundus to measure dynamic changes in the refractive error. Since mammalian accommodation is mediated by contraction of the smooth ciliary muscle, it can be stimulated by pilocarpine (Ostrin et al., 2014). For a comprehensive review of comparative accommodation in animals, the reader is referred to Ott (2006).

Humans and other primates accommodate by changing the curvature of the lens (Fig. 4.7). To view distant objects, sympathetic innervation induces relaxation of the ciliary body muscle, which in turn leads to stretching of the lens zonules. The increased tension of the zonules results in a greater pull on the lens capsule, thus causing the lens to become more discoid and decreasing its overall axial thickness and refractive power in a process of *disaccommodation* (see Fig. 4.5B and Fig. 4.7B; Glasser, 2011). To accommodate for near objects, the reverse process takes place. Parasympathetic input induces contraction of the ciliary body muscles, leading to relaxation of the zonular fibers and reduced tension on the lens capsule. In turn, this liberates the inherent elasticity of the lens, resulting in a more spherical lens possessing greater axial thickness and refractive power (Fig. 4.4A and Fig. 4.7A; Glasser, 2011; Hughes, 1977). Consequently, anterior chamber depth decreases and

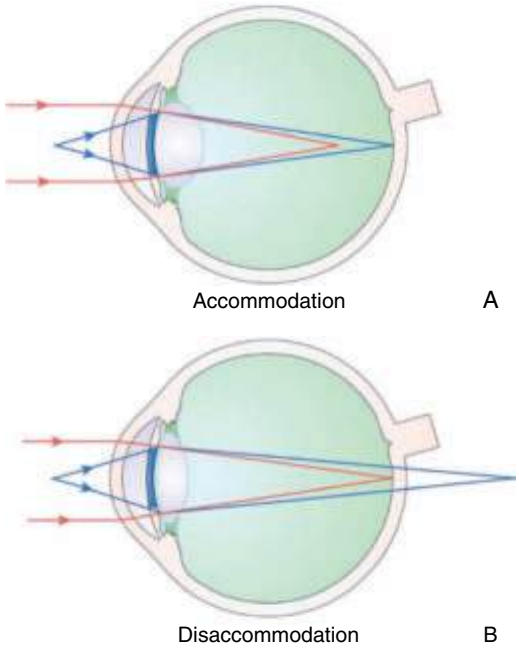


Figure 4.7 Accommodation in the primate lens. **A.** In an accommodated eye, the ciliary muscle contracts, causing the lens to become more spherical, thereby increasing its refractive power. Light from nearby objects (blue lines) is focused on the retina (emmetropia), whereas light from distant objects (parallel red lines) is focused in front of the retina (myopia, or nearsightedness). **B.** At rest the lens is discoid (flat) because of relaxation of the ciliary muscle (disaccommodation). In this state, incoming light from distant objects (parallel red lines) is focused on the retina (emmetropia), whereas light from nearby objects (blue lines) is focused behind the retina (hyperopia, or farsightedness). (Reproduced with permission from Maggs, D.J., Miller, P.E., & Ofri, R. (2018) *Slatter's Fundamentals of Veterinary Ophthalmology*, 6th ed. St Louis, MO: Elsevier.)

increases during accommodation and disaccommodation, respectively. The resulting changes in lenticular curvature allow primates such as the young (< 5 years) rhesus monkey to accommodate by as much as 34 D (Bito et al., 1982). As the animal ages, however, it gradually loses its accommodative capability in a process termed *presbyopia*, and monkeys older than 25 years can accommodate only by an average of 5 D (Bito et al., 1982). A similar and dramatic age-related reduction has been reported in the chicken, as lenticular accommodation decreases from more than 20 D at hatching to less than 5 D at 1 year of age (Choh et al., 2002b). In humans, presbyopia causes a reduction of 0.32 D per year in the refractive power (Croft et al., 2013). Mechanisms proposed for presbyopia include reduction in ciliary muscle contractility, changes in the refractive index of the lens, age-related changes in the relative position of the lens and ciliary body, and loss of the lens capsule and lens fiber elasticity (Charman, 2008; Glasser, 2011; Reilly, 2014).

As with most other aspects of vision research, the mammalian species in which accommodative capabilities have been studied most extensively is the cat. The elasticity of the feline lens capsule is only 5% of the elasticity in humans; thus, the cat is incapable of accommodating by changing its lens curvature (Fisher, 1971). Instead, *translation* (i.e., the anteroposterior movement of the entire lens) is responsible for accommodative changes in the feline eye (Glasser, 2003; Hughes, 1977; Ott, 2006; Sunderland & O'Neil, 1976). This movement is made possible by the relative abundance of meridional (i.e., longitudinal) fibers in the feline ciliary body muscle and by the relative scarcity of circular fibers, which predominate in primates (Ebersberger et al., 1993; Prince et al., 1960). Parasympathetic stimulation of the meridional muscle fibers in the cat results in anterior displacement of the lens by up to 0.6 mm (O'Neill & Brodkey, 1969), thus inducing anywhere between 2 and 4 D of accommodation (Ott, 2006). The dog's accommodative power is reportedly lower, only 1–3 D in range (Hughes, 1977; Miller & Murphy, 1995). Factoring these accommodative powers into the $D = 1/f$ formula reveals that though cats and dogs can focus on distant object (by disaccommodating), their depth of field for nearby objects is 50–25 cm (cats) and 100–33 cm (dogs). Closer objects are usually perceived using the sense of smell.

In other carnivore species, the same translation mechanism is used to achieve a significantly greater magnitude of accommodation. Anterior lens movement in the raccoon induces accommodation of up to 19 D, 6× more than in the dog (Rohen et al., 1989), while the mongoose accommodates up to 13.5 D (Ott, 2006). A similar wide range of accommodative capability also exists in other closely related species. For example, the gray squirrel does not accommodate (McBrien et al., 1993), whereas the California ground squirrel can accommodate up to 6 D (McCourt & Jacobs, 1984). It should be noted that in mammals, translation of the accommodating lens results from ciliary muscle contraction, but in teleost fish, it is affected by a specialized smooth muscle, the *retractor lentis*, which pulls the lens backward to focus on distant objects (Khorramshahi et al., 2008). Snakes also accommodate by moving their lens. However, as snakes lack a ciliary muscle, accommodation is accomplished by contraction of the iris, which causes an increase in vitreous pressure that pushes the lens anteriorly (Fontenot, 2008). And in cetaceans, anterior lens displacement is due to increased intraocular pressure mediated by contraction of the retractor bulbi muscle (Mass & Supin, 2007).

Rodents (Artal et al., 1998) and ruminants (Piggins & Phillips, 1996) are generally described as lacking accommodative capabilities. In the former, this lack of accommodation is explained by the absence of a well-defined ciliary muscle (Samuelson, 1996), though the small pupil size and short axial length in species such as the rat and mouse provide these animals with a significant depth of focus (Geng et al., 2011). Lack of accommodation in ruminants, some of which possess a more developed ciliary muscle (Samuelson, 1996; Samuelson & Lewis, 1995), is more difficult to explain, and may be a consequence of the cytoarchitecture of the lens fibers (Kuszak et al., 2006). Other ungulates also have a very limited accommodative capability. Horses, for example, can accommodate only ±1 D (Miller & Murphy, 2017; Sivak & Allen, 1975).

Another species in which accommodation has been studied extensively is the chicken, which employs several accommodative mechanisms, enabled by the presence of three ciliary muscles: anterior (*Crampton's muscle*), intermediary (*Müller's muscle*), and posterior (*Brücke's muscle*) (Tedesco et al., 2005). Lenticular accommodation in the chicken is mediated by the intermediary and posterior ciliary muscles, which (as in mammals) are parasympathetically innervated by postganglionic ciliary nerves. However, several unique anatomic adaptations combine to significantly increase the lenticular accommodative capability of the chicken compared to that of mammals (Fig. 4.8). These include very large ciliary processes, as well as a ring of columnar epithelial cells at the equatorial periphery of the lens (i.e., the annular pad), which increases the diameter of the lens and its contact area with the processes. Lenses are soft and malleable, and the corneoscleral sulcus, which exists as a consequence of the scleral ossicles, permits a greater range of movement (Choh et al., 2002a). Together, these structures make it possible for contraction of the intermediary and posterior ciliary muscles to directly squeeze the lens, as compared to the indirect effect of the mammalian ciliary muscle, which is transmitted to the lens through the zonules. Contraction of the peripheral iris (Ostrin et al., 2011), as well as the posterior and intermediary ciliary muscles (West et al., 1991), induces thickening of the lens by 0.2 mm, steepening of its curvature, and a bulging of the lens into both the anterior and vitreous chambers (Choh et al., 2002a). The cumulative results of all these mechanisms is 15–19 D of lenticular accommodation (Choh et al., 2002a).

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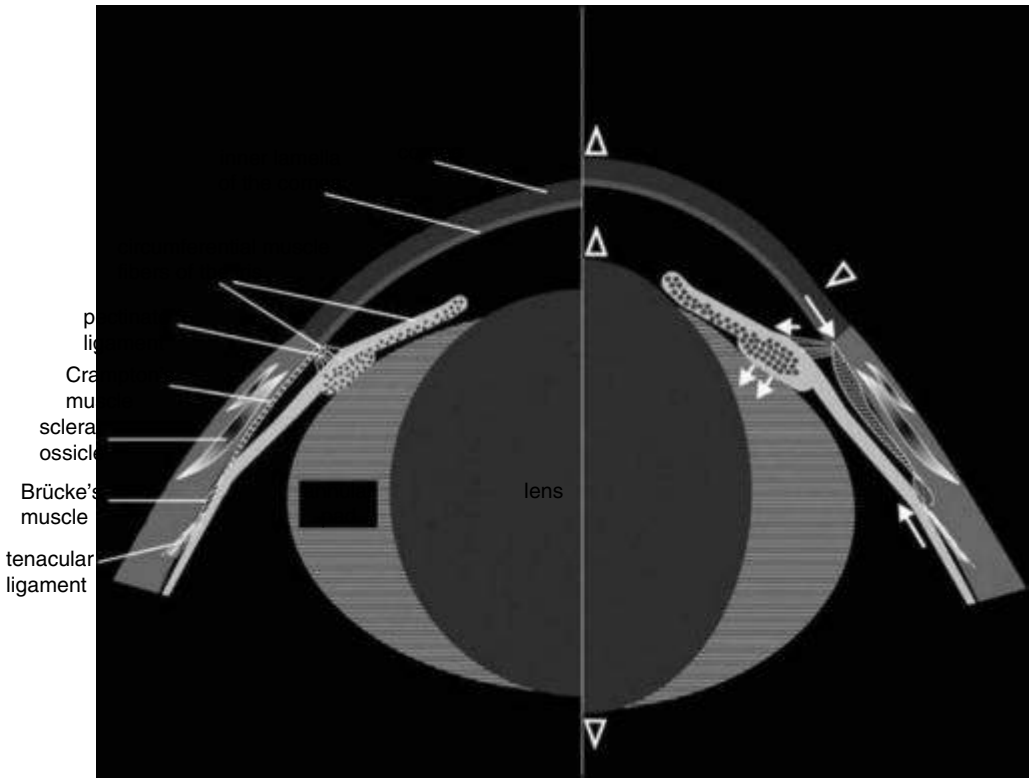


Figure 4.8 A generalized scheme of the mechanism of accommodation in birds. Left side: Relaxed state. Note the deep corneoscleral sulcus, the presence of Brucke's and Crampton's muscle (Müller's muscle not shown), the annular pad, and the lack of zonules, which allows direct contact between the ciliary processes and annular pad. All of these features contribute to the great accommodative power of the chicken eye (see text for details). Right side: An accommodated state. The black arrows show the direction of the contracting muscle forces. The open arrowheads show the resulting deformation of both the cornea and the lens. Similar mechanisms have also been found in lizards, snakes, and turtles. (Reproduced with permission from Ott, M. (2006) Visual accommodation in vertebrates: Mechanisms, physiological response and stimuli. *Journal of Comparative Physiology A*, **192**(2), 97–11.)

Unlike mammals, chickens (and possibly lizards) also accommodate by changing the corneal curvature. Corneal accommodation is mediated by the anterior ciliary muscle. Contraction of Crampton's muscle, which originates in the sclera and inserts in the cornea, flattens the peripheral cornea and increases the curvature of the central cornea (see Fig. 4.8; Chu et al., 2014; Murphy et al., 1995). Corneal accommodation is reported to play an important role in chicken accommodation, contributing 8–9 D (Glasser et al., 1994; Schaeffel & Howland, 1987). Thus, the reported combined (corneal and lenticular) accommodative power of the eye in young chicks is 25 D (Ostrin et al., 2011), compared with a maximal power of 15 D in children (Glasser, 2011). It should be noted that the chicken, as well as other avian (Schaeffel & Wagner, 1992) and reptile (Schmid et al., 1992) species, can accommodate independently in both eyes, potentially resulting in *anisometropia* (i.e., unequal degree of refraction in the two eyes) of up to 6 D. Similar corneal and lenticular mechanisms of accommodation exist in lizards (Ott, 2006).

Finally, in chickens even the choroid plays a role in focusing light on the retina. By changing its choroidal thickness, the chicken changes the distance between the retina and the cornea. The result is that in addition to bringing the focal point of incoming light onto the retina (by lenticular and/or corneal accommodation), chickens can also use "choroidal accommodation" to bring the retina into the focal point of the light (a twist on the proverb "If the mountain will not come to Mohammed, Mohammed will go to the mountain"). Once again, the choroidal "accommodation" is mediated by parasympathetic and sympathetic innervation. Transient thickening of the choroid in response to a blurred image is accomplished by changing either the volume of fluid (blood and aqueous humor) flowing through the choroid, or the tone of the choroidal smooth muscle (Nickla & Wallman, 2010). Long-lasting thickening is due to choroidal and scleral remodeling.

Additional Refraction in the Pupil and Elsewhere

The pupillary aperture is not considered to be a classic refractive structure as it has no refractive index, but it does make an important contribution to the resolving power of the eye. As the pupil dilates in dim light, the number of photons entering the eye increases, resulting in increased retinal illumination.

But there is "a price to be paid" for this increased illumination, as mydriasis also decreases the depth of focus of the eye. This means that as the pupil dilates, the range of distances at which objects remain in focus decreases. For example, in an eye that is focused at a distance of 1 m, objects at a distance of between 0.56 and 5.00 m will be in focus when pupil diameter is 1 mm; the range decreases to between 0.78 and 1.40 m when the pupil dilates to 4 mm (Duke-Elder, 1970). This is especially critical in species that have limited accommodative capability, such as the dog. Furthermore, as the pupil dilates, the relative significance of spherical and chromatic aberrations inherent in the eye increases (see the section on "Spherical and Chromatic Aberrations"), thereby reducing its resolving power. Therefore, the pupillary light reflex is, in effect, a constant balancing of two conflicting requirements for vision: maximal retinal illumination and visual resolution. In a scotopic environment, the pupil dilates to improve retinal illumination at the cost of decreased nighttime resolution (which is further attenuated by cone inactivity). In a photopic environment, pupillary constriction improves visual resolution (which is further enhanced by cone activity). As a rule of thumb, constricting the pupil by half increases visual resolution by a factor of two (Duke-Elder, 1970). The "cost" of miosis in a photopic environment is negligible, as there is sufficient retinal illumination under these conditions. This balancing of retinal illumination and visual resolution is especially dramatic in deep-diving animals, which move rapidly from one environment to another. In the Northern elephant seal (*Mirounga angustirostris*), it has been demonstrated that the pupil constricts from a giant area of 422 mm^2 in dark-adapted conditions (approximately 23 mm in diameter) to a pinhole opening of 0.9 mm^2 in light-adapted conditions; that is, the range of variation is almost 470 times (Levenson & Schusterman, 1997)!

It should be noted that light is also refracted *during* its passage through ocular structures such as the cornea and lens, not just at their interface with other structures. This refraction results from changes in refractive indices in various layers of these structures. Some of these refractive gradients are probably too small to affect the overall optical performance of the eye, however. For example, refractive indices in the various corneal layers range from 1.401 to 1.373 D in humans (Patel et al., 1995), whereas the rat retina has a refractive range of 1.369 to 1.385 D (Chen, 1993). But in other cases, regional differences are significant and must be taken into account; for example, in the goldfish eye, the refractive indices of the lens cortex and nucleus are 1.35 and 1.57 D, respectively (Axelrod et al., 1988).

Abnormal Refractive States and Optical Errors

Emmetropia and Ametropia

The "purpose" the refractive and the accommodative processes described in the previous sections is to focus an image on the outer segments of the photoreceptors. An *emmetropic* eye is one in which parallel light rays (from a distant object) are focused on the outer segments when the eye is disaccommodated. A nonemmetropic, or *ametropic*, eye is one in which the focused image (from a distant object) falls anterior to the retina (i.e., nearsighted or *myopic* eye) or posterior to it (i.e., farsighted, *hyperopic* or *hypermetropic* eye; Fig. 4.9).

Retinoscopy is the most commonly used method to determine the refractive state of the eye. It is based on two assumptions: first, that light emerging from the eye (i.e., emergent rays) follows the same optical path as light entering the eye; and second, that the fundus reflex originates at the level of the outer segments. If those two assumptions hold, then emergent rays exit an emmetropic eye as parallel rays, a hypermetropic eye as diverging rays, and a myopic eye as converging rays (Davidson, 1997). Therefore, the location of the focal point formed by the emergent rays can be used to determine the refractive state of the eye.

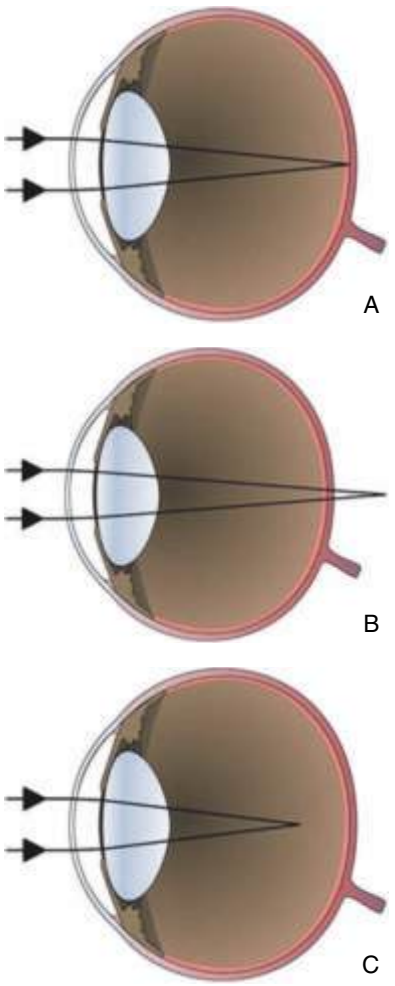


Figure 4.9 **A.** In emmetropia, parallel light rays are focused on the retina. **B.** In a farsighted (hypermetropic or hyperopic) eye, light rays are focused behind the retina. **C.** In a nearsighted (myopic) eye, the light is focused in front of the retina.

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However, it should be noted that the second assumption is not completely accurate. The fundus reflex does not originate at the outer segments but closer to the observer, most likely at the level of the inner limiting membrane (Glickstein & Millodot, 1970). Thus, there is a gap (equal to the thickness of the retina) between the point at which the reflected light is actually measured and the point at which it should be measured. This gap, termed the *artifact of retinoscopy*, results in shifting refraction values in the direction of hypermetropia and needs to be corrected using an established formula (Glickstein & Millodot, 1970). This error is relatively minor (+0.25 D) in young humans (Millodot & O'Leary, 1978) and monkeys (+1.4 D; Hung et al., 2012), but it becomes significant in small eyes, reaching values as high as +7 D in tree shrews (Norton et al., 2003). On the other hand, other researchers claim that the fundus reflex originates at the outer limiting membrane, and that the artifact's significance has been overestimated (Mutti et al., 1997).

Table 4.5 lists refractive errors in selected species. Most of these values have been determined using *streak retinoscopy*, though *autorefractors* have also been used in veterinary medicine (Groth et al., 2013; Hernandez et al., 2016; Wang et al., 2016). As can be seen, few species are truly emmetropic, though once the values are corrected for eye size, most mammals are within ±1 D of emmetropia (Hughes, 1977). A large survey found that on average, dogs are indeed emmetropic, with a mean refractive error of −0.05 D (Kubai et al., 2008). Nine dog breeds – English Springer Spaniel, German Shepherd, Golden Retriever, Siberian Husky, Shetland Sheepdog, Labrador Retriever, Border Collie, Samoyed, and "other" terriers – were found to be emmetropic (defined as having a mean refractive error < 0.5 D in either direction). Yet the same study found that 8% of all dogs were hypermetropic, with a refractive error of up to +3.25 D. Three breeds (Australian Shepherd, Alaskan Malamute, and Bouvier des Flandres) were found to have a

Table 4.5 Refractive errors in selected animal species[a]

Species	Refractive Value (D)	References
Cat by habitat		Belkin et al. (1977)
Street cat	−0.8	
Laboratory cats	1.4	
Cat by age		Konrade et al. (2012)
Kitten (≤ 4 months)	−2.45	
Adult (> 1 year)	−0.39	
Cat by coat length		Konrade et al. (2012)
DSH	−1.02	
DLH	−0.13	
Dog – mean value	−0.05 to (−0.39)	Gaiddon et al. (1996); Groth et al. (2013); Kubai et al. (2008); Murphy et al. (1992b)
Dog by habitat		Gaiddon et al. (1996)
Indoor dogs	−0.64	
Outdoor dogs	0.17	
Dog by breed	–1.87 to (+0.98)	For specific breeds see Black et al. (2008); Kubai et al. (2008, 2013); Mutti et al. (1999); Williams et al. (2011)
Horse	–0.17 to (+0.33)	Bracun et al. (2014); Harman et al. (1999); Rull-Cotrina et al. (2013)
Horizontal meridian	−0.06 to (+0.41)	Grinninger et al. (2010); McMullen et al. (2014)
Vertical meridian	0.25 to 0.34	McMullen et al. (2014)
Rabbit (New Zealand White)	1.7	Herse (2005)
Chicken (Cornell-K)	4.1, 3.7 (4 & 17 weeks old, respectively)	Wahl et al. (2015)
Guinea pig (pigmented)	0.7	Howlett & McFadden (2007)
Rat (Norway brown)	4.7, 14.2 (infant & adult, respectively)	Guggenheim et al. (2004)
Mouse (CBL75/6)	–1.5, 4.0 (10 & 102 days old, respectively)	Zhou et al. (2008)

[a] See reference list for additional refractive studies in wildlife and aquatic species.
DSH, Domestic Shorthair; DLH, Domestic Longhair.

mean refractive error that was hypermetropic. Conversely, 25% of all surveyed dogs were myopic, with a refractive error of up to −6.25 D, and four breeds (Rottweiler, Collie, Miniature Schnauzer, and Toy Poodle) had a mean refractive error that was myopic. Even breeds that were on average emmetropic had population clusters and litters that were myopic. This was especially notable in the Labrador Retriever, in which up to 31% of dogs are reportedly myopic, reinforcing the hypothesis that myopia in this breed may be inherited (Black et al., 2008). Myopia in the Labrador Retriever is caused by elongation of the vitreous chamber (Mutti et al., 1999; see Fig. 4.6), while in other breeds, including the Toy Poodle, Collie, and English Springer Spaniel, myopia is due to the presence of a steeper, more powerful lens (Kubai et al., 2013; Williams et al., 2011). The pathogenesis of myopia in the Labrador Retriever, and its mode of inheritance, could make this breed a naturally occurring large animal model for the study of myopia in humans, where vitreous elongation (see Fig. 4.6) and inheritance play a significant role (Black et al., 2008; Mutti et al., 1999).

A study in cats reported that kittens (≤ 4 months) are myopic, with a mean error of −2.45 D, while adult cats are close to emmetropia, with a mean error of −0.39 D, thus demonstrating a significant effect of age (Konrade et al., 2012). It is interesting to note that myopia decreases with age in cats, but in horses and in some dog breeds, notably the English Springer Spaniel and Beagle, it increases with age (Grinninger et al., 2010; Hernandez et al., 2016; Kubai et al., 2008; Maehara et al., 2011). Once again, there was an overall significant positive correlation between feline refractive error and axial globe length, though the correlation was insignificant when only kittens and juvenile cats were examined. Coat length was another significant factor, with domestic shorthair cats more likely to be myopic, and domestic longhair cats more likely to be emmetropic (Konrade et al., 2012). Another study found a significant effect of habitat on the feline refractive error, with hypermetropia (+1.4 D) or myopia (−0.8 D) depending on whether the cats live outdoors or indoors, respectively (Belkin et al., 1977). This is consistent with findings in humans, demonstrating the correlation between time spent outdoors and prevention of myopia (French et al., 2013).

Several large studies have shown horses to be overall emmetropic (Bracun et al., 2014; Grinninger et al., 2010; Rull-Cotrina et al., 2013). However, only 48–68% of horses are emmetropic in both eyes, with hyperopia and myopia reported in equal proportions in the ametropic horses, with errors of up to ±3 D (Bracun et al., 2014; Farrall & Handscombe, 1990; Grinninger et al., 2010). Age and breed may affect the refractive error in horses (Bracun et al., 2014; Rull-Cotrina et al., 2013). Age, habitat, and working environment have also been shown to be significant factors in other species (Belkin et al., 1977; Murphy et al., 1992b; Ofri et al., 2001, 2004). However, because of low accommodative capacity in most veterinary patients, cycloplegia has no significant effect on refraction in patients, including dogs and horses (Groth et al., 2013; McMullen et al., 2014).

A large range of retinoscopy values is reported in species with small eyes. For example, values range from +20 to −13 D in the rat (Guggenheim et al., 2004; Hughes, 1977) and from -0.7 to +13.7 D in C57BL/6J mice (Pardue et al., 2013). Such a range of results may be due to failure to correct for the artifact of retinoscopy, or because of the significant spherical aberrations (see later section) caused by the very high power of the cornea in small eyes, as shown in Table 4.3. It is recommended that retinoscopy in such small eyes be conducted using an artificial pupil, to occlude the corneal periphery.

Ametropia has also been induced in a number of experimental animals, including chickens, fish, and various mammalian species (Schaeffel & Feldkaemper, 2015). Ametropia is usually induced by visual deprivation in young animals, before the eye has completed its development. Initially, eyelid suturing was used to cause visual deprivation, though this has been replaced by exposure to various regimens of ambient light, and the use of pharmacologic agents or refractive contact lenses to degrade the quality of the retinal image. Visual deprivation leads to progressive axial elongation of the vitreous body and the eye, thereby inducing myopia (see Fig. 4.6; Norton, 2016). Additional anatomic changes in the eye induced by visual deprivation include a shallow anterior chamber, thinner lens, and changes in corneal curvature (Choh & Sivak, 2005; Ostrin et al., 2014). On the other hand, removing the lens during the same period retards axial elongation (Lambert, 2016). The aims of these experiments are to develop animal models for the study of the pathogenesis of myopia in humans, to identify molecular and cellular mechanisms controlling emmetropization, and to evaluate new therapeutic approaches (Schaeffel & Feldkaemper, 2015). Identification of genes associated with, or causing, myopia (Guggenheim et al., 2017; Li et al., 2017a) may represent a breakthrough in the prevention and treatment of what is considered to be one of the most prevalent ophthalmic disorders in humans (Morgan et al., 2018).

Aphakic Eyes and Intraocular Lenses

Because of the significant refractive role of the lens, cataract surgery (or any surgical lens extraction) resulting in aphakia leaves the eye severely hypermetropic. The aphakic eye lacks the refractive contribution of the lens; therefore, light is not sufficiently refracted, resulting in image formation "behind" the retina (Pollet, 1982). Since the early 1980s, veterinary ophthalmologists have sought to alleviate this problem by implanting IOLs in dogs' eyes following cataract extraction. The purpose of these implants is to compensate for loss of refraction by the lens, thereby returning the eye to an emmetropic state. Early attempts using 14.5–29.0 D IOLs left the implanted canine eyes hypermetropic (Peiffer & Gaiddon, 1991). Following the results of studies involving large numbers of

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dogs of various breeds, it has been determined that the canine IOL should have a power of 40.0–41.5 D (Davidson et al., 1993; Gaiddon et al., 1991, 1996). The 1.5 D range of recommended values probably results from breed differences (Kubai et al., 2008). Indeed, use of 41 D IOLs in 60 dogs resulted in an average refractive error of ≤ 1.2 D (Gift et al., 2009). However, it is important to note that though 41 D IOLs are used to bring aphakic dogs to emmetropia, this does not mean that aphakic dogs suffer from hypermetropia of 41 D. Indeed, the hypermetropia in aphakic dogs has been shown to range from 14.4 to 15.2 D (Davidson et al., 1993; Gaiddon et al., 1991). The reason that a 41 D IOL is needed to correct 15 D of hypermetropia is that an IOL is placed in the capsular bag, surrounded by aqueous humor. This environment results in a reduction of its overall refractive power (due to the small difference in refractive indices between the aqueous humor and the IOL), and therefore this power has to be higher than the aphakia it is intended to resolve. If dogs were to be fitted with spectacles to correct aphakia, then indeed these spectacles would require 15 D lenses!

While canine IOLs are widely used by veterinary ophthalmologists, their development and use in other species is lagging behind. A study in horses concluded that an IOL of 25–30 D overcorrects the aphakic equine eye (McMullen et al., 2010), even though preliminary calculations showed a theoretical power of up to 30 D is required to restore emmetropia (McMullen & Gilger, 2006; Mouney et al., 2012). Subsequent studies, supported by a calculated IOL power of 15.4 D (Mouney et al., 2012), have shown that a 14 D IOL brought five out of six horse eyes to within 0.4 D of emmetropia (Townsend et al., 2012). A 14 D IOL also brought a foal to emmetropia (Harrington et al., 2013), even though calculations showed that adult horses and foals may require different power IOLs (Townsend et al., 2013). Calculated IOL powers for bald eagles and rabbits are 16.4–17.4 and 58 D, respectively (Kuhn et al., 2015; Sanchez et al., 2017).

Studies in the cat indicate that IOLs for this species should have a power of 52–53 D (Gilger et al., 1998). The difference between the canine and feline IOL values stems from differences in the anterior chamber depth of the dog and cat (Fig. 4.10). Though the globe axial length in both species is similar, the cat has a much deeper anterior chamber, which means that the lens (and IOL) is located more posteriorly in the cat. As a result, the distance between the lens and retina in the cat is shorter, and a stronger lens is required to focus the light in the course of such a short optical path. Conversely, humans, who also have a similar size globe, have a much shallower anterior chamber and a more anteriorly located lens. This results in a longer optical path to the retina, and therefore most human IOLs have a power of only 19–22 D. Thus, it is not surprising that a study of pseudophakic dogs found a correlation between the postoperative refractive error and the distance of the IOL from the retina (Gift et al., 2009). Similarly, in Icelandic horses with multiple congenital ocular anomalies, a deeper anterior chamber is associated with myopia in older horses (Johansson et al., 2017).

Besides developing IOLs for additional species, veterinary ophthalmologists could also improve the postoperative refraction of their pseudophakic patients through preoperative calculation of the required IOL power. Such calculations rely on keratometry and intraocular dimension measurements and use established formulas to determine the IOL power (Kuhn et al., 2015; McMullen & Gilger, 2006; Mouney

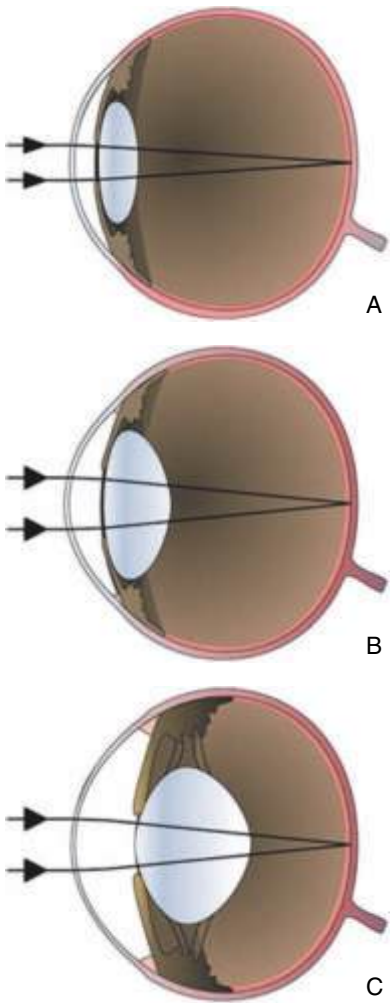


Figure 4.10 The effect of anterior chamber depth on lens curvature in a human (**A**), dog (**B**), and cat (**C**). Though the axial length in the three species is similar, they differ significantly in the depth of their anterior chambers. Humans have the shallowest anterior chamber, and consequently the location of the human lens is relatively anterior. Cats have the deepest anterior chamber, and consequently the location of the feline lens is relatively posterior. As a result, light exiting the lens has a relatively long path before it reaches the retina in a human, and a relatively short path before it reaches the retina in a cat. Therefore, the feline lens needs to have significantly greater power than the human lens, and this is made possible by its greater curvature. The dog has intermediate values in anterior chamber depth, lens location, and lens curvature.

et al., 2012; Sanchez et al., 2017; Townsend et al., 2013). This approach can be especially beneficial in dogs who suffer from vitreous chamber elongation and who may remain ametropic if implanted with a "one size fits all" 41 D IOL. Ideally, such measurements will become part of the routine preoperative evaluation, and every cataractous animal patient will be fitted with an appropriate IOL that will bring its eye to an emmetropic state. Recently introduced Fo-X IOLs with extended depth of focus of ± 1.5 D represent another approach to establishing postoperative emmetropia, but these have yet to be evaluated in clinical studies.

Though veterinary ophthalmologists have made significant progress in restoring emmetropia to pseudophakic patients, little attention has been paid to correcting ametropia in phakic patients. As noted, more than 25% of the canine population has been shown to be significantly myopic (Kubai et al., 2008), and could potentially benefit from such correction through the use of contact lenses or surgery. Indeed, it has been demonstrated that even 1.5–2 D of myopia causes significant deterioration in the visual performance of Labrador Retrievers (Ofri et al., 2012) and in the pattern visual evoked potentials of Beagles (Ito et al., 2016). Various surgical techniques, mostly involving the use of lasers to ablate the cornea, are employed to correct ametropia and astigmatism in humans, and preliminary work shows that some of these techniques are applicable in the dog (Rosolen et al., 1995) and cat (Bühren et al., 2010). Alternatively, lasers have also been used to change the refractive index of the feline cornea (Savage et al., 2014). Interestingly, Wang et al. (2016) have also shown improvement in canine refractive error following 6 months of nutritional antioxidant supplementation.

Astigmatism

Astigmatism is a state of unequal refraction of light along the different meridians of the eye. Normally, a given refractive structure of the eye (e.g., the cornea or lens) has a constant curvature radius in all its meridians (though the cornea may flatten toward the limbus). Astigmatism occurs when the horizontal and vertical meridians of the cornea or lens have different curvature radii. Because of these differing curvatures, light entering the eye through the vertical meridian may be refracted more (i.e., *direct*, or *with-the-rule*, *astigmatism*) or less (i.e., *indirect*, or *against-the-rule*, *astigmatism*) than light entering through the horizontal meridian. There are also cases of *irregular astigmatism* in which the principal meridians are not perpendicular to each other, as in keratoconus, or because of injury. Therefore, light entering along one meridian will be focused on the retina and result in high-resolution vision, whereas light from the other meridian will be unfocused, leading to blurred vision (Fig. 4.11). Such an aberration is corrected with a cylindrical lens rather than with a spherical lens that is used to correct simple ametropia.

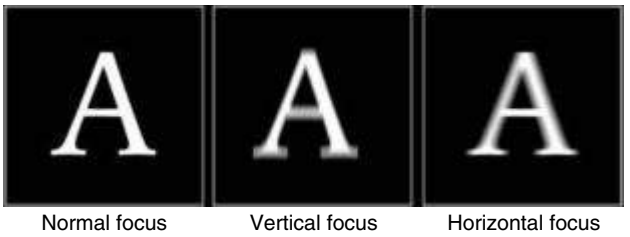


Figure 4.11 A normal eye can see focused horizontal and vertical lines (left). An astigmatic eye will see a focused line in one orientation and a blurred line along the perpendicular axis. **Vertical focus**: The horizontal lines are blurred (center). **Horizontal focus**: The vertical lines are blurred (right).

Astigmatism is diagnosed by refracting the eye in both the horizontal and vertical meridians. A difference of 0.5 D or more in the refractive power of the horizontal and vertical meridians in the same eye is defined as astigmatism. Alternatively, astigmatism can be diagnosed using a keratometer to measure the curvature of the steepest and flattest meridians of the cornea, or by use of a *corneal topographer*, which provides a map based on a large number of photographic sections of the cornea and calibrated into dioptric power (Savini et al., 2017). In humans, most cases of astigmatism result from abnormalities of the anterior surface of the cornea. Only a minority of cases result from lenticular or posterior corneal surface abnormalities (Duke-Elder, 1970). Direct astigmatism accounts for 90% of cases in young eyes, but the proportion of indirect astigmatism increases with age (Nemeth et al., 2013; Xiao et al., 2014). In humans, the prevalence of low-grade astigmatism may be as high as 63% in some populations, but the prevalence of astigmatism > 1.5 D is usually under 5% (Read et al., 2007). The prevalence of significant (> 0.5 D) astigmatism in dogs seems to be equally low, reportedly affecting 1% of all dogs; a higher prevalence of 3.3% was documented in German Shepherds (Kubai et al., 2008). On the other hand, other species are "naturally astigmatic" because of their corneal topography. In the horse, for example, the mean corneal curvature along the horizontal and vertical meridians is 21.6 D and 22.9 D, respectively. Consequently, the horse has a mean degree of 1.3 D direct astigmatism (Grinninger et al., 2010). For the same anatomic reason, 1.75–2.36 D of astigmatism is reported in pig eyes (Sanchez et al., 2011) and 0.4–0.6 D in rabbits (Wang et al., 2014). A high prevalence of astigmatism was also demonstrated in gazelles (Ofri et al., 2004) and elephants (Murphy et al. 1992a). In cows, sheep, and pigs, the lens sutures have been identified as the source of astigmatism and other aberrations (Gargallo et al., 2013).

Some pathologic processes may induce astigmatism. Corneal disease resulting in edema or scarring will inevitably lead to an uneven corneal surface, resulting in irregular astigmatism. Focal cataracts will cause refractive astigmatism

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because of variations in refractivity among different lenticular zones (Duke-Elder, 1970). In addition, cataract surgery (Eslami & Mirmohammadsadeghi, 2015), penetrating keratoplasty (Fadlallah et al., 2015), and other procedures that involve incising and suturing of the cornea often result in astigmatism because of imperfect alignment of wound edges; however, such surgically induced astigmatism frequently resolves over time. In dogs undergoing cataract extraction, surgically induced astigmatism was significantly different between right and left eyes, with values of 2.01 and 3.05 D for dorsotemporal and dorsonasal incisions, respectively (Pederson et al., 2019).

Static Accommodation

Several avian (Hodos & Erichsen, 1990), amphibian (Scheaffel et al., 1994), and reptilian (Henze et al., 2004) species possess *lower-field myopia*. The eyes of these animals are emmetropic along the horizontal and in the upper visual field, but they become progressively myopic below the horizontal (Fig. 4.12). In other words, different parts of the eye have a different refractive power because the shape of the eye is more like a flattened circle, so that the posterior focal length differs for different meridians. This adaptation can be regarded as a *static accommodation* mechanism (Ott, 2006). Rather than changing the refractive power of its lens to focus on an object (in dynamic accommodation), the animal shifts its gaze to see the object with the appropriate refractive power. Consequently, the animal can match the average viewing distances of different areas of the visual field (Schaeffel et al., 1994). This allows the animal to keep the ground in focus with relaxed accommodation while foraging for food and, at the same time, monitor the sky for predators while focused at infinity (Hodos & Erichsen, 1990). This may be why predators such as raptors do not possess this adaptation (Murphy et al., 1995). The same principle is also found in the eyes of pinnipeds (Hanke et al., 2006; Mass & Supin, 2007; Miller et al., 2010). Regional changes in the refractive powers of different parts of the cornea allow these animals to maintain high-resolution vision in both water and air (see the section on "Emmetropia and Accommodation Under Water"). Therefore, static accommodation may be an evolutionary mechanism helping animals to improve their spatial resolution capabilities in different environments (Shilo, 1977).

The horse was also believed to possess a similar, static "accommodating" mechanism, resulting from its nonsymmetric eye shape. According to the *ramp retina theory*, the superior retina was believed to be farther from the lens than the inferior retina (Farrall & Handscombe, 1999; Harman et al., 1999; Sivak & Allen, 1975). Therefore, it was argued that the horse raises its head to focus distant objects on the ventral retina and lowers it to focus nearby objects on the dorsal retina. An analogy to this would be a person with bifocal glasses trying to peer through one lens or the other to view objects at different distances, though in this case the person is aided by the different refractive powers

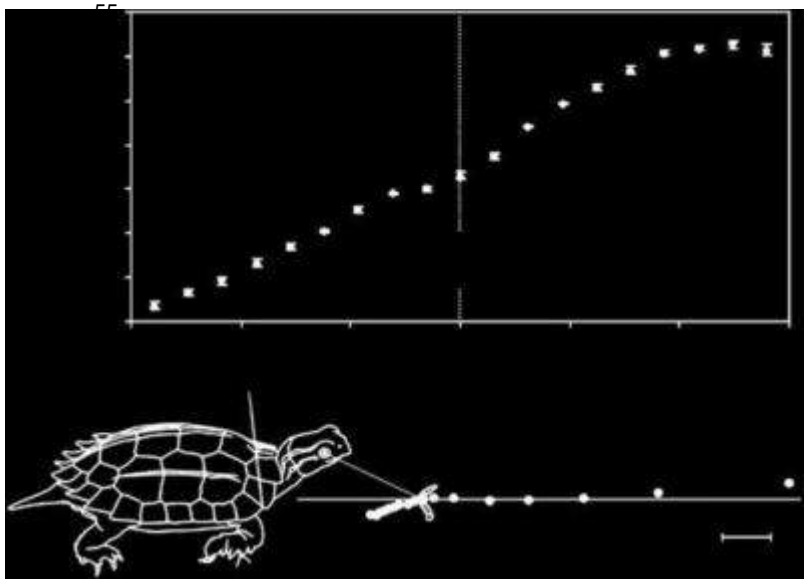


Figure 4.12 Lower-field myopia in the terrestrial turtle *Geoemyda* as an example of static accommodation. Top panel: The refractive state of the unaccommodated eye changes steadily from hyperopic values in the upper visual field to myopic values in the lower visual field. Black dots represent the focal points at various visual angles apart from the optical axis for this state of focus. Lower panel: Because the refractive power changes with the visual angle, the animal can keep the whole ground in focus, and by changing the angle of its gaze focus on its prey no matter how distant it is. (Reprinted with permission from Ott, M. (2006) Visual accommodation in vertebrates: Mechanisms, physiological response and stimuli. *Journal of Comparative Physiology A*, **192**(2), 97–111.)

of the lenses rather than by the varying axial lengths of different meridians. Anatomic measurements have now discredited this theory, and the horse is believed to possess an active (though limited) accommodation mechanism of ±1 D (Harman et al., 1999; Miller & Murphy, 2017; Sivak & Allen, 1975). The head movement previously associated with this behavioral "focusing" is now believed to occur when the horse is interchanging monocular and binocular visual fields (Harman et al., 1999). However, a "ramp retina" has been demonstrated in guinea pigs, with the ventral retina further from the lens center than the dorsal retina as a result of differing globe axial lengths and vitreous chamber depths in different quadrants (Zeng et al., 2013). Consequently, the guinea pig's inferior visual field is –6 D more myopic than the superior field. As in the case of lower-field myopia of nonmammalian species, it is proposed that this adaptation evolved to allow the ground plane to be well focused while maintaining clear vision on the horizon, presumably important to a small creature that needs to detect both food and predators.

Spherical and Chromatic Aberrations

Spherical Aberrations

The eye is not a perfect optical system. Indeed, Duke-Elder (1970) quotes Hermann von Helmholtz, the 19th-century German physicist who invented the ophthalmoscope, as saying that "if an optician should try to sell me an instrument possessing such faults, I would feel justified in using the most severe language with regard to the carelessness of his work and return the instrument under protest." Two of the most significant optical problems that affect the eye are spherical and chromatic aberrations. *Sperical aberrations* occur because in both the cornea and the lens, rays passing through the periphery are refracted more than rays passing through the center. Therefore, rays passing through the periphery are focused closer to the cornea (or lens) than rays passing through its center (Fig. 4.13). Obviously, as the image is not uniformly focused on the retina, the aberration causes blurred vision. In other words, the focusing of rays depicted in Fig. 4.5 and Fig. 4.7 is an "ideal" refraction that in reality does not take place in the eye. The difference between the focal points of the peripheral and central rays, the spherical aberration, is measured in diopters. A comparative study found significant degrees of spherical aberration in the lenses of dogs, cats, and rats, but minimal lenticular aberrations in cows, sheep, and pigs (Sivak & Kreuzer, 1983).

Both the cornea and the lens possess anatomic adaptations that are intended to minimize the extent of their inherent spherical aberrations. In the lens, the higher refractive index of the lenticular nucleus increases the refractive power of the central lens. This results in moving its focal point closer to the lens, nearer to the focal point of the peripheral lens (Fig. 4.14). A gradient variation in the refractive index of the lens would result in the formation of a multifocal lens, with a higher refractive index in the nucleus and a lower refractive index toward the equator, leading to further attenuation of the spherical aberration. Corneal spherical aberrations are minimized because the peripheral cornea is flatter than

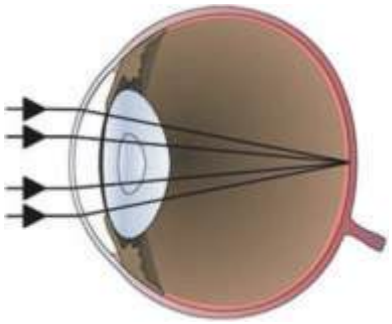


Figure 4.14 Multifocal lenses reduce the amount of spherical aberrations. A higher refractive index of the lens nucleus causes increased refraction of the central light rays (compared to the refraction of the central rays in Fig. 4.13A). Consequently, the focal point of the central rays is shifted closer to the lens and closer to the focal point of the peripheral rays, thus eliminating the spherical aberrations seen in Fig. 4.13A.

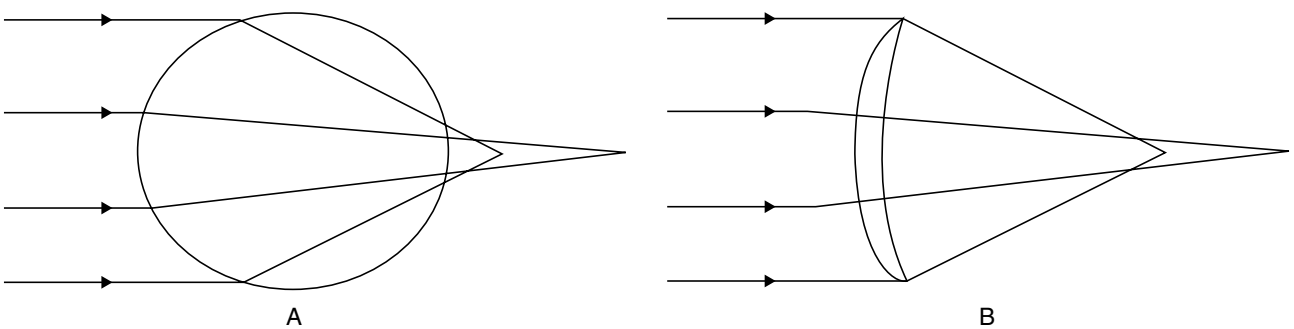


Figure 4.13 Spherical aberrations occur when light passes through the lens (**A**) and cornea (**B**). In both cases, peripheral rays are refracted (bent) more than central rays. Therefore, the focal point of the peripheral rays is closer to the lens/cornea, while the focal point of the central rays is closer to the retina. The result is a blurred image. The distance between the two focal points is called spherical aberration and is measured in diopters (D).

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the central (apical) cornea. This decreases the refractive power of the peripheral cornea and moves its focal point toward the retina and closer to that of the central cornea (Millodot & Sivak, 1979). Therefore, refractive surgeons attach great importance to centering the apical cornea so that the aberration-free zone is aligned with the pupil, thereby contributing to a high-quality retinal image (Bühren et al., 2010; Gobbe et al., 2015). A similar problem may arise in corneoscleral transposition in veterinary patients, as the flatter peripheral cornea is transposed into the steeper central cornea, potentially increasing spherical aberrations in the patient. For similar reasons, surgeons performing keratoplasty should strive to collect the donor's cornea from the same region as the intended grafting site. However, the possible effects of corneoscleral transpositions and keratoplasty on visual optics in animal patients have yet to be investigated.

Another structure that plays a critical role in reducing spherical aberrations is the pupil. Contraction of the pupil blocks rays of light that enter the eye through the most peripheral (and refractive) cornea. It also prevents light from passing through the peripheral lens. Thus, miosis allows only rays that pass through the central cornea and lens to reach the retina, thereby contributing to the formation of a well-focused image (Fig. 4.15A). A mydriatic pupil, on the other hand, allows more peripheral rays to enter the eye, and their passage through the peripheral cornea and lens increases the amount of spherical aberrations as well as all the other wavefront aberrations (Fig 4.15B). In humans, an 8 mm pupil induces 1 D of spherical aberrations (Millodot, 2018), which is the reason for the significant blurring of vision that is experienced after pupils have been pharmacologically dilated.

It is worth noting that nowadays the aberrations of the eye are analyzed by assessing the amount of deviation obtained between an output wavefront emanating from it and a theoretical ideal wavefront (Thibos et al., 2002). This stems from the fact that the eye is not a symmetric globe. These aberrations are reported as *Zernike polynomials*, of which there are more than 20 types, including astigmatism, spherical aberration, coma, trefoil, and quatrefoil. They are now routinely measured with various types of commercial *aberrometers*, and a common unit of measurement of all wavefront aberrations is the root mean square (RMS). In a large human survey, Wang and Koch (2003) found that the most significant aberration was spherical aberration, followed by coma.

Chromatic Aberrations

Chromatic aberrations result from the fact that the refractive index n (as in the equation $D = n/f$) is not constant, but rather is wavelength dependent. Once again, therefore, Fig. 4.5 and Fig. 4.7 are somewhat misleading because they portray the ideal situation pertaining to monochromatic light. However, when white light enters a prism (or a lens), each wavelength contained in that light is refracted by a different amount. The n of a given wavelength is inversely proportional to λ. Therefore, waves with a short wavelength (e.g., blue light) have a higher n than waves with a long wavelength (e.g., red light). Consequently, blue light will be more refracted than red light, and its focal point will be closer to the lens (Fig 4.16A). The distance between the focal points of the short and long wavelengths is the chromatic aberration, and once again this distance is measured in diopters. The implication is that when viewing red text on a blue background, for example, the overall image would be blurred, as the text and the background are focused on different planes in the eye. A study comparing chromatic aberrations in different species found that in most animals (including cats, cattle, sheep, pigs, rats, and fish) the amount of chromatic aberration (442–633 nm) of lenses amounts to a relatively constant 4.6% of equivalent focal length; an exception is the dog lens, with 5.7% chromatic aberrations (Kreuzer & Sivak, 1985).

As in the case of spherical aberrations, anatomic adaptations may contribute to a reduction in the effect of the chromatic aberrations. For example, fish have been shown to possess multifocal lenses consisting of concentric rings of differing refractive properties (Kröger, 2013). Thus, red light passing through one ring will be more refracted than blue

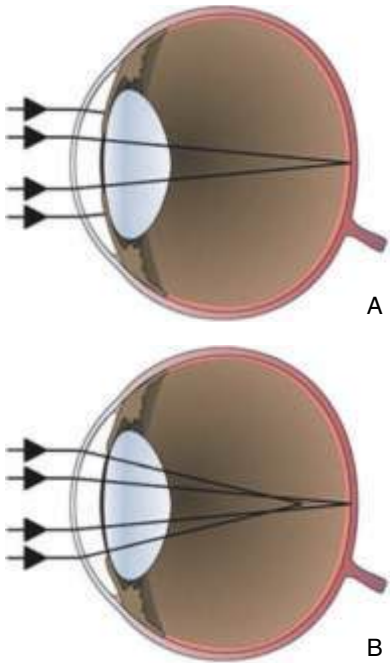


Figure 4.15 Pupillary diameter affects the magnitude of spherical aberrations. A miotic pupil (**A**) blocks the peripheral rays, thereby eliminating the spherical aberrations induced by the peripheral cornea and lens (seen in Fig. 4.13). Only central rays reach the retina, resulting in a focused image. A mydriatic pupil (**B**) admits peripheral rays into the eye, thereby increasing the amount of spherical aberrations. Panel **B** is the basis for the blurred vision experienced following pharmacologic dilation of the pupil.

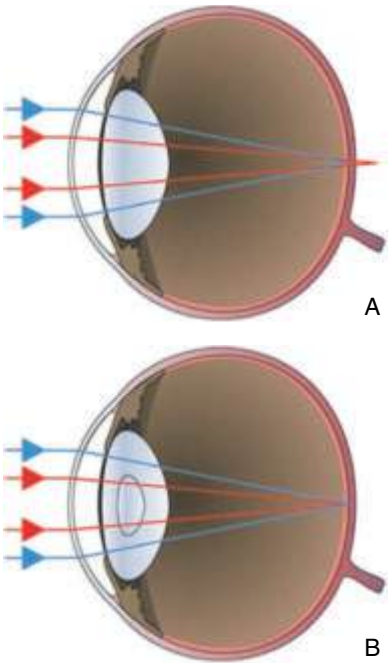


Figure 4.16 Chromatic aberrations in the lens. **A**. White light is composed of numerous wavelengths, each of which is characterized by a different refractive index (*n*). Light with a longer wavelength (e.g., red light) has a lower *n* than light with a shorter wavelength (e.g., blue light). Consequently, red light will be refracted to a lesser degree than blue light. If the blue light is focused on the retina, the red light converges behind the retina. The distance between the focal points of the short and long wavelengths is the chromatic aberration; this distance is measured in diopters. **B**. Multifocal lenses reduce the magnitude of chromatic aberrations. A higher refractive index of the lens nucleus causes increased refraction of the red light (compared to its reduced refraction in panel **A**). Consequently, the focal point of the red light is shifted closer to the lens and closer to the focal point of the blue light, thus eliminating the chromatic aberrations seen in panel **A**.

light passing through another ring, thereby compensating for the blue light's higher *n*. Consequently, the image formed on the retina will be chromatically focused (Fig. 4.16B).

It is interesting to note that in terrestrial species, multifocal lenses consisting of concentric refractive rings can be found in those species in which the miotic pupil is not round (Land, 2006; Malmström & Kröger, 2006). Such a lens has been demonstrated, for example, in the domestic cat. The vertical slit shape of the cat's miotic pupil allows light to pass through both the peripheral and central lens during constriction. Therefore, even during miosis, the cat continues to benefit from the advantage of a multifocal lens (Fig. 4.17). On the other hand, in the closely related tiger, a round pupil is associated with a monofocal lens, so that no optical properties of the lens are "lost" when the pupil constricts (Malmström & Kröger, 2006). Therefore, species with a multifocal lens have a steeper GRIN than species with a monofocal lens. In cats, for example, the refractive indices in the lens nucleus and subcapsular areas are 1.48 and 1.39, respectively; in humans, the respective figures are 1.41 and 1.38 (Pierscionek & Regini, 2012). In this context it is noteworthy that the harbor seal, which is a monochromat, has multifocal lenses; since multifocal lenses have evolved to compensate for chromatic aberrations in animals with color vision, the functional significance of such a lens in a monochromat is not understood (Hanke et al., 2008).

Additional evolutionary adaptations to decrease the detrimental effect of chromatic aberrations on visual resolution can be found in the anatomy of the retina. The human fovea, for example, contains red and green cones, but does not contain any blue cones (Chen et al., 2015). Therefore, red light, which is focused on the fovea, will be absorbed in this region. Blue light, which is not focused on the fovea, will not be absorbed, and therefore not be perceived, thus contributing to the high-resolution vision of the fovea (at the expense of

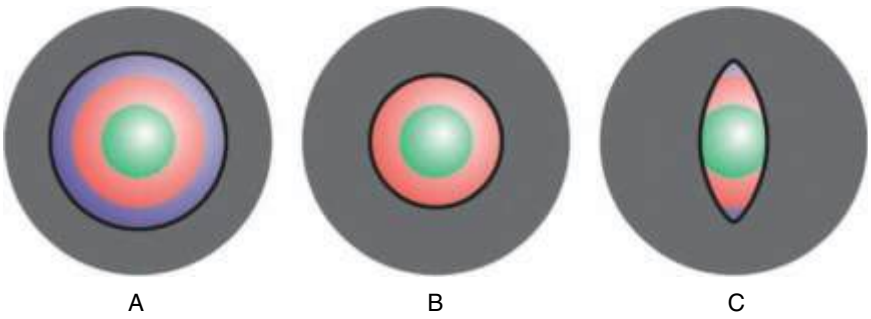


Figure 4.17 The functional significance of the slit pupil in combination with a multifocal lens. In the fully dilated state of the pupil (**A**), all zones of the lens (shown in the colors they are focusing) can be used. A concentrically constricting iris (**B**) would cover the outer zone of the lens, such that a spectral range (blue in this example) could not be focused on the retina. By contrast, all lens zones can be used if the pupil constricts to a slit (**C**). (Reprinted with permission from Malmström, T. & Kröger, R.H. (2006) Pupil shapes and lens optics in the eyes of terrestrial vertebrates. *Journal of Experimental Biology*, **209**, 18–25.)

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foveal blue color perception). This is why the fovea has been called the *blue scotoma region* of the retina (Chen et al., 2015). The chromatic aberrations induced by blue light in the macular region are further reduced by the presence of yellow macular pigment, which is abundant in carotenoids, lutein, and zeaxanthin, with a peak absorption of about 460 nm, which absorbs unfocused short wavelengths (Bernstein et al., 2016).

Obviously, chromatic aberrations are less significant in species that have limited color vision, as some of the defocused wavelengths may not be absorbed by the photoreceptors, and hence are not perceived. Thus, in many of our animal patients, who have dichromatic vision, it is possible that this aberration has minor functional implications.

Emmetropia and Accommodation Under Water

In aquatic species, the cornea is in contact with water rather than air. Because of the very small (~0.003) difference between the refractive indices of the cornea and water, the cornea of these species has virtually no refractive power. In fact, because the anterior corneal surface has lower curvature than the posterior surface (Ueno et al., 2015), under water the cornea acts as a weak divergent lens. Fish are forced to compensate for the absence of corneal refraction by increasing the refractive power of other ocular structures, usually the lens. For this reason, as noted earlier, the lenses of fish eyes are very spherical. Their increased curvature results in significantly larger refractive power. Biochemical changes in lenticular proteins also increase the refractive index of the fish lens to up to 1.66, thereby contributing to significant refraction as light passes from the aqueous humor into the lens (Sivak, 1978). In the sandlance fish, these evolutionary adaptations can increase the refractive power of the lens to as much as 500 D (Pettigrew & Collin, 1995). If it were not for these two lenticular adaptations, the absence of corneal refraction would cause fish to be severely hypermetropic under water.

The problem of refraction under water is further complicated in species that move in and out of water because it is physically impossible for an eye to be emmetropic both in air and underwater (Fig. 4.18). Eyes that are emmetropic in the air will be hypermetropic under water because the refractive power of the cornea is lost due to its submersion in water. Conversely, eyes that are emmetropic under water become extremely myopic in the air because now the cornea (due to Snell's law) contributes refraction that the eye did not possess under water. Therefore, species that live and function in both habitats must "choose" whether they will be emmetropic in the air or under water. It is very interesting to observe that both of these evolutionary strategies exist in the animal kingdom. Birds that hunt under water, such as cormorants (Katzir & Howland, 2003), the Australasian gannet (Machovsky-Capuska et al., 2012), and penguins (Sivak et al., 1987), as well as sea otters (Murphy et al., 1990), are emmetropic in the air. These species overcome the resulting underwater hypermetropia by increasing the accommodative power of the lens, thus allowing them to actively hunt and chase their prey under water. During accommodation in the cormorant, for example, the lens bulges through the pupil, forming *anterior lenticonus* that increases the lenticular axial length pathway and consequently its refractive power (Fig. 4.19) (Katzir & Howland, 2003). This combination of forward movement and change in lenticular curvature gives the cormorant lens an accommodative power of 60 D and an incredible accommodation rate of more than 600 D/s, 10 times as fast as nondiving birds (Katzir & Howland, 2003). Sea otters have also been shown to have a similar lenticular accommodative mechanism, combining forward movement and change in the curvature of the lens (Mass & Supin, 2007). As in cormorants, the result is an accommodative power of 55–60 D, which is the highest of any mammal (Murphy et al., 1990). Since the otter loses 59 D of corneal power under water, the equivalent magnitude of lenticular accommodation allows the animal to regain its visual acuity when diving. In penguins, the entire cornea is flat, consequently minimizing the alteration in refractive state when moving from air to water (Sivak et al., 1987).

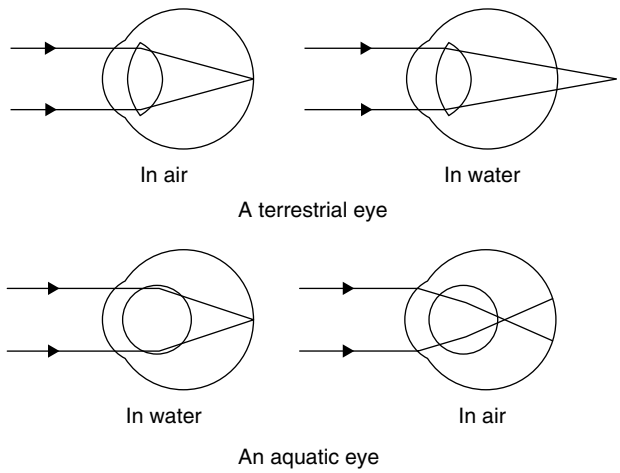


Figure 4.18 No eye can be emmetropic both in air and under water. An eye of terrestrial animals, which is emmetropic in an aerial environment, loses the refractive contribution of the cornea under water and becomes farsighted (top panel). An eye of a fish that is emmetropic under water becomes severely nearsighted (myopic) in the air because it "gained" corneal refraction that it did not possess under water (bottom panel). Note the difference in shapes of the lenses between the two species. The lens of the fish is more spherical in order to increase its refractive power (to compensate for the absence of corneal refraction under water). (Reproduced with permission from Sivak J.G. & Millodot M. (1977) Optical performance of the penguin eye in air and water. *Journal of Comparative Physiology*, **119**, 241–247.)

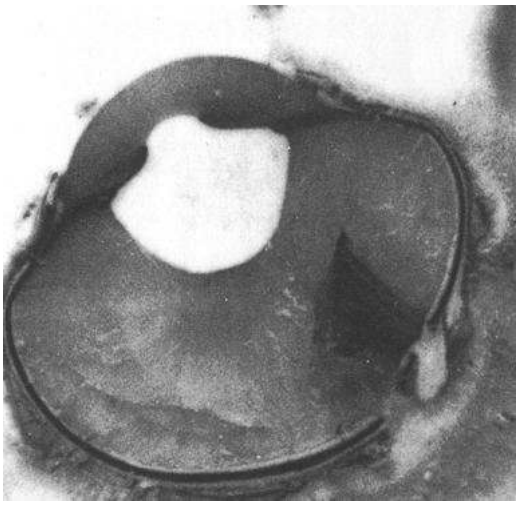


Figure 4.19 A sectioned eye of a cormorant during accommodation. The bulging of the lens through the miotic pupil into the anterior chamber is clearly illustrated. As a result, the axial length of the lens, and its refractive power, increases. This underwater accommodation allows the eye to compensate for the loss of corneal refraction during diving, and the bird can focus on its prey. But if the bird dives into deep, scotopic waters, the inevitable mydriasis will disable this accommodating mechanism. Therefore, the bird is restricted to hunting in shallow, photopic waters. (Courtesy of Gadi Katzir.)

Thus, in cormorants, otters, and penguins, the cornea is the major refractory organ on land, allowing for aerial emmetropia; the lens accommodation provides for underwater refraction. However, as usually happens with evolutionary strategies, there is a price to be paid for this well-developed underwater lenticular accommodative capability. The bulging of the lens through the pupil in these species requires miosis. This, in turn, limits the amount of light entering the eye. Therefore, these species can only hunt to a depth of about 9 m (Boyd et al., 2015). In deeper water, the inevitable mydriasis will not allow them to accommodate and focus on their prey. In this context it is worth noting that other piscivorous (fish-eating) birds, such as osprey, kingfishers, and sea eagles, do not chase their prey under water. Instead, these birds search for their aquatic prey from the air and capture it while plunging into the water, relying on momentum rather than accommodation to catch the fish (Machovsky-Capuska et al., 2012). Therefore, it is not surprising that pursuit-diving ducks accommodate, while nondiving ducks do not (Lisney et al., 2013).

On the other hand, many aquatic mammals developed an opposing evolutionary strategy (Mass & Supin, 2007). Sea lions, harbor seals, and other pinnipeds are emmetropic under water. Consequently, these animals become severely myopic when they come out of the water to breathe. Various mechanisms have evolved to make up for the increased refractive power of the eye in an aerial environment. Harbor seals have one flattened corneal meridian, with a slit-shaped pupil oriented along this flattened meridian (Hanke et al., 2006). When the animal exits the water, the bright light causes pupillary constriction along this meridian, which has minimal refractive power as it is not curved (*stenopaic vision*). Therefore, the resulting aerial myopia along this axis is attenuated significantly. Thus, in the air, the animal suffers from about −20 D myopia along the horizontal meridian, but "only" −7.5 D of myopia in the vertical meridian, the difference in refractive power of the central, flat cornea between water and air (Hanke et al., 2006). The aerial miosis also serves to minimize aberrations and increase the depth of field, thus allowing for further improvement of aerial acuity, which is comparable to the animal's underwater acuity (Hanke & Dehnhardt, 2009). Obviously, aerial visual acuity will deteriorate significantly at night, when mydriasis will allow light to enter through the highly curved and refractive quadrants of the cornea. A similar solution has evolved in the California sea lion, which has a specialized, flattened region with very low refractive power in the ventromedial cornea (Miller et al., 2010), and dolphins, which have a similar region in the medial cornea (Dawson et al., 1987). These regions provide for minimally defocused aerial vision, whereas the rest of the cornea is convex, providing for high underwater acuity. The animal shifts its head as it exits the water to allow light to enter through the flat "window" (Fig. 4.20; Dawson et al., 1987).

In both seals and dolphins, underwater mydriasis enables the eye to benefit from the highly curved and refractive quadrants of the cornea, thus allowing for emmetropia and high-resolution aquatic vision. Therefore, unlike diving birds, these animals can accommodate and hunt in deep water, as they use mydriasis, rather than miosis, for improving underwater acuity. The detrimental effect of the flat window, so beneficial in the air, is probably neutralized by underwater accommodation (Hanke et al., 2006). Therefore, what these animals lose in aerial acuity, they gain in hunting depth. More primitive amphibians (e.g., crocodiles) that lack this compensatory accommodative capability simply cannot focus. These animals are emmetropic in air and are severely hypermetropic under water, forcing them to rely on other senses when hunting under water (Nagloo et al., 2016).

Another interesting adaptation is observed when semi-aquatic garter snakes submerge in water. Contrary to expectations, their pupils constrict under water, rather than dilate. It is suggested that this constriction causes an increase in vitreous pressure in the posterior chamber and pushes the lens forward. The resulting accommodation allows the snake to compensate for the loss of corneal refractive power under water. In other words, aquatic submersion triggers a "pupillary water reflex" that is independent of light intensity; this reflex is intended to prevent hyperopia through lens accommodation, rather than to regulate the amount of light on the retina (Fontenot, 2008).

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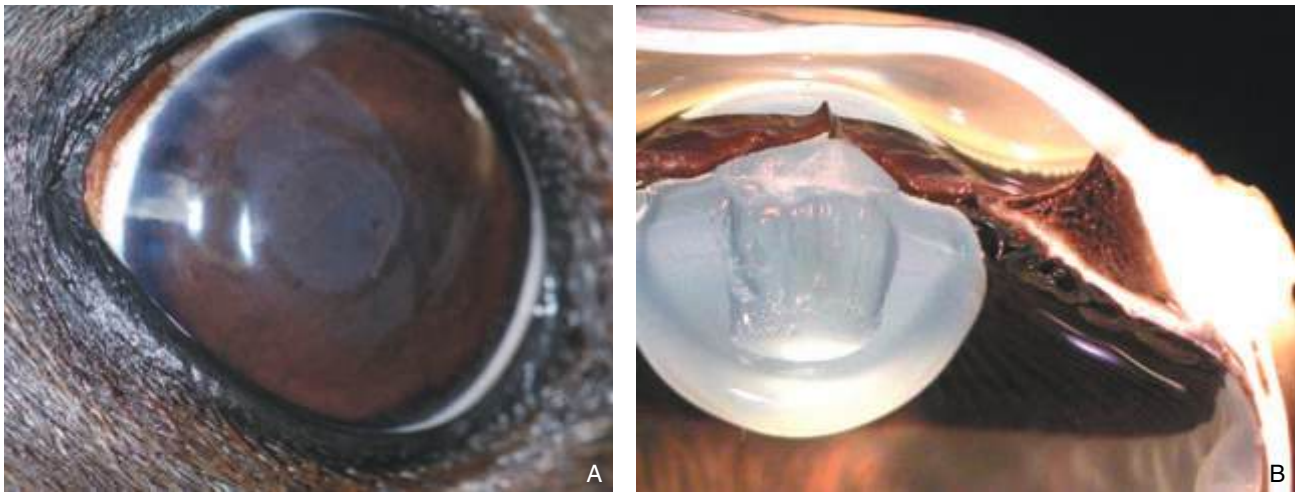


Figure 4.20 A frontal (**A**) and sectioned (**B**) view of the anterior segment of a pinniped eye. Note the flattened central cornea, which minimizes the inevitable myopia that occurs when the animal exits the water to an aerial environment. Note in panel **A** that the pupil constricts around this part of the cornea, so that only light passing through the least refractive part of the cornea will enter the eye. The pinpoint pupil minimizes spherical aberrations and increases depth of focus, further enhancing aerial acuity. (Panel **A** courtesy of Carmen M. Colitz. Panel **B** courtesy of Richard R. Dubielzig.)

Visual Processing: From Photoreceptors to Cortex

The Retina

The optical part of the visual process ends with photons striking the outer segments of the photoreceptors. The neuronal part of the visual process begins with the capture of these photons and absorption of their energy by the photopigments in the outer segments of the cones and rods, where a chain of biochemical reactions starts. In addition to these sensory neurons, the retina also contains secondary and higher-order neurons and an intricate neural circuitry that performs the initial stages of image processing, before trains of electrical impulses are transferred through the axons of the retinal ganglion cells (RGCs) to areas in the brain where secondary processing and eventually visual perception occur. A schematic representation of the retina is shown in Fig. 4.21.

The Photoreceptors

The outermost cells in the neural retina are the photoreceptors, which are divided into two classes: rods and cones. Rods and cones differ from each other in their morphology, function, and retinal distribution. Functionally, cone systems are characterized by high resolution of fine details, rapid responses, color perception, and low sensitivity to small fluctuations in light intensity (Lamb, 2016). Rod systems are characterized by poor visual resolution and no color perception, but they are extremely sensitive to minute changes in light levels and detection of motion. Therefore, cones are particularly suitable for daylight *photopic* vision, whereas rods contribute mostly to dim-light *scotopic* vision (Collin et al., 2009; Lamb, 2013; Lamb et al., 2007, 2016; Mustafi et al., 2009). Hence, a retinal mosaic containing both cone and rod photoreceptors, which appears to be ubiquitous among mammals (Peichl, 2005), forms a duplex retina, which functions in both low and bright light conditions.

These functional differences between rods and cones are partially the result of the morphologic differences discussed in Chapter 2. The rod outer segment is long and thin, about 2 μm in diameter, which permits a high density of rods, thus increasing the probability of absorbing scarce photons at night. Cones are thicker than rods, but both cones and rods in the central part of the retina are thinner than those in the periphery to permit a high photoreceptor density (Mowat et al., 2008). Rod axons are thin, which is consistent with the cell's slow response to light and fewer ribbon synapses, whereas cone axons are thick, enabling transfer of information (signals) at higher rates in multiple synapses (Hsu et al., 1998).

Cones constitute a minority of the photoreceptors in most mammalian retinas, with ranges of 0.5%–3% in nocturnal species and 5%–10% in crepuscular and arrhythmic species, whereas the proportion of cones in diurnal animals ranges from 8% to 95% (Ahnelt & Kolb, 2000). Hence, the cone-to-rod ratio roughly reflects the lifestyle of the species. There are also differences in photoreceptor concentrations in different regions of the retina. A specialized, avascular area with higher cone density providing higher spatial resolution (ability to see finer details) in the corresponding part of the visual field is often present in the retina. In diurnal species possessing high acuity, such as haplorrhine primates and many avian species, this region is called the *fovea centralis*.

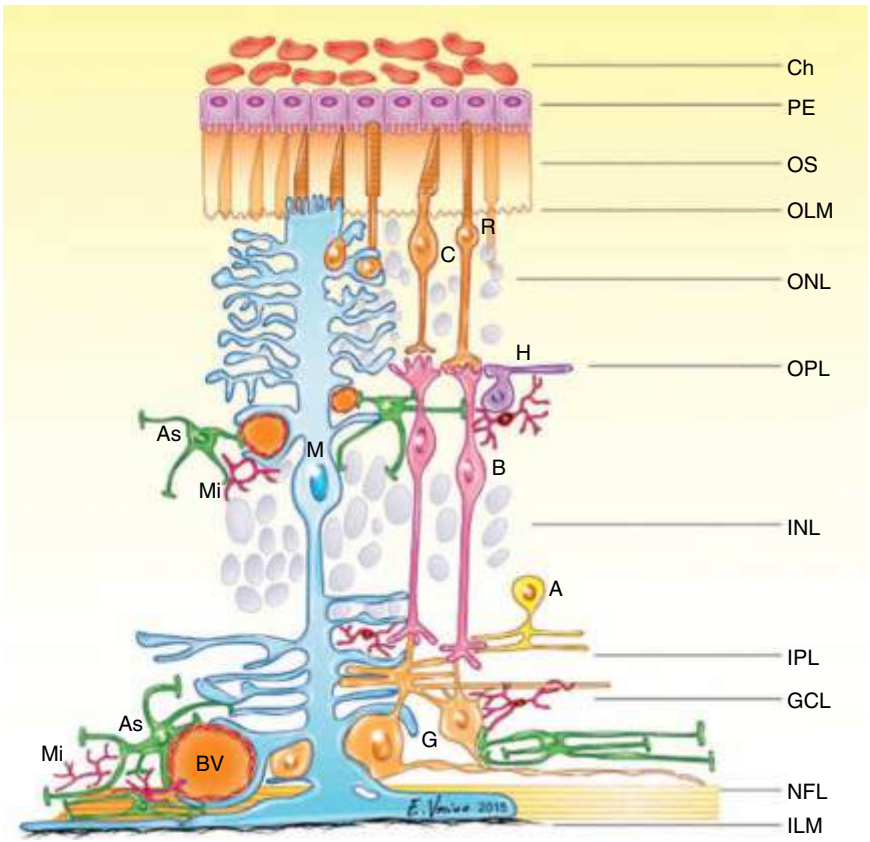


Figure 4.21 Schematic drawing of the mammalian retina with part of the choroid (Ch) on top. Below the retinal pigment epithelium (PE) are the layers of the neuroretina: the outer segments of the photoreceptors (OS), the outer limiting membrane (OLM), the outer nuclear layer with nuclei of cones (C) and rods (R), the neuropil of the outer plexiform layer (OPL), the inner nuclear layer (INL) with nuclei of horizontal (H), bipolar (B), and amacrine (A) cells, the inner plexiform layer with synapses in strata, the ganglion cell layer (G), their axons in the nerve fiber layer, and finally the inner limiting membrane (ILM) facing the vitreous. The glial elements of the retina, Müller cells (M), and microglia (Mi), as well as astrocytes (As) embracing retinal blood vessels, are shown. (Reproduced with permission from Vecino, E., Rodriguez, F.D., Ruzafa, N., et al. (2016) Glia–neuron interactions in the mammalian retina. *Progress in Retinal and Eye Research*, **51**, 1–40. doi: 10.1016/j.preteyeres.2015.06.003.)

The primate and avian fovea is actually a depression (or pit) that contains no rods or retinal capillaries, thus permitting more dense packing of cones almost individually connected to retinal interneurons and ganglion cells (Kolb & Marshak, 2003). This area subserves the highest-resolution vision of the eye. Most other species are devoid of such a highly specialized area, but a *fovea plana*–like area (a fovea without evident foveal pit) temporal to the optic nerve head has recently been identified in the dog (Beltran et al., 2014). A more diffusely outlined region with increased cone density called the *area centralis* surrounds the fovea plana in the dog and is usually seen in other mammals that are currently considered to be afoveate (Beltran et al., 2014; Mowat et al., 2008). Though this area has a higher concentration of cones, rods still outnumber the cones in the area centralis (Table 4.6). Because of their higher rod concentration, these eyes have higher sensitivity under low light conditions, albeit sacrificing visual acuity and richer color vision, as they have fewer cones. The primate fovea and area centralis in lower mammals are surrounded, respectively, by a *macula* and a *visual streak*, which are regions of decreasing cone density. In foveate primates, the macular area appears yellowish because of the macular pigments absorbing blue light and scavenging free radicals, thus protecting the retinal area providing the high visual acuity (Provis et al., 2013). The concentration of cones continues decreasing with retinal eccentricity, and the more peripheral retina is characterized by higher rod-to-cone ratios.

Cones are further subdivided into several types depending on their opsin contents (Hunt et al., 2009). Humans (as well as Old World primates) have three cone classes, with peak sensitivities to either long (552–562 nm, usually called red cones, although they are most sensitive to greenish-yellow), medium (525–533 nm, green), or short (410–450 nm, blue) wavelengths of light (Hofmann & Palczewski, 2015a). These cones, known as *L-*, *M-*, and *S-cones* or *red*, *green*, and *blue cones*, respectively, are the basis of human trichromatic vision. Most New World primates and lower mammals have

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Table 4.6 Photoreceptor concentrations in cats, dogs and humans.

	Human (Østerberg, 1935)	Cat (Steinberg et al., 1973)	Dog (Mowat et al., 2008; Beltran et al., 2014*; Yamaue et al., 2015**)
Number of rods ($\times 10^6$)	110–125		
Number of cones ($\times 10^6$)	6.5		
Maximal cone concentration ($\times 10^3$ per mm^2)	199	27	23/127*
Maximal rod concentration ($\times 10^3$ per mm^2)	160	460	501
Cone concentration at ora serrata ($\times 10^3$ per mm^2)	5	<3	7[a]
Rod concentration at ora serrata ($\times 10^3$ per mm^2)	40	250	~200**
Rod-to-cone ratio (area centralis)	No rods	11 : 1	23 : 1[b]
Rod-to-cone ratio (ora serrata)	50 : 1	100 : 1	41 : 1[a]

[a] These numbers were obtained in the periphery by Mowat et al. (2008) and not at the ora serrata;
[b] Data from Beltran et al. (2014) suggest that the rod-to-cone ratio in the area centralis is closer to 1 : 1.

two cone populations (serving dichromatic vision). Some animals have one cone population (monochromatic vision), while others have more than three cone populations (tetrachromatic vision and beyond). Morphologically, the three primate cone populations are almost identical, and immunohistochemistry or another molecular method is needed to distinguish between them. These methods reveal differences in the cone synaptic terminals and in their retinal distribution, such as the absence of S-cones in the fovea. They also reveal a high degree of evolutionary conservation between L- and M-cones. Thus, most dichromatic species will have S- and L/M-cones rather than L- and M-cones, because S- and L/M-cones, whose absorption spectra are further apart, are activated by a wider range of wavelengths and therefore able to detect more of the electromagnetic radiation being reflected off different surfaces in nature. The implications of these properties for color vision are discussed in Chapter 5.

Mammals only have one class of rods, which precludes color vision when light is too dim for cones to be activated. The peak spectral sensitivity of rods is close to 500 nm (cyan-greenish light). In the dog, the highest rod density, almost 540,000 rods/mm^2, is seen dorsal to the area centralis region, whereas the density in the peripheral retina is 2.5–2.7 times lower (Yamaue et al., 2015).

Morphologically, both rods and cones are divided into four parts (Fig. 4.22A):

1) Outer segment
2) Inner segment
3) Nucleus
4) Synaptic terminal.

The *outer segment* is the part of the cell where phototransduction, as well as disc formation and shedding, occurs; for a review see Molday and Moritz (2015). The outer segments are connected by a cilium to the *inner segment*, which is an area rich in mitochondria (ellipsoid), Golgi apparatus, and endoplasmic reticulum (myoid). Opsin is synthesized in the Golgi apparatus of the inner segment and is transported through the cilium to the base of the outer segment, where it is incorporated into the outer segment's plasma membrane, which undergoes evagination and invagination to form a new disc. In rods, the disc detaches from the membrane and the outer segment is filled with a stack of 600–1,600 free-floating discs, similar to a stack of coins (Hofmann & Palczewski, 2015b). In cones, the disc remains part of the membrane, thus exposing it to a greater supply of the recyclable, light-sensitive part of the photopigment (relative to the disconnected rod disc). Thus, the outer segments are in fact tubes full of discs (or tubes made up of discs, in the case of cones) of folded double membranes in which the visual photopigment molecules are embedded.

The outer segments undergo constant destruction due to photo-oxidative damage. The damaged tips of the outer segments are shed and then phagocytized by the retinal pigment epithelium (RPE), where they become phagosomes that are broken down by lysis (Nguyen-Legros & Hicks, 2000). This shedding of outer segments is a diurnal cycle (which takes place following morning light onset in rods, and following night onset in cones), and is *not* to be confused with the intermittent and much more frequent process of chromophore phagocytosis and regeneration. As new discs are formed at the base of the outer segment, older discs are

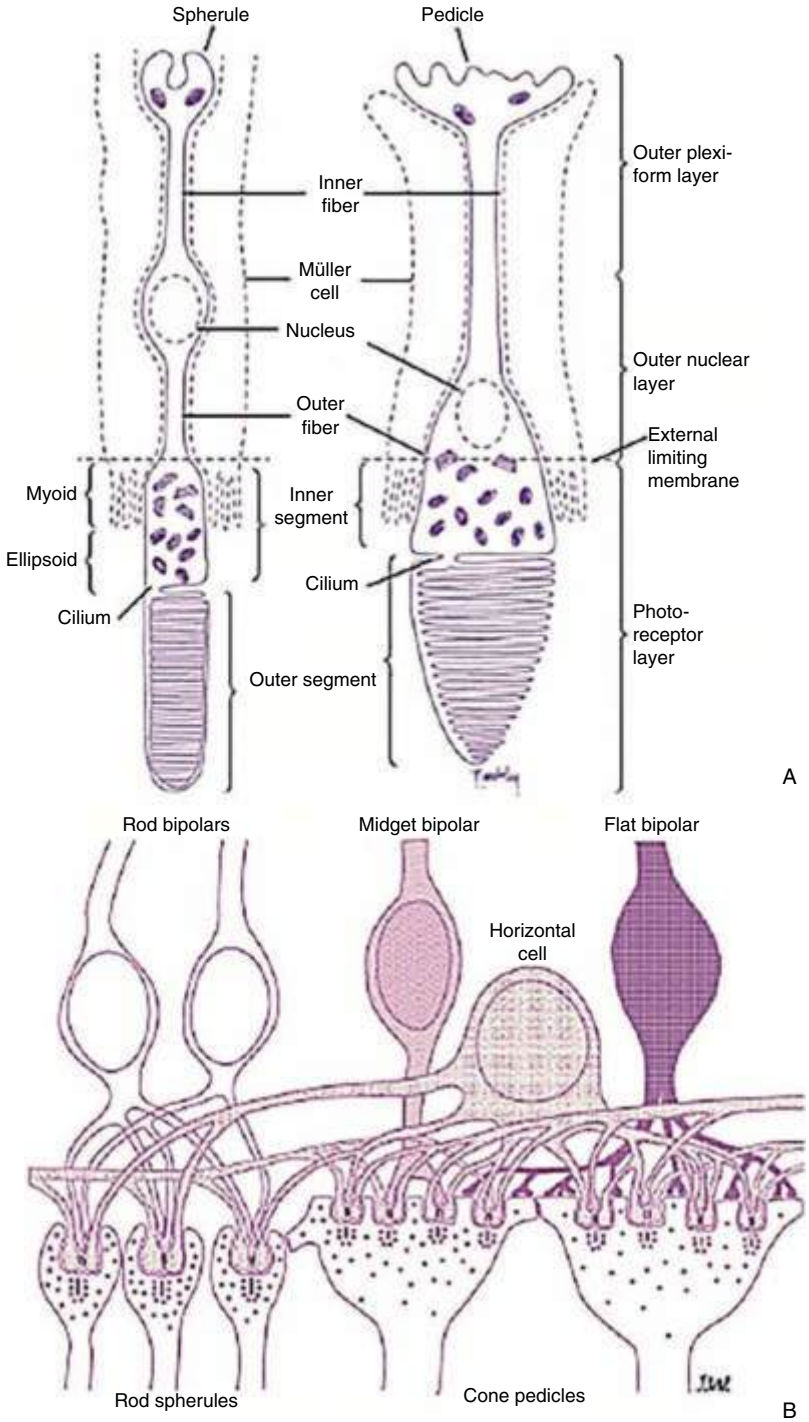


Figure 4.22 **A.** The discs of the outer segments (facing the retinal pigment epithelium) of the photoreceptors contain the photopigment required for vision. The photoreceptors' inner segments contain the mitochondria, and together with the outer segments constitute the photoreceptor layer. The rod spherule and cone pedicle are synaptic expansions where their axons synapse with dendrites of bipolar and horizontal cells in the outer plexiform layer. Portions of Müller's cells (dotted lines) are shown adjoining the rods and cones. **B.** Rod and cone bipolar cells show extensive contacts. Horizontal cells also make synapses with both rods and cones. Interconnections are shown between spherules and pedicles. (Modified and reproduced with permission from Remington, L.A. (2005) *Clinical Anatomy of the Visual System*, 2nd ed. St. Louis, MO: Butterworth-Heinemann.)

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displaced toward the distal end. Experiments in which radiolabeled precursors have been injected into the inner segments show that labeled proteins appear at the outer segment base within 2 hours; another 11 days pass before the discs containing these proteins are shed and phagocytized (Anderson et al., 1978).

The *nuclei* of the photoreceptors constitute the outer nuclear layer (ONL) of the retina, which is separated from the inner segments by an outer limiting membrane. Nuclei of cones occupy a single row directly below the membrane, with rod nuclei making up the remainder of the ONL below the cone nuclei. The *synaptic terminals* of the rods and cones synapse with dendritic processes of bipolar and horizontal cells in the outer plexiform layer (OPL; Fig. 4.22B). The synaptic terminal of a mammalian cone, which is large and flat, is called a *pedicle*. The rod terminal, which is rounder and smaller, is called a *spherule*. Both pedicles and spherules contain mitochondria, synaptic vesicles, and synaptic ribbons (Mustafi et al., 2009; Schmitz, 2009).

The Classic Visual Pigments and Phototransduction

Most of our understanding about the processes occurring in the outer segments comes from studying rhodopsin, the rod photopigment. This light-sensitive transmembrane protein comprises more than 90% of the protein content of the discs in the rod outer segments and covers approximately 50% of the disc membrane area (Hargrave, 2001; Hofmann & Palczewski, 2015b; Palczewski, 2006). It is estimated that each human rod has approximately 10^9 rhodopsin molecules (Smith, 2010), whereas the mouse has only about 10^6–10^7 molecules/rod (Palczewski, 2006).

A visual photopigment consists of two components. The first component of the photopigment is the *opsin*, which is an apo-protein that determines the wavelengths of light that the photopigment will absorb. In most mammals studied to date, maximal absorption of rhodopsin, determined by its opsin part (called *scotopsin*), occurs round 500 nm in most species, thus showing a high degree of evolutionary conservation in the molecule (Bowmaker, 1981, 2008; Palczewski, 2006). There is greater evolutionary divergence in the opsin of cones, with most mammalian species possessing at least two classes of cone opsins: those sensitive to one short wavelength (S-cones) and those sensitive to medium to long wavelengths (L/M-cones; Bowmaker, 2008; Imamoto & Shichida, 2014; Lamb, 2013). Although they are more complicated to study because of the smaller number of cones and difficulties in extraction, cone opsins such as iodopsin appear to be similar to scotopsin in both structure and function (Wensel, 2008).

The second component of the photopigment is the *chromophore*, which is the part of the photopigment that is excited when the energy from a photon is absorbed. The chromophore is covalently bound to the opsin. Both rod and cone photopigments use the same excitable chromophore, a vitamin A1 derivative, 11-*cis*-retinal (Wald, 1968). The 11-*cis*-retinal is highly conserved and found in most terrestrial and avian species.

Phototransduction in Image-Forming Photoreceptors

Phototransduction is the process by which light stimulus is converted into a neuronal signal (Fig. 4.23). Photons captured by the photopigment transfer their energy to the chromophore, causing photoisomerization of the 11-*cis*-retinaldehyde, through several intermediate compounds, into all-*trans*-retinal (Hargrave, 2001; Palczewski, 2006). This results in changes in the chromophore conformation that cause a rearrangement of the heptahelical transmembrane opsin molecule, which eventually leads to activation of subsequent steps in the phototransduction cascade (Nakamichi & Okada, 2006). This bleaching process (so called because the rhodopsin loses its purple color when activated) can be recorded as the early receptor potential of the ERG (Müller & Topke, 1987).

Stimulated neurons depolarize, but contrary to intuition, photoreceptors are depolarized in the dark, causing them to release glutamate (an excitatory neurotransmitter). This depolarized state of the photoreceptor is maintained by a *dark current*, which is generated by a constant influx of Na^+ and Ca^{++} (at an 85 : 15 ratio) into the cell and balanced by K^+ outflow. These cations enter the photoreceptor through cyclic guanosine-3,5′-monophosphate (cGMP)-gated cation channels in the outer segment plasma membrane. The end result of the phototransduction process is a decrease in cGMP levels, leading to closure of the ion channels in a millisecond or less (Yau, 1994). Even though only a small fraction of the cation channels is open in the dark, the cessation of Na^+/Ca^{++} influx leads to hyperpolarization of the photoreceptor. This hyperpolarization decreases or terminates the glutamate release at the photoreceptor synaptic terminals, a signal affecting the second-order neurons in the retina (Heidelberger et al., 2005).

The phototransduction cascade, beginning with the absorption of photon energy by the photopigment and ending with closure of the cation channels and photoreceptor hyperpolarization, involves several enzymes. The interactive form of rhodopsin, R*, activates a G-protein in the disc membrane called transducin (T) in rods, which is composed of three subunits (Tα, Tβ, and Tγ). In the dark, transducin is bound to guanosine diphosphate (GDP), but R* binds to transducin, forming a T-GDP-R* complex (see Fig. 4.23). This binding changes the affinity of the complex to GDP, which drops off and is replaced by guanosine triphosphate (GTP), leading to the formation of a T-GTP-R* complex. Additional affinity changes now occur and the complex breaks up. R* falls off and is free to activate additional T-GDP molecules at the rate of one per millisecond. Tβ-Tγ also falls off, thereby removing the inhibitory γ subunit from the Tα-GTP complex (Stryer et al., 1981). Each R*

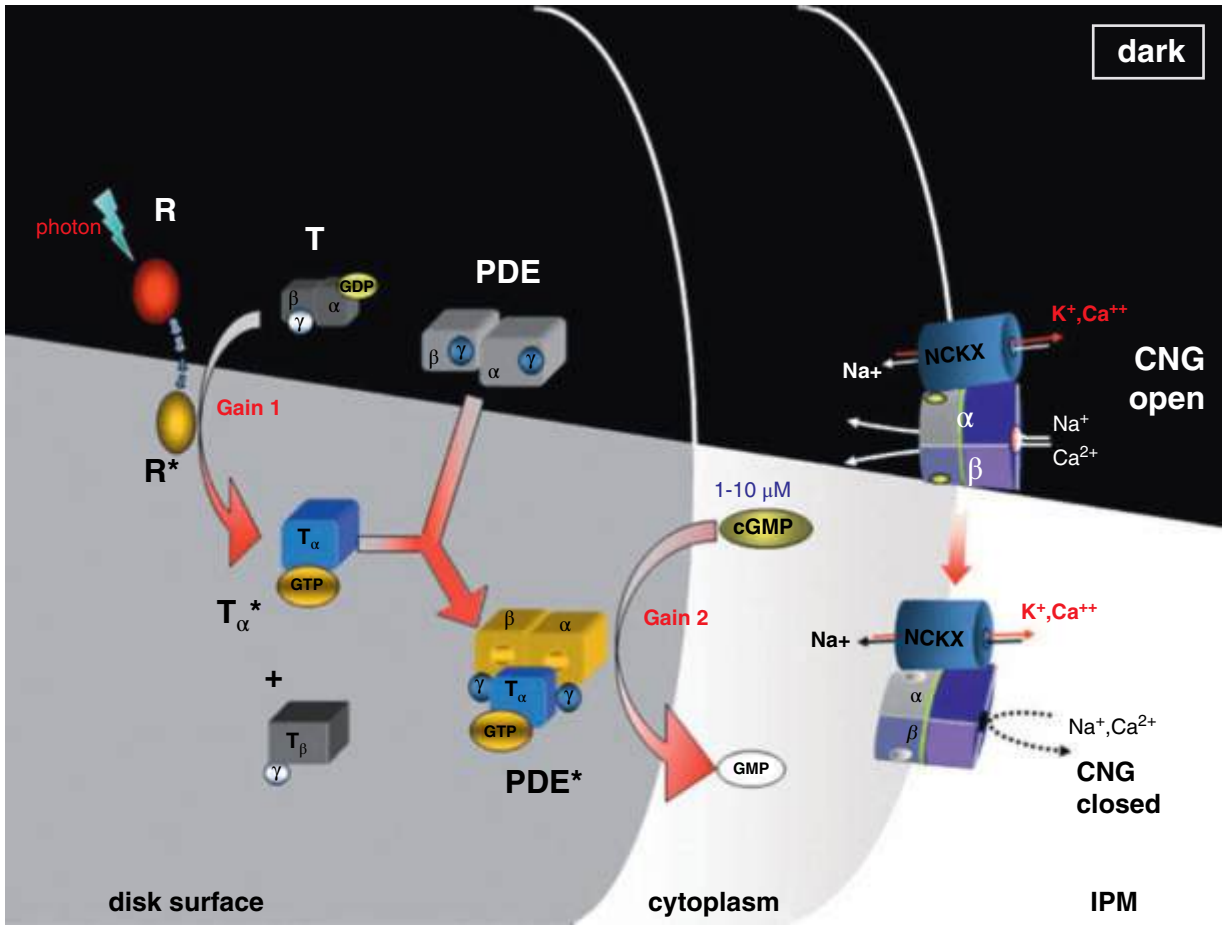


Figure 4.23 Activation of the rod phototransduction cascade. The top of the illustration shows the rod in the dark, where its depolarized state is maintained by influx of sodium and calcium through the open cyclic nucleotide-gated (CNG) cyclic guanosine-3,5′-monophosphate (cGMP)-gated cation channel (α, β). This cation influx is balanced by potassium outflow (through the NCKX Na^+/Ca^{2+}, K^+ exchanger). In the lower part of the figure, a photon has been absorbed by the rhodopsin (R). Activated rhodopsin (R*) now binds to the transducin guanosine diphosphate (T-GDP) complex, leading to reduction in affinity to GDP. GDP is replaced by guanosine triphosphate (GTP), forming an R*-T-GTP complex, leading to dissociation of R* and the transducin Tβ-Tγ subunits. The remaining Tα-GTP complexes remove the inhibitory γ-subunits from the phosphodiesterase (PDE) enzyme. The activated enzyme (PDE*), consisting of its β- and α-subunits, hydrolyzes cGMP into GMP. The reduction in cGMP levels leads to closure of the CNG channels and hyperpolarization. IPM, interphotoreceptor matrix. (Reproduced with permission from *Phototransduction in Rods and Cones*, WebVision, Moran Eye Center (http://webvision.med.utah.edu). Used under CC BY.)

molecule can activate 20 or more T-GDP complexes (Krispel et al., 2006). This is the first step of amplification of the response to the capture of a single photon in the phototransduction cascade.

The activated complex migrates to the disc membrane, where it activates the next enzyme in the cascade, phosphodiesterase (PDE), by removing its inhibitory γ-subunits. Because PDE contains two γ subunits, two Tα-GTP complexes are required for complete PDE activation. However, the density of PDE is lower than that of T in the outer segment. The activated PDE hydrolyzes cytoplasmic cGMP into GMP, resulting in decreased levels of free-floating cGMP. The activation of PDE by Tα-GTP represents no gain *per se*, but the increase in catalytic power of the activated PDE (which hydrolyzes numerous cGMP molecules) is considerable and constitutes the second step of amplification of the response (Lamb & Pugh, 2006).

Multiple cGMP-gated cation channels in the cell's plasma membrane respond by closure to the rapid decrease in cytoplasmic cGMP. Hence, a small relative change in the cGMP concentration produces a threefold larger relative change in the current through the channels. Each photoisomerization interrupts the flow of 10^5 or more cations into the cell (Burns & Baylor, 2001). Therefore, the photoreceptor membrane hyperpolarizes, which generates an electronegative signal that can be recorded at the surface of the eye as the first part of the a-wave of the ERG. The combined amplification for all steps in rods is high, allowing them to detect a single photon.

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Cones, on the other hand, need to absorb 10–100 times as many photons to generate the same current, thus accounting for their decreased light sensitivity (Baylor, 1996).

Inactivation of the Phototransduction Cascade

The cascade is eventually quenched by an equally complex chain reaction that leads to inactivation of R*, transducin, and PDE (Fig. 4.24). Initially, the enzyme rhodopsin kinase (regulated by recoverin) phosphorylates R* (Arshavsky & Burns, 2012; Burns & Baylor, 2001). This phosphorylation increases the affinity of rhodopsin to arrestin, and their binding prevents further transducin activation by R*. At the same time, Tα-GTP is hydrolyzed into Tα-GDP, thus freeing up the PDE-inhibitory γ subunit. The γ subunit rebinds to PDE, thus stopping the hydrolysis of cGMP, and Tα-GDP rebinds to Tβ-Tγ, thus deactivating the transducin molecule (Makino et al., 2003). The cessation of cGMP hydrolysis by PDE, together with increased guanylate cyclase activity in the outer segment, results in net synthesis of cGMP (Burns et al., 2002). As cGMP's concentration rises, it eventually causes reopening of the channels and photoreceptor depolarization.

The phototransduction process in rods can be regarded as a G-protein signaling pathway, with rhodopsin as its receptor, transducin as its G protein, and cGMP PDE as its effector. cGMP is the second messenger in this pathway, connecting between the "rhodopsin receptor" in the rod disc membrane and its "target channel," located in the plasma membrane (Luo et al., 2008).

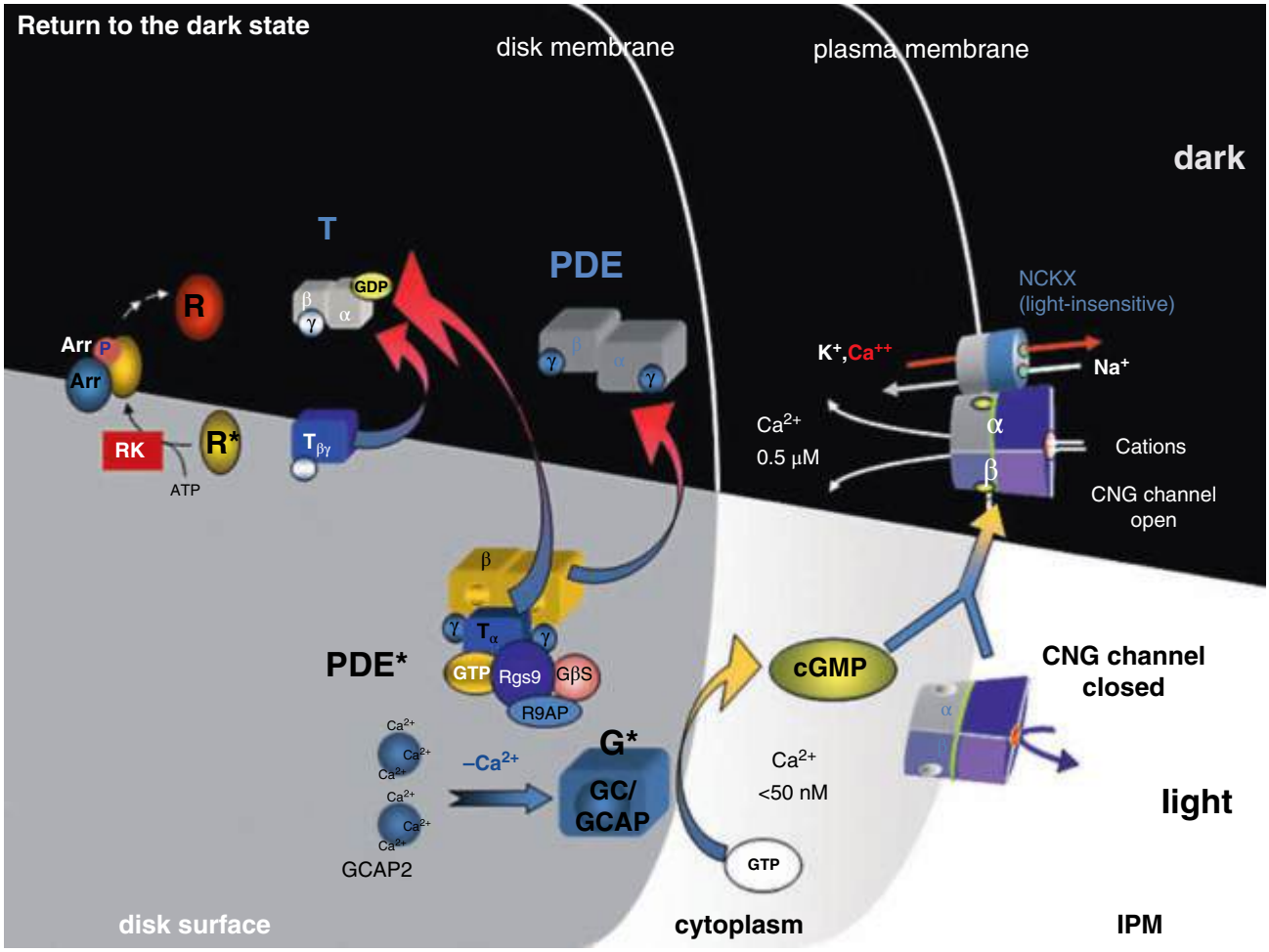


Figure 4.24 Inactivation of the rod phototransduction cascade that results in reopening of the cGMP-gated cation channels on the plasma membrane (from the light-adapted state in the bottom part to the dark-adapted state in the top part of the drawing). Initially, the enzyme rhodopsin kinase (RK, regulated by recoverin) phosphorylates the light-activated rhodopsin (R*). This phosphorylation increases the affinity of rhodopsin to arrestin (Arr), and their binding prevents further transducin activation by R*. At the same time, Tα-GTP is hydrolyzed into Tα-GDP, thus freeing up the PDE inhibitory γ-subunit. The γ-subunit rebinds to PDE, thus stopping the hydrolysis of cGMP, and Tα-GDP rebinds to Tβ-Tγ, thus deactivating the transducin molecule. The cessation of cGMP hydrolysis by PDE, together with increased guanylate cyclase (G*) activity in the outer segment, results in net synthesis of cGMP. As its concentration rises, it eventually causes reopening of the CNG cation channel and photoreceptor depolarization. See Fig. 4.23 for abbreviations. (Reproduced with permission from *Phototransduction in Rods and Cones*, WebVision, Moran Eye Center (http://webvision.med.utah.edu). Used under CC BY.)

Understanding of the molecular biology of phototransduction has led to new insights into the pathogenesis of photoreceptor dysplasias and degenerations, and is leading to new treatments of these diseases (Petersen-Jones & Komaromy, 2015; Scholl et al., 2016).

Synthesis and Regeneration of the Classic Visual Pigments

Regeneration of all-*trans*-retinal to 11-*cis*-retinal is a rather complicated process in vertebrates that mainly takes place in cells adjacent to the photoreceptors. Most of the all-*trans*-retinal is released from the opsin on the cytoplasmic side of the discs in the rod outer segments; however, the portion of the inactive form of the chromophore that enters into the disc lumen has to be transported over to the cytoplasm by an ATP-binding cassette transporter (ABCA4). Because of the reactive aldehyde group on retinal that could potentially damage the photoreceptors, the all-*trans*-retinal is rapidly reduced to all-*trans*-retinol by all-*trans*-retinol dehydrogenase (Fig. 4.25). This is the only step of the regeneration process that occurs in the outer segment of the rods; the rest occurs in the RPE (Kiser et al., 2014; Palczewski, 2014; Saari, 2000).

All-*trans*-retinol diffuses out of the outer segment into the subretinal space and makes its way to the RPE. An interphotoreceptor retinoid-binding protein (IRBP) plays an important role in the movement of all-*trans*-retinol from the photoreceptors through the subretinal space (Wu et al., 2007). Once inside the RPE, all-*trans*-retinol undergoes a three-step transformation reaction to 11-*cis*-retinal. A key enzyme in this reaction is *RPE65* (Redmond, 2009). The 11-*cis*-retinal is then translocated from the RPE back to the outer segment via IRBP, where it binds with opsin (synthesized in the inner segment) to reform the photopigment in both rods and cones (Parker et al., 2011). In addition to the recycling of the chromophore in the RPE, the cones also receive 11-*cis*-retinal through a process involving the Müller cells in the neuroretina (Das et al., 1992). This pathway supports rapid dark adaptation of cones and extends their dynamic range in background light independently of the RPE (Wang et al., 2014). Hence, cones are not completely dependent on the function of the IRBP (Kolesnikov et al., 2011).

Thus, the rods have access to 11-*cis*-retinal from three storage sites in the neuroretina and RPE. When moving abruptly from a scotopic to a photopic environment, the chromophore will be depleted from these three sites in sequential order. The first is the chromophore available in the rod outer segments; the second is the chromophore bound to IRBP in the subretinal space; and the third is the chromophore bound to *RPE65* in the RPE. The cones also have access to a fourth storage site for rapid recovery, the Müller cells. Therefore, *RPE65* plays two vital roles in the visual cycle. In light, it catalyzes the re-isomerization reaction of the chromophore back to 11-*cis*-retinal. In the dark, it serves as a chromophore binding protein and an important reserve pool of 11-*cis*-retinal.

Bleached pigment is not the only source for 11-*cis*-retinal synthesis in the RPE. Dietary uptake remains the main substrate for chromophore synthesis. Carotenoid compounds in food are oxidized into vitamin A (all-*trans*-retinol) in the wall of the small intestine. The vitamin is then esterified and transported to the liver, where it is bound to serum RBP. Retinol-bound RBP is transported through the bloodstream and eventually reaches the choriocapillaris. Specific receptors on the outer aspect of the RPE bind the serum RBP, and the retinol is taken up by the cell for processing, similar to that undergone by all-*trans*-retinol reaching the RPE from the photoreceptor. This dependence on dietary carotenoid compounds is the reason for the nyctalopia and progressive retinal degeneration observed in cases of avitaminosis A in cattle and other species (Millemann et al., 2007).

As indicated earlier, light stimulation causes bleaching of the photopigment; conversely, the pigment undergoes regeneration during darkness (Lamb & Pugh, 2006; Redmond, 2009; Wang & Kefalov, 2011; Wang et al., 2014). Prolonged and intense light stimulation will eventually bleach all of the rod photopigment, resulting in its depletion. Prolonged and total darkness will enable all of the photopigment to regenerate, which is an important part of the dark adaptation process. At intermediate levels of illumination, between these two extremes, a dynamic and continuous process of bleaching and regeneration occurs, leading to equilibrium and contributing to adaptation to existing light levels (see Chapter 5).

Physiology of Retinal Cells

Horizontal and Bipolar Cells

The soma of both the horizontal and bipolar cells are located in the inner nuclear layer (INL). Both cells serve as *second-order* neurons of the retina, connecting, directly or indirectly, the *first-order* (photoreceptors) and *third-order* neurons (RGCs).

Horizontal cells occupy the outermost layer of the INL and synapse almost exclusively in the OPL (Ahnelt et al., 2000; Bloomfield & Xin, 2000; Chapot et al., 2017; Macneil et al., 2009; Marshak & Mills, 2014; Thoreson & Mangel, 2012). They connect photoreceptors laterally across the OPL (see Fig. 4.22), serving to integrate responses from photoreceptors and increase their sensitivity to changes in illumination (i.e., brightness contrast) and color, which is a phenomenon termed *lateral inhibition*. Morphologically, horizontal cells are divided into *HI* or *B*-type cells with axons, and *HII* or *A*-type cells that are axonless. Additional types of horizontal cells are seen in animals, including primates, birds, and reptiles, with more types of cones. The horizontal cells form a mosaic with about six dendritic fields overlapping at any given point in the murine retina (Reese et al., 2005).

The physiologic equivalents of HI/B and HII/A horizontal cells have been characterized as luminosity (L) and color (C) types, respectively. The HI/B- or L-type horizontal cells

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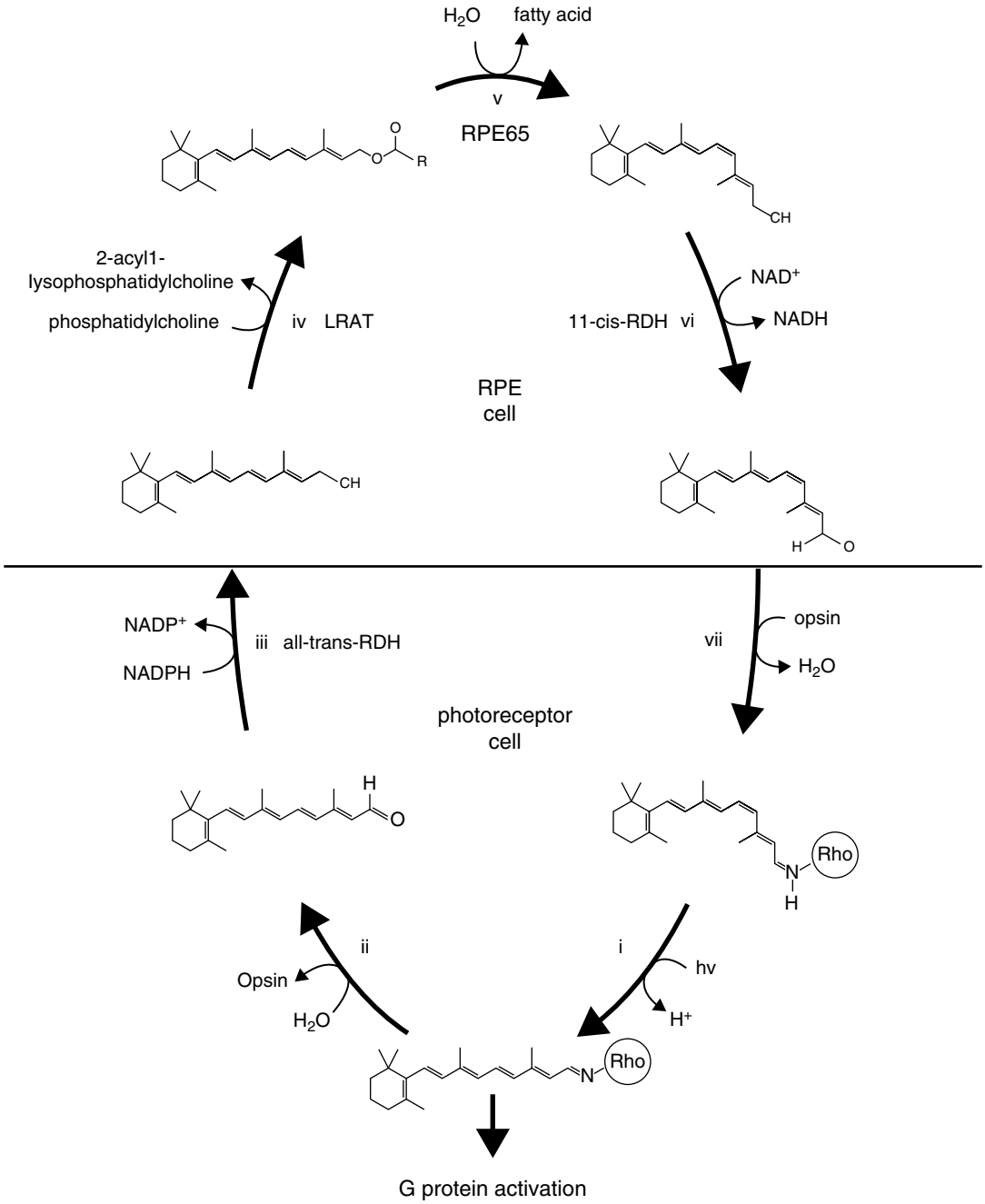


Figure 4.25 The retinoid (visual) cycle, which begins when a photon (hv) causes photoisomerization of the 11-*cis*-retinylidene chromophore of the dark-adapted rhodopsin. Subsequently, a proton is lost and rhodopsin activates G proteins (i). The isomerized chromophore is released via hydrolysis, generating free all-*trans*-retinal and opsin (ii). The all-*trans*-retinal is then enzymatically reduced (iii) to all-*trans*-retinol, which binds to interphotoreceptor retinoid-binding protein (IRBP) and is exported from the outer segment of the rod to the retinal pigment epithelium (RPE). Here all-*trans*-retinol binds to cellular retinaldehyde binding protein (CRALBP) and is metabolized by lecithin retinol acyltransferase (LRAT) to produce all-*trans*-retinyl esters (iv), which can be either stored in retinosomes or further processed. RPE65 is the key enzyme that catalyzes the conversion of all-*trans*-retinyl esters to 11-*cis*-retinol (v). 11-*cis*-retinol is finally enzymatically reduced to 11-*cis*-retinal (vi) and transported back via IRBP to the rod outer segment, where it recombines with opsin to form ground-state rhodopsin (vii). This cycle runs continuously to sustain vision under conditions where rods are primarily active. (Reproduced with permission from Kiser, P.D. & Palczewski, K. (2010) Membrane-binding and enzymatic properties of RPE65. *Progress in Retinal and Eye Research*, **29**, 428–442.)

synapse with both rods and cones. They code changes in ambient light intensity, thus regulating the adaptational and spatial responses of the photoreceptors and bipolar cells. These cells respond with graded hyperpolarizations to light stimuli (regardless of wavelength), with the amplitude and duration of the response depending on the intensity and duration of the stimulus (Svaetichin & MacNichol, 1959). The HII/A- or C-type cells only connect with cones, thus contributing to color and fine detail perception. HII/A- or C-type horizontal cells respond with different polarity to light stimuli of different wavelengths; for example, they may respond with graded depolarization to red light stimuli and with graded hyperpolarization to yellow, green, and blue stimuli. Surprisingly, the HII/A-like cells in the horse seem only to contact S-cones (Sandmann et al., 1996), which precludes color opponency.

Thus, the two types of horizontal cells serve to modulate the antagonistic center-surround receptive fields of bipolar cells, normally contributing to both their spatial and color opponency properties. Furthermore, the receptive field of horizontal cells may extend outside their dendritic fields via electric coupling through gap junctions between horizontal cells (Chapot et al., 2017).

Bipolar cell somata are also located in the INL. Their dendrites synapse with photoreceptors and horizontal cells in the OPL (see Fig. 4.22), and their axons terminate in the inner plexiform layer (IPL), where they synapse with amacrine and ganglion cells. There are several ways to classify bipolar cells. Anatomically, bipolar cells (bipolars) are divided based on whether they synapse with rods or with cones. Because most species have more rods, *rod bipolars* are numerically superior to *cone bipolars*. Only one type of rod bipolar has been described in mammals. As each rod bipolar cell can receive input from numerous rods, the rod pathway has been described as a *convergent pathway* with large receptive fields (the *receptive field* of a bipolar cell is the sum of the receptive fields of the photoreceptors from which it receives input; Fig. 4.26). Such a pathway enhances scotopic vision, because the absorption of just one photon anywhere in the receptive field is sufficient to stimulate the rod bipolar pathway.

The number of cone bipolar types in species carefully studied, such as the macaque, mouse, and rabbit, seems to be about 11–12 (Euler et al., 2014; Tsukamoto & Omi, 2016; Wässle et al., 2009). In the primate fovea, *midget bipolars* typically synapse only with one M- or L-cone in a one-to-one relationship (Jusuf et al., 2006; Wässle et al., 1994). Since each midget bipolar cell receives input from just one cone, it will have a much smaller receptive field, and form a *nonconvergent pathway* (Fig. 4.27). This feature, combined with the antagonistic center-surround properties of the receptive fields that is thought to be established at the bipolar cell level (Dacey et al., 2000), contributes to the higher visual resolution that characterizes the cone system. *Diffuse cone bipolars* receive input from as few as a handful of cones in the central retina, and as many as 20 cones in the peripheral retina. Thus, diffuse cone bipolars function much like rod bipolars, converging input from several cones, but their role in retinal processing is still largely elusive, although progress has been made (Hoon et al., 2014).

Bipolar cells are the first visual neurons exhibiting spatial organization of their receptive fields. The cells respond with opposite-voltage polarity to light stimuli illuminating either the center or the surround of the receptive field. The interactions between horizontal cells and photoreceptors that underlie this organization of spatial opponency organization are illustrated in Fig. 4.28. Specifically, direct input from photoreceptors is believed to contribute to the central response of bipolar cells, while the horizontal cells form the antagonistic surround component through modulation of photoreceptor synaptic output.

Therefore, another way of classifying bipolar cells is on the basis of the response generated by light stimulation of their central receptive field. "ON-center" cells are activated (depolarized) when their center is stimulated by light, whereas "OFF-center" cells are inhibited (hyperpolarized) in response to light stimulation in the central field.

The peripheral (i.e., toroidal) receptive field of these cells is antagonistic to the center. Thus, for example, an ON-center bipolar cell will also have OFF-surround properties and will activate (depolarize) when light is turned off in the surrounding field. Therefore, when both the central and peripheral fields of an ON-center–OFF-surround bipolar cell are stimulated by light, the central field will depolarize, and the peripheral field will hyperpolarize. The result is decreased responsiveness by the cell, because the response of the periphery will inhibit the response of the center.

However, if an OFF-field is inhibited (hyperpolarized) by light, it follows that it is activated (depolarized) by darkness. Therefore, if the same ON-center–OFF-surround bipolar cell was presented with a small light stimulus in its central field and an adjacent dark stimulus in its peripheral field, the net result would be an enhanced response, as both fields respond with activation and depolarization to their respective stimuli. This enhanced responsiveness to small, adjacent light and dark stimuli is the cornerstone of high-resolution vision.

In addition to enabling spatial center-surround antagonism, horizontal cell modulation also allows chromatic antagonism. For example, based on horizontal cell feedback, it is possible to have a red-OFF green-ON bipolar cell. Such a cell responds with hyperpolarization to red stimuli and with depolarization to green stimuli. This color opponency is generated by different types of inputs from different types of cones, in this case excitatory input from the red cones and inhibitory input from the green cones, forming the first step in chromatic visual processing.

Other Inner Nuclear Layer Cells

The INL is populated by three more types of cells, in addition to some displaced RGCs. Little is known about the *interplexiform cells*, which are neurons with processes in both the

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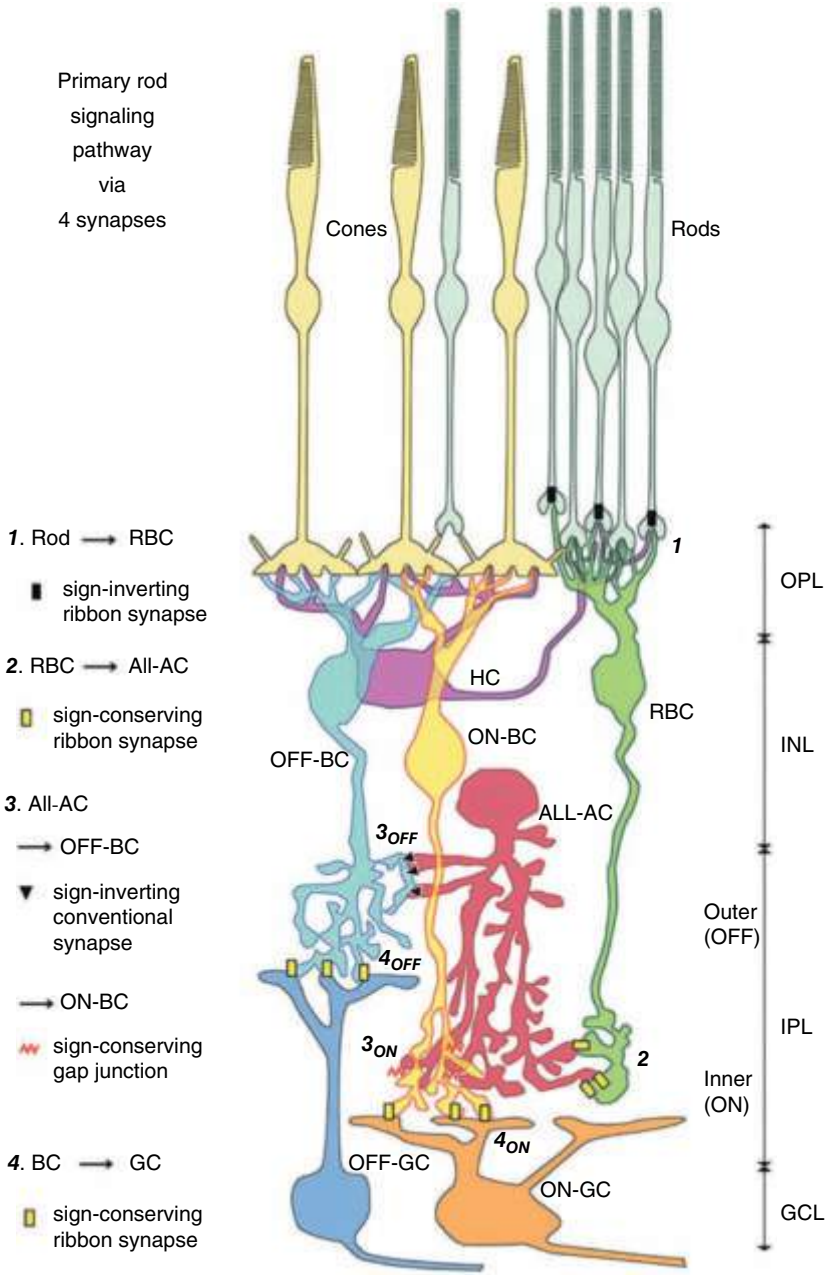


Figure 4.26 The primary rod pathway is indirect and more convergent than that of cones. A group of rods connect to a rod bipolar cell (RBC), whereas the cones connect to both ON- and OFF-cone bipolars. Furthermore, the rod signal has to pass via the amacrine and cone bipolar cells before reaching the ON-ganglion cell, whereas the cone bipolar cells synapse directly to the ganglion cells. GCL, ganglion cell layer; INL, inner nuclear layer; IPL, inner plexiform layer; OPL, outer plexiform layer. (Reproduced with permission from Tsukamoto, Y. & Omi, N. (2017) Classification of mouse retinal bipolar cells: Type-specific connectivity with special reference to rod-driven AII amacrine pathways. *Frontiers in Neuroanatomy*, **11**, 92. doi: 10.3389/fnana.2017.00092. Licensed under CC BY 4.0.)

OPL and the IPL. In the OPL, they are presynaptic to bipolar cells. In the IPL, they are pre- and postsynaptic to amacrine cells, and presynaptic to bipolar cells. Thus, it believed that they may modulate the synaptic gain between photoreceptors and their second-order neurons (Jiang et al., 2014).

Müller cells are another class of cells found in the INL, and they are the main glial cells of the retina (de Melo Reis et al., 2008; Kofuji et al., 2000; Vecino et al., 2016). Müller cells are ependymoglial cells, meaning they have both a structural support and a metabolic role. Their perikarya are located in the INL, but they extend long processes toward the inner and outer retina, where they join to form both the inner and outer limiting membranes. Therefore, the Müller cells can be regarded as retinal radial cells, extending

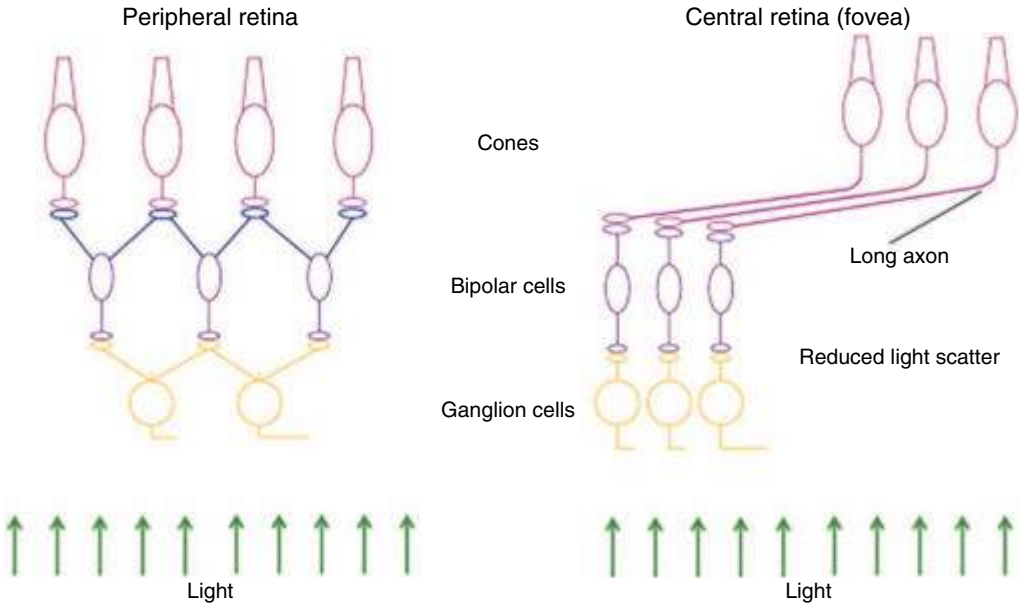


Figure 4.27 Cone pathways in the central (foveal) and in the peripheral primate retina. In the fovea, each cone photoreceptor has a private line to one retinal ganglion cell. In the peripheral retina, there is progressive convergence of several cones onto a bipolar cell. Furthermore, the long axons of the foveal cones allow light to reach the outer segment without having to pass through the neurons of the inner retina. Both of these specializations increase the resolution of details. (Reproduced with permission from Masland, R.H. (2017) Vision: Two speeds in the retina. *Current Biology*, **27**(8), R303–R305. doi.org/10.1016/j.cub.2017.02.056.)

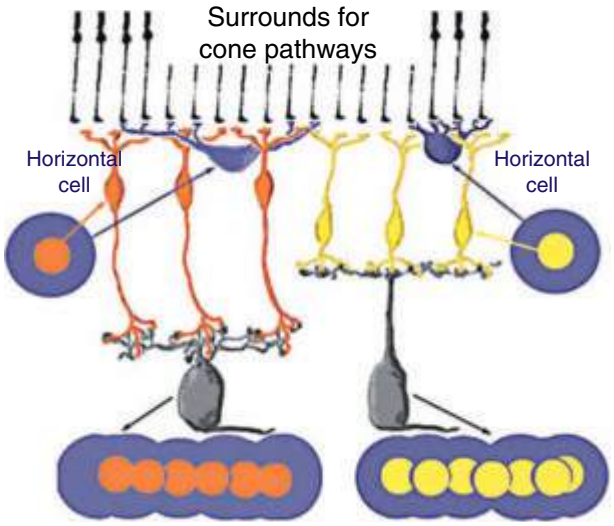


Figure 4.28 Center-surround antagonism of bipolar (and consequently ganglion) cells is due to modulation by horizontal cells. A central stimulus is relayed directly from cones (in black), through a yellow or orange bipolar cell onto a gray ganglion cell. A peripheral stimulus is relayed through an inhibitory horizontal cell (in purple). The resulting receptive fields are depicted at the bottom, with stimulated centers (yellow or orange) and inhibited surround (bluish-violet). (Reproduced from *Cone Pathways through the Retina*, WebVision, Moran Eye Center (http://webvision.med.utah.edu) with permission of Dr. Helga Kolb. Used under CC BY.)

through the retina's entire thickness and lending it architectural support. Müller cells also fill in all gaps in the neuroretina not occupied by other elements. Thus, their processes encircle intraretinal blood vessels and RGC axons in the nerve fiber layer. They also sheath dendritic processes, isolating them chemically and electrically, and surround the individual photoreceptors, insulating them from each other and keeping them properly aligned. Recently, it has also been shown that Müller cells have a circadian clock function (Xu et al., 2016).

Metabolically, Müller cells synthesize and store glycogen, which helps protect the retina from fluctuations in systemic glucose levels. These cells also help to maintain the anionic balance in the retina by taking up the K^+ secreted by the photoreceptors. Müller cells remove the excess K^+ from the retina, thus acting as a "K^+ sink" and contributing to the generation of the ERG b-wave. Müller cells are also active in uptake and metabolism of neurotransmitters, including γ-aminobutyric acid (GABA), dopamine, and glutamate (Bringmann et al., 2013). In pathophysiologic conditions, they can become activated by inflammatory mediators, and contribute to the immune response of the retina following injury (Bringmann et al., 2009). In mammals, their ability to reacquire a retinal progenitor state and regenerate neurons after retinal damage is very limited (Hamon et al., 2016).

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Amacrine cells, which are the last type of INL cells, occupy the innermost tier of this layer, though displaced amacrine cells are also found in the ganglion cell layer (Klump et al., 2009; Lee et al., 2016b; Masland, 2012; Weltzien et al., 2015). Morphologically, more than 30 types of amacrine cells have been identified in the mammalian retina. They are characterized by the fact that they do not possess any recognizable axons, and they are classified by the size (i.e., narrow, small, medium, and wide) and shape of their dendritic tree (e.g., linear, beads, starburst), or by the neurotransmitter they release (e.g., acetylcholine, serotonin, dopamine). However, as the IPL is traditionally divided into five strata, the most widely used classification of amacrine cells is based on the IPL strata in which their dendritic tree is found.

Amacrine cells are known to be inhibitory neurons containing the common inhibitory neurotransmitters GABA or glycine, but they also excite bipolar and ganglion cells through gap junctions and possibly glutamate release (Marshak, 2016; Nath & Schwartz, 2017; Roy et al., 2017). The cells form very complex networks of connections with bipolar axon terminals, with RGC dendrites, and with other types of amacrine cells (Fig. 4.29). Each type of amacrine cell seems to be functionally charged with specific tasks in the retina. The amacrine cells create contextual effects for the responses of RGCs, including the center-surround antagonism enhancing motion detection relative to a background, but also mediate gain control (Grimes et al., 2010) and alter the kinetics of the bipolar cell output (Sagdullaev et al., 2011). Some of them also exchange information between the layers of the IPL, thus sending signals between the ON- and OFF-strata. Hence, amacrine cells such as the AII cell contribute to both lateral and vertical communications in the retina (Fig. 4.30).

Amacrine cells are the target cells of centrifugal fibers from higher cortical centers, which further modulate the retinal responsiveness in birds and nonmammalian species. It is still unknown whether amacrine cells also are targeted in mammals.

Ganglion Cells

All information processed by the retina eventually converges on the RGCs, the innermost cell layer in the retina, and its final-order output neuron. Though much signal processing has already occurred in the vertical (photoreceptor to bipolar to RGC) and in the lateral (photoreceptor to horizontal cell to bipolar to amacrine to RGC) pathways, the RGCs are the most complex information processing cells in the retina (Schiller, 2010). To date, more than 30 functionally-distinct classes of RGCs have been described in the mouse (Baden et al., 2016). This means that even in the mouse, the data obtained and processed in the retina is sent to the brain in a rather large number of parallel output channels providing information about different features of the visual scene.

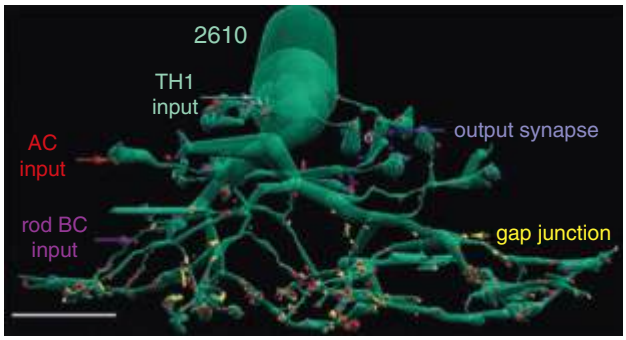


Figure 4.29 Amacrine cells (AC) form complex networks with other retinal neurons. Each colored dot represents a contact between this AII cell (labeled no. 2610) and other cells. Synapses with its rod bipolar are shown in magenta. Yellow gap junctions form electrical contacts with adjacent cells, such as cone bipolar cells (BC). A single ribbon synapse with a cone OFF-bipolar cell is marked with a white circle. Inputs from other amacrine cells are shown in red and the cyan inputs come from a tyrosine hydroxylase (TH-1) immunopositive interneuron. Glycinergic synaptic outputs from this AII cell are labeled blue. Scale bar: 10 µm. (Reproduced with permission from Marc, R.E., Anderson, J.R., Jones, B.W., et al. (2014) The AII amacrine cell connectome: A dense network hub. *Frontiers in Neural Circuits*, **8**, 104. doi: 10.3389/fncir.2014.00104. Used under CC BY.)

Traditionally, ganglion cells have been classified in three ways:

1) *Morphology*. Morphologic classification schemes have been used extensively. RGCs have been subdivided into classes such as the α-, β-, and γ-cells in cats (Boycott & Wässle, 1974). Later these classes have been further subdivided according to more detailed analysis of the cell's microcircuitry (Kolb et al., 1981; Masri et al., 2019; Rockhill et al., 2002). Midget ganglion cells in primates (corresponding to β-cells in the cat) are located in the central retina, and the small size of these cells permits denser packing, thus allowing each to receive input from fewer cones and bipolars. In species with high-resolution vision, the functional ratio of cones and bipolar cells to β-ganglion cells approaches 1:1:1 in the foveal region. Larger (α) ganglion cells are found in the more peripheral retina, and their large size permits convergence of input from many amacrine cells. Axonal diameter is proportional to the somata size; therefore, central β-cells possess smaller-diameter axons than peripheral α-cells. More recently, specific markers for individual RGC classes and molecular genetic techniques have been employed to characterize and subdivide the RGCs (Badea & Nathans, 2011; Kim et al., 2010; Siegert et al., 2009; Sweeney et al., 2019).
2) *Physiologic responses*. Physiologic classifications according to the responses generated by the RGC, which of course depend on the input the cell receives, have also been elaborated (Enroth-Cugell & Robson, 1984; Zeck &

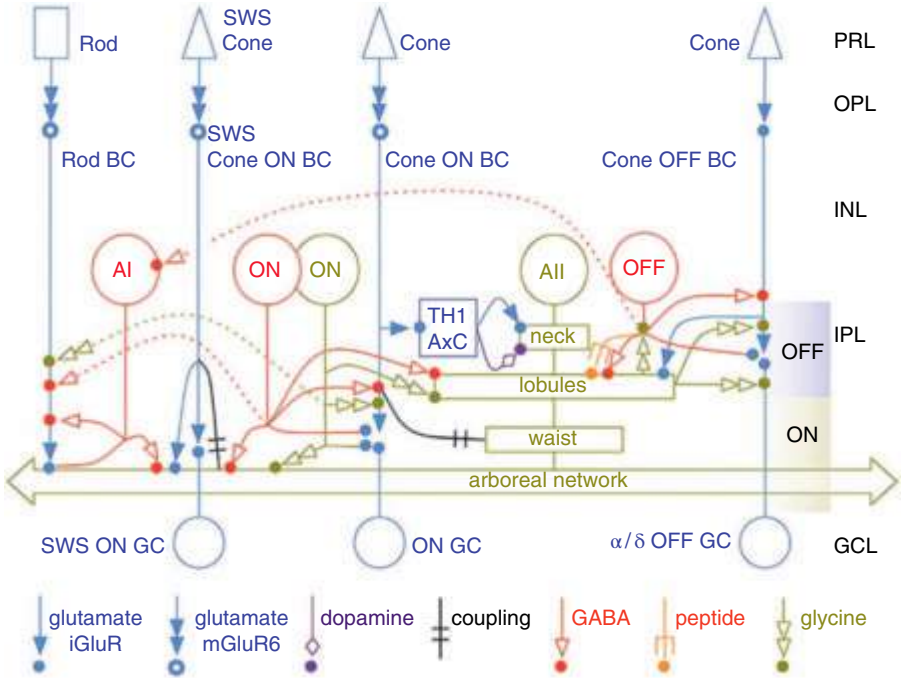


Figure 4.30 The intricate amacrine AII network contributes to both horizontal and vertical communication in the retina. The AII cell is subdivided into five parts, with the nucleus in the inner nuclear layer (INL) and the lower four representing the dendritic tree in different strata of the inner plexiform layer (IPL). The neck and lobule in the OFF-layer of the IPL do not overlap with neighboring AII cells, whereas the waist and arboreal network in the ON-layers do. The inputs to this AII cell include four types of excitatory glutamate inputs: gap junctions (electrical coupling) between cells, dopaminergic and peptide modulation, inputs from three types of wide-field GABAergic cells, and glycinergic inputs from narrow-field cells. The AII cell outputs to OFF-bipolar cells and OFF-inhibitory neurons and two types of OFF retinal ganglion cells (RGCs). Different types of pure cone bipolar cells (CBs) are lumped into single ON- and OFF-channels, as well as multiple types of ON- and OFF-amacrine cells lumped into single representative classes in the drawing. The dashed lines show cone -> rod suppressive crossover pathways. TH_1AxC shows a glutamate/dopaminergic wide-field axonal cell. GCL, ganglion cell layer; OPL, outer plexiform layer; PRL, photoreceptor layer; SWS cone, short wavelength-sensitive (blue) cone. (Reproduced with permission from Marc, R.E., Anderson, J.R., Jones, B.W., et al. (2014) The AII amacrine cell connectome: A dense network hub. *Frontiers in Neural Circuits*, **8**, 104. doi: 10.3389/fncir.2014.00104. Used under CC BY.)

Masland, 2007). Most RGCs receive input directly from bipolar cells. Therefore, the receptive fields of these cells function in a manner similar to those of their associated bipolar cells (i.e., ON-center–OFF-surround, or vice versa). These cells are called X-cells and correspond to the cat β-cells. Other RGCs (i.e., Y-type) receive input mainly from amacrine cells. RGCs are also subdivided according to their ability to detect motion in a certain direction or respond better to elongated stimuli that have a certain orientation. Motion-responsive RGCs that are directionally selective respond to stimuli moving in a preferred direction and may be completely inhibited by movement in other directions (Fig. 4.31; Borst & Euler, 2011; Fried et al., 2002). Some cells respond better to bar-shaped stimuli that have a certain angular orientation (pointing in a particular direction like a hand on a clock) and are consequently called orientation selective (Antinucci et al., 2016; Levick, 1967). RGCs are also classified on the basis of the cell to which they output. M-ganglion cells synapse in the magnocellular layers of the lateral geniculate nucleus (LGN), and P-ganglion cells terminate in the parvocellular layers. The function of the heterogenous group of K-cells synapsing in the koniocellular layer is less well understood, but the K-ganglion cells are reported to convey blue color signals and respond to rapid movements (Percival et al., 2014).

3) *Information processing*. The luminance (magnocellular) pathway both processes and relays information regarding changes in light levels and motion. The resolution (parvocellular) pathway processes information pertaining to fine details and the color of the stimulus.

Obviously, these classifications are not exclusive; rather, they constitute different descriptions of the same cells. The β-, X-, or parvo-cells are numerous, small cells that receive input from cone systems and bipolar cells. They can further be subdivided into additional types, but all have a small diameter in common, and therefore the slower-conducting axons of these cells transmit information on stimulus wavelength (color) and fine detail. The different types of RGCs

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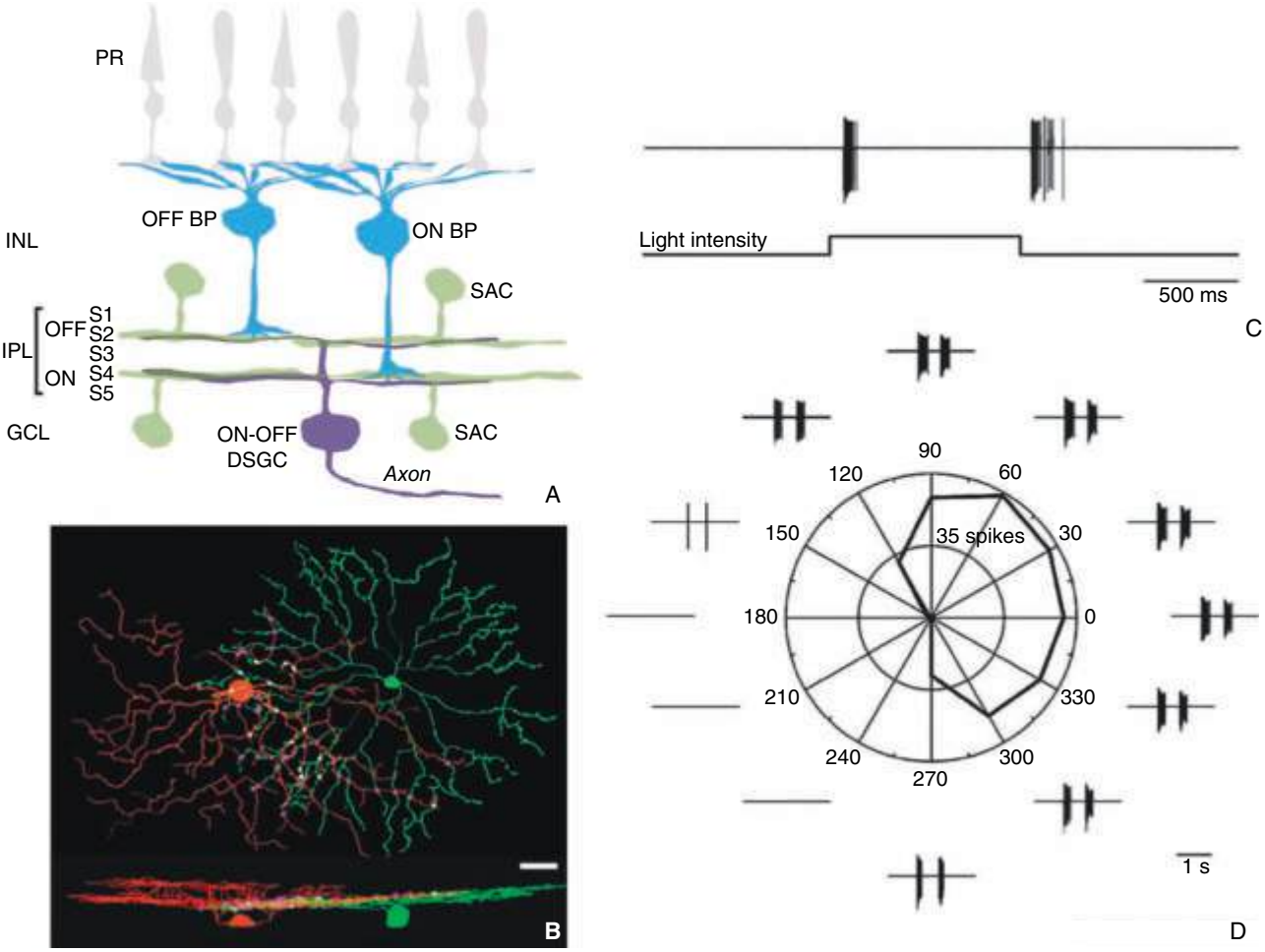


Figure 4.31 **A**. A mammalian ON–OFF direction-selective ganglion cell (DSGC) fed by ON- and OFF-bipolar cells (BP) that relay signals from photoreceptors (PR). The DSGC has a bistratified dendritic arbor in sublaminae (S) 2 and 4 of the inner plexiform layer (IPL). Two mirror symmetric populations of starburst amacrine cells (SAC) with their nuclei in the inner nuclear layer (INL) and ganglion cell layer (GCL, where they are often termed "displaced amacrine cells") modulate the signals to the DSGC. **B**. Reconstruction of contacts between a DSGC (red) and an SAC (green). Dots show dendritic contacts with putative GABAergic contacts (cofasciculation segments) on the null side in white and the rest in purple (scale bar 25 μm). **C**. Responses from recordings of an ON–OFF DSGC to a flashing spot of light. Both the onset of the light stimulus and the cessation of the stimulus trigger short bursts of spikes in this phasic cell. **D**. Recordings from the same ON–OFF DSGC in response to a bar moving in 12 different directions. Movement in the preferred directions elicits brisk bursts of spikes, whereas the cell is silent or responds very weakly when the bar is moved in nonpreferred directions. (Reproduced with permission from Wei, W. & Feller, M.B. (2011) Organization and development of direction-selective circuits in the retina. *Trends in Neuroscience*, **34**, 638–645. doi: 10.1016/j.tins.2011.08.002.)

lumped together as α-, Y-, or magno-cells are fewer in number and larger in size; these cells receive input from rod systems and amacrine cells. Their larger-diameter and faster-conducting axons relay information on subtle changes in illumination levels (i.e., contrast) and stimulus motion (i.e., temporal resolution). These cells are characterized by transient (phasic) responses, as compared to the more sustained (tonic) responses of the β-cells.

About 3%–5% and 45%–50% of the feline RGCs can be classified as α- and β-cells, respectively. They are arranged in regular, superimposed mosaics across the entire retina. Both OFF-center and ON-center classes of α- and β-cells are arranged in a paired manner, so that an ON/OFF pair receives inputs from almost the same retinal region. Naturally, both cell types have their smallest dendritic tree sizes at the area centralis. The dendritic tree size increases (and RGC density decreases) with retinal eccentricity, and consequently peripheral RGCs extend over 10× larger areas than those in the area centralis. Most of the axons of both types of cells terminate in the LGN, with only a few collateral fibers synapsing in the superior colliculus.

The remaining balance of the feline RGCs is classified morphologically as γ- (gamma) or δ- (delta). The γ-cells, also classified as W-cells, have small somata and axons, but their

response to light can be either sustained or transient. They serve in cone systems and contribute to high-resolution photopic vision. There are more than 20 types of δ-cells, classified as G4—G23 based on their size. Half of these cells project to the superior colliculus rather than to the LGN.

RGCs usually have an intrinsic, basal firing rate in darkness. Changes in the number of spikes in response to light or darkness are similar to those of the associated ON- or OFF-bipolar cells, and amacrine cells, with which they synapse in the IPL. Thus, an ON-center–OFF-surround RGC will respond to a light stimulus in the center of its receptive field with depolarization and a vigorous train of impulses due to input from its associated ON-bipolar cells (see Fig. 4.32A–C). On the other hand, a stimulus in the surround will actively inhibit the same RGC by hyperpolarizing its membrane based on input from its associated OFF-bipolar and amacrine cells (see Fig. 4.32). Conversely, OFF-center cells, which are excited at light offset in their center, have regions in the peripheral receptive field where ON excitation is evoked by light onset. As in the case of the bipolar cells, the result is a high degree of contrast perception between central and peripheral stimuli.

This antagonistic center–surround receptive field organization of RGCs is also used to code additional information about the stimulus. For example, amacrine cell modulation allows direction-selective RGCs to respond to stimuli moving in a preferred direction (see Fig. 4.31). Color opponent RGCs will change their firing rate in response to different colors. For example, in a red-OFF–green-ON center RGC, green light will excite the cell and evoke impulses, while red light will inhibit discharges (Fig. 4.33). The same cell will also have reciprocal red-ON–green-OFF surround properties. At the same time, additional RGCs code other features about the stimulus, including its size, contrast, orientation, and speed of movement.

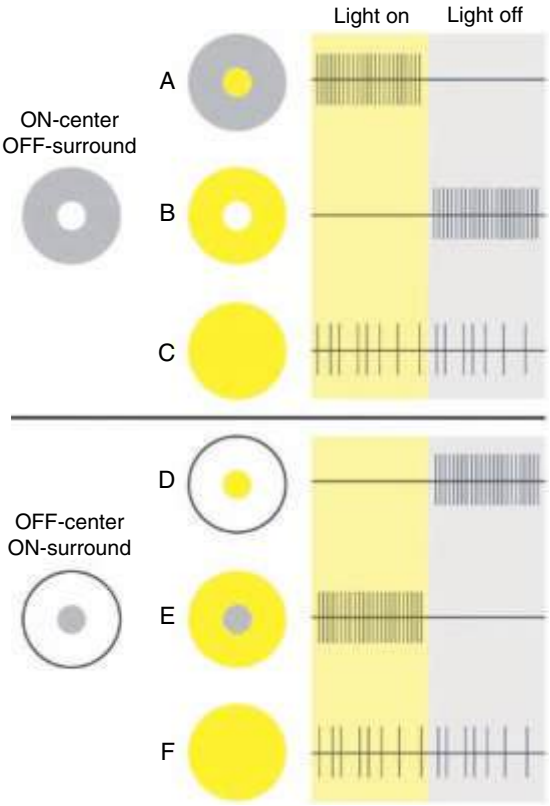


Figure 4.32 The upper half shows responses of an ON-center OFF-surround retinal ganglion cell (RGC). In (**A**), only the ON-center is stimulated by light (yellow) and a tonic train of spikes is seen throughout the stimulus. When the center is in the dark (gray) and only the surround is stimulated by an annulus of light, the cell is inhibited and starts firing first at the cessation of the annular stimulus (**B**). When both the center and surround are stimulated by light simultaneously (**C**), the RGC is spiking much less frequently because the excitatory signals from the center are counteracted by the inhibitory ones from the surround. Panels (**D**) through (**F**) show responses from an OFF-center ON-surround RGC.

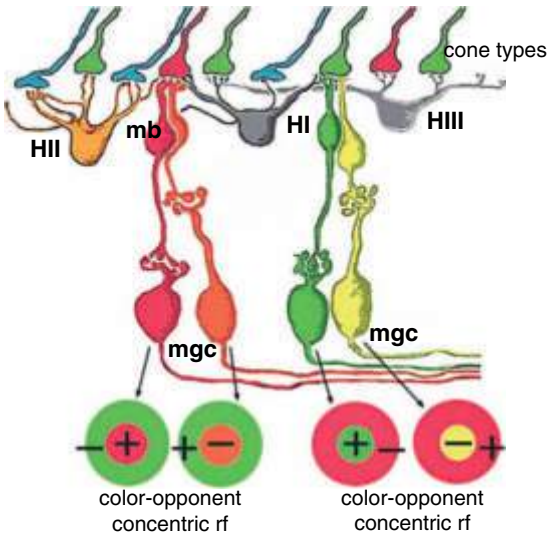


Figure 4.33 Schematic drawing of color opponent circuits in the primate fovea. A long wavelength-sensitive cone (in red; L) contacts an ON-midget bipolar cell (red mb), which connects to a L-cone midget RGC (red mgc). The same L-cone also connects to an OFF-midget bipolar cell and RGC (both in orange). Thus, an L-cone ON- (red center and green surround) and an L-cone OFF-center receptive field ganglion cell (orange center and green surround) are generated. Further to the right, a middle wavelength-sensitive cone (in green; M) is connected in a similar manner creating green ON- and OFF-receptive fields, respectively. Horizontal cells (HI through HIII) can contribute the surrounds to the L-cone center bipolar cells. (Reproduced from *Midget Pathways of the Primate Retina Underlie Resolution and Red Green Color Opponency*, WebVision, Moran Eye Center (http://webvision.med.utah.edu) with permission of Dr. Helga Kolb. Used under CC BY.)

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Intrinsically Photosensitive/Melanopsin-Expressing Retinal Ganglion Cells

In 1998, a high level of expression of another vitamin A-based opsin, melanopsin, was identified in non-photoreceptor cells in the frog retina (Provencio et al., 1998). Later, it was found that the melanopsin was expressed in a subset of RGCs with small somata, but large, sparsely branching dendritic fields (Nasir-Ahmad et al., 2019). These intrinsically photosensitive RGCs (ipRGCs) were mainly projecting to the hypothalamic suprachiasmatic nucleus (SCN), but also targeting the geniculate and the olivary pretectal nuclei (Hattar et al., 2002). Axons reaching other centers in the brain, including the superior colliculus, have been described more recently. The ipRGCs constitute up to 3% of the total RGC count. To date, six classes of ipRGCs have been identified in the mouse, whereas primates are considered to have three classes (Fig. 4.34; Hughes et al., 2016; Quattrochi et al., 2019; Sexton et al., 2012). Different types of ipRGCs appear to have both different response characteristics and, at least in part, project to different areas in the brain.

Melanopsin uses the same chromophore as cones and rods, 11-*cis*-retinal, and has a peak absorbance in the blue part of the spectrum at about 480 nm. Phylogenetic analysis indicates that mammalian melanopsin is more closely related to the invertebrate opsins than the classical vertebrate visual opsins (Provencio et al., 1998). The phototransduction cascade driven by photoactivation of melanopsin is also different from that of cones and rods (Hughes et al.,

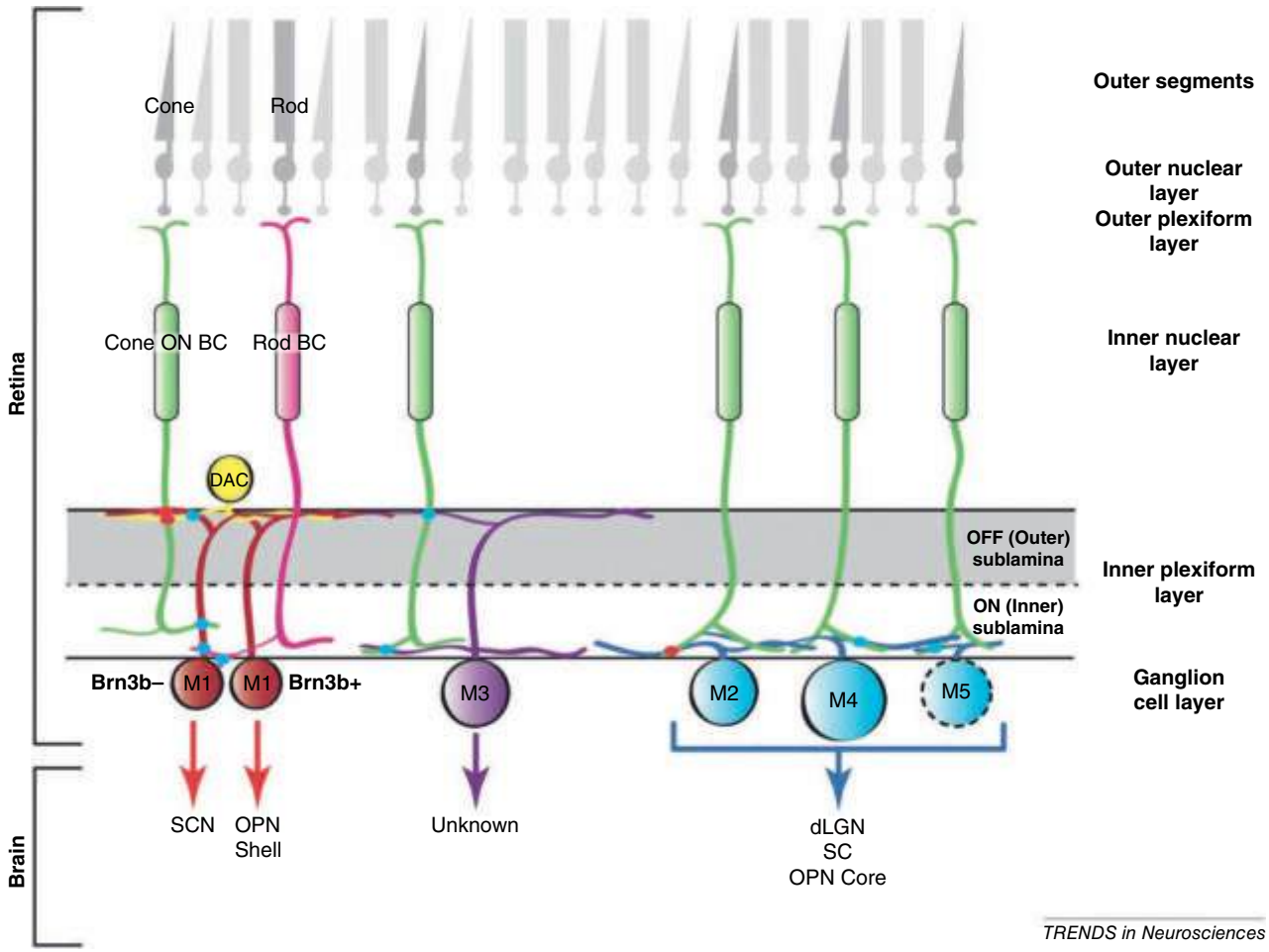


Figure 4.34 So far six distinct subtypes of intrinsically photosensitive retinal ganglion cells (ipRGCs) have been identified in the mouse (M1–M6). This figure briefly outlines the input to and targets of the first five ipRGCs. Their nuclei make up a small fraction of those seen in the ganglion cell layer of the retina (and occasionally displaced into the inner nuclear layer) and subtypes have different dendritic patterns and primary nonimage or image-forming targets in the brain. They also differ in size, with the M1 being small and the M4 having large soma. Dots indicate synapses with other retinal cells. BC, bipolar cell; DAC, dopaminergic amacrine cell; dLGN, dorso-lateral geniculate nucleus; OPN, olivary pretectal nucleus (for pupillary light reflexes); SC, superior colliculus; SCN, suprachiasmatic nucleus (for circadian photoentrainment). It has been suggested that M1 cells can be further subdivided according to their expression of the transcription factor Brn3b. (Reproduced with permission from Schmidt, T.M., Chen, S.K., & Hattar, S. (2011) Intrinsically photosensitive retinal ganglion cells: Many subtypes, diverse functions. *Trends in Neuroscience*, **34**, 572–580. doi: 10.1016/j.tins.2011.07.001.)

2012). It seems to start with activation of special G-proteins that in turn activate the enzyme phospholipase C (PLC), which leads to an influx of Ca^{2+} through transient receptor potential (TRP) channels in the cell membrane of the ipRGCs and generation of action potentials. However, the melanopsin density in ipRGCs is about 10^4 less than that of cone and rod opsins (Do et al., 2009). This implies a low probability of photon catch, which is why the phototransduction in ipRGCs mainly plays a role in relatively bright light. However, ipRGCs are not only depolarized by the activation of melanopsin by light, but also by input from circuits driven by cones and rods (Fig. 4.35; Weng et al., 2013). This expands the dynamic range and spectral sensitivity of responses driven by or through ipRGCs.

IpRGCs may play a role in image-forming vision, but most of their important functions are non-image-forming (Feigl & Zele, 2014). Their input to the SCN is essential for the body's circadian clock, whereas ipRGC axons to the intergeniculate leaflets contribute to the entrainment of the circadian rhythm. Projections to the ventrolateral preoptic nucleus are likely to play a role in the control of sleep, and ipRGCs' signals to the pretectal olivary nucleus contribute to the pupillary light reflexes (PLRs) and the sustained constriction after offset of bright, short-wavelength lights. This is why Keeler could detect PLRs in blind mice (Keeler, 1927). Furthermore, ipRGCs have been reported to be less vulnerable than other RGCs in some diseases (such as Leber's hereditary optic neuropathy), but are susceptible to other neurodegenerative diseases, such as glaucoma (Georg et al., 2017).

Retinal Synapses and Neurotransmitters

Obviously, with so many different types and classes of retinal cells, there are numerous potential pathways for transferring a signal from the photoreceptors to the RGC axons. Furthermore, new cell types, projections, and synapses are constantly being discovered.

The rod spherules and cone pedicles contain *synaptic invaginations*, in which one bipolar and two horizontal cells synapse and together form the *synaptic triad* (see Fig. 4.22). Photoreceptors usually have more than one synaptic invagination. A typical rod synapses with two triads, and a cone may have multiple contacts with three or more bipolar cells. The cone pedicle with its 20–50 presynaptic ribbons and up

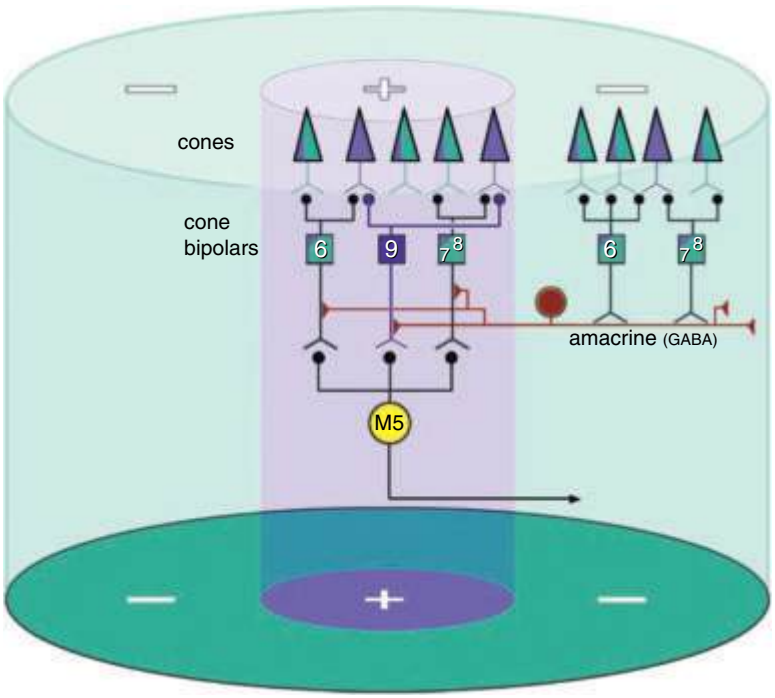


Figure 4.35 The M5 intrinsically photosensitive retinal ganglion cell (ipRGC; yellow) contains light-sensitive melanopsin, but can also be driven by the ultraviolet (UV-; violet) and M-cone (green) opsin in murine cones. In the mouse, most cones coexpress both opsins, but some only one opsin. Cone signals are relayed to the M5 cell through different subtypes of cone bipolar cells (numbered 6 through 9). In the center, the M5 cell receives input through all bipolar cell subtypes, including type 9, which contact pure UV-cones. A wide-field GABAergic amacrine cell (red) selectively samples type 6–8 bipolar cells and can thus create surround with cones relatively better driven by green light than the more UV-sensitive center. Hence, the M5 cell can send both chromatic opponent signals to the latero-dorsal geniculate nucleus of the mouse and signals driven by activation of the melanopsin in the ganglion cell itself. (Reproduced with permission from Stabio, M.E., Sabbah, S., Quattrochi, L.E., et al. (2018) The M5 cell: A color-opponent intrinsically photosensitive retinal ganglion cell. *Neuron*, **97**, 150–163.e4. doi: 10.1016/j.neuron.2017.11.030.)

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to 500 contacts to postsynaptic cells is considered to be the most complex synapse in the central nervous system (CNS; Haverkamp et al., 2000). In addition, photoreceptors send out processes to neighboring spherules and pedicles, thus providing for direct electrical junctions between photoreceptors. Because of these couplings, current can spread between adjacent photoreceptors. Therefore, the stimulation of a single rod can activate other photoreceptors, resulting (once again) in the large receptive field that converges on the bipolar cell. These junctions also allow rod signals to be transmitted through cone pathways when the light is so dim that the cones are unable to respond (see Fig. 4.26).

Traditionally, the retina has been considered to have two pathways conveying signals from the photoreceptors: the cone pathway and the rod pathway (see Fig. 4.26). The *cone pathway* typically is short, involving only two types of synapses: cone to bipolar cell to RGC, lateral processing provided by horizontal and amacrine cells in the OPL. Even though it is shorter than the rod pathway, the cone pathway is also complex, as it provides two parallel channels of processing, ON- and OFF-center (Wässle, 2004). This dichotomy is made possible by the fact that bipolar cells can respond to light and subsequent cone hyperpolarization with either depolarization (ON-center bipolar cell) or hyperpolarization (OFF-center bipolar cell; see Fig. 4.30). However, it is clear that the cone and rod pathways are more complex than outlined above and not as distinctly separated as previously believed (Pang et al., 2010; Strettoi et al., 2010). Hence, some rods contact cone bipolars and cones synapse with rod bipolars, but for enhancing the basic understanding of the retinal circuitry, the presentation has been restricted to the more traditional pathways of cone and rod signals.

OFF-center bipolar cells have excitatory, ionotropic (AMPA kainate) glutamate receptors (Puller et al., 2013). Therefore, these cells are excited (depolarized) in the dark when cone glutamate release is high. Light stimulation decreases the amount of excitatory glutamate released from the cone and consequently the OFF-center bipolar is inhibited and hyperpolarizes. This is called a *sign-conserving synapse*, as both the photoreceptor and the bipolar cell respond with hyperpolarization to light.

ON-type bipolar cells have inhibitory, metabotropic glutamate receptors (Gerber, 2003). As a result, the cells are inhibited (hyperpolarized) in the dark due to glutamate release by cones. Light stimulation and the consequent decrease in glutamate release remove the inhibition, allowing the cell to be excited and depolarize. The result is a *sign-reversing synapse*, because the response of the bipolar cell is opposite to that of the photoreceptor. Hence, the separation of signals for dark and light in the cone pathway is initiated by different glutamate receptors present in the first synapse in the retina.

The ON- and OFF-center dichotomy of cone bipolar cells is further enhanced by horizontal cell modulation in the OPL. In other words, the negative feedback signals of horizontal cells to the synaptic terminals of a cone provide lateral inhibition from surrounding cones (which are also stimulated), creating an antagonistic surround to the response in the center. This is considered to enhance the detection of edges in visual stimuli. This concentric organization is maintained in the inner retina, as ON- and OFF-center bipolar cells synapse exclusively with ON- and OFF-center RGCs, respectively. The antagonistic effect of the surrounding receptive field (OFF- and ON-surround, respectively) is once again enhanced by amacrine cell modulation and lateral inhibition in the INL (see Fig. 4.30). This arrangement improves contrast and, in combination with the dense packing of cones in the central retina, the low cone–bipolar–ganglion cell ratio, and the small size of the cone receptive fields, contributes to high spatial resolution and detection of fine details.

The traditional *rod pathway* differs from the cone pathway in several important features (Tsukamoto et al., 2001). First, there is only one type of rod bipolar cell. It has metabotropic, inhibitory glutamate receptors, similar to those of the ON-bipolar cells. Therefore, light stimulation and the consequent decrease in the amount of glutamate released by rods will remove the neurotransmitter's inhibitory effect on these receptors, leading to depolarization of rod bipolars, as it does in ON-bipolar cells.

Another significant difference between the two pathways is that rod ON-bipolar cells synapse with RGCs indirectly, through amacrine cells (see Fig. 4.26). This allows further convergence and processing of rod output, and its channeling to both ON- and OFF-center RGCs. Summation and convergence of the rod pathway are much greater than those of the cone pathway. It has been demonstrated that in the ON-pathway of the cat, about 1,500 rods synapse with 100 rod bipolars and 5 AII amacrine cells that converge on one small, β-ganglion cell. In the OFF-pathway, 75,000 rods synapse with 5,000 rod bipolars and 250 AII amacrine cells that converge on a single, large α RGC. This contrasts with the feline cone pathway, where each small, β-ganglion cell in the area centralis receives inputs from 3–4 cone bipolars, each of which, in turn, receives input from 4–8 cones (Kolb, 1979; Wässle et al., 1981). These figures further demonstrate the low visual acuity of the rod pathway compared to that of the cone pathway. When a rod RGC fires, there is no way of knowing which of the thousands of rods in its receptive field was hyperpolarized by light. Therefore, its activation provides little information about the location of the stimulus. This contrasts with the cone pathway in the central retina, where the RGC has a much smaller receptive field, and therefore its firing provides more accurate stimulus localization. Still, it is important to note that the feline cone pathway has some convergence, as opposed to the non-convergent nature of the primate, foveal cone pathway (Kolb & Marshak, 2003). This is one reason why feline visual acuity is lower than that of primates.

Several neurotransmitters are involved in lateral and vertical communication in the neuroretina. Glutamate is an excitatory, mainly "vertical" neurotransmitter relaying information from the photoreceptors, via the bipolars, to the RGCs (Wan & Heidelberger, 2011), but a subset of amacrine cells also uses glutamate to excite RGCs and contrast-sensitive circuits (Lee et al., 2016a). Acetylcholine is another excitatory transmitter released by cholinergic amacrine cells; it binds to muscarinic and nicotinic receptors in different types of amacrine cells in the mature retina (Gleason, 2012). Starburst amacrine cells are known to use acetylcholine to depolarize RGCs, although the function of these cholinergic circuits is still unclear (Taylor & Smith, 2012). Prior to the maturation of the photoreceptors, the primary source of previsional neural activity is cholinergic retinal waves (Ackman et al., 2012).

The main inhibitory neurotransmitter in the retina is GABA (Hoon et al., 2014; Wu, 2010). As such, it is used mainly for lateral processing of the signal by both horizontal and amacrine cells, which have an inhibitory function in the OPL and IPL, respectively. Together with glycine, GABA acts to inhibit RGCs by opening their Cl^- channels (Lynch, 2009)

Dopamine and serotonin are two more neurotransmitters found in amacrine cells. They probably play an important role in retinal signal processing but may also have other functions (Brandies & Yehuda, 2008; Trakhtenberg et al., 2017). Dopamine is only released from one class of amacrine cells that is driven by both cones and rods, as well as ipRGCs (Qiao et al., 2016). Dopamine can bind to D_1 and D_2 receptors, thus enabling further signal refinements. Many aspects of the role of the dopaminergic cells in the retina are still unclear or subject to contradictory reports.

Additional neurotransmitters, including substance P, adenosine, nitric oxide, somatostatin, neuropeptide Y, vasoactive intestinal peptide, corticotropin-releasing factor, and cholecystokinin, have also been described in various types of amacrine cells.

From Retina to Visual Cortex

Optic Nerve

RGC axons constitute the optic nerve fibers. These axons converge at the optic disc, where they are joined in bundles to form the nerve. As the nerve contains RGC axons but no other neuronal cell body, it can be considered a pure white matter tract. But the nerve does contain several important glial cell populations (Butt et al., 2004). These include oligodendrocytes, which contribute to its myelin sheath and formation of nodes of Ranvier, and astrocytes, which have several functions, including K^+ homeostasis and transportation and storage of metabolites (mainly glycogen) used by the axons. Microglia are CNS-specific macrophages that are smaller than the other glial cells and scan the tissues for signs of damage or distress (MacNair & Nickells, 2015). Once activated in inflamed or degenerating tissue, they can perform several tasks including phagocytosis of cellular debris, antigen presentation, and cytokine production.

RGCs (and some subtypes of amacrine cells) are the only retinal neurons that generate *action potentials*. Unlike the graded hyperpolarizing or depolarizing responses of other retinal neurons, action potentials are all-or-nothing spikes of electrical activity. This means that all of the neuronal processing of the visual signal that has taken place in the retina so far, including information about stimulus size, contrast, color, movement, and location, is coded as alterations in the firing pattern (e.g., short bursts or sustained episodes of firing) and firing rates of the RGCs (Meister et al., 1995).

In their resting state, optic nerve axons are hyperpolarized, maintaining a negative resting potential due to outflow of K^+ cations, balanced by inflow of Na^+ cations. Opening of voltage-sensitive sodium channels increases the inflow of Na^+ into the axon and causes rapid depolarization. The increased potential within the axon will cause adjacent sodium channels to open, propagating the action potential further downstream. Myelination of the optic nerve, provided by oligodendrocytes, allows for decreased capacitance and increased resistance of the nerve, as well as clustering of sodium channels in the nodes of Ranvier, providing for efficient and rapid saltatory conduction of the electrical signal (Kaplan et al., 2001).

A target anywhere in the visual field will elicit a cohort of signals generated by multiple RGCs representing different points in that particular part of the visual field. Consequently, arrangement of the axons within the optic nerve is not random. Instead, the fibers are arranged in a *retinotopic* manner, meaning that the precise spatial arrangement of the retina is maintained within the nerve. Through a carefully controlled process during development, fibers from the superior retina are made to arrive at the superior half of the optic nerve head, and those from the inferior retina form the inferior half. Fibers from the peripheral RGCs are peripheral within the nerve, and those from RGCs in the area centralis are located centrally within the nerve. This precise arrangement is a condition for the subsequent accurate projection of the visual field in both the LGN and the visual cortex (Herrera et al., 2019; Reese, 2011). However, the fibers do not necessarily work as parallel channels sending independent information about the visual scene, but may also be part of a multineural signaling system sending more complexly coded information to the brain (Ala-Laurila et al., 2011; Meister et al., 1995).

Optic Chiasm and Optic Tract

As the optic nerve approaches the optic chiasm, the location of fibers within the nerve gradually shifts in preparation for decussation at the optic chiasm (Neveu & Jeffery, 2007; Reese, 2011; see Fig. 4.36). Generally, fibers from the temporal retina remain in the ipsilateral hemisphere, and fibers

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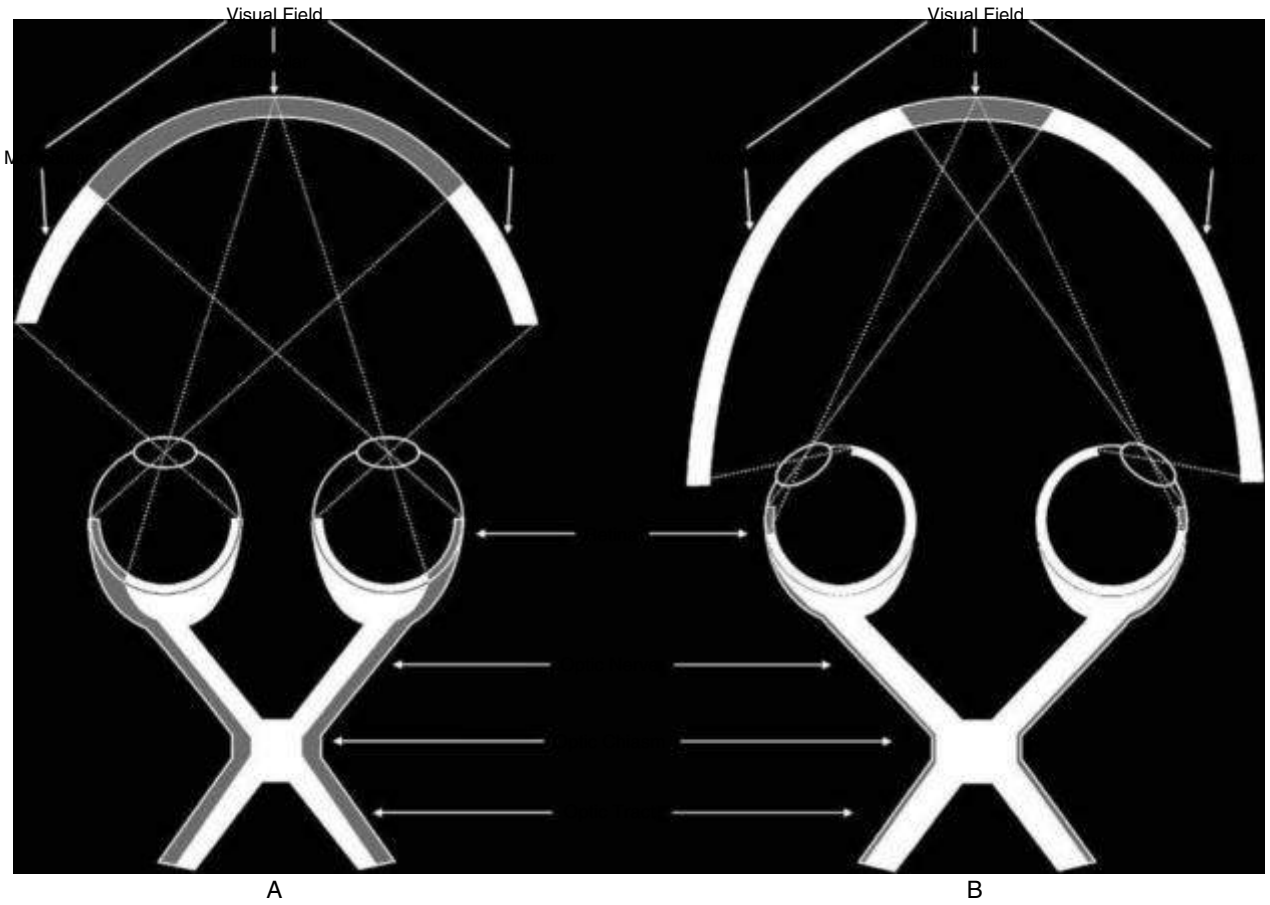


Figure 4.36 In animals with more frontally positioned eyes, such as several predatory mammals, the binocular overlap is large and consequently a large portion of the axons in the optic nerve project ipsilaterally at the optic chiasm (**A**). Animals with more laterally positioned eyes have a larger visual field, although the area of binocular overlap is smaller, resulting in fewer axons projecting ipsilaterally at the chiasm (**B**). N, nasal; T, temporal. (Reproduced with permission from Jeffery, G. & Erskine, L. (2005) Variations in the architecture and development of the vertebrate optic chiasm. *Progress in Retinal and Eye Research*, **24**, 721–753. doi: 10.1016/j.preteyeres.2005.04.005.)

from the nasal retina cross over to the contralateral side. The amount of decussation varies between species, perhaps representing a broad evolutionary scale. Birds, as well as many amphibian and reptilian species, have complete crossover of fibers to the contralateral side. A greater proportion of fibers remains on the ipsilateral side in mammals that have developed binocular vision. In the horse, 15% of the fibers stay on the ipsilateral side, as do 25% in the dog and 33% in the cat. In humans, only 50% of the fibers cross over. Partial crossover of fibers allows both hemispheres to continue receiving visual input even when one retina or optic nerve has been completely destroyed, thus enabling the animal to maintain better physiologic function and correlation with other sensory input (Fraser et al., 2011). Because the topography of decussating fibers is characterized by spatial precision in primates (Jeffery et al., 2008), lesions in different areas of the chiasm (or the optic nerve) will cause specific visual deficits.

The optic tract runs from the optic chiasm to the LGN. Because of decussation at the chiasm, fibers of the optic tract conduct information from the opposite visual field of both eyes. In humans, where roughly 50% of the axons decussate in the chiasm, the left optic tract relays the right visual hemifield of both eyes, and the right optic tract relays both left visual hemifields. In animals, where a greater percentage of fibers cross over, the left optic tract will relay a greater proportion of the right visual field from the right eye and a smaller proportion of the right visual field from the left eye.

It is important to remember that the optic tract carries only 80%–90% of the RGC axons to the LGN. The rest of the RGC axons, including those of the ipRGCs, exit the optic tract before it reaches the LGN and relay visual information to several other areas in the thalamus, midbrain, hypothalamus, and amygdala/pallidum (Martersteck et al., 2017; Morin & Studholme, 2014). In total, RGCs project to more than 50 regions in the brain of a tiny mouse. Best known are

the fibers that relay information to the pretectal olivary nucleus, and through it to the parasympathetic oculomotor nucleus, providing afferent input to the PLR. Other optic tract fibers synapse in the superior colliculus, which controls saccadic eye movement and also receives information from other sensory organs (i.e., ears and spinal cord) and is therefore involved in the correlation of sensory information. In addition, information from the retina reaches additional nuclei involved in controlling optokinetic reflexes, circadian rhythms, and endocrine activity of the hypothalamus.

Lateral Geniculate Nucleus

For most RGC axons, the first synapse occurs in the LGN, which is one of about ten targets of RGCs in the thalamus (Monavarfeshani et al., 2017). The axons maintain their retinotopic arrangement through the optic nerves, chiasm, and tracts and as they enter the LGN. Here, the RGC axons synapse with dendrites of LGN *interneurons* (which provide for signal processing) and *projecting cells* in synaptic glomeruli.

In the LGN, RGC axons segregate by eye and functional group, usually forming layers where they terminate in discrete clusters, generating a retinotopic map of the contralateral visual hemifield (with receptive fields similar in size and response properties to the retinal receptive fields). Furthermore, the somata of the projecting cells, classically subdivided into magnocellular (M), parvocellular (P), and koniocellular (K) cells, are also segregated into the same distinct LGN layers as the RGC axons (Fig. 4.37). Traditionally, it has been considered that P-cells process form information (visual acuity and contrast), while M-cells process motion and K-cells process colors. Although these descriptions are oversimplifications, corticogeniculate neurons can be segregated according to their konio-, magno-, and parvocellular properties (Briggs & Usrey, 2009).

Thus, in primates where the decussation is about 50%, three of the six LGN layers receive input from the ipsilateral visual hemifield, and three alternating layers receive their input from the corresponding contralateral hemifield. Furthermore, the six resulting monocular maps are in register, which means that an electrode vertically penetrating through the six layers would record information about the same point in the visual field in each of the layers.

The maps of the LGN also reflect the physiologic processing of the signal that has occurred in the retina. Thus, cells in the magno-layer receive input from Y- or α-type RGCs, while cells in the parvo-layers receive input from X- or β-type RGCs. Therefore, the six cells through which the abovementioned line of projection passes receive both X- and Y-type data about an identical receptive field in both eyes. Furthermore, the LGN cells also maintain the center-surround antagonism of the RGC receptive fields. This provides the basis for the additional merging of visual information that occurs in the cortex.

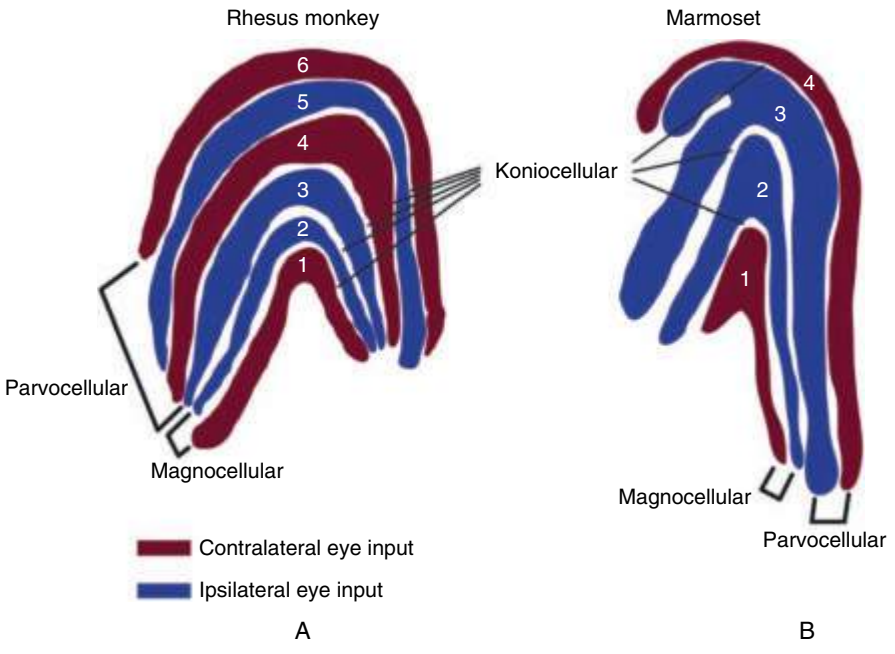


Figure 4.37 In the lateral geniculate nucleus (LGN), the parvo- and magnocellular layers are separated by thinner koniocellular layers. Each LGN receives input from the part of the retina looking at the contralateral visual field in both eyes. In contrast to humans and rhesus monkeys (**A**), the marmoset (**B**) has fewer parvocellular layers and a large proportion of binocular cells in the koniocellular layers. (Reproduced with permission from Wallace, D.J., Fitzpatrick, D., & Kerr, J.N. (2016) Primate thalamus: More than meets an eye. *Current Biology*, **26**, R60–R61. doi: 10.1016/j.cub.2015.11.025.)

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In recent years, it has been shown that rather than being a simple relay station conveying signals from the RGCs to the visual cortex, the LGN is actually a complex and multifunctional center. In fact, signals from the RGCs account only for 5%–10% of the input to projecting cells, and the LGN receives large amounts of feedback from the visual cortex and other areas. Weyand (2016) lists a multitude of putative functions of the LGN, including parsing retinal inputs for selective access for non-retinal inputs; amplifying and integrating retinal inputs; controlling contrast (luminance) gain; controlling retinogeniculate gain by state, level of arousal, and attention; implementing pattern-recognition algorithms; synchronizing saccades and retinogeniculate signaling; enhancing temporal diversity, thus potentially improving coding of natural scenes; and generating signals that are used by directionally selective cortical neurons.

Axons of projecting cells exit the LGN and form the *optic radiations*. These axons relay the visual signal from the LGN to the primary visual cortex, as well as to other visual centers, where they synapse.

The Primary Visual Cortex

Location

Brodmann (1909) demonstrated that the primary visual cortex (i.e., *area 17*) receiving the input from the LGN is located in the posterior part of the occipital lobe in a number of species. This area is now usually called *V1* (visual area 1) or the *striate cortex*, after the striae of Gennari. In contrast, all other visual areas in the cortex lacking the stria (which is a myelinated stripe where the LGN axons enter the gray matter of the V1) are termed *extrastriate*.

V1 has been mapped in several species. In the cat, it occupies the posteromedial portion of the cortex, extending from the crown of the lateral gyrus on the dorsal surface to the superior bank of the splenial sulcus on the medial surface (Tusa et al., 1978). In the dog, it is located at the junction of the marginal and endomarginal gyri (Ofri et al., 1994). The striate cortex has also been identified in the horse (Ström and Ekesten, 2016).

Neuronal Organization

Like the rest of the cerebral cortex, cells of V1 are orderly arranged in six layers. The incoming thalamic (LGN) axons synapse with cortical neurons, glutamate-containing *simple cells*, in layer 4. More precisely, magno-, parvo-, and koniocellular projections synapse in layers 4Ca, 4Cb, and 4A, respectively, thus maintaining the segregation of visual information that characterizes the visual system to this point. More superficial layers (layers 1–3) contain excitatory neurons that project to each other and to extrastriate visual areas; these layers also receive feedback from the same extrastriate visual areas (Binzegger et al., 2009). Layers 5 and 6 communicate with the superficial layers and feed back to the LGN.

The simple cells in layer 4 maintain the functional center-surround orientation of their afferent RGCs and LGN layers, but they are monocular in nature (Lehky et al., 2005). Complex cells in other layers of V1 receive binocular input from several simple cells, making them (in some species) the first neuron where input from both eyes is fused. Surprisingly, the incoming thalamic fibers provide just 5% of the excitatory synapses in layer 4 (Douglas & Martin, 2007). This small fraction of sensory input from the retina, compared to the huge number of synapses made by cortical and subcortical neurons in V1, is testimony to the complexity of the processing of the image by local and long-distance circuits in the brain (Iacaruso et al., 2017; Stepanyants et al., 2009).

Functional Architecture of the Striate Cortex

The functional architecture of the striate cortex was extensively studied by Nobel prize winners David Hubel and Torsten Wiesel (Wurtz, 2009). Here we present the organization they originally proposed. The basic cortical unit that processes an incoming signal is termed a *cortical column*, which extends through all six layers of V1. As in the LGN, vertical penetration through the six cortical layers of the column will result in passage through cells with almost identical receptive fields. Therefore, adjacent retinal receptive fields project onto adjacent columns in V1. Consequently, the entire contralateral visual hemifield, as projected on both retinas, is mapped on the surface of the cortex retinotopically, meaning that adjacent loci of the contralateral visual hemifield are projected onto adjacent loci of the cortex in a point-to-point manner (Schira et al., 2007; Wandell & Winawer, 2011). There is no difference in size between columns serving the central and the peripheral retina; rather, more columns are used to process visual input from the central retina.

There are several functional types of columns in V1. These are devoted to stimulus size, color, orientation, and ocular dominance (Fig. 4.38). In an orientation column, all the cells respond best only to one stimulus orientation; in other words, cells in a given column may fire in response to a horizontal bar, but not to a vertical or diagonal bar. Movement of 50 μm along one axis of the cortical surface will bring a shift of 10° in the orientation preference of the cells. Movement of 0.1 mm along the same axis will shift the orientation preference by 20°. Therefore, a column 0.9 mm wide will contain cells responding to a 180° change in orientation, thus containing all the possible permutations.

Movement along another axis of the cortical surface will result in movement across ocular dominance columns. A dominance column is an area approximately 0.4 mm wide in which input from one eye is dominant over that of the other eye. The dominance is strongest at the center of the column and decreases gradually, so that input is almost equally binocular at the column periphery. As movement continues into the adjacent column, there is a gradual buildup of dominance by the other eye, which, again, will be most dominant at the adjacent column's center.

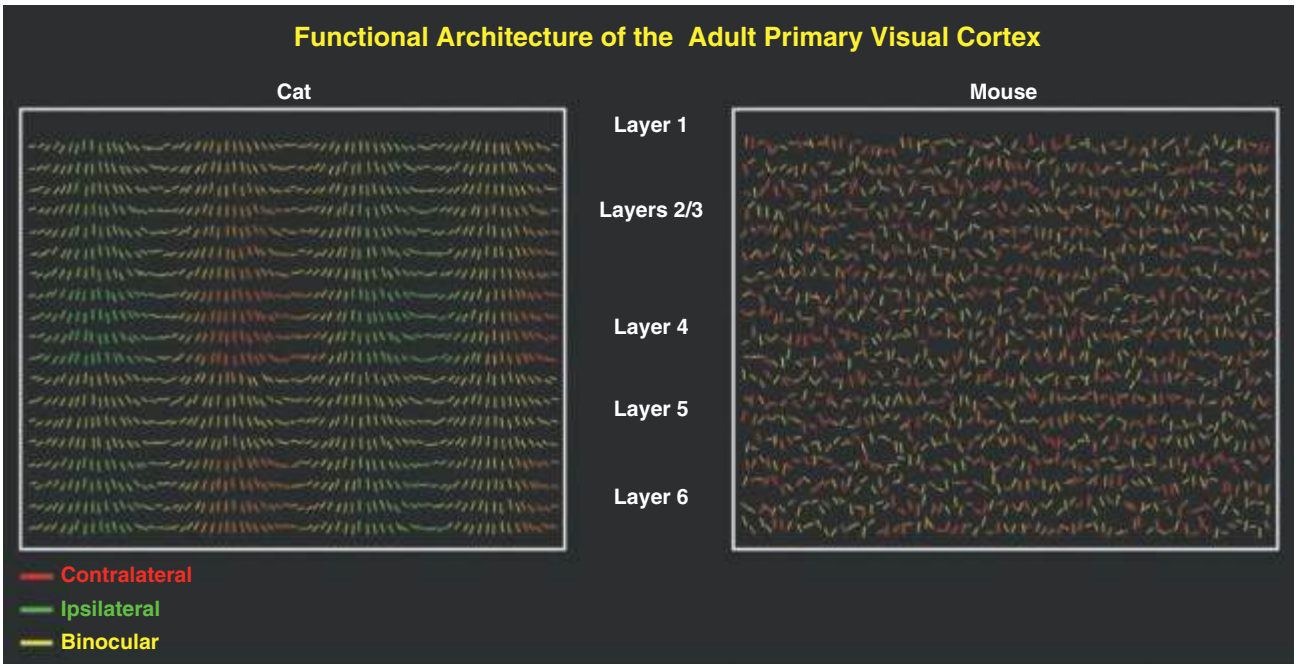


Figure 4.38 The functional architecture of the cat visual area 1 (V1) is highly structured and the neurons are highly specialized. Both specific orientation (shown by the angle of the lines) and ocular dominance properties (indicated by the color of each line) are organized into columns. The columnar organization of preferred orientation of the stimulus spans all layers, from the most superficial layer 1 to the deepest layer 6. The ocular dominance columns are not as clearly outlined throughout the layers and are most pronounced in layer 4, where many cells are driven monocularly from the lateral geniculate nucleus. The mouse also has specialized neurons in V1, but neither preferred orientation nor ocular dominance properties are organized in columns. Furthermore, in this species, where the vast majority of the axons of the retinal ganglion cells decussate at the optic chiasm, a bias in ocular dominance is seen toward the contralateral retina. (Reproduced with permission from Espinosa, J.S. & Stryker, M.P. (2012) Development and plasticity of the primary visual cortex. *Neuron*, **75**, 230–249, doi: 10.1016/j.neuron.2012.06.009.)

A *hypercolumn* is a complete set of both column types. It contains, along one axis 0.9 mm in length, all possible permutations of orientation preferences. Along a different axis 0.8 mm in length, it contains all possible ocular dominance combinations. Therefore, every given cell in a hypercolumn will respond best just to one stimulus orientation from one eye. Such a response of a given cell provides information regarding stimulus orientation, movement, direction, and binocularity.

Subsequently, it was discovered that interspaced between the hypercolumn's columns is another system responsible for processing color information. Cells belonging to this system are arranged in "blobs" (so named because of their appearance after staining for cytochrome oxidase) and respond selectively to different combinations of stimulus wavelength (Economides et al., 2011; Livingstone & Hubel, 1984). These *color opponent cells* display antagonistic center-surround properties (similar to those of bipolar and ganglion cells) regarding color.

Despite the knowledge about this basic organization of cells in V1, still little is known about the connections individual neurons make. In the mouse, a local cortical circuit (encompassing about 0.25 mm^3) contains approximately 25,000 neurons and 250 million synapses (Reid, 2012). Local signals from different types of neurons in V1 must be integrated to create a unified visual percept and the extensive interconnections between visual areas provide almost countless pathways along which signals can travel. V1 outputs to higher visual areas, where more specialized neurons respond to more complex stimuli. Both hierarchic and parallel processing are used in the visual areas and contribute different information (Ponce et al., 2008). At the same time, there is also extensive feedback activity from extrastriate areas to V1 and from there back to the LGN.

Para- and Extrastriate Visual Areas

Visual area 2 (V2) or the parastriate cortex (Brodmann's area 18) forms a concentric crescent around V1. V2 can be separated from V1 based on histologic appearance, connectivity pattern, response properties, and reversal of the retinotopic map at the border between V1 and V2 (Buckner & Yeo, 2014).

Another well-defined, more anterior area that has a binocular visual field map is the MT (middle temporal). MT is important for processing information about the motion, speed, and binocular disparity of moving stimuli (Maunsell & Van Essen, 1983a, 1983b).

There are additional maps and representations of the visual field in other extrastriate areas. Furthermore, some higher-order extrastriate areas are not as distinctly defined

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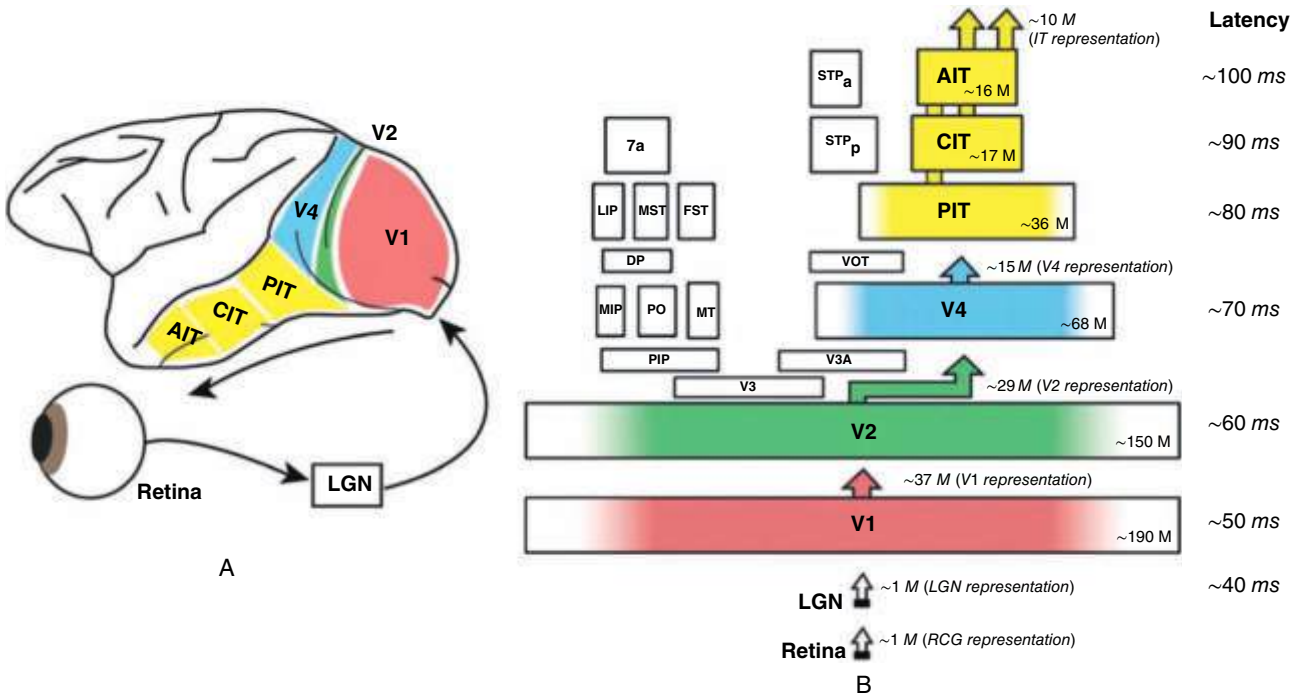


Figure 4.39 **A**. The flow of visual information from the retina to ventral stream area locations in the macaque brain. **B**. The areas plotted to their cortical surface areas; numbers in the lower right corners indicate the number of neurons in millions (M) in each area. The approximate number of neurons projecting from one area to the next is shown above each rectangle. Approximate median response latencies are listed to the right. PIT, CIT, and AIT indicate posterior, central, and anterior inferotemporal cortex (areas essential for object recognition), respectively. LGN, lateral geniculate nucleus; RCG, retinal ganglion cell. All other abbreviations refer to specific visual areas in the macaque monkey cortex. (Reproduced with permission from DiCarlo, J.J., Zoccolan, D., & Rust, N.C. (2012) How does the brain solve visual object recognition? *Neuron*, **73**, 415–434. doi: 10.1016/j.neuron.2012.01.010.)

as V1, V2, and MT, neither anatomically nor functionally, and their exact number and boundaries are still controversial (Angelucci & Rosa, 2015). This uncertainty is no surprise, because the visual input is widely spread in the brain. Even in a tiny mouse, 50 or more areas receive input from the retina (Martersteck et al., 2017).

After V2, the visual pathways diverge into two functional streams. Broadly speaking, these two pathways process information about *where* and *how* (the *dorsal pathway* or *stream* in the parietal cortex) and *what* (the *ventral pathway* or *stream* in the inferotemporal cortex) a certain visual stimulus is (Conway, 2014; Kravitz et al., 2011). The dorsal pathway is devoted to object localization, processing motion, direction, and stereoscopic depth perception, but also to unconscious visually guided behavior (like grasping a cup on a table when you are drinking coffee). It receives mostly magnocellular input from V1 and V2, relaying it through areas usually termed V3 and V5 to even higher visual areas. The ventral pathway deals with object recognition (Fig. 4.39), processing details such as form, color, orientation, and shape. It receives both magno- and parvocellular input from V1 and V2, relaying it through V4 to higher processing in several visual areas.

The complexity of the stimulus selectivity increases step by step when ascending the hierarchy of the extrastriate areas. Eventually, high-order neurons are driven only if the visual stimulus has a certain shape or other properties that contribute to object recognition. Lesions in higher visual areas can cause deficits in spatial or motion perception and visuomotor control (dorsal pathway disorders) or in color processing and object recognition (ventral pathway disorders; Barton, 2011).

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5

Fundamentals of Animal Vision

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Ability to detect light is, of course, fundamental for vision, but other aspects, such as detection of motion or determining other qualities of an object, including shape and details, color, size, and distance, help to form our visual percept. The processing of the output from the photoreceptors starts in the retina (Fig. 5.1), but countless neurons in the brain finally shape and interpret the final perceived image of the world around us.

Animal visual perception is a subject of great fascination to researchers, clinicians, and animal owners. Unfortunately, we can know neither exactly what an animal sees because they usually cannot tell us, nor precisely what there is to see because of the limitations of our own visual system. Still, understanding the physiologic basis of animal vision and what different species can potentially perceive helps both to satisfy our curiosity and to better judge the impact of an ocular condition on an animal's welfare, performance, and safety. While we often generalize about canine, feline, or equine vision, one should remember that an Irish Wolfhound, for example, may depend to a much greater extent on its vision than a typical scent hound, such as a Dachshund. Hence, individual and breed differences must also be recognized. In this context, owners may be able to help assess the quality of their animal's vision just as parents can aid in assessing the vision of their child using standardized questionnaires (Miller & Parisi, 2018), thus providing raw data for research that will improve our ability to establish better-substantiated prognoses for various conditions and treatments.

Scotopic and Photopic Vision

We have all experienced temporary loss of vision when moving from a dark room into a brightly lit outdoor environment, or vice versa. This is because at any given moment photoreceptors have a narrow operating range: they do not respond to light that is too dim, and they are saturated by light that is too bright. However, photoreceptors can respond to changes in levels of background luminance by processes of *adaptation* (Demb, 2008; Kelber & Lind, 2010; Reuter, 2011; Rieke & Rudd, 2009). The adaptation results in an extended operating range, allowing the eye optimal performance at a given illumination level. A decrease in background illumination to below 0.03 cd/m^2 will deactivate the cone system, resulting in increased light *sensitivity* (i.e., a lower *threshold*) and *scotopic* rod vision. An increase in background illumination, to 0.03–3 cd/m^2, will lead to *mesopic* vision in which both the rod and cone systems are active, for example before dawn or after sunset. A further increase in background illumination above 3 cd/m^2, to *photopic* levels, will result in rod saturation. In such an environment, cones will continue to function, albeit with a higher threshold, or with lower sensitivity.

The implication of this higher threshold is that in a bright environment, higher-stimulus intensities are required to stimulate cones. The "price" of adaptation to a bright environment, a lower sensitivity, means that the eye will not be able to detect miniscule changes in stimulus intensity, a task that is easily performed by rods in darkness. The inverse relationship between retinal sensitivity and threshold is depicted in Fig. 5.2. For example, because of light adaptation, we are able to see the glaring sand on a sunny day at the beach (high threshold), but we are unable to detect the small luminance change caused by the glow of a distant cigarette on the beach (low sensitivity). As noted in the following sections, however, what is lost in low photopic sensitivity is gained in higher visual acuity and faster responsiveness, both of which characterize cone function and output. Furthermore, a retina with more than one type of photoreceptor is a prerequisite for color vision. Because we have both rods and cones, and thanks to the adaptation of their

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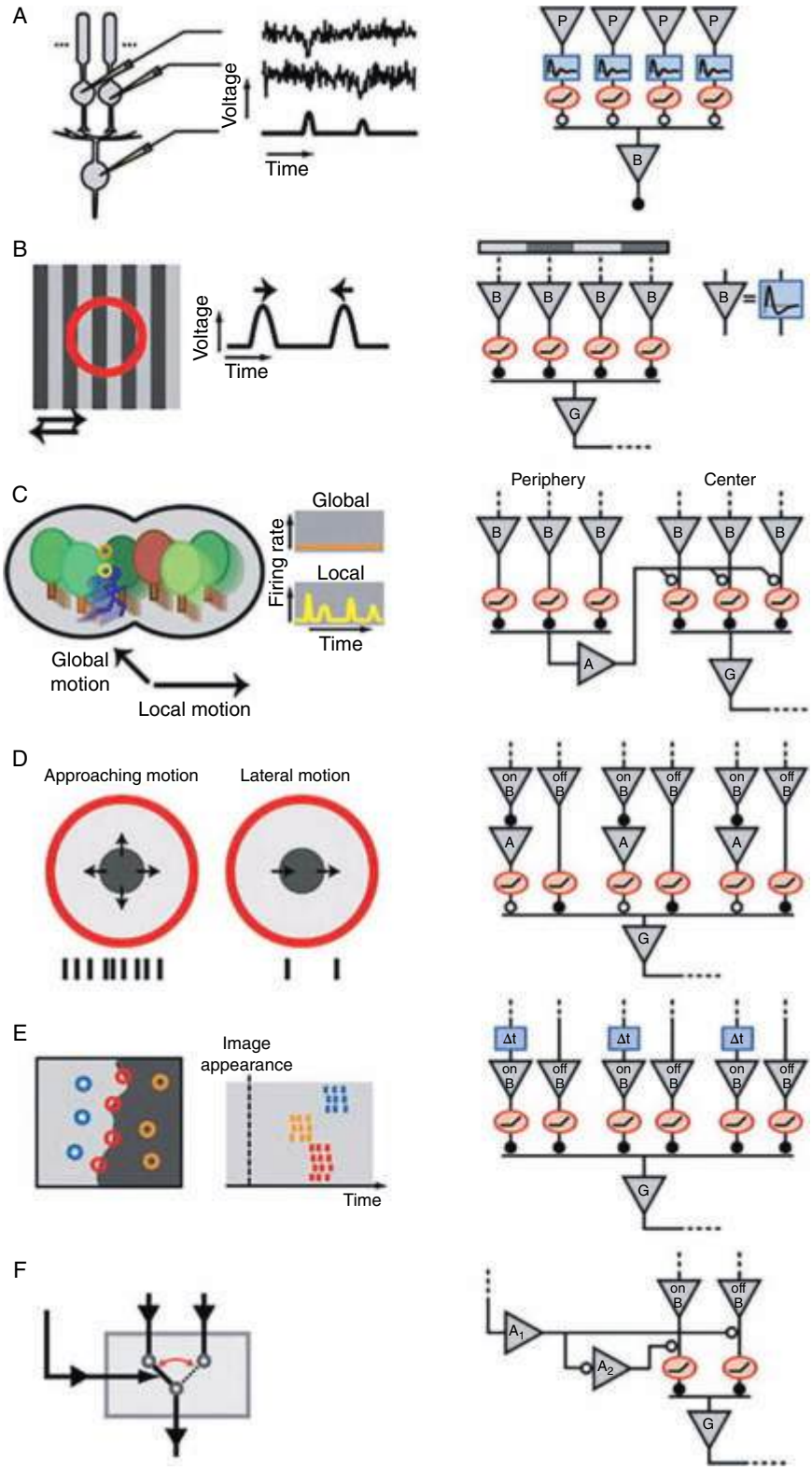


Figure 5.1 A considerable amount of processing of data from the photoreceptors is performed in the neuroretina. The left-hand panels briefly describe the purpose of the computations performed, and the right-hand column illustrates important elements of the underlying circuits schematically (triangle – neuron; A – amacrine cell; B – bipolar cell; G – retinal ganglion cell (RGC); P – photoreceptor; rectangle – temporal filter function; oval – instantaneous rectifier; closed/open circle – sign-preserving/sign-inverting synapse). **A**. The rod-to-rod pathway detects single photons. The output of each rod (noisy tracings) is sent through a band-pass temporal filter followed

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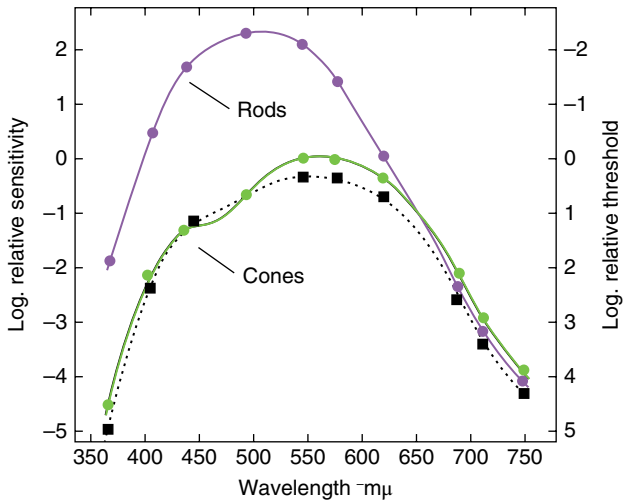


Figure 5.2 The inverse relationship between retinal threshold (right Y-axis) and retinal sensitivity (left Y-axis). Note that the units of the left Y-axis (sensitivity) are increasing, while those of the right Y-axis (threshold) are decreasing. Sensitivities and thresholds of rods (purple) and cones (foveal - green, peripheral - black) are shown as a function of wavelengths. Note that for wavelengths < 650 nm, rods are much more sensitive, and have a lower threshold, than cones (keeping in mind the logarithmic scales of both Y-axes). (Reproduced with permission from Kalloniatis, M. & Luu, C. (1995–) Psychophysics of vision. In *Webvision: The Organization of the Retina and Visual System* (eds., Kolb, H., Nelson, R., Fernandez, E., & Jones, B.), http://webvision.med.utah.edu.)

pathways described next, we are able to see on a moonless, starry night (~10^{-4} cd/m^2) as well as on a sun-drenched sandy beach (~10^5 cd/m^2), a 10^9-fold (one billion) change in illumination (see Chapter 4, Table 4.1).

Scotopic Vision

Rods and Rod Pathways

Cones are inactive in scotopic conditions, and in such an environment our fovea becomes a relative blind spot (Records & Brown, 1999). Instead, scotopic vision is possible because of the molecular and anatomic characteristics of both rods and the rod pathway. The unique features that make an individual rod more sensitive than an individual cone have been recently reviewed by Ingram et al. (2016) and are described in Chapter 4. Even though rods and cones share many proteins involved in the activation and termination of the phototransduction cascade, because of a number of differences in isoforms and/or levels of expression of certain proteins, rods both have greater gain and close the sodium channels more rapidly. Consequently their responses rise much faster per photon absorbed. For the same reasons, the responses of rods decay much more slowly than those of cones, allowing the former to process incoming photons for longer. In addition, the volume of the outer segments is much larger in rods than in cones, increasing the probability of absorption of a photon by rhodopsin (Ingram et al., 2016). All these factors contribute to significant differences in the activation and inactivation of rods and cones (Fig. 5.3). For example, in mice the response per activated photopigment molecule (R^*) is 20–30 times larger in rods than in cones (Cao et al., 2014; Reingruber et al., 2015). In cats, rods are about 200 times more sensitive than cones (Enroth-Cugell et al., 1977).

Another important feature that enables sensitive scotopic vision is the *converging* nature of the rod pathway (see Chapter 4, Fig. 4.26). In cats, it has been estimated that in the peripheral retina, the output of approximately 75,000 rod photoreceptors converges on about 5,000 rod bipolar cells, which output to 250 amacrine cells, which converge on one ganglion cell (Sharma & Ehinger, 2003). The resulting spatial (and temporal) summation of signals from numerous rods increases scotopic retinal sensitivity, as numerous responses are summed to generate a stronger signal and brighten the projected retinal image (Lamb, 2011; Taylor & Smith, 2004). At the same time, the rod pathway also has *diverging* features, with one feline rod synapsing with two rod bipolar cells that diverge to five amacrine cells and eight cone bipolar cells. Therefore, hyperpolarization of a single

Figure 5.1 (Continued) by a thresholding operation. Signals from several rods are then pooled to and summed by one rod bipolar cell, which shows distinct activations (tracings without noise). **B**. The Y-RGC is activated by texture motion in either direction over its receptive field (red circle). Each movement elicits either transient ON- or OFF-responses in the bipolar cells, but only the depolarized bipolar cells signal to the ganglion cell that fires transiently to each shift in the grating. **C**. An RGC sensitive to local motion fires when the object in its central receptive field moves in different direction than that from the background, thus detecting differential motion. This RGC is silent when the object in the center moves in the same direction as the background, because the excitatory input in the center is counteracted by inhibitory input from the surround via the amacrine cell. **D**. An RGC responds strongly (several spikes) to an approaching dark object, but only weakly to lateral motion. More OFF-bipolar cells are excited when a larger part of the receptive field is dark. When the object only moves laterally, the RGC receives both excitatory signals from the OFF-bipolars and inhibitory signals from amacrine cells activated by ON-bipolar cells. **E**. Specific RGCs use differences in spike latencies to rapidly encode the structure of an image. RGCs with receptive fields (circles) in the dark part of the image have short latencies, those in the light have long. RGCs with receptive fields containing both dark and light areas fire in between, thus indicating the position of the border. Here signals from both ON- and OFF-bipolar cells are individually rectified, and the timing difference follows from a delay (Δt) in the ON-pathway. **F**. Wide-field amacrine cells (A1) are activated during rapid shifts of the image in the retinal periphery, which suppresses the OFF-bipolar cell signal and disinhibits the ON-bipolar cell through a local amacrine cell (A2). Hence, this circuit acts like a switch, in this case enabling a signal in the more central part of the retina. (Reproduced with permission from Gollisch, T. & Meister, M. (2010) Eye smarter than scientists believe: Neural computations in circuits of the retina. *Neuron*, **65**, 150–164.

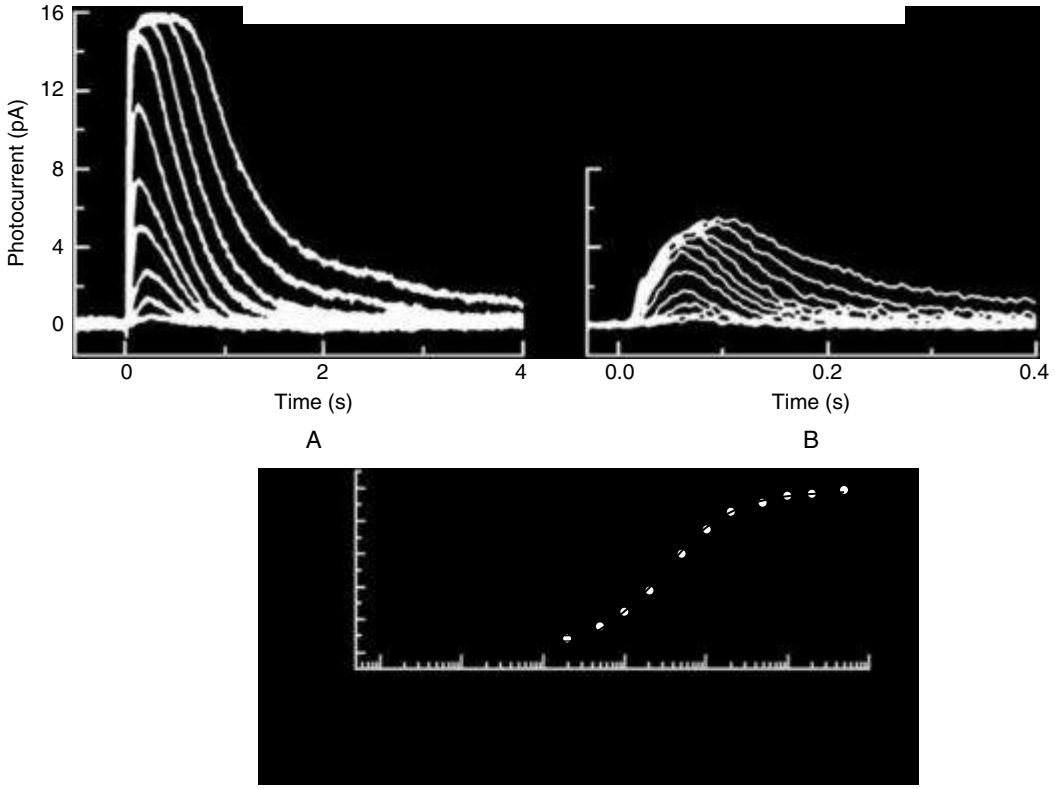


Figure 5.3 Responses of mouse rods and cones. **A**. Mean responses of mouse rods to illumination from 0.5 to 2000 photons. **B**. Mean responses of mouse cones to illumination from 200 to 500,000 photons. Note the significantly lower responses of cones, even though they are illuminated by many more photons. **C**. Mean peak amplitudes of responses of mouse rods (left, •) and cones (right, °) to increasing illumination. Note that there is only a small mesopic range of illumination where both systems are active. (Reproduced with permission from Ingram, N.T., Sampath, A.P., & Fain, G.L. (2016) Why are rods more sensitive than cones? *Journal of Physiology*, **594**, 5415–5426.)

rod in a cat can activate several retinal ganglion cells (RGCs), resulting in increased responsiveness (Sterling et al., 1988). Because of the increased sensitivity afforded by these features of the rods and rod pathway, our scotopic vision can detect small changes in light intensity that would be invisible in daytime, such as dim stars uncovered by moving clouds. In fact, the rod pathway is so sensitive that it is able to detect just a single photon (Takeshita et al., 2017).

In many animal species, the increased number and density of rods enhances scotopic vision. As can be seen in Chapter 4, Table 4.6, the maximal rod concentration in humans (found about 15° away from the fovea) is about one-third of the maximal rod concentration in cats; in the ora serrata (or ora ciliaris retinae), the ratio between the two species is 1:6. It can also be appreciated that dogs have a higher maximal rod concentration than cats, even though most people associate the latter with greater scotopic sensitivity. This discrepancy may be explained by the structure of the tapetum, which is less reflective in dogs than in cats. Nonetheless, the high concentration of rods, which evolved to allow the retina to capture every available photon at night, endows both these species with enhanced scotopic vision.

The advantages conferred by a high rod density in certain environments have resulted in some extreme evolutionary adaptations. Thus, it is not surprising that some deep-sea fish which inhabit a scotopic environment (Hirt & Wagner, 2005), and some nocturnal species such as the nocturnal gecko (Yokoyama & Blow, 2001), have a pure-rod retina. However, these are rare examples, and most nocturnal species, including mice, have cones (Musser & Arendt, 2017). Indeed, many species that were formerly believed to have a pure-rod retina, such as seals and whales (Peichl et al., 2001) and chinchillas (Sandalon et al., 2018), have been shown to be cone mono- and dichromats, respectively.

The Tapetum

One of the most fascinating adaptations for enhanced scotopic vision is the evolution of a reflective tapetum in the choroid (Fig. 5.4). Light photons striking this layer bounce back onto the retina, thus giving them a second chance to be absorbed by the photoreceptors. This second opportunity is not significant in daytime, as cones absorb enough photons during their "first pass" through the retina. In fact, the tapetum has a detrimental effect on visual acuity in broad daylight, as the light is reflected onto a photoreceptor different from the one in the original trajectory (Ofri, 2018b). However, at night this detrimental effect on visual resolution is insignificant since cones are inactive. Instead, the retina benefits from the increased probability that rods will absorb the few

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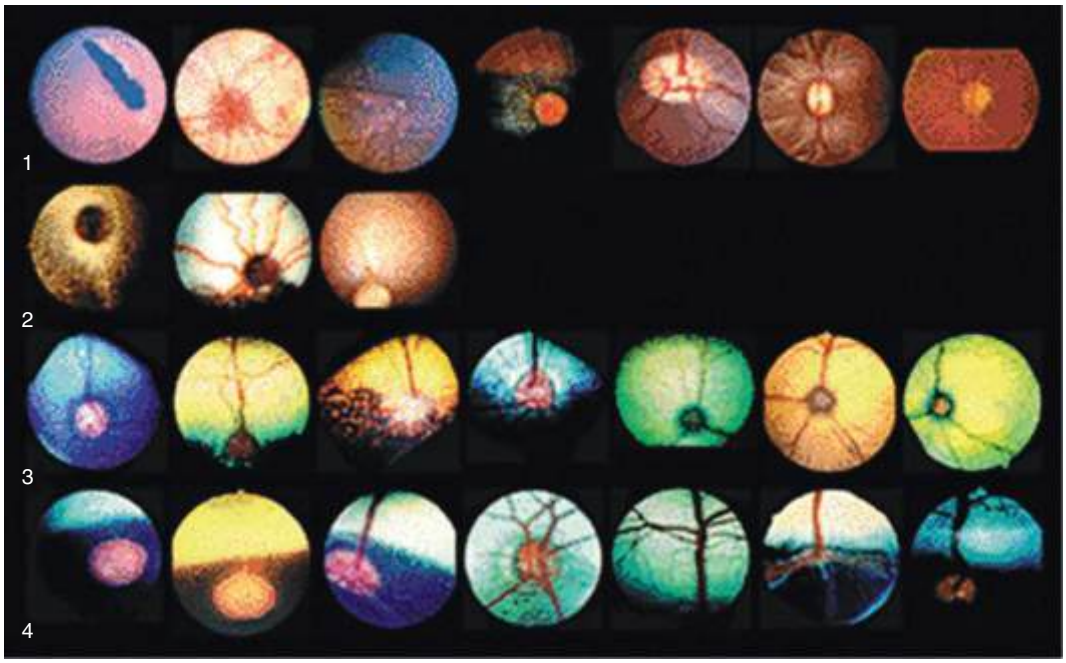


Figure 5.4 Ocular fundus of various species showing the absence or presence of a tapetum lucidum that can exhibit various colors. From right to left: Lane 1: absence of tapetum: bird, albino rat, hooded rat, red kangaroo, pig, rhesus monkey, human. Lane 2: retinal tapeta: alligator, opossum, fruit bat. Lane 3: Choroidal tapeta cellulosa: puppy, dog, cat, jaguar, leopard. Lane 4: choroidal tapeta fibrosa: foal, horse, sheep, goat, cow, deer, mouflon. (Reproduced with permission from Ollivier, F.J., Samuelson, D.A., Brooks, D.E., et al. (2004) Comparative morphology of the tapetum lucidum (among selected species). *Veterinary Ophthalmology*, **7**, 11–22.)

photons entering the eye in a dim environment, thus enhancing scotopic vision.

The composition of the tapetum varies between species, depending on the habitat and ecologic requirements of the animal. The feline tapetum, for example, is 15–20 layers thick (Ollivier et al., 2004), giving it a reflectance rate of almost 100% (Land, 1972). Indeed, the cat's eye reflects about 130 times more light than the human eye (Rodieck, 1973). However, not all wavelengths are reflected equally, as reflectivity is also affected by the dimensions and packing of the reflecting tapetal fibrils or rodlets (Ollivier et al., 2004). As noted previously, the canine tapetum is less reflective than the feline one as it has fewer layers (Yamaue et al., 2015) and suboptimal packing of the reflecting rodlets (Ollivier et al., 2004), which certainly contributes to cats having higher scotopic sensitivity than dogs.

The horse tapetum is only 4–5 layers thick, thus significantly reducing its reflectivity (Ollivier et al., 2004), but the diameter and interfibrous distance of the tapetal collagen fibrils are such that they reflect light at about 468 nm; this wavelength is more effectively absorbed by rods than by cones, minimizing the detrimental effect of tapetal scatter on equine photopic vision (Shinozaki et al., 2013). In contrast, the tapetal reflectance of the diving hooded seal selectively increases the relative ultraviolet (UV)/blue components to more than 10 times those of other wavelengths, which may have advantages in the dim, blue light-shifted environment experienced by submerged marine mammals (Hogg et al., 2015). The most dramatic example of the adaptability of the tapetum to the animal's environment is probably that of the Arctic Reindeer, which changes its tapetal reflectivity with the seasons! The reindeer tapetum is golden and less reflective in summer to enable high visual acuity during the long and bright Arctic days, but turns blue and more reflective in winter, when higher retinal sensitivity is required to detect predators in the dark Arctic night (Stokkan et al., 2013).

Globe Size

The dimensions of the ocular tissues also contribute to improved scotopic sensitivity in many species. For example, the mean diameter of the cornea in cats and humans is 16.5 and 11.7 mm, respectively (Carrington & Woodward, 1986; Rüfer et al., 2005). Consequently, much more light enters the cat's eye. Next, light must pass through the pupil. The diameter of a mydriatic pupil in cats and humans is about 12 and 8 mm, respectively (Hammond & Mouat, 1985; Gilmartin et al., 1995), translating into a pupillary aperture of 113 and 50 mm^2, respectively. As a result, far more light passes through the cornea and pupil to reach the feline retina at night, when the pupil is fully dilated. Indeed, it has been calculated that a fully dilated pupil increases the amount of light reaching the retina by 135-fold in the cat, compared to an 80-fold increase in humans (Hughes, 1977; Records & Brown, 1999). When all of these factors – a large aperture for light to enter the eye, a high concentration of rods, and a



Figure 5.5 Increased scotopic sensitivity of a cat. The same spider is seen at night, under identical scotopic conditions, by a human (**A**) and a cat (**B**). Even though both are viewing the spider under the same conditions, the cat sees a much brighter image because of its greater retinal sensitivity. The spider is seen by both observers in black and white, as no cones are active at these low intensities. (Courtesy of Dr. Shlomi Levi.)

highly reflective tapetum – are considered, it is not surprising that the scotopic threshold of cats (1.6×10^{-7} cd/m^2) is 5.5 times lower than that of humans (7.6×10^{-7} cd/m^2); that is, cats can detect light that is 5.5 times dimmer (Harmening & Wagner, 2011; Weale, 1953; Fig. 5.5).

These species differences obviously become even more dramatic in larger eyes, such as in horses. The horizontal and vertical diameters of the equine cornea are 30.3 and 21.2 mm, respectively (Badial et al., 2015). The respective diameters of the equine pupil, dilated with tropicamide, are about 22 and 25 mm (McMullen et al., 2014), giving it a surface area of approximately 430 mm^2. Consequently, a greater number of photons can enter the dilated horse pupil and reach its retina, and though data regarding rod density in the horse are lacking, it is safe to assume that the large area of the equine retina allows it to pack more rods and to capture more light, compared to other species. However, as in the case of dogs, the scotopic sensitivity of the equine eye may be affected by a suboptimal tapetum. Nonetheless, Hanggi and Ingersoll (2009) report that horses could recognize shapes when the ambient light intensity was as low as 3.4×10^{-5} cd/m^2, so dim that the researchers were stumbling into objects and their cameras were unable to capture any images!

Dark Adaptation

Dark adaptation is a process in which sensitivity of photoreceptors increases, and their threshold decreases (see Fig. 5.2). It takes place in darkness following prolonged exposure to bright light, which causes bleaching of a substantial portion of the photopigment and includes several components.

One mechanism of dark adaptation is biochemical and revolves around the resynthesis of rhodopsin from free opsin and from recycled (or newly available) 11-*cis*-retinal. Consequently, the amount of unbleached photopigment increases in the dark, and in a totally dark-adapted eye, 100% of the rhodopsin is in an unbleached form (Rushton, 1965). The rate-limiting and time-consuming step of the process is the supply and transport of 11-*cis*-retinal from the retinal pigment epithelium back to the outer segments, where it binds with opsin to reform unbleached rhodopsin (see Chapter 4, Fig. 4.25; Wang et al., 2014). Therefore, the time required for dark adaptation and photopigment regeneration is largely determined by the duration, intensity, and wavelength of the preadapting light, which dictates how much of the photopigment has been bleached, and how much remains unbleached.

Postreceptoral neuronal processes make an equally important contribution to dark adaptation (Lamb, 2011). Reciprocal synapses between bipolar and amacrine cells may regulate retinal sensitivity through feedback mechanisms (see Fig. 5.1) (Dowling, 1967; Reuter, 2011) and reorganization of RGC-receptive fields also enhances dark adaptation (Puell et al., 2014; Troy et al., 1993). Together, the biochemical and neuronal adaptation processes increase the retinal sensitivity so that light that is about 10,000× dimmer (4 log units) can be detected.

The third mechanism that plays a role in dark adaptation is pupil dilation. Mydriasis contributes about 1 log unit of adaptation in humans and most terrestrial species (Dowling, 1987). However, in diving pinnipeds, such as seals, where very fast adaptation is needed, very large pupils may contribute 2 log units of dark adaptation (Hanke & Dehnhardt, 2009). In fact, the pupillary range of three pinniped species studied correlates with the range of light levels over which their visual system has to operate during diving (Levenson & Schusterman, 1999).

Dark adaptation is a biphasic process (Fig. 5.6). Cones (and cone pathways) dark-adapt too, as their stores of unbleached photopigment also increase in darkness. This first phase is relatively fast, and cones completely dark-adapt in 5–8 minutes (Reuter, 2011). Since rod rhodopsin regenerates much

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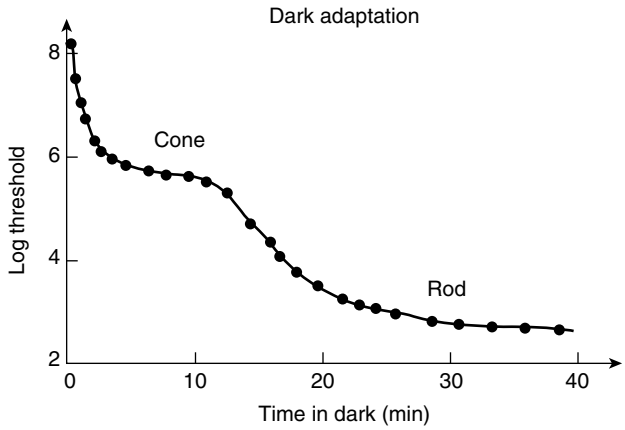


Figure 5.6 The processes of dark adaptation in humans. Cones dark-adapt for the first 5–8 minutes, increasing their sensitivity (lowering their threshold) by about 2.5 log units. Dark adaptation of rods is a much slower process, which increases retinal sensitivity by another 3–4 log units. (Reproduced with permission from Goldstein, E. B. (2005) *Blackwell Handbook of Sensation and Perception*, 2nd ed. Malden, MA: Blackwell.)

more slowly than the cone iodopsin (Wald, 1955), rod dark adaptation is a longer process, usually lasting 30–40 minutes in humans (Lamb & Pugh, 2006).

In animals, in which it is difficult to conduct psychophysical studies, dark adaptation is most often determined through electroretinographic (ERG) recordings. The aim is to establish the amount of time needed, following exposure to strong ambient light, for the scotopic b-wave to return to its maximal response to a dim stimulus. Such studies have shown that 100 minutes are needed for complete dark adaptation in albino rats (Dowling, 1960). During this time, rod sensitivity increased by 3.5 log units, while the amount of rhodopsin increased from 4% (in the light-adapted state) to about 100%, reflecting a logarithmic relation between these two parameters. In horses, scotopic b-wave amplitude reaches maximal amplitude after 20 minutes of dark adaptation (Ben-Shlomo et al., 2012). In dogs, the dark-adapted b-wave reaches maximal amplitude after 20 minutes in alert subjects (Yu et al., 2007) and after 30 minutes in sedated animals (Maehara et al., 2015). These species differences may be due to evolutionary differences in the speed at which retinal is released by the bleached photopigment (Bickelmann et al., 2015). Electroretinographic recordings of the dark adaptation process can be used for early diagnosis of outer retinal diseases in patients (Ekesten et al., 2013; Narfström et al., 2002; Fig. 5.7).

Photopic Vision

Light Adaptation

Light adaptation is a process in which cone (and rod) sensitivity decreases, and threshold increases, in response to increased background light intensity and the resulting

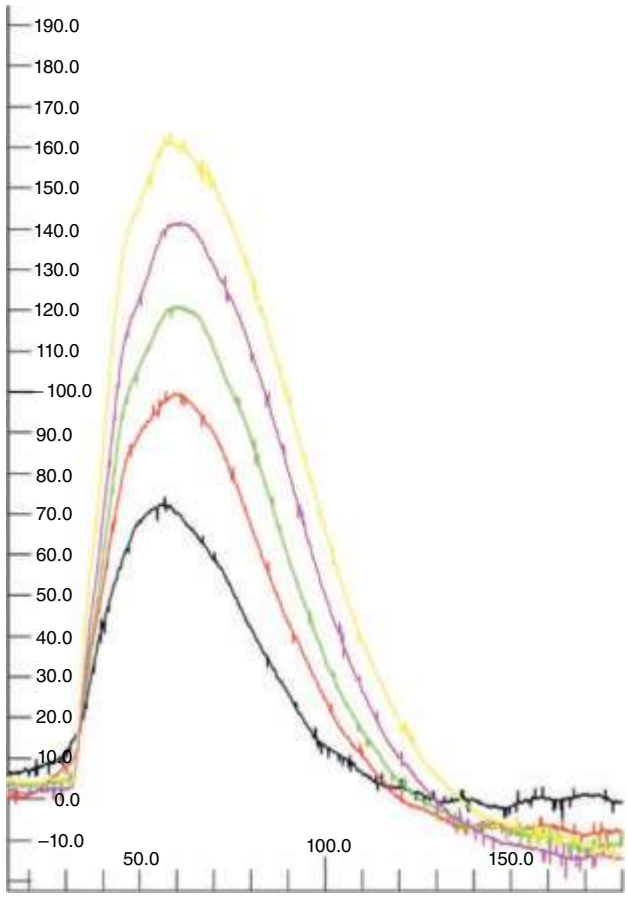


Figure 5.7 In a comprehensive canine electroretinographic (ERG) protocol, following preparation of the animal in ambient light, the light is turned off. During the next 20 minutes, the retina is stimulated with a dim flash every 4 minutes, thus generating a dark adaptation curve (Narfström et al., 2002; Ekesten et al., 2013). In a normal animal, signal amplitude will increase from one flash to the next as the retina dark-adapts (black, red, green, pink, and yellow traces represent the respective responses recorded after 4, 8, 12, 16, and 20 minutes in the dark). Failure of the signal to increase with time in the dark may be an early sign of rod dysfunction.

increased photopigment bleaching. This is a much faster process than dark adaptation. Our eyes begin light adapting within seconds to a sudden increase in background light intensity, such as that experienced when exiting a dark room. Indeed, it is suggested that the reason for the initial *photophobia* exhibited when exiting a dark room is an attempt by the eye to preserve the dark-adapted state of the retina (Records & Brown, 1999).

Several mechanisms account for light adaptation (see Chapter 4). One is the increased activity of phosphodiesterase, resulting in a shorter turnover time for cyclic guanosine-3,5′-monophosphate (cGMP) and accelerating the response kinetics of cones. Another factor contributing to light adaptation is a drop in cytoplasmic Ca^{2+} concentration. This leads to activation of guanylyl cyclase, recoverin (which

phosphorylates R^*), and calmodulin (responsible for channel reactivation), all resulting in increased opening of cGMP-gated sodium channels (Lamb, 2011; see Chapter 4, Fig. 4.24). Generally, eyes are fully light-adapted within 5 minutes, in contrast to the 30 minutes or more required for complete dark adaptation (Records & Brown, 1999).

These adaptation processes take place in both rods and cones. However, the former reach saturation at moderate levels of background light, as all the rhodopsin is bleached, thus making rods unresponsive in saturating light levels. In contrast, cones can continue functioning over an extended range of photopic intensities, albeit at a lower sensitivity (see Fig. 5.3C), and actually they never reach saturation in steady light (Lamb, 2016). Indeed, over 8 log units of background light, cone sensitivity is inversely correlated with background intensity (Burkhardt, 1994; see Fig. 5.2). This is because bleaching (and depletion) of the photopigment results in a proportional increase in the amount of light required for photoreceptor hyperpolarization. In fact, for each 1 log unit increase in light intensity there will be a 1 log unit decrease in the amount of unbleached photopigment available to absorb light, resulting in a 1 log unit reduction in photoreceptor sensitivity (Lamb, 2011).

The Pupil

As with scotopic vision, the pupil also contributes to photopic vision because miosis protects the retina from excessive and harmful amounts of light (Fig. 5.8). It is proposed that the large corpora nigra found on the superior border of the pupil in some species (and often the inferior pupil also) provides additional protection. This is because the corpora nigra supposedly decreases the amount of light entering the eye from the superior visual field (where the sun is located), further reducing glare and improving vision in bright light (Miller & Murphy, 2017). Moreover, because a miotic slit pupil can block light more efficiently than a miotic circular one, it is suggested that slit pupils have evolved in nocturnal or crepuscular species such as cats and geckos that need to function in daytime (Brischoux et al., 2010; Murphy & Howland, 1986). However, this view is challenged by others who note that some species (such as the tarsier) have round pupils that constrict very effectively, to a diameter of about 0.5 mm, while many ungulate species have rather rectangular pupils that do not close to a narrow slit in photopic conditions (Land, 2006). Instead, it is possible that slit pupils have evolved to decrease the detrimental effects of chromatic aberrations (see Chapter 4, Fig. 4.17) (González-Martín-Moro et al., 2014; Malmström & Kröger, 2006).

Flicker Detection

The temporal responsiveness of the retina has two aspects: motion detection and flicker detection. The retina responds to flashes of light as long as there is a sufficient interval between two consecutive flashes, allowing the retina to recover from one response before the next flash is presented. But as the frequency of these flashes increases, a point is reached at which the retina does not have enough time to recover between flashes, and therefore it can no longer distinguish the individual flashes. At this point, which is termed the critical flicker frequency (CFF) or flicker fusion frequency (FFF), the eye perceives a steady light even though this light is made up of numerous flickers (Ezra-Elia et al., 2014; Lisney et al., 2012). There are separate CFFs for rod-driven responses and signals generated from the different cone types, just as there are separate adaptation mechanisms for the rod and cone systems. Therefore, CFF is a function of

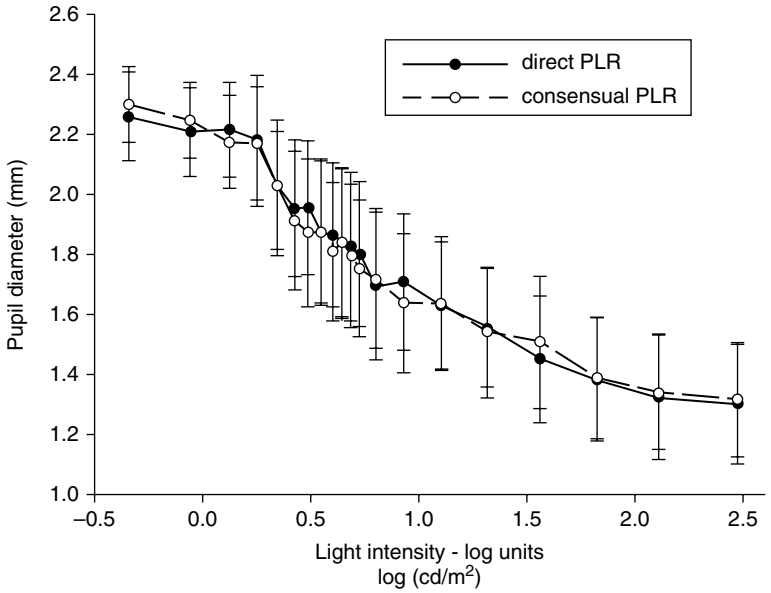


Figure 5.8 The direct and consensual pupillary light reflex in mice as a function of stimulating light intensity. (Reproduced with permission from Grozdanic, S., Betts, D.M., Allbaugh, R.A., et al. (2003) Characterization of the pupil light reflex, electroretinogram and tonometric parameters in healthy mouse eyes. *Current Eye Research*, **26**, 371–378.)

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stimulus intensity, wavelength, background light, adaptation levels, and retinal eccentricity. Figure 5.9 shows the effect of the last two variables on CFF. It can be appreciated that flickers of low-intensity light projected on the peripheral retina, and consequently stimulating the rod pathway, "fuse" at a frequency of approximately 10–20 Hz. Flickers characterized by high illumination projected onto the central retina will activate the cone pathway and therefore fuse at much higher frequencies. CFF is also determined by the location in the visual pathways at which it is measured. The CFF of the cone ERG is higher than the more processed signal detected in the visual cortex; similarly, the CFFs of channels delivering either luminance or chromatic information will also differ (Bowles & Kraft, 2012; Spitschan et al., 2016).

As noted, CFF is affected by numerous factors, and therefore it is difficult to make interspecies comparisons. However, in general, the CFF for the canine rod system is similar to that of humans (10–20 Hz). CFFs of 60 Hz or more have been reported for the feline and canine cone systems (Coile et al., 1989), whereas birds can reach values close to 150 Hz (Bostrom et al., 2016). The ability to resolve very rapid changes in luminance allows these species to view their surroundings in "slow motion" (compared to the temporal resolution of humans) and more easily to follow rapidly moving objects (such as prey) or avoid stationary obstacles (such as tree trunks and branches in a dense forest) while running or flying at high speed.

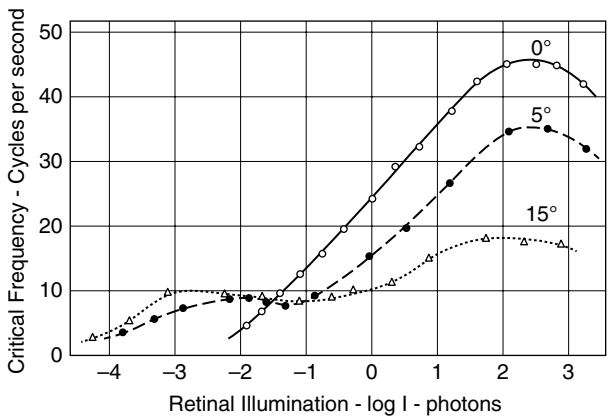


Figure 5.9 Critical flicker frequency (CFF) as a function of retinal illumination for light projected at the fovea (0°), as well as 5 and 15° above the fovea. As can be seen, the highest CFF values are attained for light flashing at the fovea, whereas the lowest values were obtained when stimulating the most peripheral location (15°). CFF values also increase with illumination (moving to the right along the X-axis). Both of these characteristics illustrate that the CFF of cones is higher than that of rods. In the foveal region of this test person (who was also the first author of the original article), using high illumination, responses of cones fuse at about 45 Hz. (Reproduced with permission from Hecht, S. & Verrijp, C.D. (1933) The influence of intensity, color and retinal location on the fusion frequency of intermittent illumination. *Proceedings of the National Academy of Science*, **19**, 522–535.)

Motion Perception

Moving through the environment produces a flow of images projected onto the photoreceptors, resulting in huge amounts of visual information necessary for navigating through a complex environment (Lee, 1980). Perception of motion is required for both directing visual attention to a certain location in the visual field and for segmenting moving objects from their background. Psychophysically, there are three ways of discerning motion (Burr & Thompson, 2011). Movement can be perceived if an object is moving across our visual field while our eyes and head are stationary. Motion can also be perceived when either the head or the eyes are moved to pursue a moving object. It is interesting to note that even though each of these perceptual mechanisms involves the use of different pathways, all three result in similar sensations and experiences.

Processing of motion across the visual field starts in the retina, typically enabled through lateral inhibition by large-field starburst amacrine cells that contribute to motion discrimination and direction detection. Directionally selective RGCs, firing robustly in response to motion in a certain direction and weakly or not at all in response to motion in other directions, make specialized synapses with these amacrine cells. However, it seems that the inhibitory amacrine cell circuits are the primary source of the directional selectivity, which is then amplified by the RGCs (Vaney et al., 2012). Signals from the RGCs, providing information about more rapidly moving targets, are relayed through the magnocellular pathway to the striate cortex, whereas the parvocellular pathway may contribute to the transfer of signals triggered by relatively slow motions (Gilaie-Dotan et al., 2013). Visual area 1 (V1) relays information about motion hierarchically to extrastriate areas, such as the middle temporal area (MT/V5) in primates and to similar areas in lower mammals, mainly through the dorsal stream. Information about fast motion is also conveyed in parallel pathways bypassing V1, thus enhancing vision of rapidly moving objects (Juavinett & Callaway, 2015; Zeki, 2015).

Subtle movement of objects with relatively high luminance is best detected by the central retina, which has a lower threshold and higher sensitivity for motion detection. Therefore, motion sensitivity is directly correlated with visual acuity. Thus, in bright light a human can detect moving objects that are 10 times slower than can a cat (Pasternak & Merigan, 1980). However, in dim light the cat's more efficient scotopic vision makes it superior to humans in detecting slow motion, though even in these conditions humans have an advantage when spatial frequencies exceed 0.5 cycles/degree (Kang et al., 2009). Furthermore, the peripheral retina perceives motion and may be more sensitive to certain speeds, directions, or objects that function as "attention-grabbing" stimuli. For example, it has been shown that the ferret's chase behavior is reflexively triggered by objects

moving at the speed of a running mouse, but not by faster or slower objects (Apfelbach & Wester, 1977).

Different gaze behaviors, including fixations on objects, gaze shifts, and constant gaze, have developed to guide animals during locomotion (Rivers et al., 2014). Fixations occur when head and/or eye movements temporarily stabilize the image of an object moving relative to the observer on the retina, thereby projecting it onto the area with best acuity and allowing more time for visual processing of its properties. Here, the optokinetic reflex allows the eye to follow objects in motion when the head remains stationary. Gaze shifts or saccades are rapid movements between fixations and episodes of constant gaze when sampling of visual information is suppressed to avoid blurring the image (Kowler, 2011). Saccades are exploratory movements used by a wide range of species, where selected locations of the visual scene are brought to the area of best vision and the visual environment is sampled during a brief period of relative image stability in between these small eye movements. Finally, constant gaze occurs when the animal looks at a fixed distance ahead, thus probably extracting visual clues from the information flow about both its own movements and objects in the environment.

Visual Fields, Binocular Vision, and Depth Perception

It is rather extraordinary to note that all vertebrate species, and many invertebrates, have two eyes. Having more than one eye is required for a large visual field, virtually 360° in some species, and for *stereopsis*, or depth perception. However, no more than two eyes are required to achieve these aims (Tyler & Scott, 1994).

Visual Fields

The extent of the visual field depends largely on the placement of the orbits within the skull (Fig. 5.10). Many mammalian prey species, as well as avian and fish species, have lateral eyes, providing almost a 360° field of view. These animals have a small, frontal *binocular* field; two large, peripheral *monocular* fields; and a small blind spot behind their head. On the other hand, most primate and predator species have frontal eyes. In these species, most of the frontal visual field is covered by extensive binocular vision; there are two small, peripheral monocular fields and a large blind spot behind the skull (Fig. 5.10). Therefore, enucleation will cause a cat, for example, to lose approximately 30° of one visual field, while in a horse the same procedure will cause a loss of about 145°.

While the two lateral (monocular) visual fields are equal in size, they may differ in their importance, a phenomenon known as *visual lateralization*. In dogs, for example, it has been shown that the right side of the brain, and subsequently the left lateral visual field, is more responsive to threatening and alarming stimuli (Siniscalchi et al., 2018). This may explain why canine left eyes were 5.3 times more likely to sustain snake-induced trauma compared to right eyes (Scott et al., 2019).

Large (monocular) visual fields are typically associated with prey species that need to detect predators. This is why these species usually have a pupil and a visual streak whose shapes are aligned with the horizon, allowing them to identify predators and conspecifics (Pettigrew et al., 2010). The horizontal visual streak in species such as the horse is augmented by a relatively high RGC concentration both temporally and nasally (Evans & McGreevy, 2007). The former serves the frontal binocular visual field of the animal, while the latter improves vision in the posterior visual field that may harbor predators (Land, 2017; Pettigrew et al., 2010). In fact, horses can detect the appearance of objects within almost 360°, and Hanggi and Ingersoll (2012) suggest that the high acuity of the posterior field (provided by the high concentration of nasal RGCs) may explain how horses can defend themselves with such well-aimed hind-leg kicks.

Obviously, in addition to horizontal visual fields, we also have vertical visual fields. The vertical visual field of horses and humans is 178° and 135°, respectively (Harwerth & Schor, 2011; Miller & Murphy, 2017). The latter is divided into 60° superiorly and 75° inferiorly, though naturally the visual perspective changes when the head is raised or lowered. In fact, in some species these vertical fields, and their enhancement by eye movement, are more important than the horizontal visual fields. In rats, for example, eye movements are mostly disconjugate, impeding horizontal binocular vision; instead, the eyes have a large area of binocular vision above the head, most likely to detect raptors overhead (Land, 2013).

Stereopsis

Many people associate stereopsis with predatory behavior, as depth vision is required to pounce on prey with precision. However, stereopsis is just as important for the prey that uses it to distinguish between a camouflaged predator and its surroundings. Though monocular stereopsis is possible thanks to various visual cues including grain, texture, brightness, contour, size, and relative motion (Ono & Steinbach, 1990), in most cases stereopsis is the result of binocular vision, and the extent to which the visual fields of the two eyes overlap. In addition, optimal stereopsis requires normal visual function and refraction, oculomotor control to maintain fixation, and sensory and neuronal mechanisms to extract and process important visual cues (Harwerth & Schor, 2011).

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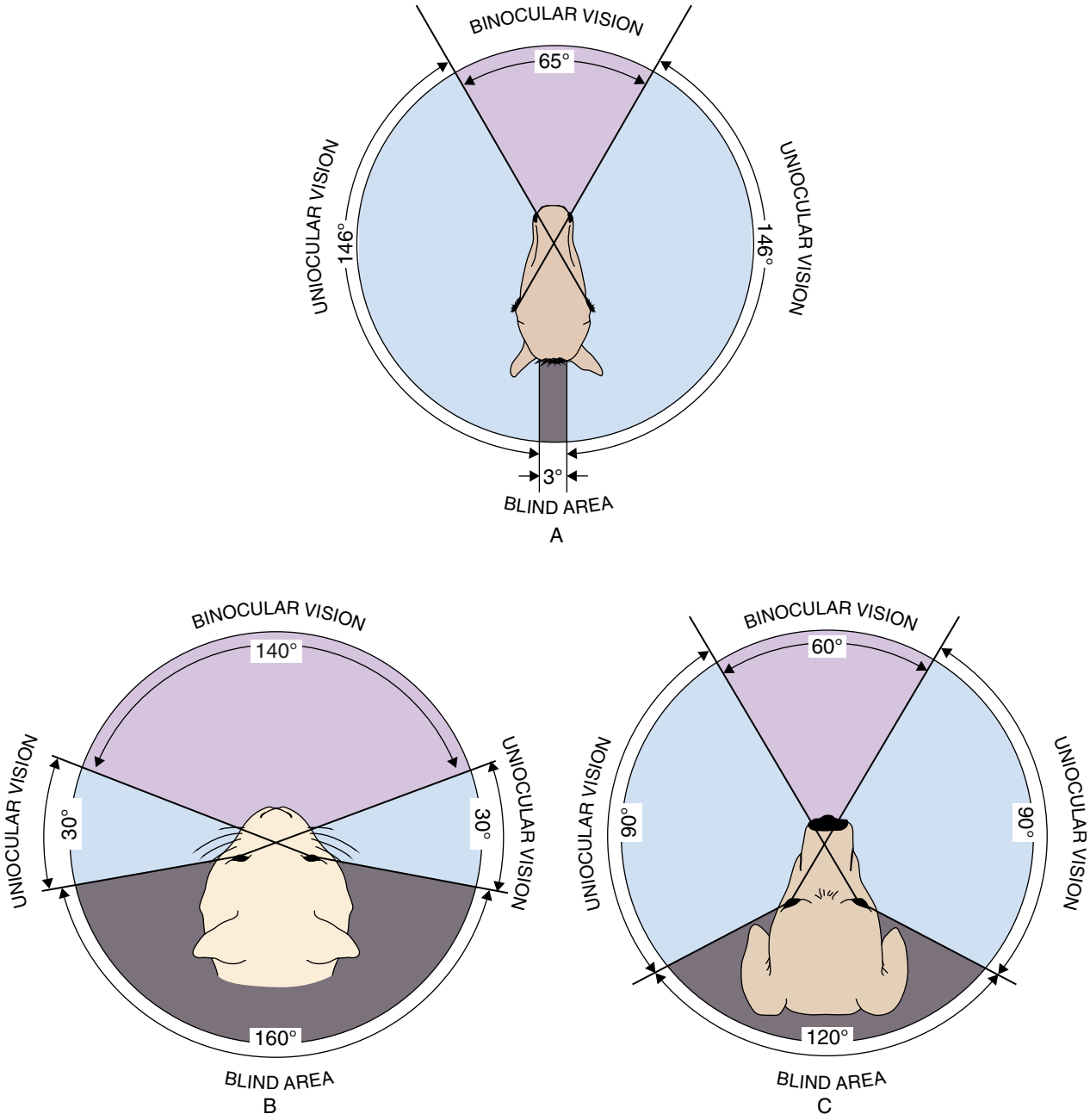


Figure 5.10 **A**. The visual field of a horse showing a frontal binocular field (65°) comparable to that of a dog, but with much larger panoramic monocular fields (each spanning 146°) and a very small posterior blind area (3°). **B**. The visual field of a cat showing a large frontal binocular field (140°) with relatively small monocular fields (each 30°) and a relatively large posterior blind area (160°). **C**. Monocular and binocular visual fields in a typical mesocephalic dog. The dog has a modest frontal binocular visual field (60°) with relatively large monocular visual fields (each 90°) and a posterior blind area of approximately 120°. (Reproduced with permission from Maggs, D.J., Miller, P.E., & Ofri, R., eds. (2018) *Slatter's Fundamentals of Veterinary Ophthalmology*, 6th ed. St. Louis, MO: Elsevier.)

Geometry and Retinal Disparity

If an object is located in the plane of fixation of both eyes, it is viewed with the same angle by both eyes (Fig. 5.11). However, objects outside the binocular plane of fixation are viewed with a slightly different angle by each eye, resulting in *disparate images*. The visual angle can serve as a "range finder." An object is deemed close if the projection lines from both eyes intersect before the plane of fixation, thus triggering a converging oculomotor response; for a distant object the projection lines intersect beyond the plane of fixation, serving as an oculomotor stimulus for divergence (see Fig 5.11). Therefore, range detection requires highly coordinated

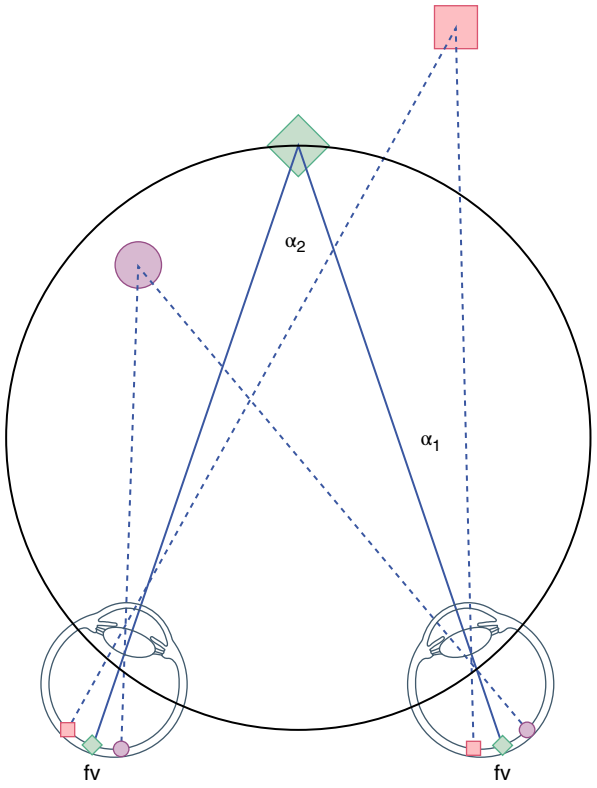


Figure 5.11 Binocular disparity and the perception of stereoscopic depth. The green diamond is on the plane of fixation of both eyes. It is therefore seen at the same angle by both eyes and projected onto both foveas (*fv*). Both the purple circle and red square are outside the plane of fixation. Therefore, they are viewed at different angles by both eyes, and projected onto disparate (but corresponding) retinal regions. The purple circle is closer than the object of fixation (the green diamond) and therefore the projection lines from both eyes intersect before the plane of fixation. The red square is further away, and the projection lines from both eyes intersect after the plane of fixation. The α angles of these projection lines, and their intersection, serve as range finders in stereoscopic depth detection. (Modified with permission from Levin, L.A., Nilsson, S.F.E., ver Hoeve, J., et al., eds. (2011) *Adler's Physiology of the Eye*, 11th ed. St. Louis, MO: Saunders Elsevier.)

movements by both eyes. However, one should remember that many species have limited eye movement and convergence, in which case head or trunk movements supply the required cues. In barn owls, for example, eye movement is limited to only 2°, but the head can turn up to 270°, thus compensating for the immobile eyes (Harmening & Wagner, 2011).

The implication of the geometric angles depicted in Fig. 5.11 is that an object in the binocular plane of fixation will be projected on both foveas (or on the same spot of both areas centralis), resulting in *haplopia*, or a single image. However, because of the disparate viewing angles, objects outside the binocular plane of fixation will be projected on two different (but corresponding) retinal areas in both eyes (see Chapter 4, Fig. 4.36). The result is two disparate retinal images. This disparity increases with the distance of the object from the plane of fixation and allows accurate determination of this distance (Wilcox & Allison, 2009). It is important to note that stereopsis is the result of horizontal (mediolateral) disparity, which allows for perceiving the relative distance, or depth, of an object. Obviously, objects may also trigger vertical (ventrodorsal) disparity, which is important in estimating elevation and height, but this does not contribute to stereopsis in humans (Duke et al., 2006; Fig. 5.12).

Processing Retinal Disparity

Retinal disparity is resolved in the visual cortex, which has the unenviable task of reconstructing a three-dimensional image from the projection of this image on two two-dimensional retinas (Tsutsui et al., 2005). As discussed in Chapter 4, the first synapse of the RGC axons occurs at the lateral geniculate nucleus (LGN); yet, though each LGN receives input from both eyes, binocular interaction typically commences in the visual cortex. The segregation between the outputs of the two eyes is still maintained at the first cortical synapse; that is, the simple cells populating layer 4 of the striate cortex. Binocular interaction begins when these cells output to adjacent layers of the striate cortex and to extrastriate visual areas, where many of the neurons receive binocular input and act as *disparity detectors* (Bridge & Cumming, 2008; Tong et al., 2006). The disparity-sensitive neurons of the occipital cortex act as "low-level" detectors of spatial disparity and process stereopsis; additional neurons in the parietal lobe, inferotemporal cortex, and other cortical areas process "high-level" cues such as texture, shading, and motion to construct a three-dimensional image of the visual field (Tsutsui et al., 2005). Thus, it can be said that some cortical neurons act to integrate disparate binocular inputs and fuse them into one image, while others use the same disparity as a stereoptic cue to process depth perception and three-dimensional vision (Backus et al., 2001; Poggio & Talbot, 1981; Read & Cumming, 2005). Disparity-selective neurons have been described in the cortices of a number of species with laterally placed eyes, including sheep, goats, and rabbits (Clarke et al., 1976; Swadlow, 1988).

However, disparity cannot always be resolved by cortical integration and fusion of two images into haplopia. Sometimes the disparity is so significant that the fusion mechanism "breaks" and normal binocular input must be suppressed. For example, such suppression may occur due to anisometropia or unilateral aphakia that produces unequal contrast perception in both eyes. The consequence of the suppression is functional loss of visual input from the eye that cannot fixate (Harwerth & Schor, 2011). In this context, it is worth remembering that Kubai et al. (2008) demonstrated anisometropia in 6% of dogs surveyed, raising questions about the potential degradation of binocular cortical vision in some veterinary patients. Failure of the

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Figure 5.12 The effect of visual perspective on vision. The same scene as viewed by a small dog with eyes located 8 inches above the ground (**A**), a tall dog with eyes 34 inches above the ground (**B**), and a person with eyes 66 inches above the ground (**C**). (Reproduced with permission from Maggs, D.J., Miller, P.E., & Ofri, R., eds. (2018) *Slatter's Fundamentals of Veterinary Ophthalmology*, 6th ed. St. Louis, MO: Elsevier.)

suppression mechanism will result in *diplopia* (i.e., double vision) or *visual rivalry* (i.e., visual confusion; Fig. 5.13).

Another form of suppression occurs when the two eyes see differing images due to a partial obstruction in the near visual field. Humans experience this when the view of a distant object is partially obstructed by the nose (Harwerth & Schor, 2011). The effect this suppression has on vision in canine, equine, bovine, and other long-nosed patients is unknown, though it probably accounts for the *anterior blind spot* that horses have below their nose (Miller & Murphy, 2017). Similarly, in birds the beak falls in the anterior blind spot. Therefore, birds that eat immobile food usually have shorter beaks, while birds that need to capture moving food require a longer beak that extends beyond the blind spot and can be seen (Lisney et al., 2013; Tyrrell & Fernández-Juricic, 2017). The former are also often characterized by lower visual acuity, a larger (monocular) visual field, and just one fovea, whereas the latter have higher acuity, a larger binocular field, and two foveas (Potier et al., 2016).

Another prerequisite for binocular vision is optic nerve decussation, which allows cortical neurons to receive input



Figure 5.13 Diplopia, or double vision, is the simultaneous perception of two images of a single object. These images may be displaced vertically, horizontally (shown in this figure), diagonally, or rotationally in relation to each other. Diplopia may be the result of failure of cortical centers responsible for suppressing disparate input, or from dysfunction of the extraocular muscles that disrupts binocular convergence. (Courtesy of Dr. Shlomi Levi.)

from corresponding areas of the retinas of both eyes. Consequently, Siamese cats and albino animals with congenital misrouting of optic nerve fibers and abnormal decussation patterns suffer from deficits in their binocular vision (Di Stefano et al., 1984). Similarly, species with no decussation at the optic chiasm, such as birds, lack the input required to generate the binocular maps in the striate and extrastriate cortex. Instead, these species rely on cerebral commissures connecting the two hemispheres to make stereopsis possible.

However, as noted earlier, various visual cues make stereopsis possible in monocular visual fields, which is why humans have depth perception even when closing one eye (Fig. 5.14). Such cues have long been thought to play a central role in providing stereopsis for animals with laterally placed eyes. Nonetheless, it has been shown that even species with lateral orbits (such as the horse) rely on binocular rather than monocular stereopsis, as the former is about 5× superior to the latter (Timney & Keil, 1999). An interesting question that remains unstudied in veterinary medicine is the effect of enucleation on stereopsis, and the extent to which one-eyed animals can learn to use such monocular visual cues (Steeves et al., 2008). The story of Patch, a one-eyed Thoroughbred who ran the 2017 Kentucky Derby (he finished 14th in a field of 20 horses), suggests that such compensation occurs.

Of course, the world is not static and therefore stereopsis is not restricted to stationary objects such as those depicted in Fig. 5.11. *Motion-in-depth* processing is necessary to catch moving prey or to avoid colliding with obstacles while running. Such processing may be facilitated by changes over time in the retinal disparity of a moving object, or by differential velocities of the retinal images (Harwerth & Schor, 2011). The cortex also processes motion-in-depth (Kim et al., 2016). This is why the segregation into magnocellular and parvocellular pathways (see Chapter 4) is also maintained in regard to stereopsis. The parvocellular pathway is associated with static stereopsis and fine disparities, and the magnocellular pathway is associated with motion stereopsis and coarse disparities (Mansilla et al., 1995). Nonetheless, motion-in-depth stereopsis is rather poor, and in humans it has only one-sixth the resolution of static stereopsis (Brooks & Stone, 2006).

Stereoacuity

Stereoacuity is the measurement of the smallest detectable stereoscopic depth. Just like visual acuity, it is measured in arc minutes or arc seconds (see the later section on "Visual Acuity"). It is largely determined by the distance of the object, as obviously smaller disparities can be detected for nearby objects than for distant objects. For example, at a distance of 25 cm some humans can detect a depth of 25 µm (Tyler & Scott, 1994). Of course, such fine discrimination is not possible for objects 100 m away. However, stereoacuity is also determined by other stimulus parameters such as color, contrast, orientation, size, duration of exposure, location (central or peripheral), and luminance (Chima et al., 2016; Harwerth et al., 2003; Simmons & Kingdom, 2002). Stereoacuity is also affected by ocular parameters such as eccentricity and by interpupillary distance, which determines the disparity of the viewing angles. And finally, it is determined by the refractive error and visual acuity, as poor acuity and optical defocusing obviously have a negative impact on stereoacuity (Nabie et al., 2017). Low visual acuity



Figure 5.14 Even though this picture is two-dimensional, various visual cues including relative size, perspective, partial obstruction, and texture gradient provide depth perception of the scene.

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may explain why horses and cats have only 5% and 10%, respectively, of the stereoacuity of humans (Miller & Murphy, 2017). However, in nearly all species stereoacuity is much finer than visual acuity, and therefore stereoacuity is also called *hyperacuity* (Harwerth & Schor, 2011). In barn owls, for example, stereoacuity is about three times higher than visual acuity (Harmening & Wagner, 2011).

Stereoacuity is also affected by ocular pathologies. For example, strabismus increases disparity and reduces stereoacuity, an effect that persists even after surgical correction (Chang et al., 2017). Lack of visual input during the critical developmental period (e.g., due to congenital cataracts or corneal opacities) also degrades stereoacuity (Jeffrey et al., 2001). Nobel Prize–winning work by Hubel and Wiesel (1970) showed that in cats, the sensitive developmental period is through 3 months of age; during this time, even one week of monocular deprivation will result in *amblyopia* and cause irreversible deficits in binocular function (Timney, 1990). The implication is that congenital ocular opacities in veterinary patients should be treated as soon as possible. Indeed, humans undergoing surgery for congenital cataract after 2 years of age (which is the critical developmental period in infants; Harwerth et al., 1990) will have visual acuity < 20/200 for the rest of their lives (Tyler & Scott, 1994).

Color Vision

Prerequisites for color vision are that the retina has both photoreceptors with different spectral sensitivities that are active under the same background light conditions, as well as circuits where signals from the different photoreceptors are compared (Kelber, 2016). In most mammals, two or three types of cones with different opsins provide the first step in color vision in daylight, but some amphibians have more than one type of rod and are therefore likely to distinguish between hues at night too (Yovanovich et al., 2017). The central part of the absorption curve of a photopigment is bell shaped, and the overlap of different photopigments' absorption curves will allow perception of intermediate hues.

Photopigments are classified according to the wavelength at which the opsin molecule has its peak absorption. As noted in Chapter 4, the most common opsin molecules of cones are the L-, M-, and S-opsins, most sensitive to either long (~560 nm, greenish-yellow light, but by convention called the L- or red opsin), medium (~530 nm, green light), or short (~420 nm, blue light) wavelengths, respectively. This means that even though peak absorbance (or maximum sensitivity) occurs at a primary wavelength, the photoreceptor can also be hyperpolarized by a relatively broad range of wavelengths. However, wavelengths further away from the absorbance peak will be weaker stimuli for the photoreceptor. In species with an overlap of two or more absorbance curves, a given light stimulus will stimulate cones of different classes. The extent of stimulation of the various cone classes will determine the color perceived. For example, the dashed vertical line seen in Fig. 5.15 would describe a yellow color, because this light stimulates green and red cones equally. A light source containing longer wavelengths would stimulate the red cones more strongly and the green (and blue) cones less, and would therefore be perceived as more orange-red by a normal human subject. In summary, the number of hues that can be perceived is a function of the number of cone classes and the degree of their overlap.

Perception of color also depends on the luminosity of the light source. Colors are best perceived in bright light, when the cone system is fully active. Under optimal conditions, humans can detect wavelength (color) differences as subtle as 1–2 nm. As the source luminosity decreases, so does the perception of color. At low illumination, when only the rod system is functional, the observer can see only varying shades of gray.

Humans and Old World primates possess three opsins, thus allowing them *trichromatic vision*. The green photopigment is the most abundant in the human retina, while the blue is the scarcest. Total color blindness, which is very rare, usually refers to *rod monochromacy* (or *achromatopsia*), where the patient has no cones at all and no color vision. Cone monochromats potentially have limited color vision under lighting conditions where both the rods and their single type of cones are active (Joesch & Meister, 2016). Most color vision–deficient human subjects have *dichromatic*

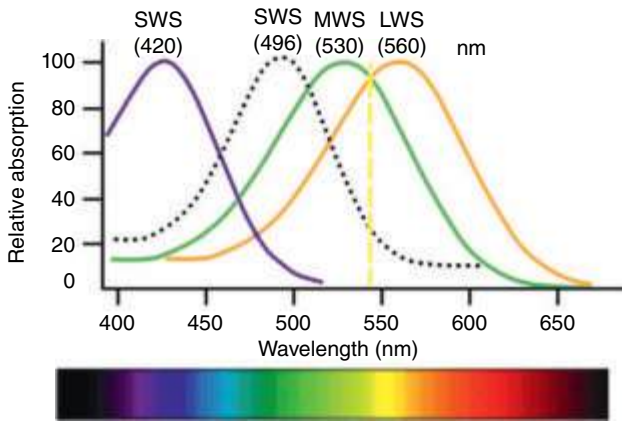


Figure 5.15 Approximate absorption spectra of human rhodopsin (rods) and cone opsins. The wavelength where each opsin has its maximal sensitivity is indicated above each curve. SWS, short-wavelength-sensitive (blue) opsin; MWS, middle-wavelength-sensitive (green) opsin; LWS, long-wavelength-sensitive (blue) opsin. The dashed, yellowish, vertical line indicates the hue detected when the green and red opsins are equally stimulated (see text for additional explanation). The colors of the visible spectrum, as perceived by a normal trichromat, are shown below the diagram. (Modified and reproduced with permission from Deeb, S.S. & Motulsky, A.G. (2013) Color vision defects. In: *Emery and Rimoin's Principles and Practice of Medical Genetics* (eds. Rimoine, D.L., Pyeritz, R.E., & Korf, B.), 6th ed., Fig. 133-1. St. Louis, MO: Elsevier.)

vision, either missing or having a mutated form of the red (*protanopia* or *protanomaly*, most frequent), green (*deuteranopia* or *deuteranomaly*), or blue opsin (*tritanopia* or *tritanomaly*, least frequent). Hence, they perceive colors but, for example, a protanope will perceive red and green objects to have very similar colors, but will readily discriminate between isoluminant blue and green (or red) objects.

Some species are monochromats. Rod monochromacy is mainly found in some fish species, whereas marine mammal species and a few terrestrial mammalian species, including the owl monkey, are cone monochromats (Hunt & Peichl, 2014; Jacobs et al., 1993b; Levenson et al., 2006).

Most mammals, including cats, dogs, horses, cattle, goats, sheep, and swine, are dichromats, just like human protanopes or deuteranopes (Jacobs, 2018; Table 5.1). Horses, for example, have cone opsins with peak absorbance in the blue and green parts of the spectrum, making their color vision comparable to human protanopes. Dogs (and cats), on the other hand, have cone opsins most sensitive to blue and greenish-yellow, making their color vision more similar to that of human deuteranopes (Siniscalchi et al., 2017; Fig. 5.16). When light stimulates the two opsins in a dichromat equally (a monochromatic light of a wavelength that coincides with the intersection of the absorption curves), the retina will not be able to distinguish this wavelength from an achromatic stimulus. This neutral point is reported at about 505 nm in the cat, and 480 nm in the dog and horse (Clark & Clark, 2016; Geisbauer et al., 2004; Neitz et al., 1989). Despite their having fewer cones than humans and being dichromats, for dogs color vision cues seem to be important during daylight conditions (Kasparson et al., 2013), and it is likely that other mammalian species also take advantage of their ability to discriminate between different wavelengths to enhance their daily lives, and particularly their sexual and feeding behavior.

Table 5.1 Cone opsin peak sensitivities in selected species.

	Cone Peak Sensitivity (nm)		
Species	**S-opsin**	**M/L-opsin**	**References**
Cat	454	561	Loop et al. (1987)
	450	550	Guenther & Zrenner (1993)
Dog[a]	429–435	555	Neitz et al. (1989); Jacobs et al. (1993a)
Horse	428	539	Carroll et al. (2001); Timney & Macuda (2001)
Pig	439	556	Neitz & Jacobs (1989)
Cow	451	555	Jacobs et al. (1998)
Sheep and goat	445	552	Jacobs et al. (1998)
Syrian gold hamster	—	508	Williams & Jacobs (2008)
Rat	358[b]	510	Jacobs et al. (2001)
Mouse	360[c]	510	Jacobs et al. (2004)
Guinea pig	429	529	Jacobs & Deegan (1994)

[a] Three species of foxes also have similar values. [b] Ultraviolet light sensitivity.

Some dichromats, including many rodents, such as the mouse, rat, gerbil, and Siberian hamster, have a specialized short-wavelength opsin that peaks in the UV range of the spectrum rather than in the blue (Peichl, 2005). Hence, they have extended the spectral range of the electromagnetic radiation that they can perceive (Gouras & Ekesten, 2004). Furthermore, some dichromats that have "regular" S- and M/L-cone pigments, such as the reindeer and dog (and most likely the cat, too), have lenses transmitting UV light, which enables them to see in the UV part of the spectrum using their regular cone pigments (Ekesten et al., 2014; Hogg et al., 2011).

Many modern-day reptilian, avian, and fish species still have all four ancestral photopigments, including an additional short-wavelength opsin with peak absorbance in the UV or violet range (355–450 nm) that humans and most domestic mammals have lost, and have thus *tetrachromatic vision* (Bowmaker, 2008).

Birds have developed additional unique mechanisms for color vision. Their *double cones* are used for fine spatial discrimination (visual acuity), while *single cones* are used for color vision. *Oil droplets* found in the cones of birds contribute to color perception by filtering out different wavelengths of incoming light and shifting the wavelength sensitivity of the photoreceptor (Toomey et al., 2015).

Although not using such a sophisticated system as a palette of oil droplets, incident light is in fact filtered in most species before reaching the photoreceptors. Transmission of UV light is profoundly reduced or blocked by the lens in several species, and the yellow macular pigment in haplorrhine primates filters out short-wavelength light. Furthermore, the yellowing of the lens in some species, such as the horse, may have a similar function, as it filters out the blue wavelengths of incoming light, although several other factors associated with aging may also contribute to age-related changes in color vision (Beirne et al., 2008).

Another extraretinal factor that determines color perception is the architecture of the LGN and visual cortex. Both areas are populated by color-sensitive cells, termed *color opponent cells*. These cells are activated in response to a given color but are inhibited by another, in a manner similar to the on–off responses characterizing the retinal bipolar and ganglion cells. For example, blue-yellow cells respond to blue light, but they are inhibited by yellow light. Other cells

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Figure 5.16 A colorful dog, as seen by a normal trichromat (**A**). In (**B**), the color information from the photograph has been extracted. The photograph has been filtered to mimic how a protanope (**C**), a deuteranope (**D**), a tritanope (**E**), and a cone monochromat (**F**) would perceive the same scene. The protanope and deuteranope can distinguish between short and long wavelengths, whereas the tritanope can subdivide the middle to long wavelengths into different hues.

may be triggered by red light and inhibited by green. *Double opponent cells* will respond in an antagonistic manner to both spatial and spectral stimuli. Thus, some cells may be "red-ON-center, green-OFF-surround," or "blue-ON-center, yellow-OFF-surround." Obviously, the number of possible double opponent cell types is potentially very large, depending on the number of cone classes (Conway, 2009; Shapley & Hawken, 2011).

Visual Acuity

Visual Acuity in the Animal Kingdom

Visual acuity is the minimal detection power of the eye, or the minimal angle that can be resolved by the eye. There are a number of ways to express visual acuity, but the best-known method is based on the Snellen chart (Fig. 5.17). This is determined by the size of letters that a subject can read at a distance of 20 ft, or 6 m. Obviously, determination of Snellen acuity requires verbal cooperation by the test subject and therefore is not applicable in veterinary medicine. In animals, visual acuity can be determined using behavioral discrimination tests (Hanggi & Ingersoll, 2009), by electrophysiologic recordings to determine the smallest pattern that elicits an ERG or cortical response (Ofri et al., 1993), or by pursuit (i.e., optokinetic) eye responses to determine the smallest stimulus that elicits a tracking eye movement (Ryan et al., 2016). Acuity is also often determined by theoretical calculations based on cone or RGC density (Coimbra et al., 2013, 2015, 2017; Pettigrew et al., 2010), though the results of these calculations may differ from those of behavioral tests (Clark & Clark, 2013; Mitkus et al., 2014).

There are two ways to express the results of such tests and calculations. Minutes of arc (MAR) describes the angle (in minutes) subtended by the narrowest bar that can be discriminated, keeping in mind that 60 MAR make up a 1° visual angle. Alternatively, cycles per degree (cpd) is the number of cycles (a dark and a white bar) that can be seen within a field subtended by a 1° visual angle. These values are inversely related (Fig. 5.18). A subject with high visual acuity can resolve very narrow bars, resulting in a low MAR value; therefore, in 1° this subject will be able to see many bars, resulting in a high cpd value. Published charts can be used to convert between MAR, cpd, and Snellen acuity units (Miller & Murphy, 1995). A human adult typically has a Snellen acuity of 20/20 or 6/6, depending on whether the nonmetric or metric system is used, respectively. These fraction values represent the size of the object that should be seen at a distance of 20 ft, or 6 m, by a person with normal vision. At this distance, the dimensions of this "gold standard" target are 1 MAR or 30 cpd. In the decimal system, a visual acuity of 20/20 or 6/6 corresponds to 1.0, whereas 20/80 equals 0.25.

Snellen acuity values for selected species are provided in Table 5.2. Fractional values < 1 represent visual acuity that is lower than that of a gold standard human. The value of 20/50 reported for the dog, for example, roughly means that a dog and a human who stand 20 and 50 ft away from a visual target, respectively, would both have the same resolution for that target. The general implication is that the resolution of the human is 2.5 times better than that of the dog, as both will be resolving and detecting the same target, even though the human is 2.5 times further away from it. In a metric system, these results are reported as 6/15, with the dog and the human standing 6 and 15 m away, respectively, from the target. Figure 5.19 shows the optical quality of the images formed by a dog's eye with 20/50 (or 6/15) vision.

As can be seen in Table 5.2 and Fig. 5.17, due to the presence of a fovea and macula, humans and nonhuman primates have the highest visual acuity among mammalian species. However, it can also be appreciated that raptors have even

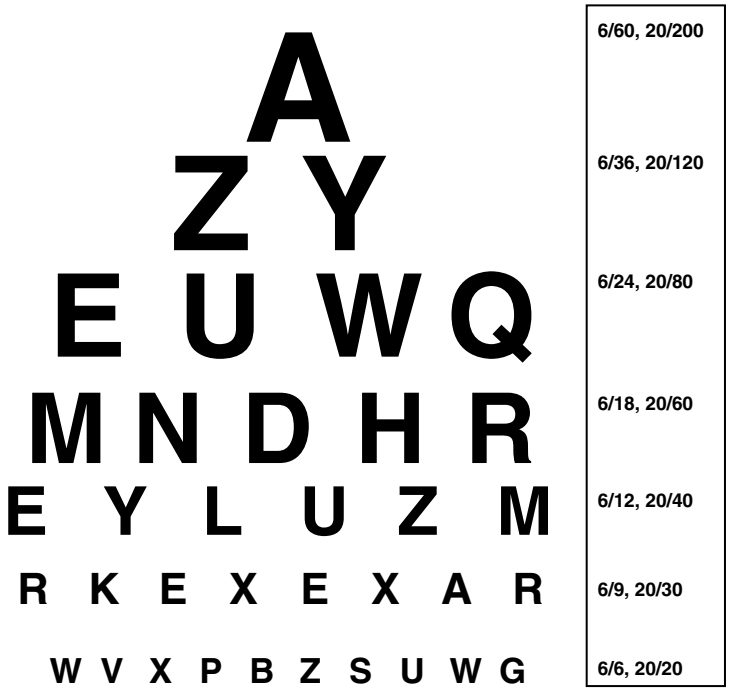


Figure 5.17 Snellen acuity chart. A normal human with 6/6 or 20/20 vision should be able to read the bottom line at a distance of 6 m or 20 ft. Humans and animals with lower acuity, as indicated by the figures on the right, can only detect larger letters at the same distance. Based on the values in Table 5.2, horses, for example, should be able to see the second line from the bottom, while rabbits can only detect the top letter.

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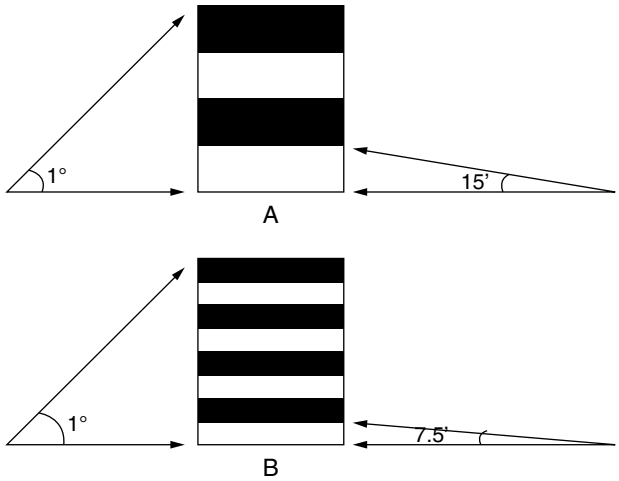


Figure 5.18 Visual acuity expressed in cycles per degree (cpd) and minutes of arc (MAR). The acuity of the observer on the left is denoted in cpd, which expresses the number of cycles (each cycle consisting of a dark and a light bar) seen within a 1° visual field. The observer on the right has an identical visual acuity, but it is denoted in MAR, which expresses the angle (in minutes) subtended by a single bar. **A.** The acuity of the observer on the left is 2 cpd (two pairs of light and dark bars). Because there are four bars in a degree, each is 15' wide; therefore, the acuity of the observer on the right is 15 MAR. **B.** The observer on the left can discriminate four pairs of dark and light bars in a 1° field and, therefore, has an acuity of 4 cpd. The width of each bar is now 7.5', however, and the acuity of the observer on the right is therefore 7.5 MAR.

higher visual resolution, with Snellen fractions > 1. The 20/5 resolution of the eagle, for example, implies that an eagle can be 4x further from a visual target than a human (20 and 5 ft, respectively), yet both species will equally resolve this target. On the other hand, it can be seen that contrary to common perception, the domestic cat has very low visual acuity, perhaps as low as 50% of the canine visual acuity. The popular belief that cats have high visual acuity may stem from the superior scotopic sensitivity of this species; however, this high scotopic sensitivity of the cat is enabled by the presence of a tapetum lucidum (which scatters light) and a rod-rich retina, two factors that have detrimental effects on visual acuity.

When looking at Table 5.2, one should keep in mind that the legal definition of blindness in humans is 20/200 (or 6/60). This means that by human standards rabbits, cows, rats, and mice are legally blind. Furthermore, the menace response requires a visual acuity of only 20/20,000, far below the threshold of legal blindness, thus casting doubts on the usefulness of this commonly used method to assess vision (Miller, 2018).

Factors Affecting Visual Acuity

Numerous factors affect visual acuity. These include both visual system- and stimulus-dependent factors. Visual system factors are further subdivided into optical, retinal, and cortical features.

Optics of the Visual System

Refractive Error

Many of the optical factors affecting visual acuity were discussed in Chapter 4. Foremost among these is the refractive error of the eye. The values presented in Table 5.2 are for an emmetropic eye, when the image is focused on the retina. Obviously, ametropia results in a blurred image on the retina, and leads to degradation of acuity. In the dog, 1.5 D (diopters) of myopia reduces visual acuity from 20/50 to 20/92, and 3 D myopia reduces it further, to 20/120 (Fig. 5.20). Such defocusing had a significant negative impact on retrieval times and performance scores of trained Labrador Retrievers (Ofri et al., 2012).

A large survey of over 1,400 dogs found that the average canine refractive error is −0.05 D, and that two-thirds of the study population was emmetropic, defined as a refractive error of <0.5 D in either direction (Kubai et al., 2008). Therefore, two-thirds of canine patients have the visual acuity values presented in Table 5.2. Yet the same study found that 8% of all dogs were hypermetropic, with a refractive error of up to +3.25 D, and three breeds (Australian Shepherd, Alaskan Malamute, and Bouvier des Flandres) had a mean refractive error that was hypermetropic. Conversely, 25% of all surveyed dogs were myopic, with a refractive error of up to −6.25 D, and four breeds (Rottweiler, Collie, Miniature Schnauzer, and Toy Poodle) had a mean refractive error that was myopic. Other researchers also confirmed a high prevalence of myopia in Toy Poodles (63.9%), English Springer Spaniels (36.4%), and Collies (35.7%; Williams et al., 2011). Thus, it would seem that a high proportion of dogs suffer from the adverse behavioral effects described for canine myopia (Ofri et al., 2012; see Fig. 5.20). Furthermore, it should be noted that if an intraocular lens is not implanted in a canine patient undergoing cataract surgery, the aphakic eye will have 14.5 D of hyperopia (Davidson et al., 1993), resulting in visual acuity of 20/800, which is well below the 20/200 legal definition of blindness in humans.

Other species may also suffer from a high prevalence of ametropia. Only 48%–68% of horses are emmetropic in both eyes, with hyperopia and myopia reported in equal proportions in the ametropic horses (Bracun et al., 2014; Grinninger et al., 2010), with errors of up to ±3 D (Farrall & Handscombe, 1990; Grinninger et al., 2010). In Icelandic horses, a mutation causing silver coat color and multiple ocular anomalies is associated with myopia (Johansson et al., 2017). Though there are no studies documenting the behavioral consequences of equine ametropia, the condition has been associated with nervousness in affected horses (Miller & Murphy, 2017).

In a survey of 98 cats, only 30% were emmetropic; 54% and 16% of the study population were myopic and hyperopic, respectively (Konrade et al., 2012). However, the results may have been skewed by the fact that only 58% of the study

Table 5.2 Visual acuity in select species.*

Species	Snellen Resolution**	Spatial Frequency (Cycles/Degree)**	Method***	References
Eagle (*Aquila audax*)	20/4	140	Behavioral and anatomic	Reymond (1985)
Falcon (*Falco berigora*)	20/8	73	Behavioral and anatomic	Reymond (1987)
Macaque monkey	20/16	38	Behavioral	Merigan & Katz (1990)
Human	20/20	30		Ravikumar et al. (2011)
Horse	20/26	23	Behavioral	Timney & Keil (1992)
	20/36	16.5	Anatomic	Harman et al. (1999)
King penguin			Anatomic	Coimbra et al. (2012)
Under water	20/30	20.4		
In air	20/40	15.3		
Alpaca	20/45	13.4	Anatomic	Wang et al. (2015)
Sheep	20/51–20/43	11.7–14	Behavioral	Sugnaseelan et al. (2013)
	20/86–20/60	7–10	Anatomic	Hughes (1977)
Camel	20/60	10	Anatomic	Harman et al. (2001)
Dog	20/140–20/52	4.3–11.6	Electrophysiologic	Odom et al. (1983); Ofri et al. (1993); Murphy et al. (1997)
	20/110–20/31	5.5–19.5	Behavioral	Lind et al. (2017)
Cat	20/190	3.2	Behavioral	Jarvis & Wathes (2007)
	20/90	6.5	Electrophysiologic	Berkley & Watkins (1971)
	20/33	18	Anatomic	Steinberg et al. (1973); Clark & Clark (2013)
Barn owl			Behavioral	Orlowski et al. (2012)
	20/190	3.2 (Mesopic)		
	20/500	1.2 (Scotopic)		
Rabbit	20/200	3	Electrophysiologic	Pak (1984)
Cow	20/460–20/230	1.3–2.6	Behavioral	Rehkämper & Görlach (1998); Rehkämper et al. (2000)
Rat			Behavioral	Prusky et al. (2002)
Pigmented	20/600–20/400	1–1.5		
Albino	20/1200	0.5		
Mouse	20/1000	0.58	Behavioral	Lehmann et al. (2012)
	20/1500	0.39	Optokinetic	Lehmann et al. (2012)

* This table mostly contains data for species commonly seen by veterinary ophthalmologists in clinical and research settings. Avian species have been included to demonstrate their high acuity (eagle, falcon) or the effects of aquatic vision (penguin) and light conditions (owl). The scientific literature reports visual acuity values for numerous other species, such as giraffes (Coimbra et al., 2013), elephants (Pettigrew et al., 2010), rhinoceros (Pettigrew & Manger, 2008), and marsupials (Dooley et al., 2012), that are beyond the scope of this book.
** Most articles report visual acuity in cycles/degree. These values have been converted to Snellen units by the author (R.O.) as most readers are more familiar with this latter scale. Values for Snellen acuity < 20/200 have been rounded.
*** Anatomic methods of assessment include counting the density or cones and/or retinal ganglion cells; electrophysiologic methods are based on recordings of the pattern electroretinogram or pattern visual evoked potentials.

population were adults. Indeed, in dogs (Kubai et al., 2008), horses (Grinninger et al., 2010), and cats (Konrade et al., 2012) as well as in wildlife species (Ofri et al., 2001, 2004), it has been shown that refractive error changes with age. Therefore, ametropia should be considered a differential diagnosis for age-related deterioration in the visual performance of animals with an unremarkable ophthalmic examination, and refraction should be added to the list of diagnostic tests performed in such patients.

Accommodation

Accommodation is another optical factor that may affect visual acuity, as it brings the images of nearby objects into focus on the retina. The process is described in detail in

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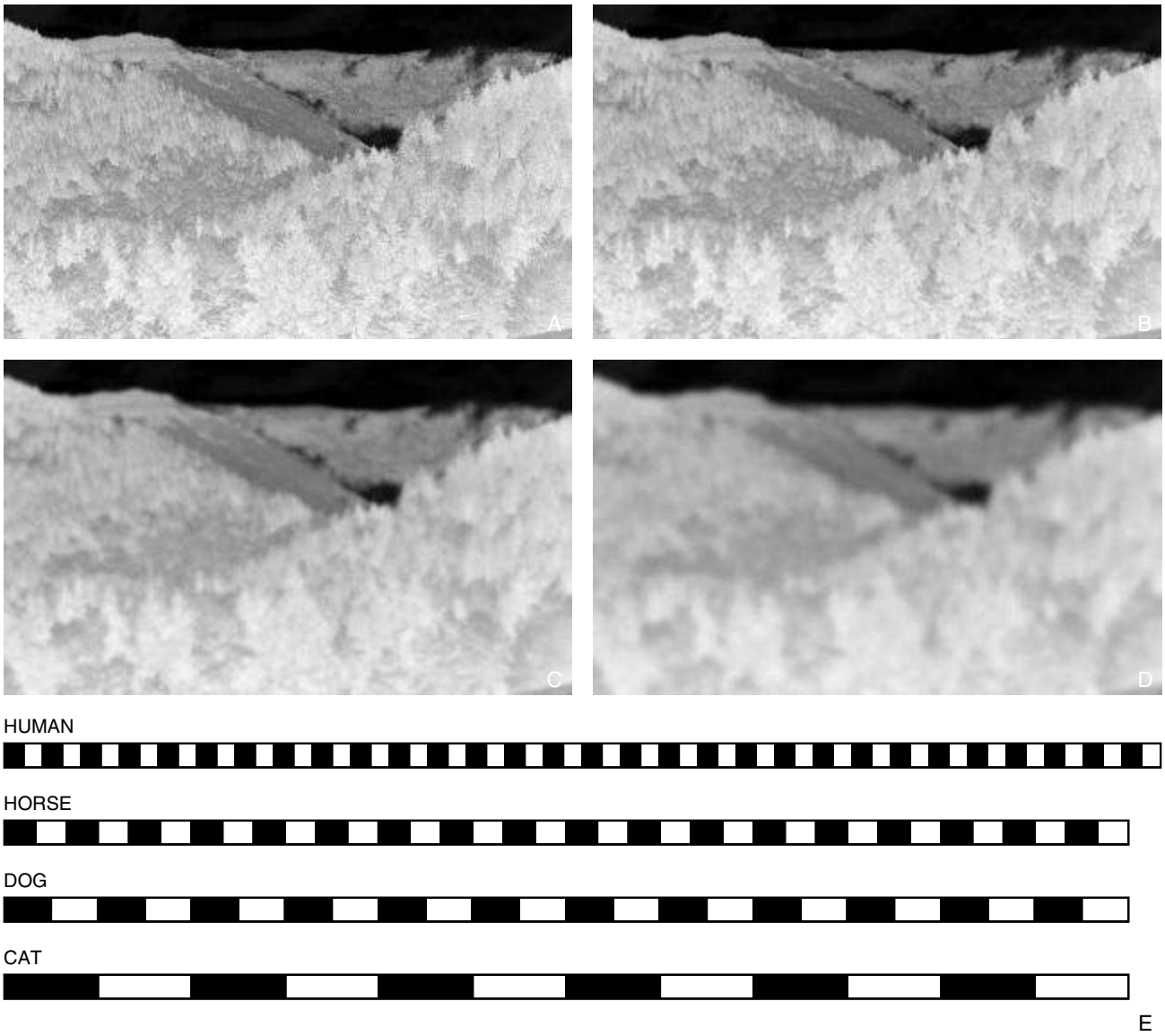


Figure 5.19 Comparative visual resolution. The same landscape is seen by (**A**) a human, (**B**) a horse, (**C**) a dog, and (**D**) a cat. The landscape is presented in black and white to avoid the confounding factor of differences in color vision between species. Differences in visual field size have also been ignored. **E**. Visual acuity depicted as cycles per degree, which means how many lines one can distinguish as being separate in 1 degree of the visual field. A cycle is a pair of a black and a white bar. Humans see 30 cycles per degree, horses 18, dogs 12, and cats 6. Therefore, acuity in cats is 0.2 times that of humans, 0.33 times that of horses, and 0.5 times that of dogs. (Panels A–D courtesy of Dr. Shlomi Levi.)

Chapter 4 (see Fig. 4.7). Briefly, during accommodation parasympathetic stimulation leads to contraction of the ciliary body muscle, allowing the eye to focus on nearby objects. In primates and birds this contraction leads to an increase in the curvature of the lens, while in carnivores it results in anterior movement of the lens in the eye. In disaccommodation, sympathetic stimulation leads to relaxation of the ciliary body muscle, allowing the eye to view distant objects. In primates and birds the relaxation results in a flatter lens with reduced refractive power, while in carnivores it results in posterior movement of the lens in the eye (Ofri, 2018b).

Children have a powerful accommodating capability, perhaps as high as 15 D, which means that they can focus on objects as close as 6–7 cm; unfortunately, humans gradually lose this capacity with age, in a process called *presbyopia*, and by 50–55 years of age they are left with virtually no accommodative power (Glasser, 2011). As detailed in Chapter 4, in diving birds and otters the accommodative power can be as high as 60 D, and accommodative powers of 10–20 D have been demonstrated in other avian species, as well as some mammals such as raccoons and mongooses. However, most mammalian species that are commonly seen

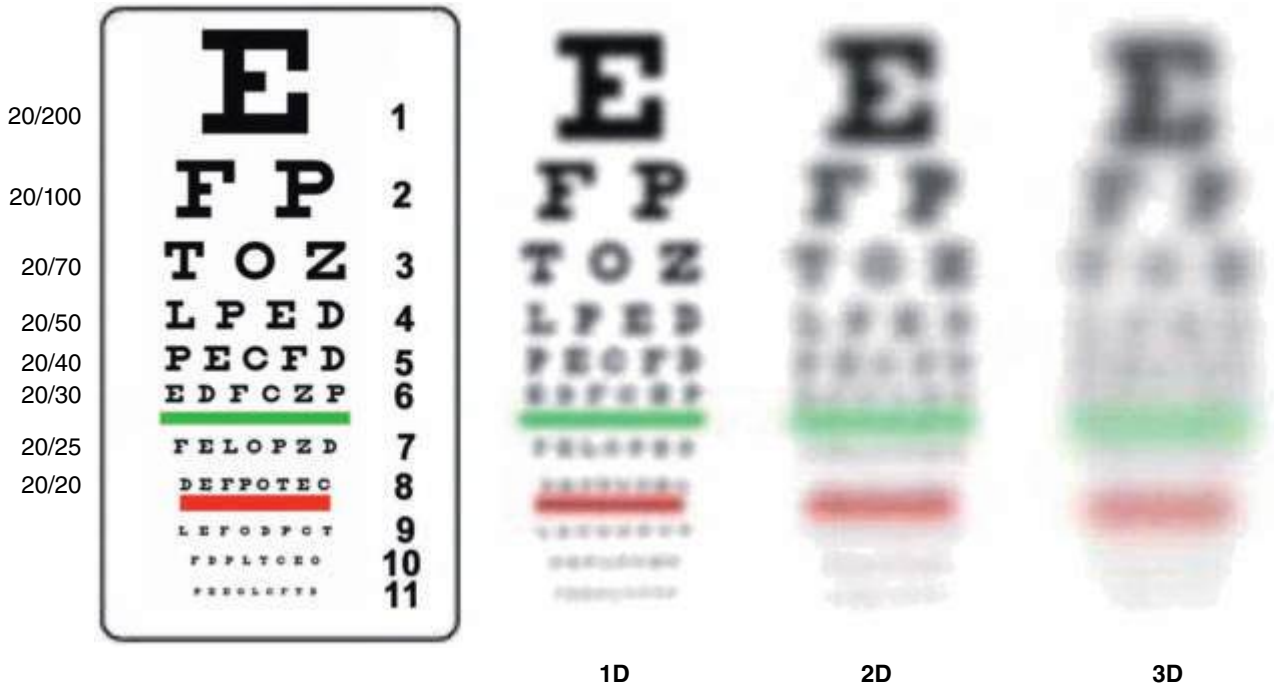


Figure 5.20 Simulated blurred vision due to myopia. 1–3 D (diopter) defocus can result in blurry vision simulated based on human subject experience. Similar blurry vision can be expected for dogs that have −1 to −3 D myopia. (Reproduced with permission from Hernandez, J., Moore, C., Si, X., et al. (2016) Aging dogs manifest myopia as measured by autorefractor. *Plos One*, **11**, e0148436.)

by veterinary ophthalmologists have very low, or no, accommodative power. Dogs and cats have accommodative power of just 1–3 D (Hughes, 1977) and 2–4 D (Ott, 2006), respectively. The implications of these numbers are that though dogs and cats can focus on distant objects (by disaccommodating), their depth of field for nearby objects is just 100–33 cm (dogs) and 50–25 cm (cats). Closer objects are very blurred and are usually perceived using the sense of smell, rather than vision. Horses can accommodate only ±1 D in either direction (Sivak & Allen, 1975), while rodents (Artal et al., 1998) and ruminants (Piggins & Phillips, 1996) generally lack accommodative capabilities. Thus, it would seem that in most veterinary patients, accommodation does not make a significant contribution to visual acuity.

The Pupil

Unlike accommodation, the pupil has a great impact on the visual acuity of many veterinary patients. As described in Chapter 4, the peripheral cornea and lens introduce significant spherical (and chromatic) aberrations into the eye. Therefore, mydriasis results in reduced visual acuity as peripheral rays reach the retina (Fig. 5.21). In humans, dilating the pupil with 1% tropicamide will decrease acuity to about 20/30 (Chew et al., 2007; Montgomery & MacEwan, 1989). While similar studies are unavailable in animals, one can assume that due to the large pupil size in some veterinary

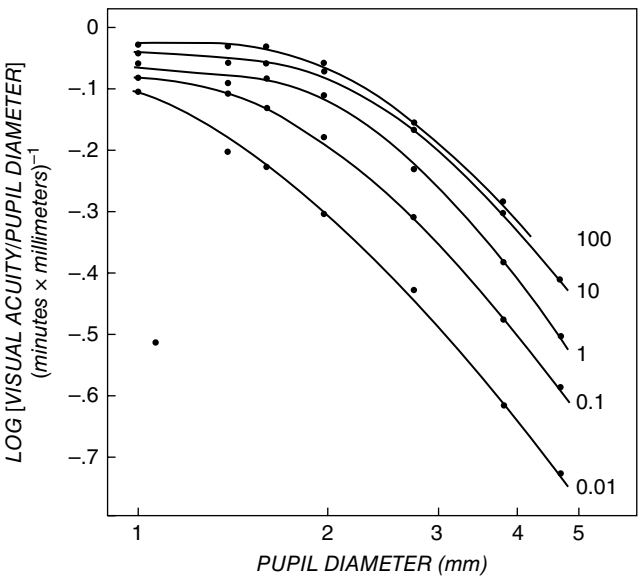


Figure 5.21 The effect of pupil diameter on visual acuity. Luminance values of the reference field are indicated at the right of the curves. Note how acuity decreases with decreasing luminance (compare top curve to bottom curve) and how it also decreases with increasing pupil diameter due to increased spherical aberrations. (Reproduced with permission from Leibowitz, H. (1952) The effect of pupil size on visual acuity for photometrically equated test fields at various levels of luminance. *Journal of the Optical Society of America*, **42**, 416–422.)

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patients, the effect of mydriasis on visual acuity could be even more detrimental. The area of a mydriatic human and feline pupil is 50 mm^2 (Gilmartin et al., 1995) and 113 mm^2 (Hammond & Mouat, 1985), respectively, allowing significant spherical aberrations and visual degradation in cats.

Conversely, miosis decreases spherical aberrations and improves visual acuity. For example, treatment with carbachol causes significant improvement in the visual acuity of human patients (Abdelkader, 2015). This is why miosis is a component in the *near reflex* triad, which also includes ocular convergence and lens accommodation, as these three mechanisms allow humans to view nearby objects of interest with high resolution (Kardon, 2011). Another beneficial effect of miosis is that it increases the depth of field of the eye; that is, the distance between the nearest and farthest objects on which the eye can focus. With a 4 mm pupil, the depth of field of the human eye is 0.78–1.40 m; constricting the pupil to a 1 mm pupil will increase it to 0.56–5.0 m (Wang & Ciuffreda, 2006). This is one instance where the eye may be compared to a camera, as miosis may be compared to the pinhole effect attained when the lens aperture is decreased, thereby increasing the photographer's depth of field, or f-stop (Harmening & Wagner, 2011).

However, there is a limit to the beneficial effects of miosis. As the pupil constricts, the diffraction of light, or its bending and scattering as it passes through the pupillary aperture, becomes more noticeable (Fig. 5.22). This has a detrimental effect on visual acuity, similar to that of the spherical aberrations associated with mydriasis. In humans, the ideal pupil size, which balances diffraction (enabled by miosis) and aberrations (enabled by mydriasis), is 3–5 mm (Smith & Atchison, 1997). Furthermore, miosis reduces the amount of light reaching the retina. Due to the stenopaeic (slit-shaped) feline pupil, miosis in cats decreases retinal illumination by 3 log units (Hammond & Mouat, 1985), compared to the 1.5 log units decrease in miotic humans (Kardon, 2011). Depending on the prevailing conditions, this decrease may result in suboptimal retinal illumination, thus affecting retinal factors that determine visual acuity, as discussed in the next section.

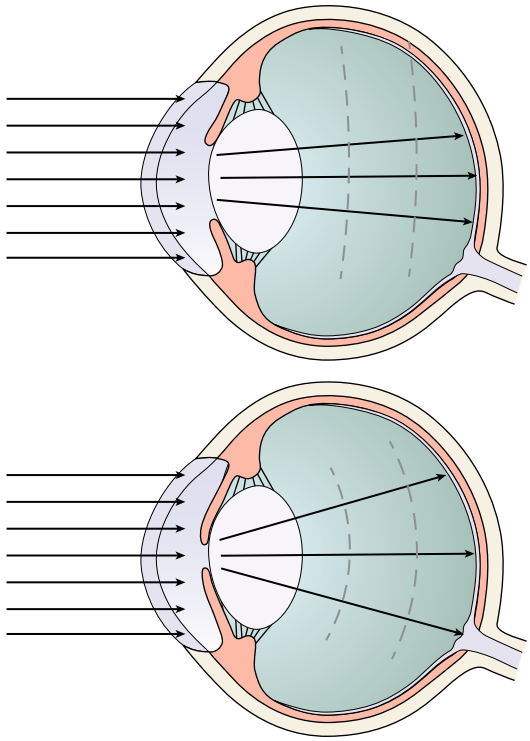


Figure 5.22 The effect of pupil size on light diffraction. Note that with the smaller pupil (bottom) light passing through the pupil is more scattered. Though miosis can improve visual resolution as it decreases spherical aberrations (see Fig. 5.21), beyond a certain threshold it can have a detrimental effect on resolution due to increased light diffraction.

Globe Size

Another optical factor influencing visual acuity is the size of the eye. A comparative study of 91 mammalian species shows that axial length and visual acuity are significantly and positively correlated (Veilleux & Kirk, 2014). This is because an increase in axial length produces a longer posterior focal distance (between the lens and the retina; Fig. 5.23). Consequently, as axial length increases a larger image is formed on the retina, an image that can be sampled by more photoreceptors and RGCs, as discussed next. Interestingly, large eyes and high visual acuity are also correlated with large semicircular canals in the inner ear; it is suggested that high acuity requires precise gaze stabilization, which is enabled by a vestibular system possessing canals with large radii and the resulting high vestibular sensitivity (Kemp & Kirk, 2014).

Retinal Factors Affecting Visual Acuity

Visual acuity is also determined, largely, by anatomic and functional differences between the rod and cone pathways (see Chapter 4). In the retina, visual acuity decreases as a function of increased eccentricity because of the decreased number of cones and RGCs in the peripheral retina (see Chapter 4, Table 4.6). This decline in the peripheral RGC population has been described in the dog (Gonzalez-Soriano et al., 1995), horse (Evans & McGreevy, 2007; Guo & Sugita, 2000), and cat (Stein & Berson, 1995; Stein et al., 1996). In the latter, the ratio of RGCs in the central and peripheral retina is 20:1 (Miller, 2018). Additionally, the peripheral retina is populated mostly by α- or Y-type ganglion cells, which are characterized by large dendritic trees (Li & Da Costa 2002; Stein & Berson, 1995; Stein et al., 1996), further contributing to the low acuity of this region. Thus, it is not surprising that dogs and horses have low visual resolution in the peripheral retina, where most information is processed by the converging rod pathway (Harman et al., 1999; Ofri et al., 1993).

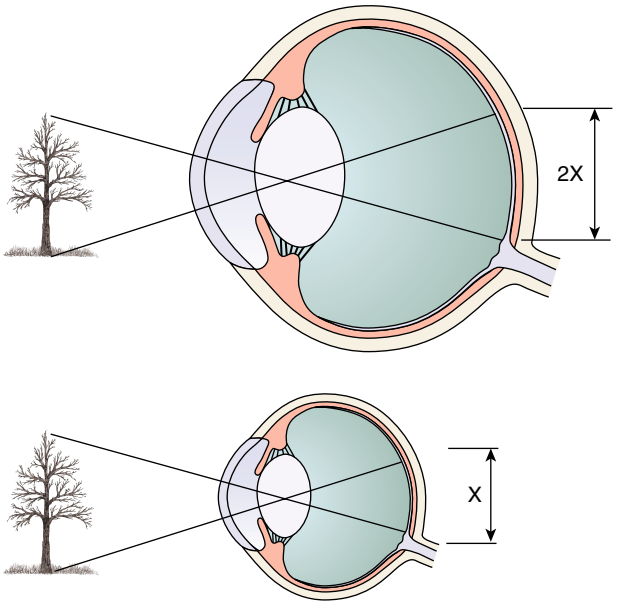


Figure 5.23 The effect of globe size on the image projected on the retina. The larger globe (top) has a longer posterior focal distance (between the lens and the retina), resulting in a larger retinal image. This results in higher visual resolution for this eye, as the image can be sampled and processed by more photoreceptors and ganglion cells than the bottom image.

Conversely, the architecture of the central retina has evolved to provide high visual acuity. It is characterized by a high density of cones and RGCs, by a low photoreceptor-to-RGC ratio, and by RGCs with small dendritic trees. In primates and some avian species, the evolution of this arrangement has culminated in the formation of an anatomic pit called the *fovea*. The central fovea contains no rods, and cones are tightly packed in a regular arrangement for maximal density (Levi, 2011). Each of these cones outputs, through a single midget bipolar cell, to a single midget RGC (Provis et al., 2013). This pathway ensures maximal resolution, as there is no convergence or summation of the cone output, and each cell projects its signal directly to the brain, providing pinpoint localization of the visual stimulus. The high density of photoreceptors, particularly the cones, and their associated bipolar and RGCs in the central retina, compared with peripheral retina, explains why the central canine retina is thicker than the retinal periphery (Ofri & Ekesten, 2020).

Though a fovea-like bouquet of cones has recently been described in dogs (Beltran et al., 2014), in other (nonprimate) mammals central vision is subserved by an *area centralis*, rather than a fovea. The principles of area centralis architecture are similar to those of the fovea: it is the retinal region containing the highest concentration of cones and associated RGCs, with small dendritic trees and minimal convergence. However, in the area centralis these principles are not as refined as they are in the fovea. Thus, even though it contains the highest concentration of cones, the area centralis is not rod free, and the presence of rods results in a lower cone density than in the fovea. Furthermore, the area centralis does not have the midget circuitry that characterizes the fovea, resulting, once again, in cellular packaging that is not as dense as in the fovea. In the cat, for example, midget RGCs are replaced by β-RGCs; though their dendritic tree is smaller than that of other feline RGCs, it is larger than the dendritic trees of the primate foveal midget RGCs (Stein et al., 1996). Just as importantly, even in the area centralis the output of several feline cones converges on a single β-RGC (Cohen & Sterling, 1992). The result is summation of cone output in the cat's area centralis, compared to the "private line" that conveys the output of each primate foveal cone to the brain.

Obviously, differences in cone-to-rod ratios and variations in RGC types are not limited to regional retinal variations in eccentricity. Such differences are also found between species, depending on their environment (diurnal vs. nocturnal), life style (herbivorous vs. carnivorous), and other evolutionary factors (see Chapter 4, Table 4.6). For example, barn owls are unique in that they have a fovea that is rod dominant, to facilitate scotopic hunting by this nocturnal raptor (Harmening & Wagner, 2011). On the other hand, other avian species, including diurnal raptors and passerines, have evolved bifoveate retinas, containing both a shallow temporal and a deeper nasal/central fovea (Coimbra et al., 2015; Inzunza & Bravo, 1993; Fig. 5.24), contributing to their high visual acuity (see Table 5.2). In diurnal raptors, the nasal/central fovea (which has a higher acuity) is used to identify distant objects during flight, while the temporal one is used to fixate on nearby prey (González-Martín-Moro et al., 2017).

In general, after controlling for eye size and phylogeny, visual acuity in mammals is associated with diurnality, even in closely related species (Veilleux & Kirk, 2014). For example, megabat species that roost outdoors and have a carnivorous diet possess a pronounced visual streak (analogous to the area centralis) of high RGC density, whereas cave-dwelling megabat species with a herbivorous diet have a less pronounced streak with lower RGC concentration. Consequently, the visual resolution of the former is twice as high as that of the latter (Coimbra et al., 2017).

Another feature of retinal anatomy that affects visual acuity is the presence of a tapetum lucidum, though its effect is negative (Fig. 5.25). Light striking the tapetum is reflected back onto the retina at various angles, resulting in light scatter and diminished acuity (Ofri, 2018a; Schwab et al., 2002). Since in most species the tapetum underlies the area centralis, this scatter occurs in a region where it would have the most detrimental effect on the animal's visual acuity. This may be why elephants have a heterogenous structure of a tapetum lucidum, with its least dense and least reflective area located behind the horizontal visual streak (Pettigrew

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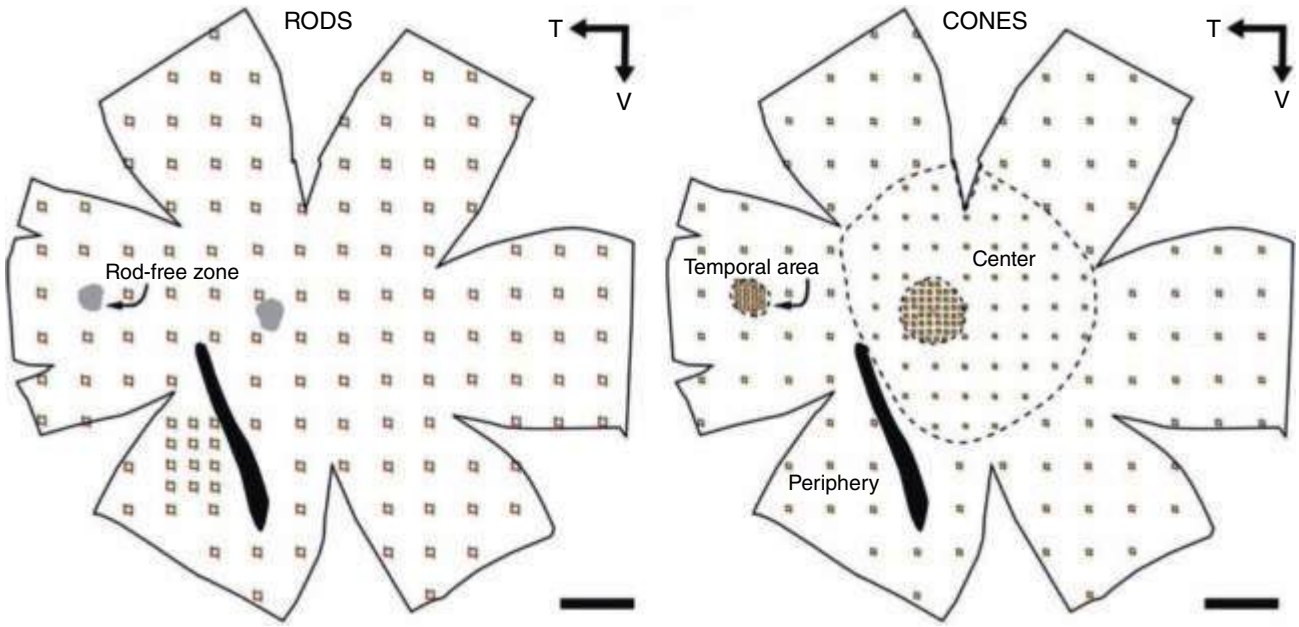


Figure 5.24 Stereologic sampling scheme used to map the topographic distribution of rods and cones in the retinal wholemounts of passerines. **A**. Rod density. The gray shaded areas mark the location of the rod-free zones in this representative retina. **B**. Cone density. The two rod-free areas in panel A are actually a central and a temporal fovea. The thick, dark diagonal line represents the pecten. T, temporal; V, ventral. Scale bars = 1 mm. (Modified with permission from Coimbra, J.P., Collin, S.P., & Hart, N.S. (2015) Variations in retinal photoreceptor topography and the organization of the rod-free zone reflect behavioral diversity in Australian passerines. *Journal of Comparative Neurology*, **523**, 1073–1094.)

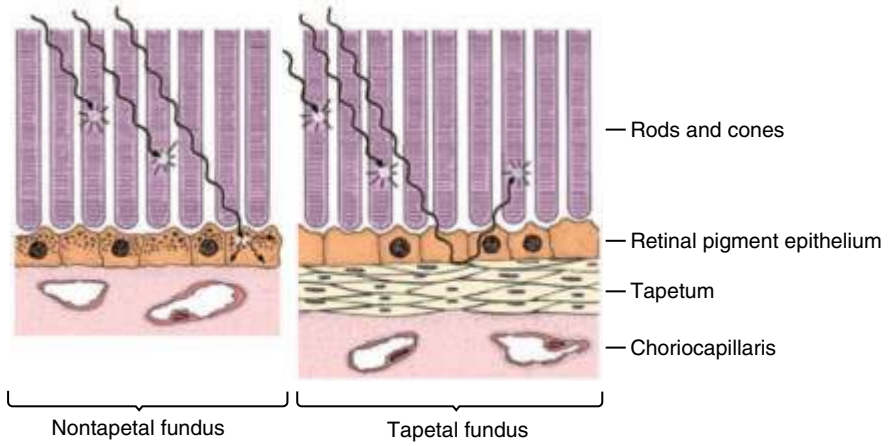


Figure 5.25 Light scatter by the tapetum. The left side of this figure represents a nontapetal section of the fundus, the right half a tapetal region. On both sides of the figure, three incoming photons are shown. Two are absorbed by the photoreceptors and contribute to visual sensation, and the third passes through the retina without being absorbed. In the nontapetal fundus (left), this photon's energy dissipates in the pigment epithelium and does not contribute to visual sensation. By comparison, in the tapetal fundus (right), this third photon is reflected back onto the photoreceptors, where it is absorbed and contributes to vision, thereby enhancing scotopic sensitivity. However, note that in this region the photon is eventually absorbed by a photoreceptor that is not in its original trajectory, and therefore the resulting image is blurred. Consequently, tapetalized eyes have low visual acuity but great scotopic sensitivity. (Reproduced with permission from Maggs, D.J., Miller, P.E., & Ofri, R., eds. (2018) *Slatter's Fundamentals of Veterinary Ophthalmology*, 6th ed. St. Louis, MO: Elsevier.)

et al., 2010). Such an anatomic arrangement would minimize the negative effect that the tapetum has on the elephant's visual acuity.

Of course, features that are a disadvantage in daytime, when the photopic cone system is active, become advantageous in dim light, when the scotopic rod system takes over (see "Scotopic and Photopic Vision"). Cats have low visual resolution because of a large pupil (and the consequent spherical aberrations) and a reflective tapetum, combined with an afoveate retina characterized by a low concentration

of cones, converging cone output, and RGCs with large dendritic trees. Because of these anatomic constraints, the low acuity values of cats can never be improved by visual aids such as glasses or LASIK surgery, contrary to suggestions by the public. After all, the feline visual resolution is poor even though the cat eye is close to emmetropia (Konrade et al., 2012). However, what cats lack in cone function they gain in rod function. The same factors – a large pupil, a reflective tapetum, and photoreceptor pathways that converge on RGCs with large dendritic trees – afford cats superior scotopic vision. Furthermore, the maximal rod concentration in cats and humans is 460,000/mm^2 and 160,000/mm^2, respectively (see Chapter 4, Table 4.6). Therefore, though their view of the world may not be as colored or as detailed as ours, cats continue to see at night, while humans are left groping in the dark (see Fig. 5.5)!

The Visual Cortex and Visual Acuity

Just like the central retina, the architecture of the visual cortex devoted to the central visual field has also evolved to enable high-resolution vision. However, there is a fundamental difference in the anatomic features that have evolved to process high-resolution vision in the retina and cortex. In the retina, each degree of the visual field is projected onto a similar-size retinal area, regardless of whether it is peripheral or central. The increased visual resolution of the central retina is obtained by increasing the density of the cones and their associated RGCs, as described in Chapter 4. In the cortex, on the other hand, the density of neurons serving the peripheral and central visual fields is identical. The increased detail with which visual input from the fovea or area centralis is analyzed by the cortex is not a result of thicker neuronal layers and increased cell density, as in the retina. Rather, this increased cortical visual discrimination is a result of the increased cortical area devoted to representing the fovea or area centralis. In other words, because of the importance of the visual input from the area centralis or fovea, large cortical areas are devoted to processing the signals originating from these regions.

The larger area devoted to processing information from the central retina results in magnification of its cortical representation. *Magnification factor* is a term coined by Daniel and Whitteridge (1961) to quantify the disproportionate amount of cortical area devoted to processing the high-resolution vision of the central visual field. In the cat, for example, the surface area of the visual cortex is 380 mm^2, 50% of which is devoted to the central 20° of the visual field (Tusa et al., 1978). Consequently, half the visual cortex is devoted to the central 20° of the feline retina, and half of it is devoted to the rest of the visual field (Fig. 5.26). In humans, the disproportionate cortical representation of the central visual field is even more striking. The fovea occupies only 0.01% of

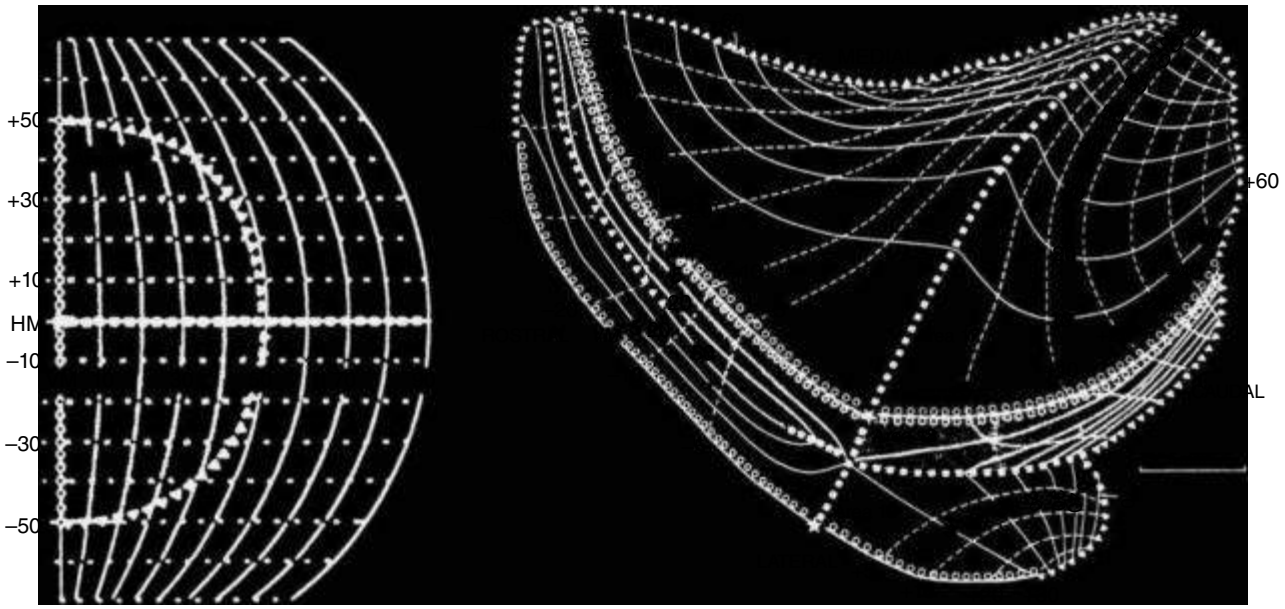


Figure 5.26 The projection of the visual field on the cat cortex. **A.** Perimeter chart showing the extent of the visual hemifield. Azimuths and elevations are illustrated by solid and dashed lines, respectively. **B.** Visual hemifield projection in areas 17 (V I), 18 (V II), and 19 of the unfolded cat cortex. Note the disproportionate large amount of cortical area devoted to processing the central 5° of the visual field, at the expense of the small areas devoted to processing input from the peripheral visual field. (Reproduced with permission from Tusa, R.J., Rosenquist, A.C., & Palmer, L.A. (1979) Retinotopic organization of areas 18 and 19 in the cat. *Journal of Comparative Neurology*, **185**, 657–678.)

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the human retina, yet its representation takes up 8% of the visual cortex (Azzopardi & Cowey, 1993). Furthermore, in primates the density of neurons in this cortical area is 2.5× greater than in nonprimates, reflecting the high acuity of the fovea that it serves (Srinivasan et al., 2015). The increased cortical "machinery" devoted to processing the output of the area centralis and fovea is another reason for the significant difference between central and peripheral acuity, and contributes a critical element to the actual perception of high-resolution vision.

Stimulus-Dependent Factors Affecting Visual Acuity

The two most important stimulus parameters affecting visual acuity are its luminance and contrast (Fig. 5.27). Visual acuity is high in photopic conditions, when the cone system is active, and decreases in scotopic conditions, when the rod system is active. In dogs, for example, behavioral studies have shown that it decreases from an average of 20/70 in the former to 20/225 in the latter. Even in the barn owl, a nocturnal raptor highly adapted to night vision, acuity decreases by 75% when transitioning from photopic to scotopic conditions (Orlowski et al., 2012). This is because of the functional and anatomic differences between the cone and rod systems (high density of cones in the fovea or area centralis, the synaptic connection of one cone to one midget bipolar cell and one midget RGC, versus the convergence and low photoreceptor and RGC density of the rod pathway).

Likewise, a high degree of stimulus contrast is required for high acuity. On a sunny day, humans can easily see dark power lines at a distance, as they sharply contrast with the blue sky, but the same lines would not be easily seen if they were blue. As with luminance, acuity decreases with log contrast (Legge et al., 1987). In harbor seals, for example, behavioral testing demonstrated a linear decrease of acuity with increased water turbidity, potentially affecting the animals' foraging ability (Weiffen et al., 2006). However, as noted earlier, contrast and luminance sensitivities are not only dictated by retinal anatomy and physiology; the visual cortex also contributes to these functions, as it has functional contrast- and luminance-modulating units (Dai & Wang, 2012).

The texture of the stimulus (De Weerd et al., 1992; Wilkinson, 1995) – that is, the density and size of its constitutive elements – and its shape are also important in determining visual perception (Fig. 5.28). For example, horses are better than chimpanzees at perceiving shapes with diagonal lines, but are worse at perceiving shapes with right angles (Tomonaga et al., 2015). Similarly, young kittens react

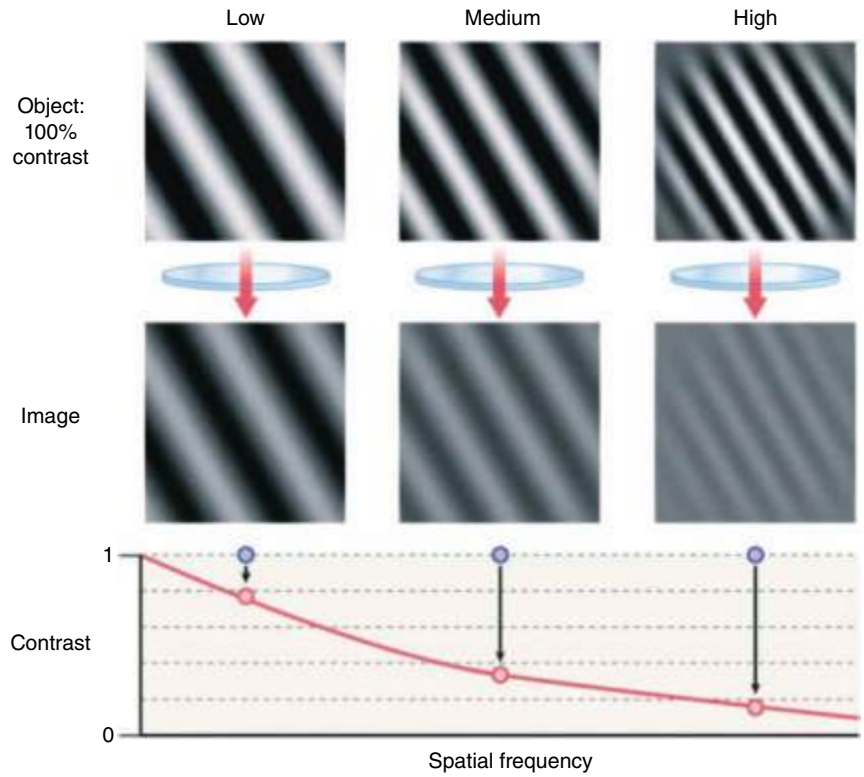


Figure 5.27 Visual acuity increases with contrast. With high contrast (top row), high visual resolution is possible (top right image). With lower contrast (middle row), the object on the right can barely be seen, and only low visual resolution is possible (middle row, left image). The linear relationship is shown in the bottom graph. (Reproduced with permission from Levin, L.A., Nilsson, S.F.E., ver Hoeve, J., et al., eds. (2011) *Adler's Physiology of the Eye*, 11th ed. St. Louis, MO: Saunders Elsevier.)



Figure 5.28 Visual texture allows the viewer to differentiate an object from its surroundings. In this image, a barn owl can be distinguished from the surrounding vegetation based on differences in the texture of the feathers, which are more homogenous and smooth than the tree trunk on the left.

strongly to horizontal lines, but not to dots (Wilkinson, 1995). Additional stimulus parameters influencing visual acuity include stimulus duration (acuity declines for brief stimuli because of insufficient retinal exposure) and stimulus movement (movement faster than the tracking response will also result in insufficient retinal exposure).

Other factors also become important when conducting behavioral tests to determine visual discrimination in animals. For example, in horses, visual discrimination is enhanced when the target is at ground level and poorer when it is at a height of 70 cm, or about 2 ft (Hall et al., 2003). In addition, the examiner should recall that most nonprimates have minimal accommodative ability, and therefore test objects should not be placed too close to the animal (Clark & Clark, 2013). For example, since horses can accommodate by only 1 D, they will fail a behavioral test if the target is closer than 1 m.

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Section II

Foundations of Clinical Ophthalmology

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6

Ocular Immunology

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Organisms have multiple mechanisms that allow successful interactions with the environment and maintenance of health. Complex, interactive biochemical pathways allow repair from mechanical damage and are critical in prevention and repair of damage by infectious organisms. These pathways are numerous with overlapping functions. The biochemical pathways critical to initiate repair of a surgical wound are also involved in the initiation of an immune response. The body has the same goal whether damaged by trauma, metabolic changes, or by an infectious disease: repair of damaged tissue and return of function.

The immune response is not a single pathway down which the body travels when trying to evade disease from a pathogen. The immune response is an accumulation of various pathways, with different evolutionary origins that influence one another. Many of these variable immune responses are elicited each time a pathogen is present. However, dependent on the molecular makeup of the pathogen, the immunogenetics of the individual, and the presence or absence of other ongoing immune processes, certain immune pathways will predominate each time an animal encounters a pathogen. Which pathways predominate ultimately determines how well the pathogen is eliminated as well as the clinical outcome of the disease.

Unlike other organs where a certain degree of regeneration is possible, and where partial damage can be accommodated and still preserve organ function, the eye has a limited tolerance for tissue damage before significant loss of function occurs. Consequently, much of ocular therapy is aimed at preventing, resolving, minimizing, and controlling unwanted inflammation and immune reactions in ocular tissues.

Architecture of an Immune Response

Initiation of Inflammation

Clinically and conceptually, it is helpful to discuss immune responses separate from inflammation. In reality, inflammation, the innate immune responses, and the antigen-specific immune response are simply a continuum of the same process. Immune responses are dependent on inflammation. Even wound healing and tissue repair are integrally related to inflammation and the chemical events that occur when tissue is damaged. But it is easier to discuss the goals of clinical therapy, and the timing of therapy, by addressing each stage as an individual process.

Inflammation is the key to an immune response. Inflammation is characterized by several acute changes in a tissue. Vasodilation of the capillaries with increased vascular permeability leading to tissue edema, swelling, redness, as well as the triggering of pain receptors and potentially other nerve stimuli such as a pruritic response are signs seen most frequently.

On a cellular level, inflammation is characterized by the release of molecules that cause vasodilation and increased local capillary permeability, expression of adhesion molecules on vascular endothelium that binds circulating leukocytes, and the release of chemoattractant factors that encourages the migration of leukocytes into the tissue. In addition, the initial cascade of released molecules by local cells stimulates resident immune cells, especially tissue macrophages, to alter their behavior. These cells begin to sample the environment more aggressively (phagocytizing molecules and organelles or pathogens), increase their expression of surface molecules critical to initiation of antigen-specific immune responses, and increase their migration to local

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lymph nodes and other primary immune organs where they can expose other immune cells to the molecules they have processed.

It is important to keep in mind that the immune system does not recognize infectious organisms or damaged tissue, it recognizes molecules: specifically, molecules that are not normally present in healthy tissue.

Molecules in the tissue microenvironment that trigger this initial inflammatory cascade of events can be grouped into endogenous and exogenous molecules. Endogenous molecules are from local tissue cells. Whether from surgery or other mechanical trauma, damage from a pathogen, or metabolic related changes, damaged cells release a variety of molecules that are recognized by surrounding cells as a sign of injury. These molecules, such as heat shock proteins and nucleic acid fragments, are critical to the body being able to recognize that damage has occurred.

Exogenous molecules are also recognized by host tissue cells, especially tissue macrophages and immune cells. These exogenous molecules are often molecules common to many infectious organisms and as such provide a broad spectrum detection system for the presence of potential pathogens.

To detect the presence of pathogenic organisms or damaged cells, tissue macrophages and other immune cells, as well as some resident epithelial cells, rely predominately on receptors on their surface known collectively as pattern recognition receptors (PRRs). These surface molecules bind to molecules found in a variety of bacteria and fungi as well as other infectious organisms. These PRRs are not antigen specific as is the adaptive immune response. However, by binding to molecules shared by many bacteria and fungi, these receptors allow tissue immune cells to constantly sample the microenvironment looking for potential pathogens.

The common molecules recognized by the PRRs are often termed pathogen-associated molecular patterns (PAMPs). Common molecules in the PAMP group that are recognized by PRRs include endotoxins, flagellin, gram-positive bacterial peptidoglycans, fungal zymosan, and nucleic acid chains found mostly in virus-infected cells or bacteria such as double stranded RNA or CpG motifs (Table 6.1). Because some of these molecules are not unique to pathogenic organisms but potentially are present in many microbes, the term MAMPs (microbial-associated molecular patterns) has been suggested as a better name for these common microbe molecular segments.

In addition, damaged-associated molecular pattern molecules (DAMPs) also bind specific receptors found on the surface of adjacent cells and local immune cells. This way tissue damaged from mechanical trauma, surgery, or metabolic changes such as ischemia (or elevated intraocular pressure) can also trigger the innate inflammatory reaction which is part of the same process responsible for healing and recovery of damaged tissue.

This is an important consideration when histopathologically evaluating damaged ocular tissue. The presence of inflammatory cells is normal whenever tissue responds to damage. These inflammatory cells may not necessarily be contributing to the pathogenesis of the disease, but simply responding to the damaged tissue.

There are several groups of PRRs that are expressed on or in different cell types in various tissues. These include Toll-like receptors, C-type lectin receptors that are predominately found on the cell surface, retinoic acid-inducible gene I like receptors, nucleotide-binding oligomerization domain-like receptors, and AIM2-like receptors which are found predominately inside of cells. Toll-like receptors are some of the best studied of the PRRs and recognize a variety of diverse pathogen and host molecules (Table 6.1).

Binding of these PRRs by immune cells leads to intracellular signals that usually involve the nuclear factor-κβ (NF-κβ), myeloid differentiation factor 88 (MyD88), activator protein-1 (AP-1), and mitogen-activated protein kinase. Activation of these intracellular signal pathways lead to the release of proinflammatory cytokines by the local immune cells, again mostly local macrophages. The release of these proinflammatory cytokines such as interleukin (IL)-1β, TNF-α, and IL-6, are what lead to the cascade of events that lead to typical inflammation. Vasodilation, vascular permeability, tissue edema, the release of chemoattractant molecules that recruit neutrophils, macrophages, and natural killer cells in circulation and from nearby tissue, the stimulation of pain receptors, the activation of fibroblasts and other cells required for the clean up and repair of damaged tissue, and the continued activation of tissue macrophages to become potent antigen-presenting cells (APCs) are all dependent on the initial binding to PRRs on local immune cells that leads to a long cascade of chemical events.

The result is that the presence of conserved molecules found in many bacteria, fungi, viruses, and damaged tissue activate local immune cells and to some degree other resident cells to start the innate immune response and tissue repair processes. This initial, non-antigen specific, broad spectrum response to a variety of common pathogen-associated molecules is the basis of the innate immune response and the main first line of defense against infectious diseases. This initial response is also key to the development of the adaptive or antigen-specific response. Suppressing inflammation and the innate immune response also suppresses the development of antigen-specific responses.

A pathogen's resistance to clearance by the host or even resistance to medical therapy can be related to the ability of PRRs to recognize molecules from the pathogen. For example, Toll-like receptor 13 (TLR-13) in mice recognizes a conserved sequence of RNA from the bacterial 23S ribosome. Macrolide antibiotics such as erythromycin work by binding to the same area of RNA on the 23S ribosome. *Staphylococcus aureus* strains resistant to erythromycin have an altered

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Table 6.1 Toll-like receptor (TLR) ligands.

TLR receptor	Ligand that the receptor binds	Source of the ligand
TLR-1	Triacyl lipoproteins	Mycobacterium and other bacteria
TLR-2	Peptidoglycans	Gram-positive bacterial cell wall
	Lipoproteins	Bacteria
	Zymosan, glucuronoxylomannan	Fungal cell walls
	Intracellular parasite molecules	Trypanosoma
	Hemagglutinin protein	Measles virus
	Undetermined molecules	Herpes simplex virus 1, cytomegaly virus
TLR-3	dsRNA	Viruses
TLR-4	LPS	Bacteria
	Mannan	Fungi
	Glycoinositolphospholipids	Trypanosoma
	Viral envelope proteins	Respiratory syncytial virus
	Heat shock proteins and fibrinogen	Damaged host cells
TLR-5	Flagellin	Bacteria
TLR-6	Diacyl lipoproteins	Mycoplasma
	Lipoteichoic acid	Bacterial (group B streptococcus)
	Zymosan	Fungi
TLR-7	ssRNA	Viruses
TLR-8	ssRNA	Viruses and bacteria
TLR-9	CpG-DNA	Bacteria
	DNA	Viruses
	Hemozoin	Plasmodium
TLR-11	Profilin-like molecule	Toxoplasma
TLR-13	Ribosomal RNA	Bacteria

Source: Adapted in part from Akira, et al. 2006; Kawasaki and Kawai 2014.

RNA sequence on the 23S ribosomes. This altered RNA sequence also no longer binds to the TLR-13 receptor, and as a result, the presence of the 23S ribosomal RNA from *Staphylococcus aureus* strains resistant to erythromycin no longer causes inflammation and does not trigger an appropriate innate immune response (Oldenburg, et al., 2012).

Unfortunately, the immune system is capable of recognizing exogenous molecules from non-pathogenic sources. Allergic reactions are often inflammatory responses to molecules associated with nonpathogenic, nonthreatening organisms such as plants. But binding of these molecules, such as various pollens, to the proinflammatory receptors on cells leads to an inflammatory response, an innate immune response, and eventually an antigen-specific response, similar to the response to a pathogen. The immune system does not recognize organisms, it only recognizes molecules.

Inflammation is self-limiting. For example, surgical-based tissue damage is a one-time event. Once the damaged cells and their molecules have been cleaned up, there are no longer molecules in the tissue driving ongoing inflammation. This has important clinical relevance. If no exogenous molecules that stimulate inflammation and innate immune responses (such as bacterial endotoxins and lipopolysaccharides) are introduced into the tissue, and no antigen-driven immune response develops to self-molecules (lens proteins or melanin), then the inflammation associated with a relatively atraumatic procedure such as lens extraction should easily resolve in 7–10 days, even without therapy. When inflammation after ocular surgery persists, the current knowledge of immune responses suggests that either exogenous pro-inflammatory molecules are present (in the form of a live pathogen, molecules from a pathogen, or foreign material capable of stimulating inflammation) or an autoimmune reaction is developing. These factors could play a role in the persistent inflammation observed in some patients after lens extraction. These same inflammatory reactions are critical in wound healing and excessive capsular opacification after lens extraction is simply a form of wound healing.

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The Innate Immune Response

The innate or non-antigen-specific immune response represents the first line of defense against many pathogens. It includes both the persistent presence of antimicrobial agents on organs exposed to the environment, such as the ocular surface, as well as the release of antimicrobial agents and recruitment of cellular effector cells whenever pathogens are detected or tissue damage occurs.

Antimicrobial peptides present in the tear film, including lysozyme, alpha lysin, lactoferrin, ceruloplasmin, and transferrin, are part of the innate immune response. Several other families of antimicrobial peptides are released by damaged cells or by innate immune cells when pathogens are detected. The antimicrobial peptide family is large, and their activity in the innate immune response as well as the antigen-specific immune response is diverse (Kropf et al., 2003).

Acute inflammation is a vital step in activation of local innate immune cells such as macrophages and natural killer (NK) cells and initiates the innate immune response. The same vascular and tissue changes that result in edema and hyperemia also lead to the expression of vascular adhesion molecules and the release of chemoattractant chemokines. The vasodilation and slowing of blood flow through inflamed tissue, the increased vascular permeability, and the expression of specific adhesion molecules lead to the migration of leukocytes from the blood into the damaged tissue.

These innate immune system effector cells, both the ones normally present in tissue and those that migrate into the inflamed tissue, release chemicals to kill potential pathogens (Table 6.2). These cells also have increased phagocytic activity and help clean up damaged tissue as well as destroy pathogens. But these defense reactions are not specific and can generate significant damage to surrounding host tissue.

A good example is a bacterially infected corneal ulcer. Although some of the collagen loss is caused by enzymes released by the bacteria, enzymes released by the invading innate immunity effector cells contribute significantly to the loss of corneal tissue. It is this response that can ultimately lead to greater fibrosis as well as synechiae and other tissue changes that can decrease ocular function.

Provided there is ongoing activation of local cells through the recognition of PAMPs and DAMPs, these local tissue cells will continue to release cytokines that activate and recruit the innate immune response effector cells. At the same time, APCs are sampling and processing all the molecules from the area of inflammation and migrating to regional lymph organs to present these molecules and trigger the antigen-specific or adaptive immune response.

The Adaptive or Antigen-Specific Immune Response

The recognition of conserved molecules commonly found in many pathogens as well as molecules released by damaged host cells is key to the initiation of inflammation and the innate or non-antigen-specific immune response. The adaptive or antigen-specific immune response, however, uses different receptors. Macrophages, dendritic cells, and other potential APCs are constantly phagocytizing and processing molecules from their environment, both extracellular and intracellular molecules. These cells combine small molecular fragments from the molecules they phagocytize, combine them with major histocompatibility complex (MHC) proteins, and express the MHC-antigen molecule on their surface. APCs and their expressed MHC–Ag complexes then travel to regional lymphoid tissues (lymph nodes or the

Table 6.2 Mechanisms of pathogen elimination by innate immune responses.

Complement activation	Activated immune cells ... complement factors capable of disrupting membrane permeability of the pathogen leading to pathogen death
Phagocytosis	The main mechanism for killing of bacterial and other smaller pathogens. Phagocytized pathogens are fused with lysosomes
	Lysosyme and acid hydrolases disrupt pathogen cell membrane
	Oxygen derived compounds (superoxide, hypochlorite, hydrogen peroxide, nitric oxide) as part of a respiratory burst to kill pathogens in lysosome
	β defensins that disrupt pathogen cell membranes
Exocytosis	Release of lysosome products (listed above) from white blood cells into the extracellular space when pathogens are too large to be phagocytized
Interferon α and interferon β	Released by epithelial cells, some connective tissue cells and resident macrophages, and migrating mononuclear cells in response to viral DNA or viral infection. Activates ssRNA nucleases and shuts down host cell protein synthesis, both often required for viral replication, in both infected cells and neighboring cells
Natural killer (NK) cells	Activated by interferons released by virally infected cells. NK cells induce apoptosis of infected cells, often targeting cells with low levels of MHC class expression. This occurs on virally infected cells and tumor cells

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spleen) to present their found pieces of molecules to T helper (Th) cells. The APCs are essentially picking up molecules from all over the host and asking the Th cells, does this look like evidence that we have a problem? The vast majority of the time, the sampled molecules are normal host molecules.

T Helper Subsets

Lymphocytes can be considered the management team or executives of the antigen-specific immune response. Based on the type of antigen receptor they express, lymphocytes are divided into three types: T cells, B cells, and NK cells. T cells can express either the alpha-beta T-cell receptor (TCR) or the gamma-delta TCR complex. T cells expressing the alpha-beta TCR can further be divided into the CD4 expressing MHC II restricted cells (their TCR binds to antigen bound to MHC II molecules on an APC) or CD8 expressing MHC I restricted cells.

The development of most immune responses is dependent upon activation and expansion of CD4+ T cells by activated APCs in lymphoid tissue. Because of their critical role in the development of the immune response and because they often determine the type of immune response based on molecules they express and release, these cells are referred to as Th cells.

Activation of Th cells often results in further differentiation of the cell into various Th subsets. These subsets are categorized based on the types of cytokines they release, expression of certain cell surface molecules, and ultimately the types of antigen-specific immune responses they promote. The understanding of these subsets is far from clear, and there is some plasticity among the subsets where differentiation may not always be in one direction. However, altering Th cell differentiation by pushing Th cells to preferentially develop into one subset versus another can greatly influence the development and severity of clinical disease created by both infectious agents as well as experimental autoimmune disorders. Consequently, manipulation of Th cell differentiation in patients could represent a vital therapeutic pathway, especially for autoimmune disorders. The immune system has several safeguards in place that help make it more likely the antigen-specific immune response recognizes molecules from pathogens and less likely it generates an unwanted autoimmune response.

The main mechanism of preventing unwanted immune responses is the requirement for two steps in the initiation of an adaptive immune response. The first step is stable binding of the MHC-Ag complex on the APC to the TCR complex on the surface of the Th cell. The repertoire of available MHC molecules possessed by APCs and the repertoire of TCR molecules limits what molecules can potentially be recognized as antigens. Individuals within a species will have slightly different MHC and TCR genes. From an evolutionary standpoint, this is critical for survival of a species. If all individuals had the same immunogenetic make up and the same MHC and TCR molecules, a single pathogen whose molecules were poorly recognized by this MHC and TCR repertoire could result in extinction of the species. Likewise, the development of debilitating autoimmune disease in all members of a species could lead to extinction. The genetic basis for susceptibility to autoimmune disorders (atopy in many breeds, chronic superficial keratitis in German Shepherds, nodular granulomatous episcleritis complex in spaniels, uveodermatologic syndrome [UDS] in Akitas, etc.) or how efficient a host is at clearing specific pathogens (the poor ability of German Shepherds to clear systemic fungal diseases or certain Rickettsial diseases) is in part because of the repertoire of MHC and TCR molecules commonly found in individuals of that breed.

T cells are further vetted to eliminate the ones capable of recognizing self-antigens through a maturation process involving mostly the thymus and also other organs such as the gastrointestinal tract. Although beneficial in preventing unwanted autoimmune reactions, limiting the molecules T cells recognize could potentially increase the odds that an individual will not adequately recognize a pathogen. Therefore, not surprisingly, this selection process does not completely eliminate T cells capable of recognizing self-molecules. Most individuals still have T cells that express TCR molecules capable of recognizing self-molecules.

The second step in activation of Th cells in the initiation of an adaptive immune response is the requirement of coactivation factors. Simple binding of MHC–antigen combinations on the surface of an APC to the TCR complex on the surface of a Th cell will not activate a Th cell and will not trigger an immune response. Simultaneous binding of coactivation molecules expressed on the APC, and/or the presence of coactivation cytokines in the local environment, is required to activate a Th cell that recognizes an antigen presented by an APC. Not only are coactivation molecules required, but also which coactivation molecules are expressed is key in determining the type of immune response that is generated.

This is where inflammation is critical. It has long been understood that local tissue inflammation at the site of the target antigen is required to generate an antigen-specific immune response. The addition of adjuvant to vaccines often serves the purpose of generating the required inflammation. Not surprisingly, many adjuvants were originally derived from bacteria because several molecules commonly found in bacteria cell walls are potent initiators of tissue inflammation. Suppression of inflammation is a successful method to limit the development of an antigen-specific immune response. The various cytokines and chemokines released when inflammation occurs are required to activate APCs so that they express surfaced-based coactivation factors, as well as release soluble activation factors. This activation is required if the presentation of Ag to Th cells to the regional lymphoid tissue is to result in activation of an antigen-specific immune response.

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Furthermore, the make-up of the cytokines released is one of the most influential steps in the afferent arm of the immune response. Which immune response pathway will predominate is greatly dependent on the cytokines present both when the APC encounters the antigen, as well as what cytokines are present and what cell surface molecules are being expressed, when the APC encounters a T cell capable of binding to its MHC–Ag complex.

Taking into account the required steps in activation of an immune response, there are several factors that ultimately determine the type of immune response that develops.

Immunogenetics. As mentioned previously, the immunogenetics of the individual determines both what antigens are recognized and what type of immune response will predominate. In addition to determining the repertoire of MHC and TCR molecules, as well as immunoglobulin, preferential expression of certain cytokines in response to inflammation is influenced by the patient's genetics. Veterinary ophthalmology is an excellent study in immunogenetics given the strong breed predisposition to certain immune-based ocular disorders such as chronic superficial keratitis (German Shepherds, sighthounds, Dachshunds), scleritis/episcleritis syndromes (spaniels and Maltese breeds), idiopathic chorioretinitis (retrievers), optic neuritis (small brachycephalic breeds), UDS (Akitas and Arctic circle breeds), and several others.

Tissue where the immune response initiates. Local tissues play a strong role in shaping the immune response. The eye is perhaps the best example because the altered immune response to antigens in the eye, termed anterior chamber-associated immune deviation (ACAID), is strikingly different than the more typical immune response generated with subcutaneous antigen exposure. But many other organs, namely the blood, the gastrointestinal tract, and the renal capsule, are also capable of altering the immune response. Many characteristics of these tissues alter the immune response, both the initiation of the response as well as the effector mechanisms. The release of cytokines by local tissue cells often alters the types of coactivation molecules expressed by resident APC which ultimately influence the type of immune response. In addition, receptors critical for initiation of inflammation and activation of innate immune responses are differentially expressed in different tissues. Binding to these innate immune receptors is often the first step in generating an immune response, and different receptors trigger the release of different cytokines and therefore direct the immune response down different pathways.

Nature of the antigen. This can influence not only the antigenic scope of the immune response, in other words what antigens and crossreacting antigens the immune response will recognize, but will also greatly influence the type of immune response. Different molecules from even the same pathogen can elicit different types of inflammation and immune responses (Reiner & Locksley, 1995). The type of receptor on innate immune cells that the antigens bind to can direct the immune response. They also influence the immune response by which MHC molecules and TCR molecules are capable of recognizing the antigen. Certain MHC and TCR combinations are preferentially associated with the activation of different immune responses.

Other immune reactions. Other immune reactions, mainly widespread systemic reactions, alter the level of cytokines present throughout the body but especially at the local microenvironment of the lymphoid tissue where most immune activation occurs. The presence of a certain pattern of cytokines from other immune responses can influence the type of immune response triggered by an antigen and pathogen (Erb et al., 1998; Hansen et al., 2000; KuoLee et al., 2008; Rodríguez et al., 2003; Sayers et al., 2004). A good example is that stimulation of an ocular surface allergic reaction prior to transplantation significantly decreases the survival of allogenic corneas by altering the normal immune privilege response afforded the cornea (Belvin & Anderson, 1996).

Ramping Up the Antigen-Specific Immune Response

Once APC expressing MHC-Ag complexes and appropriate cofactors on their surface activate a Th cell capable of recognizing the antigen, the antigen-specific immune response has officially begun. The activated Th cells replicate to expand the pool of cells cable of recognizing the antigen. This occurs in the local lymph nodes and/or spleen. In addition, these Th cells release cytokines and express surface molecules that lead to activation of effector T cells (CD8+ cytotoxic cells, NK cells), regulatory T cells responsible for controlling and shutting down the immune response, and the activation of B cells expressing antibody that are also capable of binding to presented antigens.

The expanded pool of activated antigen-specific T cells and B cells enter the circulation from the local lymph nodes and spleen. These activated lymphocytes express surface molecules that bind to endothelial cells expressing adhesion molecules which occur in areas of inflammation. Effector cell migration is not specific, meaning these cells will migrate into almost any area that has inflammation. However, only inflamed areas that contain the antigen capable of binding to the T-cell receptor of surface antibody on these activated lymphocytes will stimulate further replication and activation of the cells.

Once in the target tissue and further activated by binding of the TCR or surface antibody to the specific antigen, these activated lymphocytes employ a large array of effector mechanisms. Effector mechanisms vary in the level of inflammation generated. Some effector mechanisms such as neutralizing antibodies or cytotoxic T cells can prevent pathogen spread and kill infected or abnormal cells with almost

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no tissue inflammation. Pathogen clearance using non-complement binding antibodies or cytotoxic lymphocytes results in damage only to the pathogen or infected cell, with minimal damage to adjacent cells and minimal tissue inflammation. By contrast, complement binding antibodies and delayed type hypersensitivity (DTH) reactions eliminate pathogens by upregulating the innate immune response in areas where the antigen is found. Upregulating the innate immune response entails activation of neutrophils and macrophages in the area. The mechanisms that neutrophils and macrophages use to kill pathogens or infected cells are less specific than noncomplement binding antibodies or cytotoxic lymphocytes and result in more tissue inflammation and greater potential for damage of adjacent healthy cells.

In ocular tissue, the downside of inflammation-based immune responses is the potential for bystander tissue damage and loss of visual acuity caused by fibrosis and opacification of the visual axis. Effector mechanisms that do not generate significant tissue inflammation are therefore preferred in the eye. The wide array of effector mechanisms employed by the antigen-specific immune response, as well as the development of immune tolerance or suppression to certain antigens, often develop simultaneously. A pathogen rarely leads to only one or two types of effector immune responses. However, each effector mechanism is not equally expressed and within a specific host, a handful of effector mechanisms will predominate the immune response to a particular pathogen or antigen. The predominate type of immune response, or more appropriately, the ratio of the different effector immune mechanisms that are generated, determines the efficiency of an immune response in clearing a pathogen. Furthermore, the predominating immune effector mechanisms determine the amount of unwanted tissue damage or loss of organ function that occurs during the process of clearing a pathogen.

Shutting Down an Immune Response

Termination of an immune response, both innate and antigen specific, is dependent upon two mechanisms. Immune cells do not remain active perpetually and eventually either become quiescent or go through cell death. Persistence of an immune reaction is therefore dependent upon continued proliferation and activation of immune cells. Because this process is driven by the immune system recognizing either specific antigens or at least PAMP/DAMP and other stimulatory conserved molecules, elimination of the pathogen, and therefore elimination of the antigens and PAMPs associated with the pathogen, leads to shutting down of an immune response. Unfortunately, this is also why autoimmune disorders are so difficult to control because the antigen is continually being produced by some poor host cell.

The second mechanism for shutting down an immune response is the generation of specific regulatory cells that suppress the immune response. These cells work through a variety of pathways, often involving the release of cytokines at local sites of tissue inflammation that essentially deactivate activated immune cells or lead to apoptosis or death of activated immune cells. The successful use of certain immunosuppressive medications in autoimmune disorders and organ transplantation is in part because of their ability to promote the development of antigen-specific suppressor cells (Sewgobind et al., 2008).

Manipulating the Immune Response

There are several potential ways to alter the immune response.

Limit tissue trauma. Because local tissue macrophages and other resident cells release inflammatory mediators when molecules from damaged local cells bind to PRRs, minimizing surgical-based tissue damage directly decreases the magnitude of inflammation and any immune response.

Avoid introduction of PAMPs. Even sterile procedures can introduce inflammatory molecules into tissue. Introduction of nanomolar amounts of endotoxins or other potent PAMPs can result in inflammation that persists for weeks to months. Bacterial cell products in particular are ubiquitous in the environment. Using gloves to handle all instruments for cleaning and packaging, making sure to use water free of endotoxins or other proinflammatory contaminants, and using sterilization techniques that do not introduce additional molecules to instruments can all contribute to less inflammation associated with surgical procedures.

Minimize autoantigen generation. It has been speculated that one cause of persistent inflammation after surgery on the lens is the release of lens proteins by persistent lens epithelial cells. Directly inhibiting the production and release of lens proteins through medical therapy or surgical technique could lead to less postoperative inflammation.

Blocking the formation of proinflammatory molecules. Blocking molecules directly involved in inflammation is by far the most common approach to controlling inflammation and therefore immune responses. Arachidonic acid metabolites such as prostaglandins and leukotrienes, as well as histamines, garner the most clinical attention because of both their importance in inflammation and also the fact that these pathways have the greatest therapeutic options (corticosteroids, NSAIDs, antihistamines). Blocking the release or effect of molecules directly responsible for inflammation is the quickest way to suppress inflammation. Perhaps the greatest future potential for inhibiting tissue inflammation is to target the molecular pathways used by innate immune receptors such as Toll-like receptors (TLRs). This would block the inflammatory cascade higher up the pathway. Manipulation of second messenger pathways used by PRR involved in inflammation is emerging. Jannus kinase inhibitors such as oclacitinib (Apoquel, Zoetis Inc., NJ, USA) are

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already in use in veterinary medicine. New therapies to block the MyD88 pathway, which is critical to the function of several PRRs and the initiation of inflammation, are in development.

Blocking molecules important for immune cell activation. Another strategy is to block the function or release of molecules required to stimulate immune cells. These methods are not blocking the inflammatory component of the immune system but more the antigen-specific immune response. These techniques are therefore more targeted. Calcineurin inhibitors such as cyclosporin and tacrolimus are the most commonly used medications in this class.

Monoclonal antibodies that inhibit certain cytokines are widely used for autoimmune diseases in humans. Inhibition of tumor necrosis factor-alpha (TNF-α) function, a critical molecule in both inflammation and immune activation, is successfully used in humans with autoimmune disorders including autoimmune skin disease, gastrointestinal disease, and uveitis. Humanized monoclonal antibodies that block TNF-α function or contain a fusion protein consisting of the TNF-α receptor, are given by injection on a monthly basis. Biologic response modifiers targeting other key cytokines in immune responses are also used in humans. These include monoclonal antibodies against the IL-2 receptor, the IL-1 receptor, and lymphocyte surface protein CD-52, as well as cellular adhesion molecules (Yeh et al., 2008).

Monoclonal antibody therapy in dogs that blocks IL-31 is now available for treating atopic dermatitis (Cytopoint, Zoetis Inc., NJ, USA). IL-31 is responsible for triggering the pruritic response in neurons in areas with allergic reactions. Blocking IL-31 has almost no effect on the immune response or allergic inflammation but by eliminating pruritus, greatly decreases the morbidity of the disease.

Antimetabolite and antimitotic therapy. Immune cells require a high level of cell proliferation to maintain an active immune response. One of the least targeted but still effective mechanisms to inhibit immune reactions is to inhibit cell proliferation. Alkylating agents, nucleotide analogs, and other antimetabolite, antimitotic drugs limit immune cell function and proliferation. These drugs, such as azathioprine, chlorambucil, cyclophosphamide, and others are the original immunosuppressive therapies that have been used for decades. Although beneficial, they simply target active or dividing cells and because of their nonspecificity, have numerous side effects.

The ultimate goal of better understanding the molecular pathways involved in inflammation and immune responses, is the ability to clinically target much more specific aspects of the immune response. Not only for the suppression of inflammation, but more importantly to direct the immune response down a beneficial, nondestructive path. The ability to generate tolerance to a self-antigen would be much more beneficial than simply global immunosuppression which is the current therapy for immune-mediated diseases. Furthermore, pushing the immune response of a patient away from a nonbeneficial destructive immune response, such as a predominate non-neutralizing antibody response in cats with systemic coronavirus infections, and toward a more effective immune response capable of clearing the pathogen, such as better cytotoxic lymphocyte (CTL) responses to coronavirus, could greatly limit the morbidity of infectious disease.

Ocular Immune Responses

The eye follows the same basic protocol for an immune response. However, the eye is a unique organ and therefore has unique immune requirements. The eye is a high pathogen and antigen exposure organ like the gastrointestinal and respiratory tracts. Yet it also represents a neurologic tissue with limited regenerative capabilities and is not tolerant of significant inflammation or fibrosis. Like the gastrointestinal tract and respiratory system, it has a secretory function to help minimize pathogen exposure and decrease pathogen entrance, and it also strongly modulates immune reactions that are initiated in ocular tissues.

To protect the sensitive ocular structures, the ocular surface mucosal immune system must have a robust specific immune response to invading organisms. However, an overzealous inflammatory response to an antigen would likely result in overt damage to the eye and possible blindness. Therefore, the ocular surface immunity is a combination of the innate immune and adaptive immune systems designed to prevent microbial invasion while minimizing damage to delicate ocular tissue. The innate immune system uses a variety of methods to minimize microorganism invasion, including mechanical tissue barriers and production of antimicrobial peptides (e.g., tear lysozyme). The adaptive immune system functions through the fine-tuned eye-associated lymphoid tissue that uses both effector lymphocytes that migrate to the lacrimal gland and diffuse conjunctival lymphoid tissue to express secretory IgA. Tolerance of normal ocular flora is achieved by the presence of a minimal number of professional APCs, immunosuppressive substances in tears (e.g., TGF-β), and the strategic intra- and intercellular location of the TLRs (i.e., away from the apical surface of the epithelial cells). Autoimmune diseases are common on the ocular surface, and with contributions of environmental and genetic factors, autoantigens are presented to the adaptive immune response usually during upregulation of cytokines and costimulatory molecules during chronic infectious disease processes. TLRs are the link between the innate and adaptive immune response and are likely key components of the response of ocular tissue to

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infectious organisms and in the initiation and perpetuation of autoimmune disease.

Components of Ocular Surface Innate Immunology

Epithelium and Mucins

The physical action of eyelid closure and tear washout is the first barrier to ocular microorganism invasion. The ocular surface is also lined with nonkeratinized stratified epithelial cells, whose superficial layers are in contact with microorganisms (i.e., the ocular flora). The epithelium itself acts as a barrier to invasion of microorganisms because of the presence of epithelial intercellular tight junctions and by the rapid renewal of epithelial cells with frequent shedding of superficial layers of potentially invaded epithelium (Hodges & Dartt 2013).

Mucins on the ocular surface serve several physiologic roles in the maintenance of ocular health. Transmembrane mucins anchor the ocular tear film to the external corneal epithelium, and thus act as a transition between the hydrophobic epithelium and the aqueous tear film. Mucins also prevent bacterial colonization and help eliminate surface foreign material (Guzman-Aranguez & Argueso, 2010; Hodges & Dartt, 2013). There are several types of mucins, and they commonly include the MUC1, 2, 3, 4, and 5, MUC5AC, and MUC5B mucins (Jumblatt et al., 1999; Umeda et al., 2010). Two secreted and two membrane-bound mucins have been detected in the canine conjunctiva (Hicks et al., 1997). Mucin production and secretion by goblet cells are stimulated by cytokines, such as IL-6 and γ-IFN, from dendritic cells in inflamed conjunctiva (Berry & Radburn-Smith, 2005). O-glycosylated serine and threonine residues in mucin contribute to maintaining their highly extended and rigid structure and contribute to the protection of corneal and conjunctival epithelia by preventing bacterial adhesion through interactions with galectin-3, promoting boundary lubrication, and maintaining the epithelial barrier function (Ablamowicz & Nichols, 2016; Guzman-Aranguez & Argueso, 2010). Abnormalities in mucin-type O-glycosylation have been identified in many disorders where the stability of the ocular surface is compromised (Guzman-Aranguez & Argueso, 2010; Guzman-Aranguez et al., 2009) and has shown to be altered and/or depleted in canine keratoconjunctivitis sicca (KCS) (Hicks et al., 1998). Restoration of conjunctival goblet cell mucin production has been demonstrated after topical cyclosporine treatment of dogs with KCS (Moore, 1990).

Antimicrobial Peptides

To assist in the prevention of invasion of microorganisms, epithelial cells of the conjunctiva, lacrimal sac, and nasolacrimal surface constitutively produce several small molecular weight cationic peptides with a wide range of activity against viruses, bacteria, fungi, and parasites (Gilger, 2008; Mohammed et al., 2017). These peptides include lysozyme, lactoferrin, lipocalin, angiogenin, and secretory phospholipase A2. Lysozyme peptides function by binding to the outer membrane of the bacteria, inserting full thickness through cell membranes, and ultimately creating a pore that leads to cell death. Lactoferrin binds reversibly with iron, which is required for microbial metabolism and growth. Lipocalin (tear-specific prealbumin) scavenges bacterial products, and angiogenin has general antimicrobial effects (Knop & Knop, 2007). Inducible APCs, that is, those that become active during inflammation or infection, may be produced by resident neutrophils (alpha defensins 1-3) or by epithelium (beta defensin 2). The production of these APCs are induced by IL-1β, TNF-α, and gram-negative bacteria LPS, and the mechanism is likely through the TLR complex. Induced APCs also alert the adaptive immune system of a potential infection by T lymphocyte chemoattraction induced by alpha and beta defensins. In dogs with KCS, a disruption of the normal pattern of conjunctival goblet cells was seen with preservation of the pattern of lectin binding observed in normal animals (Corfield et al., 2005; Davidson et al., 1994).

Ocular Surface Adaptive Immunology

In systemic immunity, mucosal lymphocytes form a common mucosal immune system called the mucosal-associated lymphoid tissue (MALT). The lacrimal gland, conjunctiva-associated lymphatic tissue (CALT), and the lacrimal drainage-associated lymphatic tissue (LDALT) also form a functional mucosal immunologic group, a component of MALT, called the eye-associated lymphoid tissue (EALT) (Knop & Knop, 2005a; Steven & Gebert, 2009). MALT is divided into two forms, an organized lymphoid tissue where lymphocytes are in follicles, and an extensive diffuse lymphoid tissue. In lymphoid follicles (i.e., organized lymphoid tissue), antigen is taken up from the environment by overlying follicle-associated epithelium (FAE) (via conjunctival M cells) and presented to naive lymphocytes by APCs. The conjunctival M cell is a morphologically and functionally distinct epithelial cell found in the FAE above organized lymphoid tissue of the conjunctiva (Knop & Knop, 2005b). This antigen uptake by the FAE leads to lymphocyte activation, proliferation, and eventual differentiation into effector cells, that is, B or T cells. These activated lymphocytes leave the follicle and migrate to afferent lymphatic vessels, regional lymph nodes, bloodstream, and eventually to effector organs: the lacrimal gland and conjunctiva (Knop & Knop, 2005b; Fig. 6.1).

The effector cells of mucosal immunity are composed of the diffuse form of lymphatic tissue that is interspersed along most mucous membranes and their associated glands (including the lacrimal gland and conjunctiva) (Gilger, 2008). These consist of intraepithelial lymphocytes and plasma cells. Lymphocytes are located in the basal epithelial layer and lamina propria of the conjunctiva and lacrimal

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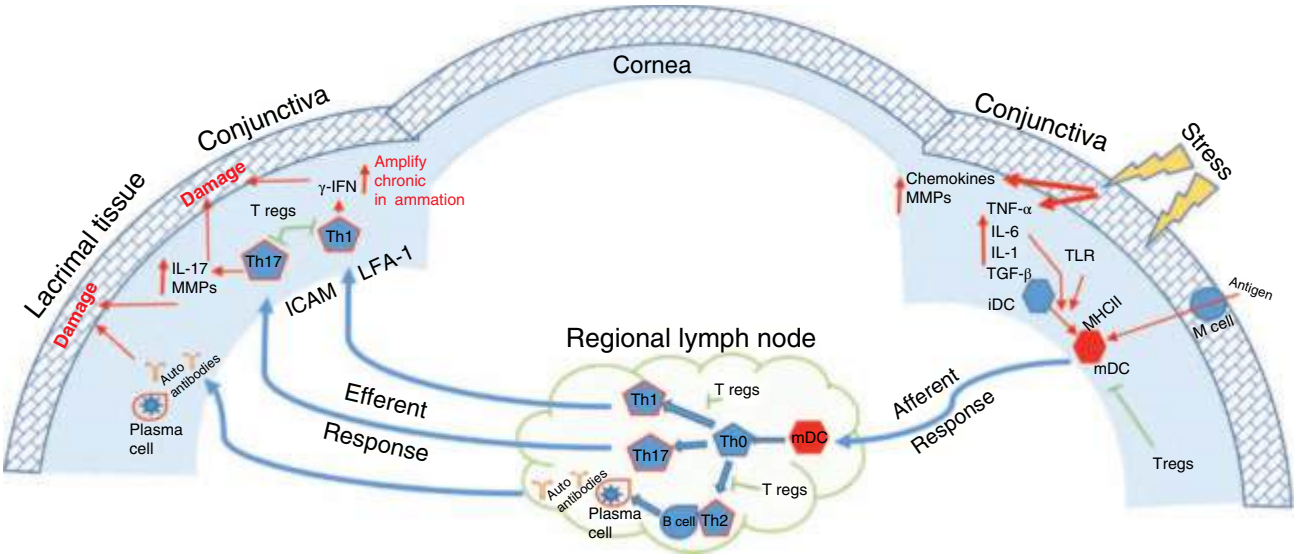


Figure 6.1 Ocular surface adaptive immune response. Antigen presentation through the conjunctival M cell or recognition of autoantigens during stress-induced chronic inflammation, induces an upregulation of proinflammatory cytokines (e.g., TNF-α, IL-6, IL-1, TGF-β) that allows immature dendritic cells (iDC) to convert to mature DC (mDC) and thus uptake environmental antigens (via conjunctival M cells) or autoantigens. The activated mDC present the antigens to naïve T cell (Th0) which differentiate into Th1, Th2, Th17, depending on the type of antigen presented. The activated T cells and/or autoantibodies travel back to the conjunctival surface and lacrimal gland to cause tissue damage. ICAM, intercellular adhesion molecule; LFA-1, lymphocyte function associated antigen 1; MMP, matrix metalloproteinases; TLR, Toll-like receptor; MHC II, major histocompatibility complex II.

gland and are predominantly CD8+ suppressor/cytotoxic T cells and fewer CD4+ Th cells (Knop & Knop, 2005a, 2005b; Knop & Knop, 2010). The CD8+ cells likely promote an immunosuppressive environment. Plasma cells in mucosal tissues contribute to secretory immunity, one of the main immune effector mechanisms, by production of specific immunoglobulins (e.g., IgA), which pass through the overlying epithelium with the help of secretory component epithelial transporter molecules to form a surface layer of IgA. IgA-secreting plasma cells predominate in the lacrimal gland, and secretory IgA are released into the tear film and ocular surface. The lacrimal gland has a mixture of IgA-positive plasma cells and lymphocytes in the loose connective tissue between the secretory acini. Therefore, both the lacrimal gland and conjunctiva are involved in the local production of secretory IgA (Knop & Knop, 2005b). Also, at effector organs such as the lacrimal gland and conjunctiva, these primed lymphocytes (CD4+) monitor for antigens. When exposed again, clonal expansion of the cells occurs with differentiation into B lymphocytes and plasma cells or T lymphocytes. Therefore, through the EALT functional mucosal immune unit, lymphoid follicles detect antigen and produce effector cells in the lacrimal gland and conjunctiva. Local detection of antigens then provides the ocular tissues with effector cells and the lacrimal gland with specific IgA plasma cells (Knop & Knop, 2005b).

Recent studies have also demonstrated that desiccating stress to the ocular surface, such as seen in KCS, stimulates Th17 cell differentiation by the production of cytokines by corneal and conjunctival epithelia through a dendritic cell-mediated pathway (Stern et al., 2010; Zheng et al., 2010; see Fig. 6.1).

Antigen-Presenting Cells

APCs are classified based on their level of constitutive expression of MHC II antigen. APCs are considered "professional" if they have high expression of MHC II antigen (and costimulatory molecules). Examples of these include dendritic cells, macrophages, B lymphocytes, and epithelial Langerhans cells (Dana, 2005). APCs are considered "nonprofessional" if they have low expression of MHC II antigen and include vascular endothelial cells and mesenchymal cells. Nonprofessional APCs may be induced to express MHC II antigen with inflammatory stimuli. APCs, including dendritic cells and macrophages, capture antigens then migrate via draining lymph nodes to prime naïve T lymphocytes (Dana, 2005).

The central cornea is mostly devoid of professional APCs (specifically dendritic cells and Langerhans cells), which may contribute to the immune privileged (immunologic nonresponsive) nature of the cornea (see later). However, with inflammatory processes (e.g., infectious keratitis), APCs are recruited from the limbus to the cornea. This recruitment of APCs is preceded by infiltration of neutrophils and macrophages, overexpression of ICAM-1, and subsequent release of cytokines such as IL-1 and TNF-α (Dana, 2005). Furthermore, with inflammation, there is an upregulation in the expression of MHC II and costimulatory molecules

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(i.e., CD80 and CD86) by resident corneal mesenchymal and endothelial cells. Rejection of corneal transplants is mediated mainly by corneal dendritic cells that travel to the regional lymph nodes to initiate the immune reaction (Knop & Knop, 2007).

Mucosal Tolerance, Ignorance, and Privilege

As mentioned above, the cornea is considered an "immune privileged site" (Knop & Knop, 2007). There are multiple active and passive mechanisms that contribute to this phenomenon, including the lack of corneal vasculature and lymphatics, reduced MHC II positive APCs, and reduced corneal expression of MHC I (Cursiefen, 2007). Immune privilege is provided by the processes of immune ignorance, immune tolerance, and the development of an immunosuppressive microenvironment (Knop & Knop, 2007). Ignorance is when the presentation of an antigen to the immune system is impeded. This occurs in the cornea, for example, by the strategic intracellular or basal epithelial positioning of TLRs, which respond to microorganisms that have penetrated the surface epithelium and play a major role in the initiation of the immune response (Ueta et al., 2004). Lack of TLRs on the epithelial surface, however, minimizes the presentation of antigens to APCs and immune recognition of surface antigens, and thus allows ignorance (Ueta et al., 2004). Mucosal tolerance, although not well described in the ocular mucosa, is the active induction of immune unresponsiveness of the systemic immunity to antigens (e.g., normal ocular flora) present on mucosal surfaces. A similar phenomenon, called the anterior chamber associated immune deviation (discussed later), is known to protect the anterior chamber from antigenic stimulation and uncontrolled inflammatory response. The ocular surface immunosuppressive microenvironment likely occurs because of the presence of substances such as TGF-β, surface-bound Fas ligand, vasoactive intestinal peptide, alpha melanocyte-stimulating hormone, lipocalin, and/or angiogenin (Knop & Knop, 2007). Ocular surface secretory IgA, which is constitutively deposited on the ocular surface and present in the tear film, also contributes to the immune privilege of the ocular surface because it prevents invasion of microorganisms (Knop & Knop, 2007).

If tolerance or ignorance is impaired because of damage to the surface epithelium or decrease in production of IgA, inflammatory cytokines are produced, and uncontrolled access to antigens by the immune system can result.

Toll-like Receptors and Ocular Surface Immunity

TLRs are part of the body's innate immune system and constitute the first line of defense against many pathogens, including bacteria, fungi, viruses, protozoa, and helminths (Chaudhuri et al., 2005). As described in the innate immune section previously, PAMPs from different classes of pathogens stimulate different TLRs and induce distinct patterns of cytokines appropriate for that specific pathogen (see Table 6.1; Fig. 6.2). Thus, TLRs function to both trigger and modulate the activation of the adaptive immune response (Chang et al., 2004). TLRs have been identified in the human eye, and the uvea, retina, choroid, and conjunctiva have been shown to constitutively express TLR-4 (Chang et al., 2004). Equine-specific TLRs 2 and 4 mRNA sequences have been reported (Figueiredo et al., 2009; Kwon et al., 2010) and TLRs 2, 3, 4, 6, and 9 have been shown to be expressed in a variety of equine ocular tissues (Gornik et al., 2011).

TLRs are likely to play a pivotal role in the ocular surface immune response, especially in the interplay between the innate and adaptive immune response and in the immunologic tolerance of ocular surface and environmental antigens. In fact, TLR regulation may be a main player in ocular tolerance of surface antigens. In a recent study, it was found that human corneal epithelial cells expressed TLRs 2 and 4 intracellularly, but not at the cell surface, suggesting that this placement of TLR in the normal cells helps to create an "immunosilent condition" to prevent unnecessary inflammatory response to normal bacterial flora (Ueta et al., 2004). Another study found that the expression of TLR-5 is located at the basal and wing cell layers of human corneal epithelium, but not at the apical layers, again suggesting a potential mechanism by which the corneal epithelium may remain inactive (i.e., ignorant) in response to nonpathogenic bacteria at the apical surface (Zhang et al., 2003). However, if the outer epithelial layers are breached and the wing and basal layers are exposed, an organism would then trigger a TLR-mediated innate immune response (Zhang et al., 2003). In fact, activation of TLR-4 was shown to be a critical step in the pathogenesis of endotoxin (LPS)-induced keratitis in mice (Khatri et al., 2002). However, excessive TLR activation in response to pathogens, which may occur in some viral infections (e.g., Epstein-Barr virus, human T-lymphotrophic virus), provide an innate link to activation of autoreactive lymphocytes and subsequent autoimmune surface disease (Stern et al., 2010).

Anterior Chamber-Associated Immune Deviation

It has been known for over 100 years that tissues and antigens introduced via the anterior chamber of the eye result in an unusual immune response (Van Dooremaal, 1873). Medawar termed the anterior chamber an immune privilege site because tissue normally rejected by the immune system in other locations would survive for extended periods of time in the eye (Medawar, 1948). In addition to the eye, several locations in the body demonstrate a level of immune privilege where allogenic tissue enjoys prolonged survival and an altered immune response. But the extent of immune privilege afforded by the eye is unique.

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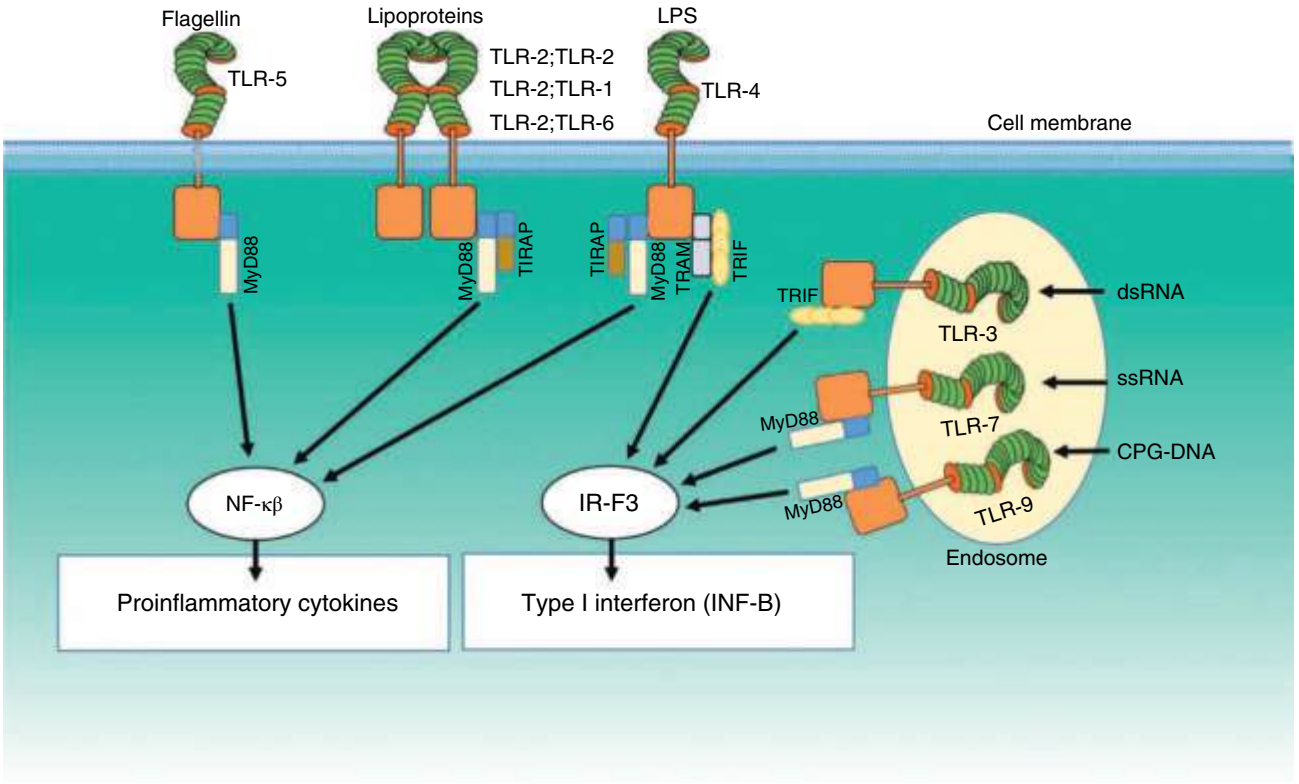


Figure 6.2 Toll-like receptor (TLR) signaling. TLR ligands and signaling. TLR receptors recognize different microbial components: TLR-4 recognizes lipopolysaccharide (LPS); TLR-2 recognizes lipoproteins together with TLR-1 or TLR-6; TLR-5 recognizes flagellin, a major component of flagella; TLR-3 recognizes double-stranded RNA (dsRNA); TLR-7 recognizes single-stranded RNA (ssRNA) and TLR-9 recognizes viral and bacterial DNA (CpG DNA). The signaling pathways of TLRs are mediated by adaptor molecules, MyD88, TRIF, TIRAP and TRAM. Nucleic acid-recognizing TLRs (TLR-3, TLR-7, TLR-9) are present in the endosome. IR-F3, interferon regulatory factor 3; INF-B, interferon beta; NF-κβ, nuclear factor-κβ;

The immune response to tissue and antigens introduced via the anterior chamber is robust and not absent. However, compared with introduction of the antigen via other routes such as subcutaneous injection, the response to intraocular antigens is characterized by the selective absence of certain effector mechanisms and by the enhanced generation of tolerance to the antigen. This form of immune privilege is termed ACAID (Streilein & Niederkorn, 1981).

Characteristics of Anterior Chamber-Associated Immune Deviation

The generation of an immune response to tissues introduced into the anterior chamber is characterized by minimal DTH reactions and minimal production of complement binding antibody isotypes. CTL generation is intact and noncomplement antibody isotypes are produced. Both delayed-type hypersensitivity reactions and complement-fixing antibodies can result in significant damage of host tissue during clearance of a pathogen. Although both mechanisms are antigen specific and antigen driven, they employ the release of inflammatory and cytotoxic molecules into the local tissue in the presence of the target antigen. Both mechanisms can be thought of as antigen-driven upregulation of an innate effector mechanism. These effector processes can unfortunately also be cytotoxic for neighboring uninfected cells and produce prolonged inflammation. Inflammation is a driving force for fibrosis and for both loss of ocular clarity as well as other unwanted developments such as vitreal membranes and cataracts.

ACAID is not a lack of an immune response; it is an immune response that is directed toward specific effector mechanisms. T lymphocytes, B cells, and antibodies specific for the antigen introduced via the eye can be found throughout the body, and the immune response is robust.

The ACAID response is systemic, and the alteration of the immune response is not limited to the eye. Tissue transplanted into the anterior chamber or cornea enjoys prolonged survival without immune rejection. Likewise, the same tissue subsequently transplanted to the skin also enjoys prolonged survival. Several adoptive transfer studies in mice have shown that cells critical to the initiation of the immune response (the afferent arm) as well as cells responsible for the altered effector mechanisms (efferent arm) are generated and present outside ocular tissue (Ferguson & Kaplan, 1987;

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Stein-Streilein & Streilein, 2002; Streilein et al., 1997; Waldrep & Kaplan, 1983; Wilbanks et al., 1991).

Induction of this privileged or atypical immune response is not limited to the anterior chamber. Introduction of antigens or tissue into the central cornea, vitreal cavity, and subretinal space also generates an ACAID-like immune response (Streilein et al., 2002; Stein-Streilein & Streilein, 2002; Zamiri et al., 2007).

The presumed purpose of the eye having a unique immune response is preservation of function. In most organs, damage of adjacent tissue during clearance of a pathogen does not result in long-term loss of function because of either the size of the organ, the ability of the organ to regenerate, or the ability of the organ to function despite the presence of significant fibrosis. But this is not the case with ocular tissue. Limited regeneration and the loss of function associated with ocular fibrosis and opacification results in much greater morbidity when effector mechanisms involving greater tissue inflammation are employed to eliminate a pathogen.

The lack of robust DTH reactions and minimal complement-fixing antibody generation potentially increases the eye's susceptibility to certain infectious agents. However, ACAID is not absolute. Several chronic inflammatory conditions of the eye are caused by immune reactions normally suppressed in ACAID. Persistent inflammation mediated in part through TLR-2 signaling and γ-IFN expression, a pathway often suppressed in ACAID, occurs in animal models of *Onchocerca volvulus* keratitis (Gentil & Pearlman, 2009). Similarly, TLR-2 receptor binding plays a role in the persistent DTH reaction and inflammation that generates corneal fibrosis and loss of vision in animal models of herpetic keratitis (Kurt-Jones et al., 2004; Sarangi et al., 2007). Consequently, the normal ACAID-generating immune activation pathways can be circumvented, leading to a more traditional immune response. Autoimmune disorders such as chronic superficial keratitis of German Shepherds or eosinophilic keratitis in cats and horses likely represent immune reactions that have circumvented the normal pathways of immune activation in the eye, leading to chronic inflammation.

Molecular and Physiologic Basis of Anterior Chamber-Associated Immune Deviation

Several soluble factors, membrane-bound molecules, and anatomical properties of the eye are vital for generation of the immune privilege response. In addition, several organs participate in ACAID development. It is known that removal of the eye, the spleen, or the thymus within 3 days of intraocular antigen injections or chemical sympathectomy within 4 days prevents ACAID development and results in a traditional immune response (Niederkorn & Streilein, 1982; Streilein & Niederkorn, 1981; Wang et al., 1997).

Limited Lymphatic Drainage and Tight Vascular Junctions

It is clear that antigens introduced into the eye are not sequestered or hidden from the immune system because of the blood ocular barriers. However, these barriers do appear important and may decrease peripheral APC migration early in an immune response and therefore increase the likelihood that antigens are processed by APCs native to the eye. Resident APCs within ocular tissues have been influenced or conditioned by soluble factors released in the eye. These APCs express specific coactivation factors that lead to the generation of ACAID-inducing Th responses when these conditioned APCs present their antigen to CD4+ T cells in regional lymphoid tissue. The presence of preexisting inflammation or other changes that alter the blood ocular barriers or the level of vascularization (particularly in the cornea) allow greater migration of blood-based APCs which may not have been conditioned by ocular media and will promote a more traditional immune response when they present antigen to Th cells.

In addition, there is a paucity of lymphatics draining intraocular tissues. Whereas some antigens or cells introduced into the eye do make it to regional lymph nodes (Camelo et al., 2006), the majority of immune cells leave the eye via the blood. This makes the spleen the first major lymphoid organ encountered by most APCs leaving the eye. Indeed, removal of the spleen prior to introducing antigens of allogenic tissue into the eye prevents the generation of ACAID and the privileged immune response.

Limited MHC I expression might also help ocular tissue avoid immune damage. MHC I is expressed on almost all nucleated cells in the body. Cytotoxic T cells target and kill infected cells by recognizing antigen bound to MHC I on the infected cells. NK cells kill cells that do not express MHC I as a mechanism to eliminate unhealthy (such as infected) cells or tumor cells. The corneal endothelium and most retinal cells do not express typical MHC I molecules recognized by CTLs. This decreases the potential for cytotoxic T-cell recognition. However, they do express MHC Ib molecules, which can interact with NK cells and prevent NK cell attack (Le Discorde et al., 2003; Niederkorn et al., 1999).

Ocular Tissues Influence Resident Antigen-Presenting Cells

The other crucial aspect of generating the ACAID-afferent immune response is alteration of APC function by factors secreted by ocular tissue. APCs that process antigens from the eye and travel to the thymus and spleen are capable of interacting with T cells in a way that preferentially leads to the generation of antigen-specific T suppressor cells, minimal DTH effector cells, and minimal stimulation of B cells to produce complement-fixing antibody isotopes.

Several soluble factors released by ocular tissues and found in aqueous humor are critical in the conditioning of APC and generation of the eyes' unique immune response (Table 6.3). The presence of TGF-β is perhaps the most

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Table 6.3 Soluble factors contributing to the development of anterior chamber-associated immune deviation.

Transforming growth factor-beta (TGF-β)	Alters antigen-presenting cell (APC) coactivation of T cells, inhibits natural killer (NK) cells
Alpha-melanocyte stimulating hormone (α-MSH)	Inhibits gamma-interferon (γ-IFN) production by T cells, suppresses neutrophil activation, promotes T regulator cell differentiation
Vasoactive intestinal peptide (VIP)	Suppresses T cell activation
Calcitonin gene-related peptide (CGRP)	Inhibits APC, in part by inhibiting γ-IFN or lipopolysaccharide-associated activation
Macrophage migration inhibitory factory (MIF)	Inhibits NK cytotoxicity activity
Complement regulatory proteins (CRPs)	Inhibit antibody-mediated complement lysis

Source: Hori et al. (2010); Niederkorn & Larkin (2010); Stein-Streilein & Streilein (2002).

critical. Incubating APC from non-ocular tissue with aqueous humor or supernatant from cultured uveal cells generates APC capable of generating an ACAID-like immune response. Blocking TGF-β in these cultures prevents the generation of an ACAID-like response. Furthermore, incubation of non-ocular APC with TGF-β allows the APC to generate an ACAID-like response similar to aqueous humor (D'Orazio & Niederkorn, 1998; Hara et al., 1993; Jiang et al., 2009; Streilein, 1997; Streilein & Cousins, 1990; Streilein et al., 1992, 1997; Wilbanks & Streilein, 1992; Wilbanks et al., 1992). These findings all point to TGF-β as one of the critical soluble factors in generation of ACAID.

Another soluble factor important in directing the immune response is alpha melanocyte-stimulating hormone (α-MSH). The α-MSH stimulates the generation of CD4+ CD25− T reg cells that participate in generating systemic antigen-specific tolerance or immune suppression (Delgado et al., 2005; Edling et al., 2011; Namba et al., 2002; Streilein & Cousins, 1990; Streilein et al., 1992).

Ocular Antigen-Presenting Cell Traffic to the Thymus and Spleen

Conditioned APCs leave the eye and travel to the spleen and thymus via the blood. ACAID-type immune response can be adoptively transferred by harvesting these APCs from the blood and injecting them into other individuals (Wilbanks & Streilein, 1991). Despite the presence of antigen in both the spleen and lymph nodes within 24 hours of intraocular injection in mice (Camelo et al., 2006), it takes an amazingly low number of these conditioned APCs to adoptively transfer the ACAID response to mice who have never seen the antigen.

APCs entering the spleen from the eye do not localize in the T cell-rich areas of lymphoid follicles as would normally be expected, but instead are found in the more B cell-rich marginal zones. The eye-conditioned APCs have specific characteristics. APCs processing Ag from the intraocular spaces of the eyes in mice express CD1d (Lin et al., 2005; Sonoda & Stein-Streilein, 2002), an alternative MHC I molecule required for interaction with natural killer T (NKT) cells, but they do not express MHC II. They must also express complement 3b receptor because binding of the complement C3 factor iC3b to the complement receptor on APCs is required to successfully induce ACAID (Sohn et al., 2003).

Conditioned APCs produce IL-10, IL-13, macrophage inflammatory protein-2 (MIP-2), and TGF-β. But the production of IL-12, required for Th1 differentiation, is suppressed during APC activation of CD4+ cells (D'Orazio & Niederkorn, 1998). They express CD-1d on their surface (an MHC I-like molecule that is required for interaction with NKT cells). The release of MIP-2 attracts CD4+ NKT cells which in turn produce RANTES, which further recruits cells to the marginal zone, including B cells, CD4+ Th cells, gd T cells, and CD8+ T cells that ultimately become one of the antigen-specific T suppressor cells critical to ACAID development (Faunce & Stein-Streilein, 2002; Faunce et al., 2001; Nakamura et al., 2003, 2005; Sonoda & Stein-Streilein, 2002; Sonoda et al., 2001, 2002).

Afferent and Efferent T Regulatory Cells Are Produced

The resultant immune response stimulated by the interaction of conditioned APCs carrying antigen from the eye and T cells, B cells, and NKT cells in the marginal zones of lymphoid aggregates in the spleen is the generation of antigen-specific T reg cells (Niederkorn, 2006; Streilein, 2003). Studies have shown that NKT cells from the thymus, and NKT expressing an invariant alpha chain on their TCR (iNKT cells), are in part responsible for suppressor cell development. ACAID cannot be generated in mice that lack functional iNKT cells (Sonoda et al., 1999).

One of the T reg cells that develops in ACAID is represented by a CD4+ T cell capable of altering the activation of other T cells in regional lymphoid tissue and therefore considered an afferent T reg cell (Skelsey et al., 2003). In corneal transplant studies in mice, this T reg cell is a CD4+ CD25+ Foxp3+ T cell which is critical for long term allograft survival (Chauhan et al., 2009; Cunnusamy et al., 2011). The other T reg cell is more of a classic T suppressor cell because it is a CD8+ cell. It inhibits DTH factions against antigens presented within the eye and can even downregulate existing DTH responses. It is therefore altering the efferent arm of the immune response (Stein-Streilein & Streilein, 2002).

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The development of suppressor or regulatory cells is also important in the development of the immune tolerant response of the eye. Antigen-specific CD4− CD8+ T suppressor cells are generated when antigens are processed via the anterior chamber (Stein-Streilein & Streilein, 2002).

Local Factors in the Eye Alter Immune Effector Cell Function

The function of effector cells is also altered by factors released by ocular tissue. TGF-β not only participates in altering APC function and immune initiation, it suppresses activation of T cells, NK cells, and macrophages that traffic to the eye. Activation of effector cells is required for these cells to participate in both antigen driven but also innate immune responses and their participation in upregulating tissue inflammation through the release of cytokines. Likewise, vasoactive intestinal peptide (VIP) and α-MSH directly inhibit DTH reactions and can inhibit the release of inflammatory mediators by macrophages.

Calcitonin gene-related peptide (CGRP) is present in aqueous humor and is required for ACAID. It is found at the nerve synapses in the uveal tract that are in proximity to tissue APCs (Adamek-Kotowicz & Lutjen-Drecoll, 2003). CGRP inhibits the release of several proinflammatory mediators by macrophages. Somatostatin inhibits the release of γ-IFN from T cells and γ-IFN is critical in the activation of other T cells as well as macrophages and is critical for DTH reactions. The ability of NK cells to induce cytolysis is inhibited by macrophage migration inhibitory factor in aqueous humor, and soluble FasL inhibits neutrophil migration and activation. Lastly, the presence of complement regulatory proteins (CRPs) in aqueous humor and ocular tissue inhibits complement activation and cell lysis (Streilein et al., 2002; Wilbanks & Streilein, 1990).

Innervation of the eye also plays a role in ACAID development. Chemical sympathectomy or removal of the superior cervical ganglion inhibits normal ACAID development (Li et al., 2004). Denervation of the central cornea also alters the ability to generate ACAID, further suggesting a role for neural regulation of this unique immune response (Streilein et al., 1996). Part of the reason that endothelial stripping is associated with less immune rejection of endothelial cells than can be found with penetrating keratoplasties could be related to maintenance of normal corneal innervation (Price et al., 2016).

The higher rejection rate of subsequent corneal transplants after failure of the initial transplant is in part related to corneal denervation (Paunicka et al., 2015). Grafting into denervated corneas fails to induce a robust T reg response leading to higher graft rejection. Likewise, corneal denervation inhibits the normal induction of an ACAID response to intraocularly injected antigens. This loss of immune privilege is mediated in part by substance P (SP) because injection of SP into the eye at the time of antigen injection blocks ACAID as well (Mo et al., 2017). The lack of T reg development after corneal transplant or intraocular antigen injection could be caused by the activation of dendritic cells in the eye, cells known to have a receptor for SP that results in activation of the DCs and leads to a robust Th-1 dominated immune response. Here again is an example of how local tissue greatly influences the immune response by altering what costimulatory molecules APCs express when they present antigen to Th cells (Mo et al., 2017).

Immune Responses in Clinical Ocular Disease

A significant number of ophthalmic diseases involve immune reactions in their pathology. Several ocular disorders in domestic animals are accepted as immune mediated and potentially autoimmune and are similar to human disorders. The individual diseases are discussed in other chapters. However, it is worth noting the level of understanding of the immune response in a select few of these disorders.

Keratoconjunctivitis Sicca

KCS is a common disease in dogs and humans. Original studies in dogs suggested a potential immune-mediated basis for the disease based on the immune cell infiltrates in the tear glands of affected dogs and a potential increase in autoantibodies (Kaswan et al., 1983, 1984, 1985). Although the initial evidence was circumstantial, it led to a critical clinical discovery that topical calcineurin inhibitors such as cyclosporin and tacrolimus increase tear production (Berdoulay et al., 2005; Hendrix et al., 2011; Morgan & Abrams, 1991; Olivero et al., 1991; Sansom et al., 1995), but the actual immunopathogenesis of canine KCS is unknown.

There are several mouse models of dry eye disease (DED), the most common of which is a model induced by low humidity and high air flow environments, with or without the additional use of scopolamine (Barabino et al., 2004; Barabino et al., 2005; Daull et al., 2016). The extended environmental stress to the surface of the eye of these mice disrupts the normal ocular immune tolerance and immunohomeostasis (Barabino et al., 2012), as described previously. These mice models have been used to study the immunopathogenesis of dry eye and the initial evaluation of therapeutics. Other induced models of DED in rodents, which may be less immunopathologic in origin, include lacrimal gland excision or injections of toxins or antigens such as botulinum toxin or concanavalin A. Genetic models, such as the MRL/lpr mouse, manifest multiple autoimmune disorders and can be helpful to study diseases such as systemic lupus erythematosus and Sjögren's syndrome. There are numerous knockout and transgenic mice strains that are commonly studied that also may have signs of DED (Schrader et al., 2008). In rats, the most commonly described dry eye model is the extraorbital lacrimal gland excision model (with or without use of scopolamine) (Fujihara et al., 2001; Meng

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et al., 2015). Like other models of induced dry eye, this rat lacrimal-excision model likely does not develop, substantially, an immunologic pathogenesis and therefore may not be as effective for evaluation of immunosuppressive therapies as naturally occurring models of dry eye. All of these rodent models of dry eye are similar in that they can be used to determine proof of principal of therapeutic response to a drug, but all have similar disadvantages of having orbital and lacrimal anatomy and eye size that differs from the human eye. Rabbit or dog models are more commonly used to evaluate dry eye signs and response to therapy because they have easily measured decreased tear production and develop ocular surface changes.

Domestic canines develop spontaneous dry eye that clinically and immunopathologically is similar to dry eye in humans. Not only do dogs spontaneously develop dry eye symptoms of ocular discomfort, conjunctival hyperemia, and corneal scarring, these symptoms correlate directly with reduced aqueous tear production, a reduction readily measured using a standard Schirmer tear test strip. Furthermore, dogs with dry eye have a reduced tear breakup time and increased corneal staining, all abnormalities also observed in humans with DED. The pathogenesis of dry eye in dogs appears similar to that of humans, where an apparent immunologic inflammation occurs with progressive lymphocytic infiltration and damage to the lacrimal gland with subsequent decreased production of the aqueous tear film. With chronicity, the ocular surface becomes progressively more desiccated and inflamed, the cornea vascularizes and scars, and ultimately the dog loses vision. Initial proof of concept of commonly used immunosuppressive eye drops was first demonstrated to be effective in this spontaneous dog model, including topical cyclosporine, tacrolimus, and LTF-1 inhibitors. Decreased aqueous production of the tears results in an increase of tear electrolytes, proteins, and inflammatory mediators, resulting in damage to the surface ocular tissues, decreased visual acuity, and ocular discomfort. The relative decrease in aqueous tears on the ocular surface in patients with DED causes chronic stress to the ocular surface that disrupts the normal ocular immune tolerance. With breakdown of ocular surface tolerance and immune-homeostasis, autoimmunity develops through activation of NK cells and Toll-like receptors, followed by release of proinflammatory factors such as IL-1α, IL-1β, TNF-α, and IL-6. These mediators amplify activating APCs, which internalize autoantigens and migrate to the draining cervical lymph node where autoreactive Th1 cells, Th17 cells, or B cells (i.e., in Sjogren's syndrome) undergo expansion. Efferent trafficking of these autoreactive T cells to the ocular surface is directed by adhesion molecules (e.g., lymphocyte function associated antigen 1 [LFA-1]) and chemokine receptors. Autoreactive T cells in ocular surface tissues potentiate the chronic autoimmune response resulting in epithelial cell apoptosis, reduced goblet cell density, and squamous metaplasia of epithelium (see Fig. 6.1).

Corneal Transplantation

As part of the ACAID response, allogenic corneal grafts enjoy a high rate of acceptance in humans and cats (Bahn et al., 1982). Allogenic corneal transplantation in humans often results in long-term graft survival and clarity without selecting MHC compatible tissue and with minimal immunosuppressive therapy (Hori & Niederkorn, 2007). This enhanced survivability is dependent on several properties of the cornea.

The presence of corneal vascularization has long been shown to decrease allograft survival. Lymph vessels develop concurrently with corneal vascularization, and it is the presence of these lymph vessels that leads to graft rejection (Dietrich et al., 2010). Corneal epithelial cells and keratocytes secrete soluble vascular endothelial growth factor 2 receptor (sVEGF2) which helps prevent lymphangiogenesis in the normal cornea. However, inflammation can overwhelm the ability to inhibit lymphatic development. In models of corneal inflammation, allograft survival is enhanced by intracorneal injection of sVEGF2 complexes that inhibit lymphogenesis (Albuquerque et al., 2009). The lack of lymphatics in the cornea forces APCs processing allogenic antigens from the graft to be influenced by the immune privilege of the anterior chamber versus migrating via lymphatics to a regional lymph node, as they would if the graft was present in the eyelid or other sites with more typical immune processing.

The ability of normal corneal epithelium and, to a lesser degree, stroma to inhibit corneal lymphogenesis may be one reason that allogenic grafts survive longer when covered with host tissue. Transplanting a partial lamellar donor graft (endothelium, Descemet's membrane, and minimal deep corneal stroma) under a flap of the host's anterior cornea stroma and epithelium significantly enhances graft survival (Klebe et al., 2009; Melles et al., 1998).

The importance of ACAID in the survival of corneal grafts is further evidenced by studies that alter or enhance the normal response to intraocular antigens. If the molecular pathways responsible for the normal development of an immune privilege response to allogenic antigens introduced via the anterior chamber are blocked, corneal graft survival significantly decreases. For example, blocking the development of CD1d-reactive NKT cells leads to a lack of detectable T reg cell for allogenic antigens after allogenic corneal grafting and significantly decreases corneal graft survival (Bora et al., 1993; Sonoda et al., 1993, 2002; Yamada et al., 1999). Likewise, generation of an ACAID response by injecting alloantigens into the anterior chamber weeks prior to corneal transplantation enhances allogenic corneal graft survival (Niederkorn & Mellon, 1996; She et al., 1990). T reg cells are known to be critical in both ACAID and the survival of corneal allografts. Interfering with the function of CD25+ T reg cells leads to corneal allograft rejection, although altering of the CD8+

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T reg cells generated in ACAID does not lead to greater allograft rejection (Cunnusamy et al., 2010).

In addition to altering the type of antigen-specific immune response that develops after allogenic corneal transplantation, the cornea is able to blunt effector responses as well. Corneal tissue expresses both the FasL (CD88L) molecule and the programmed death ligand-1 (PD-L1). FasL binds to Fas expressed on leukocytes including neutrophils and T cells and induces apoptosis. This limits the function of these immune cells and subsequently enhances graft survival (Griffith et al., 1995; Stuart et al., 1997; Yamagami et al., 1997). Similarly, PD-L1 binds to PD-1 on T lymphocytes, inhibiting the release of γ-IFN (critical for many steps in the generation of innate and antigen-specific immune responses, especially DTH reactions, and activation of effector cells) as well as inhibiting T cell proliferation and stimulating apoptosis. Not surprisingly, the expression of PD-L1 has been shown to be important in the normal survival of corneal allografts (Hori et al., 2006; Shen et al., 2007). The ability of the cornea to both destroy migrating immune cells and inhibit the local activation of immune cells greatly limits the normal ability of the immune response to recognize and destroy non-self tissue.

Although the exact role of antibodies against allogenic antigens in mediated corneal graft rejection is controversial, the cornea is able to mitigate antibody-directed, complement-mediated tissue damage. CTLs are the primary effector cells which directly attack cells bearing foreign antigen. In addition to the adaptive immune response, NK cells and macrophages of the innate immune response also play a role in corneal graft rejection. Long-term survival of corneal grafts is dependent on the development of CD4+ CD25+ Foxp3+ regulatory T cells that have a high expression of Foxp3 and are effective in suppression of T cell proliferation.

There is a significant need for corneal transplantation in veterinary patients. Although keratoconus, a leading cause of penetrating keratoplasty in humans, is a rare disease in domestic animals, severe corneal fibrosis secondary to previous infectious keratitis and endothelial degeneration are common disorders where corneal transplantation could greatly improve visual acuity. Indeed, the need for deep anterior lamellar keratoplasties, where an opacified stroma is replaced, but the patient's endothelium is left intact, is likely greater in dogs than in humans. But allogenic corneal transplants in dogs and horses are predominately performed to salvage a globe, not to improve visual acuity. Cats are fortunate that they enjoy a high level of penetrating keratoplasty success and clarity, similar to humans (Bahn et al., 1982; Cohen et al., 1990; Melles et al., 1998).

Immunogenetics of veterinary species compared with humans likely plays a role in the reduced clinical success in some species. However, patient selection is a large factor as well. By human standards, veterinary patients undergoing corneal transplantation are often at high risk for rejection. Many veterinary patients receiving grafts have experienced previous corneal ulcers and erosions, which invariably induces some level of corneal lymphangiogenesis and vascularization. In domestic animals, corneal transplantation is often pursued far later in the disease course, when secondary changes such as vascularization are more likely to have occurred. Ironically, transplantation is often pursued later in domestic animals because of the lower success rate, yet earlier transplantation could significantly improve success rates.

Bacterial Keratitis

The same factors, especially a lack of blood vessels, which enhance the survivability of allogenic tissue in the cornea, potentially increase the risk of microbial growth. A healthy cornea, however, rarely develops bacterial infections. The antimicrobial properties of the tear film, the continued clearing of microbes as the tear film turns over, and the physical barrier of healthy corneal epithelial cells provide an excellent barrier to bacterial and fungal keratitis. Patients with reduced or abnormal tear film, or reduced epithelial cell health and adhesion, are consequently at high risk of developing secondary bacterial infections.

In addition, the immunogenetic makeup of the patient greatly influences the clinical outcome of a bacterial infection of the cornea. Therapies for most acute bacterial infections of the cornea appropriately focus on elimination of the bacteria and pain management. Global protease inhibitors to help minimize stromal loss from bacterial or host-derived proteases are also used. However, studies have clearly shown that altering the immune response to the bacterial infection greatly impacts the clinical outcome.

Innate immune responses are the predominate mechanisms for clearing an acute bacterial infection. Certain bacteria, via induction of marked inflammation and an aggressive innate immune response can, however, cause significant damage and loss of clarity when they are allowed to colonize the cornea. A significant amount of the corneal damage, fibrosis, and loss of clarity that occurs with these infections is the direct result of host molecules released as part of the innate immune response. Endotoxins and other molecules released by the multiplying bacteria, as well as molecules released by damaged epithelial cells and keratocytes, stimulate the release of proinflammatory cytokines from local cells. This is mediated in part by TLRs and leads to the release of IL-1, TNF-α, IL-6, as well as many other proinflammatory and chemoattractant factors and upregulation of adhesion molecules (Huang & Hazlett, 2003). The latter are critical in recruiting and allowing leukocytes to migrate to the infected cornea. Infiltrating neutrophils release proteolytic enzymes, oxygen-derived free radicals, and nitric oxide compounds that are not only effective at killing bacteria but also cause collagen necrosis and loss of glycosaminoglycans in the cornea.

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Murine models of *Pseudomonas* keratitis have demonstrated how the immunogenetic background of the animal and therefore the type of immune response determines the outcome. BALB/c mice often are able to clear experimental corneal *Pseudomonas* infections whereas C57Bl/6 mice often have a persistent infection and progression to corneal perforation. BALB/c mice are better at generating immune responses that clear the bacterial infection, as well as inhibiting excessive inflammation in the cornea (Hazlett et al., 2000).

C57B1/6 mice express higher levels of chemoattractant factors during the infection. These factors lead to a greater and more prolonged recruitment of neutrophils and the release of proteases and inflammatory mediators that lead to stromal degeneration and loss (Kernacki et al., 2000; McClellan et al., 2006).

Not surprisingly, signaling through TLR might play a role in the clinical outcome of experimental *Pseudomonas* keratitis. Murine and human corneal epithelial cells express TLR-4. Gram-negative LPS, such as produced by *Pseudomonas*, bind to TLR-4 causing a cascade of activation (Huang et al., 2006; Khatri et al., 2002). TLR-4 expression is upregulated in resistant BALB/c mice after *Pseudomonas* infection, and blocking TLR-4 function increases susceptibility to corneal perforation (Khatri et al., 2002). Interestingly, in mice, B-defensin-2 binds to TLR-4, as does gram-negative bacterial LPS. B-defensin-2 is an antimicrobial peptide released by many cells such as corneal epithelial cells and some immune cells as part of the innate immune response. In BALB/c mice that are capable of clearing *Pseudomonas* corneal infections, B-defensin-2 expression after infection is much higher than in C57B1/6 mice. Furthermore, blocking the expression of B-defensin-2 in BALB/c mice results in a more severe infection (Wu et al., 2009).

Many other factors influence the innate immune response to bacterial infections of the cornea and could be therapeutic targets for improving clinical outcome. For example, the level of expression of macrophage inhibitory factor (MIF) determines the clinical outcome in experimental *Pseudomonas* keratitis. Despite its name, MIF is a potent stimulator of proinflammatory molecules (TNF-α, IL-1β, γ-IFN, arachidonic acid metabolites, nitric oxide byproducts, and others). Experiments have demonstrated that mice deficit in the expression of MIF have a significantly less severe *Pseudomonas* keratitis with faster clearance of the infection and less corneal collagen loss and fibrosis (Gadjeva et al., 2010).

Because of the common genetic background between members of the same breed, the establishment of predictable immunogenetic profiles and expected clinical immune responses would be relatively easy in veterinary medicine compared with human medicine and would allow for breed-specific therapies for diseases such as melting ulcers.

Immune Keratitis/Nonulcerative Keratopathies

Presumed immune-mediated disorders of the cornea, sclera, and episcleral tissues are common in humans, dogs, cats, and horses (Gilger et al., 2008; Matthews & Gilger, 2009). They are presumed immune-mediated because no infectious agent can be identified, they often respond to anti-inflammatory and immunosuppressive therapy, and many are recurrent or persistent. Like many immune-mediated disorders, certain breeds are predisposed to these diseases, further suggesting an immunogenetic influence.

Several studies have looked for the presence of various immune cells and the expression of important immune molecules in these immune-mediated syndromes. For example, studies of tissue from dogs with one of the originally described immune-mediated disorders of the cornea, chronic superficial keratitis of German Shepherds, has demonstrated the presence of immunoglobulin in the conjunctiva and less so in the cornea, the presence of CD4+ T cells and, to a lesser degree, CD8+ T cells, and at least some γ-IFN expression (Campbell et al., 1975; Eichenbaum et al., 1986; Jokinen et al., 2011; Peiffer et al., 1977; Williams, 1999, 2005). The finding of immunoglobulin, T cells, and enhanced MHC expression are expected results in almost all immune-mediated disorders. But the predominance of CD4+ T cells and γ-IFN is most consistent with a Th1-mediated DTH response to a local antigen. Although the pathogenesis of immune scleritis/episcleritis in dogs is also unknown, Breaux and colleagues demonstrated that in dogs with episcleritis/episclerokeratitis that had a high percentage of B cells, a more prolonged clinical disease was present (Breaux et al., 2007).

Certainly, innate immune receptors such as TLRs likely play a role in initiating these immune-mediated conditions (Knop & Knop, 2007; Kreig & Vollmer, 2007; Rifkin et al., 2005). However, the actual immunopathogenesis of these disorders, as is the case with almost all immune-mediated disorders in veterinary species, is unknown. The finding of B cells, T cells, upregulated MHC expression, and common proinflammatory cytokines is to be expected with nearly all immune reactions. But these studies are at least the first steps in understanding these diseases. If these disorders are truly autoimmune in nature, determining the targeted self-antigens, and determining what initiates the development of the autoimmune reaction, will provide insight into understanding the pathogenesis of these disorders. More importantly, understanding the molecular pathways involved in the persistence of inflammation with these diseases will be critical in developing new clinical therapies.

Lens

The various proteins found in the lens are known to elicit immune responses. In humans, antibodies to alpha, beta, and gamma-crystallins are found at a significantly higher

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level in the sera of patients with cataracts compared with the sera of individuals with normal lenses (Ranjan et al., 2008). Denis and colleagues (2003) demonstrated a decrease in prevalence of anti-lens crystallin antibodies in dogs with cataracts compared with dogs without cataracts. The prevalence of antibodies further decreased with maturity of the cataract. This decrease in peripheral antibodies could reflect a change in type of immune response and not necessarily an overall decrease in the immune response to lens proteins with cataract onset.

The antigenic nature of lens proteins is proposed as the mechanism that leads to persistent inflammation after lens damage and lens protein exposure within the eye. Phacolytic uveitis occurs as lymphocytic plasmacytic inflammation often associated clinically with rapid onset of a cataract in younger dogs, or dogs with diabetes mellitus. It often begins even before a complete cataract is visualized and the peracute nature is suggestive of a possible triggering of innate immune responses. Phacoclastic uveitis, a granulomatous inflammation that occurs after lens capsule rupture, is characterized by both a mononuclear cell infiltrate as well as a neutrophil infiltrate in dogs and is often more severe (Wilcock & Peiffer, 1987). Although the timing of the inflammation in phacoclastic uveitis, occurring 7–14 days after lens damage, suggests an antigen-specific immune response plays a role in these inflammatory conditions, the actual pathogenesis or immune mechanisms involved are unknown.

Immune reactions to lens proteins could play a more significant clinical role after cataract surgery. Phacoemulsification lens extraction leaves behind lens epithelial cells. These cells are capable of proliferation and the production of lens proteins, and potentially lead to capsular membranes and plaques that form posterior capsular opacification after lens extraction. In dogs, persistent intraocular inflammation and eventual secondary glaucoma caused by fibrovascular membrane formation is a significant problem after cataract surgery. It is possible that immune reactions to lens proteins that are persistently produced after lens extraction play a role in this form of persistent uveitis.

Several factors indirectly suggest a role for an immune reaction to lens proteins as a possible cause of persistent uveitis post lens extraction. First is the biphasic nature of the uveitis in many patients. The initial inflammation associated with surgical manipulation of the ocular tissues is often resolved within days. Even with patients who receive no postoperative anti-inflammatory therapy, the level of aqueous flare, iridal edema, and corneal edema is often minimal to absent after 4–5 days. The more persistent inflammation often begins weeks after the surgery, consistent with the development of an antigen-specific immune response, and would fit with the production and release of lens proteins by remaining lens epithelial cells. In addition, chronic uveitis is exceptionally rare in patients that receive intracapsular lens extraction and have no remaining lens epithelial cells (unpublished data).

Several of the crystallin proteins found in the lens are expressed in non-ocular tissue. Indeed, alpha A-crystalline and alpha B-crystalline are expressed in many tissues throughout the body and are members of the heat shock protein family (Robinson & Overbeek, 1996). Immune recognition of crystallins might play a role in several immune-mediated disorders. Humans with persistent uveitis have elevated antibody levels to alpha A-, alpha B-, and beta B-crystallins (Chen et al., 2008; van Noort et al., 1995, 2010).

Investigation into the immune reactions to lens proteins post lens extraction could lead to novel therapies for preventing both significant lens capsule opacification as well as the development of low-level inflammation, fibrovascular membranes, and secondary glaucoma.

Uveitis

Persistent or recurring uveitis occurs in nearly all domestic animals and is well characterized in humans. These syndromes are suspected to have an underlying autoimmune pathology based on the lack of identifiable infectious disease, the lack of clinical response to anti-infectious agents, the identifications of autoreactive antibodies and T cells in patients with the disease, and the long-term response to immunosuppressive therapy (Gilger et al., 2000, 2006).

Like the immune response to a pathogen, immune responses to autoantigens must meet the same criteria for immune activation, namely the presence of inflammation and activation of the innate immune response, the subsequent presence of activated APC capable of binding and expressing the autoantigen in MHC complexes, and T cells expressing TCRs capable of recognizing the autoantigen–MHC complex on the APC. There are several pathways by which such criteria occur. A well-documented pathway is through molecular mimicry. Several pathogens express antigens that generate immune responses capable of crossreacting with self-antigens. These pathogen-derived molecules are mimicking self-molecules, and unfortunately, antibodies and T cells capable of reacting to the pathogen-derived molecules can bind to self-antigens. However, the presence of self-reacting antibodies or T cells alone does not mean an autoimmune disease will develop. Self-reactive antibodies and lymphocytes are found in a large portion of humans and likely animals. It is likely the presence of persistent inflammation at the site of the potential autoantigen, as well as the type of autoreactive lymphocytes (T reg cells, vs. DTH stimulating, vs. CTLs, etc.) that develop determines if autoimmune disease will occur.

Other mechanisms that can lead to autoimmune reactions include epitope spreading. Damage to host cells as the result of a persistent infection and inflammation leads to the release of damaged self-molecules. These damaged or altered self-molecules can lead to the exposure of epitopes, the specific short peptide sequences that antibodies or TCRs recognize,

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normally hidden by the tertiary structure of the molecule. An immune response to these minor epitopes can ultimately lead to immune recognition of more major epitopes on the same molecule or similar molecules. Eventual recognition of these major epitopes ultimately leads to clinical disease (Miller et al., 1997; Ott et al., 2004).

Simple persistent inflammation has also been postulated to lead to activation of autoreactive lymphocytes. An infectious agent might not contain crossreactive antigens. But by causing persistent inflammation and activation of APC, chronic inflammatory diseases might allow activated APC to present autoantigens while expressing the necessary coactivation factors that lead to T-cell activation and an antigen-specific immune response.

Experimental Autoimmune Uveitis

Uveitis can be generated in several species using autoantigens. By evaluating the presence of antibodies and/or T cells in humans with uveitis that are capable of recognizing normal ocular molecules, several potential autoantigens have been identified over the last few decades. Injection of some of these autoantigens into rodents, combined with bacterial adjuvants, results in **experimental autoimmune uveitis** (EAU). EAU is a primarily posterior uveitis (or panuveitis) that is induced by immunizing susceptible rodents with retinal antigens (e.g., S-antigen [S-ag], interphotoreceptor binding protein [IRBP], recoverin, rhodopsin/opsin); whereas experimental melanin–protein-induced uveitis, a predominantly anterior uveitis, is elicited by immunization with melanin (from retinal pigment epithelium) or tyrosinase-related proteins 1 and 2 (Caspi, 2006). The predominant animal model is the Lewis rat, but other animals, such as guinea pigs or mice have also been used. EAU does not develop without the use of adjuvants. The use of complete Freund's adjuvant (*mycobacterium* cell wall product) or pertussis toxin is necessary to stimulate the innate immune response to develop inflammation (Agarwal et al., 2012; Chen et al., 2015; Silver et al., 2015). This ultimately generates activated APCs capable of presenting the injected autoantigen with the coactivation factors required to activate T cells capable of recognizing the antigen. In naturally occurring uveitis, infectious diseases such as leptospirosis or onchocerciasis can both generate the persistent ocular inflammation that allows activated APCs to stimulate self-reacting T cells, as well as generate immune responses to pathogen antigens that mimic self-antigens.

These models have been helpful in identifying potential autoantigens, and in evaluating the benefits of various therapeutic interventions. However, they often do not mimic the naturally occurring disease. Unlike naturally occurring uveitis in humans and domestic animals, many of the rodent experimental models of uveitis are not recurrent. They often elicit a single, albeit prolonged, course of uveitis that eventually resolves. Therefore, the immunologic pathways involved in the development of these rodent models might not be the same as in naturally occurring uveitis. Despite this limitation, these experimental models still offer great insight into the mechanisms that play a role in generating uveitis. Indeed, understanding why the disease is often self-limiting in EAU may help identify new immunomodulating therapies for clinical patients. In addition, these models are critical in evaluation of therapies, particularly broader immunosuppressive therapies, for treating uveitis.

Equine Recurrent Uveitis

In domestic animals, the immunopathology of equine recurrent uveitis (ERU) is perhaps the best studied. Immunohistochemical studies have demonstrated that T cells are the predominate mononuclear inflammatory cells infiltrating ocular tissues in horses with naturally occurring chronic uveitis, with a significant number being CD4+ cells (Deeg et al., 2001; Gilger et al., 1999; Romeike et al., 1998). Recruitment of proinflammatory cells as well as autoreactive lymphocytes could be driven in part by the expression of the chemokine RANTES in the ciliary body (Gilger et al., 2002).

Several potential autoantigens have been identified in horses that could play a role in the development of autoimmune uveitis. T cells isolated from the eyes of horses with ERU proliferate in response to two commonly used autoantigens in rodents: S-Ag and IRBP (Deeg et al., 2001). In addition, several additional potential autoantigens were identified by analyzing antibodies in the sera of ERU that reacted with retinal proteins. These include recoverin, cellular retinaldehyde-binding protein (CRALBP), and malate dehydrogenase. Although all these potential autoantigens are capable of inducing experimental uveitis in rodent models, only CRALBP and IRBP consistently produce uveitis in outbred horses (Deeg, 2009; Deeg et al., 2006b).

Several studies have pointed to a potential role for *Leptospira* infections as a potential cause of ERU. In addition to persistent inflammation caused by lack of clearance of the pathogen and the subsequent chronic immune response, *Leptospira* infections might be capable of generating autoimmune uveitis. Studies of horses with ERU have also helped elucidate how *Leptospira* infections induce immunological uveitis, specifically autoimmune uveitis (Lucchesi et al., 2002; Lucchesi & Parma, 1999; Verma et al., 2005). Field studies of horses in the 1950s after an outbreak of acute leptospirosis caused by *L. interrogans* serogroup *pomona* demonstrated that one of the six horses (17%) developed intraocular inflammation during acute leptospiral disease and all horses developed ERU 18–24 months after the initial infection. Subsequent studies demonstrated crossreactivity between equine ocular tissues and *Leptospira* antigens (Lucchesi et al., 2002; Lucchesi & Parma, 1999), and horses with uveitis associated with *L. interrogans* infections had

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high levels of IgA and IgG in their intraocular fluids that reacted to two *Leptospira* lipoproteins, LruA and LruB (Verma et al., 2005; Verma et al., 2010). Furthermore, antibodies to LruB crossreacted with a 30 kDa molecule from equine retinal extracts, and antibodies to LruA crossreacted with 65 kDa molecule from the equine ciliary body and a 22 kDa molecule from equine lens extracts. These antibodies were also subsequently discovered in the serum of human leptospiral uveitis patients (Verma et al., 2008).

Studies of spontaneous ERU have helped elucidate the immunopathogenesis of recurrent uveitis. In autoimmune disease, several autoantigens, or epitopes, participate in the immunopathogenesis; *epitope spreading* is accountable for disease induction, progression, and inflammatory relapses (Deeg et al. 2006a). Epitope spreading is defined as the diversification of epitope specificity from the initial focused, dominant, epitope-specific immune response, directed against a self or foreign protein to cryptic epitopes on that protein (intramolecular spreading) or other proteins (intermolecular spreading) (Deeg et al., 2006a). The shifts in immunoreactivity, or epitope spreading, has been documented in ERU and is thought to be responsible for the recurring character of ERU.

ERU, as a model of spontaneous immune-mediated uveitis, has also led to the study of promising therapeutics. For example, several sustained release ocular implants have shown much promise in the treatment of ERU (Gilger et al. 2001; Gilger et al. 2000). Evaluation of drug delivery to the suprachoroidal space has been shown to control ERU and prevent recurrences (Gilger et al. 2006; Gilger et al. 2010). Triamcinolone injections into the suprachoroidal space are currently under development for treatment of human uveitis.

Canine and Feline Uveitis

Little is known about the immunologic background of potentially immune-mediated uveitis in dogs or cats. Feline recurrent uveitis is a leading cause of blindness in cats and is characterized not only by anterior uveal infiltrates of immune cells, but also by sometimes marked inflammatory cells in the anterior and peripheral vitreous (Maggs, 2009; Townsend, 2008). Like horses, persistent uveitis in cats has been associated with several infectious diseases. However, whether a persistent infectious agent is responsible for the inflammation or an initial infectious disease leads to a true autoimmune uveitis is unclear. It is interesting to note that the accumulation of immune cells in feline uveitis is around the lens and that intracapsular lens extraction often results in a marked reduction or resolution of the uveitis (unpublished observations). This is suggestive that immune reactions to lens-associated molecules may play a role in the immunopathogenesis of the disease.

Control of immune-based ocular diseases will ultimately require a two-pronged attack. Critical to long-term resolution of any immune-mediated, potential autoimmune disorder is to push the immune response toward suppression of active disease. When the antigens stimulating an immune response cannot be eliminated, as is the goal in immune responses to a pathogen, the best long-term therapy is to generate a suppressive immune response. Cells capable of downregulating and inhibiting inflammation toward an antigen likely develop in all antigen-specific immune responses. They are responsible for the generation of tolerance toward an antigen. Therapeutically pushing an autoimmune response toward the generation of T suppressors and T regulating cells and inducing tolerance toward the self-antigen is the best long-term therapy for immune-mediated disorders. Unfortunately, although the understanding of the molecular events involved in the generation of tolerance are consistently expanding, current knowledge of T reg cell development is insufficient to allow the development of viable therapeutic intervention.

The other aspect of treating immune-based ocular disorders is inhibition of active inflammation. Because the eye has limited regenerative capabilities, and even minimal fibrosis and tissue damage can lead to loss of organ function, rapid control of inflammation is needed. Even when strategies to push the immune response toward tolerance become available, directing the immune response will take months to years. Therefore, control of ongoing inflammation is critical. Because of accessibility and, to some degree, its isolation, the eye is amenable to therapeutic strategies not available to other organs, such as intraocular delivery of immunomodulating drugs and biologic agents.

Indeed, our current therapies for immune-mediated ocular diseases are limited to controlling inflammation. Most therapies are broad based, nonspecific immunosuppression and anti-inflammatory. They are helpful and critical to saving vision. However, they often have unwanted systemic side effects and because of their untargeted approach, they are not always effective. More recent therapies aimed at inhibiting slightly more specific immune reactions are in clinical use. TNF-α inhibitors have been used for treatment of refractory uveitis associated with systemic autoimmune disorders (Suhler et al., 2005; Tugal-Tutkun et al., 2005). The use of slow release intraocular cyclosporin has provided an enhanced ability to treat uveitis in horses (Gilger et al., 2010). These therapies both target the continued activation of the immune response as well as suppression of effector mechanisms. In addition, long-term use of systemic calcineurin inhibitors/IL-2 inhibitors such as cyclosporin and tacrolimus has been shown to increase the presence of antigen-specific T suppressor cells and increase tolerance (Fujino et al., 1988; Kawashima et al., 1990; Sugita et al., 2011).

Future therapies will look at inhibiting the key factors in generation of tissue inflammation, namely the inhibition of the release of the multiple proinflammatory molecules (beyond just cyclooxygenase products), blocking of the effector function of innate and antigen-specific immune cells,

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blocking the migration of immune cells into the target tissue, and preventing the development of unwanted side effects (fibrosis, cell death, vascularization) that result from persistent inflammation.

Idiopathic persistent uveitis is less common in canines compared with horses or cats. An uncommon but well-described immune-mediated disorder in dogs is UDS, a disease closely related to Vogt–Koyanagi–Harada (VKH) disease in humans. In humans, the presence of a large number of CD4+ Th cells expressing type 1 cytokines, especially γ-IFN, and the presence of activated macrophages, strongly suggests that a DTH-like immune response toward melanocytes plays a prominent role in the pathology of ocular changes (Gocho et al., 2001; Maezawa et al., 1982; Sakaguchi et al., 1998). As in dogs, there is a strong genetic predisposition in humans, with individuals expressing HLA-DR4/DR53 or HLA-DRB1*45 having a much greater risk of developing VKH (Goldberg et al., 1998). Immune reactions against several proteins important in the production of melanin have been identified in humans, including tyrosinase, tyrosinase-related protein 1, and tyrosinase-related protein 2, as well as others (Damico et al., 2009). However, what triggers the immune response to these self-molecules is unclear. Although flu-like disease is reported by many patients prior to VKH onset, a correlation between a specific viral disease and VKH development does not exist.

UDS in dogs is associated with a similar immune-mediated attack on melanocytes in the eye and skin. Macrophages with engulfed pigment are a hallmark of the disease in dogs as it is in humans. In contrast to findings in humans, Carter et al. (2005) reported immunohistochemical staining consistent with predominately B cells in the eyes of two dogs with UDS, with minimal T cells. Serum antibodies to a surface protein associated with melanocytes was found in several species of animals, including dogs, with vitiligo (Naughton et al., 1986). These findings, the clinical loss of pigment, the similarities with VKH, and the finding that in dogs with heterochromia irides the nonpigmented eye is not inflamed with UDS (Sigle et al., 2006), suggest an immune response to pigment cells is the basis for the disease. However, detailed studies on the immune response in UDS are lacking.

Akitas in the United States, a breed commonly affected with UDS, have strikingly minimal genetic diversity at the DQA1 allele, and it has been postulated that the expression of this haplotype might be a predisposing factor for UDS (Angles et al., 2005).

Retina

Immune-mediated retinopathies are poorly defined in dogs. Immune mechanisms might be a key factor in the various acute retinal degeneration syndromes in dogs collectively grouped as sudden acquired retinal degeneration (SARD). In humans, autoimmune retinopathies (AIRs) are associated with neoplastic diseases (cancer-associated retinopathy and melanoma-associated retinopathy), but nonparaneoplastic retinopathies with a suspected immune basis also exist (Chan, 2003; Heckenlively et al., 2000; Thirkill et al., 1989). The diagnosis of AIRs in humans is dependent on clinical findings similar to the criteria used in the diagnosis of SARD in dogs: a sudden alteration in vision with little to no anatomical changes on fundoscopy, abnormal electroretinogram findings, and the presence of antibodies against retinal antigens. Immunoreactivity against the retinal proteins recoverin and alpha-enolase are best characterized in AIR but are not the only autoantigens recognized by AIR patient sera (Adamus et al., 1998; Ohguro et al., 1999; Thirkill et al., 1987, 1989). Expression of recoverin by small cell carcinomas provided a potential mechanism by which autoantibodies could be generated (Matsubara et al., 1996; Yamaji et al., 1996). However, expression of a normal self-molecule on an abnormal cell does not preclude the development of an immune response. The immunological steps that lead to the development of autoimmune paraneoplastic disease are unknown. Paraneoplastic autoimmune disorders are exceptionally uncommon in patients with neoplastic disease. Furthermore, not all patients with a clinical diagnosis of AIR have detectable antibody reactivity against normal retinal proteins, and the pattern of antiretinal reactivity does not always correlate with clinical outcome (Heckenlively & Ferreyra, 2008). Although originally diagnosed as a paraneoplastic syndrome, many patients with AIR have no identifiable neoplastic disease (Shiraga & Adamus, 2002). Unfortunately, the visual prognosis is better for AIR associated with neoplastic disease because it usually requires lower levels of immunosuppression to control the disorder. Patients with AIR not associated with a neoplastic disease are more likely to have a history of other immune-mediated disorders, suggesting a potential genetic predisposition (Heckenlively & Ferreyra, 2008; Jankowska et al., 2004). Local as well as systemic immunosuppressive therapy can prevent complete loss of vision in humans when the disease is detected early. Several weeks to months of therapy are often required before vision stabilizes and potentially lifelong immunosuppressive therapy is required (Heckenlively & Ferreyra, 2008).

The role of antiretinal antibodies is less clear in SARD in dogs. Although an initial study suggested that antiretinal antibodies may play in dogs with retinal degeneration (Bellhorn et al., 1988), other more recent serologic studies indicate that both normal dogs and dogs with SARD have detectable antibodies to S-Ag as well as CRALBP (Braus et al., 2008; Gilmour et al., 2006; Keller et al., 2006). However, sera from patients with SARD had detectable antibodies to neuron-specific enolase, present in the retina, whereas sera from normal patients did not (Braus et al., 2008). This is the only published data to date that suggests an immune-mediated role for SARD. Whether these antibodies play a role in the development of SARD is unknown.

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Non-peer-reviewed data have suggested that immune mechanisms play a role in SARD. Grozdanic and colleagues reported finding plasma cells and complement activity in the retinas of dogs with SARD. Furthermore, they reported clinical improvement in vision when dogs with acute SARD are treated with aggressive immunosuppressive therapy such as intravenous immunoglobulin (Grozdanic et al., 2008).

Unfortunately, even if an immune mechanism is elucidated for SARD, immunosuppressive therapy is less likely to restore vision or halt continued loss of vision in dogs compared with humans because of the late stage of detection. Most humans with AIR still have reasonable functional vision on presentation, whereas most canine patients do not present until marked vision loss is noted. With apoptosis being a documented mechanism of photoreceptor loss in SARD, saving vision would require halting of the underlying mechanisms leading to apoptosis early in the disease process (Miller et al., 1998).

Immunologic mechanisms may play a role in the development of age-related macular degeneration (AMD), a leading cause of vision loss in humans. Activated macrophages and several activated complement components are found in the retinal tissue and even drusen from patients with AMD (Mullins et al., 2000; Nozaki et al., 2006). In addition, humans with alterations in CRP expression or genetic alterations in the complement factor H gene are more likely to develop AMD (Edwards et al., 2005; Hageman et al., 2005; Haines et al., 2005; Klein et al., 2005). Although the presence of activated complement components and epidemiological relationships between the expression of complement factors and AMD development suggest a role for immune activation in the development of AMD, the mechanisms that ultimately lead to retinal damage and whether complement plays an active or passive role is unknown.

AMD is not a described disease in domestic animals. However, age-related, poorly characterized retinal degenerations are observed in canines. Although the characteristic presence of drusen is not a common finding in dogs, it is possible that age-related retinal degenerations could have a similar immunopathogenesis as human AMD.

In summary, many clinical diseases in veterinary ophthalmology are believed to have an immune-mediated, potentially autoimmune basis. However, little is known regarding the actual immune mechanisms that generate these immune disorders. The lack of knowledge is both because of an incomplete understanding of immune processes and also a lack of therapeutic options that involve targeting specific aspects of the immune response. The eye represents a unique organ where the potential to modulate the immune response is great. Ophthalmology will continue to lead the way in the development of novel immunotherapies as the knowledge of the immunopathologic mechanisms of common clinical disorders increases.

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7

Clinical Microbiology and Parasitology

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Ocular Virology

Introduction

Viruses can be categorized in three main groups based on their nucleic acid composition: DNA viruses, RNA viruses, and viruses which utilize both DNA and RNA for replication. For each group, characteristics of the fully assembled infective virus (virion) are used to assign them into four main hierarchical levels that are denoted by a specific suffix: family (suffix—*viridae*), subfamily (suffix—*virinae*), genus (suffix—*virus*), and species. This assignment is based primarily on the type and nature of the genome (e.g., linear, double-stranded), the structure of the virion (e.g., size, presence, or absence of envelope), and the site (e.g., nucleus, cytoplasm), as well as mode of viral replication (see later).

Because viruses have no inherent replicative ability, they must enter host cells and utilize host cell processes for their own replication. Understanding the stages of viral replication is important for understanding viral pathogenesis and infection. The classic stages of viral replication are attachment, penetration, uncoating, transcription, translation, replication, assembly, and release (Quinn et al., 2011a).

Viruses are usually very specific in their mechanisms for infecting a target cell. As a virion comes in contact with a target cell, it interacts with and attaches to specific receptors or components of the cell membrane, usually via specific glycoproteins. After attachment, viruses enter the host cell through receptor-mediated endocytosis or other mechanisms such as fusion of the viral envelope with the cell membrane or direct introduction or translocation of viral genomes into the cytoplasm. Uncoating is the next process, by which the viral capsid is degraded by viral or host enzymes resulting in the release of the viral genome in a form suitable for transcription, translation, and nucleic acid replication processes. Transcription, translation, and replication of viral nucleic acid occur in a specific order and vary between each virus group.

DNA viruses are often transcribed to mRNA and translated to viral proteins shortly after uncoating and prior to beginning DNA replication. The replication and transcription of RNA viruses is more complicated. The genome of nonretroviral RNA viruses contains nucleic acid with positive or negative polarity. RNA of positive strand RNA viruses is similar to mRNA and is transcribed and translated prior to replication. A complementary or negative strand of RNA is then created as a template for replication of the positive strand RNA genome. RNA of negative strand RNA viruses, however, must be converted to a positive strand mRNA by RNA-dependent RNA polymerase (RDRP) before transcription and translation into proteins can begin. Then RDRP uses the positive strand RNA as a template to create the negative RNA strands to be included in the new virions (Quinn et al., 2011a).

Retroviruses get their name from their unique method of genome replication. Upon uncoating of the virus, the viral protein reverse transcriptase creates a DNA template from the viral RNA genome. This proviral DNA is incorporated in the host genome where it is replicated to RNA via transcription, and RNA is used for translation and new viral genomic material.

After viral genome replication and formation of viral structural proteins, progeny virions are assembled within the host cell and released. Release of progeny virus occurs by budding through the host cell membrane or through rupture (lysis) of the host cell. Enveloped viruses typically "bud" and during the budding process acquire the phospholipid envelope containing the embedded viral glycoproteins from the host cell membrane.

The method by which viruses induce injury to ocular tissues is quite variable. Many directly destroy ocular cells in the process of replication, as is typical for alphaherpesviruses.

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Alternatively, other viruses indirectly damage ocular cells by inciting an immune or inflammatory response that is deleterious to tissues, inducing tumor formation, or causing tissue injury via immunosuppression.

Diagnostic Methods

The most commonly used and clinically useful laboratory methods for the diagnosis of viral infections in swabs and tissue biopsies are live virus isolation (VI), diagnostic serology, and polymerase chain reaction (PCR) (Evermann et al., 2012; Lappin, 2009; Quinn et al., 2011b). Histopathology, in combination with immunohistochemistry and the methods mentioned above can also be used on samples collected after enucleation or postmortem examination.

Live Virus Isolation

The presence of live virus in the sample collected from the animal under investigation is confirmed when the virus replicates on specific cell lines producing characteristic cytopathic effect on the cells. Usually, the nature of the toxic effect and the cell type that facilitates the growth of the virus are sufficient to achieve a diagnosis of viral infection (Fig. 7.1). VI is a sensitive and specific method when viruses are not labile and when the sample transport and cultural conditions are optimal. The main disadvantage of VI is that it is unsuitable for in-clinic use because it is technically demanding and labor-intensive. A number of blind passages may be required before a virus becomes adapted to a specific cell line, and therefore, test results may not be available for some weeks. Although VI has largely been superseded by PCR, there are instances when VI is clinically useful. For example, reverse transcription PCR (RT-PCR) for calcivirus can be hampered by the high variability of its viral genome so the PCR test used must be optimized against a large panel of strains of the virus, and for this reason, RT-PCR could be negative, but VI could be positive.

Serology

Serology has long been used for diagnosis of several viral infections by detecting antibodies against a specific virus or by detecting a specific protein (antigen) of the virus. Immunofluorescence (IF), enzyme-linked immunosorbent assays (ELISAs), and/or immunochromatography are the most commonly employed technologies (Radford & Dawson, 2005).

IF can be performed in a direct or indirect manner. The fundamental principle of IF is that the sample to be tested for viral antigens or the presence of antibodies is fixed on a slide, and a fluorescent molecule is attached to the viral antigen or antibody through one or more viral-specific antibodies. The direct method uses a single antibody (or a single application of polyclonal antibodies) with a conjugated fluorescent molecule to react with the sample. The indirect IF method is used more commonly; first, it uses a nonfluorescent antibody to react with the sample (the primary antibody) and then utilizes a secondary fluorescent antibody (FA) with an affinity for the first antibody. A fluorescent microscope is required for examination of the slides. Immunochromatography and ELISA are routinely employed for serological testing in external veterinary laboratories but have also been adapted for creating tests suitable for in-clinic use (Fig. 7.2 and Fig. 7.3) (Digangi et al., 2011; Sand et al., 2010). In general, serological tests can detect specific types of antibodies (e.g., IgG, IgM), and the generated results can be quantitative (expressed as titers) and/or qualitative (positive or negative).

It should be noted that a "positive" test result for an antibody against a certain infectious agent does not always indicate clinical disease, and that the magnitude of the antibody

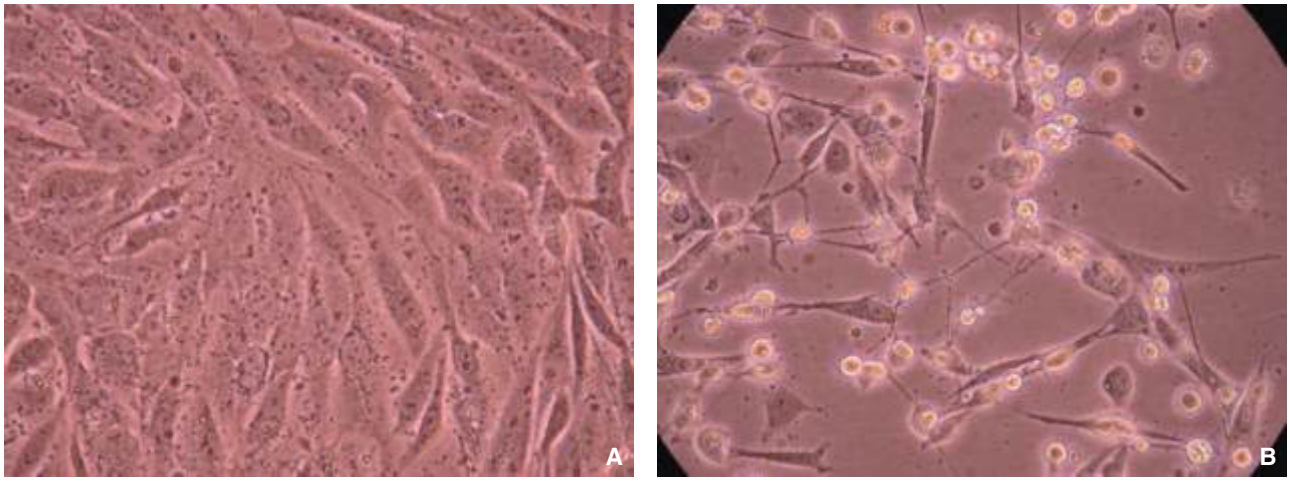


Figure 7.1 **A.** A sheet of intact cells. **B.** The round, oval, and rarely triangular in shape bright orange, granular areas indicate destruction of the cells caused by the growth, in this case, of feline calici virus.

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Figure 7.2 The SNAP® device (Idexx Laboratories, Inc., Westbrook, ME, USA) uses enzyme-linked immunosorbent assays (ELISA) technology for the detection of antibodies or antigens. The test result in this photo is positive, as in addition to the positive control (blue dot in the middle), there is a second lighter blue dot on the left indicating, in this case, the presence of antibodies against feline immunodeficiency virus.



Figure 7.3 The Witness® device (Synbiotics Co., Kansas, MO, USA) uses immunochromatography for the detection of antibodies or antigens. The result for sample 1178 is positive, as in addition to the positive control line (position 3), there is a second line in position 2 indicating, in this case, the presence of FeLV antigen. The result for sample 1428 is negative.

titer does not always correlate with active or clinical disease. The diagnostic utility of some antibody tests is limited because they do not distinguish between vaccination, active infection, or exposure. The presence of maternally derived antibodies can give positive antibody results in animals younger than 14 weeks of age that are not infected. False-positive and false-negative results can occur with ELISAs. IF tests can generate false-positive results if the prepared slides are thick or are read incorrectly by inexperienced technicians; technicians must tediously examine numerous cells and subjectively determine if the magnitude of cell fluorescence is above that which would be considered "background" fluorescence.

Because methodologies and antibody titer results can differ between various laboratories, direct comparison of results generated by different laboratories cannot be made, and interpretation of titers must be guided by the laboratory used.

Polymerase Chain Reaction

The major advantage of PCR is its inherent exponential amplification of small amounts of DNA to a detectable signal (Tasker, 2010). The key to this exponential molecular amplification is that the target DNA sequence is doubled during each of approximately 30 cycles of the amplification reaction. Thus, one viral copy, under ideal conditions, would be amplified to 5.37×10^8 copies in 30 cycles of amplification. The PCR effectively acts as a "DNA photocopier" (Fig. 7.4).

The general concept behind PCR is that a simple double-stranded template DNA is reacted with oligonucleotide primers, free nucleotide bases to be used in constructing new DNA molecules, and DNA polymerase. These components are mixed in a sample tube with appropriate salt concentrations and buffers. The sample is heated to approximately 90°C to melt or separate the double-stranded DNA, cooled to allow annealing of the oligonucleotide primers to the template DNA, and heated slightly to allow DNA polymerase to build new DNA strands from the oligonucleotide primers,

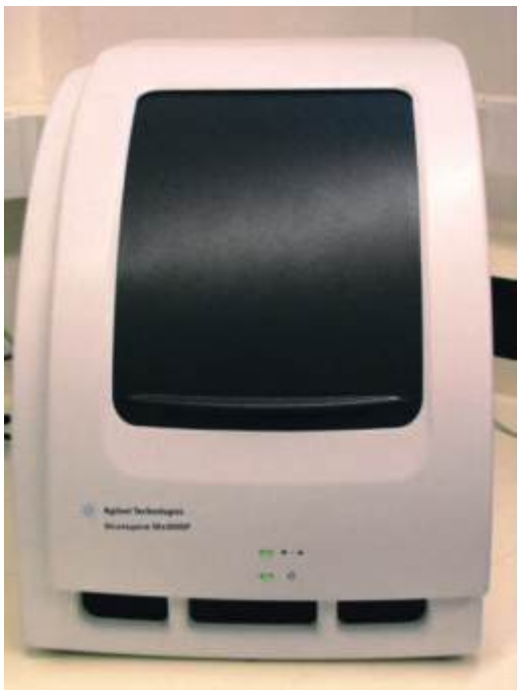


Figure 7.4 A polymerase chain reaction (PCR) instrument. (Courtesy of Dr. Chris Helps, Langford Vets, Molecular Diagnostic Unit, University of Bristol, UK.)

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template DNA, and nucleotides. This series of reaction temperatures constitutes one cycle of the PCR reaction. The entire PCR reaction is composed of numerous cycles (typically 25 to 40) to amplify exponentially the target DNA sequence.

Three common variations of PCR methodology are *nested PCR*, *RT-PCR*, and *real-time PCR*:

- *Nested PCR* utilizes a second set of oligonucleotide primers, directed at a sequence internal to the first amplified sequence, and repeats the cycling program a second time. The major advantage of nested PCR is increased sensitivity. Increased sensitivity, however, may have adverse effects in some situations, as discussed later.
- *RT-PCR* (reverse-transcriptase PCR) is a method of amplifying RNA for detection. DNA polymerases used in PCR will not amplify RNA sequences. Therefore, RNA sequences must first be reverse transcribed to DNA so that standard PCR can be performed. This technique is frequently utilized to detect mRNA sequences transcribed from DNA, but it is also used to detect RNA of certain RNA viruses.
- *Real-time PCR* differs from conventional PCR in that it is quantitative (QPCR), enabling the clinician to know how much target DNA is present in a sample. During QPCR, the amount of PCR product formed is measured each cycle and reported in fluorescence units. The more target DNA present in a sample, the more quickly the PCR product (and therefore fluorescence) is generated. A sample is positive if the amount of fluorescence produced rises above the threshold level. The threshold cycle (Ct) value (Fig. 7.5) denotes how many PCR cycles are required for the sample fluorescence to reach the threshold level. Thus, the more target DNA present in a sample, the lower the Ct value will be, because the threshold is reached sooner. QPCR results are reported by stating the Ct value for the sample.
- *Next-generation sequencing*, currently a research tool only, differs from conventional PCR in that the method does not use primers of known sequence. DNA is amplified to billions of bases and analyzed to identify novel genomes. This method has allowed identification of new viral pathogens (Datta et al., 2015).

Because PCR assays detect DNA from live and dead organisms, a "positive" test result does not always indicate clinical disease or that the treatment has been ineffective. In addition, some PCRs may not be able to discriminate vaccinal from field viral strains. PCR is an unsuitable method for in-clinic use because it is technically demanding. Even so, there is lack of established/recognized external quality assurance schemes for veterinary laboratories, so the quality of the generated results depends on the quality of the laboratory. Established and reputable veterinary PCR laboratories always run QPCRs for internal control genes, depending on animal species, on submitted samples to ensure that faulty or inadequate sampling does not result in a false-"negative" result.

Pathogenic Feline Viruses

Feline Herpesvirus-1

Characteristics, Clinical Relevance, and Epidemiology

Feline herpesvirus-1 (FHV-1) is member of the Herpesviridae family, subfamily Alphaherpesvirinae. These are double-stranded DNA viruses characterized by their short replication cycle, rapid cell-to-cell spreading, tendency to induce cell lysis, and persistence in sensory ganglia of their host (Gould, 2011; Pennington et al., 2017).

The virus is relatively unstable in the environment, persisting up to 18 hours in moist conditions and less in dry conditions. It is susceptible to most disinfectants, antiseptics, and detergents. The main source of transmission between cats is by direct transfer of bodily fluids, in particular respiratory secretions, which are passed via sneezing,

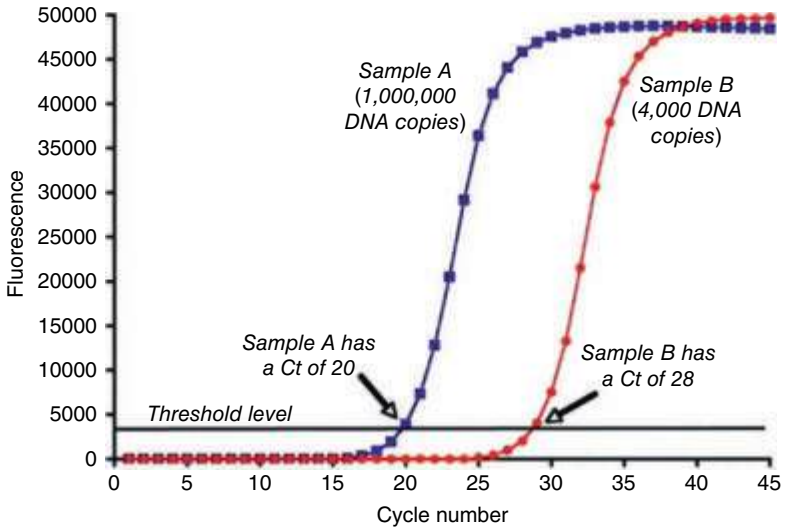


Figure 7.5 Quantitative polymerase chain reaction (QPCR) traces for two samples and generation of Ct values. Sample A contains *250* times more target DNA than Sample B, so it reaches the threshold level at a lower cycle number (*20*) than Sample B (*28*). Samples containing no target DNA never reach the threshold level. (Courtesy of Dr. Chris Helps, Langford Vets, Molecular Diagnostic Unit, University of Bristol, UK.)

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contaminated fomites, or via unhygienic handling practices (Gaskell et al., 2012).

FHV-1 is a significant cause of feline morbidity worldwide. In addition to its role in feline upper respiratory tract disease, it is a major cause of feline ocular disease. It is widespread in the global feline population, with reported serological prevalence rates of up to 97% (Maggs et al., 1999a). After exposure, more than 80% of cats become persistently infected and, of these, 45% will subsequently shed virus spontaneously or as a result of natural stress situations, and around 70% will shed virus in response to corticosteroid administration (Gaskell & Povey, 1977).

Globally, there is little genomic variation between FHV-1 strains, with only three main genotype groups recognized. A recent study analyzing 26 FHV-1 isolates collected over 40 years (including two vaccine strains) revealed less than 0.01% diversity (Vaz et al., 2016). Despite this, experimental infection studies have shown that there is significant variation in virulence between field isolates of the same strain, which may in part explain the variation in severity of clinical signs that is recognized clinically.

Disease Pathogenesis

Primary infection Primary infection occurs most frequently among kittens and adolescent cats, because maternal antibodies decline from around 8 weeks of age. However, even vaccinated cats remain at some risk because FHV-1 vaccines, both parenteral and intranasal, confer only partial immunity against clinical signs and no protection against reactivation/shedding. FHV-1 preferentially infects mucoepithelial cells of the tonsils, conjunctiva, and nasal mucosa, but there is also significant infection of corneal epithelial cells (Gaskell & Povey, 1979; Nasisse et al., 1989). The resultant lytic infection is characterized by rapid replication and acute cellular damage leading to cytolysis. Clinical signs develop 2–6 days after infection. Ocular signs associated with this phase are acute conjunctivitis and epithelial keratitis characterized by the formation of punctate and dendritic epithelial ulcers that persist up to 24 days in experimental infections (Nasisse et al., 1989).

Latency During primary infection, FHV-1 virions invade sensory nerve endings of the trigeminal nerve within the host tissue and travel to the trigeminal ganglion. Here FHV-1 develops a latent state in which the genome persists in episomes within the cell nuclei of the trigeminal ganglia (Gaskell et al., 1985). Although this is a clinically quiescent phase, there is transcription of latency-associated transcripts, which are RNA species that play an as yet incompletely understood role in maintaining latency and allowing recrudescent disease (Bloom, 2006; Ohmura et al., 1993).

Recrudescent infection Latent FHV-1 virus can reactivate to cause recrudescent clinical disease. This has been recorded spontaneously or in association with various stressor conditions including systemic corticosteroid administration, coinfection with other agents, change of housing, parturition, and lactation (Gaskell & Povey, 1977). The molecular mechanism behind viral recrudescence is poorly understood, but it results in viral replication and migration down the sensory axons to epithelial tissues. This may result in subclinical shedding, lytic infection (with signs similar although usually less severe than those of the primary infection), or development of immunopathological disease (chronic stromal keratitis) as the host mounts an immune response against viral antigens within the cornea.

Ocular Signs

Conjunctivitis In primary infections, acute conjunctivitis occurs in conjunction with rhinotracheitis, after an incubation period of 2–6 days (Nasisse et al., 1989). The conjunctivitis is usually bilateral, with signs of hyperemia, serous ocular discharge, and a variable degree of chemosis. Areas of conjunctival ulceration can develop secondary to viral-induced epithelial necrosis. In the majority of cases, the clinical signs resolve by 10–20 days postinfection. Recurrent acute conjunctivitis is a feature of viral recrudescence. FHV-1 is also a major cause of chronic conjunctivitis (Nasisse et al., 1993).

Dendritic corneal ulceration The presence of dendritic corneal ulcers is considered pathognomonic for FHV-1 infection (Nasisse et al., 1989). FHV-1 infection of the corneal epithelial cells in acute primary infection leads to corneal ulceration, which typically manifests as linear or branching epithelial defects.

Geographic corneal ulceration Larger areas of geographic corneal ulceration also can develop as a result of primary infection (Nasisse et al., 1989). These may be single or multiple. In recrudescent infections, either dendritic or geographic corneal ulceration is often a clinical feature.

Chronic stromal keratitis After multiple bouts of recrudescent disease or periods of chronic ulceration, the corneal stroma can develop chronic inflammatory changes including neovascularization, inflammatory cell infiltration, pigmentation, scarring, and fibrosis presumed to be a result of an immune response to viral antigens sequestered within the cornea (Nasisse et al., 1995).

Other ophthalmic manifestations In addition to conjunctivitis and keratitis, FHV-1 has also been linked to a multitude of other ocular diseases including ophthalmia neonatorum (Bistner et al., 1971), symblepharon, keratoconjunctivitis sicca (Nasisse et al., 1989), tear film instability (Lim et al., 2009), eosinophilic keratitis (Morgan et al., 1996; Nasisse et al., 1998), corneal sequestration (Morgan 1994; Nasisse et al. 1989, 1998; Stiles et al., 1997a), calcific band keratopathy

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(Nasisse et al., 1989), periocular dermatitis (Hargis et al., 1999), and anterior uveitis (Maggs et al., 1999b).

Diagnostic Testing

Polymerase Chain Reaction The PCR test identifies FHV-1 by amplifying specific sequences of viral DNA. It has, in theory, 100% specificity and extremely high sensitivity. Various PCR testing protocols have been developed for FHV-1 diagnosis (Hara et al., 1996; Helps et al., 2003; Stiles et al., 1997a, 1997b). Most are based on DNA amplification of sections of the highly conserved viral thymidine kinase gene. Conventional (single round) PCR, nested PCR, and real-time PCR testing are offered by different commercial diagnostic testing laboratories. Because of its exquisite sensitivity, nested PCR carries a higher risk of contamination than conventional PCR, and because nested and conventional PCR methods show good correlation (Volopich et al., 2005), most UK laboratories now offer only conventional or real-time PCR as their standard test for FHV-1. PCR testing can be performed on dry conjunctival or corneal swabs without the need for viral transport medium. As with VI, ocular swabs may be submitted in combination with pharyngeal swabs in primary lytic disease.

PCR testing for FHV-1 poses some difficulty because of the relatively high frequency of normal cats that are reported to test positive for FHV-1. Different PCR-based studies have calculated the incidence of such false-positive cases as being between 3% and 49% (Low et al., 2007; Maggs et al., 1999a). Conversely, a significant number of cats with a high index of suspicion of herpesvirus disease will test negative for FHV-1. Possible reasons for this include intermittent viral shedding by infected cats, inadequate sample collection, degradation of the DNA sample during transport, or reduced sensitivity of the PCR test. Diagnostic testing results must therefore be interpreted with caution because both false-negative and false-positive testing is common. Because of this, it is important to consider the overall clinical picture when attempting to make a diagnosis of FHV-1 ocular disease.

Fluorescent antibody testing FA testing is performed on conjunctival or corneal tissue. To maximize cell numbers and quality, conjunctival cells should be harvested using a cytobrush. Corneal cells can be collected using a Kimura spatula or the blunt handle end of a scalpel blade. After application of topical anesthetic to the sample site, the cytobrush should be gently rolled over the tissue then rolled onto a clean glass slide, air-dried, and submitted to the testing laboratory. Because most FA tests use fluorescein-conjugated antibody to detect FHV-1 antigen within the submitted tissue, topical fluorescein should be avoided prior to collection. FA has largely been superseded by PCR testing, although some diagnostic laboratories still offer the service.

Virus isolation Because VI identifies live virus, it has traditionally been accepted as the diagnostic "gold standard" for active infection. Swabs are collected from the conjunctival or corneal surface and then transported in viral transport media, which is available from commercial testing laboratories. Although topical anesthetics are often used prior to sample collection, it should be noted that after an hour's incubation in proparacaine, FHV-1 does not remain infectious, raising the possibility that the use of topical anesthetics prior to sampling could reduce sensitivity (Storey et al., 2002). In primary acute lytic disease, ocular swabs may be submitted in combination with pharyngeal swabs. A disadvantage of VI is the inevitable delay while awaiting viral culture results. This inconvenience, coupled with the fact that PCR testing is more sensitive than either VI or FA testing, means that PCR is now the most commonly performed diagnostic test for FHV-1 (Stiles et al., 1997b).

Feline Calicivirus

Characteristics, Clinical Relevance, and Diagnostic Testing

Feline calicivirus (FCV) is a single-stranded RNA virus of the family Caliciviridae. It is an important cause of feline upper respiratory tract and gingivostomatitis but is not a major primary ocular pathogen (Gaskell et al., 2012; Nakanishi et al., 2018; Ormerod et al., 1979; Radford et al., 2007; Wardley & Povey, 1977a, 1977b). One study identified conjunctival erosions in 30 of 99 FCV-infected cats, but all of these had concurrent oral ulceration and signs of upper respiratory disease (Gerriets et al., 2012). Diagnosis is by PCR of swabs from affected tissues.

Feline Coronavirus

Characteristics, Clinical Relevance, and Epidemiology

Feline coronavirus (FCoV) is a single-stranded RNA virus of the family Coronaviridae. It can remain stable and infective outside the host for up to 7 weeks under dry conditions, although it is rapidly destroyed by most household detergents (Andrew, 2000).

The virus is ubiquitous in the domestic cat population, with the feline small intestine acting as the likely reservoir for infection (Pedersen, 2009, 2014). All cats are susceptible to infection, but clinical disease is most commonly seen in younger cats between 3 months and 3 years of age, because kittens less than 3 months of age derive some protection from infection via maternal antibodies (Andrew, 2000). In the majority of FCoV-infected cats, the virus is either asymptomatic or causes only mild enteritis. However, up to 12% of FCoV-infected cats go on to develop feline infectious peritonitis (FIP) (Addie et al., 2009). FIP is the major infectious cause of mortality in cats (Addie, 2012).

There is some debate about what triggers conversion of such a previously benign enteric coronavirus into a fatal pathogenic strain within an individual cat. An "*in vivo* mutation transition" hypothesis is generally accepted, which proposes that spontaneous virus mutation occurs *in vivo* to induce viral pathogenicity, with immunosuppression or

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stress predisposing to disease development (Addie et al., 2009; Poland et al., 1996; Vennema et al., 1998). An alternative hypothesis suggests that distinct avirulent and virulent strains exist (Brown, 2011).

Disease Pathogenesis

FIP signs are classically described as effusive ("wet" FIP, caused by vasculopathy resulting in abdominal and thoracic effusions) or noneffusive ("dry" FIP, characterized by pyogranulomatous lesions in affected organs), although these really reflect the two extremes of a wide clinical spectrum and mixed signs are commonly encountered. The disease is almost always fatal, although cats suffering from noneffusive FIP tend to have a more chronic disease course than cats with effusive FIP.

Ocular signs are more common in noneffusive FIP than in effusive FIP, being reported in 36% of the former compared with less than 5% of the latter (Andrew, 2000).

Disease pathology results from a number of pathogenic mechanisms. Immune complex deposition results in vasculitis, with resultant increased vascular permeability allowing formation of exudative effusions. Hyperglobulinemia caused by chronic antigen stimulation can lead to hyperviscosity syndrome. A cell-mediated immune response results in the formation of pyogranulomatous lesions within body organs, leading to widespread systemic pathology.

Ocular Signs

The most common ocular signs associated with FIP are anterior uveitis, chorioretinitis, retinal blood vessel tortuosity and perivascular effusions, retinal hemorrhage, and retinal detachment (Addie, 2012; Andrew, 2000; Stiles, 2012).

Diagnostic Testing

No single diagnostic test for FIP is available. Without histopathological examination of affected tissue, antemortem diagnosis of FIP is presumptive, relying on a combination of history and signalment, clinical findings, and interpretation of clinical laboratory results (Addie, 2012).

- Typical hematological findings include lymphopenia, neutrophilia usually with a left shift, and a mild to moderate normocytic, normochromic anemia.
- Serum biochemistry findings often include hyperglobulinemia, hypoalbuminemia (an albumin:globulin ratio <0.4 makes FIP very likely, whereas a ratio >0.8 makes it very unlikely), and elevated alpha-1 acid glycoprotein (AGP).
- Serum antibody tests for FCoV include ELISAs, indirect immunofluorescence antibody tests, and rapid immunomigration tests. Although FIP cats tend to have higher antibody titers than non-FIP cats, there is considerable overlap and therefore an elevated FCoV titer in itself is of limited diagnostic value.
- Analysis of effusion samples can be very helpful. FIP effusions are typically protein-rich, comprising >50% globulins with a low albumin:globulin ratio and elevated AGP levels. Serum antibody testing of effusion samples for FCoV titers is unreliable and not recommended (Tasker, 2018).

Definitive diagnosis of FIP is by immunohistochemistry (IHC) of formalin-fixed tissues to identify FCoV antigen. A positive IHC result is diagnostic for FIP, although a negative result does not rule it out because FCoV antigen can be variably distributed within lesions.

Immunostaining of FCoV antigen in effusion samples is also possible but has lower sensitivity than IHC of tissues, meaning that false-negative results can occur. Immunostaining of FCoV antigen in aqueous humor samples from postmortem FIP cases has recently been described. This showed a sensitivity of 64% and specificity of 82%, limiting the use of this technique as a diagnostic tool for FIP (Felten et al., 2018).

RT-PCR assays are also available for FCoV mRNA detection from effusions, blood, tissue, cerebrospinal fluid (CSF) or aqueous humor, but these are not specific for FIP (Tasker, 2018). Furthermore, a study using RT-PCR to detect FCoV mutations in effusions showed high specificity but poor sensitivity (Barker et al., 2017).

Feline Immunodeficiency Virus

Characteristics, Clinical Relevance, and Epidemiology

Feline immunodeficiency virus (FIV) is a single-stranded RNA virus of the family Retroviridae, subfamily Lentivirinae, and is a significant cause of feline morbidity and mortality worldwide (Elder et al., 2010; Pedersen et al., 1987; Willis, 2000a). The virus is unstable outside its host and is rapidly deactivated by common hospital disinfectants, although retroviruses in dried biological deposits can remain viable for up to 1 week (Levy et al., 2008).

FIV seroprevalence rates in healthy cats are generally less than 5%, but in clinically ill cats and in certain populations at high risk of exposure (such as feral cats or cats in rehoming shelters), seroprevalence rates above 10% are recorded (Burling et al., 2017; Gates et al., 2017; Stavisky et al., 2017). There is a higher incidence in male cats, in cats over 6 years of age, and in cats with a free-roaming lifestyle. The predominant mode of transmission is in saliva or blood via fight wounds although it can also be transmitted vertically via prenatal and postnatal routes (Elder et al., 2010; Pedersen et al., 1989; Sellon & Hartmann, 2012; Willis, 2000a; Yamamoto et al., 1989).

Whilst an FIV vaccine is commercially available, there is some doubt as to its efficacy, with a study showing no difference in FIV prevalence rates between control and FIV-vaccinated cats (Westman et al., 2016).

Disease Pathogenesis

The major clinical manifestations associated with FIV infection in cats include chronic oral cavity infections (56%), chronic upper respiratory tract disease (34%), chronic enteritis

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(19%), and chronic conjunctivitis (11%) (Pedersen et al., 1989; Yamamoto et al., 1989).

Experimentally inoculated kittens develop a transient fever and neutropenia, beginning 4–8 weeks after infection and lasting 2–14 days, which is associated with a generalized lymphadenopathy that can persist for up to 9 months (Pedersen et al., 1989). After this acute viremic phase, infected cats then enter a clinically asymptomatic period of variable duration. This is not true latency, however, because FIV replication continues and virus can still be recovered from blood, CSF, semen, and lymphoid tissues (Sellon & Hartmann, 2012). As time goes on, FIV infection leads to progressive depletion of CD4+ helper T-lymphocytes, and later on CD8+ T cells and B cells. Ultimately, in some cats this leads to a terminal phase which has been described as feline acquired immunodeficiency syndrome (feline AIDS). This period is associated with severe secondary infections, neurological dysfunction, and neoplastic disease. Common clinical findings in affected cats include stomatitis, respiratory infections, chronic enteritis, and weight loss. However, a recent study found that FIV-seropositive status alone did not significantly affect longevity, although life expectancy was lower in cats coinfected with FIV and FeLV, especially in those anemic at the time of diagnosis (Spada et al., 2018).

Ocular Signs

Ocular signs reported in FIV infection include acute and chronic conjunctivitis, anterior uveitis, pars planitis, glaucoma, retinopathy, neuro-ophthalmic abnormalities, and intraocular neoplasia (Sellon & Hartmann, 2012).

Conjunctivitis

Specific pathogen-free (SPF) cats inoculated with FIV develop a lymphocytic conjunctivitis (Callanan et al., 1992). In clinical practice, one retrospective study of chronic conjunctivitis reported that 8.5% of affected cats were FIV positive, compared with 2.6% of normal cats (Nasisse et al., 1993), whereas a study of FIV-infected cats showed that 11% had signs of chronic conjunctivitis (Yamamoto et al., 1989). However, in neither clinical study was it determined whether the conjunctivitis was a primary effect of FIV or caused by secondary infection with another pathogen.

Anterior uveitis and pars planitis

SPF cats infected with FIV develop a lymphocytic-plasmacytic uveitis in the absence of opportunistic infections, suggesting that FIV can be a primary cause of feline uveitis (Callanan et al., 1992; Loesenbeck et al., 1996). In addition, because FIV infection predisposes to secondary infection with organisms such as *Toxoplasma gondii*, many clinical cases of anterior uveitis in FIV-infected cats might represent such opportunistic infections (Davidson et al., 1993a; English et al., 1990).

Pars planitis has also been reported in FIV-infected cats and manifests as an accumulation of white inflammatory infiltrates in the peripheral anterior vitreous, giving a "snowbanking" effect when viewed ophthalmoscopically (English et al., 1990).

Glaucoma has also been reported in FIV-infected cats but is likely secondary to chronic uveitis rather than a primary manifestation of FIV (Willis, 2000a).

Retinopathy

An FIV retinopathy, manifest as large geographic areas of retinal degeneration, has been described in both experimentally and naturally infected cats. Retinal perivasculitis and hemorrhage are also reported (English et al., 1990, 1994). These may well represent primary FIV pathology because similar findings are reported in HIV infection in humans. Proposed mechanisms include intravascular immune-complex deposition, direct infection of the vascular endothelium, increased plasma viscosity, or induction of neurotoxin release by glial cells (Willis, 2000a).

Neuro-ophthalmic abnormalities

Experimental infection with FIV can cause primary neurological disease, and therefore, neuro-ophthalmic abnormalities reported in FIV-infected cats, such as anisocoria and nystagmus, are likely to be ocular manifestations of central nervous system disease (English et al., 1994).

Neoplastic ocular disease in FIV-infected cats

FIV-infected cats are at higher risk of developing lymphoma compared with noninfected cats, although because FIV provirus is rarely detected in tumor cells, the link is likely to be indirect (English et al., 1994; Sellon & Hartmann, 2012). Although the exact mechanism is unknown, it is likely that FIV-associated immunosuppression and resultant reduced immune surveillance predisposes to disease development or progression (Willis, 2000a).

Coinfection with cats with FIV and other ocular pathogens

During the terminal phase of disease, FIV-infected cats are at an increased risk of a variety of opportunistic infections. FIV has been shown to prolong or worsen clinical signs in cats experimentally infected with *T. gondii* and with *Chlamydophila psittaci* (Davidson et al., 1993a; O'Dair et al., 1994). However, in FIV-infected cats there appears to be no increased risk of infection with some other pathogens including feline leukemia virus (FeLV), *Cryptococcus neoformans*, or *Bartonella henselae* (Pedersen et al., 1989; Sellon & Hartmann, 2012).

Diagnostic Testing

The mainstay for clinical screening of FIV is ELISA testing for FIV-specific antibodies, for which a variety of "in-house"

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testing kits are available. Although most kits have good sensitivity and specificity, there is significant variability between different manufacturers' kits. Negative test results are highly reliable because of high-test sensitivity and low FIV prevalence in most cat populations. However, because of lower specificity of most tests and because the consequences of a positive test result are significant, cats with positive results via in-house FIV testing should always be retested to confirm the diagnosis, by repeat antibody testing, Western immunoblotting, or viral culture (Hosie et al., 2009; Levy et al., 2008).

Feline Leukemia Virus

Characteristics, Clinical Relevance, and Epidemiology

Feline leukemia virus (FeLV) is a single-stranded RNA virus of the family Retroviridae, subfamily Oncornovirinae. It is a significant cause of feline morbidity and mortality worldwide, although since the widespread introduction of vaccination programs, its prevalence and clinical impact has reduced. As with other retroviruses, FeLV is unstable in the environment and is quickly deactivated by common hospital disinfectants, although it can remain viable for up to a week in dried biological deposits (Hartmann, 2012; Levy et al., 2008).

Reported FeLV prevalence rates in healthy cat populations in the United States are around 2%, although in ill cats and in those at increased risk, rates of 6%–33% have been reported. Risk factors for infection include male gender, adulthood, and access to outdoors (Levy et al., 2008; O'Connor et al., 1991).

FeLV can pass both vertically and horizontally. Vertical transmission from infected queens to their kittens can occur either transplacentally or via saliva during grooming in the neonatal period. Horizontal transmission occurs through close contact between FeLV-shedding and susceptible cats. Virus concentration is high in saliva (even in infected cats that are clinically healthy) and thus, transfer most commonly occurs among close living communal cats via mutual grooming and sharing of food and water bowls, or via fighting (Hartmann, 2012). FeLV susceptibility is age dependent, with a higher risk of infection in kittens younger than 16 weeks of age (Hoover et al., 1976).

Disease Pathogenesis

After exposure to the virus, FeLV first infects local lymphoid tissue and from there spreads via monocytes and lymphocytes into the peripheral circulation (Rojko et al., 1979). The FeLV provirus integrates into the host genome of infected cells, and so infection is likely to be lifelong (Cattori et al., 2006). However, by no means will all infected cats go on to develop clinical disease, and many will develop regressive infection, in which a vigorous host immune response is able to contain viral replication. In such cats, FeLV remains integrated into the cat's genome, but no viral shedding occurs, and the cats are unlikely to develop FeLV-associated disease. In cats with progressive infection, however, the virus is not contained by the host immune system, and extensive viral replication occurs within lymphoid tissue, bone marrow, and mucosal and glandular epithelial tissues. These cats usually progress to develop fatal FeLV-associated diseases within a few years of infection (Levy et al., 2008).

The main systemic diseases linked to FeLV are hemopoietic neoplasia, myelosuppression, and infectious diseases. In order of frequency, FeLV-infected cats most commonly present with secondary infections (FIP, upper respiratory tract infections, FIV, hemotrophic mycoplasmosis), stomatitis, anemia, lymphoma, leukopenia, thrombocytopenia, leukemia, and myeloproliferative disease (Hartmann, 2012). The life expectancy of FeLV-positive cats is significantly lower than that of controls (Spada et al., 2018).

FeLV is not a major cause of feline ocular disease, with one study showing that only 1.5% of 714 cats presenting with ocular problems were FeLV positive (Brightman et al., 1991). The same study, however, reported that 11.3% of FeLV-positive cats had ocular disease (a twofold increase in ocular disease compared with FeLV negative cats), which suggests a direct or indirect link and implies that all FeLV positive cats should undergo ophthalmic examination. Ocular conditions attributed to the disease include ocular lymphoma, retinal dysplasia, anemic retinopathy, and spastic pupil syndrome (Brightman et al., 1991).

Ocular Signs

Ocular lymphoma

One retrospective study of 49 cases of feline ocular lymphoma reported that 41% of cats tested were positive for FeLV (Corcoran et al., 1995), although since that time the widespread introduction of screening and vaccination programs means that the incidence of FeLV-associated ocular lymphoma is nowadays likely to be less. Ocular lymphoma usually presents as a component of multicentric disease. Anterior uveal lymphoma is the most common ocular presentation, but it can also manifest as infiltrative disease in the conjunctiva, cornea, orbit, or eyelids (Willis, 2000a).

Retinal dysplasia FeLV infection of fetal and newborn kittens leads to the development of retinal dysplastic lesions. Histopathologic changes include diffuse intraocular inflammation, retinal pigment epithelium proliferation and pigment migration, progressive retinal disorganization, and necrosis, leading to the development of dysplastic rosette structures (Albert et al., 1977).

Anemic retinopathy Anemic retinopathy may occur when hemoglobin concentration falls below 5 mg/dL, inducing local hypoxia and increased blood vessel fragility and leading to retinal hemorrhage (Fischer, 1970).

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Neuro-ophthalmic disease Anisocoria or spastic pupil syndrome (D-shaped or reverse D-shaped pupil) have been reported and are likely to be caused by lymphoma infiltration of cranial nerves or iris stroma (Brightman et al., 1991; Nell & Suchy, 1998). FeLV-associated nystagmus is presumed to be caused by lymphoma infiltration of central nervous system (CNS) tissue (Brightman et al., 1991).

Diagnostic Testing

In-house testing kits that detect soluble circulating FeLV p27 antigen in peripheral blood are most commonly used to test for FeLV infection, but since development of antigenemia following exposure can take 30 days or longer, repeat testing is advised if recent infection cannot be ruled out (Levy et al., 2008). Other tests include PCR to detect provirus and IF tests on blood or bone marrow smears to detect p27 antigen within infected blood cells. Because the consequences of a positive screening test are significant, confirmatory testing is advised. Negative screening tests are highly reliable because of the high-test sensitivity and low prevalence rate (Levy et al., 2008).

Feline Sarcoma Virus

Characteristics, Clinical Relevance, and Epidemiology

Feline sarcoma virus (FeSV) is a member of the family Retroviridae, subfamily Oncornovirinae. It is a hybrid virus that forms when FeLV DNA provirus inserts near a host proto-oncogene and incorporates it into the provirus genome. FeSV is an acutely transforming virus, inducing rapidly growing and multicentric sarcomas, mostly in young cats. However, its clinical relevance with respect to ocular disease is unclear.

FeSV is replication deficient, requiring FeLV as a helper virus for replication, and cats with FeSV always test positive for FeLV. Natural transmission of FeSV between cats has not been reported (Modiano & Breen, 2007).

Experimental intraocular injection of FeSV in neonatal kittens is capable of inducing invasive anterior uveal melanoma formation (Albert et al., 1981). PCR testing of 36 naturally occurring feline uveal melanomas identified FeLV/FeSV DNA in three cases (Stiles et al., 1999). Another study, however, failed to identify FeSV/FeLV in 10 cases of feline diffuse iris melanoma (Cullen et al., 2002). Thus, the clinical significance of the role of FeSV/FeLV in the development of feline uveal melanoma remains unclear.

To date, studies have failed to identify FeSV or FeLV in any cases of feline ocular sarcoma (Cullen et al., 1999, 2002).

Feline Panleukopenia Virus

Characteristics, Clinical Relevance, and Epidemiology

Feline panleukopenia virus (FPV) is a single-stranded DNA virus of the family Parvoviridae, genus *Parvovirus*. It is very stable in the environment, able to survive for 1 year at room temperature in organic material, and capable of surviving disinfection with 70% alcohol and a number of disinfectants, although it is inactivated by bleach in 10 minutes at room temperature (Greene, 2012a).

FPV is shed from all body secretions during active infection, and because of its environmental stability, it is ubiquitous and is a significant cause of feline morbidity and mortality in unvaccinated cats. Its main ocular pathology is retinal dysplasia associated with intrauterine infection.

Disease Pathogenesis

In adult cats, FPV infects rapidly dividing cells such as lymphoid tissue, bone marrow, and intestinal mucosal cells, causing a wide range of clinical signs including fever, anorexia, vomiting, leucopenia, and secondary infections. Late fetal and early neonatal infection, however, tends to result in widespread central nervous system involvement including the cerebrum, retina, and optic nerves. Ophthalmic findings include retinal dysplasia and rosette formation, retinal thinning, and optic nerve hypoplasia (Percy et al., 1975).

Diagnosis

Presumptive diagnosis is usually based on history of exposure and suggestive clinical signs. Diagnosis can be confirmed by histopathological examination of affected tissue or virus identification. Serological testing is of limited value.

Pox Virus

Pox viruses (family Poxviridae) are large double-stranded DNA viruses. Cowpox (genus *Orthopoxvirus*) can cause conjunctivitis, blepharitis, and severe ulcerative dermatitis in cats, which can be fatal (Möstl et al., 2013; O'Halloran et al., 2016). Despite its name, rodents (primarily mice and voles) are the main reservoir host. Transmission of cowpox from cats to humans has also been reported (Gaskell et al., 1983; Lawn, 2010; O'Connor et al., 1990; Świtaj et al., 2015). Diagnosis is via PCR or VI from tissue samples.

Pathogenic Canine Viruses

Canine Herpesvirus-1

Characteristics, Clinical Relevance, and Epidemiology

Canine herpesvirus-1 (CHV-1) is a double-stranded DNA virus of the family Herpesviridae, subfamily Alphaherpesvirinae. It is relatively unstable in the environment and is susceptible to most disinfectants, antiseptics, and detergents.

The virus is widespread in the canine population, with serological surveys suggesting infection rates from 30% to as high as 100%. It is a significant cause of fetal and neonatal mortality, but infection of older dogs usually results in only mild clinical disease. Most infected dogs go on to develop lifelong latent infection, with the virus persisting in ganglionic and lymphoid tissues of the oronasal and genital mucosae

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(Greene, 2012b). Viral recrudescence can occur spontaneously or secondary to physiological or pharmacological stress. Infection is via direct contact with mucosal secretions.

Disease Pathogenesis

Infection *in utero* or in the early neonatal period can result in fatal disseminated viral replication within the parenchymal organs and CNS. Older dogs, however, rarely show clinical signs or develop only mild clinical illness such as transient upper respiratory disease or vaginitis.

Ocular Signs

Ocular signs of experimental CHV-1 infection in newborn puppies include keratitis, panuveitis, retinal necrosis, and optic neuritis (Albert et al., 1976).

In adult dogs, CHV-1 has been associated with a self-limiting conjunctivitis in both experimental and naturally acquired infections (Ledbetter et al., 2009a, 2009b, 2009c). Dendritic, punctuate, and geographic corneal ulceration has been reported in naturally acquired CHV-1 disease (Ledbetter et al., 2006, 2009c) and after experimental reactivation of latent CHV-1 with immunosuppressive doses of prednisolone (3 mg/kg/day) (Ledbetter et al., 2009d). Topical ocular corticosteroids administered to experimentally infected dogs did not induce CHV-1 reactivation, nor did topical cyclosporine (Ledbetter et al., 2010, 2012; Pennington et al., 2017). However, a single case report describing CHV-1 associated dendritic ulceration in a dog treated with topical prednisolone acetate and tacrolimus suggests that local as well as systemic immunosuppression might play a role in reactivation of CHV-1 in some dogs (Gervais et al., 2012).

Diagnosis

Diagnosis of CHV-1 can be made via PCR or VI.

Canine Distemper Virus

Characteristics, Clinical Relevance, and Epidemiology

Canine distemper virus (CDV) is a negative stranded RNA virus of the family Paramyxoviridae, genus *Morbillivirus*. It is relatively unstable in the environment, surviving for around 3 hours at room temperature, and is susceptible to most hospital disinfectants. It is a significant cause of canine morbidity and mortality, especially in unvaccinated weaned puppies between 3 and 6 months of age. CDV is highly contagious, and infection is usually via aerosol droplets from respiratory secretions (Greene & Vandevelde, 2012).

In pregnant bitches, transplacental infection of puppies can also occur. Depending on stage of pregnancy, this may lead to abortion, stillbirth, or the birth of weak or immunodeficient puppies.

Disease Pathogenesis

After aerosol infection, CDV replicates in the epithelial and lymphoid tissues of the upper respiratory tract and from there spreads to most epithelial and CNS tissues. The immune status of the host and the pathogenicity of the viral strain determine the severity of the resultant clinical disease.

Systemic signs can vary from mild to severe. More than 50% of infections are thought to be subclinical (Greene & Vandevelde, 2012). Mild disease is common and is characterized by transient oculonasal serous discharge, lethargy, fever, inappetance, and cough from which affected dogs quickly recover. Severe generalized disease can occur at any age but can be found most commonly in unvaccinated puppies from 12 to 16 weeks of age. Acute conjunctivitis, fever, anorexia, and a dry cough that rapidly becomes productive is followed by vomiting, diarrhea, and severe bronchopneumonia which may prove fatal.

Neurological disease can occur in CDV infection. Young puppies or immunodeficient dogs can develop acute fatal encephalomyelitis (Krakowka & Koestner, 1976). Older immunocompetent dogs can develop immune-mediated demyelinating disease or chronic progressive encephalomyelitis ("old dog encephalitis") after apparent recovery from acute CDV disease. CNS signs include hyperesthesia, seizures, ataxia, myoclonus, cerebellar and vestibular signs, paraparesis, or tetraparesis (Willis, 2000b).

Ocular Signs

- Acute conjunctivitis is the first clinical sign of acute CDV infection. A bilateral serous or catarrhal ocular discharge becomes mucopurulent over a period of days.
- Acute keratoconjunctivitis sicca is also seen in acute CDV infection and is caused by dacryoadenitis. It is usually transient and typically resolves over a period of weeks (de Almeida et al., 2009; Kaswan et al., 1985; Sansom & Barnett, 1985; Stiles, 2012; Willis, 2000b).
- Intraocular disease is frequently reported with CDV infection. Chorioretinitis lesions are common in cases of CDV encephalomyelitis, with one study identifying them in 40% of cases that received an ophthalmic examination. They are most frequently identified in the non-tapetal fundus and manifest as perivascular cuffing, retinal edema, and retinal blood vessel congestion in acute disease (Fischer, 1971; Jubb et al., 1957; Thomas et al., 1993). Optic neuritis can also develop, usually in association with neurological signs (Jubb et al., 1957; Richards et al., 2011). Mild asymptomatic anterior uveitis has been described in experimental infections but is seldom a significant problem in natural infections (Fischer, 1971; Willis, 2000b).

Diagnosis

Suggestive clinical history, signs, and signalment are sufficient to make a presumptive diagnosis of distemper in many cases. Hematological and serum biochemical findings are nonspecific but might include thrombocytopenia and regenerative anemia. In acute disease, CDV inclusion bodies can be identified in conjunctival scrapes and can be confirmed

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by FA staining (Stiles, 2012). In cases with neurological signs, CSF analysis might show elevated protein and cell count (primarily lymphocytes). The presence of anti-CDV antibody within the CSF is considered diagnostic as long as there is no blood contamination during the collection procedure (Greene & Vandevelde, 2012). RT-PCR testing for CDV DNA is commercially available and can be performed on CSF samples (Frisk et al., 1999).

Canine Adenovirus-1

Characteristics, Clinical Relevance, and Epidemiology

Canine adenovirus-1 (CAV-1) is a DNA virus of the family Adenoviridae, genus *Mastadenovirus*. It is environmentally stable, surviving for days in organic material at room temperature and for many months below 4°C. It is resistant to a number of disinfectants but is inactivated by iodine, phenol, and sodium hydroxide or by heating to above 50°C for 5 minutes.

Serological surveys have demonstrated a high level of exposure to CAV-1 in feral and wildlife dog populations worldwide. It is the cause of infectious canine hepatitis and as such is a significant cause of morbidity and mortality in dogs and other *Canidae*. Dogs younger than 1 year of age are most commonly affected although it can affect unvaccinated dogs of all ages. CAV-1 is transmitted via the oropharyngeal route and can be spread by direct contact, contaminated fomites, and possibly via ectoparasites. The virus is present in all body tissues and secretions during the acute phase of infection and continues to be excreted in the urine for 6–9 months postinfection (Greene, 2012c).

Disease Pathogenesis

After oropharyngeal exposure, CAV-1 localizes in the tonsils before spreading via regional lymph nodes and lymphatics to the bloodstream. Viremia develops between 4 and 6 days after infection and leads to rapid systemic dissemination of the virus. Parenchymal cells of the liver, glomerular endothelial cells of the kidney, and corneal endothelial cells are prime viral targets. Clinical signs during the early stages of infection include fever, abdominal pain, vomiting, diarrhea, hematemesis, petechiation of mucous membranes, and lymphadenopathy. A strong antibody response from day 7 allows viral clearance from the blood and liver, but if this does not develop, then fatal hepatic necrosis may ensue.

Ocular Signs

Twenty percent of naturally infected dogs and 0.4% of dogs given a modified live CAV-1 vaccine develop ophthalmic disease (Curtis & Barnett, 1983). Afghan hounds have been reported to be at increased risk of CAV-1-induced ocular disease (Curtis & Barnett, 1981). Unilateral ocular signs are most common, but bilateral disease also occurs (Willis, 2000b).

Ocular signs of CAV-1 infection are biphasic. During the viremic phase of disease, virus enters the anterior chamber to infect and replicate in corneal endothelial cells. Blood–aqueous barrier breakdown during this stage results in an influx of inflammatory cells and resultant anterior uveitis, which tends to be mild. Histologically, this phase is characterized by mononuclear cell infiltration of the iris stroma and trabecular meshwork. During this phase, virus can be isolated from the aqueous humor, and replicating virus can be identified within corneal endothelial cells. The second phase of disease, which typically develops between days 7 and 21 postinfection, is more clinically severe and is associated with an extensive corneal edema that can lead to functional blindness in some cases. In this phase, active viral replication is not present; instead, the pathology is caused by a Type III hypersensitivity (Arthus) reaction in which immune complex deposition and complement fixation on the endothelial cell surface induces endothelial decompensation. In the majority of cases, this is self-limiting, and endothelial cell recovery leads to gradual resolution of edema from around 21 days postinfection. (Aguirre et al., 1975; Carmichael, 1964, 1965; Carmichael et al., 1975; Curtis & Barnett, 1983; Greene, 2012c).

Diagnosis

In clinical practice, diagnosis is usually presumptive and is based on suggestive history, signalment, and clinical signs. Hematological findings during the initial viremic stage of infection are nonspecific but can include lymphopenia, neutropenia, and thrombocytopenia. Increased liver enzyme parameters might be present depending on the degree of hepatic necrosis. Bilirubinuria and proteinuria (primarily albuminuria) is often present. Serological testing, viral isolation, and IFA testing are available but are not commonly performed in clinical practice (Greene, 2012c).

Acute unilateral or bilateral corneal edema developing 1–3 weeks after a period of transient systemic disease or after vaccination against infectious canine hepatitis is suggestive of CAV-1-induced ocular disease.

Canine Adenovirus-2

Characteristics, Clinical Relevance, and Epidemiology

Canine adenovirus-2 (CAV-2) is a DNA virus of the family Adenoviridae, genus *Mastadenovirus*, closely related to CAV-1. It is one of the agents implicated in canine infectious laryngotracheobronchitis ("kennel cough"). Young and unvaccinated animals in close contact are most at risk, although vaccinated dogs can still develop clinical signs. The virus replicates in the epithelium of the nasal mucosa, pharynx, tonsils, trachea, and bronchi. Transmission is via oronasal contact (Ford, 2012).

Disease Pathogenesis and Ocular Signs

After infection and replication in the epithelial cells of the upper respiratory tract, CAV-2 causes a mild, self-limiting upper respiratory disease in dogs. Clinical signs are usually

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limited to acute onset coughing in an otherwise healthy dog. CAV-2 has been isolated from cases of idiopathic canine conjunctivitis, suggesting it may be a causal agent (Ledbetter et al., 2009b).

Tick-Borne Encephalitis Virus

Tick-borne encephalitis virus (TBEV) is an enveloped RNA virus (family Flaviviridae, genus *Flavivirus*) that is the major cause of tick-transmitted viral encephalitis in humans in Europe and Asia. Dogs are susceptible to infection with TBEV, but they are accidental hosts that are unable to further disseminate the virus. Serological surveys suggest a significant and increasing incidence of infection in dogs across Europe (Beugnet & Marié, 2009; Csángó et al., 2004; Klimes et al., 2001). Most canine infections are asymptomatic, but in some cases, the disease is fatal. Clinical signs are neurological in origin and include paresis, ataxia, myoclonus, tetraplegia, facial nerve paralysis, anisocoria, nystagmus, and optic neuritis (Pfeffer & Dobler, 2011; Stadtbäumer et al., 2004).

Canine Papilloma Virus

Papillomaviruses (family Papillomaviridae) are species specific, double-stranded DNA viruses that induce papilloma formation in their host species. In addition to skin and oral lesions, canine papilloma virus (CPV) has been associated with ocular papilloma development in dogs (Nicholls & Stanley, 1999; Sansom et al., 1996). However, in older dogs, conjunctival papilloma is not associated with CPV (Beckwith-Cohen et al., 2015)

Pathogenic Equine Viruses

Equine Herpesvirus-1 and Equine Herpesvirus-2

Equine herpesvirus-1 (EHV-1) is a double-stranded DNA virus of the family Herpesviridae, subfamily Alphaherpesvirinae. It is the cause of equine rhinopneumonitis, abortion, and neurological disease (Patel & Heldens, 2005). Experimental infection induces mild multifocal chorioretinitis lesions which develop after clinical signs of upper respiratory tract disease have resolved (Hussey et al., 2013; Slater et al., 1992). It has also been linked to a wide variety of other ocular signs, most likely secondary to neurological disease, including blindness, strabismus, ptosis, keratoconjunctivitis sicca, optic neuritis, and neuroparalytic keratitis (Andrew & Willis, 2005; Hughes, 2010; Maggs, 2003).

Equine herpesvirus-2 (EHV-2) (family Herpesviridae, subfamily Betaherpesvirinae) is a common respiratory pathogen of horses and has been implicated as a cause of equine keratoconjunctivitis in both foals and adult horses. Ocular findings described include multifocal subepithelial punctate corneal opacification, lace-like corneal opacities, and conjunctivitis (Andrew & Willis, 2005; Collinson et al., 1994; Kershaw et al., 2001). However, EHV-2 can also be identified in ocular samples from clinically healthy horses, so its role as a primary ocular pathogen must be questioned.

Viral isolation or PCR from ocular or nasopharyngeal swabs can be used to confirm the presence of EHV-1 or EHV-2. Given the high prevalence of both viruses in the equine population, serology is of limited value.

Borna Disease Virus

Borna disease virus (family Bornaviridae, genus *Bornavirus*) is an enveloped RNA virus with a worldwide distribution. It causes sporadic cases of meningoencephalomyelitis, primarily in horses and sheep, although it is also capable of infecting a wide range of warm-blooded species including, among others, cattle, goats, rabbits, deer, cats, birds, and humans (de la Torre, 1994; Hatalski et al., 1997; Reeves et al., 1998; Richt et al., 1997). The mode of transmission is uncertain, but because horizontal transmission between infected horses or sheep does not occur, a reservoir host is suspected, and rats have been implicated in transmission via nasal infection from contaminated urine (Sauder & Staeheli, 2003). Ophthalmic signs include abnormal pupillary light reflexes and blindness. These signs could be in part caused by CNS disease, but the virus has also been shown to cause extensive photoreceptor degeneration in naturally infected horses (Dietzel et al., 2007).

African Horse Sickness Virus

African horse sickness virus (AHSV) (family Reoviridae, genus *Orbivirus*) is an RNA virus that, like the closely related blue tongue virus, is transmitted by *Culicoides* midges (Maclachlan & Guthrie, 2010; Mizukoshi et al., 1992). It presents in a variety of ways, from peracute disease with mortality rates exceeding 90%, to clinically inapparent infections. The condition primarily affects the circulatory and respiratory systems, causing hemorrhagic and effusive disease. Ocular signs include conjunctival petechiation and vascular congestion and edema of the supraorbital fossa (Mellor & Hamblin, 2004).

Equine Infectious Anemia Virus

Equine infectious anemia virus (EIAV) (family Retroviridae, genus *Lentivirus*) is an RNA virus that is transmitted by mosquitoes and biting flies. It causes cyclical anemia and thrombocytopenia which can lead to conjunctival petechiation and intraocular hemorrhage (Maclachlan & Guthrie, 2010; Sellon, 1993).

Equine Viral Arteritis

Equine viral arteritis (EVA) (family Arteriviridae) is an enveloped RNA virus of horses that is transmitted via inhalation or via sexual transmission. It causes a panvasculitis, with systemic signs of fever, depression, dependent edema, oculonasal discharge, and abortion. Ophthalmic signs of conjunctivitis, photophobia, and periorbital edema might be observed (Del Piero, 2000; Glaser et al., 1996).

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Equine Encephalomyelitis Viruses

These related viruses (family Togaviridae, genus *Alphavirus*) are arthropod (mostly mosquito)-transmitted RNA viruses with zoonotic potential. New-world alphaviruses, including Venezuelan equine encephalitis (VEE), Eastern equine encephalitis (EEE), and Western equine encephalitis (WEE) cause potentially fatal encephalitis in both horses and humans in the Americas. VEE virus often causes massive epizootics in horses and spillover epidemics in humans, whereas EEE virus and WEE virus typically result in individual cases or limited outbreaks in both horses and humans (Steele & Twenhafel, 2010). Clinical signs include ataxia, stupor, hyperesthesia, paralysis, aggression, strabismus, pupillary dilation, and blindness.

Equine Adenovirus-1

This double-stranded DNA virus (family Adenoviridae) primarily causes pneumonia in immunocompromised Arabian foals but can also cause conjunctival and lacrimal gland epithelial necrosis and panuveitis (McChesney & England, 1975).

West Nile Virus

West Nile Virus (family Flaviviridae, genus *Flavivirus*) is a mosquito-transmitted RNA virus of birds that occasionally infects and causes disease in other vertebrates, including humans and horses. Signs in horses are primarily neurological, including ataxia, paresis and hyperesthesia, facial nerve paralysis, and blindness. In humans, panuveitis has also been reported, and the condition can be fatal in both species (Castillo-Olivares & Wood, 2004; Gerhardt, 2006; Murray et al., 2010).

Pathogenic Production Animal Viruses

Bovine Herpesvirus-1

Bovine herpesvirus-1 (BHV-1) is a double-stranded DNA virus of the family Herpesviridae, subfamily Alphaherpesvirinae, and is the cause of infectious bovine rhinotracheitis (IBR). It has also been associated with infectious pustular vulvovaginitis, abortion, and mastitis. It is widespread in the cattle population and is a significant cause of morbidity worldwide (Muylkens et al., 2007).

IBR usually occurs in outbreaks within a cattle herd. Direct nose-to-nose transmission between animals is the usual route of infection although aerosol transmission over short distances has been demonstrated (Mars et al., 2000). Cattle of all ages can be affected. Clinical signs, which develop between 2 and 6 days after infection, are mostly restricted to the upper respiratory tract and trachea. Fever and anorexia develop in association with coughing, ulceration of oronasal mucous membranes, hypersalivation, and oculonasal discharge that progresses from serous to mucopurulent. Secondary bacterial infections can ensue and prove fatal in some cases. In cattle that survive, a lifelong latent infection is established in sensory ganglia, and recrudescent disease allows maintenance of infection within a cattle herd.

Although conjunctivitis is the most common ocular sign associated with IBR, keratitis and anterior uveitis are also described (Rebhun et al., 1978; Timoney & O'Connor, 1971).

Clinical signs of IBR are fairly characteristic, but diagnosis should be confirmed by viral isolation from swabs taken early in the course of disease. Rising serum antibody titers can also be used to aid diagnosis.

Malignant Catarrhal Fever

Malignant catarrhal fever (MCF) is caused by the ruminant gamma-herpesviruses alcelaphine herpesvirus-1 (AlHV-1) and ovine herpesvirus-2 (OvHV-2). These viruses establish latency in B lymphocytes in their reservoir hosts (wildebeest for AlHV-1 and sheep for OvHV-2) where they cause asymptomatic infection, although virus excretion occurs at low level either constantly or intermittently, creating a source of infection for reservoir and nonreservoir hosts.

Where reservoir hosts are kept in close proximity to nonreservoir but MCF-susceptible species, including cattle, deer, bison, water buffalo, and pigs, the virus may cross-infect to cause clinical disease. In such animals, a fatal lymphoproliferative disease commonly ensues. MCF either presents as sporadic disease, affecting a small number of animals within a herd, or as epizootic outbreaks (Ackermann, 2006; Barton et al., 2011; Callan & Van Metre, 2004; Russell et al., 2009).

The disease pathogenesis in susceptible animals is incompletely understood but is triggered by invasion of host tissues by predominantly CD8+ T lymphocytes, some of which contain virus. Extensive tissue destruction then ensues as a result of indiscriminate cellular killing by cytotoxic T lymphocytes and natural killer cells (Russell et al., 2009). Clinically, this shows as acute and fatal pansystemic vasculopathy.

MCF presents in a variety of forms. Peracute disease, which can be found more commonly in deer than in cattle, can result in sudden death before clinical signs become apparent. In the acute form of the disease, ocular signs are one of the earliest presentations. Corneal edema, corneal ulceration, and panophthalmitis develop secondary to a severe lymphocytic vasculitis. Additional signs include fever, lymphadenopathy, oronasal ulceration, and hemorrhagic enteritis. In the chronic form of the disease, ulcerative skin lesions are common, and the disease may have a waxing and waning course. The majority of cattle ultimately die, although around 5% do recover.

Clinical signs of MCF are fairly characteristic, although the disease can mimic other infectious diseases including anthrax, mucosal disease (MD), foot and mouth disease, and IBR. Postmortem findings reveal extensive lymphocytic vascular infiltrates affecting many body systems. PCR to detect viral DNA is the diagnostic test of choice.

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Bovine Viral Diarrhea Virus

Bovine viral diarrhea virus (BVDV) is a member of the family Flaviviridae, genus *Pestivirus*. Pestiviruses are small, enveloped RNA viruses that infect animals of the order Artiodactyla (which includes cattle, sheep, camelids, antelope, and deer). They have relatively poor environmental stability and are inactivated by all common disinfectants. BVDV is the cause of MD, a fatal condition.

The virus has a worldwide distribution and is arguably the most widespread cattle virus in the world (Peterhans et al., 2010). Despite its extremely high prevalence, morbidity rates are low because the majority of infected cattle show no clinical signs of disease.

BVDV has two biotypes, cytopathic (cp) and noncytopathic (ncp). The ncp type (but not the cp type) can establish persistent infection in the fetus when vertically transmitted from the dam early in gestation (between the second and fourth month of the 9.5-month gestation period) before maturity of the adaptive immune system. The fetus is unable to mount an immune response against the virus and remains persistently infected. Infection results in abortion, stillbirth, congenital malformations, or the birth of clinically normal but persistently infected calves. Although such animals account for only 1% of cattle in an infected region, they ensure viral persistence in the population. Viral shedding from persistently infected cattle via the feces allows infection of naïve cattle within the same herd. These may develop mild respiratory signs or diarrhea but are only transiently infected because an effective immune response eliminates the virus, and after seroconversion, they are protected from reinfection for life. Should they become infected between the second and fourth month of pregnancy, they can pass the infection to their fetus which will then become permanently infected (Peterhans et al., 2010).

In persistently infected cattle, spontaneous mutation of ncp virus into cp virus can trigger the development of MD. This is a fatal condition causing fever, leukopenia, diarrhea, dehydration, erosive oronasal lesions, and death within a few days of onset.

Ocular signs and CNS defects can be seen in fetuses infected during the second trimester of gestation. These include cataracts, retinal dysplasia, optic nerve gliosis, microphthalmia, cerebellar hypoplasia, microencephaly, and hydrocephalus (Bistner et al., 1970; Kahrs et al., 1970).

Clinical signs, postmortem findings, and viral isolation are required for diagnosis. Because of the high seroprevalence rate of BVDV, a single serological test is not helpful, although rising titers in paired serum samples taken more than 2 weeks apart can verify recent infection.

Bluetongue Virus

Bluetongue virus (family Reoviridae, genus *Orbivirus*) is a nonenveloped RNA virus of ruminants which is transmitted by biting midges of the genus *Culicoides*. It infects vascular endothelial cells, mononuclear phagocytes, and lymphocytes within lymphoid tissues, lungs, skin, and other tissues (Maclachlan et al., 2009). Among domestic livestock, bluetongue most commonly causes clinical disease in sheep, whereas asymptomatic infection is observed in cattle within endemic regions. However, certain serotypes can cause outbreaks of severe clinical disease in cattle (Darpel et al., 2007; Maclachlan et al., 2009). Until recently, bluetongue was restricted to a geographical band between approximately 40°N and 35°S, but a northward extension within Europe has been observed, and the disease is now of significant economic impact in the countries of northern Europe, spreading as far north as the United Kingdom (Gloster et al., 2008; Maclachlan & Guthrie, 2010; Wilson & Mellor, 2009).

Disease pathogenesis involves vascular damage within target tissues. Clinical signs can be mild but prove fatal in up to 30% of cases and include: oral and upper gastrointestinal ulceration and hemorrhage; coronitis; skeletal and cardiac muscle necrosis; pulmonary and subcutaneous edema; and pericardial, pleural, and abdominal effusions (Maclachlan et al., 2009). Transplacental infection during the first trimester of pregnancy, or vaccination of ewes or cows with a live attenuated virus vaccine during this period, can lead to abortion or the birth of offspring affected with ocular and CNS abnormalities including ataxia, blindness, and necrotizing retinitis (Osburn et al., 1971a, 1971b).

Clinical signs and postmortem findings are usually characteristic, but definitive diagnosis requires VI or the identification of viral RNA by PCR.

Bovine Leukemia Virus

Bovine leukemia virus (BLV) (family Retroviridae, genus *Deltaretrovirus*) is the cause of enzootic bovine leukosis. Although vertical transfer can occur, it is primarily transmitted horizontally through transfer of infected B lymphocytes via direct contact, through milk and possibly via insect bites (Burny et al., 1978; Gillet et al., 2007; Hopkins & DiGiacomo, 1997). BLV is now almost completely eradicated from the European Union but is of major economic impact in many parts of the world, including the United States and Canada (Rhodes et al., 2003; Scott et al., 2006). Orbital lymphoma induced by BLV often leads to progressive unilateral or bilateral exophthalmos (Rebhun, 1982).

Bovine Papillomavirus

Bovine papillomavirus (BPV) has been implicated as a possible etiological factor in the development of bovine ocular squamous cell carcinoma (OSCC); although no direct link has been found between BPV and OSCC, it is possible that the virus plays a role in initiation of tumor development (Ford et al., 1982; Rutten et al., 1992).

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Pseudorabies Virus

Suid herpesvirus-1 (family Herpesviridae, subfamily Alphaherpesvirinae) is the cause of pseudorabies (Aujeszky's disease) in pigs, but the virus is able to infect and cause clinical disease in a wide range of other nonhost species including cattle, sheep, goats, dogs, and cats as well as a number of wildlife species. Infection is via inhalation of aerosolized virus, which can be transmitted up to 2 km by airborne spread. Adult pigs are usually asymptomatic, but the disease has a high mortality rate in piglets and is invariably fatal in nonhost species. Neurological signs predominate, and ocular signs are likely to be related to these. In experimentally infected pigs, keratoconjunctivitis, corneal ulceration, and anterior uveitis are reported (Schneider & Howarth, 1973). A case series of pseudorabies in the dog reported blindness, abnormal pupillary light reflexes, ptosis, facial paresis, excessive lacrimation, and photophobia (Monroe, 1989).

Hog Cholera Virus

This virus (family Flaviviridae, genus *Pestivirus*) causes classic swine fever or hog cholera. The route of transmission is uncertain, although direct contact, airborne spread, and indirect spread via fomites are reported (Ribbens et al., 2004). Clinical signs are indistinguishable from those of African swine fever (family Asfarviridae). Both are highly infectious and cause potentially fatal hemorrhagic disease with ocular signs including conjunctivitis, severe ocular discharge, blepharitis, panuveitis, and optic neuritis (Saunders et al., 1958).

Pig Paramyxovirus

Pig paramyxovirus (family Paramyxoviridae) is the cause of blue eye disease of pigs. In young piglets this causes corneal edema and CNS signs caused by anterior uveitis and encephalomyelitis. In older animals, corneal edema and reproductive failure are more commonly seen (Stephan et al., 1988).

Pathogenic Avian and Exotic Animal Viruses

Marek's Disease Virus

Marek's disease virus (family Herpesviridae, subfamily Alphaherpesvirinae) is an oncogenic virus that can induce T lymphocyte transformation and cause lymphoproliferative tumors in chickens. The virus is shed from feather follicles and is highly contagious, leading to severe outbreaks of disease primarily affecting younger birds, with mortality rates up to 80%. Clinical signs include depression, paralysis, blindness, and death (Ficken et al., 1991). Histopathological examination of affected eyes reveals malignant lymphocytic infiltration of optic and ciliary nerves and the uveal tract, leading to a severe panuveitis and retinal necrosis (Pandiri et al., 2008; Smith et al., 1974).

Avian Encephalomyelitis Virus

Avian encephalomyelitis virus (AEV) (family Picornaviridae) is a neurotrophic virus that infects chickens, quail, turkeys, pheasants, and pigeons (Marvil et al., 1999; Shafren & Tannock, 1991). Infection is via horizontal or vertical transmission. The virus causes ataxia and tremors in young chickens, with mortality rates around 5%, although this can be significantly higher in some outbreaks. Pathological findings show lymphocytic infiltration of nervous tissue leading to gliosis and neuronal degeneration. Ocular signs reported include cataract and blindness (Welchman et al., 2009).

Poxviruses

Avian poxvirus (family Poxviridae, genus *Avipoxvirus*) causes blepharitis and conjunctivitis in psittacine birds (Boosinger et al., 1982; Katoh et al., 2010).

Myxoma virus (family Poxviridae, genus *Leporipoxvirus*) is the cause of myxomatosis, a fatal arthropod-borne disease of rabbits. Ocular signs include conjunctivitis and blepharedema that can be severe enough to cause functional blindness (Krogstad et al., 2005; Patton & Holmes, 1977; Spiesschaert et al., 2011).

Ocular Bacteriology

Introduction

Bacteria are prokaryotic organisms consisting of a *cell membrane* (i.e., cell wall or envelope), *cytoplasm*, and in some instances, specialized surface structures such as *capsules* and *fimbriae*. Bacterial *cell walls* are composed of phospholipids and proteins that contain the electron transport system, serve as an osmotic barrier, and regulate transport of solutes. The cell wall is also the site of many antigenic determinants for various bacteria, whereby variability of surface polysaccharides allows serologic differentiation of isolates. Endotoxin, when present, is located within the cell wall, where a lipid component (i.e., lipid A) is primarily responsible for toxicity. Bacterial *cytoplasm* contains a single, circular strand of DNA, plasmids (smaller molecules of DNA), and ribosomal RNA. Plasmids carry information for drug resistance (R factors), or code for toxins that can affect host cellular functions. Fimbriae (or pili) are short, hairlike extensions of the cell membrane that mediate adhesion to specific surfaces. Fimbriae aid in the initial colonization of the host, but they may also increase susceptibility of bacteria to phagocytosis (Quinn et al., 2011c, 2011d).

Because bacteria lack both a nucleus and a mitotic apparatus, they reproduce by asexual binary fission, involving ingrowth of the cell wall and cleavage of the intracellular compartment with division of cell contents.

The bacterial growth cycle typically consists of four phases: the lag phase, the logarithmic growth phase, the

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stationary growth phase, and a decline phase. Bacteria vary in their temperature requirements for growth and can be divided into psychrophiles (0–20°C), mesophiles (20–40°C), and thermophiles (40–90°C). Most bacteria are mesophiles, with some important mesophiles, such as *Staphylococcus* sp., capable of growth at temperatures below their normal growth range. Others, such as *Streptococcus* and *Proteus* sp., possess the ability for psychrophilic growth.

Iron is an essential nutrient for bacteria. Iron availability affects bacterial growth and can influence the nature of a bacterial infection. The fact that the eye is iron-deficient might aid in its resistance to bacteria. Bacteria can undergo phenotypic changes, however, and develop ways to acquire iron from infected tissue. Under conditions of iron-restricted growth, pathogenic bacteria may produce exotoxins and thereby acquire iron from damaged host cells (Griffiths, 1987).

General Pathogenic Mechanisms and Host Responses

The infectivity of a microorganism is greatly influenced by its ability to initiate the infectious process. Bacterial adhesion to epithelial cells is recognized as a critical initial stage in the colonization of mucosal surfaces and in the pathogenesis of ocular infections (Smith, 1995). Adhesins (i.e., protein determinants of adherence) have been identified for most bacterial pathogens and have been shown to function *in vivo* (Razin & Jacobs, 1992; Rhem et al., 1996). Some adhesins are expressed in bacterial fimbriae (Wu et al., 1995).

Host cell receptors that form linkages with bacterial adhesins have been identified as carbohydrates or carbohydrate moieties of cell membrane glycoproteins (Beachey, 1981). Sialic acid is reported to be a receptor molecule for bacterial adhesion (Ramphal & Pyle, 1983). Basal and migrating corneal epithelial cells have different cell membrane sugars than superficial cells, thus accounting for the differences in susceptibility of adherence by organisms to these cells (Gipson et al., 1983). The capacity of an organism to cause tissue inflammation and destruction depends on production of one or more virulence factors such as proteases, elastases, hemolysins, and cytotoxins.

Mechanisms of Antibacterial Drug Resistance

Resistance does develop to commonly used antimicrobials (Keller & Hendrix, 2005; Sauer et al., 2003). Mechanisms that can produce drug resistance include reduction of bacterial cell permeability to the drug, production of enzymes by bacteria that can inactivate, inhibit, or destroy the drug, and structural alteration of the site (e.g., cell membrane, ribosomal protein) that the drug acts upon (Quinn et al., 2011e).

Diagnostic Methods

The laboratory methods that can be employed include microscopic examination, bacterial culture, bacterial detection and identification by PCR, and serology. Results of cultures are more sensitive than microscopic examination results, but microscopy often gives immediate information about the causative organism, thus allowing prompt, focused therapy. Because polymicrobial eye infections are common among animals, culture, bacterial speciation, and antimicrobial susceptibility testing are essential to the successful management of ocular infections.

Microscopic Examination

This is one of the most important and cost-effective laboratory procedures which is often underutilized during initial diagnostic investigations. The procedure is performed on glass slides that contain smeared material from swabs or cytobrushes (e.g., conjunctival, corneal), tissue biopsies, fluids (e.g., vitreous), or secretions. The aim of microscopy, after staining of the smears, is to determine the bacterial number, their morphology, and staining characteristics, and to identify any inflammatory response (Fig. 7.6). This information is used as a basis for assessing the clinical significance of subsequent culture results. The stains of choice are the Gram stain and the Romanowsky stains (e.g., Leishman's, modified Wright-Giemsa). Gram-negative bacteria often appear pink to light red, and when there is pink background from material such as mucus, the bacteria cannot be detected easily. Generally, bacteria can be visualized easier with Romanowsky stains as both gram-positive and gram-negative organisms are stained uniformly dark blue. However, stain precipitate, commonly present with rapid Romanowsky stains for in-clinic use (e.g., Diff-Quik) (Fig. 7.7), can also easily be mistaken for bacteria. Some bacteria such as mycoplasmas do not stain well with Gram stain, whereas acid-fast organisms such as *Mycobacterium* sp. require staining with the Ziehl–Neelsen stain (Fig. 7.8).

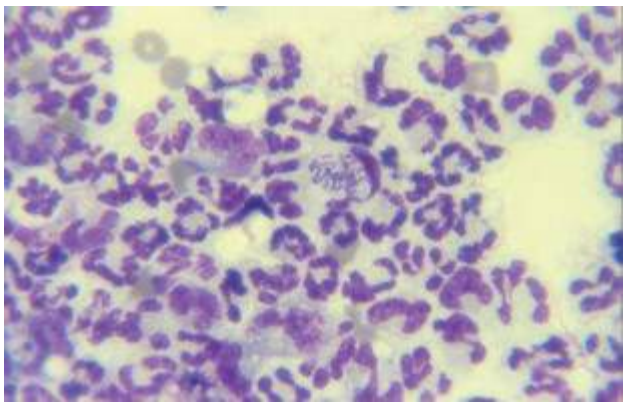


Figure 7.6 Impression smear prepared from a conjunctival swab. Microscopic examination revealed the presence of numerous neutrophils and some macrophages; The neutrophil in the center exhibits intracellular, variable in size, bacterial rods. (Original magnification 1000×; modified Giemsa stain.)

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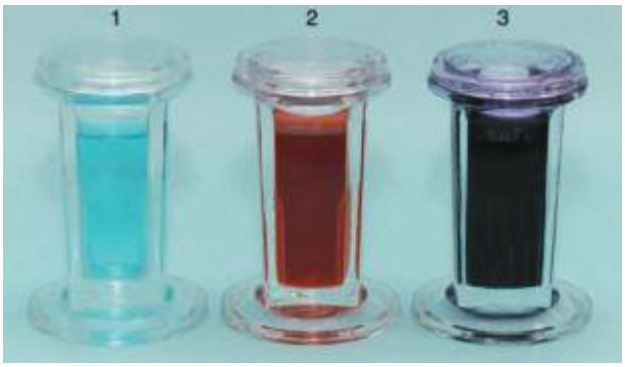


Figure 7.7 Diff-Quik stain: jar 1 contains the fixative reagent (methanol and triarylmethane dye), jar 2 contains the eosinophilic (xanthene dye), and jar 3 the basophilic stain (thiazine dye). (Courtesy of Diane Hendrix.)

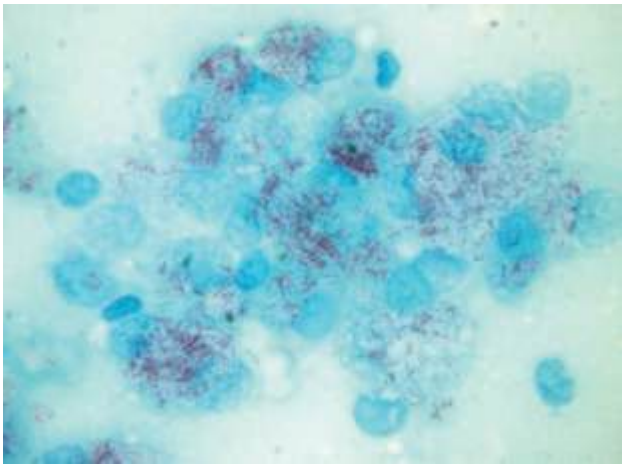


Figure 7.8 Numerous positively stained acid-fast organisms (red rods). (Original magnification 1000×; Ziehl–Neelsen stain.)

Culture

Bacterial culture is the most important laboratory method for the isolation and identification of bacteria. Collected material is inoculated into plates with culture media (agar) which facilitates the growth of isolated colonies. Routine isolation of many bacteria involves the use of blood and MacConkey agar plates after incubation for 24–48 hours. Definitive identification and speciation of a potential pathogen involves subculture of an isolated colony to obtain a pure growth that can then be used for biochemical testing. Biochemical tests aim to identify bacteria based on the presence of cytochrome oxidase C in their cell membrane and their ability to produce catalase and ferment various sugars. All veterinary laboratories utilize mini versions of biochemical tests in the form of a strip of plastic capules which contain the requisite reagent for each test (Fig. 7.9). A suspension of the pure bacterial colony is added into each test capule and the identity of the organism is based on the pattern of test reactions. Strips are available for different categories of bacteria (e.g., streptococci, nonenteric gram-negative organisms). More recently matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) has been used within the commercial environment; this analyzer has an extensive database of organisms and is able to provide further identification where standard biochemical techniques may fail (Rodrigues et al., 2017). Identification of a bacterium should be interpreted in association with the clinical signs, the presence of normal flora, the conditions of sample transportation, and the amount of bacterial growth. Quantitation of the growth is expressed as scant/light, moderate, or heavy/profuse. Profuse growth (high number of colonies) of a single bacterium is a strong indication of clinical significance. In contrast, scant growth in most cases is of questionable clinical significance as this most likely indicates normal flora, contaminant, or suppression of growth by antibiotics.

Antimicrobial Susceptibility Tests

These are *in vitro* tests for determining the most suitable antimicrobial for the effective treatment of bacterial infections. The most commonly used methods are the agar-disk-diffusion test and the minimum inhibitory concentration (MIC).

Agar-Disk-Diffusion Test (Kirby-Bauer Test)

On the basis of human pathogens and human standards, the agar-disk-diffusion test measures the inhibition of bacterial growth against a concentration of antimicrobial agent that diffuses from an impregnated paper disk placed on agar (Clinical and Laboratory Standards Institute, 2008). Typically, six to eight disks are added to one plate. The diameter of the zone of inhibited microbial growth correlates inversely with the susceptibility of the bacterium (Fig. 7.10). Limitations of this test include inoculation variables and interpretation of zone sizes (diameter). Inoculation variables include depth of agar, incubation time, and preparation (i.e., contents) of the agar. Because antimicrobials diffuse at different rates throughout the agar, published standards must be used to interpret the sensitivities. It has been reported that results with this test are reproducible between laboratories when standardized procedures are employed.

Minimum Inhibitory Concentration Determination

This test measures the minimal inhibitory concentration of an antimicrobial agent (in micrograms per milliliter) for each bacterial isolate. Advantages of using the MIC are that more antimicrobials can usually be tested and that susceptibility and resistance versus drug concentration can be directly correlated. This pharmacokinetic information is used to relate dosages to achievable serum drug concentrations. Determination of resistance versus susceptibility via the MIC is considered to be a better predictor than the agar-disk-diffusion test of clinical outcome (Moore et al., 1995). There are automated analyzers employed in some commercial laboratories for MIC testing such as the VITEK 2 analyzer; this

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Figure 7.9 Strip for the identification of bacteria (see text).



Figure 7.10 Agar-disk-diffusion for testing antimicrobial susceptibility. The bacterium is not susceptible to the antimicrobials contained in the disks positioned at 3, 6, and 7 o'clock on the plate, but susceptible to the remaining five antimicrobials (see text).

analyzer monitors growth of organism at various concentrations of antimicrobial agent over an average of 9 hours, thus significantly cutting the time for reporting a result (Vincza et al., 2014).

Limitations of Susceptibility Testing

Susceptibility testing does not usually test for antimicrobial combinations, and potentially synergistic combinations can be missed. Trimethoprim-sulfonamides and amoxicillin-clavulanate are notable exceptions; their respective synergies are widely recognized. Sensitivity tests assume equal plasma and tissue concentrations and underestimate the activity for topical treatments. In addition, sensitivity tests do not reflect local factors, such as normal or reflex secretions, exudates, or local oxygen tensions that may affect antimicrobial activity. Generally, the *in vitro* susceptibility testing is most useful in predicting failure of an antimicrobial to treat an infection *in vivo*.

Detection and Identification by Polymerase Chain Reaction

The principle of the PCR method, as well as the advantages and disadvantages for the diagnosis of bacterial infections are similar to those reported above for viral infections (see previously discussed section). The most common bacterial infections for which PCR is routinely used for their diagnosis are discussed in the sections below.

Serology

The principle and interpretation of serological testing are similar to those reported above for viral infections (see previously discussed section). The more common bacterial infections for which serological tests can be useful include *Borrelia burgdorferi*, leptospirosis, and rickettsial infections; there are in clinic tests available which test for multiple organisms (Maggi et al., 2014).

Commensal Ocular Surface Flora

The normal ocular surface is home to a wide range of both commensal and transient bacterial and fungal populations (Table 7.1). Individual species identified vary depending on the host species, age, geography and climate, season, local environment, and sampling/culture techniques. These noninvasive organisms are thought to play an important homeostatic role by competing with pathogenic species for space and nutrients to thus limit their ability to colonize the ocular surface. It follows that indiscriminate use of topical antimicrobials may disrupt this balance and predispose to overgrowth of pathogens.

In certain circumstances, nonpathogenic bacteria may become pathogenic, for instance in an immunocompromised host, after breach of an epithelial surface, or via coinfection with another agent. In the latter instance, organisms that are individually incapable of inducing disease can in combination exert a cumulative or synergistic effect that leads to clinical disease. Examples of opportunistic bacteria isolated from clinical cases of conjunctivitis include *Staphylococcus epidermidis*, *Bacillus* sp., *Corynebacterium* sp., *Escherichia coli*, *Klebsiella* sp., *Enterobacter* spp., *Serratia* sp., *Acinetobacter* sp., and some *Pseudomonas* sp. (Galle & Moore, 2007).

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Table 7.1 Bacteria and fungi isolated from clinically normal eyes.

Host species	Common bacterial and fungal isolates
Dogs	Bacteria can be cultured from the conjunctival sac of 39%–87% of normal dogs. Of these, greater than two-thirds are gram-positive. Predominant gram-positive isolates: *Staphylococcus* sp., *Corynebacterium* sp., *Streptococcus* sp., *Bacillus* sp. Predominant gram-negative isolates: *Acinetobacter* sp., *Neisseria* sp., *Moraxella* sp., *Pseudomonas* sp., *Escherichia coli*. Fungi isolated from the conjunctival sac of 22% normal dogs, most commonly *Penicillium* sp., and *Cladosporium* sp. (Galle & Moore, 2007; McDonald & Watson, 1976; Prado et al., 2005; Samuelson et al., 1984; Urban et al., 1972; Wang et al., 2008; Whitley, 2000)
Cats	Bacteria can be cultured from the conjunctival sac of 4%–67% of normal cats. Of these, the majority are gram-positive. Predominant gram-positive isolates: *Staphylococcus* sp., *Corynebacterium* sp., *Streptococcus* sp., *Bacillus* sp. Predominant gram-negative isolates: *Pseudomonas* sp., *Chlamydophila felis*, *Mycoplasma* sp., *Parachlamydia acanthamoebae* Fungi isolated from the conjunctival sac of 40% of normal cats, most commonly *Penicillium* sp., *Cladosporium* sp. (Campbell et al., 1973; Di Francesco et al., 2004a, 2004b; Espínola & Lilenbaum, 1996; Richter et al., 2010; Samuelson et al., 1984; Shewen et al., 1980)
Horses/donkeys	Bacteria can be cultured from the conjunctival sac of 52% of normal horses. Of these, the majority are gram-positive. Predominant gram-positive isolates: *Corynebacterium* sp., *Staphylococcus* sp., *Streptococcus* sp., *Bacillus* sp., *Streptomyces* sp. Predominant gram-negative isolates: *Moraxella* sp., *E. coli*, *Acinetobacter* sp., *Neisseria* sp., *Enterobacter* sp. Fungi isolated from the conjunctival sac of 95% of normal horses. Predominant species: *Aspergillus* sp., *Cladosporium* sp., *Penicillium* sp., *Scopulariopsis* sp., *Acremonium* sp., *Trichoderma* sp., *Mucor* sp., *Absidia* sp., *Chrysosporium* sp., *Alternaria* sp., *Fusarium* sp. (Andrew et al., 2003; Johns et al., 2011; Moore et al., 1988; Nardoni et al., 2007; Rosa et al., 2003; Samuelson et al., 1984)
Cows	Bacteria can be cultured from the conjunctival sac of 87% of normal cows. Predominant gram-positive isolates: *Corynebacterium* sp., *Streptococcus* sp., *Staphylococcus* sp., *Bacillus* sp. Predominant gram-negative isolates: nonhemolytic *Moraxella bovis*, *Mycoplasma* sp., *Branhamella* sp., *Neisseria* sp., *Acinetobacter* sp., coliforms, *Actinobacillus* sp. Fungi isolated from the conjunctival sac of 100% of normal cows, most commonly *Cladosporium* sp., *Penicillium* sp., *Aspergillus* sp. (Barber et al., 1986; Samuelson et al., 1984; Sgorbini et al., 2010; Wilcox, 1970)
Sheep	Bacteria can be cultured from the conjunctival sac of 40% of normal sheep. They include gram-positive: *Staphylococcus* sp., *Corynebacterium* sp., *Streptococcus* sp., *Bacillus* sp., *Micrococcus* sp. Gram-negative: *Moraxella* sp., *Achromobacter* sp., *Branhamella ovis* (formerly *Neisseria ovis*), *E. coli*, *Mycoplasma* sp., *Acholeplasma* sp. (Egwu et al., 1989; Spradbrow, 1968)
Camelids	Bacterial species isolated from the normal camelid conjunctival sac included Gram-positive isolates: *Staphylococcus* sp., *Bacillus* sp., *Streptomyces* sp., *Streptococcus* sp., *Corynebacterium* sp., *Micrococcus* sp. Gram-negative isolates: *Pseudomonas* sp., *Pasteurella* sp., *Klebsiella* sp., *E. coli*. Predominant fungal species: *Aspergillus* sp., *Fusarium* sp., *Rhinocladiella* sp., *Penicillium* sp., *Mucor* sp., dematiaceous fungi (Gionfriddo et al., 1991, 1992)
Pigs	Bacteria can be cultured from the conjunctival sac of 98% of normal pigs. Gram-positive organisms were most commonly isolated, with *Streptococcus* sp. and *Staphylococcus* sp. most predominant. Of gram-negative isolates, chlamydial sp. were most commonly isolated. (Davidson et al., 1994)
Rabbits	Bacteria can be cultured from the conjunctival sac of 98% of normal rabbits. Gram-positive organisms predominate, including: *Staphylococcus* sp., *Micrococcus* sp., *Bacillus* sp., *Stomatococcus* sp., *Corynebacterium* sp., *Streptococcus* sp. Gram negative isolates: *Neisseria* sp., *Pasteurella* sp., *Moraxella* sp. (Cooper et al., 2001)
Birds	Bacterial species isolated from the conjunctival sac of up to 85% of normal birds. The type of organisms most commonly identified depends on the bird's environment. Gram-positive organisms most frequently isolated from psittacines and raptors. Isolates include: *Staphylococcus* sp., *Streptococcus* sp., *Micrococcus* sp., *Bacillus* sp., *Corynebacterium* sp. Gram-negative organisms most frequently isolated from aquatic birds. Isolates include: *Enterobacter* sp., *Pasteurella* sp., *Actinobacillus* sp., *E. coli*, *Klebsiella* sp., *Pseudomonas* sp., and *Proteus* sp. Fungal species isolated less commonly (14% in one study), and include: *Aspergillus* sp., *Cladosporium* sp. (Abrams et al., 2002; Chalmers & Kewley, 1985; Cousquer et al., 2010; Dupont et al., 1994; Miller et al., 1995; Silvanose et al., 2001; Wolf et al., 1983; Zenoble et al., 1983)
Exotics	A wide variety of gram-positive and gram-negative bacterial species and fungal isolates have been reported from the normal conjunctival sac of a range of exotic animal species. (Cullen, 2003; Montiani-Ferreira et al., 2008; Myers et al., 2009; Pinard et al., 2002; Spinelli et al., 2010; Taddei et al., 2010)

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Pathogenic Gram-Positive Aerobic Bacteria

Staphylococcus *sp.*

Staphylococci are gram-positive, facultatively anaerobic, nonmotile cocci that are indigenous inhabitants of the skin and mucous membranes of mammals and birds. Cytologically, they appear as individual cocci, in small groups, or as grape-like clusters.

In dogs, *Staphylococcus intermedius* is the predominant staphylococcal species. However, there are over 36 species of staphylococci, nine of which contain subspecies, and although coevolution of animal hosts with their species of *Staphylococcus* occurs, host-adapted species can colonize another host species when contact between hosts is frequent or when an underlying disease is present (Weese, 2012). As such, the zoonotic potential of staphylococcal species, in particular methicillin-resistant *Staphylococcus aureus* (MRSA), has received scientific attention in recent years (Anderson et al., 2008; Hanselman et al., 2006; Weese et al., 2006). Humans may also act as a source of infection to pets, and human to canine transfer of MRSA has been recorded (Rutland et al., 2009).

Although all staphylococcal species isolated from normal animals have the potential to be pathogenic, they are not inherently invasive and usually colonize intact epithelium of healthy animals without causing disease. However, if the host epithelium becomes compromised (for example, by trauma, other infections, or clinical disease such as immunosuppression or keratoconjunctivitis sicca), then staphylococci are able to invade damaged epithelium to cause clinical disease. The exact host and/or bacterial factors that trigger pathogenicity are unknown. A number of bacterial enzymes and factors have been linked to pathogenicity, including coagulase, hemolysin, various exotoxins, Protein A, and adherence factors, but none have been consistently implicated in clinical infections, and neither does there appear to be a particular staphylococcal genetic profile associated with disease. Although coagulase-negative staphylococci are generally considered to be less pathogenic than coagulase-positive species, they are recognized as being increasingly important opportunistic pathogens (Otto, 2004; Pyörälä & Taponen, 2009).

Staphylococcal species can cause eyelid and ocular surface disease and are the most commonly isolated bacteria in cases of canine bacterial conjunctivitis (Gerding et al., 1988; Prado et al., 2005; Varges et al., 2009). Staphylococci are also cultured from cases of feline conjunctivitis in the absence of other pathogens, suggesting a primary role in this species too (Hartmann et al., 2010). They are also commonly implicated in equine and bovine conjunctivitis (McLaughlin et al., 1983; Yeruham et al., 2001).

Staphylococcal isolates most commonly recovered from cases of canine external eye disease are the coagulase-positive species *S. intermedius* and *S. aureus* and the coagulase-negative species *Staphylococcus epidermidis* and *Staphylococcus simulans* (Murphy et al., 1978; Prado et al., 2005; Tolar et al., 2006; Varges et al., 2009). Methicillin resistant staphylococci (MRS) can also be isolated, with one study showing that dogs belonging to owners employed in veterinary or human healthcare fields were four times more likely to have MRS keratitis than dogs owned by clients with different professions (LoPinto et al., 2015).

Streptococcus *sp.*

Streptococci are gram-positive, aerobic or facultatively anaerobic, nonmotile cocci that are commensal microflora of the oral cavity, nasopharynx, skin, and genital and gastrointestinal tracts. Cytologically they appear as pairs or in chains.

A large number of streptococcal species are pathogenic and cause localized to widespread pyogenic infections. Several classification schemes have been developed based on culture characteristics, biochemical features, or antigenic differences in cell wall carbohydrates (the Lancefield classification). The action of streptococci on red blood cells in culture allows classification according to hemolysis patterns. Alpha-hemolytic strains oxidize hemoglobin but leave erythrocytes intact. Beta-hemolytic strains cause complete lysis of erythrocytes, whereas other strains are nonhemolytic (Greene & Prescott, 2012). In general, beta-hemolytic strains of streptococci tend to be the most pathogenic, whereas nonhemolytic and alpha-hemolytic strains are commonly found on mucous membranes and skin of healthy animals.

Streptococci have been implicated in both ocular surface and intraocular disease in animals. After staphylococci, they are the next most commonly isolated pathogen in canine external eye diseases, with beta-hemolytic strains predominating (Gerding et al., 1988; Murphy et al., 1978; Prado et al., 2005; Tolar et al., 2006). They are also commonly isolated from cases of equine, bovine, and feline extraocular disease (Hartmann et al., 2010; Hindley et al., 2016; Keller & Hendrix, 2005; McLaughlin et al., 1983; Sauer, et al., 2003; Wada et al., 2010; Yeruham et al., 2001). In horses, *Streptococcus equi* can cause conjunctivitis, panophthalmitis, and chorioretinitis in association with outbreaks of strangles (Timoney, 1993). Beta-hemolytic *S. equi* has also been associated with severe keratomalacia in horses (Brooks et al., 2000a).

Corynebacterium *sp.* and Rhodococcus *sp.*

These are gram-positive, aerobic or facultatively anaerobic, pleomorphic bacilli that are closely related to *Nocardia* and *Mycobacterium*. They live in the gastrointestinal tract but can survive in soil for long periods of time.

Corynebacteria are common ocular surface commensal organisms, especially in equine and production animals (Moore et al., 1988). Because of their ubiquitous nature, their pathogenic role is unclear. However, they are commonly isolated from corneal ulcers, usually as part of a mixed infection. Virulence factors associated with these

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organisms include hemolysin, phospholipase, and cholesterol oxidase (Galle & Moore, 2007).

Rhodococcus equi is an important cause of bronchopneumonia and septicemia in foals. Anterior and posterior uveitis may develop as a complication of the septicemia (Colitz & Davis, 2005).

Mycobacteria

Mycobacteria are gram-positive, aerobic or facultatively anaerobic nonmotile acid-fast bacteria. A large number of mycobacterial species have been identified including, among others, *Mycobacterium tuberculosis*, *M. bovis*, *M. microti*, *M. leprae*, *M. lepraemurium*, *M. simiae*, and *M. avium-intracellulare complex* (*MAC*). Clinically, they are divided into tuberculous mycobacteria (including *M. tuberculosis*, *M. bovis*, and *M. microti*); lepromatous mycobacteria (including *M. leprae* and *M. lepraemurium*); and opportunistic, nontuberculous mycobacteria (including *M. simiae* and *MAC*) (Greene & Gunn-Moore, 2012).

In cats, the nontuberculous mycobacteria, *M. malmoense*, *M. simiae*, and a novel species closely related to *M. simiae* have been isolated from cases of conjunctival, corneal, and intraocular disease (Dietrich et al., 2003; Fyfe et al., 2008; Gunn-Moore et al., 2010; Gunn-Moore et al., 2011). Additionally, *M. tuberculosis, M. bovis, M. microti,* and *MAC* have been associated with uveitis, scleritis, optic neuritis, and retinal detachment (Formston, 1994; Stavinohova et al., 2019).

Listeria *sp.*

Listeria monocytogenes is a pathogenic gram-positive, aerobic, or facultatively anaerobic rod. It is a ubiquitous saprophyte that is commonly found in soil, sewage, water, and decaying vegetation. It differs from nonpathogenic species in that it possesses a beta-hemolytic toxin, a factor thought to contribute to its virulence. It is also able to exist as a facultative intracellular organism within macrophages, allowing it to evade the humoral arm of the immune system (Greene & Prescott, 2011). The bacterium causes encephalitis, abortion, and septicemia in humans and animals, and in ruminants it has also been associated with mastitis (Erdogan, 2010).

Neuro-ophthalmic signs such as facial nerve paralysis and ptosis can develop secondary to *L. monocytogenes* encephalitis. The organism has also been cultured from cases of bovine and ovine keratoconjunctivitis (Akerstedt & Hofshagen, 2004; Morgan, 1977) and, more recently, equine keratoconjunctivitis (Revold et al., 2015). In addition, it has been linked to anterior uveitis in silage-fed cattle (Erdogan, 2010).

Other Gram-Positive Pathogens

A wide range of other gram-positive bacteria may be cultured from cases of conjunctivitis or ulcerative keratitis across many species. These include *Bacillus* sp., *Actinomyces* sp., *Micrococcus* sp., *Enterococcus* sp., and *Streptomyces* sp. (Akerstedt & Hofshagen, 2004; Andrew & Willis, 2005; Murphy et al., 1978; Salisbury et al., 1995; Whitley, 2000). However, their role in disease pathogenesis is not clear. They may simply represent opportunistic infections or may present as a coinfection with other more pathogenic bacteria.

Pathogenic Gram-Negative Aerobic Bacteria

Gram-negative bacteria are distinguished from gram-positive species by the presence of a complex outer membrane containing lipopolysaccharide (LPS or endotoxin). The lipid portion of LPS (lipid A, the active component of endotoxin) is embedded in the outer membrane, whereas the polysaccharide portion (O antigen) protrudes from the surface. In addition to conferring a gram-negative staining pattern, these structures partly determine antibiotic susceptibility and are important virulence factors (Koenig, 2012).

Pseudomonas *sp.*

These are ubiquitous, gram-negative bacteria found in soil, water, and decaying vegetation. They can also be isolated from the skin, mucous membranes, and occasionally gastrointestinal tracts of healthy animals. Cytologically, they appear as rods which are morphologically indistinguishable from other gram-negative bacteria, although they tend to be slightly larger.

Pseudomonas aeruginosa is the most important pathogen in this genus and is associated with a severe and progressive keratitis characterized by acute stromal collagenolysis. It can also cause a range of other ocular and periocular diseases including blepharitis, conjunctivitis, dacryocystitis, orbital cellulitis, and endophthalmitis.

The bacterium is essentially an opportunistic pathogen, gaining access to the corneal stroma via abrasions in the corneal epithelium. Bacterial pili (fimbriae) and exozyme S allow adhesion of the bacterium to the host epithelial cell. LPS within the outer membrane protects the bacterium from phagocyte attachment and attack by complement. A number of virulence factors are then produced that aid colonization and further spread of the organism within infected tissue. These include collagenase, various proteases (including alkaline protease, elastase, protease IV), hemolysin, phospholipase C, and various toxins (exoenzymes –S, –T, –U, and –Y, and exotoxin A). Exotoxin A, a cytotoxin that induces tissue necrosis, allows the organism to persist and to penetrate deeper into infected tissue (Koenig, 2012; Ledbetter et al., 2009f; Pillar & Hobden, 2002).

P. aeruginosa is primarily regarded as an extracellular bacterium, but some strains are able to invade and live within host epithelial cells without killing the host cell. Experimental studies have shown that there are two bacterial phenotypes: invasive *P. aeruginosa*, which can enter and live in corneal epithelial cells; and cytotoxic *P. aeruginosa*, which is acutely cytotoxic. Both types induce severe keratitis, but the invasive strain is most commonly associated with corneal ulceration,

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whereas the cytotoxic strain is most commonly associated with corneal edema (Cole et al., 1998). In dogs, the invasive phenotype predominates, accounting for 80% of isolates from dogs with naturally occurring *P. aeruginosa* ocular infections (Ledbetter et al., 2009f). This finding has therapeutic consequences, suggesting that aminoglycosides, which are non-cell permeable, could be less effective against such invasive *P. aeruginosa* phenotypes than the cell-permeable fluoroquinolones.

Moraxella *sp.*

Moraxella sp. are large, gram-negative coccobacilli that are commensal inhabitants of the oral cavity and gastrointestinal tracts of small animals, production animals, and horses. They can cause ocular infections in small ruminants and horses, but their major significance, both pathologically and economically, is in cattle, in which *M. bovis* is the primary cause of infectious bovine keratoconjunctivitis (IBK) (Barner, 1952; Killinger et al., 1977; Slatter et al., 1982).

M. bovis is transmitted via direct contact, aerosol, or fomites, but the primary mechanical vector is the face fly, *Musca autumnalis* (Brown & Adkins, 1972). External factors that contribute to pathogenicity include season, environmental irritants, and ultraviolet light. Host factors include concurrent infections, periocular pigmentation, nutritional status, age, breed, and immune status of the host (Alexander, 2010; Brown et al., 1998).

M. bovis exists in two forms: a nonpiliated ("smooth"), nonhemolytic form, which is nonpathogenic; and a piliated ("rough"), hemolytic form which is pathogenic (Sandhu et al., 1974; Simpson et al., 1976). The nonpiliated form may persist in healthy animals which can act as carriers and shedders of the organism, and transformation between nonpiliated and piliated forms may occur (Bovre & Froholm, 1972). The pili promote adhesion of the bacteria to host epithelial cells and allow establishment of infection (Ruehl et al., 1993a, 1993b). *M. bovis* has been classified into serogroups based on pilus antigens, and emergence of a novel pilus type may be associated with outbreaks of IBK (Moore & Lepper, 1991; Vandergaast & Rosenbusch, 1989). *Moraxella* sp. also produce biofilms which can increase its pathogenicity (Ely et al., 2019).

Other factors produced by *M. bovis* that are most likely involved in IBK disease pathogenesis include leukocidin, hemolysin, and LPS. In addition, iron-binding ligands have been identified in the outer membrane of *M. bovis* that are able to bind lactoferrin, a bacteriostatic agent that is present in the bovine tear film. The bacteriostatic effects of lactoferrin are thought to be via its role as an iron-chelating agent, an essential bacterial growth element. By binding lactoferrin, *M. bovis* might thus be able to acquire a source of iron for growth (Brown et al., 1996, 1998; Fenwick et al., 1996; Hoien-Dalen et al., 1990).

Although *M. bovis* is the most consistent pathogen associated with IBK, others have been implicated. A related species, *Moraxella bovoculi*, has been identified in IBK cases in northern California and Canada (Angelos, 2010; Angelos et al., 2007; Galvão & Angelos, 2010). *M. bovoculi* has also been associated with keratoconjunctivitis in horses (Liu et al., 2014).

Bartonella *sp.*

Bartonella sp. are small, vector-transmitted, gram-negative, hemotropic bacteria. Within the genus, each species has become highly adapted to a preferential mammalian reservoir host in which they usually cause a long-lasting and often nonpathogenic intraerythrocytic bacteremia (Breitschwerdt & Chomel, 2012; Guptill-Yoran, 2012). Diagnosis is via culture or PCR (Pennisi et al., 2013).

Bartonella henselae is a feline-adapted species that can be commonly isolated from apparently clinically healthy cats. The cat flea *Ctenocephalides felis felis* is the main vector, although ticks have also been implicated (Chomel et al., 1996; Cotté et al., 2008; Shaw et al., 2004). In humans, *B. henselae* is the cause of "cat scratch fever" characterized by lymphadenopathy, fever, meningoencephalitis, neuroretinitis, retinochoroiditis, and endocarditis (Cunningham, 2000).

In cats, *B. henselae* has been linked to anterior uveitis (Lappin & Black, 1999). Intraocular production of *B. henselae*-specific IgG with a C value >1 was identified in seven of 49 cats with idiopathic uveitis and in four of nine cats experimentally infected with *B. henselae*, compared with none of 49 healthy controls. The same study also found *B. henselae* DNA in the aqueous humor of three of 24 cats with uveitis and in four of nine experimentally infected cats, compared with one of 49 healthy cats (Lappin et al., 2000). However, the significance of these findings in relation to feline anterior uveitis is not clear, especially because C values >8 are considered a more rigid criterion for the determination of local antibody production. Furthermore, a later study showed no difference in *Bartonella* seroprevalence rates between cats with uveitis and healthy cats, and another study of 104 cats with naturally occurring uveitis failed to identify *B. henselae* DNA within any aqueous humor samples (Fontenelle et al., 2008; Powell et al., 2010). In summary, the significance of *B. henselae* in the etiology of feline uveitis is debatable and, given the widespread prevalence of the organism in healthy cats, there is little evidence that it is a major uveitis pathogen in cats (Stiles, 2011).

Bartonella vinsonii subspecies *berkhoffi* has been reported to be a possible cause of anterior and posterior uveitis in dogs (Breitschwerdt et al., 2004; Michau et al., 2003).

Haemophilus *sp.*

Haemophilus somnus is a small, gram-negative, coccobacillus that is a commensal of bovine mucosal surfaces, commonly the respiratory tract, reproductive tract, and circulatory

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system (Kwiecien & Little, 1991). The organism prefers an intracellular location and commonly invades alveolar macrophages and monocytes, in which it can survive and replicate (Harris & Janzen, 1989). It is an opportunistic pathogen that is the cause of thrombotic meningoencephalomyelitis (TME) (previously called thrombo-embolic meningoencephalomyelitis, TEME). TME occurs in feedlot cattle and in addition to peracute and often fatal meningoencephalitis, it can cause chorioretinitis, retinal detachment, or central blindness. Isolated cases and outbreaks of disease occur (Descarga et al., 2002). The primary pathogenic lesion is *in situ* thrombus formation. Once the organism has localized to a particular site, it causes endothelial cells of blood vessels to separate, and the exposed underlying basement membrane induces local thrombus formation (Harris & Janzen, 1989). Virulent *H. somnus* strains are biochemically and antigenically similar to avirulent strains. However, virulent strains possess a number of features that seem to confer pathogenicity, including the production of immunoglobulin Fc binding proteins, lipo-oligosaccharides that mediate apoptosis of host cells, and factors that allow intraphagocytic survival (Siddaramppa & Inzana, 2004).

Other Gram-Negative Aerobic Bacteria

Coliform bacteria are a diverse group of gram-negative bacteria found in the normal gastrointestinal tract, as well as in soil and sewage. They include members of the genera *Escherichia*, *Salmonella*, *Citrobacter*, *Shigella*, *Klebsiella*, *Enterobacteria*, *Serratia*, *Proteus*, and *Yersinia*. They are not primary pathogens but can be opportunistic invaders of the eye and have been cultured from cases of conjunctivitis, ulcerative keratitis, dacryocystitis, orbital infections, anterior uveitis, and chorioretinitis (Gerding et al., 1988; Moore et al., 1983; Prado et al., 2005; Salisbury et al., 1995; Whitley, 2000).

Neisseria sp. are gram-negative cocci that colonize mucosal surfaces, including the conjunctiva, to cause clinical disease. Pathogenic features include the presence of surface pili, oxidase, protease, and a variety of endotoxins.

Branhamella ovis (formerly known as *Neisseria ovis*) is a gram-negative diplococcus that can be isolated from the conjunctival sac of healthy small ruminants. It causes conjunctivitis and keratoconjunctivitis in sheep and goats, either as a sole agent or as a coinfection with mycoplasmal or chlamydial organisms (Dagnall, 1994a, 1994b; Jansen et al., 2006). *B. ovis* produces one or more heat-labile toxins that display cytotoxic activity against corneal epithelial cells (Cerny et al., 2006). The organism has also been implicated in cattle as an etiological agent in IBK, although usually it causes only a mild, transient conjunctivitis in calves and only rarely are corneal lesions observed (Nagy et al., 1989).

Acinetobacter sp. are gram-negative bacilli that are often normal inhabitants of the conjunctiva of domestic and production animals. They have been isolated from cases of infectious equine keratitis (Moore et al., 1983, 1995).

Pasteurella multocida is a gram-negative coccobacillus that is a major cause of conjunctivitis and dacryocystitis in rabbits, often in conjunction with upper respiratory tract disease (Deeb & DiGiacomo, 2000; DiGiacomo et al., 1983).

Leptospira interrogans is a small gram-negative spirochete with a number of antigenically distinct serovars, many of which cause clinical disease in veterinary species. The serovars are maintained in nature by a wide range of subclinically infected wild and domestic animal reservoir hosts that act as a source of infection for incidental animal hosts or humans via contact with contaminated urine (Greene et al., 2012c). *L. interrogans* is a recognized cause of anterior uveitis in a number of species and is strongly implicated as an etiological factor in equine recurrent uveitis (ERU) (Dwyer et al., 1995; Faber et al., 2000). *L. interrogans var pomona* is the main serovar linked to ERU in the United States, whereas *L. interrogans var grippotyphosa* is more common in central Europe. Sporadic reports have also associated a number of other serovars with equine uveitis, including *australis*, *autumnalis*, *icterohaemorrhagiae*, and *sejroe* (Dwyer & Gilger, 2005; Gilger, 2010; Lowe, 2010; Matthews, 1987; Spiess, 2010).

Borrelia burgdorferi is a small gram-negative spirochete that is the cause of Lyme disease in humans, dogs, horses, and cats (Greene et al., 2012b). Unlike *Leptospira* spp., *B. burgdorferi* is unable to survive as a free-living organism in the environment. Instead it is transmitted between its wild animal reservoir host (rodents, small mammals, and birds) and its incidental animal or human host via a tick vector, primarily *Ixodes* sp. Infection rates are proportional to contact time between the tick and host, and once inoculated, the organism spreads mainly by tissue migration rather than hematogenously. Infection in dogs is often asymptomatic, but a wide range of signs have been reported, including fever, polyarthropathy, protein-losing nephropathy, and cardiac and neurological disease (Fritz & Kjemtrup, 2003; Krupka & Straubinger, 2010; Little et al., 2010; Littman, 2003). Ocular signs in dogs include anterior and posterior uveitis (Cohen et al., 1990; Munger, 1990), whereas a single case report identified the organism in the eye of a pony with arthritis and panuveitis (Burgess et al., 1986). Diagnostic testing options for borreliosis include ELISA, IF, Western blotting, and PCR testing (Gerber et al., 2009; Johnson et al., 2008; Littman et al., 2006; Straubinger, 2000).

Brucella canis is a small gram-negative coccobacillus that causes abortion, epididymitis, and lymphadenomegaly in dogs (Greene & Carmichael, 2012). It rarely causes anterior and posterior uveitis in dogs in the absence of overt systemic disease (Ledbetter et al., 2009e; Vinayak et al., 2004).

Pathogenic Obligate Intracellular Bacteria

Chlamydiaceae *and* Parachlamydiaceae

The genomic classification of the family Chlamydiaceae (order Chlamydiales) has undergone major revisions since 1999, and now is divided into two genera, *Chlamydia* and

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Chlamydophila (Table 7.2). Prior to 1999, only the *Chlamydia* genus was recognized, and most of the organisms relevant to veterinary species were classified as *C. psittaci* variants (Stiles, 2012). However, because of the genomic similarities between the genera and because no easily recognizable phenotype such as host preference or tissue tropism is available, it has been proposed to once again combine the genera (Sachse et al., 2015).

Chlamydiaceae are gram-negative, obligate intracellular bacteria that require the metabolic machinery of host cells for survival and replication. They possess a cell wall like that of other gram-negative bacteria except that they lack peptidoglycan. They are relatively labile, although they can survive a few days in the environment at room temperature. Their developmental cycle involves both extracellular (elementary body) and intracellular (reticulate body) forms. Elementary bodies are small, metabolically inactive infectious particles with rigid cell walls that travel extracellularly to infect new cells. Once within the cytoplasm of a host cell, they transform into the larger reticulate bodies, which replicate by a process of binary fission within membrane-bound cytoplasmic vacuoles. Rapid proliferation then ensues as the reticulate bodies transform into a large population of elementary bodies, which are then released after lysis of the host cell and go on to infect new cells (Gruffydd-Jones et al., 2009; Stiles, 2012).

The organisms can be found in the ocular, respiratory, gastrointestinal, and urogenital mucous membranes of apparently healthy animals, which can act as carriers. Spread is via direct contact or aerosol.

Chlamydophila felis is an important feline pathogen. Seroprevalence studies have shown that the organism is widespread in the worldwide feline population, with more than 10% of unvaccinated household cats and up to 64% of cattery cats having antibodies against *Chlamydophila* (Di Francesco et al., 2004a, 2004b; Gunn-Moore et al., 1995; Holst et al., 2006; Yan et al., 2000). Despite this high exposure rate, *C. felis* can be isolated from the conjunctiva of only around 6% of clinically healthy cats (Wills et al., 1988).

C. felis is a significant cause of conjunctivitis in cats, with two studies isolating the organism from 30% to 56% of cats with conjunctivitis, respectively (Hartmann et al., 2010; Wills et al., 1988). Another study, however, isolated it only from around 7% of cats with active conjunctivitis (Low et al., 2007). *C. felis* can also be present as part of a mixed infection with FHV-1, calicivirus, *Mycoplasma* spp., or aerobic bacteria (Fernandez et al., 2017; Hartmann et al., 2010; Low et al., 2007).

Clinical disease is most commonly seen in cats less than 1 year of age. Clinical signs, primarily conjunctivitis, develop after an incubation period of between 2 and 5 days. Transient fever and inappetance may develop, but most cats remain well and continue to eat. Respiratory and other systemic signs are uncommon. However, the organism can be shed from the gastrointestinal and urogenital tracts, and this can act as a source of infection to other cats (Gruffydd-Jones et al., 2009).

Conjunctival shedding of *C. felis* usually stops from around day 60 postinfection, although untreated cats can shed the organism for up to 215 days and some develop persistent infection (Gruffydd-Jones et al., 2009; O'Dair et al., 1994). Host immunity involves both cellular and humoral responses, and increasing immunity establishes with age (Longbottom & Livingstone, 2006; Stiles, 2012).

In sheep, chlamydial species have been isolated from cases of infectious ovine keratoconjunctivitis, as well as polyarthritis, pneumonia, orchitis, epididymitis, and abortion (Dagnall, 1994b; Wilsmore et al., 1990). However, it should be noted that *Chlamydophila abortus* and *C. pecorum* can also be isolated from the conjunctiva of healthy sheep, and one study showed no significant difference in isolation rates between flocks affected with conjunctivitis and healthy flocks (Polkinghorne et al., 2009).

Chlamydophila sp. also causes conjunctivitis in cattle (Otter et al., 2003), swine (Rogers et al., 1993; Schautteet & Vanrompay, 2011), guinea pigs (Lutz-Wohlgroth et al., 2006; Strik et al., 2005), and koalas (Cockram & Jackson, 1981).

Table 7.2 The Chlamydiaceae family.

Genus	Species	Host	Preferential tissues
Chlamydia	*trachomatis*	Humans	Conjunctiva, urogenital tract, neonatal respiratory tract
	muridarum	Rodents	Internal organs
	suis	Swine	Conjunctiva, respiratory, and gastrointestinal tracts
Chlamydophila	*psittaci*	Birds	Urogenital and respiratory tracts, internal organs
	felis	Cats	Conjunctiva
	pecorum	Cattle, sheep	Conjunctiva, brain, joints
	pneumoniae	Humans, koalas, horses	Respiratory tracts, joints
	abortus	Sheep	Placenta, intestines
	caviae	Guinea pigs	Conjunctiva, urogenital system, spleen

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In general, chlamydial species are considered to have a restricted host range. However, *C. psittaci* and *C. abortus* are well-recognized as serious zoonotic pathogens, and there have also been reports documenting transmission of *C. felis* from cats to humans (Hartley et al., 2001; Rohde et al., 2010). In addition, *C. psittaci* has also been isolated from sheep (Lenzko et al., 2011) and *C. pneumoniae* was identified in cases of feline conjunctivitis (Sibitz et al., 2011).

Parachlamydial organisms (order Chlamydiales, family Parachlamydiaceae) are Chlamydial-like bacteria that naturally infect amoeba. *Parachlamydia acanthamoebae* infects the protozoan *Acanthamoeba*, the cause of amoebic keratitis in humans, but is also able to infect and multiply in human macrophages (Marciano-Cabral & Cabral, 2003). *P. acanthamoebae* has been found in the eyes of both healthy cats and those with keratitis or conjunctivitis (Richter et al., 2010). Another parachlamydial organism, closely related to *Neochlamydia hartmannellae*, was previously identified in ocular samples from cats with and without conjunctivitis (von Bomhard et al., 2003). The clinical significance of these findings is unknown.

Diagnosis of chlamydiosis is most commonly via PCR of conjunctival swabs.

Ehrlichia, Anaplasma, and Rickettsia *sp.*

Prior to 2001, the genera *Ehrlichia, Anaplasma*, and *Rickettsia* were all classified as members of the family Rickettsiaceae. However, molecular characterization studies led to the reclassification of *Ehrlichia* and *Anaplasma* as members of family Anaplasmataceae (Harrus et al., 2012).

Ehrlichia sp. are gram-negative, nonmotile, aerobic, obligate intracellular coccobacilli that are transmitted by ticks. They primarily infect leukocytes (monocytes, macrophages, granulocytes).

Ehrlichia canis, which is transmitted by the tick vector *Rhipicephalus sanguineus*, causes canine monocytic ehrlichiosis (Harrus et al., 2012). During an incubation period of 8–20 days, the organism multiplies in monocytes by a process of binary fission and spreads throughout the body. After the incubation period, three phases of clinical disease are recognized. The acute phase lasts 2–4 weeks and is characterized by fever, anorexia, lethargy, petechiation of mucous membranes, and lymphadenomegaly. Laboratory abnormalities include thrombocytopenia, mild leucopenia, and mild anemia. Ocular signs during the acute phase are related to acute vasculitis and thrombocytopenia and include conjunctival hyperemia, anterior uveitis, chorioretinitis, retinal hemorrhage, and optic neuritis (Komnenou et al., 2007; Leiva et al., 2005b; Panciera et al., 2001). Untreated dogs will then enter a subclinical disease phase, with apparent recovery and resolution of clinical signs, although platelet counts may remain below reference range. This phase can last months to years and during this period, *E. canis* is thought to remain dormant within the spleen. Infected dogs subsequently eliminate the organism, remain symptomless lifelong carriers, or progress to the chronic phase of infection. In the chronic phase, hyperviscosity syndrome can develop as a consequence of a monoclonal gammopathy. This, along with thrombocytopenia, result in ocular signs including hemorrhage and retinal detachment. Eventually bone marrow suppression results in an often fatal pancytopenia.

Anaplasma platys (formerly known as *Ehrlichia platys*) is a gram-negative, nonmotile, aerobic, obligate intracellular bacterium that is presumed to be tick-transmitted, although a vector has not yet been conclusively identified (Dantas-Torres, 2008; Harrus et al., 2012). It infects canine platelets, and experimental infections often lead to only very mild clinical disease. Some strains, however, can cause more severe signs including fever, lethargy, weight loss, petechiation of mucous membranes, and lymphadenomegaly. Uveitis has been reported after natural infection (Glaze & Gaunt, 1986).

Rickettsia rickettsii is the cause of Rocky Mountain spotted fever in dogs. It is an obligate intracellular bacterium that replicates in endothelial cells of smaller arteries and venules (Greene et al., 2012a). It is transmitted by ticks (predominantly *Dermacentor andersoni* and *Dermacentor variabilis*, although *Amblyomma americanum* and *Rhipicephalus sanguineus* are also implicated) and causes an acute febrile illness in dogs, characterized by a multifocal vasculitis. Clinical signs include fever, lymphadenomegaly, peripheral edema, joint swelling, hemorrhage of the mucous membranes, icterus, tachypnea, tachycardia, and sometimes neurological signs secondary to meningoencephalomyelitis. Ocular signs include scleral congestion, conjunctival hemorrhage, anterior uveitis, retinal hemorrhage, and optic neuritis (Davidson et al., 1989).

Mycoplasma *sp.*

Mycoplasmas are divided into hemotrophic and nonhemotrophic types, but only the nonhemotrophic types are involved in ocular disease.

Mycoplasmas are the smallest free-living microorganisms, with replicating cells as small as 300 nm. They lack a true cell wall and instead are enclosed in a plasma membrane composed of protein, glycoprotein, glycolipid, and phospholipid. The lack of a cell wall makes mycoplasmas relatively fragile outside their host but resistant to lysozyme and cell wall inhibiting antibiotics such as penicillins. Their genome contains as few as 700 genes, which is sufficient to allow for an extracellular existence but restricts their metabolic capability. For this reason they require a rich environment in order to flourish, which they find on mucous membranes of the respiratory and urogenital systems of their hosts, although they are able to survive in the environment for variable time periods depending on the temperature and humidity (typically 7–14 days under dry conditions at 30°C) (Messick & Harvey, 2012).

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Mycoplasmas are commonly isolated from mucous membranes of healthy animals, but their increased rate of isolation in disease suggests that they also play a pathogenic role under some circumstances. Pathogenic mechanisms include the production of hemolysin, proteases, and nucleases. They tend to be host specific.

In cats, *Mycoplasma* sp. are rarely isolated from the conjunctival sac of healthy animals, with surveys reporting either an absence of *Mycoplasma* sp. or isolation rates of less than 3% (Haesebrouck et al., 1991; Low et al., 2007; Shewen et al., 1980). However, in cats with conjunctivitis, isolation rates between 16% and 49% have been reported, frequently in the absence of other pathogens, thus suggesting a pathogenic role (Haesebrouck et al., 1991; Hartmann et al., 2010; Low et al., 2007). *Mycoplasma felis* is the predominant pathogenic species, but other species isolated from cases of feline conjunctivitis include *M. canadense*, *M. gateae*, *M. lipophilum*, *M. hyopharyngis*, and *M. cynos* (Haesebrouck et al., 1991; Hartmann et al., 2010).

In sheep and goats, *Mycoplasma conjunctivae* can be cultured from the conjunctival sac of healthy animals but is more frequently isolated from cases of conjunctivitis and keratoconjunctivitis. Experimental inoculation into the conjunctival sac confirms its role in the etiology of conjunctivitis in this species (Akerstedt & Hofshagen, 2004; Dagnall, 1994b; Degiorgis et al., 2000; Egwu et al., 1989; Giacometti et al., 1998; Jansen et al., 2006; McCauley et al., 1971; Motha et al., 2003; ter Laak, 1988a, 1988b).

In cattle, *Mycoplasma bovoculi* has been implicated as an etiological agent in IBK (Rosenbusch, 1983). In birds, *Mycoplasma gallisepticum* can cause outbreaks of severe conjunctivitis and upper respiratory tract disease (Dhondt et al., 1998; Nunoya et al., 1995).

Pathogenic Anaerobic Bacteria

Obligate anaerobes constitute a large group of gram-positive or gram-negative rods or cocci that exist not only in the environment but also as commensal organisms on the mucous membranes of humans and animals, primarily in the gastrointestinal tract, where they play an important role in the protection of mucosal surfaces from pathogenic bacteria (Jang & Walker, 2012).

Anaerobic bacteria can become pathogenic after compromise of a mucosal surface or inoculation of an anaerobic organism into a normally sterile site. They are commonly involved in deep tissue infections, often as part of a mixed infection with facultatively anaerobic organisms such as *Staphylococcus*, *Streptococcus*, *Escherichia*, or *Pasteurella* sp. A variety of anaerobic bacteria have been isolated from orbital infections in animals, including *Bacteroides* sp., *Clostridium* sp., *Actinomyces* sp., *Fusobacterium* sp., *Peptostreptococcus* sp., and *Porphyromas* sp. (Wang et al., 2009).

Tetanus is caused by the action of a neurotoxin produced by the gram-positive soil-dwelling anaerobe *Clostridium tetani*. Cranial nerve motor nuclei are commonly affected, resulting in hypertonicity of their respective musculature. Ocular signs are among the most common presenting signs of tetanus, with third eyelid protrusion and enophthalmos developing as a result of globe retraction secondary to retractor bulbi muscle hypertonicity (Burkitt et al., 2007).

Botulism is caused by a neurotoxin produced by *Clostridium botulinum*, a gram-positive anaerobic bacterium that is found in decaying organic matter. The neurotoxin causes inhibition of acetylcholine release at cholinergic synapses, disrupting both autonomic and skeletal muscle function. Ingestion of neurotoxin leads to systemic absorption and progressive clinical signs including ascending flaccid paralysis of the limbs, abnormal cranial nerve motor reflexes, inability to swallow, and excessive salivation. Ocular signs include mydriasis and reduced pupillary light reflexes (Critchley, 1991).

Ocular Fungal and Algal Diseases

Introduction

Fungi are eukaryotic, nonphotosynthetic organisms that grow as either single-cell yeasts or multicellular molds. Molds grow as branching filaments called *hyphae* (2–0 μm in diameter) whereas yeasts are unicellular, have oval or spherical appearance (3–5 μm in diameter) and reproduce by budding. Depending on the environment, some species of fungi can grow as either yeast or mold forms, and these species are described as dimorphic. Interestingly, some fungi exhibit multiple forms simultaneously, including budding, pseudohyphae, and hyphae; therefore, these species are described as polymorphic. Environmental temperature, nutrient factors, and genetic factors determine the type of growth observed (Quinn et al., 2011f).

Fungi grow aerobically, and many are strict aerobes. The reproductive cycle of fungi is sexual, asexual, or both. The sexual form of a fungal organism is referred to as a telemorph; the asexual form is referred to as an anamorph. The entire fungal replication process, consisting of all known reproductive forms, is referred to as a holomorph. In sexual reproduction, propagules arise through a process of plasmogamy, which is followed by karyogamy of compatible nuclei and subsequent meiosis. The point at which meiosis occurs varies among species. In contrast to meiotic reproduction, asexual reproduction is characterized by propagules formed directly from existing nuclei through mitosis. Via asexual reproduction, molds produce aerial fruiting hyphae that bear spores, the dispersion of which is chiefly through air currents, water, and animals.

The optimum temperature for growth of fungi is 20°C–30°C, but pathogenic fungi causing systemic mycoses can tolerate 37°C. Fungal growth is by simple mitosis of

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somatic nuclei and budding or apical extension of the cell wall. Elongation of buds with persistent attachment of cells in some yeasts produces filamentous forms known as pseudohyphae. In filamentous fungi, as hyphae grow by apical extension, they can intertwine to form a mycelial network or colony. Hyphae are often divided at regular intervals by cross partitions called septa, which have one or more small pores that allow for cytoplasmic communication. Chitin is a primary component of the cellular structure of many fungi. Chitin is composed of *N*-acetylglucosamine residues linked by glycosidic bonds similar to those found in cellulose. Fungal cell wall structures, which contain ergosterol, other lipids, and glycoproteins, serve as unique targets for antifungal drugs.

Fungi have been placed in their own kingdom. Fungi are nonmotile and most are strictly aerobic. Because fungi are nonphotosynthetic, they must obtain nutrition by secreting enzymes and absorbing the digested substrate. Medically important fungi have been separated into four traditional classes: *Basidiomycetes* sp., *Ascomycetes* sp., *Zygomycetes* sp., and *Deuteromycetes* sp. (or Fungi Imperfecti).

General Pathogenic Mechanisms and Host Responses

Fungi are commonly recovered from the eyelids and conjunctiva of normal animals, and they are believed to reflect random environmental exposure. Fungi do not appear to be permanent floral residents of the ocular surface but only transient colonizers of the external eye. Filamentous fungi are the predominate fungal isolates reported from the eyes of normal animals.

Local defenses to fungi are generally quite effective because ocular infection is not common unless anatomic barriers are compromised. An intact corneal epithelium provides excellent resistance to fungal penetration and infection. Normal ocular surface flora, normal lacrimal flow, and mechanical movements of the eyelids (and third eyelids) create an environment unfavorable to the growth of many opportunistic fungi. In addition, because many fungi will not grow at elevated temperatures, normal body temperature is high enough to prevent some from becoming pathogenic. The lower temperature of the cornea relative to the rest of the body and the eye, however, may partially explain the predilection for keratomycosis as the most common ocular infection with fungi. The role of local antibodies and complement in protection against ocular fungal infection is unclear.

A breach of the intact corneal epithelial barrier is usually a prerequisite for keratomycosis, and penetrating injuries can result in direct inoculation of fungi into the cornea. After trauma, colonization of an ocular wound by fungi may occur, particularly when corticosteroids have been administered, whether alone or in combination with antibacterial agents. The clinical observation that topical corticosteroids enhance the risk of fungal ocular infections suggests that local immune factors may be important in protecting the eye from fungal invasion. Local immunosuppression by corticosteroids possibly results primarily from effects on cellular immune mechanisms because immunity to fungal infections is considered to be more cell-mediated than antibody-mediated. Systemic or topical antibacterial agents alter normal flora and can decrease natural microbial barriers as well as encourage colonization and growth of fungi.

The second avenue for fungal invasion of the eye is endogenous (i.e., via the bloodstream). Systemic mycoses often occur in otherwise healthy animals living in endemic areas. In animals, intraocular fungal disease most often results from systemic mycoses contracted through respiratory tract exposure.

The host inflammatory response to oculomycosis is generally suppurative in acute cases and pyogranulomatous in chronic cases. Host tissues can be damaged directly by inflammatory processes (i.e., by elaborating inflammatory mediators and oxidative products) or by enzymes produced directly by the fungal organisms.

Diagnostic Methods

The laboratory methods employed for diagnosis include microscopic examination, fungal culture, PCR (for fungal detection and identification), and serology (Jagger, 2005; Jang & Walker, 2012; Sparagano & Foggett, 2009).

Microscopic Examination

Significant fungal elements can be identified by cytological and histological examination of slides containing material from scraped surface lesions, fluids, and/or biopsies.

Direct smears can be prepared for cytology as fixed stained smears and/or wet mounts (stained or unstained). Gram and Romanonwsky-type stains (e.g., Leishman's, Giemsa, Wright's, Diff-Quik) are routinely used for the cytological detection of fungi, especially yeasts, on direct smears with the fungal cell walls appearing as unstained halos (Fig. 7.11). Regarding cytological examination of wet mounts, there is a useful but less generally available fluorescent method; the collected material is mixed with equal volumes of 10% potassium hydroxide and 0.5% calcofluor white powder on a slide. Calcofluor is a fluorescent material that binds to chitin in fungal cell walls and when excited by light at a wavelength of 500 nm, the bound calcofluor fluoresces blue–green.

Some fungal elements can be detected in histological sections with hematoxylin and eosin, but employment of specific stains such as periodic acid-Schiff (PAS), Gomori's methenamine silver, and Meyer's mucicarmine allows confirmation of fungal infection and differentiation between yeast and hyphal forms.

Culture

Sabouraud dextrose agar is the medium most commonly used for culturing ocular fungi from swabs, scrapings,

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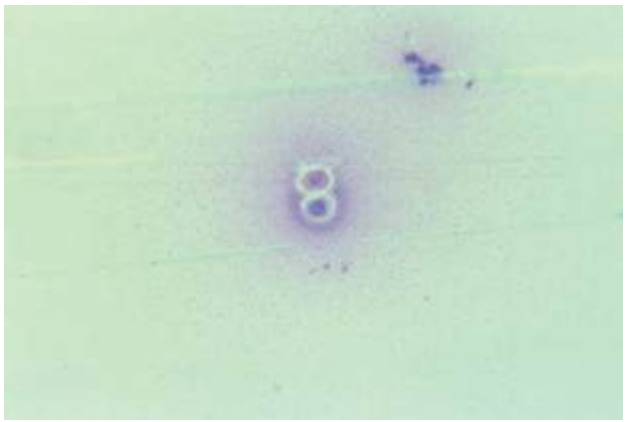


Figure 7.11 Smear prepared after centrifugation of vitreous fluid which was aspirated from the right eye of a 12-year-old cat which was presented with blindness and exophthalmia. Microscopic examination revealed the presence of two fungal organisms with their cell wall appearing as an unstained halo. (Original magnification 1000×; modified Giemsa stain.) Serological testing demonstrated a high antibody titer against *Cryptococcus* as well as the presence of *Cryptococcus* antigen.

fluid, and tissue samples. Enriched media such as brain-heart infusion agar with 5% blood is used for dimorphic fungi. When incubated at 37°C, mycelial fungal growth may convert to the yeast phase of the dimorphic organism. Gentamicin or chloramphenicol are useful additions to culture media to suppress bacterial overgrowth, but media should not include cycloheximide, which inhibits fungal growth.

Specimens from external infections of the ocular surface should be collected with a spatula and inoculated directly onto culture media. Scrapings or biopsy specimens from corneal ulcers or aspirates from the anterior chamber or the vitreous cavity should be directly inoculated onto Sabouraud agar, brain-heart infusion broth medium, and blood agar plates. Incubation should be from 24°C to 30°C for at least 30 days. Definitive identification is often made on the basis of the morphologic structure of the organism, including the direct microscopic appearance of the fungus in the clinical specimen, the morphology of the colony and type of pigmentation, the microscopic appearance of the fruiting heads and spores from mold colonies, and the morphology of the yeast and type of budding. Commercially available identification systems utilizing biochemical testing can be used for yeasts and, to a more limited extent, to identify some molds (Pincus et al., 2007).

In vitro susceptibility testing of fungi to antifungal drugs has been performed by measuring a suitable concentration end point (i.e., the MIC) for various antifungal drugs (Ledbetter et al., 2007; Pearce et al., 2009; Weinstein et al., 2006). The MIC is the amount of drug (micrograms per milliliter) that inhibits essentially all visible growth in treated test wells compared with duplicate, untreated test wells (see Ocular Bacteriology section previously). Standardized *in vitro* susceptibility test criteria are not available, though attempts have been made to estimate MIC susceptibility versus resistance on the basis of correlating clinical responses to antifungal therapy (Brooks et al., 1998).

Polymerase Chain Reaction

The ease with which PCR diagnostics can be performed, the relatively minimal expense of such testing, and the rapidity with which results can be delivered make PCR testing for fungal ocular infections desirable (Garner et al., 2010). However, the high sensitivity of PCR may, in fact, be a limiting factor in the applicability of PCR to diagnosis of keratomycosis in veterinary species. Fungal organisms are often part of the commensal flora depending on geography, season, and environment; standard PCR cannot distinguish transient fungal flora from those that are involved in pathogenesis of disease.

Serology

A number of serological techniques are available for the diagnosis of systemic mycoses (Jackson, 1986).

Complement-Fixation Test

The complement-fixation (CF) test is used for the diagnosis of histoplasmosis, blastomycosis, and coccidioidomycosis. Cross-reactivity between *Histoplasma* sp. and *Blastomyces* sp. occurs. CF titers for mycotic agents are often low (e.g., 1:8, 1:16), and nonspecific anticomplementary activity can be problematic. Appropriate controls must be used, and acceptable limits of complement activity established. Titers of 1:8 or greater offer presumptive evidence of histoplasmosis, blastomycosis, and coccidioidomycosis. Lower titers (e.g., 1:2, 1:4) might also be important, but a supplementary gel diffusion precipitation test should be performed. CF titers can serve as a prognostic aid. When titers decrease over a period of several weeks, the prognosis is usually good; if titers continue to increase over 8 weeks or longer, the prognosis is more guarded.

Gel Diffusion Precipitin

The gel diffusion precipitin (GDP) test is an immunodiffusion test with less cross-reactivity than the CF test. The test is based on the reaction in agar gel of specific antibody to fungal cell extracts or culture filtrates. In addition to its specificity, it is relatively simple to perform. The GDP has been developed for blastomycosis, histoplasmosis, coccidioidomycosis, aspergillosis, candidiasis, and sporotrichosis. In cases of mixed infections, false-negative results can be problematic. In addition, the GDP test is not useful in the diagnosis of advanced histoplasmosis in the cat.

Latex Agglutination

The slide latex agglutination (LA) test is rapid, sensitive, and specific for the presence of fungal antigen. This test has been developed for the diagnosis of cryptococcosis, coccidioidomycosis, sporotrichosis, candidiasis, and histoplasmosis,

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and it has been used extensively to detect antigen in body fluids (e.g., cryptococcal antigen in CSF). The course of disease can also be monitored during therapy by quantitating the antigen in fluids.

Fluorescence

Fluorescein-labeled antibodies can be used to identify fungi rapidly in tissues and culture, and this test can also be used on fixed specimens. It is particularly useful in the absence of culture and when serum is not available. Fluorescein-labeled lectins with defined specificity for different sugars also have been used to identify fungi in paraffin sections for surgical and postmortem specimens. The indirect FA test can also be used to detect antibody to fungal agents when other procedures are unavailable.

Agglutination

The tube agglutination test is a sensitive procedure for the diagnosis of sporotrichosis and cryptococcosis using yeast cells as antigen. It is used in conjunction with the LA antigen test to quantitate anticryptococcal antibody for prognostic purposes.

Enzyme-Linked Immunosorbent Assay

Detection of antibodies employing an enzyme-linked immunosorbent assay (ELISA) test has been reported for the diagnosis of sporotrichosis in cats (Fernandes et al., 2011).

Immunofluorescence

The fluorescent immunoassay is an immunochemical procedure used to detect antibodies to *Candida* sp., *Histoplasma* sp., *Blastomyces* sp., and *Coccidioides* sp. This test compares favorably with conventional methods in correlating clinical response and predicting relapse of disease.

Pathogenic Fungi

Dermatophytes

Dermatophytes are keratinophilic fungi that cause clinical disease in a wide range of animal species. Although many different dermatophyte species have been isolated from animals, a limited number of species are responsible for the majority of cases of clinical disease. They typically cause localized or generalized skin disease that involves the eyelids and periocular skin. Transmission is via direct contact or from contaminated fomites, with an incubation period of 1–3 weeks. The organisms have a relatively wide host range and are significant zoonotic pathogens (Chermette et al., 2008; Drouot et al., 2009; Moriello et al., 2017; Ramsay, 2011; Warner, 1984).

Dermatophytosis is more common in hot, humid environments. The high environmental resistance of arthrospores, the wide range of host species, and the close contact between susceptible animals can all contribute to disease spread and persistence, such that the disease can become enzootic in certain environments, particularly farms and breeding establishments. Pathogenic mechanisms include the production of keratinase, elastase, and collagenase that are thought to aid initiation and progression of infection (Viani et al., 2007).

Microsporum canis, *Trichophyton mentagrophytes*, and *Microsporum gypseum* are responsible for the vast majority of canine and feline dermatophyte infections worldwide. Cats are considered to act as reservoirs of *M. canis*, with surveys of healthy cats showing carrier rates of around 2% (Patel et al., 2005). The reservoir host of *T. mentagrophytes* is thought to be rodents, although cats also act as carriers (Patel et al., 2005). *M. gypseum* is a geophilic organism; exposure is therefore by digging in contaminated soil (Moriello & DeBoer, 2012).

In cattle, *Trichophyton verrucosum* is most commonly isolated, followed by *T. mentagrophytes* and *M. gypseum*. In horses, *T. equinum* is the predominant isolate, with *Microsporum equinum* and *T. mentagrophytes* less common. Ringworm is rare in sheep and pigs (Chermette et al., 2008; Soltys & Sumner-Smith, 1969).

Diagnosis of dermatophytosis is via direct microscopic examination of skin scrapes or, preferably, fungal culture. Approximately half of all *M. canis* strains are reported to fluoresce under examination of the haircoat with ultraviolet light, wavelength 320–400 nm (Wood's lamp examination) (Kefalidou et al., 1997).

Ocular Surface Fungal Pathogens: Aspergillus, Penicillium, Alternaria, Cladosporium, Fusarium, *and Related Species*

These are ubiquitous free-living saprophytic fungi that are commonly found as commensal flora on the skin and mucous membranes, including the conjunctiva, of animals (see Table 7.1). They act as opportunistic pathogens, and a wide range of species have been implicated in ocular surface disease. Presumably caused by environmental housing conditions, fungal ocular surface disease is more commonly seen in horses and production animals than in companion animals (Andrew et al., 1998, Brooks et al., 1998; Gaarder et al., 1998; Gerding et al., 1988; Marler et al., 1994; Reed et al., 2013). Fungal keratitis is more commonly seen in hot and humid environments and is a particularly significant problem in horses, in which it can cause devastating corneal disease (Andrew et al., 1998; Gaarder et al., 1998). The organisms require an epithelial defect to allow colonization of the corneal stroma, and tear film instability could predispose to infection (Brooks et al., 2000b). Once inoculated, pathogenic mechanisms include release of proteases and factors that promote adherence and penetration (Hua et al., 2010; Jackson et al., 2007).

Although primarily extraocular pathogens, these organisms also cause intraocular disease in association with systemic disseminated spread, or via local extension from the

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sinuses via the orbit (Clercx et al., 1996; Willis et al., 1999; Wooff et al., 2018).

Systemic Fungal Pathogens: Blastomyces, Histoplasma, Coccidioides, and Cryptococcus *sp.*

Blastomyces dermatitidis, *Histoplasma capsulatum*, and *Coccidioides immitis* are free-living saprophytic fungi that grow filamentously in the environment and produce conidia (asexual spores). Conidia are environmentally robust spores that are thought to be infectious via airborne spread. Their small size (typically 1–4 μm) allows them to enter the alveoli where they establish local infection. Once there, systemic spread ensues via hematogenous or lymphatic routes. Pathogenic fungi possess a large number of virulence factors that allow them to establish themselves in host tissue and to escape host defenses, although to allow systemic spread, some degree of host immunosuppression is usually required (Hogan et al., 1996).

Blastomyces dermatitidis

B. dermatitidis prefers sandy, acidic soils with close proximity to water, supported by decaying animal and plant material. Even in endemic regions, the organism is not widely distributed but appears to require an ecological niche of some sort for survival.

In contrast to other systemic fungal infections, subclinical infection is rare. Virulence factors for *B. dermatitidis* include a number of cell wall-associated factors including α-1,3-glucan and WI-1 adhesin/antigen (Hogan et al., 1996).

Blastomycosis is primarily a disease of North America, with an endemic distribution comprising Mississippi, Missouri, the Ohio River Valley, the mid-Atlantic and southern states, and southeast Canada. It is primarily a disease of dogs; cats are rarely infected. Up to 50% of dogs with blastomycosis have ocular lesions, primarily chorioretinitis, anterior uveitis, and optic neuritis. Hematogenous spread is thought to be the main route by which the organism gains access to the choroid (Arceneaux et al., 1998; Brömel & Sykes, 2005; Krohne, 2000; Legendre, 2012).

Histoplasma capsulatum

H. capsulatum grows preferentially in nitrogen-rich soil such as that contaminated with bird or bat excrement. It prefers warm, moist, and humid environmental conditions and is endemic in many parts of the world.

Virulence factors include cell wall α-1,3-glucan, relative thermotolerance, and an ability to modulate local pH and thus inactivate hydrolases released from host phagosomes. Of particular pathogenic relevance is the ability of *H. capsulatum* to persist and actively replicate within host macrophages once phagocytosed. As well as providing protection against humoral and cell-mediated host defenses, this "Trojan horse" approach allows spread of the organism within the host, as unwittingly infected macrophages migrate from the lungs to other parts of the body, carrying the fungus with them (Hogan et al., 1996).

In the United States, most clinical cases of histoplasmosis can be found in the regions of Ohio, Missouri, and Mississippi (Brömel & Greene, 2012). Up to two-thirds of infected dogs develop ocular lesions. Chorioretinitis is the most common ocular manifestation, although optic neuritis and anterior uveitis also occur (Krohne, 2000; Salfelder et al., 1965). In cats, histoplasmosis is the second most common systemic mycosis after cryptococcosis. Twenty-four percent of cats with histoplasmosis are reported to have ocular signs, primarily chorioretinitis (Brömel & Sykes, 2005; Davies & Troy, 1996; Gionfriddo, 2000).

Coccidioides immitis

C. immitis prefers sandy, alkaline, dry, and warm soils at low elevation and is primarily found in the southwestern United States, Central America, and parts of South America. Virulence factors include the production of extracellular proteinases (Hogan et al., 1996). As with other systemic mycotic infections, ocular involvement primarily manifests as chorioretinitis. The condition is more common in dogs than in cats (Gionfriddo, 2000; Graupmann-Kuzma et al., 2008; Greene & Troy, 1995; Krohne, 2000; Shubitz & Dial, 2005).

Cryptococcus *sp.*

Cryptococcosis in dogs and cats is caused by one of two encapsulated yeast species, *Cryptococcus neoformans* and *Cryptococcus gattii*. In contrast to other systemic mycoses, cryptococcosis is less common in dogs than in cats, in which it is the most frequently recognized systemic fungal infection (Gionfriddo, 2000; Sykes & Malik, 2012; Trivedi et al., 2011).

C. neoformans has a worldwide distribution, prefers nitrogen-rich soils, and is commonly found in soil contaminated with bird (especially pigeon) excrement. *C. gattii* is restricted to tropical and subtropical climates. It is found in high concentrations within decaying plant material, and in Australia, koalas are thought to be sentinel hosts for infection (Sykes & Malik, 2012).

In animal tissues, the organisms exist as round to oval yeast with a characteristic polysaccharide capsule which provides protection from host phagocytes and is a key virulence factor (Zaragoza et al., 2009). Additional virulence factors include the cell wall-associated oxidative enzyme laccase (Zhu & Williamson, 2004; Zhu et al., 2001) and the production of melanin, mannitol, superoxide dismutase, proteases, and phospholipases (Buchanan & Murphy, 1998).

The route of infection is thought to be via inhalation of airborne dehydrated yeast cells or spores. In humans, primary infection is established in the lung. This is usually asymptomatic in healthy individuals, but in immunocompromised patients, hematogenous spread via macrophages allows dissemination to other tissues including the nervous system (Botts & Hull, 2010).

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In contrast to humans, the nasal cavity is the primary site of infection in cats, dogs, koalas, and psittacine birds. Here it causes local disease or disseminates, usually to the central nervous system to cause meningoencephalitis. Intraocular spread is presumed to be via the optic nerves, although infection via the hematogenous route also occurs (Sykes & Malik, 2012). The primary ocular manifestation is chorioretinitis (Gionfriddo, 2000; Sykes & Malik, 2012; Trivedi et al., 2011).

Prototheca *sp.*

Prototheca is a saprophytic alga that is related to the green algae of the genus *Chlorella*. Unlike *Chlorella*, however, *Prototheca* lacks chlorophyll and is a saprophytic organism (Hollingsworth, 2000; Pressler, 2012). Three species are recognized: *Prototheca stagnosa*, *P. wickerhamii*, and *P. zopfii*. Of these, *P. wickerhamii* and *P. zopfii* have pathogenic potential. *P. zopfii* is more often associated with disseminated disease than is *P. wickerhamii* (Pressler, 2012; Stenner et al., 2007).

The organisms are found in sewage, animal waste, and decaying vegetable matter. They are opportunistic pathogens, causing disease if they are ingested or come into contact with damaged skin or mucous membranes. It is thought that some degree of host immunosuppression is required to allow disseminated infection, with cell-mediated immunity playing a major role in host defense mechanisms. In dogs there is an apparent breed predisposition, with an increased reported incidence in Collies and Boxers. Young adult spayed females are also overrepresented (Hollingsworth, 2000; Stenner et al., 2007). In cats, only cutaneous protothecosis has been reported, and disseminated disease does not seem to occur.

The most commonly reported clinical sign in dogs is colitis, which is usually intermittent and chronic in nature. Systemic dissemination leads to renal, hepatic, cardiac, CNS, and ocular disease. Ocular disease occurs in three-quarters of reported cases and can be the presenting sign. Chorioretinitis, retinal hemorrhage, retinal detachment, and anterior uveitis are reported (Pressler, 2012; Hollingsworth, 2000).

Other Fungal Pathogens

Other fungal species have been sporadically documented to cause opportunistic ocular diseases, including anterior uveitis, chorioretinitis, endophthalmitis, and orbital disease (Clercx et al., 1996; Gionfriddo, 2000; Krohne, 2000; Wooff et al., 2018).

Ocular Protozoal Diseases

Introduction

The most common protozoa responsible for ocular disease are *Toxoplasma*, *Neospora*, *Leishmania*, *Babesia*, and *Encephalitozoon*. For information on the individual organism's replication and pathological mechanisms, see the respective sections that follow.

Diagnostic Methods

Diagnosis is based on a combination of clinical signs, clinicopathological abnormalities, and more specific diagnostic tests (Little & Lindsay, 2012; Murphy & Papasouliotis, 2005). These tests are best either in the detection of the organism itself (microscopic examination, culture, PCR, histology) or immunological tests that detect specific proteins of the organism (antigens) and/or the host's immune response to the organism (antibodies).

Microscopic Examination

Organisms can be detected in dried smears prepared from fresh and anticoagulated blood samples (e.g., *Babesia*), other body fluids, and fine needle aspirates of affected organs, as well as impression smears from tissue biopsies (e.g., *Neospora*, *Toxoplasma*, *Leishmania*, *Encephalitozoon*). The most commonly used stains are Giemsa, Wright, and Wright–Giemsa. Diff-Quik can also be used, but both detection and subsequent morphological identification is more difficult. The use of immunocytochemical methods may increase the sensitivity of direct identification, but its commercial availability is very limited.

Culture

Culture of whole blood, tissue aspirates, biopsies, or body fluids is not commonly performed because protozoa are generally very difficult to grow *in vitro*; those that can grow are very slow, and the methodologies are technically demanding and offered by a very limited number of diagnostic laboratories.

Polymerase Chain Reaction

The principle of the PCR method, as well as the advantages and disadvantages for diagnosing protozoal infections are similar to those reported above for viral infections (see Ocular Virology section previously). The most common protozoal infections for which PCR is routinely used for their diagnosis are discussed later. At present, PCR assays can be performed on blood, CSF, or aqueous humor samples collected in tubes containing ethylenediaminetetraacetic acid (EDTA) anticoagulant.

Histology

Organisms can often be seen during histological examination of biopsies with routine hematoxylin and eosin staining or with electron microscopy. Protozoa can also be identified on frozen sections if an immediate diagnosis is required, but only if the tissue samples have been collected and submitted to laboratory quickly. Biopsies for electron microscopy should be placed in a glutaraldehyde-based fixative. The use of immunohistochemical methods may increase the sensitivity of direct identification, but its commercial availability is not extensive.

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Immunological Tests

Immunological tests can be performed in serum samples and less commonly in aqueous humor (Lappin et al., 1992). Measurement of serum antibody titers are commonly available for all ocular protozoal diseases, and the most commonly used techniques are IF, ELISAs, and agglutination/hemagglutination. For some organisms, point-of-care ELISAs for the detection of serum antibodies are also available, offering reliable results (Couto et al., 2010).

For most protozoal diseases, serology detects the presence of IgG. Although for the diagnosis of toxoplasmosis, serological tests detecting IgM are also available. In clinical practice, there are two main approaches in the use of serology for the diagnosis of infection; single measurement of IgM and/or IgG titers and measurement of IgM and/or IgG titers in paired serum samples.

Single Antibody Titer Measurement

High titers of antigen-specific IgM are believed to indicate active or recent infection. IgM is of particular value in the diagnosis of endemic diseases when a high proportion of the animal population may have been exposed to the infection and therefore may have antigen-specific IgG detectable. Limitations of the single measurement of antibodies include the detection of antibodies in vaccinated animals that are not diseased, the absence of antibodies in acutely infected animals that did not have time to produce antibodies, and that detection of IgG antibodies can reflect to the organism and not necessarily active infection.

Measurement of Antibody Titers in Paired Samples

A fourfold or greater increase in antibody titer in two samples collected over a 2-week period has been suggested to indicate active infection. However, it should be noted that antibody titers might not increase in immunocompromised animals and maximum antibody levels could have been reached by the time clinical signs develop. In addition, titers from different laboratories vary, and titers can vary between assays performed on different days. For these reasons and in an ideal situation, paired samples should be assayed together (i.e., repeat assay on the first sample) as a fourfold or greater increase is unlikely to be caused by laboratory variability.

Pathogenic Protozoa

Toxoplasma gondii

Toxoplasma gondii (phylum Apicomplexa, family Sarcocystidae) is an obligate intracellular protozoal parasite that infects almost all warm-blooded animal species and is one of the most common parasitic infections in humans and animals worldwide. Domestic cats and other Felidae are its definitive hosts and shed infective oocysts via feces. Nonfeline species are intermediate hosts that carry tissue cysts but do not shed oocysts, because they do not support a gastrointestinal life cycle (Davidson, 2000; Davidson & English, 1998; Dubey & Lappin, 2012; Dubey et al., 2009).

There are three major routes of infection: ingestion of infected tissue, ingestion of oocyst-contaminated food or water, and congenital infection. Minor routes of infection include lactational, via organ or tissue transplantation, and via transfusion of infected body fluids.

In cats, after ingestion of *T. gondii*-infected intermediate hosts (usually rodents or birds), bradyzoites are released from tissue cysts into the stomach and small intestine after degradation of the cyst wall by stomach acids. They penetrate the epithelial cells of the small intestine where they undergo asexual or sexual phases of reproduction. The asexual phase involves transformation into tachyzoites, which then spread via the bloodstream to CNS and ocular tissues, skeletal muscle, and visceral organs where they encyst as bradyzoites. The sexual phase is confined to the intestinal epithelial cells. Bradyzoites transform into merozoites and then into either male (micro-) or female (macro-) gamonts. Fertilization of a macrogamont by a microgamont leads to the formation of an oocyst. This is excreted in feces as an unsporulated and noninfectious oocyst. After exposure to air and moisture for 1–5 days, the oocyst sporulates. A sporulated oocyst contains two sporocysts, each with four sporozoites, which are the infectious form of the parasite. They are resistant to extreme environmental conditions and can remain infectious for many months.

The enteroepithelial (coccidian) life cycle is completed in 3–10 days after ingestion of tissue cysts and occurs in 97% of infected cats. In contrast, after ingestion of sporulated oocysts, only 20% of cats will progress to patency, and the life cycle takes 18 days or longer to complete. Thus, bradyzoites are more infectious to cats than are oocysts, and it is thought that bradyzoites are the natural precursors for the enteroepithelial life cycle (Dubey & Lappin, 2012).

In non-Felidae species, only the asexual extraintestinal life cycle occurs. After ingestion of tissue cysts (containing bradyzoites) or sporulated oocysts (containing sporozoites) the parasite transforms into tachyzoites. These disseminate systemically and encyst as bradyzoites in muscle, CNS, ocular tissue, and visceral organs where they are thought to persist for the lifetime of the host. In pregnant animals and people, tachyzoites are capable of crossing the placenta to infect the fetus, where they can lead to abortion or developmental defects.

Toxoplasmosis describes clinical disease associated with *T. gondii*. Risk factors for seroreactivity and clinical disease include age, a raw meat diet, and an outdoor environment. *T. gondii* does not produce toxins, and damage to the host is via cell necrosis after intracellular growth of the parasite. Tachyzoites are capable of growing in almost any cell type, and rupture of an infected cell leads to release of more tachyzoites which can then go on to infect and damage other cells either locally or at distant sites. Tissue cysts containing

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bradyzoites can also grow and cause host cell necrosis. The host immune response also contributes to local tissue damage, especially in the eye where autoantibody production can develop in response to infection and damage of host cells, thus perpetuating uveitis even in the absence of active organisms (Davidson & English, 1998).

Many *T. gondii* infections are subclinical, and the reasons why some infected animals develop clinical toxoplasmosis whereas others remain healthy are not fully understood. Age, host species, strain of *T. gondii*, infectious load, concurrent infections, and the status of the host immune system are all likely contributory factors (Davidson, 2000; Davidson et al., 1993a; Powell & Lappin, 2001). Both cell-mediated and humoral immune responses are important host defenses, and immunosuppression or concomitant illness will predispose to clinical disease in an infected individual.

Clinical signs of toxoplasmosis are wide-ranging. In naïve infected cats, transient diarrhea is associated with the initial phases of the enteroepithelial replication. Systemic signs are most commonly seen in transplacentally or lactationally infected kittens, where overwhelming tachyzoite spread and replication can prove fatal. CNS, ocular, hepatic, and respiratory disease can develop. Chorioretinitis is the most common ocular sign in kittens. In adult cats, signs develop caused by tachyzoite spread after acute primary infection or via reactivation of latent tissue cysts after immunosuppression. Most commonly reported signs are pulmonary, CNS, hepatic, pancreatic, cardiac, and ocular disease. Anterior uveitis and chorioretinitis are the principal ocular manifestations (Davidson et al., 1993b).

In dogs, clinical signs are also wide-ranging, commonly affecting the neuromuscular, respiratory, or gastrointestinal systems. Ocular signs include chorioretinitis, anterior uveitis, and optic neuritis (Davidson, 2000; Dubey, 1985; Dubey et al., 2009).

Diagnosis of toxoplasmosis can be difficult. Clinical signs and hematological and biochemical parameters are nonspecific. Serological diagnosis is seldom definitive, because surveys show that *T. gondii* is common, with around 30% of healthy dogs and cats in the United States having positive *T. gondii* IgG antibody titers (Dubey & Lappin, 2012).

Because an IgM response develops early in the course of the disease and is generally short-lived, positive IgM titers indicate recent infection. After experimental infection, approximately 80% of cats will develop an IgM antibody response. This usually develops within 1–3 weeks of infection and typically disappears by 12–16 weeks postinfection (Davidson, 2000; Lappin, 1996; Lappin et al., 1989). However, caution should be exercised when interpreting IgM results because not all infected cats will develop an IgM response, whereas in other cases the IgM response may last months to years (Dubey & Lappin, 2012; Powell & Lappin, 2001). Additionally, the IgM titers are not specific for *T. gondii*.

An IgG response develops later than the IgM response, and IgG levels are present for months or years after infection. Thus, whereas a positive IgG titer is evidence of exposure to *T. gondii*, it is not proof of recent exposure. Rising IgG titers are used as evidence of recent infection. However, the initial IgG response may not be detectable until 4–6 weeks after infection and, after initial detection of IgG, maximal titers may develop in as little as 2 weeks, leaving a narrow window for demonstration of rising titers (Dubey & Lappin, 2012).

For ocular toxoplasmosis, elevated *T. gondii*-specific aqueous humor antibody levels compared with serum levels indicates ocular production of *T. gondii* antibodies, and therefore possibly local infection (Chavkin et al., 1994; Lappin, 1996; Lappin et al., 1992). PCR testing of blood and aqueous humor samples has also been reported (Powell et al., 2010).

Neospora *sp.*

N. caninum (phylum Apicomplexa, family Sarcocystidae) is a protozoan parasite that, until 1998, was misdiagnosed as *T. gondii* (Dubey et al., 1988). Its definitive host is the domestic dog, which sheds infective oocysts after an enteroepithelial sexual life cycle similar to that of *T. gondii* in cats. *N. caninum* is a significant cause of abortion in cattle and of neurological disease in dogs. Ocular signs in dogs are associated with neurological disease and include blindness, anisocoria, optic neuritis, chorioretinitis, anterior uveitis, and extraocular myositis, although there are very few clinical reports in the veterinary literature (Dubey & Lappin, 2012; Dubey et al., 1990, 2007).

Leishmania *sp.*

Leishmaniasis is caused by protozoan parasites of the phylum Euglenozoa, family Trypanosomatidae. Around 30 leishmanial species are recognized worldwide, and around 20 of these cause clinical disease in humans. The majority of these are zoonotic, and dogs are important disease vectors in areas of the world where the disease is endemic. *Leishmania infantum* and its New World homologue *Leishmania chagasi* are the main causative agents of canine leishmaniasis (Baneth, 2012).

Leishmaniasis is uncommon in cats, but *L. infantum* causes feline leishmaniasis within endemic areas of Europe (Martín-Sánchez et al., 2007; Pennisi & Persichetti, 2018). In other parts of the world, different species cause disease in cats, including *L. chagasi*, *L. mexicana*, *L. amazonensis*, and *L. braziliensis* (Petersen, 2009; Trainor et al., 2010; Vides et al., 2011).

In humans, three forms of clinical diseases are recognized: cutaneous leishmaniasis; mucocutaneous leishmaniasis; and visceral leishmaniasis. Dogs and cats typically develop a combination of visceral and cutaneous disease (Baneth, 2012; Leiva et al., 2005a; Trainor et al., 2010; Vides et al., 2011).

The parasite is transmitted by sandflies (*Phlebotomus* sp. in the Old World, *Lutzomyia* sp. in the New World), which transmit leishmania promastigotes to humans and animals during a blood meal. Once inoculated, the parasites are

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phagocytosed by host macrophages, in which they transform into an amastigote form that replicates by binary fission, leading to rupture of the macrophage and release of amastigotes which can then infect new cells. The amastigotes can also be ingested by sandflies, where they transform into an extracellular flagellated promastigote form which undergoes replication within the gastrointestinal tract of the sandfly before being inoculated via saliva into their vertebrate host when the female sandfly feeds.

Canine visceral leishmaniasis is a chronic disease, with clinical signs developing from 3 months to 7 years after infection. Clinical signs are vague and wide-ranging, and include lymphadenomegaly, splenomegaly, pale mucous membranes, skin disease, weight loss, lethargy, anorexia, diarrhea, vomiting, epistaxis, melena, and respiratory disease. Cutaneous lesions can be found in up to 90% of dogs and include progressive and symmetric alopecia with exfoliative dermatitis (Baneth, 2012; Ciaramella et al., 1997). Around 25% of affected dogs develop ocular or periocular signs, most frequently anterior uveitis, periocular dermatitis, and keratoconjunctivitis. Approximately 15% of dogs develop only ocular signs with no evidence of systemic involvement (Peña et al., 2000). Histopathological examination shows granulomatous inflammatory lesions developing in the conjunctiva, cornea, sclera, limbus, ciliary body, iridocorneal drainage angle, iris, choroid, and optic nerve (Peña et al., 2008).

Feline ocular leishmaniasis is rare, but has been associated with anterior uveitis, panuveitis, and corneal ulceration (Hervás et al., 2001; Leiva et al., 2005a).

Definitive diagnosis of leishmaniasis is by microscopic demonstration of parasites in histopathological samples, serology, culture of the organism in appropriate culture medium, or detection of DNA via PCR testing (Baneth, 2012).

Babesia *sp.*

Babesia sp. (phylum Apicomplexa, family Babesiidae) are tick-borne protozoal parasites of red blood cells that cause fever, hemolytic anemia, jaundice, and hemoglobinuria in a wide range of mammalian host species (Birkenheuer, 2012; Chauvin et al., 2009). Ophthalmic signs develop secondary to systemic disease and include eyelid swelling, subconjunctival and third eyelid hemorrhage, and serous ocular discharge (Sippel et al., 1962; Taylor et al., 1969).

Encephalitozoon cuniculi

E. cuniculi (phylum Microsporidia, family Unikaryonidae) is an obligate intracellular protozoal parasite of rabbits and other small mammals. Mature spores are small and oval (1.5 µm × 2.5 µm) and contain a distinctive coiled polar tubule that is used to inoculate the parasite into the host cell. Infection of mammalian hosts is by ingestion or inhalation of spores from contaminated urine or fecal material shed from infected hosts, although vertical transmission is also a significant route of infection (Wasson & Peper, 2000). Once internalized, the polar tubule inoculates the parasite into the host cell where it develops within a host-derived membrane and replicates by schizogony (a form of binary fission) before rupture of the host cell allows release of infectious spores (Didier et al., 2012).

E. cuniculi is a major pathogen in rabbits, where its primary target organs are the kidney, brain, and eye (Ashton et al., 1976; Giordano et al., 2005; Künzel & Joachim, 2010; Smith & Florence, 1925; Wasson & Peper, 2000). In the eye, it causes cataract formation with lens capsule rupture leading to phacoclastic uveitis. It has also been reported to cause cataracts and central nervous system pathology in mink and in blue fox puppies (Bjerkås, 1987, 1990).

Experimental inoculation of *E. cuniculi* into cats leads to infection and damage of the kidneys and brain, although the organism does not appear to be a clinically important cause of renal disease in practice (Hsu et al., 2011; Pang & Shadduck, 1985). However, the organism was reported to cause anterior uveitis and cataract in a case series of 19 eyes of 11 cats, with infection confirmed by serology, PCR of aqueous humor/lens, and cytological confirmation of spores within lens tissue (Benz et al., 2011).

Ocular Parasitic Diseases

Introduction

The most common parasitic ocular diseases are caused by infection with mites, nematodes, dipteric larvae, or tapeworms. For information on an individual organism's replication and pathological mechanisms, see the respective sections that follow.

Diagnostic Methods

Diagnosis is based on a combination of clinical signs, clinicopathological abnormalities, and more specific diagnostic tests. The most commonly employed laboratory methods include microscopic examination, fecal examination techniques (Baermann, flotation) (Schnyder et al., 2011a), PCR (Gioia et al., 2010; Wijesundera et al., 1999), and histology or immunological tests that detect antibodies against the organism and/or specific protein antigens of the organism (Schnyder et al., 2011b). The principles of these methods are similar to those reported above (see Ocular Virology and Ocular Bacteriology sections previously). The fecal examination techniques have variable diagnostic yield (Dunkel et al., 2011; Schnyder et al., 2011a). Immunological methods for the detection of serum antigen have been designed for in-clinic use, but their diagnostic performance is variable (Lee et al., 2011; Schnyder et al., 2014).

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Parasitic Mites

Demodex sp. (phylum Arthropoda, order Trombidiformes, family Demodicidae) are commensal parasitic mites of the skin and hair of mammals. They spend their entire life cycle on the host, being directly transmitted from the dam to her offspring within 2–3 days of birth. There is no evidence of horizontal transmission between adult hosts. *Demodex* mites undergo four stages of development: a fusiform egg, a six-legged larva, an eight-legged nymph, and an eight-legged adult. Most species, including *Demodex canis*, *D. cati*, *D. equi*, *D. caballi*, and *D. bovis*, live within hair follicles and sebaceous glands, although a few species are found within the epidermis. They feed on dead skin cells, sebum, and cellular debris. In small numbers, the mites are nonpathogenic, but in some hosts, they multiply and cause localized or generalized demodicosis. Immunosuppression, stress, genetic predisposition, poor nutrition, and concurrent infection may all be contributory factors to clinical disease, and T-cell deficiencies have been implicated in the etiopathogenesis of disease in dogs (Gortel, 2006). Localized periocular demodicosis is relatively common and is typically characterized by bilaterally symmetrical nonpruritic alopecia and scaling.

Other skin mites include *Sarcoptes scabei*, *Notoedres cati*, *Otodectes cynotis*, *Haematopinus asini*, *Werneckiella equi*, *Cheyletiella* sp., and *Psoroptes* sp. Unlike *Demodex* sp., they are unlikely to cause localized periocular dermatitis, but eyelid involvement can be seen as part of generalized skin involvement.

Parasitic Nematodes

Angiostrongylus vasorum *(Lungworm)*

Angiostrongylus vasorum (phylum Nematoda, order Strongylida, family Metastrongylidae) is a parasite of the heart and pulmonary circulation of dogs and foxes that was originally a clinical problem primarily in southwestern France but has since been recorded in many countries across Europe, Africa, Asia, and the Americas. In recent years, an increased incidence has been particularly noted in the United Kingdom and Scandinavia (Bolt et al., 1994; Helm et al., 2010; Morgan & Shaw, 2010).

Male and female adult worms live in the right side of the heart and the pulmonary arterial circulation. Here they reproduce to create eggs which hatch to first-stage larvae (L1) that are then carried to the pulmonary capillaries, where they penetrate the alveoli and are coughed up into the oropharynx before being swallowed and passed in the feces. Intermediate hosts are gastropod mollusks (slugs or snails) in which further larval development to infective stage three larvae (L3) takes place. If the intermediate host is eaten by a dog or fox, the larvae penetrate the intestinal wall and are carried via the bloodstream and/or lymphatic system to the heart and pulmonary arteries, where they mature to adult worms.

The major clinical signs of *A. vasorum* infestation are coughing, dyspnea, lethargy, and hemorrhagic diatheses (Chapman et al., 2004). Extensive subconjunctival hemorrhage is a common clinical finding in affected dogs. The mechanism of the coagulopathy is poorly understood, but anemia, thrombocytopenia, antiplatelet antibodies, increased clotting times, hyperglobulinemia, reduced activity of clotting factors VIII and V, and von Willebrand factor deficiency have all been documented, suggesting a consumptive coagulopathy (Cury et al., 2002; Gould & McInnes, 1999; Morgan & Shaw, 2010; Morgan et al., 2005; Whitley et al., 2005). Aberrant migration of L3 larvae can lead to ocular penetration, and larvae may be found in the anterior chamber or vitreous, where they can stimulate a severe granulomatous uveitis (Manning, 2007).

Definitive diagnosis of *A. vasorum* infestation is by demonstration of L1 larvae in the respiratory tract via bronchoalveolar lavage, or within the feces via Baermann or FLOTAC examination (Barçante et al., 2008; Humm & Adamantos, 2010; Schnyder et al., 2011a).

Dirofilaria immitis *(Heartworm)*

Dirofilaria immitis (phylum Nematoda, order Spirurida, family Onchocercidae) lives in the pulmonary arteries of dogs, although it may infest other species including cats and humans (Litster & Atwell, 2008; McCall et al., 2008; Ware, 2003). It is widespread in areas of the world where its mosquito intermediate host is endemic, in particular the eastern and gulf coasts and the Mississippi River valley of the United States, Australia, and southern Europe (Dantas-Torres et al., 2009; McCall et al., 2008; Ware, 2003).

Adult female worms within the pulmonary arterial system release microfilariae (L1) into the blood stream which are ingested by mosquitoes during a blood meal. The L1 larvae undergo two maturations within the mosquito over a period of 2–2.5 weeks as they develop into the infective L3 stage larvae, which are then inoculated into a host at the next blood meal. L3 larvae migrate within subcutaneous tissues of the host, molting into L4 then L5 larval stages. These then enter the bloodstream approximately 100 days after infection and are transported to the pulmonary arteries where they mature to adult worms. From the time of infection to development of mature heartworms, a period of 6 months or longer is usually required (Bowman & Atkins, 2009; Ware, 2003).

Heartworm disease in dogs is a major cause of pulmonary hypertension (cor pulmonale) which develops secondary to progressive damage to the pulmonary arteries. Periarterial edema, vasculitis, and proliferation of smooth muscle cells within the arterial walls lead to arteriolar narrowing and increased local vascular hypertension. Many dogs are asymptomatic at diagnosis, but clinical signs can include lethargy, dyspnea, cough, hemoptysis, weight loss, and progressive right-sided congestive heart failure. Migration of microfilariae may also cause permanent liver damage and cirrhosis,

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whereas circulating antibody–antigen complexes may induce glomerulonephritis.

Aberrant migration of L4 larvae may lead to ocular infiltration, where the parasites develop to L5 and immature adult forms, inducing a severe anterior uveitis (Dantas-Torres et al., 2009; Eberhard et al., 1977; Lavers et al., 1969; Mallett et al., 1971).

Diagnosis of dirofilariasis can be confirmed via heartworm antigen testing kits. It should be noted, however, that in some cases of ocular dirofilariasis, antigen testing has proven negative, presumably because of a low worm burden in such animals. In these cases, diagnosis is made by direct observation of the parasite within the anterior chamber (Dantas-Torres et al., 2009).

Onchocerca *sp.*

Onchocerca cervicalis (phylum Nematoda, order Spirurida, family Onchocercidae) is a nematode parasite of horses transmitted by a *Culicoides* midge or *Simulium* fly vector. These inoculate microfilariae into the skin, which then migrate to the nuchal crest where they develop to mature adults. Adult worms release microfilariae that migrate within the dermis and subcutaneous tissues and are ingested by biting midges or flies, in which they develop to the infectious L3 stage in around 25 days (Mellor, 1973a, 1973b; Mellor, 1974a, 1974b; Schmidt et al., 1982a; Webster & Dukes, 1979).

The parasite is common and has a worldwide distribution. However, and presumably because of increased use of antiparasiticide treatments in horses, studies have shown a significant reduction in prevalence rates in recent years. For example, prevalence rates in the eastern, southeastern, and midwestern United States reduced from around 50% to 24% between 1985 and 2000 (Cummings & James, 1985; Lyons et al., 2000).

Ocular onchocerciasis occurs when microfilariae migrate to the conjunctival and periocular tissues of infected horses. Ocular involvement has been reported in 18%–49% of horses with onchocerciasis (Lloyd & Soulsby, 1978; Moran & James, 1987). The most commonly reported ocular and periocular lesions associated with the parasite are conjunctivitis, blepharitis, punctate scleral opacities, temporal scleral vitiligo, and uveitis (Cello, 1971; Moran & James, 1987; Schmidt et al., 1982b).

Ocular onchocerciasis occurs in many other species, including cattle, camelids, deer, swine, dogs, and humans. Canine ocular onchocerciasis is most commonly reported in southern Europe but has also been identified in the United States (Komnenou et al., 2002; McLean et al., 2017; Otranto et al., 2015; Sréter & Széll, 2008; Zarfoss et al., 2005). Acute canine ocular onchocerciasis is associated with conjunctivitis, chemosis, erythema, and periorbital swelling. In chronic cases, the parasites form granulomatous nodules within the retrobulbar space, eyelid, nictitans, conjunctiva, and sclera.

Thelazia *sp.*

Thelazia sp. (phylum Nematoda, order Spirurida, family Thelaziidae) are common commensal parasites of the conjunctival fornix and nasolacrimal duct of horses and cattle. *Thelazia lacrimalis* affects horses, whereas in cattle, *T. lacrimalis*, *T. gulosa*, *T. rhodesi*, and *T. skrjabini* are reported. Flies, in particular the face fly *Musca autumnalis*, act as mechanical vectors and transfer larvae to the eyes during feeding. Prevalence rates above 40% have been reported in both horses and cattle at necropsy (Arbuckle & Khalil, 1978; Lyons et al., 2000). In dogs *Thelazia callipaeda* is a common ocular parasite in Asia and is reported increasingly in other parts of the world, including Europe (Graham-Brown et al., 2017; Miró et al., 2011; Ruytoor et al., 2010).

Thelazia spp. are usually asymptomatic, but the parasites may induce conjunctivitis, dacryocystitis, and ulcerative keratitis (Miró et al., 2011).

Habronema *sp.*

Habronema microstoma, *H. muscae*, and *Draschia megastoma* (phylum Nematoda, order Spirurida, family Habronematidae) are parasites that inhabit the equine stomach. Larvae are passed in the feces and are ingested by maggots of the intermediate host *Stomoxys calcitrans*, the stable fly. Here, the larvae develop to the infective L3 microfilaria stage before being deposited around the mouth of the horse where the stable flies congregate. Microfilariae migrate or are mechanically transferred into the mouth before being swallowed to complete the life cycle. The parasite has a worldwide distribution, with postmortem studies in various countries identifying it in 4% to more than 40% of horses (Borgsteede & van Beek, 1998; Bucknell et al., 1995; Lyons et al., 1983).

Ocular habronemiasis results from aberrant microfilarial migration. Lesions typically appear as raised yellow gritty plaques in the palpebral and bulbar conjunctivae, or as eyelid granulomas or blepharitis (Rebhun et al., 1981).

Setaria *sp.*

Setaria sp. (phylum Nematoda, order Strongylida, family Filaroideae) parasitize the abdominal cavity of ungulates including horses, cattle, and sheep. *Setaria digitata* and *S. equina* are reported in horses, and *S. digitata* and *S. marshalli* are reported in cattle. The parasites are common across Asia and parts of Africa, with a prevalence of up to 70% in some areas (Shin et al., 2002). Aberrant migration of microfilariae can lead to ocular involvement, with immature adult worms developing in the anterior chamber (Marzok & Desouky, 2009; Muhammad & Saqib, 2007; Shin et al., 2002).

Halicephalobus deletrix

Halicephalobus deletrix (phylum Nematoda, order Rhabditida) is a free-living nematode found in soil and decaying organic matter. Rarely, infection of humans and horses has been reported, involving a wide range of organs and tissues including

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the kidneys, oral and nasal cavities, lymph nodes, spinal cord, and CNS tissue. The route of infection is presumed to be via contamination of open wounds. Migration to the eye has been reported to lead to severe granulomatous chorioretinitis in association with fatal encephalitis (Rames et al., 1995).

Toxacara canis

Toxacara canis (phylum Nematoda, order Ascaridiidia, family Toxocaridae) is a common intestinal parasite of the dog with a worldwide distribution. The adult worm lives in the small intestine, where it produces eggs that are excreted in the feces. Larval development to the infective L2 stage occurs within the egg in the environment. When swallowed, L2 larvae are released into the small intestine and penetrate the intestinal wall to enter the portal blood stream to the liver and lungs. In the lungs, development to the L3 stage takes place before the larvae are coughed up and swallowed. Two further molts to adulthood occur in the intestine. This life cycle occurs predominantly in young dogs, whereas in adult dogs, L2 larvae migrate to skeletal muscle, liver, brain, and other tissues where they remain dormant. In pregnant bitches, they mobilize and migrate to the fetal lungs a few weeks prior to parturition. Infection of newborn puppies may also occur via ingestion of infected milk.

Aberrant L2 migration in dogs and in nonhost species, including humans, may lead to ocular larval migrans. In dogs, the parasite has been shown to cause focal granulomatous lesions within the fundus and has also been suggested to cause more extensive retinal degeneration (Hughes et al., 1987; Johnson et al., 1989; Rubin & Saunders, 1965).

Ancylostoma caninum

Larvae of the canine hookworm *Ancylostoma caninum* (phylum Nematoda, order Strongylida, family Ancylostomatidae) infect the host via penetration of the skin, hematogenous migration to the lungs, and passage into the gastrointestinal tract. Aberrant migration of the larva has been reported to cause granulomatous endophthalmitis in a dog (Gaunt et al., 1982).

Parasitic Dipteric Larvae

Ophthalmomyiasis describes aberrant migration of fly (order *Diptera*) larvae within the ocular or periocular structures. Ophthalmomyiasis caused by *Cuterebra* sp. (the rabbit or rodent botfly) has been reported in humans, dogs, and cats (Baird et al., 1989; Brooks et al., 1984; Crumley et al., 2011; Delgado, 2012; Gwin et al., 1984; Harris et al., 2000; Johnson et al., 1988; Ollivier et al., 2006; Stiles & Rankin, 2006; Wyman et al., 2005).

The normal life cycle of *Cuterebra* involves the laying of eggs on vegetation near the nesting areas of rabbits and rodents. The eggs hatch into larvae that invade the skin of the host species. After completion of three developmental stages (instars) within cutaneous and subcutaneous tissues, the larvae exit the host and complete their development in the soil (Baird et al., 1989).

Ophthalmomyiasis involves the periocular structures (ophthalmomyiasis externa), the anterior segment (ophthalmomyiasis interna anterior), or the posterior segment (ophthalmomyiasis interna posterior). Migrating larvae cause acute inflammatory disease, especially when involving the periocular structures or anterior segment (Delgado, 2012; Harris et al., 2000; Stiles & Rankin, 2006). Cases involving the posterior segment incite less inflammation and are more commonly identified as an incidental finding on ophthalmoscopic examination. The most commonly reported lesions are curvilinear tracts within the tapetal and non-tapetal fundus (Brooks et al., 1984; Gwin et al., 1984).

Tapeworm Disease

Echinococcus granulosus granulosus (phylum Platyhelminthes, order Cyclophyllidea, family Taeniidae) is a tapeworm of wild and domestic dogs, for which equids are the intermediate host. The larval stage of the tapeworm forms hydatid cysts in tissues of the intermediate host. Hydatid cysts have been reported to affect the equine orbit, leading to exophthalmos or blindness (Barnett et al., 1988; Summerhays & Mantell, 1995).

Taenia solium (phylum Platyhelminthes, order Cyclophyllidea, family Taeniidae) is a tapeworm of humans, for which the pig is the natural intermediate host. The larval stage, *Cysticercus cellulosae*, can invade the orbit or globe to cause orbital or intraocular cysts, the latter giving rise to a severe granulomatous panuveitis in pigs (Cárdenas-Ramírez et al., 1984).

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8.1

Clinical Pharmacology and Therapeutics

Part 1: Ocular Drug Delivery

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In ocular therapy, drug choice is based on knowledge of pharmacodynamic potency and pharmacokinetic properties of therapeutic agents to select the most suitable route of administration and dosage regimen. These parameters should be aimed at ensuring the presence of an effective drug concentration in the target biophase for an appropriate period of time while limiting diffusion of the drug to other ocular structures or parts of the body. In veterinary ophthalmology, the dosage regimen and route of administration may also have to be adapted in order to maximize owner compliance.

The dosage forms currently used for the treatment of eye disease in veterinary patients include ophthalmic solutions, suspensions, ointments, and gels, but depending on the clinical context, drugs may also be delivered to the eye via the periocular or systemic route. Unique functional and structural protective mechanisms of the eye act as major obstacles to the access of xenobiotics to the targeted ocular tissues. Therefore, conventional ocular drug delivery systems have several drawbacks, including short duration of action, low ocular bioavailability, and the need for repeated administrations. Research into ocular drug delivery has become an increasingly important field that has led to novel strategies to overcome many of today's therapeutic dilemmas in human ophthalmology, but has also served to improve the medical treatments of ocular disorders in animals (Kompella et al., 2010; Patel et al., 2013; Weiner & Gilger, 2010; Weng et al., 2017; Yellepeddi & Palakurthi, 2016).

Barriers to Ocular Drug Delivery

Compared with drug delivery to other organs of the body, ocular drug delivery is a major challenge because of the presence of permeability barriers depending upon the route of administration. The ocular barriers refer to anatomical and physiological ocular structures that have protective functions for maintaining ocular homeostasis and represent natural defense mechanisms against the entry of xenobiotics into the eye.

Corneal Membrane Barriers

For topically applied drugs, the corneal route has been assumed to be the major route of entry into the eye. The cornea consists of three primary layers: the epithelium, stroma, and endothelium, representing distinct barriers to absorption organized as an aqueous phase (stroma) sandwiched by two lipid layers (epithelium and endothelium). Kinetic studies using *in vitro* and *in vivo* techniques have shown that passage of drugs through the corneal epithelium can occur both across the cells (transcellular route) and between the cells (paracellular route) (Grass & Robinson, 1988a, 1998b). However, the paracellular route is blocked by one type of specialized intercellular junction, the tight junction or *zonula occludens*, characterized by multiple sites of fusion between the plasma membrane of adjoining cells which completely surround and seal the most apical epithelial cells of the cornea to all but the smallest hydrophilic molecules (Sasaki et al.,1999). It is thus anticipated that the transcellular drug penetration will be related to oil/water (o/w) partition coefficient of molecules because of the lipophilic nature of the epithelium, whereas paracellular movement will more likely be related to characteristics such as molecular size and aqueous diffusivity (Grass et al., 1988; Maurice & Mishima 1984). As a consequence, the transcellular route across the lipid cell membrane will contribute to the epithelial transfer of lipophilic drugs, whereas very low molecular-weight hydrophilic (polar) compounds will diffuse through the intercellular space, which represents the aqueous pore pathways of the corneal epithelium (Grass et al.,1988; Sasaki et al., 1997). The intercellular space has a size ranging from 0.6 nm to less than 3 nm at its most confined point, and because of the negatively charged carboxylic groups of the tight junction components, it has a repulsive interaction with the negatively charged molecules

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(Grass & Robinson, 1988a; Nettey et al., 2016). Thus, drug penetration through the cornea shows a lipophilicity, molecular weight, and charge dependency on the permeability of the corneal epithelium to transferred compounds (Prausnitz & Noonan, 1998).

If the epithelial layer is a rate-limiting barrier for highly polar drugs, at the opposite, the stroma with its 78% water content allows the free passage of compounds possessing high aqueous solubility and acts as a barrier to lipophilic molecules (Hegeman et al., 1984). Theoretically, the cube root of the molecular weight is the most important factor of stromal penetration, but because ophthalmic drugs have a relatively narrow molecular weight range, their stromal penetration is nearly the same (Schoenwald, 1997). Although the endothelium is cellular, its permeability displays a strong dependence on both o/w partition coefficient and molecular size. This indicates that the endothelium does not provide significant resistance to lipophilic and hydrophilic ophthalmic drugs (Prausnitz & Noonan, 1998). The significant permeability of the endothelium likely relates to the fact that it is only one cell thick and that these cells are connected by junctional gaps that do not provide any barrier for drug penetration (Bartlett & Cullen,1984; Hegeman et al., 1984).

Conjunctiva and Sclera Membrane Barriers

There is evidence that penetration across the bulbar conjunctiva, and then sclera, contributes significantly to the intraocular penetration of certain topically applied drugs (Schoenwald, 1997). The conjunctiva is more permeable than the cornea through a significant paracellular route, which makes its permeability to molecules of varying physicochemical characteristics, such as β-blockers, hydrophilic macromolecules, and [^{3}H]mannitol, 2–30 times higher than that of the cornea (Ashton et al., 1991; Hämäläinen et al., 1997; Sasaki et al., 1997; Wang et al., 1991). In addition, there is not a large difference between the permeability coefficients of ionized (polar) and unionized (nonpolar) forms, which can also be explained by the richness of paracellular routes of the conjunctival membrane (Sasaki et al. 1996). Several reports have concluded that the scleral permeability is approximately 10 times higher than that of the cornea with a direct relationship between the ability of a drug to penetrate the sclera and both the thickness and total surface area of this tunic, and that the molecular radius is a better predictor of scleral permeability than the molecular weight (Ambati et al., 2000a, 2000b; Hämäläinen et al., 1997; Prausnitz & Noonan, 1998). However, with molecules of similar radii, the scleral permeability is higher for the more hydrophilic molecules than for the lipophilic ones and greater for negatively charged molecules than for positive ones (Cheruvu & Kompella, 2006). In consideration of the sclera and the underlying layer, it appears that the choroid-Bruch's layer is a greater barrier than the sclera for the intraocular transport of lipophilic molecules delivered by the periocular route (Cheruvu & Kompella, 2006). The primary route for solute transport through the sclera is by passive diffusion through the interfibrillar aqueous media of the gel-like proteoglycans (Geroski & Edelhauser, 2001). Transscleral diffusion is unaffected by the intraocular pressure at pressures ranging from 0 to 60 mmHg, and allows the transfer of compounds with a molecular weight as high as 150 kDa (Ahmed & Patton, 1995; Cruysberg et al., 2005). Other *in vitro* findings indicate that if a topically applied drug is preferentially absorbed by the scleral route, its transfer will be more rapid through the sclera than it would be through the cornea (Achim & Woodward, 2004). Scleral permeability can be enhanced with exposure to prostaglandins (PGs) or PG analogues, such as latanoprost, suggesting that PG cotreatment might allow sufficient transscleral transport to provide delivery of macromolecules, such as trophic factors, to the retina (Aihara et al., 2001; Kim et al, 2001).

Blood–Ocular Barriers

Following systemic administration, penetration of drugs into the eye is limited by several barriers localized either in epithelia or vascular endothelia. More precisely, the concept of blood–ocular barriers refers to the permeability restriction associated with morphological characteristics of the endothelial cells of iridial and retinal vessels and epithelial cells of the ciliary body and retinal pigment epithelium (RPE) (Nettey et al., 2016). In these barriers, the paracellular route is blocked because the clefts between the endothelial or epithelial cells are sealed by impermeable tight junctions responsible for inhibiting the entry of solutes into the ocular environment (i.e., aqueous humor and vitreous body) (Raviola, 1977). The blood–aqueous barrier (BAB) is located in the anterior segment of the eye and is formed by iridal blood vessels' endothelial cells, as well as the nonpigmented cell layer of the ciliary epithelium (Fig. 8.1.1). In the iris, the blood vessels' endothelial cells represent one anatomic location of the BAB because they lack fenestrae and are joined by tight junctions, therefore preventing movement of macromolecules from the lumen of the iridial vessels into the iris stroma and then into the anterior chamber (Raviola, 1977). In the stroma of the ciliary processes, circulating macromolecules escape through the capillary walls, but their transfer to the posterior chamber is blocked by the tight junctions that interconnect the apices of the nonpigmented cells of the overlying epithelium (Raviola, 1977). They are impermeable to exogenous markers such as peroxidase and represent the other anatomic component of the BAB (Smith & Rudt, 1973). In the posterior segment, the blood–retinal barrier (BRB) provides restricted

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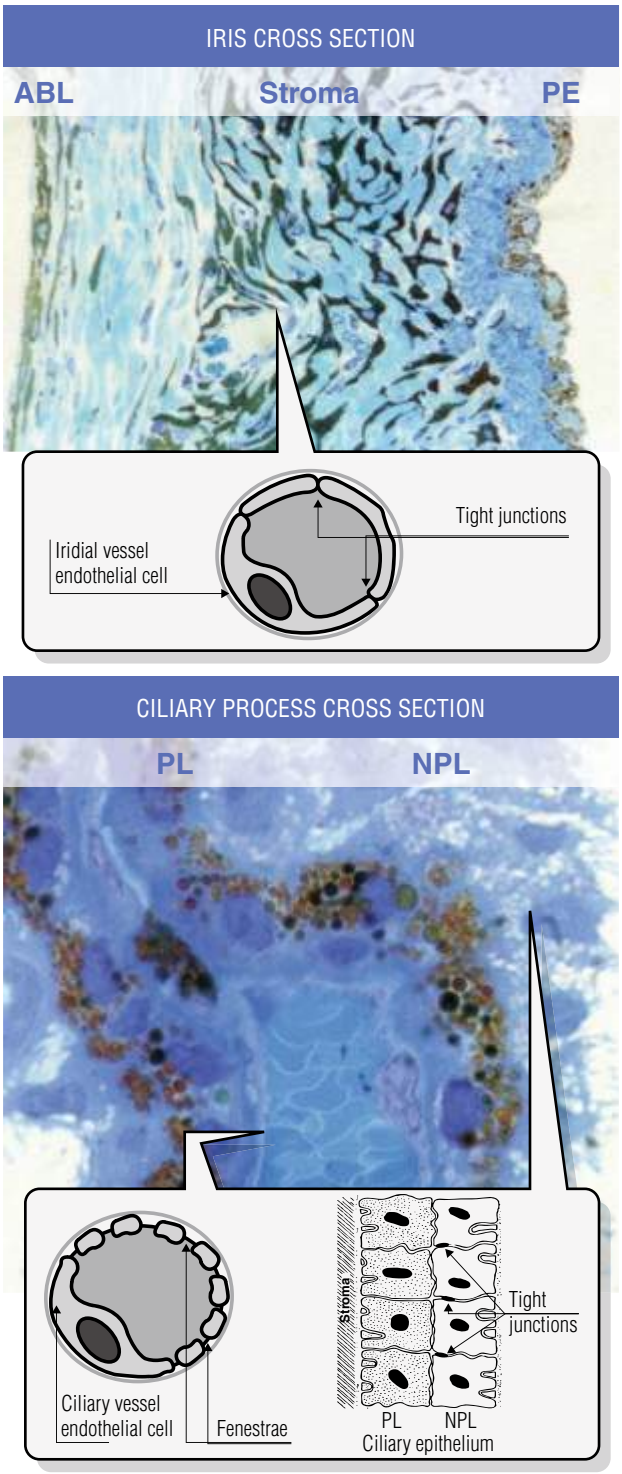


Figure 8.1.1 Schematic illustration of the blood–aqueous barrier (BAB). In the anterior segment, the endothelial cells of the iris blood vessels and the nonpigmented cell layer of the ciliary epithelium possess tight junctional complexes and form the BAB. ABL, anterior border layer; NPL, non-pigmented layer of the ciliary epithelium; PE, posterior epithelium; PL, pigmented layer of the ciliary epithelium.

penetration into the retina and includes the endothelial cells of the retinal vessels and the cells of the RPE, forming the outer and inner BRB, respectively (Fig. 8.1.2). The retinal vessels are nonfenestrated and have tight junctions, creating an obstruction to movement of substances from plasma into the retina and vitreous (Nettey et al., 2016). Experimentally, it was shown that the tight junctions which connect the endothelial cells of the retinal vessels are not only impermeable to circulating macromolecules, but also block the reverse diffusion of markers injected into the vitreous body (Raviola, 1977). The outer BRB is produced by the tight junctions between the RPE cells, so that substances leaking out from the extremely permeable capillaries of the choriocapillaris encounter this barrier of junctional complexes between RPE cells (Nettey et al., 2016). The morphologic characteristics of the blood–ocular barriers are basically similar in all species investigated to date, and there are no differences between the immature and mature animal (Bellhorn, 1991). Even though it may seem logical to deliver a drug to the intraocular structures via systemic administration because of the presence of the highly vascular uveal tunic, it is still a challenge because of the blood–ocular barriers, which restricts drug permeation from the blood to the inner eye. The blood–ocular barriers have anatomic and functional properties similar to those of the blood–brain barrier (Raviola, 1977; Toda at al., 2011).

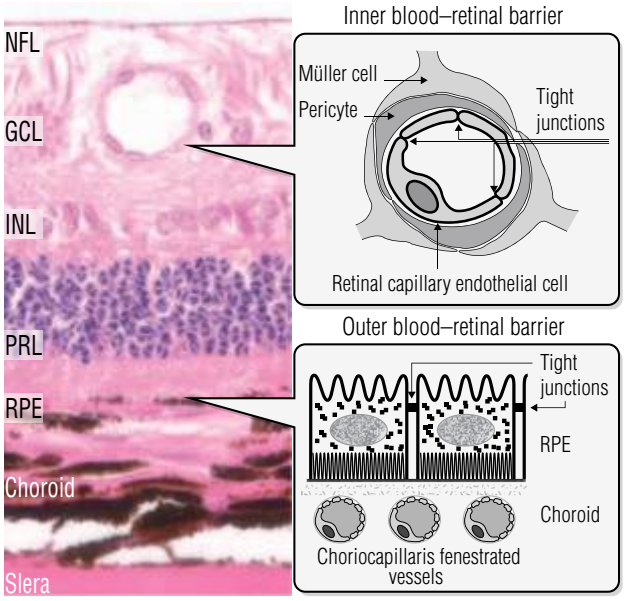


Figure 8.1.2 Schematic illustration of the blood–retinal barrier (BRB). In the posterior segment the BRB operates at two levels, the endothelium of the retinal capillaries and the retinal pigment epithelium. These cell layers display tight junctions responsible for restricting the movements of circulating molecules into the retina. NFL, nerve fiber layer; GCL; ganglion cell layer; INL, inner nuclear layer; PRL, photoreceptor layer; RPE, retinal pigment epithelium. (*Source:* Adapted from Tomi & Hosoya, 2008.)

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Drug Efflux Transporters

Other than cellular tight-junctional complexes in epithelia and endothelia, the eye possesses homeostatic mechanisms regulating the entry and exit of endogenous substrates. They can contribute to the barrier properties of ocular membranes by restricting absorption of ophthalmic xenobiotics (Gunda et al., 2008). Efflux transporters (also named efflux pumps) are membrane-bound proteins found in various ocular tissues and are reported to have a major impact on drug tissue penetration and distribution. These transporters lower drug bioavailability by actively expelling the molecules out of the cell membrane and cytoplasm, and therefore constitute significant barriers to the entry of drug molecules (Gaudana et al., 2010). Two multidrug efflux transporters responsible for the development of chemoresistance have been identified in ocular tissues, including the P-glycoprotein (P-gp), and multidrug resistance protein (Gaudana et al., 2010). P-gp is involved in the active efflux of lipophilic compounds and has been reported in various cell lines and tissues of the conjunctiva, cornea and RPE, whereas multidrug resistance proteins, implicated in the effluxing of conjugated compounds and organic anions, have been identified in human RPE cell line, human corneal epithelium, and rabbit cornea (Gaudana et al., 2009). In studies comparing permeability of various drugs across BAB and BRB in rats, it was found that low-lipophilic molecules showed the highest permeability across BAB, whereas high-lipophilic compounds more readily crossed BRB than BAB. In these experiments, it was also shown that P-gp contributed more to efflux transport of drugs at BAB than at BRB (Toda et al., 2011). Modulation of drug efflux transporters activity has been studied to improve the pharmacological properties of various drugs. Studies in rabbits showed that ocular bioavailability of erythromycin is enhanced in the presence of P-gp inhibitors such as cyclosporin, quinidine, and verapamil (Gunda et al., 2008). A prodrug strategy developed to escape efflux pumps efficiently is being explored, and in coming years may play an important role in the design of ophthalmic drugs with better ocular penetration (Gunda et al., 2008). Genetic polymorphism of efflux transporters has been recognized as a cause of interspecies differences in ocular pharmacology. In the cat, for example, genetic anomalies in the ABCG2 transporter, present in the luminal membrane of endothelial cells of the inner blood–retinal membrane, favor the accumulation of fluoroquinolones in the retina, which may lead to iatrogenic retinal degeneration (Ramirez et al., 2011).

Topical Route of Administration

Topical delivery is the most common mode of administration for ophthalmic drugs because of its advantages, including simplicity of application and convenience to reach both extra- and intraocular tissue targets. The pharmacokinetic profile of topically applied ophthalmic drugs is influenced by precorneal factors (i.e., lacrimation, drainage) and the specific characteristics of the formulation itself that will determine the amount of drug penetrating the eye.

Conventional Eye Drops

Ophthalmic solutions and suspensions represent the dosage form most widely used in ophthalmology. Ophthalmic solutions are formulations in which the drug is totally dissolved in a given solvent. Typically, they are low-viscosity aqueous solutions that are mixable with the aqueous tear film. Thus, the drug must be, at least to some degree, water soluble. Some exceptions exist, like compounded preparations of cyclosporine in corn or olive oil (Frangie, 1995). To minimize irritation of the eye, ophthalmic solutions should ideally have an osmolality (tonicity) of about 300 mOsm/kg, a value corresponding to the average tonicity of normal human tears (Craig et al., 1995), and in the range of the tear osmolality values measured in cats, dogs, and horses (Davis & Townsend, 2011; Best et al., 2015; Sebbag et al., 2017). Although it is said that eye drops should be isotonic with tears, various studies have shown that the eye can tolerate solutions with an osmolality in the range of 200–600 mOsm/kg, or 0.2%–2.0% in NaCl equivalents (Bar-Ilan & Neumann, 1997; Malmberg & Lupo, 2004). Sodium chloride, boric acid, and dextrose are used to adjust tonicity of eye drop formulations. Ophthalmic solutions must fall within a pH between 4.5 and 9, but are usually pH adjusted in the range of 7.0–7.7, corresponding to human tear pH (Fischer & Wiederholt, 1982), to be comfortable for patients and not induce tearing and blinking reflexes (Malmberg & Lupo, 2004). The adjusted pH of most ophthalmic solutions and suspensions is also within the range of physiological tear pH values for small and large animals (Beckwith-Cohen et al., 2014). To improve stability and sterility, ophthalmic solutions are formulated with appropriate vehicles that may contain buffers, organic or inorganic carriers, emulsifiers, and wetting agents. The advantages of solutions include relative ease in dispensing and use. In addition, most agents are well tolerated, cause little discomfort, and do not affect vision (Bartlett & Cullen, 1984). When frequent applications of ophthalmic solutions are required in horses, a subpalpebral lavage system is necessary to provide frequent instillations with minimum handling (Martin, 2005).

Pharmaceutical derivatives of low aqueous solubility, such as acetates and alcohols used as topical corticoids, require formulations as ophthalmic suspensions (Frangie, 1995). Brinzolamide, used to reduce intraocular pressure, and rivoglitazone, a new treatment for dry eye disease in human patients, are also formulated as ophthalmic suspensions. Ophthalmic suspensions are sterile products containing solid particles of active ingredient dispersed in a liquid

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vehicle, which includes dispersing and suspending agents, intended for application to the eye. Ophthalmic suspensions generally contain particles relatively insoluble in the aqueous vehicle, but the vehicle can also be considered as a saturated solution of the drug. The drug particles contained in suspension must be less than 10 µm, uniform in size, and micronized for optimum local tolerance and therapeutic efficacy (Bar-Ilan & Neumann, 1997; Wilson, 1999). The suspensions should be formulated at a tonicity and pH that are safe for the ocular surface, but because they are heterogenous systems, their stability is dependent on the physicochemical features of the suspended solids, and they present problems with regard to methods of sterilization and drug concentration. Unstable dispersed systems can lead to changes in particle size, leading to agglomeration of dispersed particles affecting their uniform dispersion in the vehicle (Ali & Lehmussaari, 2006). Drug concentration can be manipulated by increasing the number of particles, or by the reformulation of ophthalmic suspensions as solutions, either by formulating water-soluble derivatives of the parent drugs (i.e., sodium phosphate salts for glucocorticoids) or complexing poorly water-soluble compounds with drug carriers, such as cyclodextrins, to increase their water solubility (Davies et al., 1997). From a practical point of view, potential disadvantages of ophthalmic suspensions include the possibility of irritation caused by suspended crystals or particles, and the need to be adequately shaken before use to disperse drug particles evenly throughout the vehicle and avoid incorrect dosing (Ali & Lehmussaari, 2006; Frangie, 1995; Kwon et al., 1996).

All multidose eye preparations must include a bacteriostatic preservative (i.e., benzalkonium chloride, benzethonium chloride, methylparaben, propylparaben, mercurial compounds, thimerosal) to prevent or inhibit microbial growth during clinical use (Malmberg & Lupo, 2004). At appropriate concentrations, these preservatives must be safe, be compatible with the other ingredients of the preparation, and remain effective throughout the period of use of the eye drops. In a human clinical setting, it has been observed that preserved eye drops in multidose containers do not become heavily contaminated for up to 1 month after opening, enabling these eye drops to be used for 4 weeks without increasing the risk of ocular infection (Høvding & Sjursen, 1982). In the same way, it has been reported that multidose eye drops vials of proparacaine hydrochloride, tropicamide, and eye wash bottles did not experience significant aerobic bacterial contamination over a 2-week period of administration in a veterinary hospital (Betbeze et al., 2007). Although they are useful to prevent bacterial contamination of multiuse ophthalmic solutions and suspensions, preservatives can, however, exert deleterious toxic effects to the ocular surface, as reported in animals and humans. Using canine corneal epithelial cells in tissue culture, it has been shown that both benzalkonium chloride (at concentrations ranging from 0.025% to 0.01%) and thimerosal (at concentrations ranging from 0.0125% to 0.1%) induce severe morphologic changes at all concentrations evaluated (Hendrix et al., 2002). Experimentally administered to rabbits at concentrations ranging from 0.004% to 0.02%, which are those used in most commercially available eye drops, benzalkonium chloride induced significant inflammatory infiltration of the limbus, conjunctiva, and trabecular meshwork (Burstein, 1980; Liang et al., 2008). Of primary concern with their frequent or prolonged use, is their potential toxicity to the ocular surface epithelium, disruption of tear film stability, and hypersensitivity reactions (Baudoin et al., 2010). As preservatives are present in most antiglaucoma agents, the surface changes resulting from long-term topical antiglaucoma treatment in human patients directly influence the outcome of filtering surgery by increasing the risk of postoperative fibrosis. In patients who experience ocular signs compatible with poor tolerance or allergy to preserved eye drops, changing to preservative-free eye drops rapidly leads to significant decrease in local side effects (Baudoin et al., 2010). Unpreserved eye drops are available in multidose bottles or unit dose containers. Those supplied in multidose bottles should be stored at 2°–8°C after opening to reduce the rate of replication of any microbial contaminants, and they should not be kept in use for more than 7 days (Oldham & Andrews, 1996). An innovation for the prevention of bacterial contamination of the multidose eyedropper has been the development of the Novelia® bottle (Nemara, La Verpillière, France), which has a tip with a one-way valve and a silicone membrane to avoid any potential retrograde contamination of the bottle (Strauss et al., 2019). Recent data show that it may decrease microbial contamination of plasma eye drops used in canine patients (Strauss et al., 2019).

Drug Disposition After Eye Drop Application

As indicated in Fig. 8.1.3, an ophthalmic drug topically applied to the eye is distributed in three ways. It is drained by

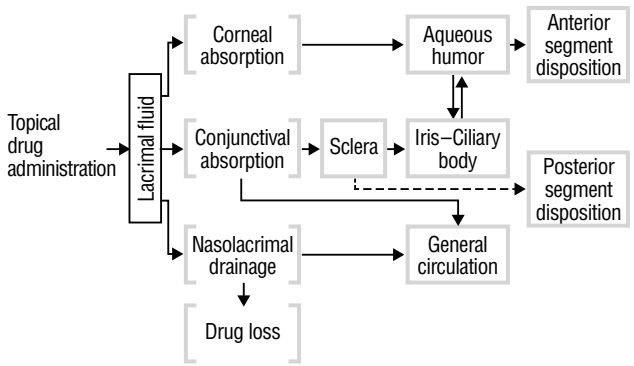


Figure 8.1.3 Disposition of ophthalmic drugs after topical application to the eye. Only a small portion of a topically applied drug may reach the posterior segment (dashed lines).

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the nasolacrimal apparatus, may penetrate into the eye through the corneal and/or noncorneal routes, and is absorbed into the systemic circulation via the conjunctiva and nasopharynx.

Nasolacrimal Drainage and Tear Washout

When eye drops are administered onto the ocular surface, they first mix with the tear film, the volume of which is about 7–10 µL (with 1 µL covering the cornea and about 3–4 µL residing in each conjunctival sac), as estimated in humans and rabbits (Maurice, 1995; Shell, 1982). These values are lower than those recently reported for dogs and cats, with a median basal tear volume of 65 µL (range: 42–87 µL) and 32 µL (range: 29–39 µL), respectively (Sebbag et al., 2019a). The drop volume delivered by many ophthalmic dropper bottles is about 40 µL on average (Lederer & Harold, 1986), but actually it varies within a range of 25–70 µL depending on the design of the dropper tip, the physicochemical properties of the medication to be dispensed, and the manipulation of the dropper bottle (Van Santvliet & Ludwig, 2004). With an average drop volume of 35 µL, it has been estimated that the drug concentration at the ocular surface is immediately diluted by threefold in dogs and twofold in cats upon mixing with the tear film (Sebbag et al., 2019a). Since the palpebral fissure is capable of holding only 25–30 µL of fluid, the volume of most ophthalmic drops largely exceeds the volume of the cul-de-sac, so complete retention of this drop volume is unlikely to occur (Mishima et al., 1966). As a consequence, the sudden increase of volume created by instillation of an eye drop will be diminished rapidly by escape of a large proportion of the instilled fluid (approximately 80%–90%) into the nasolacrimal system and spillage over the lower eyelid (Agrahari et al., 2016; Hegeman et al., 1984). Scintigraphic studies of ophthalmic solution elimination has shown that, as a result of rapid drainage, most of the instilled solution is lost within the first 15–30 seconds in humans (Shell, 1982; Wilson, 1999). The extra solution volume that enters the nasolacrimal apparatus will then flow to the nasopharynx, where part of the drained fraction may be absorbed and contribute to some systemic side effects (see paragraph on systemic absorption) or may induce salivation caused by a bitter taste (e.g. atropine). Following removal of a substantial proportion of the drug subsequently to administration of such an excess volume, a second mechanism of clearance, represented by continual turnover of the tear film, will prevail until restoration of the normal tear volume occurs (Davies, 2000). In normal, nonirritated human eyes, the secretion and drainage of tears occur at a rate of approximately 1 µL/min corresponding to a 15% turnover of the tear film per minute (Davies, 2000). This washout results in almost complete disappearance of the applied fluid remaining on the ocular surface via lacrimal drainage within approximately 10 minutes (Davies, 2000). This conclusion also applies to dogs and cats, which tear turn-over rate is similar at about 11%–12% per minute (Sebbag et al., 2019a). The tear volume and tear flow rate in horses have been reported to be 230 µL, and 33 µL/min, respectively (Chen & Ward, 2010). Assuming an instillation volume of 0.2 mL via a subpalpebral lavage system (Martin, 2005), it has been estimated that the drug concentration in the tear film is diluted by more than half immediately upon instillation, suggesting that increased dosing regimens or continuous infusion techniques for topical administration of ophthalmic drugs would be indicated when treating severe equine corneal disease (Chen & Ward, 2010).

Factors Influencing the Nasolacrimal Drainage

The rate at which a topically applied ophthalmic solution is eliminated from the ocular surface because of nasolacrimal drainage is influenced by four main factors: the size of the drop delivered to the eye, the blinking frequency, the viscosity of the ophthalmic solution, and the tear flow dynamics. Within the cul-de-sac, the drainage rate of an instilled volume has been shown to be proportional to the volume of the drop that is above the normal lacrimal fluid volume. The larger the volume instilled, the more rapidly it is drained through the nasolacrimal system (Bartlett & Cullen, 1984). Pharmacokinetic models indicate that tear drainage within the first minute after topical application is 13 µL/min and 30 µL/min for a 25-µL and a 50-µL eye drop, respectively (Chrai et al., 1973). As a result, 90% of a topically instilled dose in a rabbit eye is cleared within 2 minutes for an instilled volume of 50 µL, 4 minutes for an instilled volume of 25 µL, and 7.5 minutes for an instilled volume of 5 µL (Chrai et al., 1974). Thus, a strategy for minimizing the rate of drug loss through drainage would be to reduce the volume instilled to 5–15 µL (Patton, 1977). Instillations of 10-µL drops of phenylephrine 10%, or 15-µL drops of clonidine 0.25% and 0.5% in human eyes, have the same ocular pharmacological effects as 30-µL to 70-µL drops of the same concentrations (Petursson et al., 1984; Whitson et al., 1993). Similarly, instillation of one drop immediately after another will reduce the availability of the first drug instilled because it will suffer a loss caused by nasolacrimal drainage that is proportional to the time interval between instillations (Schoenwald, 1997). A recent fluorophotometric study on the tear turn-over rate in dogs showed that ocular instillation of two drops (70 µL) introduces too large a volume of fluid that induces an excess lost by spillage over the eyelid margin and accelerated nasolacrimal drainage (Sebbag et al., 2019b). As an instilled drop is removed in about 10 minutes, dosage guidelines therefore recommend to apply only one drop upon the ocular surface, and that successive instillation of drops of different medications should be spaced by at least a 10-minute period (Shell, 1982). This recommendation has been extrapolated from data in humans and rabbits, but the recent findings on the canine and feline tear turn-over rates demonstrate that it also applies in dogs and cats (Sebbag et al., 2019a, 2019b).

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Blinking and tear flow dynamics may also alter the drug residence time in the precorneal compartment if the instilled medication is an irritant by virtue of its pH and/or tonicity. As previously discussed, the pH of an ophthalmic preparation should be kept as close to the physiological pH as possible to avoid local irritation or foreign body sensation with enhanced lacrimation and blinking that will promote drug clearance through the lacrimal system (Shell, 1982). In dogs and cats, it has been found that reflex tearing results in a fivefold increase in tear turn-over rate (50% per minute) compared with the basal value (11%–12% per minute), suggesting that a topically applied ophthalmic solution would be rapidly cleared from the ocular surface if it induces lacrimation for any reason (e.g., caused ocular irritation) (Sebbag et al., 2019).

Penetration Across the Cornea

After topical ocular application, drugs may be absorbed into the inner eye through the corneal or conjunctival–scleral route. The rate and extent of absorption through one route or the other is dependent both on transport characteristics of the cornea, conjunctiva, and sclera and on the physicochemical properties of the drug itself. Generally, the cornea has been regarded as the main route of absorption for clinically used ocular drugs because most of them have been developed with adequate properties for corneal absorption (Lee & Robinson, 1986).

As shown previously, the cornea is a complex barrier to drug entry into the eye because it has layers with different partitioning properties. Transfer through the epithelium is the rate-limiting step for absorption of hydrophilic compounds, whereas transfer through the stroma is rate-limiting for lipophilic compounds. Thus, in order for an ophthalmic drug to penetrate the cornea, it must exhibit intermediate solubility characteristics, being soluble to some degree in both oil and water to penetrate the epithelium and stroma (Bartlett & Cullen, 1984). It is postulated that a good predictor of corneal penetration rate of drugs is the o/w partition coefficient and that maximal corneal penetration is obtained with drugs whose o/w partition coefficient range from 10:1 to 1000:1 (Grass & Robinson, 1984). For moderately lipophilic drugs such as timolol and dexamethasone, the corneal epithelium contributes 50% to the total resistance to transport whereas the stroma and endothelium each contribute 25% (Lee & Robinson, 1986). After topical application, a very lipophilic drug (i.e., cyclosporine) may be sequestrated in the corneal epithelium from which it is then gradually released (Agrahari et al., 2016). For hydrophilic drugs such as epinephrine, pilocarpine, gentamicin, tobramycin, prednisolone sodium phosphate, dexamethasone sodium phosphate, cromolyn, and idoxuridine, the corneal epithelium contributes more to the total resistance to transport, and these molecules will penetrate the epithelium slowly or not at all because of the paracellular pathway predominance (Lee & Robinson, 1986; Schoenwald, 1997). In humans, ocular bioavailability is predicted to be 5%–7% at maximum for lipophilic drugs (o/w partition coefficient >1) and to be less than 0.5% for hydrophilic ones (o/w partition coefficient <0.01) (Gunda et al., 2008).

Most ophthalmic drugs, being weak acids or bases, are present in solutions as both the unionized and ionized forms of the molecule. The ionized form can be a cation or an anion and is in equilibrium with the unionized form, also called the free-base form of the drug. Penetration of ionizable drugs through the cornea follows the pH partition theory because they are hydrophilic in the ionized form and lipophilic when unionized (Bartlett & Cullen, 1984; Hegeman et al., 1984). When such a drug is applied on to the eye, its unionized form predominantly penetrates the epithelium (Fig. 8.1.4). Since negatively charged molecules experience inhibition in transfer through the pores of the corneal epithelium, as stated above, the paracellular pathway allows for only a small degree of permeation by the ionized form (Nettey et al., 2016). Once the free base reaches the stroma, its abundance drives the reaction to convert the unionized form to the ionized form, which is the favored stromal diffusion. Upon reaching the endothelium, another equilibrium is found, and penetration is achieved by both the ionized and unionized forms, because the endothelium is relatively permeable to drugs (Bartlett & Cullen, 1984; Friedrich et al., 1993).

Factors Influencing Corneal Absorption

In the case of ionizable drugs, the pH of the ophthalmic preparation and of the tear fluid affect ocular drug penetration by influencing the ratio of the ionized and unionized forms of the molecule in equilibrium. The degree of ionization of a drug in solution, and hence its capacity to diffuse

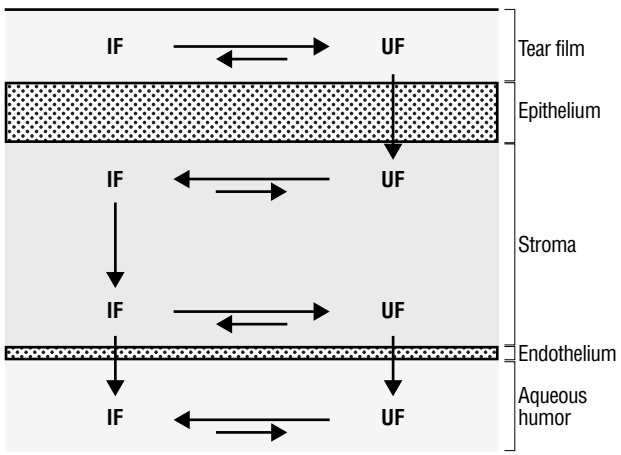


Figure 8.1.4 Equilibrium reactions and transcorneal diffusion of ionizable drugs after topical application to the eye. IF, ionized form; UF, unionized form.

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across cellular barriers, is determined by its dissociation constant (pKa) and the solvent's pH. The dissociation constant is governed by the following relationship: pH = pKa + log[base]/[salt]. Thus, small changes in the pH can significantly affect the degree of drug dissociation in the formulation (Shell, 1982). If we consider the activity of tropicamide and atropine on the isolated iris sphincter, tropicamide has 1/70th the affinity of atropine for muscarinic receptors. Both drugs topically applied as a 1% solution, however, are equally effective as mydriatics because a larger proportion of tropicamide (pKa = 5.4) compared with atropine (pKa = 9.7) will exist as unionized at tear pH and will be rapidly transferred through the cornea to intraocular target tissues (Patil, 1984). By using buffer solutions, the pH can be adjusted to increase the proportion of the unionized fraction, the more lipophilic species of the drug molecule, thereby facilitating penetration across the lipid barrier of the corneal epithelium. For example, penetration of pilocarpine, a weak base, increases more than 10-fold when its pH is changed from 7 to 9.5. However, the pH of pilocarpine formulations must be kept within 4.5 to 5.5 to ensure long-term drug stability (Patil, 1984).

Protein binding of topical drugs is known to occur in the precorneal tear film, rendering the bound fraction no longer available for absorption. As local inflammation increases tear protein content, drug loss by this route may gain significance during topical treatment (Hegeman et al., 1984; Agrahari et al., 2016). A 75- to 100-fold reduction in pupillary response to pilocarpine was found in rabbits by addition of 3% albumin to tear fluid, and conversely, an increase in the ocular bioavailability was observed when this drug was coadministered with agents such as cetylpyridinium that compete with the pilocarpine binding site to lacrimal proteins (Shell, 1982).

Although penetration through the cornea is controlled by the gradient of drug concentration, the possible increase of drug concentration in the formulation is limited because instillation of a hyperosmotic solution will induce lacrimation, and will remove fluids osmotically from the surrounding ocular tissues, resulting in complete dilution to isotonicity (Shell, 1982). Hydrophilic drugs that penetrate poorly through the intact epithelium may reach high levels in the cornea when the epithelium is damaged or inflamed. In the case of a corneal ulcer, a drug is further retained by the craterlike effect of irregular tissue margins. For example, penetration into the cornea and anterior chamber of a topically applied hydrophilic antifungal agent is increased up to ninefold when 25%–50% of the surface area of the corneal epithelium is removed (Johnson et al., 1995). The possible clinical implication of these findings is that corneal epithelial debridement may be performed in some situations (i.e., keratomycosis or corneal abscess beneath an intact epithelium) to allow better penetration of therapeutic drugs into the deep corneal stroma and anterior chamber (Johnson et al., 1995). Conversely, the effect of epithelial damage should be low or negligible for lipophilic drugs, which normally penetrate the epithelium very readily (Maurice & Mishima, 1984). As discussed in a later section, the permeability of corneal epithelium may also be altered by chemical action of compounds such as surfactant or chelating agents, referred to as penetration enhancers.

Penetration Via the Conjunctiva/Scleral Route

In the last decades, studies have shown that the conjunctival/scleral absorption of ocularly applied drugs contributes to the ocular absorption known as noncorneal absorption. The noncorneal absorption route through bulbar conjunctiva and sclera is important mostly for very hydrophilic and large molecules that are not able to penetrate through the corneal barrier, because the conjunctival epithelium is leakier and has a surface area 20 times greater than that of the cornea (Ahmed & Patton, 1985; Hämäläinen et al., 1997; Prausnitz & Noonan, 1998).

The conjunctiva is more permeable than the cornea through a significant paracellular route which makes its permeability to molecules of varying physicochemical characteristics, such as beta-blockers, hydrophilic macromolecules, and [^{3}H]mannitol, 2–30 times higher than that of the cornea (Ashton et al., 1991; Hämäläinen et al, 1997; Maurice & Polga, 1977; Sasaki et al., 1997; Wang et al., 1991). The richness of paracellular routes in the conjunctival membrane also explains that there is not a large difference between the permeability coefficients of ionized and unionized forms (Sasaki et al., 1996).

Once the drug penetrates the bulbar conjunctiva, there are two different possibilities for it to reach the intraocular target tissues. Drug entry directly into the anterior chamber can result from lateral diffusion into the sclera and then the cornea (Schoenwald et al., 1997). Since the sclera also contains arterial vessels leading to the uvea, another possibility for drug penetration through the conjunctival/scleral pathway is that once the drug is absorbed into the scleral tissue, a significant portion enters scleral vessels that supply the uvea, particularly the anterior ciliary arteries, and deposits within the ciliary body (Schoenwald et al., 1997). Although the proportion of drug entering the eye by the two routes of the conjunctival/scleral pathway is unknown, vessel uptake and deposition at the iris-ciliary body was found to be significant for drugs such as the topical carbonic anhydrase inhibitors (Schoenwald et al., 1997). Although less plausible than vessel uptake or lateral diffusion into corneal stroma, drug entry into the eye could occur by first penetrating the conjunctiva, proceeding through the sclera, ciliary muscle, ciliary processes, and finally by diffusing into the anterior chamber (Schoenwald et al., 1997). If the ciliary body is the target tissue of the topically applied drug, it seems reasonable to assume that the conjunctiva/scleral pathway is more likely to achieve higher drug concentrations than lateral diffusion through the cornea and entry into the anterior chamber (Schoenwald et al., 1997).

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No ophthalmic drug delivery systems have been designed specifically to promote noncorneal drug penetration, but it is possible that this end result can be obtained from the inserts because they are placed in the fornices. When timolol is applied to rabbit eyes as an ophthalmic insert, the drug concentration in the conjunctiva and the amount of drug penetrating the iris-ciliary body and aqueous humor are significantly higher than those measured after eye drop instillation. It was suggested that after placement of the insert in the fornix, the iris and ciliary body would absorb the drug that has penetrated through the conjunctiva and sclera (Friedrich et al., 1996). Transfer through the conjunctival/scleral pathway may also be favored when the drug is instilled with a mucoadhesive polymer vehicle, which has a prolonged contact time with the underlying bulbar conjunctiva (Lehr et al., 1994).

Systemic Absorption

After eye drop administration, systemic absorption may occur through the conjunctival and nasolacrimal mucosa, as well as the nasopharynx after passage through the lacrimal drainage system (Fig. 8.1.5). The portion of the topically applied drug that is absorbed systemically can cause drug loss, lowering ocular bioavailability, and give rise to systemic adverse effects (Bartlett & Cullen, 1984; Shell, 1982). However, for larger molecules such as peptide drugs, topical application to the eye can represent an efficacious method of systemic delivery.

The conjunctiva is the first site where topically applied drugs may reach the systemic circulation. Drug absorption results from uptake by the fenestrated blood vessels located in the conjunctiva and episclera and is increased by the leaky nature of the conjunctival epithelium and its large surface area (Ahmed & Patton, 1985). As many ophthalmic drugs are small organic molecules with a molecular weight less than 500 kDa, they can easily be absorbed through the conjunctiva, thus representing a main site of systemic drug absorption (Urtti & Salminen, 1993). In the case of topical ophthalmic beta-blockers, it was shown that their corneal application results in very low plasma levels compared with those observed after conjunctival and scleral applications (Bartlett & Cullen, 1984; Hegeman et al., 1984; Sasaki et al., 1996).

The epithelium of the nasolacrimal duct has been reported to be able to absorb lipophilic substances in rabbits, and its vascularized walls may represent potential sites for systemic diffusion (Paulsen et al., 2002). The mucosa of the nasolacrimal passage is also suspected to represent a significant site for the systemic absorption of topical ocular drugs in other species, although specific data are lacking (Urtti & Salminen, 1993; Paulsen et al., 2002). Following passage through the nasolacrimal system, part of the instilled drug comes in contact with the nasal and pharyngeal mucosa, which may contribute to systemic absorption because their permeability is in the same range as that of the conjunctiva (Urtti & Salminen, 1993). The significance of circulatory system access by topical agents is that drugs absorbed through the conjunctiva and nasolacrimal mucosa are not subject to the first-pass metabolism in the liver. The administration of eye drops has therefore been compared with a slow intravenous injection, which can account for the systemic toxicity of some topically applied ophthalmic drugs (Urtti & Salminen, 1993). Knowledge of these potential systemic adverse effects in human patients enabled clinical recommendations to be provided on the use of some topical drugs, particularly in infants and older patients (Lama, 2005). Awareness of this risk is also important in small animals, because systemic absorption and potential side effects have been reported with topical phenylephrine, glucocorticoids, atropine, and timolol in dogs (Glaze et al., 1988; Greenberg et al., 2015; Herring et al., 2004; Pascoe et al., 1994; Plummer et al., 2006; Smith et al., 2010), as well as topical diclofenac in cats

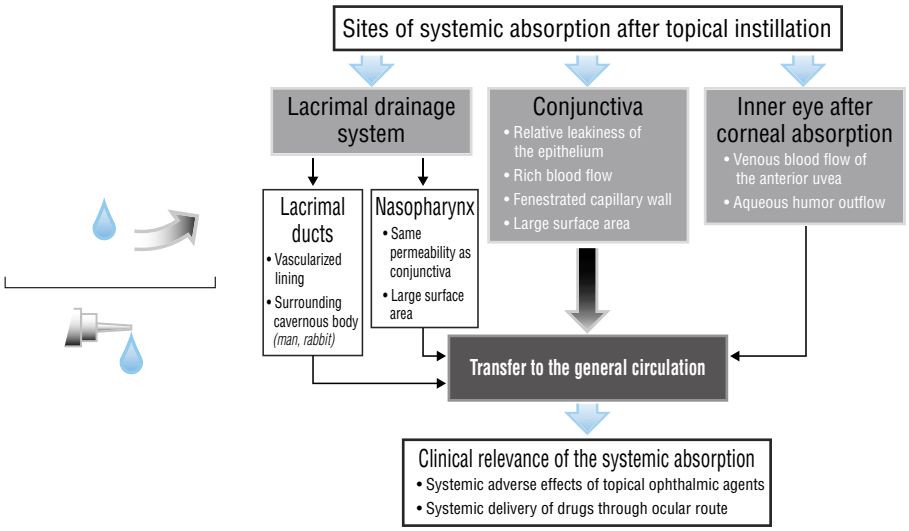


Figure 8.1.5 Topically applied medications can enter the systemic circulation through conjunctival absorption, drainage via the nasolacrimal system, and absorption through the nasopharyngeal mucosa. After transcorneal penetration, minor routes of systemic drug transfer involve aqueous humor outflow and diffusion into the iris.

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(Hsu et al., 2015). Although contribution of vascular absorption of topical ocular drugs to systemic adverse effects would probably be lower in horses, because the apparent volume of drug distribution is much greater than in small animals, this risk is not absent because systemic diffusion has been observed with topical dexamethasone and atropine in this species (Spiess et al., 1999; Williams et al., 2000). In human patients, nasolacrimal occlusion and eyelid closure just after eye drop instillation have been recommended to reduce the severity of adverse systemic effects by minimizing the amount of drug delivered to the lacrimal and nasopharyngeal mucosa. This results in enhanced intraocular drug penetration and decreased systemic diffusion, as shown with topical timolol whose systemic bioavailability is reduced more than 60% and ocular absorption is increased by 70% in patients practicing these maneuvers (Ellis et al., 1992). The effect of nasolacrimal occlusion on systemic absorption is probably best for drugs that are mostly absorbed from the nasopharyngeal mucosa, because it has no effect on systemic absorption via conjunctiva (Urtti & Salminen, 1993). After topical drug application in one eye, significant contralateral effects may sometimes be observed, and they are generally attributed to the systemic uptake of the drug and crossover effect (Maurice, 2002). Changes in intraocular pressure in the contralateral eye have been noted with unilateral topical application of various antiglaucoma agents and were particularly documented for beta-blockers (Piltz et al, 2000). In cats and dogs, timolol applied topically to one eye was found to lower intraocular pressure in both treated and untreated eyes (Wilkie & Latimer, 1991a, 1991b).

Since part of the instilled drugs is absorbed systemically, drug delivery into systemic circulation via the ocular route has been studied as an alternative to repeated injections, which are poorly accepted by patients (Chiou, 1994). The conjunctiva and nasal mucosa are permeable to small peptides such as thyrotropin-releasing hormone (molecular weight 360) and luteinizing hormone-releasing hormone (molecular weight 1200), which are readily absorbed by the ocular route (Chiou, 1994). Larger polypeptides, such as insulin (molecular weight 6000), need to be combined with permeation enhancers or emulsants, like saponin, nonionic surfactants, and certain alkylglycosides to penetrate ocular membranes after topical application (Chiou & Li, 1993). Systemic delivery of insulin through the ocular route has been shown in healthy cats and dogs (Morgan, 1995; Morgan & Huntzicker, 1996), but to the author's knowledge, this mode of administration is not used currently in diabetic small animals. Conversely, systemic delivery of antidiuretic hormone through the ocular route is exploited in the treatment of canine diabetes insipidus. Another application of systemic delivery through the ocular route in dogs is apomorphine-induced emesis from an ocular insert containing the drug (Cote et al., 2008).

Pharmacokinetics of Conventional Eye Drops

Tear Drug Kinetic Profile

From a pharmacokinetic standpoint, the time course of drug concentration in the tear film after topical instillation follows a first-order kinetic (Fig. 8.1.6), characterized by an initial high drug concentration observed just after instillation, followed by a rapid and exponential decline as the therapeutic agent is lost through the nasolacrimal system, absorption across the cornea and conjunctiva, and tear washout (Hegeman et al., 1984). As a consequence, most topical liquid

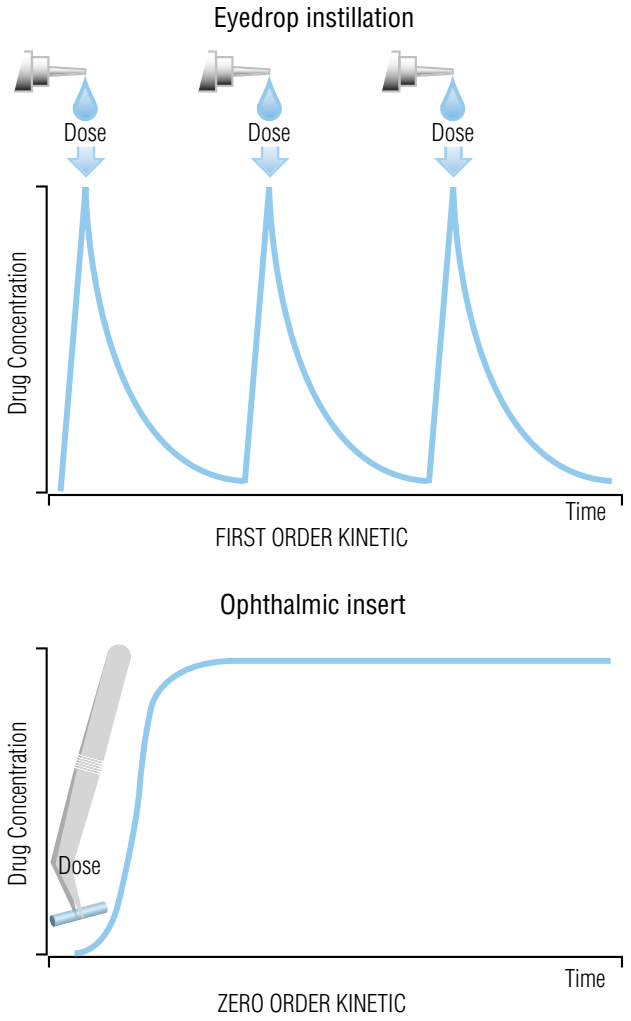


Figure 8.1.6 Differences in kinetic profiles of ophthalmic drugs applied as eye drops or as a sustained-release delivery device. Following application of eye drops, a maximum of drug concentration is achieved locally, and then drug levels exponentially decline (first-order kinetic) to subtherapeutic tissue concentration until the next instillation. With some sustained-release delivery (i.e. nonbiodegradable ophthalmic inserts and implants), a plateau level of drug distribution is achieved (zero-order kinetic) allowing constant drug release over time.

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formulations have a short half-life of about 4 minutes on the surface of the eye (Gaudana et al., 2010; Paugh et al., 2008). Ciprofloxacin residence in the tear film after topical application has been described in dogs and horses (Hendrix et al., 2007; Hendrix & Cox, 2008), and topical tobramycin was found to have a half-life of 11.7 minutes in tear fluid of horses after single application (Czerwinski et al., 2012). An important consideration in topical ocular treatment with conventional eye drops is thus the frequency of administration because it directly influences drug concentrations in the target ocular tissues. With ophthalmic suspensions, the drug administration is also pulsed, but suspensions are said to be advantageous compared with solutions because particles tend to accumulate in the cul-de-sac, prolonging contact time with the ocular surface, and their dissolution will allow the drug concentration to persist in the tear fluid longer than after instillation of a solution (Frangie, 1995). Dissolution occurs gradually to a concentration governed by the drug's solubility in tear film as well as the size and quantity of particles. As previously mentioned, the particles of an ophthalmic suspension should be small enough to be well tolerated by the ocular surface, but from a pharmacokinetic point of view, they should not be too small because their dissolution rate into the tear film would be more elevated because of the increased surface area of exposed drug at the tear–drug interface. Thus, the advantage of suspensions over solutions would be diminished (Sasaki et al., 1996b; Shell, 1982). Actually, suspension formulations show enhanced ocular bioavailability over solutions if the dissolution rate of the particles is greater than their rate of clearance from the precorneal area (Sieg & Robinson, 1975).

Due to the rapid drug clearance from the ocular surface, it is generally considered that for ophthalmic drugs, less than 1% to no more than 10% of the dose topically applied enters the eye, depending on the lipophilicity or hydrophilicity of the molecule as discussed in a previous section (Gunda, et al., 2008). Some examples, documented by experimental studies in rabbits, indicate that as little as 2% of pilocarpine, 1.6% of clonidine, and 7%–10% of flurbiprofen is absorbed after topical application (Schoenwald, 1997). By comparison, bioavailability of systemic drugs is usually more than 75%.

Intraocular Drug Distribution

Following intraocular penetration of topically applied drugs, their subsequent distribution and retention at the target site is critical to their therapeutic success. Those drugs that diffuse through the cornea enter the aqueous humor first, where the peak concentration occurs from 0.5 to 3 hours after instillation and was estimated in human patients to be about a 150,000 dilution of the drop for a hydrophilic drug, and a 1,500 dilution for a lipophilic one (Kessler et al., 1991; Maurice et al., 1996). From the aqueous humor, the drugs are distributed to the anterior segment ocular tissues, but their effective transfer to the posterior segment of the eye is hindered by various physical and metabolic barriers. Hence, it is difficult to achieve therapeutic drug concentration in the posterior segment of the eye with topical drug application (Patel et al., 2013).

The iris tissue possesses a large surface area that is highly vascular, and highly porous because its anterior face is not covered by a cell layer. As such, it is able to equilibrate rapidly with drugs dissolved in the aqueous humor. The iris is a target site for miotics and mydriatics, and because of the anatomic location of the sphincter and dilator muscles and porosity of iris stroma, drug diffusion into these muscles most likely occurs from the anterior surface (Sherman et al., 1978; Schoenwald, 1997). Once inside the iris, the lipophilic drugs can penetrate across the endothelial walls of the iridial vessels to be eliminated by the venous blood flow of the anterior uvea (Urtti, 2006). For topically applied drugs that penetrate the eye via the noncorneal route of entry, higher peak concentrations may be observed in the iris and ciliary body than in the aqueous humor, and may be reached before they occur in the aqueous humor because scleral penetration permits the drug to reach the target tissue first without entering the aqueous humor (Schoenwald et al., 1997; Shell, 1982).

If drug levels reached in the iris and ciliary body are similar or higher to those achieved in the aqueous humor, levels in the lens are usually lower because the primary barrier to drug entry into the lens is the anterior epithelial cell layer. Consequently, hydrophilic drugs are expected to poorly penetrate this layer (Schoenwald, 1997; Shell, 1982). Drugs that are lipophilic can partition into the lens from the aqueous humor and then diffuse around the cortex (Maurice, 2002). In the rabbit, measurable quantities of timolol and imirestat, an aldose reductase inhibitor, have been found in the lens after the instillation of a single drop (Ahmed et al., 1989; Brazzel et al., 1990). Once drugs enter the lens, the most significant rate-determining step to accumulation is diffusion through the densely packed fibers and the nucleus. Distribution within the lens from the aqueous humor is crucial for anticataract therapies (i.e., aldose reductase inhibitors) whose target tissue is the lens cortex, and for iatrogenic cataract formation. This can occur with both topically or systemically administered drugs, and chronic use of amiodarone, chlorpromazine, corticosteroids, gold salts and psoralen is considered potentially responsible for the formation of cataracts in humans (Prokopich et al., 2008).

It is generally stated that when a drug is topically applied onto the eye, only very little of the administered dose reaches the posterior segment of the eye (Maurice, 2002). This is illustrated by data on the ocular distribution of topical dexamethasone in cats and dogs, demonstrating therapeutically relevant drug concentrations only in the anterior ocular structures (Kaiser et al., 2008; Bessonova et al., 2011).

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However, studies in rabbits suggest that access to the posterior segment of the eye is possible through the sclera for hydrophilic drugs or may take place across the conjunctiva and retrobulbar space (Maurice, 2002; Sasaki et al., 1996b). Observed and calculated pharmacokinetic data from a rabbit model suggest that the transscleral route is a major pathway for drug penetration to the posterior segment of the eye after ofloxacin instillation (Shikamura et al., 2011). This experiment also showed that to a lesser extent, the drug can be absorbed into the systemic circulation and then gain access to the retinal vessels (Shikamura et al., 2011). These transfers may explain the distribution of brimonidine, betaxolol, dorzolamide, nepafenac, and alpha-luminol into the posterior ocular tissues, reported after topical administration (Da Sylva et al., 2011; Gaudana et al., 2010). For those drugs that enter the vitreous at its anterior zone, presumably through the noncorneal route of penetration, they can progress further to the fundus by diffusion through the vitreous when it is formed or by convection when it is liquefied (Maurice, 2002). Modeling of drug movement in the human vitreous allowed to estimate that if a mass, D, is released near the hyaloid membrane, it will reach a concentration at the optic nerve head of 0.06 D/mL for a drug to which the retina is impermeable or 10 times less for a drug with a high retinal elimination (Maurice, 2002).

Drug Elimination from the Anterior Chamber

Aqueous outflow is presumed to be the primary route of drug elimination from the eye, although loss of drug may occur by additional pathways (i.e., retinal blood flow) or processes such as metabolism and drug binding to distinctive tissues (Shell, 1982). It has been established that once drugs are absorbed into the anterior chamber, they are eliminated mostly by aqueous humor turnover, which was estimated to be 1.5–5 μL/min in humans (Coakes & Brubaker, 1979) and about 5 μL/min in dogs (Ward et al., 2001). Although drug elimination from the anterior chamber has not been extensively determined for topically or systemically administered drugs, it is considered that a clearance rate value close to that of the aqueous humor flow rate suggests that drug elimination can be explained by aqueous humor turnover (Schoenwald, 1997). In healthy dogs, aqueous marbofloxacin clearance rate was evaluated to be 6 μL/min, suggesting that its elimination from the anterior chamber mostly occurred via aqueous outflow (Regnier et al., 2003). For drugs with a clearance rate higher than the aqueous humor turnover, a strong tissue binding is likely to occur, whereas for those with a clearance rate lower than the aqueous turnover, metabolism and uptake by iris blood vessels are likely pathways for elimination (Schoenwald, 1997).

Drug Melanin Binding

The affinity of drugs to melanin present in different ocular tissues, such as the iris and ciliary body for the anterior segment, can influence the pharmacological effect of instilled ophthalmic drugs, because melanin binding decreases the free drug concentration available for target tissues leading initially to smaller pharmacological effects (Agrahari et al., 2016; Sasaki et al., 1996b). As a result, the pigmented tissues form a drug reservoir from which the drug is slowly released during the elimination phase, resulting in a prolonged duration of action. This explains the fact that the higher the amount of melanin in the eye, the smaller the initial effect on pupil size of topical atropine and pilocarpine, but the longer their duration of action is (Salazar et al., 1976; Urtti et al. 1984). Affinity to melanin of the iris and ciliary body was reported for various antibiotics and for timolol (Eiferman & Stagner, 1982; Fukuda & Sasaki, 1994; Tabbara, et al., 1983; Salazar-Bookaman et al., 1994). The reduced hypotensive ocular effect of timolol observed in people with darker irides was attributed to melanin binding (Katz & Berger, 1979).

It is also known that the resistance to solute transport across the sclera–choroid–RPE is not only correlated to the tissue thickness, but also depends on the melanin content of the choroid–RPE, which may represent the principal barrier to transscleral transport, as shown for topical beta-blocker antiglaucoma agents (Gaudana et al., 2010; Kadam et al., 2011). By affecting the bioavailability of topically applied drugs, ocular pigmentation may also decrease their local toxic effects (Salazar-Bookaman et al., 1994). The protection of the retina of pigmented rabbits from gentamicin-induced toxicity most likely reflects binding of the drug by melanin, which thereby reduces the concentration of the free gentamicin (Zemel et al., 1995).

Drug Ocular Metabolism

Although many oxidoreductase, hydrolytic, and conjugating enzymes that exist in systemic tissues are expressed in various ocular tissues, little is known about the extent of local metabolism. Ocular drug metabolism was a neglected area of research until the discovery that topically applied drugs may be metabolized during or after corneal transport, and that metabolism can be exploited to design new ophthalmic drugs to improve corneal permeability using the prodrug concept (Sasaki et al., 1996b). Enzymes of the cytochrome P450 monooxygenase system, in addition to crucial roles in either biosynthesis or degradation of endogenous substrates, contribute to xenobiotic metabolism (Attar & Shen, 2008). Other oxidoreductase systems (i.e., aldehyde oxidase, ketone reductase) expressed in conjunctiva, cornea, and iris and ciliary body epithelia have been involved in the metabolism of topical brimonidine and levobunolol, two antiglaucoma agents (Attar & Shen, 2008). Esterases are hydrolytic enzymes, identified in various ocular tissues with the highest activity in the iris and ciliary body, followed by the cornea and the aqueous humor (Sasaki et al., 1996b). Depending on the nature of the drug, these enzymes contribute to either an

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inactivating or activating effect. The former metabolic process results in loss of activity of the drug, whereas the latter relates to the synthesis of active metabolite(s) or activation of prodrugs. After pilocarpine instillation in the rabbit, about 40% of the original compound in the cornea and 75% of that in the anterior chamber are breakdown products of pilocarpine, mainly pilocarpic acid (Maurice & Mishima, 1984). Topical idoxuridine is also subject to metabolic breakdown in the corneal epithelium, where it is converted to 2'-deoxyuridine and iodouracil, which can be recovered from the anterior chamber (Maurice & Mishima, 1984).

Improvement of Topical Ocular Drug Delivery

Different strategies have been developed to enhance ocular bioavailability of topically administered ophthalmic drugs from less than 10% to at least 15% to 20%, and can be separated into the physical and chemical approaches (Lee, 1990; Yellepeddi & Palakurthi, 2016). As discussed in a previous section, the extent of intraocular absorption of topically applied drugs is hindered by the lacrimal drainage with a rate estimated to be about 100 times more rapid than the absorption rate, and by the cornea that represents a rate-limiting barrier to hydrophilic compounds (Schoenwald, 1997). Therefore, some strategies to improve eye drop formulation included adding additives such as viscosity enhancers to prolong eye drop residence time at the ocular surface, and as penetration enhancers or cyclodextrins to improve drug transcorneal permeation (Patel et al., 2013). In parallel, use of semisolid (i.e., ophthalmic ointments, gels, and *in situ* gel-forming systems) and solid (i.e., contact lenses and ophthalmic inserts) forms to allow drugs to stay longer in the precorneal area, as well as formulation of topical drugs into prodrugs to facilitate transcorneal penetration, have also become classical approaches to improve the bioavailability of topically applied ocular drugs. More recently, emulsions and nanotechnology-based ophthalmic formulations provided innovative means to improve intraocular penetration of topically applied drugs (Kaur & Smitha, 2002; Patel et al., 2013; Yellepeddi & Palakurthi, 2016).

Enhancement of Drug Absorption Across the Cornea

Penetration Enhancers

Penetration enhancers are additives that increase drug penetration through the ocular epithelia by affecting the paracellular and/or transcellular pathways of transfer. Benzalkonium chloride, the surfactant-type preservative, enlarges intercellular spaces in the superficial layer of the corneal epithelium at concentrations as low as 0.001%. Therefore, it facilitates drug absorption via the paracellular route; however, because it forms defects in the lipid layer of the cell membranes, it also enhances drug penetration via the transcellular route (Sasaki et al., 1999). This mechanism of action is also the basis of its potential local toxic effects, as previously discussed (Baudoin et al., 2010). Chelating agents, such as EDTA, and sodium salts of medium-chain fatty acids, such as caprylate and caprate, similarly enlarge the space between the apical corneal epithelial cells and increase the corneal penetration of hydrophilic compounds (Morimoto et al., 1989; Sasaki et al., 1999). Due to their potential adverse effects on the epithelial cells, penetration enhancers should be selected with great caution. Cationic polymers such as aminated gelatin, chitosan, and poly-L-arginine have been reported to dissociate tight junctions between epithelial cells without producing significant cellular damage and might be useful penetration enhancers in the future (Nemoto et al., 2007).

Cyclodextrin Complexation

A chemical approach to enhance corneal permeation of topically applied drugs is the use of cyclodextrins, which are a family of cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. Cyclodextrin complexation can be useful for the formulation of a variety of hydrophobic molecules in aqueous solution (Patel et al., 2013). Used in eye drop formulations, cyclodextrins remain in aqueous solution whereas the hydrophobic drug is absorbed by the epithelium of the ocular surface. Corticosteroids, cyclosporine, and carbonic anhydrase inhibitors are good examples of such poorly water-soluble drugs. Conversely, cyclodextrins do not seem to afford a real improvement for hydrophilic drugs (Davies, 2000; Loftsson & Stefánsson, 1997). Cyclodextrin complexation also favors topical drug delivery to the retina and choroid, as shown with dexamethasone, suggesting that this approach might be very valuable in the long-term treatment of the posterior segment diseases in human patients (Kristinsson et al., 1996; Sigurdsson et al., 2007). Eye drop formulations of diclofenac (Voltaren® ophthalmic, Novartis, Basel, Switzerland), indomethacin (Indom®, Alfa Intes Industria Therapeutica, Casoria, Italy), and chloramphenicol (Clorocil®, Edol, Oeirces, Portugal) containing cyclodextrins are currently available in some countries (Agrahari et al., 2016; Kompella et al., 2010).

Ophthalmic Prodrugs

Prodrugs are defined as pharmacologically inactive derivatives of drug molecules that are chemically or enzymatically converted to the active parent drugs (Ding, 1998). They are designed to increase lipophilicity of hydrophilic molecules to overcome the resistance to their transport across the corneal epithelium and improve their ocular bioavailability. Ester prodrugs derived from carboxylic and hydroxyl functional groups were developed by chemical modification of

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hydrophilic parent drugs to improve their partition coefficient, and hence their penetration through the corneal epithelial barrier. Once in the corneal epithelium, the ester prodrug is enzymatically converted by esterases to permit access of the active moiety to the anterior chamber (Fig. 8.1.7) (Ding, 1998; Urtti, 2006). An ideal ocular ester prodrug should be stable and soluble in aqueous solutions to enable formulation, sufficiently lipophilic to pass the corneal barrier, well tolerated, and capable of releasing the active moiety within the eye at a rate corresponding to the therapeutic need (Sasaki et al., 1999). Steroids were perhaps the first class of ophthalmic drugs to which the ester prodrug concept was applied; the acetate prodrugs of dexamethasone and prednisolone were designed to improve corneal absorption and were found to increase the anti-inflammatory efficiency by a factor of 1.5 to 2.0 compared with their parent drugs (Sasaki et al., 1999). Dipivalyl epinephrine (or dipivefrin), developed as an epinephrine prodrug in the late 1970s, is formed by esterification of the hydroxyl groups of the epinephrine molecule. The major advantage of dipivefrin is that a 10-fold lower dose has a therapeutic effect comparable to that produced by epinephrine with a significant lowering of systemic side effects and reduction of dose (Sasaki et al., 1999). Topical latanoprost, travoprost, and bimatoprost are all prodrugs of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), with the former two being isopropyl ester prodrugs whereas the latter being an ethanolamine amide prodrug (Kompella et al., 2010). They have been synthetized to improve corneal penetration and decrease side effects associated with the autacoid activity of the PGs (Alm, 1998). Nepafenac, the amide prodrug of amfenac, a nonsteroidal agent, is another example of prodrug derivatization used to enhance drug lipophilicity in order to overcome the corneal permeability barrier (Weiner & Gilger, 2010). *In vitro* studies have shown a sixfold greater corneal penetration of nepafenac compared with diclofenac (Ke et al., 2000).

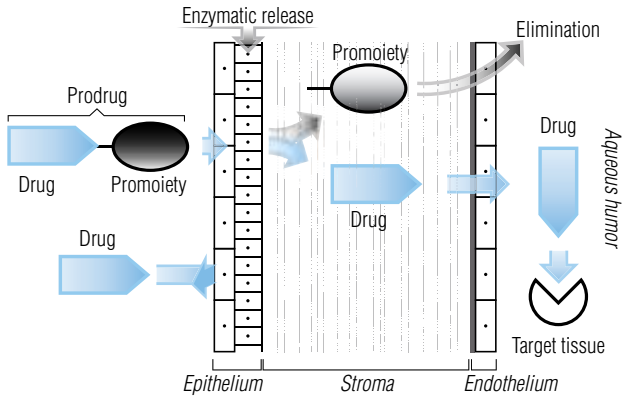


Figure 8.1.7 Following topical application onto the eye, ester-prodrugs penetrate the corneal epithelium where they undergo enzymatic transformation to release the active parent drug, which can then exert the desired pharmacological effect.

Currently, prodrugs targeted to specific transporter proteins are being investigated for enhanced ocular drug delivery (Attar & Shen, 2008). They are synthetized to have affinity for influx transporters, which are membrane-bound proteins expressed by various ocular tissues such as conjunctival and corneal epithelium. These transporters can bind and carry specific-targeted ligands attached to drug moieties, in order to facilitate the absorption of poorly permeating parent drugs across the biological membranes where the conjugate is cleaved by a biotransformation process to release the parent drug (Gunda et al., 2008). The most commonly applicable influx transporters for ocular drug delivery are amino acid and peptide transporters, and various prodrugs targeting these influx transporters have been evaluated (Gaudana et al., 2010). For example, amino acid and peptide prodrugs of acyclovir (i.e., valine-valine-acyclovir) and ganciclovir (i.e., valine-ganciclovir, tyrosine-valine-ganciclovir, glycine-valine-ganciclovir) were observed to be substrates of various amino acid and peptide transporters expressed on the corneal tissue and shown higher permeability when compared with the parent drug (Gunda et al., 2008).

Enhancement of Drug Residence Time at the Ocular Surface

Continuous Infusion of Topical Drugs

With a simple eye drop, it is not possible to maintain therapeutic drug concentration in equine eyes and the continuous infusion technique offers the advantage of maintaining constant drug concentrations in the tear film, hence allowing better drug bioavailability when treating acute anterior uveitis and infectious corneal ulcers. With a constant rate of 0.14 mL/h delivered through an infusion pump attached to a subpalpebral lavage system, it was shown that a stable drug concentration, a mean of 20% of the applied concentration, was maintained at the ocular surface of equine eyes throughout the 72 hours of the infusion (Myrna & Herring, 2006). A non-erodible micro-osmotic pump implanted subconjunctivally has been evaluated for this purpose (Blair et al., 1999), but to our knowledge, this drug delivery device is not currently marketed. Use of a battery-operated pump available at a pre-set delivery rate of 0.06 1 mL/h and with a 10 mL reservoir volume (Infu-Disk™, Med-e-Cell, San Diego, USA) is currently a convenient and reliable method of continuous ocular delivery to horses (Smith et al., 2014). Developed for single use, the pump is replaced as often as necessary during the treatment period. Elastomeric pump systems with a preset flow regulation device and a reservoir volume of 50 mL (EasyPump ST/LT™, B. Braun Melsungen AG, Germany) are alternatives to the continuous-delivery pump. The limiting factors for continuous infusion are drug stability over time and drug compatibility when several drugs are combined for a treatment. Drugs placed in the reservoir or the

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pump should not precipitate, as reported with 1% voriconazole solution (Smith et al., 2014).

Viscosity Enhancers

Attempts to increase ocular residence time of eye drop formulations via enhanced viscosity has become a popular strategy, and research has developed around the use of polymers able to lengthen precorneal residence time and improve ocular bioavailability of hydrophilic drugs (Bar-Ilan & Neumann, 1997). It has been determined that the improvement in ocular drug delivery reaches a maximum level at a viscosity of about 12–15 centipoises, and that higher viscosity formulations cause ocular irritation with an increase in reflex tears and blinks leading to rapid elimination of the instilled drug (Sasaki et al., 1996b). Hydrophilic polymers such as hydroxymethylcellulose, hydroxypropylmethylcellulose, polyvinyl alcohol, polyethylene glycols, and polyvinylpyrrolidone are currently used as viscosifying agents in some eye drop formulations (Yellepeddi & Palakurthi, 2016).

Ophthalmic Emulsions

For ophthalmic delivery, oil-in-water emulsions are preferred over water-in-oil emulsions and they are particularly useful in the delivery of water-insoluble drugs such as cyclosporine (Patel et al., 2013). The oily droplets of these emulsions consist of an outer aqueous phase, a lipophilic internal phase in which the hydrophobic drug is solubilized, and a surfactant phase with sometimes a cosurfactant to act on the homogeneity and stability of the dispersed system (Garrigue et al., 2017). Oil-in-water emulsions are used as topical ocular drug delivery carriers because they have a higher residence time, they enhance epithelial permeability of lipophilic drugs, they are not very viscous, and they are transparent because blurred vision caused by oils is minimized by the water in the external phase (Ding, 1998; Sasaki et al., 1999; Vandamme, 2002). A formulated cyclosporine 0.05% ophthalmic emulsion for treatment of dry eye (Restasis®, Allergan, Irvine, CA, USA), a difluprednate 0.05% ophthalmic emulsion to treat ocular inflammation (Durezol®, Alcon, Fort Worth, TX, USA), and an azithromycin 1% ophthalmic emulsion for treatment of bacterial conjunctivitis (Azasite®, Akorn, Lake Forest, IL, USA), showed clinical efficiency and safety, and are examples of these novel ocular dosage forms (Agrahiri et al. 2016; Patel et al., 2013; Tang-Liu & Acheampong, 2005).

Nondrug loaded emulsions for eye lubrification are commercially available in some countries (Refresh-Endura®, Allergan, Irvine, CA, USA; Soothe®XP, Bausch and Lomb, Rochester, NY, USA) to improve dry eye signs and increase lipid tear film stability (Garrigue et al., 2017). Cationic emulsions are biphasic formulations of positively charged oil nanodroplets, which interact with the negatively charged mucins and cell membranes of the ocular surface (Guarrigue et al., 2017). Cationic ophthalmic emulsions are available in some countries for symptomatic treatment of mild-to-moderate forms of dry eye in humans (Cationorm®, Santen Pharmaceutical Co., Osaka, Japan), and for the sustained delivery of topical cyclosporine (Vekacia®, Santen Pharmaceutical Co.; Cyclokat®, Santen Pharmaceutical Co.) (Barar et al., 2016; Garrigue et al., 2017).

Ophthalmic Nanosuspensions

Applications of nanotechnology currently represent a very exciting field of research for development of new systems to deliver drugs into both the anterior and posterior segments of the eye. Nanosuspension refers to incorporation of drugs into inert, biodegradable, and biocompatible polymeric systems, which are formulated as submicron colloidal dispersion in a liquid vehicle and with a viscosity similar to eye drops (Yellepeddi & Palakurti, 2016). A wide variety of components have been evaluated as potential nanosytems and are selected according to their drug-loading efficiency, capacity to provide longer duration of drug release, and ability to cross membrane barriers to improve ocular bioavailability compared with conventional eye drops. Their physicochemical features, as well as their pharmaceutical and pharmacological properties, have been discussed in detail in several recent reviews (Bhattacharjee & Bedi, 2013; Garrigue et al., 2017; Nagarwal et al., 2009; Patel et al., 2013; Sahoo et al., 2008; Weng et al., 2017; Yellepeddi & Palakurthi, 2016; Zafar et al., 2016). To date, various nanosuspensions are being evaluated in preclinical studies.

Nanoparticles are colloidal carriers with a range of 10–1000 nm, composed of natural (i.e., chitosan, albumin, alginate) or synthetic (i.e., polylactic acid [PLA], polylactide-co-glycolide [PLGA], polycaprolactone) polymers, including nanocapsules and nanospheres. In the former, the drug is encapsulated inside the polymeric shell whereas in the latter, the drug is distributed throughout the polymeric matrix (Patel et al., 2013). The potential use of nanoparticles as an ophthalmic drug delivery system has been extensively evaluated for various hydrophilic and hydrophobic drugs including pilocarpine, amikacin, betaxolol, carteolol, cyclosporine, and indomethacin, loaded into or on nanoparticles of different polymers. Results showed that these nanocarriers generally produced significantly higher corneal penetration and enhanced ocular bioavailability of topical drugs (Patel et al., 2013; Wang et al. 2013b). In addition, it was found that using the property of natural polymers, such as chitosan, polysaccharides, and hyaluronic acid, to penetrate into the conjunctival and corneal epithelium, made it possible to improve gene delivery to the anterior segment of the eye (Yellepeddi & Palakurthi, 2016). Dendrimers are another polymeric carrier currently under investigation for use as ocular drug delivery vehicles because their highly branched architecture allows incorporation of hydrophobic as well as hydrophilic drugs (Zafar et al., 2016).

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Lipid-based nanocarriers include liposomes and solid lipid nanoparticles. Liposomes are vesicles (0.01–10 μm) composed of one or more phospholipid bilayers separated by aqueous compartments containing aqueous core. They were first introduced as a drug delivery vehicle to enhance ocular bioavailability of topically applied drugs, but nondrug loaded liposome formulations were more recently proposed as lid sprays for the treatment of dry eye disease in human patients (Garrigue et al, 2017; Gaudana, 2009). Several liposomal sprays are currently marketed (i.e., Tears Again®, Optima Pharmazeutische, Hallbergmoos, Germany; Clarymist® or Eye Logic®, Optima Swiss Medical AG, Zug, Switzerland; Vyséo Sensitive®, Vyséo, Lyon, France) to be applied on the outside of the closed eyelids with the aim of renewing the tear film lipid layer (Garrigue et al., 2017). For drug-loaded liposomes, lipophilic drugs can be trapped in the lipid layer and hydrophilic medications in the aqueous compartment, allowing both types of medication to be delivered to the eye (Eljarrat-Binstock et al., 2010). Some data suggest that liposomes improve corneal absorption by binding to the corneal surface and direct transfer of the drug from liposomal to epithelial cell membrane (Sahoo et al., 2008). This explains that almost every class of topically applied ophthalmic drug has been studied in liposomal formulation. Experimental studies showed the potential of liposomes as ocular drug delivery systems for various antibiotics, antivirals, anti-inflammatory agents, and immunosuppressive drugs with promising penetration and pharmacokinetic results (Bennett, 2016a; Patel et al., 2013; Shafaa et al., 2011). However, at this time, only a few nondrug loaded liposomal formulations are available, because some problems such as difficulties in preparation, storage and stability, as well as the expense of their large-scale production, are yet to be overcome (Ebrahim et al., 2005).

Another class of lipid nanocarriers is the solid lipid nanoparticles (SLNs) composed of natural lipids like liposomes which can be loaded with hydrophobic and hydrophilic drug molecules. SLNs can be modified to control drug release rate, but because they are smaller than liposomes, they have a limited drug-loading efficiency (Wang et al., 2013b). Experimentally, topical application of tobramycin, cyclosporine, and timolol loaded into SLNs resulted in significantly improved transcorneal permeation (Attama et al., 2009; Cavalli et al., 2002; Gokce et al., 2009).

Ophthalmic Ointments

In the past, ointments were the only answer to achieving prolonged delivery for topically applied drugs. The thick, oleaginous bases of ophthalmic ointments are primarily mixtures of white petrolatum and liquid petrolatum (mineral oil) with or without a water-miscible agent such as lanolin (Bartlett & Cullen, 1984; Yellepeddi & Palakurthi, 2016). The mineral oil is added to the petrolatum to allow the vehicle to melt at eye temperature, whereas the lanolin is added to the nonemulsive ointment base in order to absorb water and allow for water-soluble drugs to be retained in the delivery systems (Bartlett & Cullen, 1984). Hydrophilic drugs are dispersed in the base as particles, like in suspensions, whereas lipid-soluble drugs are dissolved in the ointment base. Ophthalmic ointments must contain preservatives in order to prevent bacterial contamination during use, and effects of pH and tonicity should be controlled as previously discussed for ophthalmic solutions and suspensions (Bar-Ilan & Neumann, 1997).

After application to the eye, the ointment is retained in the cul-de-sac until the base melts and exposes drug particles, thereby delivering the drug to the tear fluid (Frangie, 1995). Although these preparations melt at the temperature of the ocular surface and disperse with tear fluid, studies in humans and rabbits have clearly shown that petrolatum-based ointment is retained longer at the ocular surface than certain viscosifying agents such as methylcellulose or polyvinyl alcohol used for some eye drop formulations (Hardberger et al., 1975). A first explanation is that the large molecules of the petrolatum–mineral oil base ointment are not easily removed by the lacrimal drainage system and a second factor of prolonged retention is the physicochemical relationship between the ointment base and the tear film. The fact that ointment bases and the tear film both have nonpolar oil components may allow oil bases to be readily absorbed by the preocular tear film (Hardberger et al., 1975). The overall result is that the precorneal disappearance rate of drugs administered in an ointment has been reported to be as low as 0.5% per minute (Sasaki et al., 1996b), and gamma scintigraphic studies confirmed that significant amounts of ointment are retained 4 hours after dosing (Greaves et al., 1993).

The fact that the ointment must first melt and dissolve at the ocular surface implies peak drug concentration (C_{max}) in the tear fluid to be lower and time at which peak concentration (T_{max}) is achieved in ocular tissues to be later than when a drop of solution or suspension is applied (Maurice & Mishima, 1984). Total bioavailability, however, is significantly greater than that from aqueous solution or suspensions because less drug is immediately lost to drainage (Patel et al., 2013). The prolonged residence time of ophthalmic ointments is particularly suitable when frequent instillations of solutions or suspensions are impractical. Ointment formulations are usually administered in dosage frequencies of twice daily, but depending on the response to therapy, they may be administered as often as every few hours. When both drops and ointments should be used, it is suggested from experimental data that the eye drop should be given either before the ointment or at least 2 hours after ointment application to obtain the highest intraocular drug concentrations (Ellis & Riegel, 1989). Ointment use should be avoided in eyes with impending corneal perforations or deep or flap-like corneal lacerations, before or during intraocular surgery, because of the irritative properties of

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white petrolatum and mineral oil (Bar-Ilan & Neumann, 1997; Bartlett & Cullen, 1984). Disadvantages of ophthalmic ointment application include imprecise dosing and formation of a film on the cornea, which partially obstructs vision (Bartlett & Cullen, 1984).

Ophthalmic Gels

Gel formation is an extreme case of viscosity enhancement through the use of natural gums, hyaluronic acid, polyacrylic acids, or cellulosic components such as sodium carboxymethylcellulose (Bar-Ilan & Neumann, 1997). Carbopols and polycarbophils are polyacrylic acid derivatives, but carbopols are crosslinked with allyl sucrose whereas polycarbophils are crosslinked with divinyl glycol (Kaur & Smitha, 2002). An example is carbopol 934P which has a molecular weight of 3,000,000 Da and is readily soluble in aqueous solutions (Le Bourlais et al., 1998). The use of ophthalmic gels as a vehicle for hydrophilic drugs can enhance drug retention at the ocular surface because of both the increased viscosity and the bioadhesive properties of these high molecular weight molecules (Kaur & Smitha, 2002). The concept of bioadhesion was developed when some polymers used in viscous vehicles were recognized to attach to the mucin layer of the tear film (Ludwig, 2005). The mucin layer of the tear film can be considered as a diffusional barrier for negatively charged polymers, presumably attributable to formation of strong noncovalent bonds with the carbohydrate pendant chains of the mucin molecule (Saettone et al., 1994). Using lacrimal dacryoscintigraphy in humans, it was shown that at 8 minutes postdosing, the label levels retained in the precorneal area were 7% and 42% for saline and polyacrylic acid-based gel respectively. At 35 minutes, approximately 20% of the labeled carbomer was retained at the ocular surface, suggesting stabilization of tear film for a considerable time (Wilson et al., 1998). Sodium hyaluronate has molecular similarities to ocular mucus glycoproteins and therefore has a mucoadhesion value close to that obtained with a standard mucin-mucin (Herrero-Vanrell et al., 2000). Fusidic acid formulated with a carbopol (Fucithalmic® 1%, Leo Pharma, Ballerup, Denmark) is currently available as an ophthalmic gel to give a long-lasting antibiotic efficiency. DuraSite® (InSite Vision Ltd, Alameda, CA, USA) is a polycarbophil-based polymer that entraps water and the drug molecule in a bioadhesive matrix. With this delivery system, drug release from the matrix takes place over a period of up to 6 hours (Bowman et al., 2009). Topical formulations of azithromycin (AzaSite®, Akorn, Lake Forest, IL, USA), azithromycin/dexamethasone (AzaSite Plus®, InSite Vision Ltd., Alameda, CA, USA), and bromfenac (BromSite®, InSite Vision Ltd, Alameda, CA, USA) using this bioadhesive system became recently available (Barar et al., 2016).

Ophthalmic gels containing sodium hyaluronate 0.1% (SafeDrop® gel or Hylovision® gel, Omnivision GmBH, Puchein, Germany) have also been accepted as tear substitutes because of their prolonged residence time on the ocular surface.

In Situ Gel-Forming Systems

In situ gelling systems are ophthalmic solutions that undergo gelation on contact with the ocular surface. Such a change in viscosity can be triggered by changes in external factors such as temperature, pH, or electrolyte concentration (Weiner & Gilger, 2010). Gelrite® (Merck KGaA, Darmstadt, Germany) is a polysaccharide vehicle derived from gellan gum, which forms a clear gel in the presence of mono- or divalent cations found in the tear fluid (Laurence et al., 1993). Using dacryoscintigraphy in healthy human patients, it was shown that 21 minutes after instillation, Gelrite® maintained 39% of the tracer on the ocular surface compared with only 12% and 17% when the tracer was added to a solution containing no viscosity enhancer or a hydroxyethylcellulose solution, respectively (Meseguer et al., 1996). A gel-forming preparation of timolol 0.5% with Gelrite® as the vehicle (Timoptic XE®, Merck & Co., West Point, PA, USA) allows a once-a-day administration for glaucoma treatment in human patients. Polymeric aqueous solutions, such as poloxamers, in which gelation is activated by the tear pH of 7.2–7.4 or by the temperature of the ocular surface (32–34°C) have also been investigated experimentally (Bar-Ilan & Neumann, 1997). A reversibly thermogelling timolol formulation was found to be better retained at the ocular surface of human eyes than was conventional aqueous timolol (Ishibashi et al., 2003). Xanthan gum exhibits a sol-gel transition by interacting with large proteins present in the tear fluid such as lysozyme (Weiner & Gilger, 2010), and is currently used in a formulation of tobramycin 0.3% and dexamethasone 0.05% (TobraDex ST®, Alcon).

Solid Ophthalmic Forms

Soft Contact Lenses

Soft contact lenses used for the treatment of a variety of corneal diseases as a support bandage can also serve as nonerodible vehicles for progressive drug release into the tear pool. They are typically composed of nonbiodegradable hydrophilic polymers, such as poly-hydroxyethylmethacrylate (pHEMA) or hydroxyethylmethacrylate (HEMA), and 50%–75% water. When soaked in a solution, they absorb the drug which is then released according to first-order kinetics when the lens is placed on the cornea. Drug delivery is characterized by a relatively brief period of rapid drug release (burst release) followed by a longer period of slower release (Kumari et al., 2010; Weiner & Gilger, 2010). Although some studies show the improved delivery of certain medications via presoaked contact lenses, these devices do not maintain a constant rate of drug delivery over time and because the initial burst release cannot be adequately controlled, it may expose the eye and patient to toxic concentrations of the therapeutic

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agent and preservatives (Bar-Ilan & Neumann, 1997). As contact lenses soaked in drug solution cannot be used for long-term drug delivery, efforts were made to increase the duration of drug delivery. Drug release can be prolonged and side effects can be reduced by use of contact lenses made from silicone hydrogel material able to release the drug at near zero order for several days (Fig. 8.1.6), or by loading pHEMA lenses with drug molecules entrapped in vesicles such as liposomes or nanoparticles (Sahoo et al., 2008; Kompella et al., 2010). This type of sustained drug delivery device might be useful for the treatment of ocular surface and anterior segment disease in veterinary patients (Weiner & Gilger, 2010). Besides the fact that contact lenses can serve for topical drug delivery to the eye, at the opposite, they can affect ocular penetration of topically applied drugs when they are used as bandages for corneal healing, as shown recently with topical latanoprost in dogs (Hatzav et al., 2015).

Collagen Shields

An alternative to contact lenses is the use of collagen corneal shields fabricated from porcine scleral tissue or bovine dermal collagen which contain mainly collagen type I and some collagen type III (Willoughby et al., 2002). Upon hydration, they form a clear, thin (0.1 mm in thickness) film that conforms to the corneal surface that then undergoes hydrolysis within 12, 24, 48, or 72 hours depending on the degree of collagen crosslinking determined during the manufacturing process. A collagen shield with a dissolution time of 72 hours is currently available for veterinary use (Vet Shield™, Oasis, San Dimas, CA, USA). The natural absorptive capacity and biodegradability of collagen have led to the assessment of collagen shields as sustained drug delivery devices for antibiotic and anti-inflammatory agents (Bennett, 2016; Willoughby et al., 2002). Like drug-soaked soft contact lenses, collagen shields have, however, the potential to cause ocular toxic reactions on the basis of their pulse-dose drug delivery profile (Le Bourlais et al., 1998a; Willoughby et al., 2002).

Ophthalmic Inserts

Ophthalmic inserts are solid or semisolid drug-loaded devices, the size and shape of which are designed for application in the lower conjunctival cul-de-sac. Their main objective is to maintain therapeutic concentrations at the ocular surface for a prolonged duration by sustained-release mechanisms (Kumari et al., 2010). They are classified as soluble and insoluble inserts, which are furthermore divided into diffusional and osmotic systems. The physicochemical properties of the ophthalmic inserts have been reviewed in detail in the current literature (Kumari et al., 2010; Lee et al., 2010; Rathore & Nema, 2009). The most popular insoluble diffusional insert is a system designed for controlled release of pilocarpine for 7 days (Ocusert® Pilo, Alza Corporation, Mountain View, CA, USA) and has been approved for the treatment of glaucoma in human patients (Kumari et al., 2010). A nonbiodegradable ophthalmic insert containing 5.4 mg phenylephrine and 0.28 mg tropicamide (Mydriasert®, Meditec-Zeiss, Iena, Germany), which is equivalent to one 10% phenylephrine and 0.5% tropicamide drop, is currently available in some countries to induce mydriasis in human patients who undergo cataract surgery (Morgado et al., 2010). The soluble inserts are made from biodegradable polymers and are placed in the cul-de-sac where they are moistened by the tear fluid to become a gel that adheres to the ocular surface. Drug release occurs by gradual dissolution of the polymer matrix which takes place by either hydrolysis or enzymatic erosion, eliminating the need for removing the implant after complete drug release (Rathore & Nema, 2009). From a pharmacokinetic standpoint, the advantages of an ocular insert delivery system include constant delivery rate, which means zero-order pharmacokinetics (Fig. 8.1.6), and prolonged drug residence time in the tear fluid. This was illustrated by studies in rabbits showing that the precorneal residence time of gentamicin varied from 5.1 to 21.9 hours when the drug was administered with different soluble ophthalmic inserts made of various cellulose derivatives compared with 0.08 hours when the drug was instilled as standard eye drops (Bayens et al., 1998).

A soluble insert made with hydroxypropyl cellulose has been marketed for the treatment of dry eye in human patients (Lacrisert®, Bausch & Lomb, Rochester, NY, USA). Ocular bioerodible minitablets and minidiscs containing various antibiotics were found to have prolonged drug release properties and have been considered useful for the therapy of bacterial keratitis in people (Bennett, 2016a; Weyenberg et al.,2004). Difficulty of placement, risks of loss, and mechanical irritation made ocular inserts unpopular in human and veterinary ophthalmology (Gelatt et al.,1979).

Punctal Plugs

Punctal plugs used for symptomatic relief of dry eye by occlusion of the lacrimal puncta can be specifically designed for long-term drug delivery to the eye with the advantages of enhanced availability, and hence efficacy, compared with eye drops. The lacrimal punctal plug delivery system has an outer shell made up of material impermeable to the drug and tear fluid, a polymeric core containing the drug, and a head portion in contact with the tear fluid when the plug is inserted into a lacrimal punctum. The drug is released through the head portion that has one or more pores (Kompella et al., 2010). A zero-order kinetic drug release (see Fig. 8.1.6) is observed with this type of delivery system and pilot studies indicate that latanoprost ocular delivery can be provided safely and efficiently for up to 3 months in human patients (Kompella et al., 2010). In dogs, punctal plugs (0.4–0.6 mm in diameter) may be retained for 8–23 days (Gelatt et al., 2006), but their usefulness as sustained drug delivery devices has been investigated but not reported (K. Gelatt, personal communication, 2017).

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Periocular Drug Delivery

The subconjunctival, sub-Tenon's, peribulbar, and retrobulbar routes of administration are used to improve the delivery of drugs to intraocular structures. Their selection depends on the inability of a drug to penetrate the ocular surface and/or the location of the target site. In veterinary patients, the subconjunctival route is commonly used for administration of antibiotic and anti-inflammatory agents, whereas the sub-Tenon's and retrobulbar routes are mainly used for local anesthesia of the globe. In humans, periocular drug delivery can potentially provide a safer alternative to intraocular administrations for delivering drugs to the inner eye tissues.

Subconjunctival Administration

Subconjunctival administration may be indicated for infectious or inflammatory conditions of the cornea and anterior segment because of the expected high and/or sustained drug levels that can be achieved in these ocular structures. For subconjunctival injection, the medication should be administered below the bulbar conjunctiva. Several mechanisms have been proposed to explain the drug movements from the injection site to the anterior segment of the eye: (a) the drug may diffuse directly into the cornea and sclera and penetrate the anterior chamber or underlying tissues; (b) the drug may regurgitate through the conjunctival injection puncture hole and then mix with tears before entering the eye transcorneally; and (c) the drug may be absorbed into conjunctival blood vessels with subsequent hematogenous dissemination and recirculation back into the uvea (Barza et al., 1981; Conrad & Robinson, 1980) (Fig. 8.1.8). Although it is generally assumed that subconjunctival administration delivers higher drug concentrations to anterior ocular structures compared with those of the posterior segment, some data suggest that effective drug delivery to the vitreous body and choroid/retina can be achieved and will most likely result from direct diffusion through the sclera (Ghate et al., 2007; Lee & Robinson, 2001). A direct relationship exists between the ability of a drug to diffuse through the sclera and both thickness and total surface area of the sclera (Ambati et al., 2000a, 2000b). In humans, the pars plana-pars plicata region is considered to be the zone of least resistance to transscleral drug delivery after periocular injections (Ghate et al., 2007). On the other hand, in dogs and horses the sclera is thinner at the equator than at the limbus, suggesting that drugs delivered by subconjunctival or sub-Tenon's injection at the equatorial region could more easily diffuse to intraocular structures in these species (Gilger et al., 2005).

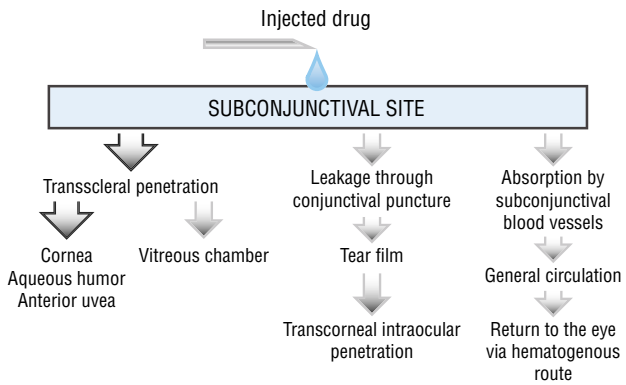


Figure 8.1.8 Routes of drug distribution after subconjunctival injection.

The ability to deliver effective concentrations of antibiotics to the anterior segment of the eye (cornea, iris, aqueous humor) by subconjunctival injections is supported by experimental data (Barza, 1986). A comparison of topical and subconjunctival routes of treatment for bacterial corneal ulcers has shown that subconjunctival administration produces transiently high antibiotic levels in the cornea and that concentrations after eight hours are similar to those achieved by hourly topical applications (Baum & Barza, 1983). Therefore, subconjunctival injection may be indicated when there is a need to obtain high tissue concentrations of antibiotics in emergency management of acute anterior segment infection, and as such, may be used as part of the antimicrobial therapy in ulcerative and nonulcerative bacterial keratitis in conjunction with topical and systemic antibiotic administration (Callegan et al., 1994). The subconjunctival route was found equivalent to retrobulbar injection in penetrating inflamed vitreous humor and may be considered as an adjunctive therapy in the treatment of bacterial endophthalmitis (Barza, 1986). Only hydrophilic antibiotics should be injected subconjunctivally and the recommended dosages have been previously published (Martin & Brooks, 2012).

Subconjunctival injections of glucocorticoids may be used as a supplement to parenteral administration in cases of posterior segment inflammatory disease (i.e., chorioretinitis) or to reduce the need for frequent instillation of drops in case of anterior segment inflammation (i.e., immune-mediated keratitis, anterior uveitis) (Martin & Brooks, 2012). Drug release from the injection site is primarily regulated by the biochemical composition of the glucocorticoid. Phosphate esters (i.e., dexamethasone phosphate) are water-soluble products that are rapidly absorbed from the injection site and are short acting (Schoenwald, 1997). By contrast, acetate and diacetate esters (i.e., methylprednisolone acetate, triamcinolone acetonide) are poorly water-soluble compounds that form a depot when injected under the conjunctiva. Therefore, drug absorption from these suspensions is slow and maintain therapeutic levels for 2–3 weeks (Castrén et al., 1964). However, data in humans suggest that a significant amount of active glucocorticoid may remain up to 13 months in subconjunctival depots (Kalina et al., 1995). These formulations are administered

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by the subconjunctival route for prolonged release of steroid, but their main drawbacks include increased risk of local infection (fungal or bacterial), and in cases of secondary complications, the impossibility of removing the drug once injected (McMullen & Fischer, 2017).

Subconjunctival injection of drug-loaded liposomes or polymeric systems have been investigated to understand if it is possible to provide prolonged residence time for therapeutic drug levels in the anterior segment of the eye (Ebrahim et al., 2005; Niesman, 1992). A subconjunctival implant of silicone MED-4750 (a nonbiodegradable polymer) loaded with penciclovir has been developed to prevent feline herpesvirus-1 (FHV-1) recurrence over the long-term. Sustained release of penciclovir for 50 days was observed in the *in vitro* studies and observed drug concentrations were able to suppress primary FHV-1 infection in cell culture (Semenkow et al., 2014). A subconjunctival nonbiodegradable implant of latanoprost (Latanoprost SR implant®, Pfizer Inc., New York, NY, USA) was designed for 3–6 months of drug release and is currently undergoing clinical evaluation in human glaucomatous patients (Kuno & Fujii, 2011). More recently, a thermosensitive biodegradable hydrogel suitable for subconjunctival injection has been evaluated for long-term delivery of voriconazole in horses. This ophthalmic form was easy to inject beneath the bulbar conjunctiva and *in vitro* studies showed significant scleral and corneal drug absorption for more than 21 days (Cuming et al., 2017).

Because a fraction of the injected dose is absorbed by the conjunctival vasculature, subconjunctival administration may be responsible for systemic side effects as observed with methylprednisolone acetate in dogs (Regnier et al., 1982) and atropine in horses (Williams et al., 2000). In dairy cows, antibiotic residues were detected in the milk for up to 22 hours after a single subconjunctival injection of procaine penicillin G, reflecting the systemic absorption of part of the injected dose (Liljebjelke et al., 2000).

Sub-Tenon's Administration

In a sub-Tenon's injection, the drug is injected with a cannula in a cavity between Tenon's capsule and sclera where transscleral diffusion of hydrophilic drugs is thought to occur. It is considered to be safer and less invasive than intravitreal injection. Experimental data in rabbits indicate that this route can be effective for delivering corticosteroid into the anterior and posterior segment of the eye (Huang et al., 2017) and that sub-Tenon's injection of a long-acting corticosteroid every 6–8 weeks would be able to treat chronic inflammatory chorioretinal diseases (Nan et al., 2010). Sub-Tenon's injection of corticosteroids is indicated in human patients with chronic equatorial and posterior uveitis and those with cystoid macular edema after cataract surgery or diabetic macular edema (Bartlett, 2008). Anecorvate acetate suspension (Retaane® 15 mg, Alcon, Fort Worth, USA) is an analog of cortisol acetate that inhibits angiogenesis and when injected by posterior sub-Tenon's route, it forms a juxta-scleral depot from which the drug is delivered over a period of 12 months. It is indicated for the treatment of exudative age-related macular degeneration (Augustin, 2006).

In the dog, sub-Tenon's injection of lidocaine provides excellent mydriasis and globe akinesia compared with retrobulbar lidocaine administration (Ahn et al., 2013). Sub-Tenon's anesthesia may also be an alternative to retrobulbar block in horses. Preliminary studies on equine cadaver eyes showed that volumes of 7 mL and 10 mL lidocaine have the same distribution around the globe after sub-Tenon's injection (Stadler et al., 2016).

Episcleral Implants

Like the sub-Tenon's administration, placement of a drug on the episcleral surface of the eye has been considered a potential way for delivering drugs to the posterior segment of the eye (Berezovsky & Edelhauser, 2013). After delivery on the episcleral surface, the drug molecule may be absorbed by the episcleral blood and lymphatic vessels to be eliminated and may enter the sclera to move to the choroid, Bruch's membrane, and retina, move in a lateral direction, or remain bound to the scleral matrix (Berezovsky & Edelhauser, 2013; Lee et al., 2010). Although various experimental studies have shown that transscleral delivery of small and large molecules to the posterior segment tissues may be achievable, drug absorption by periocular lymphatics and blood vessels is considered as a major barrier to transscleral drug delivery (Berezovsky & Edelhauser, 2013; Robinson et al., 2006). It has been suggested that this barrier can be circumvented by increasing the dose of drug delivered to the scleral surface or using a sustained-release device to maintain a concentration gradient that moves the drug across the sclera (Robinson et al., 2006). Although no specific episcleral delivery system has been approved for drug delivery to the posterior segment, episcleral cyclosporine A (CsA) implants have been evaluated to achieve therapeutic drug levels in the anterior segment. In the last decade, silicone matrix episcleral CsA implants have been designed for sustained delivery of immunosuppressive drug levels to the cornea (Gilger et al, 2006). One device has been evaluated for its potential to prevent human corneal rejection after high-risk keratoplasty (Lee et al., 2007) and another is currently used for the treatment of immune-mediated keratitis in horses (Gilger et al., 2014). The implant, made from a medical grade silicone, is 12 mm long, 2 mm wide, and 1 mm in height, and is implanted 5 mm posterior to the limbus inside a pocket formed by blunt dissection in the episcleral space. It is loaded with 12 mg of CsA and the drug release rate is characterized by an initial phase of 2–5 μg/day over 5 months, followed by a steady-state release of 1–2 μg/day for a minimum of 400 days (Lee et al., 2007). Results of a pilot study in horses showed that this

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implant was well tolerated and that superficial and endothelial immune-mediated keratitis significantly improved with this procedure (Gilger et al., 2014).

Retrobulbar and Peribulbar Administrations

Retrobulbar and peribulbar injections are used to introduce a drug into the orbital cavity. Periocular involves injections in the orbital regions surrounding the globe, whereas retrobulbar represents injection through orbital fascia for placing the drug in the retrobulbar space (Agrahari et al., 2016). These routes are primarily indicated for the delivery of local anesthetic agents prior to ocular surgery. Techniques of injection have been described for cats and dogs and evaluated in terms of the consistency of the drug distribution within the orbital tissues and retrobulbar cone (Accola et al., 2006; Shilo-Benjamini et al., 2013). In horses and cattle, different approaches have been reported for retrobulbar delivery of local anaesthetic drugs to provide akinesia and analgesia of the globe prior to ophthalmic surgery in standing sedated animals (Labelle & Clark-Price, 2013; Pearce et al., 2003).

Potential complications of retrobulbar block include globe perforation, optic nerve injury, extraocular muscle injury, and orbital hemorrhage (Dutton, 2001). Although peribulbar anesthesia has been advocated as a safer alternative to retrobulbar anesthesia, globe perforation has been reported as a rare complication of this injection technique in humans (Joseph et al., 1991).

Suprachoroidal Drug Delivery

The suprachoroidal space is, under normal conditions, an area of weak adhesions that can be expanded to incorporate injected fluids. This space normally permits the posterior flow of aqueous humor (called uveoscleral outflow). Located at the interface between choroid and sclera, the suprachoroidal space has recently been proposed to deliver drugs to the posterior ocular tissues (Berezovsky & Edelhauser, 2013). Due to its proximity to the choroid and retinal pigment epithelium, this route of administration has the advantage to give higher drug concentrations in the choroid and retina than the subconjunctival and intravitreal routes, and is expected to induce fewer changes in the vitreous body than intravitreal injections (Bansal et al., 2016; Tyagi et al., 2012). Animal studies have shown that suprachoroidal injection can increase the duration of drug effects for up to 4 months. The iTrack® microcatheter (iScience Interventional, Menlo Park, CA, USA) and hollow microneedles have been designed to deliver particulate-designed formulations into the suprachoroidal space (Bansal et al., 2016; Patel et al., 2012). The microneedle length for suprachoroidal drug delivery has been determined in horses (see paragraph on microneedles later) and there are ongoing studies aiming to evaluate the feasibility and efficacy of suprachoroidal injection of a long-acting corticosteroid for the treatment of nonresponsive equine uveitis (Gilger, 2016).

Equine recurrent uveitis (ERU) is a T-cell-mediated autoimmune disease that may require local immunosuppressive therapy for its control over the long term. Cyclosporine A is a potent immunosuppressive drug that inhibits lymphocyte activation via blockade of cytokines especially IL-2. Therefore, development of an intraocular implant to provide prolonged activity with controlled CsA release was considered as an approach to prevent recurrence of the uveitis episodes. Placement of this device in the suprachoroidal space was chosen to facilitate drug delivery to intraocular structures because of the lack of significant penetration of cyclosporine through the equine sclera and failure to control naturally occurring ERU when the CsA implant was placed in the episcleral space (Gilger et al., 2006). Cyclosporine release from this nonbiodegradable implant is about 6 µg/day at the steady state phase, thereby allowing a projected duration of release rate of 3.18 years (Gilger et al., 2006). *In vivo* experiments in healthy horses showed that when this device was implanted in the deep sclera adjacent to the suprachoroidal space, therapeutic levels of CsA could be reached in vitreous, ciliary body, choroid-retina and optic nerve, which are target tissues of ERU treatment, and no abnormalities could be noted on histopathological examination of the eyes 12 weeks after implantation (Gilger et al., 2006). In clinical equine patients with ERU treated with a 6-mm diameter, 25 mg CsA implant constructed as those previously evaluated, the frequency of uveitis episodes was significantly decreased after surgery with 79% of the treated eyes being still visual at last follow-up (13–85 months) (Gilger et al., 2010). Although theoretical CsA depletion from this device is about 3 years, clinical observation that treated horse eyes were relatively well controlled up to approximately 36–48 months suggested that a repeat suprachoroidal implant may be required at or before 48 months after initial surgery (Gilger et al., 2006, 2010).

Intraocular Drug Delivery

Intraocular administration of therapeutic agents has optimal bioavailability and represents an alternative to periocular injection and suprachoroidal administration to target intraocular tissues. However, it is more invasive with a higher risk of ocular complications.

Intracameral Injection

Intracameral administration involves delivering a drug directly into the anterior chamber of the eye (Bartlett, 2008). Most commonly, injection or irrigation of the anterior chamber is used to control iris hemorrhage or pupil size with

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viscoelastic substances and/or epinephrine during intraocular surgery. Intracameral injection is the usual mode of administration of tissue plasminogen activator in small and large animals. Doses of 25 µg/0.1 mL are effective and safe to lyse anterior chamber fibrin clots associated with ocular trauma, uveitis, and gonioimplant surgery used for treating canine glaucoma (Gerding et al., 1992). Carbachol can also be administered intracamerally at the completion of cataract surgery in the dog. Intracameral injection poses a significant risk for local drug toxicity because local intolerance may result in corneal endothelial damage with corneal edema and damage to the iris and lens (Bartlett & Cullen, 1984). Use of intracameral unpreserved 1% lidocaine has been introduced as a method of supplementing topical anesthesia during cataract surgery in humans (Bartlett, 2008). Results of an experimental study indicate that intracameral administration of unpreserved 1% or 2% lidocaine does not induce morphological changes of the corneal endothelium and would be safe for intraocular pain management in dogs (Gerding et al., 2004). Conversely, a toxic effect on the corneal endothelium has been reported in rabbits after intracameral injection of lidocaine 2% with preservative (Schellini et al., 2007).

In the dog, which has an anterior chamber volume of approximately 0.80 mL, an injection volume of 0.1 mL is suggested after an equivalent volume of aqueous humor has been aspirated to prevent transient increase in intraocular pressure (Gerding et al., 2004). In the horse with an anterior chamber volume of approximately 3 mL (Gilger et al., 2005), the injection volume theoretically should be higher to reach aqueous humor drug concentrations comparable with those obtained in the dog, provided the drug dosage is not toxic to the corneal endothelium.

Intravitreal Injection

The vitreous body is an avascular gel-like medium in which drug delivery by the vascular route is generally low because of the blood–ocular barriers and tight junctions of the retinal pigment epithelium, which severely restrict the passage of drugs from the blood flow to the vitreous humor. Similarly, therapeutic drug levels cannot be readily achieved in the posterior pole of the eye after topical application of conventional topical formulations, because drug transfer from the anterior segment is slow and reduced (Meredith, 1994). For these reasons, direct administration of a drug solution or suspension into the vitreous body is a more appropriate method to provide effective concentration at intraocular tissues and is currently used in the treatment of various posterior segment diseases in human patients (Le Bourlais et al., 1998). In veterinary ophthalmology, this route of administration was used initially for chemical ablation of the ciliary epithelium in end-stage glaucomatous eyes, but in recent years, it became a common mode of drug administration in horses with uveitis (McMullen & Fischer, 2017). Although intravitreal injection offers advantages because the therapeutic agents are directly administered into the vitreous body, drug distribution into the vitreous is not uniform and depends on the injection position and volume, physicochemical features of the drug as well as the pathophysiological condition of the vitreous body. Prior to intravitreal injections, an equal volume of liquid and/or gel vitreous is removed. After placement in the vitreous, drug molecules distribute through the vitreous body and then are lost by first-order kinetics via the anterior or the posterior route depending on their molecular weight and lipophilicity. Elimination of intravitreal drugs by the anterior route follows a diffusion pattern that moves the drug between the lens and ciliary body (annular gap) to the anterior chamber, whereas a retinal pump mechanism has been described for active transport of drugs out of the retina and then direct elimination into the systemic circulation (Tojo & Ohtori, 1994). Using a dynamic mathematical model, it has been reported that small molecules are eliminated by both the anterior and posterior routes (Tojo & Ohtori, 1994) and because most of the intravitreally administered drugs in solution have a molecular weight less than 500 Da, their half-life is likely to be shorter than 3 days (Maurice, 2001). The more hydrophilic compounds with low retinal permeability, such as aminoglycosides, leave the vitreous humor via the anterior chamber and have a half-life of elimination of 20 to 30 hours. By contrast, lipophilic molecules, such as corticosteroid agents, particulate systems less than 300 nm, and high-molecular weight proteins, such as anti-vascular endothelial growth factor (VEGF) antibodies, tend to be eliminated across the retina (Behar-Cohen, 2013; Liu et al., 1998; Macha & Mitra, 2001).

Injection location can also affect the time during which efficient drugs levels can be maintained in the vitreous. Experimental studies show that the mean drug concentration remaining in the vitreous 24 hours after an intravitreal injection varied by up to a factor of 3.8 depending on the initial location of the injected drug (Friedrich et al., 1997). Whatever the drug elimination route from the vitreous, the highest drug concentrations measured 24 hours after administration were observed after injections in the center of the vitreous body compared with those achieved after injection in the anterior and posterior vitreous (Friedrich et al., 1997). From a clinical standpoint, these findings indicate that a careful control of the conditions of an intravitreal injection could improve drug bioavailability and reduce treatment variability (Friedrich et al., 1997). Another well-known factor that may influence the half-life of drugs in the vitreous humor includes the presence of inflammation and infection and the presence or absence of lens (Ben-Nun et al., 1989; Maurice & Mishima, 1984).

As drugs in the form of solution are rapidly eliminated from the vitreous and need frequent administrations,

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crystalline formulations or nanoparticulate systems are preferred for sustained drug release because the slow rate of dissolution of the crystals or nanoparticles into the vitreous results in prolonged delivery of local drug levels. Triamcinolone acetonide, which is in a suspension form, has a half-life of approximately 19 days after intravitreal injection in human eyes that have undergone vitrectomy, whereas drug levels are present in vitreous for up to 3 months in non-vitrectomized human eyes (Beer et al., 2003; Mason et al., 2004). In horses, significant drug concentrations were found in the vitreous 21 days after a single intravitreal injection of 10, 20 or 40 mg of vehicle-free triamcinolone acetonide (Yi et al., 2008). In addition to being exploited as topical ophthalmic forms, nanoparticulate systems have been widely investigated as intravitreal injectable systems for delivery of various drug molecules to the posterior segment of the eye, as reported in a recent review (Famili & Kompella, 2013). After injection into the vitreous, nanoparticulate systems act like drug reservoirs that release drugs over weeks to months. The potential usefulness of liposomal preparations of antibiotics and antiviral agents, of microspheres made of lactic and glycolic acid polymers loaded with various drugs, and of nanoparticle-based systems loaded with antivascular VEGF has been investigated in animal models of diverse human vitreoretinal diseases and offered promising results (Ebrahim et al., 2005; Eljarrat-Binstock et al., 2010; Famili & Kompella, 2013). Injected into the vitreous, the particulate systems efficiently release drugs for about 1–2 months (Behar-Cohen, 2013). A feature that makes these systems very attractive for drug delivery to the posterior system is that, depending on their physicochemical properties, they can target a certain cell type after cellular uptake by a dynamic internalization process (Behar-Cohen, 2013; Famili & Kompella, 2013). Studies in rats show that targeting drugs to RPE cells was possible with biodegradable PLA nanoparticles injected intravitreally, suggesting that particulate systems for sustained drug release to the neuroretina might also be designed (Gaudana et al., 2009).

In human patients, the intravitreal route is indicated for administration of antibiotics for prophylaxis or treatment of bacterial endophthalmitis, triamcinolone acetonide for the treatment of wet age-related macular degeneration and diabetic macular edema, and ganciclovir for the treatment of cytomegalovirus retinitis (Bartlett, 2008; Kompella et al., 2010). Over the last years, intravitreal injection of therapeutic peptides and proteins, including anti-VEGF agents (i.e., ranibizumab, becavizumab), neurotropic growth factors (i.e., ciliary neurotropic factor, brain-derived neurotropic factor), and cytokines (interferon gamma) have been used for the treatment of proliferative vitreoretinopathy, retinal degenerative diseases, and infectious retinitis, respectively (Behar-Cohen, 2013; Bennett, 2016b). Cortiject® (Santen SAS, Evry, France) is a preservative- and solvent-free emulsion of oily carrier and phospholipid, encapsulating a corticosteroid prodrug that is activated at the level of the retina. Clinical trials are ongoing to evaluate its safety and efficacy in patients with age-related macular degeneration (Bansal et al., 2016). In veterinary ophthalmology, intravitreal injection of gentamicin (4 mg, preservative free) or triamcinolone acetonide (2.5–5.0 mg) is a current medical procedure adapted to the treatment and prevention of recurrent bouts of intraocular inflammation in horses (McMullen & Fischer, 2017).

In human patients, the common clinical practice is to deliver the desired dose of the drug in 0.05–0.10 mL of solution or suspension (Raju & Weinberg, 2002), whereas in dogs and horses drug volumes of up to 0.20 mL and 1 mL, respectively, have been injected in the vitreous without overt problems (Molleda et al., 2008; Yi et al., 2008). The safety of the drug, its vehicle, and its concentration reaching the retina must be taken into account to avoid toxicity. A well-known example is benzyl alcohol, the vehicle of triamcinolone acetonide, which is toxic to intraocular tissues and should be replaced with 0.9% sterile saline solution before intravitreal injection (Jermak et al., 2007). Any intravitreal injection is associated with the risk of bacterial endophthalmitis, vitreous hemorrhage, retinal detachment, and possible lens damage. In addition, intravitreal injection should not be viewed as a purely local treatment because part of the injected drug may diffuse in the systemic circulation and may be associated with systemic side effects (Amiran et al., 2013; Rankin et al., 2016).

Intraocular Implants

Advances in biomedical engineering methods and ocular surgery procedures led to the development of polymeric implants specifically designed to be placed in intracameral or intravitreal region with the benefit of providing prolonged and controlled drug release within the eye after a single administration (Bennett, 2016a; Jervis, 2017). Several intraocular nonbiodegradable (or non-erodible) and biodegradable implants have been developed for ocular drug delivery, especially for the treatment of chronic vitreoretinal diseases in human patients (Wang et al. 2013a).

Nonbiodegradable Implants

Current marketed products include intravitreal implants for delivery of fluocinolone acetonide (Iluvien®, Alimera Sciences Inc., Alpharetta, GA, USA; Retisert®, Bausch & Lomb Inc., Rochester, NY, USA), ganciclovir (Vitrasert®, Bausch & Lomb Inc., Rochester, NY, USA), and triamcinolone acetonide (Surmodics I-Vation®, Surmodics, Eden Prairie, MN, USA). A cyclosporine implant (Lumitect®, Lux BioSciences Inc., Jersey City, NJ, USA) was designed to prevent corneal transplant rejection but was not FDA approved after completion of phase-III clinical trials. Developed for the treatment of diabetic macular edema, Iluvien® and Retisert® implants deliver fluocinolone acetonide for over

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2.5–3 years (Jervis, 2017). The former is injected into the vitreous using a 25G needle, whereas the latter should be surgically placed. The Vitrasert® implant is also placed through a pars plana incision and suspended in the vitreous by being anchored onto the sclera with sutures. It releases ganciclovir at a rate of 1.4 μg/h over a period of 7–8 months and has been approved for treatment of cytomegalovirus retinitis in AIDS patients (Bansal et al., 2016). The I-Vation® implant releases triamcinolone acetonide for 2 years because of its helicoidal coil shape that increases the surface area available for drug coating (Bansal et al., 2016). The NT-501® and NT-503® (Neurotech Pharmaceuticals, Cumberland, RI, USA) are nonbiodegradable intravitreal implants sutured onto the sclera that use encapsulated cell technology. The NT-501® implant contains human retinal pigment epithelial cells genetically modified to produce ciliary neurotrophic factor, whereas the NT-503® is loaded with cells releasing VEGF receptor-Fc fusion protein (Bansal et al., 2016; Barar et al., 2016). They are currently in clinical trials for the treatment of age-related macular degeneration and retinitis pigmentosa. Invasive surgery, requirement for removal after the drug supply has been exhausted, and adverse events related to surgical implantation and removal represent limitations with the use of intravitreal nonbiodegradable implants.

Biodegradable Implants

These drug delivery formulations are composed of biocompatible polymers which degrade into nontoxic byproducts or polymers that solubilize and can be eliminated safely from the intraocular structures (Lee et al., 2010). They are constructed from a variety of synthetic polymers including polyglycolic acid (PGA), PLA, and the PLGA. The safety and biocompatibility of these polymers were first shown through their use in the production of the absorbable suture materials Dexon® (PGA) and Vicryl® (PLGA) (Ethicon Inc. Sommerville, NJ, USA). Drug release from PGA and PLGA-based delivery systems follows a three-phase mechanism: the burst phase occurs first after implantation, followed by the phase during which the water molecules penetrate deeper into the implant allowing efflux of the drug, followed by a final phase of biodegradation that occurs when the polymer begins to structurally break down into fragments and less drug is available for release (Lee et al., 2010). The degradation rate of these polymers can be modulated to allow for the desired drug release profile to take place for months to years (Eljarrat-Binstock et al., 2010). Surodex® (Allergan, Inc., Irvine, CA, USA) is a rod-shaped (1.0 × 0.5 mm) biodegradable implant consisting of dexamethasone (60 mg) and a matrix of PLGA with hydroxypropyl methylcellulose. Inserted in the anterior chamber or the ciliary sulcus of human eyes at completion of cataract surgery, it provides sustained release of dexamethasone for 7–10 days and was found safe and clearly superior to 0.1% dexamethasone eye drops for controlling postsurgical inflammation (Tan et al., 2001).

Ozurdex® (Allergan Inc.) is a biodegradable intravitreal implant containing 0.7 mg dexamethasone within a rod-shaped matrix (6.5 × 0.45 mm) of polylactic and polyglycolic acid. Inserted into the vitreous body through a 22G needle, it releases peak drug concentrations for 2 months followed by lower concentrations for up to 4 additional months (Wang et al., 2013a). This drug delivery device has been approved for the treatment of macular edema and chronic uveitis in humans (Jervis, 2017).

Verisome® (Ramscor, Inc., Irvine, CA, USA) is an injectable, biodegradable delivery system for sustained intraocular administration of therapeutic agents (Lee et al., 2010). Once injected into the vitreous, the material coalesces to form a spherule that slowly degrades and releases the drug. Triamcinolone acetonide and ranibizumab formulated with this system were reported to be safe and effective for the treatment of chronic cystoid macular edema and vascular age-related macular degeneration, respectively (Wang et al., 2013a).

Biodegradable scleral plugs have been investigated for sustained delivery of corticosteroids, antiviral drugs, or immunosuppressive agents to the posterior segment. Studies in different animal models indicate that they represent systems to facilitate transscleral diffusion resulting in high and prolonged drug concentrations in the vitreous and retina (Peng et al., 2010, Sakurai et al., 2003; Yasukawa et al., 2001).

Systemic Administration

In veterinary ophthalmology, systemically administered drugs are used for the treatment of eyelid diseases (e.g., bacterial blepharitis), orbital infections (i.e., orbital cellulitis or abscesses), infectious and/or ulcerative keratitis when topical ophthalmic drug administration is challenging or impossible, and intraocular conditions such as bacterial endophthalmitis. The rationale for parenteral administration of antibiotics in the treatment of infectious keratoconjunctivitis in sheep and cattle has been based on observation that some antimicrobial agents can diffuse into the lacrimal fluid after parenteral administration and that this mode of administration can be clinically effective. Secretion of drugs in tears after systemic administration is dependent upon the volume of distribution, binding to plasma proteins, and lipophilicity of the administered molecules (Monaco et al., 1979; van Haeringen, 1985). These features likely explain that the level of tear secretion after parenteral administration varied from 9% with intramuscular kanamycin in calves (George et al., 1986) to 40% with intramuscular florfenicol in sheep (Regnier et al., 2013). Parenteral administration of a long-acting formulation of oxytetracycline led to low drug levels

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in tears of sheep and calves (George et al., 1985; Nouws & König, 1983), whereas orally administered doxycycline, which is more lipophilic, was secreted in equine tear fluid at concentrations effective for antiprotease activity (Baker et al., 2008). In human patients, mean tear plasma ratios ranging from only 4% to 8% have been reported after intravenous administration of gentamicin, tobramycin, amikacin, and netilmicin, which are hydrophilic compounds (Woo et al., 1985).

Drug accessibility to targeted intraocular tissues is also limited after systemic administration and like drug secretion in tears, mostly depends on the drug lipophilicity (Bartlett & Cullen, 1984). Drugs with higher liposolubility, such as minocycline, doxycycline, chloramphenicol, and trimethoprim, may achieve high levels in the eye after systemic administration, whereas drugs that are less lipid soluble, such as beta-lactams and aminoglycosides, are thought to penetrate poorly into the aqueous humor of noninflamed eyes (Barza, 1978; Meredith, 1997). Plasma protein binding is not an absolute determinant of drug penetration into the ocular tissues after systemic administration because many drugs that have low protein binding in plasma penetrate poorly across the blood–eye barrier, whereas others that are highly protein-bound in plasma may diffuse more easily into the eye. For example, penicillins show low protein binding in plasma (20%–30%), yet ocular penetration is poor with standard doses. In contrast, chloramphenicol plasma protein binding is about 50% to 60%, yet ocular penetration is far superior (Rolinson, 1980). In fact, it is more accurate to state that the rate of drug transfer from the plasma across the blood–eye barriers is enhanced as the free fraction in the plasma increases, whereas the extent to which the drug will ultimately penetrate is determined by pharmacokinetic parameters related to its systemic distribution. In general, the molecular weight affects less the penetration of drugs across barriers. The ability to pass through membranes is related to the square root of the molecular weight and in theory, the higher the molecular weight, the less readily the molecule can cross the blood–ocular barriers. As most drugs fall in a narrow range of between 100 and 400 Daltons, this physical feature is less important than drug lipophilicity in determining the penetration of drugs across the blood–ocular barriers (Meredith, 1997). Ionized molecules at physiological pH, such as cephalosporins, are less able to travel across the blood–ocular barriers, which affects their intraocular penetration (Meredith, 1997).

Factors that induce breakdown of the blood–ocular barriers, such as ocular inflammation, ocular infection, and ocular trauma, promote intraocular penetration of systemically administered drugs (Bar-Ilan & Neumann, 1997). It is well established that intraocular inflammation plays a major role in the breakdown of the blood–ocular barriers by disrupting tight junctions, increasing both transendothelial vesicles and pinocytosis, and enhancing the formation of microvilli by endothelial cell luminal membranes (Meredith, 1997). The ability of ceftazidime (Walstad et al., 1987), ciprofloxacin (Alfaro et al., 1996), ofloxacin (Öztürk et al., 2000), and marbofloxacin (Regnier et al., 2008) to penetrate into the eye when the blood–ocular membranes are inflamed has been shown using endotoxin- or trauma-induced models of endophthalmitis in rabbits. This raises the question: would some systemic drugs used in the clinical setting for the treatment of infectious and/or inflammatory intraocular diseases be able to achieve therapeutic concentrations inside the eye. This is an important consideration when treating ERU with systemic medications. In horses, repeated oral administrations of doxycycline did not reach therapeutic drug levels in the aqueous humor and vitreous of noninflamed eyes (Gilmour et al., 2005), but intravenous enrofloxacin was able to penetrate into eyes with induced blood–aqueous barrier disruption, to achieve concentrations above the reported MIC for *Leptospira pomona* (Divers et al., 2008). As for anti-inflammatory drugs, it was shown that firocoxib penetrates the aqueous humor better than flunixin meglumine in non-inflamed equine eyes (Hilton et al., 2011).

Other Methods of Ocular Drug Delivery

Iontophoresis

Ocular iontophoresis, a noninvasive technique that utilizes low electric currents to enhance the penetration of ionized drugs across tissue barriers, has received attention in the last decade to deliver drugs to both the anterior and posterior segments of the eye (Bansal et al., 2016). The ionized substances are driven into the corneal and scleral tissues by electropulsion at either the anode for positively charged drugs or the cathode for negatively charged molecules. The drug is contained in a cup-shape device (5–10 mm in diameter), bearing the same charge as the drug and placed over the eye, whereas the return electrode with an opposite charge is submerged into the solution. The electric field enhances penetration of ionized molecules across the cornea and sclera by three mechanisms: movements of ionic species (electrophoresis), convective solvent flow (electroosmosis), and alteration of the tissue barrier (electroporation) (Weiner & Gilger, 2010). Transcorneal iontophoresis is used to enhance corneal penetration of ionized compounds with low bioavailability after topical administration, whereas transscleral iontophoresis delivers drugs directly to the retina and choroid and overcomes the risk of side-effects associated with intraocular injections and implants (Souza et al., 2013). Experimental and clinical studies have shown the potential of ocular iontophoresis in

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successfully delivering dexamethasone phosphate, triamcinolone acetonide, gentamicin, ciprofloxacin, ketoconazole, and ranibizumab to both anterior and posterior segments of the eye (Souza et al.,2013; Bansal et al., 2016). In recent years, various types of iontophoretic systems, such as EyeGate®II (EyeGate Pharmaceuticals, Waltham, MA, USA), Ocuphor® (Iomed Inc., West Salt Lake City, UT, USA) and Visulex® (Aciont Inc., Salt Lake City, UT, USA) have been developed for ocular drug delivery in human patients. An iontophoretic device is also available for small animals (Iontofor-Vet®, Opia Technologies, Paris, France) and was reported to improve transcorneal riboflavin penetration in collagen corneal crosslinking for treatment of canine melting ulcers (Famose, 2014). As the iontophoretic eye cup should be maintained in place over the eye using slight suction, this technique can be performed only in sedated or anesthetized animals.

Sonophoresis

Early *in vitro* studies indicated that 20-kHZ ultrasound application for 1 hour allowed enhancement of transcorneal penetration of beta-blocker antiglaucoma agents, such as timolol, betaxolol, carteolol, and atenolol, by two to four times (Zderic et al., 2002). Using a higher frequency of 880-kHZ for 5 minutes, the same investigators observed a 10-times increase in the transfer of hydrophilic drugs through the cornea with minor changes in the corneal epithelium (Zderic et al., 2004). More recently, a combination of sonoresis and microbubbles was experimentally assessed to transfect the ciliary muscles of rat eyes and results showed significant gene expression in treated eyes compared with control and plasmid alone groups (Kowalczuk, et al., 2011). This finding suggested that application of ultrasounds combined with microbubbles may allow intraocular production of proteins for the treatment of various retinal diseases in human patients (Kowalczuk, et al., 2011). To the author's knowledge, no preclinical or clinical studies demonstrating the efficacy of this approach for delivering ophthalmic drugs have been reported.

Microneedles

Drug-coated solid or hollow microneedles with a length of 500–750 µm have been developed as a minimally invasive method of drug delivery to the posterior segment of the eye (Thrimawithana et al., 2011). Because of their small size, they can be used to deliver drug or carrier system into the sclera or suprachoroidal space (Patel et al., 2013). A study showed that intrascleral hollow needles may be employed for scleral infusion of soluble molecules, nanoparticles, and microparticles with minimal invasion (Jiang et al., 2009). Experimental data in the rabbit also showed that insertion of coated microneedles into the cornea is minimally invasive and is effective to deliver a drug to treat corneal neovascularization with a dose 400 times smaller than that injected subconjunctivally to achieve the same response (Kim et al., 2014). Preliminary studies on freshly enucleated eyes using a precision ocular injection device indicated that intracorneal injections can be achieved with a needle length of 650 µm and 650–750 µm in the pig and horse eye, respectively. A needle length of 1200 µm appeared appropriate for suprachoroidal delivery in both species (Walsh et al., 2015).

Light-Activated Drugs

Photodynamic therapy (PDT) is a light-induced system that has been developed to localize a photosensitizer in the target tissue, followed by its activation using light of a specific wavelength (Dougherty et al., 1998). Visudyne® (Novartis) is a liposomal formulation containing verteporfin, a photosensitizer, which is used in PDT to eradicate neovascular membranes associated with wet age-related macular degeneration in human patients (Thrimawithana et al., 2011). The drug also showed great potential in the treatment of periocular squamous cell carcinoma in horses (Barnes et al., 2010; Giuliano et al., 2014). Activation of verteporfin by a 689 nm wavelength light causes the production of singlet oxygen ($^1O_2$) and free radicals that leads to an apoptotic response in the target tissue, making PDT a useful procedure for treating both neoplastic and non-neoplastic ocular conditions (Bartlett, 2008). Because the highly cytotoxic $^1O_2$ has limited migration from its site of formation, sites of cell photodamage of PDT are closely related to the localization of the photosensitizer which should penetrate inside the target cells (Dougherty et al., 1998).

Corneal collagen crosslinking (CXL) is another kind of photooxidative technique, which was developed initially to treat keratoconus in human patients (O'Brart et al., 2011; Wollensak et al., 2003). This technique involves the combined action of topically applied riboflavin (vitamin B2) as a photosensitizer and irradiation of the cornea with ultraviolet-A (UV-A) light. The photochemical process creates free radicals to induce additional intrafibrillar and interfibrillar covalent bonds, bridging amino groups of stromal collagen fibrils, thereby increasing the corneal collagen fiber diameter and strengthening corneal tissue (Wollensak et al., 2004). The main indication for CXL in human ophthalmology has been the management of keratectasia formation, such as keratoconus, pellucid marginal degeneration, and post-keratomileusis (LASIK) ectasia (O'Brart et al., 2011; Salgado et al., 2011). Results of a prospective study in cats, dogs, and horses provided evidence in relation to efficacy and safety of CXL in the management of infectious and noninfectious melting disorders of the cornea in these species (Hellander-Edman et al., 2013; Pot et al., 2014).

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8.2

Clinical Pharmacology and Therapeutics

Part 2: Antibacterial Agents, Antifungal Agents, and Antiviral Agents

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Antibacterial Agents – General Principles of Therapy

The use of antibacterial agents is important in the successful management of ocular diseases, with general principles guiding the implementation of therapy. The most fundamental of these principles requires that the clinician have a solid understanding of each individual's condition, enabling him or her to determine whether antibiotic therapy is indeed indicated, and whether it is necessary either prophylactically or therapeutically. If prophylactic use is indicated, additional factors that should guide the selection of antibiotics include the spectrum of activity of the drug relative to organism(s) of concern, the potential for development of resistant organisms, and possible adverse reactions or toxicities. If therapeutic use is indicated, every attempt should be made to determine the causative organism(s) to enable targeted therapy with the most effective antibiotic agent available, while also considering the potential for development of resistance or adverse reactions or toxicities. Regardless of whether prophylactic or therapeutic administration is indicated, it is important that the route of administration selected will achieve therapeutic drug levels at the desired site of action while providing the lowest risk of side effects or complications to the patient. Additionally, drug–drug interactions should be considered, which may alter the therapeutic effectiveness of individual drugs or exacerbate toxicities or side effects.

The antibacterial effects of antibiotics are based upon structural or functional differences between bacterial and mammalian cells, which provide various degrees of selective toxicity. First among these is the presence of a cell wall in bacterial organisms, which is absent in mammalian cells. Cell wall-inhibiting antibiotics target an essential component of the cell wall, the peptidoglycan, impairing the integrity of the cell wall and leading to lysis. Antibiotics may also affect the bacterial cell membrane. However, structural similarities with mammalian cell membranes decrease the selectivity of such drugs and may increase toxicity to the recipient. Antibiotics may selectively target the bacterial ribosome, which differs in size and shape from mammalian ribosome, inhibiting bacterial protein synthesis. Inhibition of bacterial cell folic acid synthesis is an additional antibacterial mechanism, because bacterial cells synthesize their own folic acid whereas mammalian cells do not. Finally, the function of bacterial DNA gyrase or topoisomerase IV, enzymes absent in mammalian cells, may be inhibited.

The mechanism of action of a particular antibiotic in combination with the drug concentration reached at the site of infection results in either bactericidal (cell death) or bacteriostatic (decreased replication) effects. One advantage in the treatment of ocular infections is the ability of the route of administration (i.e., topical, subconjunctival, intracameral) to be tailored to maximize the antibacterial drug concentration at the desired site of action, thus increasing the potential for bactericidal effects while minimizing the potential for systemic toxicities. It is imperative to consider, however, that local ocular toxicities may occur in response to the specific drug or its vehicle when such targeted routes are employed. When selecting a particular antibiotic, bactericidal drugs should be used in patients with impaired defenses, because bacteriostatic drugs depend more upon interaction with the natural defenses of the host for maximal efficacy. The potential for synergistic or antagonistic effects should be considered when administering multiple drugs, and it is generally considered that bactericidal antibiotics should be combined with other bactericidal antibiotics, and bacteriostatic drugs should be combined with bacteriostatic drugs (Table 8.2.1).

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Table 8.2.1 Classification of antibiotics commonly used in veterinary ophthalmology.

Bacteriostatic	Bactericidal
Chloramphenicol	Aminoglycosides
Macrolides	Bacitracin
Sulfonamides	Cephalosporins
Tetracyclines	Fluoroquinolones
Trimethoprim	Gramicidin
	Penicillins
	Polymyxin B
	Vancomycin

Drugs That Inhibit Bacterial Cell Wall Synthesis

Drugs that inhibit bacterial cell wall synthesis include the penicillins, cephalosporins, bacitracin, and vancomycin.

Penicillins

Penicillins are composed of a thiazolidine ring and a β-lactam ring connected to a side chain. The side chain determines pharmacokinetic parameters, spectrum of activity, and susceptibility to destruction by gastric acid or β-lactamase enzymes, whereas the β-lactam ring is responsible for antibacterial activity by inhibiting bacterial transpeptidase enzymes (Yolton & Haesaert, 2008). Transpeptidases cross-link the polysaccharide chains to form the peptidoglycan portion of the cell wall, thus their inhibition results in absence of a complete cell wall and bacterial cell death. Bacteria may develop resistance to penicillins by altering their transpeptidases or by inactivating the β-lactam portion of the drug through production of β-lactamases. "Penicillinases" are the subgroup of bacterial β-lactamases that preferentially inactivate penicillins (vs. cephalosporins).

Penicillins may be broadly classified into four categories based on their antibacterial activity: agents with gram-positive activity, penicillinase-resistant agents, extended spectrum penicillins, and antipseudomonal penicillins (Yolton & Haesaert, 2008).

Agents with Gram-Positive Activity

The two primary members of this group are penicillin G (inactivated by gastric acid and thus administered parenterally) and penicillin V (orally administered). Unfortunately, these drugs are highly susceptible to organisms that produce β-lactamases, including most strains of *Staphylococcus aureus* and *Staphylococcus epidermidis*. There is a high prevalence of antibiotic resistance genes in *Staphylococcus pseudointermedius* isolated from the ocular surface of dogs, with more than 50% of the isolates resistant to penicillin (Kang et al., 2014). Additionally, *Streptococcus pneumoniae* and viridans streptococci are acquiring increasing resistance through altering their intrinsic transpeptidases (Drawz & Bonomo, 2010).

Relating to treatment of ocular diseases, the low lipophilicity of penicillin G restricts its passage through the blood–ocular barriers, thereby limiting its efficacy for intraocular infections (Mauger, 1994; Rowley & Rubin, 1970). The use of penicillins for treating ocular surface disease in people has been advocated. However, ocular surface irritation may result (Yolton & Haesaert, 2008). In cattle, administration of penicillin G topically or subconjunctivally, with or without added procaine, achieves therapeutic ocular surface or tear film drug levels, sustained for up to 67 hours (Abeynayake & Cooper, 1989a, 1989b; Binkhorst, 1987). In sheep, subconjunctival administration of procaine penicillin led to detectable drug levels in tears (Nouws & Konig, 1983). However, clinical efficacy versus *Moraxella bovis*, the primary agent of infectious bovine keratoconjunctivitis, as well as *Moraxella bovoculi* and *Moraxella ovis,* are variable (Allen et al., 1995; Eastman et al., 1998; George, 1990; Maboni et al., 2015). When considering use in the treatment of orbital infections, less than 40% of aerobic gram-positive and gram-negative isolates from dogs with orbital disease were susceptible to penicillin (Wang et al., 2009).

Penicillinase-Resistant Agents

Penicillinase-resistant drugs, including methicillin, oxacillin, cloxacillin, dicloxacillin, and nafcillin, are able to resist bacterial β-lactamases because of alterations to their chemical structures, thus making them effective against *S. aureus* and *S. epidermidis* infections. However, these bacteria have begun to acquire an alternate mechanism of resistance through modification of intrinsic transpeptidases, creating "methicillin-resistant" strains (i.e., methicillin-resistant *S. aureus* [MRSA]) that are resistant to all penicillins and cephalosporins, and frequently to other antibiotics as well (Yolton & Haesaert, 2008).

Extended-Spectrum Penicillins

Ampicillin and amoxicillin are the two members of this group, whose spectrum extends beyond gram-positive organisms to include gram-negative rods, and are inactivated by β-lactamases. However, addition of sulbactam to ampicillin and clavulanic acid to amoxicillin imparts resistance to β-lactamases by irreversibly binding the bacterial enzymes, making these two combinations more effective in the treatment of *S. aureus* and *S. epidermidis* infections.

Consistent with the expected spectrum of this group of penicillins, 100% of *Streptococcus equi* isolates from horses with bacterial keratitis were susceptible to ampicillin in two studies (Keller & Hendrix, 2005; Sauer et al., 2003), whereas a separate report noted susceptibility in six of 11 (55%) equine corneal isolates (Brooks et al., 2000). A study of antibiotic susceptibility of isolates from the ocular surface of older dogs found increasing resistance to both cloxacillin

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and amoxicillin-clavulanic acid among *Staphylococcus intermedius* but not *S. aureus* isolates (Hoekstra & Paulton, 2002). However, the clinical significance of this is unknown. Additionally, of the 50 strains of *Staphylococcus pseudointermedius* isolated from the ocular surface of dogs, most (94%) were susceptible to amoxicillin-clavulanic acid (Kang et al., 2014). In cats, orally administered amoxicillin-clavulanic acid was as clinically effective as orally administered doxycycline for the treatment of experimentally induced chlamydial conjunctivitis (Sturgess et al., 2001). Of aerobic bacterial isolates from dogs and cats with orbital disease, 78% and 100%, respectively, were susceptible to amoxicillin-clavulanic acid (Wang et al., 2009).

Antipseudomonal Penicillins

Carbenicillin, mezlocillin, piperacillin, and ticarcillin are effective against *Pseudomonas aeruginosa* and some *Proteus* and *Enterobacter* species, gram-negative organisms that are resistant to most other penicillins. Ticarcillin has shown *in vitro* efficacy versus gram-positive bacterial isolates from equine eyes with bacterial keratitis (Moore et al., 1995), as well as aerobic bacterial isolates from dogs and cats with orbital disease (Wang et al., 2009).

Side Effects and Contraindications of Penicillins

Penicillins are primarily known for inducing hypersensitivity reactions (type I, II, III, or IV) in susceptible individuals. Once such a reaction occurs, which may manifest in the dermatologic, hematologic, urogenital, or other systems, no further use of penicillins is advised. Penicillins may also alter the enteric microflora, producing gastrointestinal upset (vomiting, diarrhea, nausea). Prior hypersensitivity to any penicillin or a cephalosporin is the primary contraindication to use.

Cephalosporins

Cephalosporin antibiotics are composed of a dihydrothiazine and a β-lactam ring connected to a side chain. As with penicillins, cephalosporins interfere with peptidoglycan crosslinking in the formation of the bacterial cell wall, with the β-lactam ring providing antibacterial activity and the side chain determining spectrum of activity. Cephalosporins are inactivated by β-lactamases produced by some gram-negative bacteria. However, they are able to resist inactivation by the penicillinase subset of β-lactamases, such as those produced by *S. aureus*. The division of cephalosporins into generations is based upon the spectrum of activity conferred by various side chains.

First-Generation Cephalosporins

Cephalexin, cefadroxil, cefazolin, cephalothin, and cephradine are first-generation cephalosporins, all with good efficacy versus gram-positive organisms and only marginal efficacy versus gram-negative organisms. These cephalosporins are generally effective against *Streptococcus* spp. However, *S. pneumoniae* is developing increasing resistance in human ocular infections (Yolton & Haesaert, 2008). Administration of cefazolin subconjunctivally in human patients and rabbits produced therapeutic aqueous humor (AH) concentrations (Saunders & McPherson, 1980), whereas cephradine reached therapeutic AH levels after systemic administration in human patients (Axelrod & Kochman, 1981), indicating possible efficacy in the treatment of bacterial endophthalmitis. Cefazolin may be administered topically (100 mg/mL diluted in artificial tear formulations to 50 mg/mL and refrigerated) for the treatment of bacterial keratitis (Callegan et al., 1992).

Evaluating isolates from dogs and horses with bacterial keratitis, cephalothin shows good *in vitro* activity versus β-hemolytic *Streptococcus* (Brooks et al., 2000; Keller & Hendrix, 2005; Tolar et al., 2006) and *S. intermedius* (Tolar et al., 2006), with no efficacy versus *P. aeruginosa* (Keller & Hendrix, 2005; Tolar et al., 2006). Approximately 70% and 100% of aerobic bacterial isolates from both dogs and cats with orbital disease showed *in vitro* susceptibility to cefazolin and cephalothin, respectively (Wang et al., 2009). Although cefazolin may be administered topically, a significantly deleterious effect on the morphology and wound closure rates of cultured canine epithelial cells has been noted after exposure to 5–25 mg/mL cefazolin (Hendrix et al., 2001). Intravenous administration of cefazolin in dogs may result in therapeutic AH concentrations (Whelan et al., 2000), thus serving as a potential route of therapy for cases of bacterial endophthalmitis versus susceptible organisms.

Second-Generation Cephalosporins

Cefaclor, cefuroxime, cefoxitin, and cefotetan are second-generation cephalosporins, which have increased gram-negative activity relative to the first generation. Cefoxitin reaches therapeutic AH levels after systemic administration in human patients (Axelrod & Kochman, 1980). Among dogs and cats with orbital disease, 73% and 100% of isolates, respectively, were susceptible to cefoxitin (Wang et al., 2009).

Third-Generation Cephalosporins

Ceftiofur, cefotaxime, ceftriaxone, and ceftazidime are third-generation cephalosporins with increased activity versus enteric gram-negative bacteria. They have been used in human patients via intravitreal injection as a treatment for endophthalmitis (Kwok et al., 2002; Lim & Campochiaro, 1992; Penha et al., 2010). However, gram-positive bacteria causing endophthalmitis have shown increased resistance to third-generation cephalosporins such as ceftazidime, and combination empiric therapy is recommended (Kodati et al., 2017; Reddy et al., 2015). Aerobic bacterial isolates from dogs with orbital disease identified 100% susceptibility of isolates to ceftiofur (Wang et al., 2009).

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Fourth-Generation Cephalosporins

Cefepime has a broad spectrum of activity against both gram-positive and gram-negative organisms, including *Pseudomonas* spp. and other strains resistant to aminoglycosides and third-generation cephalosporins. Like cefazolin, buffered aqueous solution containing cefepime (1% and 5%) may be compounded for ophthalmic use, and is reported to remain stable for up to 2 weeks if stored at 4°C (Kodym et al., 2011).

Fifth-Generation Cephalosporins

Ceftobiprole and ceftaroline are promising drugs for the treatment of MRSA infections. These antibiotics have broad spectrum activity against gram-negative and gram-positive bacteria, and are FDA-approved for skin and soft tissue infections in human patients (Greninger et al., 2016).

Side Effects and Contraindications

Hypersensitivity reactions are the most common side effect after administration of cephalosporins. Cross-hypersensitivity is more likely to occur between penicillins and first-generation cephalosporins, so patients with a known hypersensitivity to penicillins may be able to safely take a later-generation cephalosporin. Alterations in the enteric microflora may lead to gastrointestinal upset (vomiting, diarrhea, nausea), as well as vitamin K deficiency and subsequent bleeding abnormalities. Renal impairment may also develop in patients with a predisposition (i.e., concurrent aminoglycoside administration, previous renal disease) (Yolton & Haesaert, 2008). The administration of intravenous ceftriaxone to two horses experimentally infected with *Borrelia burgdorferi* caused anaphylactic reactions which led to colic syndrome and laminitis (Basile et al., 2015).

Bacitracin

Bacitracin inhibits bacterial cell wall synthesis by inhibiting the movement of a peptidoglycan precursor from the cytoplasm through the cell membrane. Its spectrum of action is primarily gram-positive, with good activity versus *S. intermedius* isolates from dogs with bacterial keratitis (Tolar et al., 2006) and β-hemolytic *S. equi* isolates from dogs and horses with bacterial keratitis (Brooks et al., 2000; Sauer et al., 2003; Tolar et al., 2006) (Table 8.2.2).

Bacitracin is a common component of triple antibiotic ophthalmic ointments, but is unstable in solution. Its combination with neomycin and polymyxin B (both having greater gram-negative efficacy) produces a good broad-spectrum preparation commonly used for prophylaxis (corneal ulcerations) or therapy (nonspecific ocular surface infections). Bacitracin has no appreciable transcorneal penetration, and therefore is of limited value in deep corneal or intraocular infections (Mauger, 1994).

Side Effects and Contraindications

The primary side effect of bacitracin that is a potential concern is a local hypersensitivity reaction, and patients with a history of such a reaction should not receive preparations containing bacitracin. It is not administered systemically because of nephrotoxicity (Yolton & Haesaert, 2008).

Vancomycin

Vancomycin inhibits bacterial cell wall synthesis by inhibiting incorporation of the peptidoglycan into the cell wall (Howden et al., 2010). It is effective versus gram-positive organisms, particularly *Staphylococcus* spp. (including MRSA) (Kotlus et al., 2006) and *Streptococcus* spp., as well as *Clostridium difficile*. It is extremely important to note, however, that resistance to vancomycin is developing among MRSA isolates (Appelbaum, 2006; Hiramatsu et al., 1997) as well as among enterococcal organisms also resistant to β-lactam antibiotics (Murray, 1997). Because of its spectrum of activity and the development of resistance among organisms highly resistant to other antibiotics, it is imperative to exercise extreme caution in the use of vancomycin in veterinary patients.

Ophthalmic use of vancomycin has included topical administration for infectious keratitis and intraocular administration for bacterial endophthalmitis. Although there is no commercially available ophthalmic formulation, vancomycin (0.1%–0.5%) is the current gold standard topical therapy, and drug of last resort, in cases of MRSA keratitis in human patients (Eguchi et al., 2009; Tas et al., 2013). Vancomycin is widely used in the treatment of postoperative and posttraumatic endophthalmitis as an intravitreal injection (1 mg) (Major et al., 2010; Pijl et al., 2010), or continuous infusion during pars plana vitrectomy (Rejdak et al., 2016).

Side Effects and Contraindications

The primary toxicities associated with parenteral, long-term vancomycin therapy in human patients include ototoxicity and nephrotoxicity, which may produce a permanent deafness or fatal uremia. Vancomycin is contraindicated in patients with a known hypersensitivity to it.

Drugs That Disrupt the Bacterial Cell Membrane

As bacterial and mammalian cell membranes are quite similar, few antibiotics are able to selectively and effectively target this cellular component without inducing patient toxicity. Polymyxin B and gramicidin are the two most readily used.

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Table 8.2.2 Recommended ophthalmic antibiotic choices based on *in vitro* susceptibility of organisms isolated from clinical bacterial keratitis cases. Antibiotic (# resistant/total # isolates evaluated, % resistant in reference indicated).

	Canine			Equine		
Organism	**Tolar et al. (2006)**	**Ledbetter et al. (2007a)**	**LoPinto et al. (2015)**	**Brooks et al. (2000)[a]**	**Sauer et al. (2003)[a]**	**Keller & Hendrix (2005)**
Staphylococcus intermedius	Bacitracin (0/30, 0%) Chloramphenicol (1/34, 3%) Ciprofloxacin (0/9, 0%) Neomycin (2/31, 6%) Polymyxin (1/31, 3%) Tobramycin (3/31, 10%)	N/A	N/A	N/A	N/A	N/A
Methicillin-resistant *Staphylococcus* spp.	N/A	N/A	Amikacin (0/17, 0%) Chloramphenicol (0/17, 0%) Gentamicin (0/17, 0%) Neomycin (5/17, 29%)	N/A	N/A	N/A
Streptococcus spp.	Bacitracin (0/19, 0%) Chloramphenicol (0/19, 0%) Ciprofloxacin (0/3, 0%)	N/A	N/A	Bacitracin (0/11, 0%) Chloramphenicol (0/11, 0%)	Bacitracin (0/12, 0%) Chloramphenicol (0/13, 0%) Enrofloxacin (2/13, 15%)	Chloramphenicol (0/17, 0%) Ciprofloxacin (0/5, 0%) Erythromycin (1/17, 6%) Gentamicin (3/17, 18%) Tetracycline (2/17, 12%)
Pseudomonas aeruginosa	Ciprofloxacin (1/15, 7%) Gentamicin (0/25, 0%) Neomycin (3/22, 14%) Polymyxin (0/22, 0%) Tobramycin (0/22, 0%)	Ciprofloxacin (0/27, 0%) Ofloxacin (2/27, 7%) Levofloxacin (0/27, 0%) Gatifloxacin (1/27, 4%) Moxifloxacin (3/27, 11%)	N/A	N/A	Polymyxin (0/14, 0%) Neomycin (4/14, 29%) Enrofloxacin (0/14, 0%)	Ciprofloxacin (0/6, 0%) Gentamicin (0/6, 0%) Neomycin (0/3, 0%) Polymyxin (0/2, 0%) Tobramycin (0/2, 0%)

[a] Fluoroquinolones available as ophthalmic preparations were not evaluated.

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Polymyxin B

Polymyxin B disrupts bacterial cell membrane phospholipids, increasing cell permeability and leading to cell death. Its spectrum is limited to gram-negative organisms, with good activity versus *P. aeruginosa* isolates from horses and dogs with bacterial keratitis (Keller & Hendrix, 2005; Sauer et al., 2003; Tolar et al., 2006) (Table 8.2.2). Its penetration through an intact corneal epithelium is poor (Mauger, 1994). Following topical ocular administration, local hypersensitivity reactions may occur, and patients exhibiting such a reaction should not receive the drug subsequently. Although a causal association has not been proven, anaphylactic events after application of ophthalmic medications containing polymyxin B have been reported in cats, with 8/61 cases in one retrospective study resulting in death within minutes after application of the antibiotic (Hume-Smith et al., 2011). Therefore, topical medications containing polymyxin B should be used with caution in feline patients.

Gramicidin

Gramicidin alters cell membrane permeability, and its spectrum is directed toward gram-positive organisms. Its stability in solution enables its substitution for bacitracin in triple antibiotic ophthalmic preparations. In combination with neomycin and polymyxin B at various concentrations lower than commercially available preparations, gramicidin deleteriously altered morphology and wound healing of cultured canine epithelial cells, although the overall effects were less than those of cefazolin, ciprofloxacin, and gentamicin (Hendrix et al., 2001). Like bacitracin, it is not administered systemically because of toxicities (hemolytic anemia) (Mauger, 1994).

Drugs That Affect Bacterial Protein Synthesis

This group of antibiotics includes aminoglycosides, tetracyclines, oxazolidinones, macrolides, lincosamides, and chloramphenicol.

Aminoglycosides

Aminoglycosides inhibit the 30S bacterial ribosome translation of mRNA into protein and are administered topically or parenterally because of poor oral absorption. In general, the spectrum of activity is strong versus gram-negative organisms (*P. aeruginosa*, *Proteus*, *Escherichia coli*, *Enterobacter*, etc.) (Shakil et al., 2008), whereas efficacy versus gram-positive organisms is restricted to *S. aureus* (Kotlus et al., 2006), with the exception of MRSA. Anaerobic bacteria are resistant to aminoglycosides because uptake of drug into the cell requires energy, which anaerobes are less able to provide. Acquired resistance to aminoglycosides by aerobic bacteria may develop through deactivation of the drug or reduction of its intracellular concentrations, or alteration of the ribosomal target or binding site (Shakil et al., 2008). An additive or synergistic effect may be achieved when an aminoglycoside is used in combination with a β-lactam antibiotic (Callegan et al., 1992; Helm et al., 1997) or vancomycin (Tsuji & Rybak, 2005). However, β-lactam antibiotics may inactivate aminoglycosides, so combination of drugs into the same vial should be avoided when coadministering these two classes (Mauger, 1994).

Neomycin

Neomycin, a component of common ophthalmic triple-antibiotic preparations, is primarily used for prophylaxis in superficial corneal ulceration, or for nonspecific treatment of ocular surface infections. Its primary side effect is contact hypersensitivity, and therefore is contraindicated in patients with a history of such a reaction. It has limited to no corneal penetration in the presence of an intact corneal epithelium (Rowley & Rubin, 1970).

Consistent with general aminoglycoside susceptibility patterns, *S. intermedius* isolates from dogs with bacterial keratitis are highly susceptible to neomycin (Tolar et al., 2006), methicillin-resistant Staphylococcus corneal isolates are mostly susceptible (71%) (LoPinto et al., 2015), *Pseudomonas* isolates show good susceptibility (Keller & Hendrix, 2005; Sauer et al., 2003; Tolar et al., 2006), and β-hemolytic *Streptococcus* isolates are highly resistant (Brooks et al., 2000; Keller & Hendrix, 2005; Sauer et al., 2003; Tolar et al., 2006) (see Table 8.2.2).

Gentamicin

Gentamicin, administered topically or subconjunctivally, is used in the treatment of infectious keratitis, particularly that caused by *P. aeruginosa*. The commercially available concentration (3 mg/mL) or fortified solutions (13.6 mg/mL) may be utilized in the presence of infection. The ability of gentamicin to provide prophylactic protection is limited because of its gram-negative spectrum of activity, whereas primary agents of concern from the ocular surface tend to be gram-positive organisms. Additionally, in rabbit models of corneal wound healing and in canine corneal epithelial cell cultures, gentamicin in various concentrations, including less than the commercially available preparation, deleteriously affected wound healing (Hendrix et al., 2001; Nelson et al., 1990; Petroutsos et al., 1983; Stern et al., 1983). Gentamicin achieves limited transcorneal penetration in normal corneas. However, therapeutic levels are more readily reached in the presence of inflammation (Insler et al., 1987; Rootman et al., 1992). Subconjunctival injection may increase ocular drug levels, although systemic absorption has been reported, emphasizing the need for awareness of

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possible confounding systemic conditions (Mathalone & Harden, 1972; Trope et al., 1979).

Reports vary significantly regarding development of resistance to gentamicin, either indicating increased resistance of *P. aeruginosa* and *S. equi* isolates from horses with infectious keratitis (Sauer et al., 2003), or indicating no change in resistance (Keller & Hendrix, 2005). Isolates from dogs with bacterial keratitis showed no overall increase in resistance between 1993 and 2003. However, as would be expected, β-hemolytic *Streptococcus* strains were more likely to be resistant to gentamicin than were *S. intermedius* or *Pseudomonas* strains (Tolar et al., 2006) (see Table 8.2.2). In a study evaluating the prevalence of methicillin-resistant *Staphylococcus* species (MRS) isolated from dogs with bacterial keratitis, 100% of the MRS isolates were susceptible to gentamicin (LoPinto et al., 2015). With regard to the treatment of infectious keratoconjunctivitis caused by *Moraxella bovis*, *M. bovoculi*, and *M. ovis*, gentamicin has one of the best susceptibility profiles for all three species (Maboni et al., 2015).

Tobramycin

The spectrum of activity and indications for use of tobramycin are similar to those of gentamicin. Nevertheless, a recent study indicates that its efficacy versus *Pseudomonas* isolates from horses with bacterial keratitis has declined (Sauer et al., 2003), whereas *Pseudomonas* isolates from dogs with bacterial keratitis were uniformly susceptible (Tolar et al., 2006). As would be expected, efficacy versus *Streptococcus* isolates is very poor (Brooks et al., 2000; Keller & Hendrix, 2005; Sauer et al., 2003; Tolar et al., 2006), whereas efficacy versus *S. intermedius* isolates is good (Tolar et al., 2006) (see Table 8.2.2). Subconjunctival administration results in therapeutic intraocular drug levels. However, systemic administration is generally not useful for ocular infections (Gorden & Cunningham, 1982; Petounis et al., 1978; Woo et al., 1985). Reports regarding epithelial toxicity of tobramycin are conflicting, with tissue culture assays showing minimal negative effect (Hendrix et al., 2001; Nelson et al., 1990), whereas use of an *in vivo* rabbit model of corneal wounding identified a significant prolongation in time to healing of 0.3% and 1.36% tobramycin relative to 5% cefazolin (Stern et al., 1983).

Amikacin

Amikacin is not available as a topical ophthalmic preparation. Nonetheless, its administration topically has led to therapeutic corneal levels which may be useful in treating patients with ocular infections caused by gram-negative bacilli that are resistant to gentamicin or tobramycin (Regnier, 2007). Subconjunctival and parenteral administration produce highly variable intraocular levels (El-Massry et al., 1996; Radda et al., 1983). Of the aminoglycosides, amikacin and kanamycin are the least toxic to the retina, indicating their potential in the treatment of endophthalmitis (D'Amico et al., 1985).

Side Effects and Contraindications

Auditory and vestibular neurotoxicity, as well as nephrotoxicity, may result from administration of aminoglycosides systemically. Hypersensitivity reactions may also occur in patients who have received topical aminoglycosides, with crossreaction among agents possible. Intravitreal injection of gentamicin is toxic to the retina and the ciliary body, and in fact forms the basis for a treatment for end-stage glaucoma (Gelatt et al., 2007). Intravitreal injection of gentamicin in eyes with chronic glaucoma resulted in detectable plasma levels in dogs (Rankin et al., 2016). Caution should be exercised when administering intravitreal gentamicin in small patients and those with renal dysfunction.

Tetracyclines

Like the aminoglycosides, tetracyclines interact with the 30S ribosomal subunit to inhibit bacterial mRNA translation. They may be classified as short-acting (tetracycline, oxytetracycline), intermediate-acting (demeclocycline), or long-acting (doxycycline, minocycline). Although they have a broad spectrum of bacterial coverage, their clinically relevant spectrum of activity is relatively narrow, due in part to development of efflux mechanisms within bacteria that actively pump drug out of the cells, creating resistant strains. Activity versus rickettsial organisms, *Borrelia burgdorferi*, *Mycoplasma* spp., *Chlamydophila* spp., and *Moraxella* spp., is consistently strong, whereas *Staphylococcus* spp. and *Streptococcus* spp. may be developing increased resistance (Breitschwerdt et al., 1999; Keller & Hendrix, 2005; Maboni et al., 2015). *P. aeruginosa* is generally considered resistant to tetracyclines, which has been supported by an evaluation of isolates from horses with bacterial keratitis (Keller & Hendrix, 2005) (see Table 8.2.2). Tetracyclines may be administered topically, orally, or parenterally in patients with ocular disease, with oral administration beneficial for organisms that sequester in non-ocular sites (*Chlamydophila felis* or *Mycoplasma* spp. in cats, *M. bovis* in cattle) (Donati et al., 2005; Sparkes et al., 1999), as well as for administration to large populations of cattle. When administered systemically, doxycycline concentrations have been detected in the tear film of several species, including cats, dogs, horses, and northern elephant seals (Baker et al., 2008; Collins et al., 2016; Freeman et al., 2013; Hartmann et al., 2008). With the exception of doxycycline, orally administered tetracyclines are generally poorly absorbed from the gastrointestinal tract.

Additional pharmacologic benefit provided by the tetracyclines is their ability to inhibit matrix metalloproteinases and other mediators of inflammation that digest corneal proteins leading to keratomalacia (D'Agostino et al., 1998; Durson et al., 2001; Hanamaaijer et al., 1998; Kuzin et al., 2001; Solomon et al., 2000). Doxycycline is the most effective matrix metalloproteinase inhibitor through its ability to chelate zinc, a necessary cofactor for many enzymes

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(Griffin et al., 2010). Tetracyclines also act as reactive oxygen species scavengers and have antiapoptotic and anti-inflammatory effects, all leading to clinical improvement beyond that expected with their antibacterial spectra (Griffin et al., 2010).

In dogs with refractory corneal ulcers treated with various combinations of systemically administered doxycycline (5 mg/kg PO q 12 hours), topically administered oxytetracycline/polymyxin B (q 8 hours), systemically administered cephalexin (22 mg/kg PO q 12 hours), or topically administered neomycin/polymyxin B/bacitracin (q 8 hours), a significantly shorter time to healing was reported in dogs receiving topical oxytetracycline (Chandler et al., 2010). Additionally, a nonsignificant trend in shorter time to healing in dogs receiving oral doxycycline relative to other medication combinations was noted, with both effects potentially attributable to increased expression of prohealing transcription factors within epithelial cells, induced by modulating effects of tetracyclines (Chandler et al., 2010).

In cats, oral doxycycline (5 mg/kg PO q 12 hours or 10 mg/kg PO q 24 hours) has been shown to more effectively control chlamydiosis than topical administration of chlortetracycline (Sparkes et al., 1999). However, it must be given in conjunction with water and/or food to avoid esophageal stricture (German et al., 2005). Additionally, long-term therapy is often necessary to eliminate the organism, as determined by real-time polymerase chain reaction (PCR) on conjunctival swab samples of experimentally infected cats (Dean et al., 2005).

In horses, results are conflicting regarding the intraocular penetration of doxycycline after oral administration. In one study, administration of doxycycline (10 mg/kg PO q 12 hours, for 5 days) to normal horses did not produce detectable AH drug levels and led to subtherapeutic (vs. *Leptospira* spp.) vitreous humor levels on the fifth day (Gilmour et al., 2005). In contrast, administration of a higher dose (20 mg/kg PO q 12 hours, for 5 doses), also to normal horses, produced detectable AH levels (Davis et al., 2006a).

In cattle, an intramuscular injection was clinically successful in treating *M. bovis* ocular disease (Smith & George, 1985), whereas therapeutic tear film drug levels were maintained for up to 72 hours after a single subconjunctival injection of a long-acting oxytetracycline formulation (George et al., 1985). Oxytetracycline is usually the first choice of antimicrobial treatment for infectious bovine keratoconjunctivitis. Although reports of strains of *M. bovis* and *M. ovis* resistant to oxytetracycline exist (Maboni et al., 2015; Shryock et al., 1998), oral and parenteral treatment remains effective overall (Eastman et al., 1998).

Side Effects and Contraindications

Tetracyclines are known to induce photosensitivity reactions, gastrointestinal upset, and discoloration of teeth during development. They also may interact with other drugs or compounds, causing potentially significant variation in absorption and therefore effect. Administration with food may decrease signs of gastrointestinal upset. However, this may significantly impact the absorption of tetracyclines, with the exception of doxycycline. Tetracyclines form complexes with divalent cations (iron, calcium, magnesium, aluminum), which markedly decreases absorption from the gastrointestinal tract; this is particularly important when considering mixing tetracyclines with molasses (very high iron content) for administration to horses.

Oxazolidinones

This class of synthetic antibiotics is active against a large spectrum of gram-positive bacteria, including methicillin- and vancomycin-resistant isolates, and anaerobes (Bozdogan & Appelbaum, 2004). Linezolid is the first oxazolidinone available that acts by inhibiting protein synthesis at the initial phase by binding to the 50S ribosomal subunit. Topical linezolid (1–2 mg/mL) showed activity against MRSA keratitis in rabbits that was comparable to vancomycin (Tas et al., 2013).

Macrolides and Lincosamides

Erythromycin, azithromycin, and clarithromycin are macrolide antibiotics that bind the 50S bacterial ribosomal subunit, preventing elongation of the peptide chain in bacterial mRNA translation. They are primarily effective versus gram-positive bacteria. However, their ability to accumulate intracellularly makes them effective treatments for *Chlamydophila*, *Mycoplasma*, and *Bartonella* infections. Organisms may acquire resistance by altering their ribosomal RNA, resulting in reduced binding affinity of the drug.

Erythromycin

Organisms pertinent to veterinary ophthalmology effectively treated with erythromycin include *Mycoplasma* spp. and *Chlamydophila* spp. Isolates of *S. equi* from horses with bacterial keratitis were highly susceptible to erythromycin (Keller & Hendrix, 2005) (see Table 8.2.2). In contrast, various aerobic bacteria species isolated from dogs and cats with orbital disease identified only 40% susceptibility in dogs (9 of 22 isolates), and 0% susceptibility in cats (0 of 3 isolates). Conversely, differences in susceptibility patterns of gram-positive versus gram-negative organisms were not reported (Wang et al., 2009).

Azithromycin

Azithromycin is a newer derivative of erythromycin that is rapidly absorbed after oral administration and has an increased spectrum of activity toward gram-negative organisms, in particular *B. burgdorferi* and *Bartonella henselae*, relative to that of erythromycin (Peters et al., 1992). Emerging information indicates that its clinical efficacy in veterinary

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medicine is relatively poor, however. Experimental inoculation of dogs with *Rickettsia rickettsii* followed by treatment with azithromycin (3 mg/kg PO q 24 hours) documented a poorer clinical response than that achieved with systemic doxycycline or trovafloxacin therapy (Breitschwerdt et al., 1999). A recent report evaluating its use in cats indicated that azithromycin had lower efficacy versus *Bartonella* than pradofloxacin or enrofloxacin (Biswas et al., 2010b), and that resistance to azithromycin develops with relative ease (Biswas et al., 2010a). It has also been advocated as systemic treatment for disease caused by *Chlamydophila psittaci* in cats (50 mg PO q 24 hours × 21 days) (Ketring et al., 2004). However, its efficacy has been shown to be lower than that of doxycycline (Owen et al., 2003). Topical administration of 2 mg/mL or 4 mg/mL azithromycin to rabbits reached measurable corneal tissue levels (Kuehne et al., 2004), whereas administration of a 1% solution reached sustained therapeutic conjunctival tissue levels but subtherapeutic AH levels (Stewart et al., 2010). Studies of the pharmacokinetics of topical ocular azithromycin in other animal species have not been reported.

Clarithromycin

Clarithromycin is a newer derivative of erythromycin and is not inactivated by gastric acid (as erythromycin is), thus making it a more viable option for oral administration in appropriate cases. A report of its use in a cat with ocular manifestations of systemic *Mycobacterium simiae* infection documented successful resolution in combination with enrofloxacin and rifampicin (Dietrich et al., 2003). Additionally, clarithromycin had lower minimum inhibitory concentrations (MICs) versus *Bartonella* spp. isolates from cats in comparison to other macrolides (Dorbecker et al., 2006). In contrast to topically administered azithromycin, clarithromycin (10 mg/mL) did not reach measurable corneal tissue levels in rabbits (Kuehne et al., 2004).

Clindamycin

Clindamycin is a lincosamide antibiotic, which also has inhibitory effects on the 50S ribosomal subunit of susceptible bacteria. It has good effect in the treatment of cats infected with *Toxoplasma gondii* (Lappin, 2010) and has been shown to prevent repeat shedding of oocysts in experimentally infected cats, even under conditions of immunosuppression (Malmasi et al., 2008). Of aerobic bacterial isolates from dogs and cats with orbital disease, 50% (6/12) and 0% (0/2), respectively, were sensitive to clindamycin (Wang et al., 2009).

Side Effects and Contraindications

Gastrointestinal irritation is the most common side effect reported in people receiving oral macrolides. Erythromycin has also been linked to cholestatic hepatitis in people, as well as hearing loss. Hypersensitivity reactions also may occur.

Chloramphenicol

Chloramphenicol also inhibits the 50S bacterial ribosomal subunit. It is broad-spectrum, with activity versus *Rickettsia*, *Chlamydophila*, and *Mycoplasma*, as well as gram-positive and gram-negative agents, with the exception of *P. aeruginosa*. Consistent with these general patterns, *Staphylococcus* and *Streptococcus* isolates from dogs with bacterial keratitis were susceptible to chloramphenicol whereas *Pseudomonas* isolates were resistant (Tolar et al., 2006; Kang et al., 2014), with the same trends in horses with bacterial keratitis (Brooks et al., 2000; Keller & Hendrix, 2005; Sauer et al., 2003) (see Table 8.2.2). All MRS isolates (100%) from dogs with bacterial keratitis were susceptible to topical and systemic chloramphenicol (LoPinto et al., 2015), and this medication should be considered for use in veterinary patients before vancomycin. Topically administered chloramphenicol penetrates poorly through the cornea in eyes with intact corneal epithelium (Rowley & Rubin, 1970), with the ointment formulation providing greater corneal and AH drug levels (Ismail & Morton, 1987). Chloramphenicol's effects on morphology and wound closure in canine corneal epithelial cell culture were less deleterious than those of cefazolin or ciprofloxacin (Hendrix et al., 2001).

Side Effects and Contraindications

The primary restriction to the use of chloramphenicol is the development of two variants of hematopoietic disorders, which have occurred after both systemic and topical ocular administration of the drug. A dose-related toxic effect may lead to bone marrow depression associated with inhibited mitochondrial protein synthesis, and this may be reversed when therapy is discontinued. The more severe reaction is a fatal aplastic anemia, which is considered to be an idiosyncratic reaction, rather than a predictable toxicity. This may occur weeks to months after discontinuation of therapy (Yolton & Haesaert, 2008), and the risk with topical ocular administration is very low (Laporte et al., 1998).

Drugs That Alter Bacterial Folate Metabolism

These antibiotics include sulfonamides, pyrimethamine, and trimethoprim, and are frequently used in combination with one another because of additive effects. A bacteriostatic effect is achieved through inhibition of bacterial folate production, a necessary cofactor for cellular functions. In the production of folate, sulfonamides competitively inhibit the enzyme dihydropteroate synthase, involved in the conversion of para-aminobenzoic acid (PABA) to dihydrofolic acid, whereas pyrimethamine and trimethoprim reversibly inhibit the enzyme dihydrofolate reductase, involved in the reduction of dihydrofolic acid to tetrahydrofolic acid. The first step in the

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pathway is particular to bacterial cells, leading to minimal host toxicity. Toxicity may occur with the second step, because mammalian cells also have dihydrofolate reductase. However, the binding affinity of trimethoprim is much stronger for the bacterial form of the enzyme, limiting toxicity.

The spectrum of activity generally includes gram-positive organisms with some gram-negative organisms (Huovinen, 1997). However, resistance mechanisms acquired by bacteria are numerous, including overproduction of PABA, reduction in enzyme affinity or bacterial permeability to the drugs, and inactivation of the drugs by bacteria (Huovinen, 1997; Skold, 2001). The activity of trimethoprim-sulfa combinations versus *Streptococcus* isolates from horses with ocular disease is good (Brooks et al., 2000; Keller & Hendrix, 2005; Sauer et al., 2003). However, *Pseudomonas* isolates have been documented to be 100% resistant (Keller & Hendrix, 2005; Sauer et al., 2003). Ninety-six percent and 100% of aerobic bacterial isolates from dogs and cats with orbital disease were susceptible to trimethoprim-sulfamethoxazole (Wang et al., 2009). Transcorneal penetration of topically administered sulfonamides and intraocular penetration of systemically administered sulfonamides is highly variable among species and individual drugs. However, orally administered trimethoprim-sulfadiazine has been noted to maintain therapeutic aqueous and vitreous humor levels in dogs (Sigel et al., 1981).

Side Effects and Contraindications

Systemic reactions may occur with the use of sulfonamides, including gastrointestinal disturbances, allergic skin reactions, renal complications, and blood dyscrasia, as may local reactions such as irritation and dermatitis (Trepanier, 2004).

In dogs, multiple sulfonamides are known to cause keratoconjunctivitis sicca, postulated to be associated with a direct toxic effect on lacrimal acinar cells by the nitrogen-containing pyridine and pyrimidine rings (Slatter, 1973). This reaction may occur in a dose-dependent or idiosyncratic manner and is reproducible experimentally by structurally similar salicylic acid compounds (Barnett & Joseph, 1987; Trepanier, 2004). The estimated incidence is 15%–25% in dogs treated with sulfas, and may occur with variable dosing levels and durations, developing potentially months to years after treatment (Berger et al., 1995; Trepanier, 2004). Frequently, dogs have other signs of toxicity (i.e., hepatopathy). If discontinued early, there is a chance of recovering adequate tear production (Trepanier et al., 2003). In contrast to dogs, evaluation of the effect of long-term systemic trimethoprim-sulfadiazine therapy in horses did not identify a reduction in tear production in that species (Rothschild et al., 2004).

Sulfonamides are contraindicated in patients with a known hypersensitivity to any members of the folate metabolism inhibitor class of antibiotics, as well as in patients with a history of blood dyscrasia. Although not necessarily a contraindication for the use of sulfonamides, it should be noted that any other drug that has PABA as part of its molecular structure may interact with and therefore decrease efficacy of sulfonamides, as may purulent diseases (purulent exudate provides an exogenous source of PABA for bacteria).

Drugs That Affect Bacterial DNA Synthesis

Nalidixic acid and related fluoroquinolones (FQNs) inhibit DNA gyrase (topoisomerase II) and/or topoisomerase IV, enzymes specific to bacteria that maintain the bacterial DNA superhelix during replication, thus exerting bactericidal effects (Blondeau, 2004). The spectrum of activity of FQN varies with generation (first, second, third, or fourth, although the classification scheme is not standardized), with newer generations generally providing greater gram-positive efficacy through greater inhibition of topoisomerase IV (Blondeau, 2004). Resistance develops through bacterial enzyme modification or reduction in bacterial drug concentration through decreased cell membrane permeability or through multidrug resistant membrane-associated efflux pumps that actively remove drug from the bacterial cell (Hirai et al., 1987; Hooper, 1999).

First-Generation Fluoroquinolones

Nalidixic acid is considered the first-generation FQN and has moderate gram-negative and gram-positive activity, with weak activity versus *P. aeruginosa* (Rubin et al., 2008).

Second-Generation Fluoroquinolones

Second-generation FQNs generally include lomefloxacin, norfloxacin, enrofloxacin, ciprofloxacin, and ofloxacin. Their spectrum of activity is strong toward *P. aeruginosa* and some gram-positive organisms. However, increasing resistance is developing, particularly by *Streptococcus* spp. and *Pseudomonas* spp. in human ophthalmic patients (Chaudhry et al., 1999; Miller & Alfonso, 2004). Despite increased resistance, fluoroquinolones remain a reasonable first choice for empirical therapy in most cases of suspected bacterial keratitis in human patients because they are equally effective as combined fortified antibiotics (Hanet et al., 2012).

In dogs with bacterial keratitis, 100% of *Staphylococcus* spp. and *Streptococcus* spp. isolates were susceptible to ciprofloxacin and enrofloxacin (Tolar et al., 2006), whereas only 35% of methicillin-resistant *Staphylococcus* corneal isolates from dogs with keratitis were susceptible to ciprofloxacin (LoPinto et al., 2015). Susceptibility of *Pseudomonas* isolates from dogs with bacterial keratitis to ciprofloxacin ranged from 93% (Tolar et al., 2006) to 100% (Ledbetter et al., 2007a),

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with 100% susceptible to norfloxacin (Ledbetter et al., 2007a), 93% susceptible to ofloxacin (Ledbetter et al., 2007a), and 87% susceptible to enrofloxacin (Tolar et al., 2006). In horses with bacterial keratitis, 85% of *Streptococcus* spp. isolates and 100% of *Pseudomonas* isolates were susceptible to enrofloxacin (Sauer et al., 2003) (Table 8.2.2). Lomefloxacin ophthalmic solution (0.3%) was safe and effective for the treatment of bacterial keratitis and conjunctivitis in 54/64 horses, with the majority of cases culturing *Staphylococcus* spp. and *Streptococcus* spp. (Hidaka et al., 2015).

Comparison of the pharmacokinetics of topically applied ciprofloxacin and ofloxacin in dogs prior to cataract surgery identified that one drop every 15 minutes (eight drops total) of ciprofloxacin resulted in significantly lower AH concentrations than those resulting from the same treatment protocol for ofloxacin (Yu-Speight et al., 2005). The concentrations of ofloxacin achieved were much more likely to be therapeutic against potential ocular pathogens *E. coli*, *Bacillus* spp., and *Staphylococcus* spp. than were the concentrations of ciprofloxacin. In horses, intravenous administration of enrofloxacin (7.5 mg/kg once daily for 4 days) resulted in potentially therapeutic AH concentrations relative to reported MICs for *Leptospira* serovars (Divers et al., 2008).

Third-Generation Fluoroquinolones

Third-generation FQNs include sparfloxacin, gemifloxacin, and levofloxacin. Comparison of *in vitro* activity of levofloxacin with ciprofloxacin and ofloxacin toward *Streptococcus* isolates from human patients with keratitis and endophthalmitis reveals variable results, with levofloxacin either stronger (Miller & Alfonso, 2004) or comparable (Ramakrishnan et al., 2010). *P. aeruginosa* isolates from dogs with bacterial keratitis were 100% susceptible to levofloxacin (Ledbetter et al., 2007a) (see Table 8.2.2). Topical gemifloxaxin for the treatment of experimental *Staphylococcus aureus* keratitis in rabbits significantly lowered clinical severity and reduced the bacterial load recovered from the corneas (Wu et al., 2012).

Fourth-Generation Fluoroquinolones

Fourth-generation FQNs include gatifloxacin, moxifloxacin, and besifloxacin. Their gram-positive spectrum is increased relative to that of earlier FQN. However, their efficacy versus *Pseudomonas* spp. may be limited (Duggirala et al., 2007; Schlech & Alfonso, 2005; Soussy et al., 2003). All three show favorable therapeutic profiles in experimental ocular infections in rabbits (Norcross et al., 2010; Proksch & Ward, 2010; Sanders et al., 2010). Of 27 *P. aeruginosa* isolates from dogs with bacterial keratitis, one and three were resistant to gatifloxacin and moxifloxacin, respectively (Ledbetter et al., 2007a) (Table 8.2.2). Although development of resistance to fourth-generation FQN is more difficult because of the requirement that mutations in both topoisomerase II and topoisomerase IV enzymes develop, it is currently recommended that use of these agents be restricted to serious ocular surface bacterial infections. However, an argument has been presented that use of these agents early in the course of infection will minimize the development of resistance (Smith et al., 2002).

In addition to potentially marked variation in the spectrum of individual FQNs, the intraocular penetration varies as well. In human patients and rabbits, moxifloxacin has consistently shown superior intraocular penetration to other FQN (Solomon et al., 2005; Soussy et al., 2003; Yagci et al., 2007). In normal horses, moxifloxacin achieved greater AH concentrations than did ciprofloxacin after repeated topical ocular administration in two separate studies (Clode et al., 2010; Westermeyer et al., 2011), while also reaching statistically significantly greater corneal tissue concentration (Westermeyer et al., 2011). Measurable concentrations of both ciprofloxacin and moxifloxacin were detected in the tears of normal horses after repeated topical administration, and although statistical significance was not reached, likely because of wide interindividual variation, moxifloxacin showed a tendency toward greater concentrations (Westermeyer et al., 2011). Following experimental keratectomy in rabbits, moxifloxacin and gatifloxacin showed no significant deleterious effect on epithelialization, relative to balanced salt solution (BSS) control (Williams et al., 2008). Besifloxacin was developed exclusively for ophthalmic use, and its ophthalmic suspension contains a mucoadhesive polymer that may contribute towards its ability to maintain concentrations in both cornea and AH, possibly by reducing elimination caused by lacrimation (Chung et al., 2012; Deschenes & Blondeau, 2015).

Side Effects

Ciprofloxacin, ofloxacin, and norfloxacin have been shown to be cytotoxic and have antiproliferative effects on stromal keratocytes (Leonardi et al., 2006; Seitz et al., 1996). A transient white crystalline precipitate is reported to develop on the corneal surface of 13%–17.6% human patients treated with topical ciprofloxacin (Hanet et al., 2012). A similar corneal plaque developed in a dog after 2 weeks of treatment with levofloxacin (Park et al., 2015).

Parenteral enrofloxacin may cause irreversible generalized retinal degeneration in cats when administered at dosages higher than 5 mg/kg once daily (Gelatt et al., 2001). Cats older than 12 years who are systemically ill are at greater risk for occurrence, which is manifested initially by gray tapetal discoloration in the area centralis, followed by generalized tapetal hyperreflectivity and retinal vascular attenuation (Gelatt et al., 2001). Significant reductions in a- and b-wave amplitudes on electroretinogram are noted, along with rod photoreceptor loss (Dubielzig et al., 2003; Ford et al., 2003).

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When administered at the recommended dose of 2.5–7.5 mg/kg, orbifloxacin does not produce the same effects. However, subtle changes were noted in cats receiving 45 and 75 mg/kg once daily for 30 days (Kay-Mugford et al., 2001). Marbofloxacin at 20 times the recommended dose did not produce retinal degeneration (Wiebe & Hamilton, 2002).

Antifungal Agents – General Principles of Therapy

Medically significant fungi exist as either yeasts (single cells, reproduce by budding), molds (cylindrical hyphae, reproduce by branching and apical extension, form multicellular filamentous mass in culture called mycelium), or as dimorphic forms (yeast phase in host tissues, mycelial phase in culture media). Fungi are eukaryotic, with a rigid outer cell wall composed of chitin and polysaccharides (glucans and mannans), inner cell membranes that surround organelles, nucleic acids stored within a nucleus, and soluble cytoplasmic carbohydrates and storage compounds for energy. In contrast to bacteria, fungal organisms are more complex and share more structural commonalities with mammalian cells, making selective pharmacological targeting more difficult. Considering the potential for greater toxicity to the patient, and more variable susceptibility patterns (as well as unclear correlations between *in vitro* and *in vivo* susceptibility profiles), antifungal medications are generally indicated only in the presence of confirmed infection (Yolton & Haesaert, 2008).

Antifungal drugs fall into one of four classes – polyenes, pyrimidines, azoles, or echinocandins – all of which act primarily on the fungal cell wall, with the goal being greater selectivity for the fungal organism versus the host.

Polyenes

The polyenes (amphotericin B, natamycin, and nystatin) bind fungal cell membrane sterols, most commonly ergosterol, and form a polyene-sterol complex. With natamycin, the complex alone is toxic to the fungal organisms, whereas with amphotericin B, the complex induces leakage of vital intracellular constituents (i.e., monovalent ions such as K^+, Na^+, H^+, and Cl^-). Their action is concentration-dependent, with the potential for fungicidal activity at higher concentrations.

Amphotericin B

Amphotericin B is a broad-spectrum antifungal agent that exhibits strong *in vitro* activity versus most fungal organisms responsible for invasive systemic disease processes (i.e. *Aspergillus* spp., *Blastomyces* spp., *Candida* spp., *Coccidioides* spp., and *Cryptococcus* spp.). However, other strains are poorly susceptible (*Trichosporon* spp., *Geotrichum* spp., *Scedosporium* spp.) (Herbrecht et al., 2005; Ozdemir et al., 2012). Amphotericin B has poor bioavailability when administered orally, and the deoxycholate colloidal suspension (Fungizone) is associated with significant systemic toxicities (renal, hematologic, hepatic) after intravenous (IV) administration (Herbrecht et al., 2005). Liposomal, lipid complex, and colloidal dispersion formulations of amphotericin B, developed for systemic administration, reduce systemic toxicities without adversely affecting the spectrum of activity, and appear to have comparable clinical efficacy when administered for invasive systemic fungal infections (Steimbach et al., 2017).

Amphotericin B has been evaluated experimentally and clinically in people as treatment for surface ocular fungal infections when administered topically (Mahdy et al., 2010), subconjunctivally (Carrasco & Genesoni, 2011; Kaji et al., 2009), intrastromally (Qu et al., 2010), and intracamerally (Sharma et al., 2015; Hu et al., 2016; Yoon et al., 2007). A topical ophthalmic formulation is not commercially available. However, preparations ranging from 0.15% to 3% can be compounded for administration (Kaur et al., 2008) using sterile water (amphotericin B is incompatible with saline), after which the solutions are stored in the refrigerator and protected from light (Mauger, 1994) (Table 8.2.3). Although topically administered amphotericin B has been effective in the treatment of fungal conjunctivitis, scleritis, and keratitis (Bernauer et al., 1998; Hirose et al., 1997; Tanure et al., 2000; Wong et al., 1997), corneal penetration is limited in the presence of an intact corneal epithelium (Kaji et al., 2009; O'Day et al., 1986), and ocular surface irritation and discomfort are potential side effects (Foster et al., 1981; Mauger, 1994). Limited penetration through an intact corneal epithelium was also noted with subconjunctival injection of 1.5 mg amphotericin B in the deoxycholate and lipid formulations in rabbits, with less local inflammation induced by the lipid formulation (Kaji et al., 2009). A microemulsion formulation that has recently been developed shows promise for topical administration, both improving penetration and decreasing side effects (da Silveira et al., 2016). In clinical cases, subconjunctival injection of amphotericin B in human patients with recalcitrant fungal keratitis has produced improvement. However, injection-related pain was also reported (Carrasco & Genesoni, 2011). Intrastromal injections in rabbits led to potentially therapeutic corneal amphotericin B concentrations for 7 days after the injection (Qu et al., 2010), whereas clinical efficacy was reported with combined intrastromal and intravitreal amphotericin B in a human patient with recurrent *Candida* keratitis (Garcia-Valenzuela & Song, 2005).

Reports of the clinical use of amphotericin B to treat surface ocular fungal infections in veterinary ophthalmology have been limited to horses. The use of concentrations above 0.3% is reportedly irritating when administered topically

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(Bistner & Riis, 1979). Subconjunctival injection in horses with corneal stromal abscesses nonresponsive to aggressive antifungal therapy has produced good clinical outcomes, though local inflammation and irritation is frequently marked (B.C. Gilger, personal communication; 0.2 mL of 0.5 mg/mL solution q 48 hours × three doses) (see Table 8.2.3). Administration of amphotericin B intrastromally has also been reported in horses with nonresponsive fungal stromal abscesses (Cutler, 2010).

Although not commonly reported in veterinary ophthalmology, fungal endophthalmitis is a significant sight-threatening condition in human patients, treated in part by intravitreal injection of amphotericin B. Experimental evaluation in rabbits and primates documents variable toxicity associated with these injections, which appears to be minimized by the use of lipid formulations (Barza et al., 1985; Cannon et al., 2003; Tremblay et al., 1985). In clinical reports, typical doses range from 5 to 10 μg, administered in conjunction with systemic therapy (Riddell et al., 2011).

Natamycin

As the only approved topical ophthalmic antifungal agent (5% suspension), natamycin has an improved spectrum of action relative to that of amphotericin B, particularly versus filamentous organisms common in keratomycosis (i.e., *Fusarium, Aspergillus, Curvularia, Acremonium*) (Mauger, 1994; O'Brien, 1999) (see Table 8.2.3). It is well tolerated and induces fewer ocular toxicities after topical application, but it did show greater adverse impacts on morphology and proliferation of cultured equine keratocytes than did itraconazole (Mathes et al., 2010). In addition, natamycin has poor transcorneal penetration, limiting its use in deep corneal or intraocular infections (Mauger, 1994). In a randomized trial of human patients with fungal keratitis, significantly increased visual acuity, decreased perforation rate, and decreased corneal transplant rate were noted in patients receiving topical natamycin versus those receiving topical voriconazole, with the difference attributable to improved efficacy of natamycin against *Fusarium* spp. (Prajna et al., 2013).

Intraocular injections of natamycin have been evaluated experimentally in animals, and overall produce significant adverse effects. Although intracameral injection of a single 250 μg dose of natamycin in normal rabbit eyes was well tolerated, a single 500 μg dose led to vision- and globe-threatening changes in normal eyes (Ellison & Newmark, 1976) and in eyes with *Aspergillus* endophthalmitis (Ellison & Newmark, 1976). Experimental intravitreal injection of natamycin in rabbits is also unfavorable, because a 25 μg dose was nontoxic but unlikely to be therapeutic versus *Aspergillus*, whereas a 50 μg dose was markedly toxic to the retina (Ellison, 1976).

Natamycin is frequently used in the treatment of equine fungal keratitis and has shown strong *in vitro* activity versus isolates from horses with clinical disease, particularly *Fusarium* (Brooks et al., 1998; Ledbetter et al., 2007b; Pearce et al., 2009) and *Candida* (Ledbetter et al., 2007b), with generally lesser but still potentially therapeutic efficacy versus *Aspergillus* (Brooks et al., 1998; Ledbetter et al., 2007b; Pearce et al., 2009). In contrast, however, a study comparing the fungistatic versus fungicidal effects of silver sulfadiazine with those of natamycin found greater fungicidal effects with silver sulfadiazine against *Fusarium* isolates from horses with clinical disease (Betbeze et al., 2006). When evaluated in combination with tobramycin 0.3%, cefazolin 5.5%, and equine serum, MICs for natamycin 3.33% versus equine disease isolates were significantly lower versus *Aspergillus* and *Fusarium* isolates than those for natamycin alone (Scotty et al., 2008). This effect was most likely caused by the dilution effect of the drug combination. However, in a different study, all fusarium isolates were sensitive to a drug combination of equal portions of natamycin 3.33%, tobramycin 0.3%, and cefazolin 5.5%, whereas one of the isolates was resistant to natamycin alone (Ben-Shlomo et al., 2013); this is most likely because of synergy between the antimicrobial drugs, and without the extra dilution effect of the serum added in Scotty's study (Scotty et al., 2008).

Nystatin

Nystatin is a polyene with relatively broad-spectrum fungistatic activity, but its use in the treatment of keratomycosis is somewhat limited because of minimal corneal penetration when administered topically, as well as local toxicity (Mauger, 1994).

Pyrimidines

Flucytosine (5-fluorocytosine, 5-FC), a cytosine analogue, exerts antifungal activity via derivatives produced within the fungal cell that inhibit protein synthesis through incorporation into fungal RNA, and inhibit DNA synthesis by reducing activity of enzymes involved in synthesis (Vermes et al., 2000). Flucytosine has the greatest effect versus yeasts such as *Candida* and *Cryptococcus*, yet intrinsic resistance may be significant and resistance may also develop during the course of therapy (Vermes et al., 2000). Although generally not used as treatment for keratomycosis in human patients, evaluation of flucytosine as an agent for the treatment of experimentally induced keratomycosis in rabbits (O'Day et al., 1983) and naturally occurring keratomycosis in horses (Coad et al., 1985) indicated lesser efficacy relative to other more commonly administered antifungal agents. More recent comparison of *in vitro* efficacy of flucytosine versus isolates from horses with keratomycosis indicated 50% resistance of yeast isolates (five of 10) versus 37% resistance of filamentous isolates (18 of 49) (Ledbetter et al., 2007b).

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Table 8.2.3 Antifungal medications used to treat keratomycosis.

Drug	Spectrum[a]	Concentration/dose	Route	Complications	Other
Amphotericin B	Good versus yeast Good versus filamentous	0.15%–0.3%[b]	Topical	Corneal toxicity	Limited corneal penetration
		0.5%	Subconjunctival (every 48 hours × three doses)	Local irritation Discomfort	
Natamycin	Good versus filamentous	5%	Topical	Minimal	Limited corneal penetration
Ketoconazole	Poor versus filamentous	1%–5%[b]	Topical	Minimal	Slower onset Good corneal penetration
Miconazole	Good versus filamentous	1%–2%[b]	Topical	Minimal	Good corneal penetration
Fluconazole	Good versus yeast Poor versus filamentous	2 mg/mL[b] 14 mg/kg once, followed by 5 mg/kg every 24 hours	Topical Oral	Minimal	Good corneal penetration Good intraocular penetration
Itraconazole	Good versus filamentous (except *Fusarium*)	1% in 30% dimethyl sulfoxide [b] 5 mg/kg every 24 hours	Topical Oral	Minimal	Good corneal tissue levels Poor corneal penetration Poor intraocular penetration
Voriconazole	Good versus yeast Good versus filamentous	1%[b] 3–4 mg/kg every 12–24 hours	Topical Oral	Minimal	Good corneal penetration Good precorneal tear film levels
Caspofungin	Good versus yeast Good versus filamentous (except *Fusarium*)	0.5%–0.7%[b]	Topical	Minimal	Good corneal penetration with epithelial defect

[a] In relation to organisms relevant to keratomycosis in veterinary patients.
[b] Not commercially available as an ophthalmic preparation.

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Azoles

The azoles are antifungal agents with fungistatic activity that, like polyenes, target the fungal cell membrane component ergosterol. Inhibition of the cytochrome P450-dependent enzyme 14α-sterol demethylase decreases synthesis of ergosterol, which leads to accumulation of toxic sterol precursors, inhibits fungal growth, and increases membrane permeability. Additionally, azoles inhibit mitochondrial oxidative and peroxidative enzymes, leading to accumulation of other toxic intracellular products. Because of action on cytochrome P450, azoles may affect other mammalian metabolic pathways utilizing that enzyme system, increasing the potential for drug interactions and systemic toxicities.

Imidazoles

Ketoconazole and miconazole are azoles based on the imidazole parent ring structure.

Ketoconazole

Relative to other azoles, ketoconazole has a more limited spectrum, greater risk for systemic toxicities, and slower onset of clinical effect (see Table 8.2.3). While topical ophthalmic formulations are not available, it is well absorbed when administered systemically (Kaur et al., 2008). When administered topically as a compounded preparation, it has good corneal and intraocular penetration and minimal toxicity (Foster et al., 1981; O'Day et al., 1983; Savani et al., 1987).

In the treatment of equine keratomycosis, ketoconazole shows consistently inferior activity relative to polyenes and other azoles (Brooks et al., 1998; Ledbetter et al., 2007b; Pearce et al., 2009). In an *in vitro* comparison of multiple azoles and natamycin versus ocular isolates of *Aspergillus* and *Fusarium* from horses in the midwestern and southern United States, ketoconazole was consistently the least effective (Pearce et al., 2009). Against isolates from horses in the northeastern United States, only fluconazole was less effective versus filamentous organisms, with 56% of isolates (35 of 62) susceptible to ketoconazole (Ledbetter et al., 2007b). Efficacy versus yeast isolates was greater, with 75% of isolates (nine of 12) susceptible to ketoconazole (Ledbetter et al., 2007b).

In dogs with ocular manifestations of blastomycosis, systemically administered ketoconazole in combination with amphotericin B was as effective in achieving clinical improvement as itraconazole alone (Arceneaux et al., 1998). A side effect of oral ketoconazole administration in dogs is the development of cataracts, which occur with long-term (up to 37 months) therapy, at dosages ranging from 6 to 30 mg/kg/day (DaCosta et al., 1996).

Miconazole

Miconazole is a broad-spectrum azole frequently administered topically as a 1% compounded suspension (Foster et al., 1981), or as the 2% dermatologic or 2% vaginal creams (Regnier, 2007) (see Table 8.2.3). Topical application and subconjunctival injection of miconazole reach measurable and potentially therapeutic corneal and intraocular levels in rabbits (Foster & Stefanyszyn, 1979). However, clinical therapeutic efficacy is variable (O'Day et al., 1983, 1991; Segal et al., 1981). Although generally considered to cause minimal topical ocular toxicity, miconazole produced deleterious effects on cultured equine keratocyte cell proliferation and morphologic parameters comparable to those induced by natamycin, and significantly more than those induced by itraconazole (Mathes et al., 2010).

Miconazole has been used frequently in the treatment of equine keratomycosis, either as the compounded preparation or as a topical cream, in part because of availability and comparative ease of ocular administration. Miconazole showed good *in vitro* activity when compared with other antifungal drugs versus *Aspergillus* and *Fusarium* isolates from horses with ocular disease in the midwestern and southern United States (Pearce et al., 2009). However, efficacy was considerably lower versus both filamentous and yeast organisms from horses in the northeastern United States (Ledbetter et al., 2007b). Miconazole has been reported as part of the successful treatment of keratomycosis caused by *Curvularia* in a dog (Ben-Shlomo et al., 2010). However, it was not effective versus *Acremonium* keratomycosis in a cat (Binder et al., 2011).

Triazoles

Fluconazole, itraconazole, voriconazole, posaconazole, and ravuconazole are examples of azoles based on the triazole parent ring structure.

Fluconazole

Fluconazole has a spectrum of activity limited primarily to yeast, such as *Candida* and *Cryptococcus*, with minimal efficacy versus filamentous fungal organisms. Although its spectrum is more limited than that of most other azoles, fluconazole exhibits an excellent pharmacokinetic profile (Kaur et al., 2008). Following oral administration to rabbits, fluconazole was detectable in the cornea, AH, vitreous, and choroid and retina (O'Day et al., 1990, 1992; Savani et al., 1987), whereas after topical administration to rabbits with and without corneal epithelial debridement, relatively high concentrations were identified in both the cornea and AH (Yee et al., 1997). As would be expected based on its general spectrum, the use of fluconazole in experimental keratomycosis associated with filamentous fungal organisms in rabbits has produced variable results (Avunduk et al., 2003; O'Day et al., 1992), whereas topical administration in humans produces AH levels that are potentially therapeutic versus *Candida* strains (Abbasoglu et al., 2001).

Oral administration of fluconazole in the treatment of equine keratomycosis is supported by its strong pharmacokinetic profile, with AH levels of 11.39 ± 2.83 μg/mL achieved

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after oral administration (14 mg/kg once, then 5 mg/kg q 24 hours × 10 days) to healthy horses (Latimer et al., 2001). However, it is limited because of its narrow spectrum of activity (Ledbetter et al., 2007b; Pearce et al., 2009) (see Table 8.2.3). In a comparison of the activities of various azoles and amphotericin B versus filamentous organisms *Aspergillus fumigatus* and *Eurotium amstelodami* isolated from the conjunctiva of horses without ocular disease in Switzerland, fluconazole consistently showed the highest MICs (Voelter-Ratson et al., 2014). Additionally, isolates of filamentous organisms from horses with keratomycosis in the northeastern United States showed 87% resistance to fluconazole, versus 14% resistance for yeast organisms (Ledbetter et al., 2007b), whereas fluconazole and ketoconazole had comparably poor *in vitro* efficacy versus isolates from horses in the midwestern and southern United States (Pearce et al., 2009). Consistent with its spectrum of activity, clinical efficacy was reported with the use of topical fluconazole in a horse with *Histoplasma* spp. keratitis (Richter et al., 2003). Also consistent with its spectrum of activity, oral fluconazole therapy was associated with resolution of meningitis and optic neuritis in a horse that was caused by *Cryptococcus neoformans* (Hart et al., 2008).

Because of its inhibition of the cytochrome P450 enzyme CYP3A4, which is involved in metabolism of anesthetic drugs, fluconazole has been implicated in association with prolonged recoveries from anesthesia in horses undergoing ocular surgical procedures (Krein et al., 2014). The association was evident in horses receiving midazolam as part of the premedication protocol, because of the fact that midazolam relies solely upon CYP3A4 for metabolism.

Itraconazole

Itraconazole has a broad spectrum of activity, particularly toward filamentous fungal organisms. However, *Fusarium* species isolated from human cases of ocular disease are more resistant to itraconazole than to other azoles (Lalitha et al., 2007; Ozdemir et al., 2012). In addition, delivery of itraconazole to the desired site of action can be difficult, in spite of high lipophilicity and moderate protein binding that would be expected to lead to good absorption and concentration in lipid-rich tissues after oral administration. For example, in dogs, the specific formulation administered is associated with significant variation in pharmacokinetic parameters, with neither generic nor compounded itraconazole demonstrating bioequivalence to the reference innovator itraconazole (Mawby et al., 2014). In other species, absorption after oral administration may be more predictable, but intraocular penetration of itraconazole tends to be poor (Cauteren et al., 1987; Savani et al., 1987) (see Table 8.2.3). Pharmacokinetic parameters are similar in horses, with bioavailability of the commercial solution higher and more consistent than that for capsules dissolved in corn syrup. Nevertheless, a single 5 mg/kg dose still fails to achieve detectable drug concentrations in the AH of horses without ocular inflammation (Davis et al., 2005). In addition, intraocular penetration of itraconazole after topical administration is poor, thus formulations of itraconazole have been developed to improve intraocular penetration. Of these, 1% itraconazole compounded in 30% dimethyl sulfoxide (DMSO), evaluated in normal horses, produces significantly greater corneal tissue levels than those achieved with 1% itraconazole without DMSO (Ball et al., 1997b). Importantly, neither formulation produced measurable AH levels. To alleviate difficulties encountered with ocular delivery of itraconazole, polymeric micelles containing itraconazole and loaded into a gel for topical ocular application were evaluated for drug capacity, irritation, and release characteristics, and showed favorable *in vitro* parameters, thus indicating future *in vivo* evaluations are appropriate (Jaiswal et al., 2015). Regarding toxicity, when applied to cultured equine keratocytes, itraconazole produced fewer deleterious effects on cell proliferation and morphologic parameters than miconazole or natamycin (Mathes et al., 2010).

Consistent with its expected spectrum of activity, itraconazole showed good efficacy versus filamentous fungal organisms (*Eurotium amstelodami* and *Aspergillus fumigatus)* isolated from horses without ocular disease in Switzerland, with MICs comparable to, or slightly higher than, those of voriconazole; comparable to, or lower than, those of amphotericin B, and significantly lower than those of miconazole or fluconazole (Voelter-Ratson et al., 2014). In horses with ocular disease in the northeastern United States, itraconazole showed reasonable *in vitro* activity, with overall resistance levels of 28% of filamentous organisms (11 of 40) and 11% of yeast organisms (one of nine) (Ledbetter et al., 2007b). Importantly, of the six *Fusarium* isolates evaluated, five were resistant and one showed intermediate susceptibility (Ledbetter et al., 2007b). Similarly, *Fusarium* isolates from horses in the midwestern and southern United States were significantly more susceptible to natamycin than itraconazole, with *Aspergillus* isolates demonstrating stronger susceptibility to itraconazole (Pearce et al., 2009). The use of 1% itraconazole-30% DMSO compounded topical ophthalmic ointment in horses with keratomycosis documented resolution in eight of 10 eyes, with greater efficacy versus *Aspergillus* spp., *Mucor* spp., *Candida* spp., and *Trichosporon* spp., whereas development of a resistant *Fusarium* strain occurred in one eye (Ball et al., 1997a).

Voriconazole

Voriconazole, a derivative of fluconazole that has a significantly improved spectrum of activity, is used to treat invasive fungal infections caused by both filamentous and yeast organisms (Kaur et al., 2008), with *in vitro* activity comparable to that of amphotericin B (Lalitha et al., 2007; Ozdemir et al., 2012). When administered orally in people, it is highly bioavailable (90%) (Herbrecht et al., 2005), with variable, but

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potentially therapeutic, intraocular (AH and vitreous) drug levels (Hariprasad et al., 2004; Riddell et al., 2011; Vemulakonda et al., 2008). In combination with other antifungals, oral voriconazole has been reported to contribute to successful resolution of endophthalmitis associated with *Candida* and filamentous fungal organisms (Breit et al., 2005; Hariprasad et al., 2008; Varma et al., 2005).

Versus fungal isolates from cases of equine ocular disease, *in vitro* evaluation confirms significantly greater activity of voriconazole relative to that of other azoles: *Fusarium* and *Aspergillus* isolates from horses in the midwestern and southern United States were consistently significantly more susceptible to voriconazole than to other azoles, and only natamycin surpassed voriconazole in efficacy versus *Fusarium* isolates (Pearce et al., 2009). Voriconazole showed consistently lower MICs than fluconazole, itraconazole, miconazole, and amphotericin B to *Aspergillus fumigatus* and *Eurotium amstelodami* organisms isolated from conjunctiva of horses without ocular disease in Switzerland (Voelter-Ratson et al., 2014).

Pharmacokinetic studies of voriconazole in dogs indicate plasma drug concentrations capable of treating susceptible infections after a single oral dose of 6 mg/kg (Roffey et al., 2003), thus leading to the recommendation of 4–5 mg/kg twice daily as an appropriate dose for systemic infections (Graupmann-Kuzma et al., 2008; Schultz et al., 2008). Regarding intraocular infections, however, daily oral dosing of 6 mg/kg voriconazole to normal dogs achieved 0.43 µg/mL AH concentration, which is likely to be effective only in treatment of intraocular infections caused by organisms with MICs ≤0.5 µg/mL (Lemetayer et al., 2015).

Pharmacokinetic studies of voriconazole in cats have not included investigation of intraocular penetration. However, intravenous voriconazole administration (1 mg/kg) is associated with a half-life of 12 hours, and oral administration of 4 mg/kg produced plasma concentrations within the target range of 1–4 µg/mL (Vishkautsan et al., 2016). Hypersalivation and miosis were noted with long-term (14 days) administration.

Pharmacokinetic studies of voriconazole in horses indicate good bioavailability, with single oral (4 mg/kg or 10 mg/kg) or IV (1 mg/kg or 10 mg/kg) doses being well tolerated and resulting in potentially therapeutic serum or plasma concentrations occurring within minutes and lasting up to 24 hours (Colitz et al., 2007; Davis et al., 2006b) (see Table 8.2.3). Additionally, likely therapeutic precorneal tear film levels were reached after twice daily administration of 3 mg/kg orally for 10 days (Colitz et al., 2007). Administration of 0.5%, 1%, or 3% voriconazole topically to normal equine eyes every 4 hours resulted in potentially therapeutic AH drug concentrations, with the 1% formulation avoiding signs of irritation (Clode et al., 2006).

In order to improve efficacy and minimize the intensiveness of therapy, alternate methods of ocular voriconazole delivery have been evaluated. Use of a continuous infusion pump connected to a subpalpebral lavage catheter (SPL) showed precipitation of voriconazole within the SPL tubing within 1 day, thus both blocking the SPL and altering the volume and concentration of voriconazole delivered (Smith et al., 2014a). Recently, a voriconazole-loaded thermogel injected subconjunctivally was documented to provide sustained release of voriconazole over 21 days, with released concentrations resulting in moderate to good inhibitory activity against *Aspergillus flavus* isolates (Cuming et al., 2017). Injection in normal horse eyes did not result in signs of toxicity.

Various protocols utilizing intrastromal voriconazole injection have been associated with improvement of equine fungal keratitis in clinical case reports. Published protocols include intrastromal injection of 1.5–2 mg (150–200 µL of 1% voriconazole), in conjunction with 4–5 mg (400–500 µL) injected subconjunctivally (Tsujita & Plummer, 2013), and injection of 22.5 mg of a 5% solution (Smith et al., 2014b). Corneal toxicity has not been investigated.

Topical administration of voriconazole in dogs (Grudnon et al., 2010; Ledbetter & Starr, 2016; Newton, 2012; Nevile et al., 2016; Pucket et al., 2012) and cats (Labelle et al., 2009) with keratomycosis has shown clinical efficacy. Oral administration of 5–10 mg/kg once daily was effective in cats with orbital aspergillosis, but treatment-limiting side effects (lethargy, inappetance, azotemia, cutaneous reaction) occurred, possibly attributable to systemic voriconazole (Smith & Hoffman, 2010).

Echinocandins

Echinocandins (caspofungin, micafungin, anidulafungin) inhibit the enzyme glucan synthase, which is responsible for the formation of the essential fungal cell wall component glucan (Sucher et al., 2009). Inhibition of this enzyme is fungistatic or fungicidal, depending upon the organism involved: fungicidal effects are present versus most *Candida* species responsible for invasive fungal diseases in people (Pfaller et al., 2008). However, effects are generally fungistatic for *Aspergillus* and other filamentous organisms (Kim et al., 2007), because of a lower glucan content (Patil & Majumdar, 2017). With the exception of most species of *Candida*, the activity of echinocandins versus other dimorphic fungi (i.e., *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*) is less versus the yeast form (Nakai et al., 2003), which predominates in infected tissue, thus potentially limiting their efficacy in the treatment of invasive systemic disease. Also of importance is the poor activity of echinocandins versus *Fusarium* spp. (Sucher et al., 2009).

Caspofungin

Caspofungin is the first FDA-approved echinocandin, with consistently strong activity versus *Candida* spp., *Aspergillus* spp., and other azole-resistant organisms, but poorer efficacy

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versus *Fusarium* (Lalitha et al., 2007). Ocular distribution after a single IV dose of caspofungin to rats without ocular inflammation was markedly lower than that to other body tissues (Stone et al., 2004), whereas single and multiple IV doses of caspofungin resulted in undetectable ocular drug concentrations in rabbits (Goldblum et al., 2007). Administration of IV caspofungin to rabbits with unilateral experimentally induced uveitis documented potentially therapeutic AH and corneal drug concentrations up to 8 and 24 hours, respectively, after a single dose, supporting the necessity of blood–ocular barrier breakdown for intraocular penetration, as well as the potential for the cornea to be an efficient drug reservoir (Goldblum et al., 2007). Topical administration of a 7 mg/mL solution of caspofungin to normal rabbit corneas did not achieve detectable AH drug concentrations, whereas potentially therapeutic AH drug concentrations were reached in rabbits after creation of epithelial defects (Vorwerk et al., 2009) (see Table 8.2.3). Treatment of experimentally induced *Candida* keratitis in rabbits with topical 0.5% caspofungin was of comparable clinical efficacy to 0.15% amphotericin B, whereas 0.15% caspofungin was inferior (Goldblum et al., 2005). No signs of ocular toxicity were noted after the aggressive treatment protocol (Goldblum et al., 2005). Although the *in vitro* efficacy of caspofungin to *Fusarium* isolates is limited, treatment of experimentally induced *Fusarium solani* keratitis in rabbits with 1% caspofungin administered topically was of comparable efficacy to that of 0.15% amphotericin B (Ozturk et al., 2007). Evaluation of efficacy of caspofungin versus *Candida* spp. isolated from the nasolacrimal duct of horses in Brazil showed resistance of only one isolate to caspofungin, versus resistance of eight isolates to both fluconazole and itraconazole (Brilhante et al., 2016).

Micafungin

Micafungin is also effective versus *Candida*, with some efficacy versus *Aspergillus* and minimal efficacy versus *Fusarium*. Micafungin shows minimal intraocular penetration after systemic administration in rabbits, with undetectable AH and vitreous humor concentrations and low retina-choroid tissue levels after IV administration (Groll et al., 2001; Suzuki et al., 2008). Toxicological evaluation of topical ocular 0.1% micafungin in rabbits documented no difference in intraocular pressure, endothelial cell density, or tear lactate dehydrogenase activity between treated and saline control animals. A slight but significant and reversible decrease in corneal thickness was identified in treated animals, though (Hiraoka et al., 2005) (see Table 8.2.3). Intravitreal injection of micafungin in rabbits inoculated with *Aspergillus* intravitreally documented greater preservation of the b-wave on electroretinogram relative to saline control, with the suggestion of lower toxic effects relative to amphotericin B or voriconazole (Harrison et al., 2005). Subconjunctival injection of micafungin in rabbits with experimentally induced *Candida* keratitis showed superior clinical response to that of fluconazole, with no ocular side effects (Hiraoka et al., 2007).

In clinical cases, topical administration of 0.1% micafungin in one eye each of three human patients with refractory fungal ulcers associated with *Candida* spp. or unidentified yeast resulted in satisfactory improvement when conventional antifungal therapy failed (Matsumoto et al., 2005).

Anidulafungin

Anidulafungin is fungicidal and effective versus *Candida* strains, as well as amphotericin B- and azole-resistant strains. No clinical reports of efficacy in ocular disease exist at this time. However, an *in vivo* study of IV anidulafungin in rabbits with *C. albicans* endophthalmitis showed no toxicities or side effects at 5, 10, or 20 mg/kg, dose-dependent penetration into the vitreous humor without penetration into the AH, and fungistatic action at the 20 mg/kg dose (Livermore et al., 2013).

Antiviral Agents – General Principles of Therapy

Although the sizes and morphologies of viruses are highly variable, the common basic structure is that of single- or double-stranded DNA or RNA contained within a protein coat (capsid), with or without a surrounding lipid envelope. Following infection of the host cell, viral DNA or RNA replication occurs through use of either virus-specific or host cell enzymes, ultimately resulting in abundant copying of the viral genome. Antiviral agents pharmacologically target this viral replication cycle within the host cell, resulting in a virostatic, rather than virocidal, effect. Drugs currently used in veterinary ophthalmology are nucleoside analogues, which mimic either the pyrimidine (cytidine, thymidine) or purine (adenosine, guanosine) nucleic acid building blocks to disrupt viral genome synthesis. Additionally, L-lysine may decrease viral replication, whereas interferons (IFNs) may be used to stimulate the host immune response targeting the virus. Considering the involvement of host cell enzymes and machinery in the viral replication process, toxicity is a concern when administering antiviral medications of any class.

The primary indication for antiviral therapy in veterinary ophthalmology is the treatment of feline herpesvirus-associated (FHV-1) ocular diseases, although equine (EHV-2) and canine (CHV-1) herpesvirus-associated ocular diseases may on occasion necessitate antiviral therapy. It is important to emphasize that the virostatic nature of current antiviral medications as well as the ability of herpesviruses to establish latency indicate that eradication of viral infections is not possible. Additionally, currently available antiviral medications are not developed to specifically target FHV-1, EHV-2, or CHV-1.

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Specific Antiviral Agents

Pyrimidine (Thymidine) Analogues

Drugs in this class include idoxuridine and trifluridine, both of which are thymidine analogues. Following intracellular phosphorylation, idoxuridine competitively inhibits incorporation of thymidine into viral DNA, resulting in a virus that cannot effectively replicate (DeClercq, 2004). Trifluridine is also phosphorylated intracellularly, allowing it to inhibit thymidylate synthase, an enzyme necessary for DNA synthesis (DeClercq, 2004). Both of these medications lack sufficient specificity for viral versus host enzymes, rendering them too toxic for systemic use, and topical administration is generally necessary four to six times daily.

Idoxuridine shows strong *in vitro* specificity for FHV-1 (Maggs & Clarke, 2004; Nasisse et al., 1989). However, it has poor ocular penetration (Yolton & Haesaert, 2008), rendering it less clinically effective for stromal disease. Idoxuridine can be compounded as a 0.1% solution, or up to a 0.5% ointment (Malmberg & Lupo, 2004), and is generally well tolerated for topical administration to cats, although no clinical trials in cats have been performed (Gould, 2011; Maggs, 2010).

Trifluridine also has good *in vitro* specificity for FHV-1 (Maggs & Clarke, 2004; Nasisse et al., 1989), and is reported to have good ocular bioavailability in the presence of disease (Pavan-Langston & Nelson, 1979). Because of its superior efficacy in treating herpetic ocular disease in human patients (Yolton & Haesaert, 2008), it is marketed commercially as a 1% solution. Although no clinical trials have been performed in cats, it is reportedly poorly tolerated (Gould, 2011; Maggs, 2010).

Successful resolution of ocular lesions associated with EHV-2 in horses and foals is reported after ophthalmic instillation of both idoxuridine and trifluridine (Maxwell, 2017). In one report, horses were administered topical antiherpetic drugs every 2–4 hours while corneal lesions were present, and then the frequency decreased to every 4–6 hours for an additional 3–4 days (Matthews, 2009).

Clinical reports indicate successful treatment outcomes with the topical application of 0.1% idoxuridine or 1% trifluridine ophthalmic solutions in dogs with ocular CHV-1 infections (Ledbetter et al., 2006). Additionally, dogs with experimentally induced recurrent ocular CHV-1 have improved clinical signs and reduced viral shedding compared with a placebo after topical application of 1% trifluridine six times daily for 2 days, then four times daily for 12 days (Spertus et al., 2016). Trifluridine is well tolerated in dogs with no signs of ocular irritation or discomfort after application (Spertus et al., 2016).

Pyrimidine (Cytosine) Analogue

Cidofovir is a cytosine analogue that requires two (rather than three) phosphorylation steps, both of which are catalyzed by host rather than viral enzymes. The phosphorylated form then shows relatively high specificity for subsequent inhibition of viral DNA polymerase (DeClercq, 2004). Although principally utilized intravenously or intravitreally in human patients for the treatment of cytomegalovirus-induced retinitis (Yolton & Haesaert, 2008), it has shown strong activity versus FHV-1 *in vitro* (Maggs & Clarke, 2004; Meulen et al., 2006; Sandmeyer et al., 2005a). A significant advantage of cidofovir over the thymidine analogues is its clinical efficacy, necessitating only twice daily topical administration of a 0.5% compounded solution, which is thought to be caused by the long intracellular half-life of the active metabolite (Neyts et al., 1991). Evaluation of this twice-daily dosing regimen in cats experimentally infected with FHV-1 showed significantly reduced viral shedding and severity of clinical signs (Fontenelle et al., 2008). Mild cytopathologic effects (reduction in cell number and viable cell counts) were noted *in vitro* when concentrations of cidofovir ranging from 0.0005 to 0.05 mg/mL were incubated with cultured feline corneal epithelial cells (Sandmeyer et al., 2005a). The primary clinical side effect noted in human patients and rabbits is stenosis of the nasolacrimal duct system (Inoue et al., 2009; Sherman et al., 2002), which has not been reported in cats on long-term clinical therapy. Other side effects noted in a dose-dependent manner in both human patients and rabbits include conjunctivitis, blepharitis, conjunctival pseudomembrane formation, and superficial punctate keratitis (Gordon et al., 1994; Hillenkamp et al. 2002). Twice daily administration of 0.5% cidofovir ophthalmic solution in dogs experimentally induced with recurrent ocular CHV-1 infection reduces the duration of ocular viral shedding. However, this medication is poorly tolerated (Ledbetter et al., 2015). Local ocular toxicity after administration of cidofovir in dogs is characterized by worsening conjunctivitis, ulcerative blepharitis, and extensive conjunctival pigmentation (Ledbetter et al., 2015).

Purine Nucleoside Analogues

Acyclovir and its prodrug valacyclovir, penciclovir and its prodrug famciclovir, and ganciclovir are acyclic nucleoside guanosine analogues that require three phosphorylation steps to become active. The initial phosphorylation requires viral thymidine kinase, with subsequent phosphorylation utilizing host enzymes (DeClercq, 2004). The use of the viral enzyme confers relatively low host toxicity, along with relatively high specificity for human herpesviruses. Their activity in cats is more variable, in part because of differences in the viral thymidine kinase associated with FHV-1 (Hussein et al., 2008), as well as differences in feline versus human host cell enzymes and metabolism (Maggs, 2010).

Although acyclovir is a valuable medication in the treatment of human herpetic diseases, it shows low *in vitro* efficacy versus FHV-1 (Maggs & Clarke, 2004; Meulen et al., 2006; Nasisse et al., 1989) and poor bioavailability after oral administration in cats (Owens et al., 1996). Both acyclovir

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and valacyclovir are associated with systemic toxicity in cats, manifesting as hepatic and renal necrosis, as well as bone marrow suppression (Nasisse et al., 1997). Additionally, valacyclovir did not decrease viral shedding or severity of signs of clinical disease in experimentally infected cats (Nasisse et al., 1997). Evaluation of a topically administered 0.5% acyclovir ointment to cats with presumed herpesvirus-associated corneal lesions was associated with resolution of disease in a median of 12 days, with greater improvement noted in cats receiving five times daily treatment (Williams et al., 2005). Taken together, the poor efficacy, low bioavailability, and potential for systemic toxicities indicate that acyclovir and valacyclovir are of limited use as systemically administered antivirals in cats (Maggs, 2010). In contrast, ganciclovir is a guanosine analogue with excellent *in vitro* efficacy versus FHV-1 (Maggs & Clarke, 2004). Ganciclovir is available as 0.15% ophthalmic gel. However, it has not been evaluated clinically in the cat.

Famciclovir is the oral prodrug of penciclovir, which has good *in vitro* activity versus FHV-1 (Hussein et al., 2008; Maggs & Clarke, 2004) because of its selectivity for the FHV-1 thymidine kinase (Hussein et al., 2008). Following oral administration of famciclovir, which is preferred because of poor bioavailability of penciclovir, penciclovir is produced by di-deacetylation and oxidation by hepatic aldehyde oxidase (Clarke et al., 1995; Filer et al., 1994). Although the pharmacokinetics of famciclovir are relatively predictable in human beings (Cirelli et al., 1996), the activity of hepatic aldehyde oxidase in cats is minimal (Dick et al., 2005), resulting in complex and nonlinear pharmacokinetics after oral administration in cats (Sebbag et al., 2016; Thomasy et al., 2007, 2011, 2012a, 2012b). A single oral dose of 40 or 90 mg/kg famciclovir in cats resulted in similar plasma concentrations and areas under the plasma concentration-time curve for penciclovir (Thomasy et al., 2012b). Although one study reports potentially therapeutic concentrations of penciclovir within the tears of cats after oral administration of 40 mg/kg famciclovir three times daily (Thomasy et al., 2012a), a second, more comprehensive study indicates that this dose did not result in adequate tear concentrations of penciclovir (Sebbag et al., 2016). Therapeutic and comparable plasma and tear concentrations of penciclovir were achieved in cats administered 90 mg/kg famciclovir by mouth twice daily (Sebbag et al., 2016).

The efficacy of famciclovir has been evaluated at various dosages and frequencies in cats with FHV-1. In cats with experimentally inoculated FHV-1, the administration of 90 mg/kg famciclovir by mouth three times daily significantly improved systemic, ophthalmic, clinicopathologic, virologic, and histologic outcomes compared with placebo-treated cats (Thomasy et al., 2011). A retrospective assessment of client-owned cats with naturally occurring FHV-1 reveals the median time to improvement of clinical signs was significantly shorter, and the degree of improvement was significantly greater in cats receiving 90 mg/kg famciclovir orally three times daily compared with cats receiving 40 mg/kg famciclovir at the same frequency (Thomasy et al., 2016). Overall, owners were satisfied with their cat's treatment (29/32; 91%) regardless of the dose of famciclovir, and few adverse effects, such as vomiting, diarrhea, anorexia, and polydypsia, were attributed to treatment (Thomasy et al., 2016). Taken together, these studies indicate that the overall pharmacokinetics of famciclovir and penciclovir in the cat are complex, and further studies are required to determine an ideal dosing regimen. Future treatment directions may include a long-term steady-state penciclovir delivery system via a silicone polymer implant that could be placed in the subconjunctival space to provide constant FHV-1 suppression (Semenkow et al., 2014).

Vidarabine is an adenosine analogue that interferes with DNA polymerase, blocking viral DNA replication. Its specificity for viral enzymes is limited, leading to substantial host toxicity if administered systemically. Similar to idoxuridine and trifluridine, when administered topically as a 3% ophthalmic ointment, it must be used four to six times per day. Although no clinical trials utilizing vidarabine in cats have been performed, anecdotal evidence suggests it may be tolerated by cats better than idoxuridine or trifluridine (Maggs, 2010).

Interferons

Interferons are glycoprotein cytokines released by infected cells in response to pathogen invasion that subsequently influence neighboring, uninfected cells to induce an antiviral state. Type I IFNs (primarily IFN-α, IFN-β, and IFN-ω) share structural homology, are produced by most cells in response to viral infection and bind the same cell surface IFN receptor (IFNAR1/2) (Bonjardim et al., 2009). The type II IFN (IFN-γ) is considered a more powerful immunomodulatory cytokine, because it is produced by natural killer, CD4+ helper, and CD8+ cytotoxic cells, and binds its own receptor (IFNGR1/2) (Bonjardim et al., 2009). IFNs influence antiviral effects within cells through inducing gene transcription, the products of which inhibit viral genome translation, lead to degradation of viral nucleic acids, and stimulate innate cellular immunity (Samuel, 2001). When administered orally, IFNs are degraded in the gastrointestinal tract (Eid et al., 1999). However, clinical antiviral efficacy has been noted after oral dosing in humans and animals, thought to be associated with induction of a mucosal immunologic response (Cummins et al., 2005).

In vitro, recombinant human IFN-α (rHuIFN-α) has been shown to decrease cytopathic changes and FHV-1 titers significantly when applied at a concentration of 10^5 U/mL to cultured feline corneal epithelial cells (Sandmeyer et al., 2005b). Additionally, rHuIFN-α alone at concentrations of 10^2–10^6 U/mL did not induce cytotoxic effects on the feline corneal epithelial cell cultures

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(Sandmeyer et al., 2005b). In feline embryo cell cultures, addition of 10–100 U rHuIFN-α/mL led to an eightfold reduction in the dose of acyclovir required to achieve maximal inhibition of FHV-1 (Weiss, 1989). Comparison of the effects of recombinant human IFN-α2b (rHuIFN-α2b) and recombinant feline IFN-ω (rFeIFN-ω) on cultured Crandell-Rees feline kidney (CRFK) cells showed a significant reduction in number of viral plaques after incubation with 100,000 U/mL and 500,000 U/mL of rFeIFN-ω relative to untreated control, with comparable reduction in plaque size among cultures incubated with rHuIFN-α2b and rFeIFN-ω (Siebeck et al., 2006).

In vivo evaluation of the biological response to rFeIFN-ω has been evaluated utilizing expression of Mx protein, an antiviral cellular protein induced in response to exposure to type I IFNs (Ronni et al., 1993). Mx protein expression in white blood cells and conjunctival cells after topical administration of rFeIFN-ω to the eyes of specific pathogen-free (SPF) cats was dose-dependent, with positive expression in conjunctival cells for up to 21 days and in white blood cells for up to 45 days in eyes receiving the highest dose (10,000 U rFeIFN-ω) (Bracklein et al., 2006). Following oral administration of 200–20,000 U rFeIFN-ω, Mx protein was not detected in conjunctival cells but was detected in white blood cells in a dose-dependent manner for 3–42 days (Bracklein et al., 2006).

In evaluation of clinical efficacy, pretreatment with 10,000 U rFeIFN-ω administered topically to both eyes of SPF cats twice daily for 2 days in conjunction with oral administration of 20,000 U rFeIFN-ω once, followed by inoculation with FHV-1, did not reduce the severity or duration of clinical signs, nor the viral shedding in treated versus untreated cats (Haid et al., 2007). Additionally, in cats with naturally occurring viral keratoconjunctivitis, ocular administration of high doses of rFeIFN-ω (10^6 U/mL) or rHuIFN-α2b (10^6 U/mL) twice daily for 14 days did not improve clinical disease or virus shedding, compared with treatment with saline solution (Slack et al., 2013). Further clinical trials with client owned (Ballin et al., 2014) and shelter-housed (Fenimore et al., 2016) cats treated with subcutaneous injections of rFeIFN-ω or rHuIFN-α, respectively, did not have significant treatment effects. Overall, there is little evidence to support the topical or subcutaneous use of IFN in the management of FHV-1 (Thomasy & Maggs, 2016).

Oral administration of low dose cytokines may be a more effective approach to the treatment of herpetic disease. Low doses (10 fentograms/mL) of sequential kinetic activated human interleukin (IL)-12 plus HuIFN-γ were orally administered to cats naturally infected with FHV-1 every 12 hours for 6 months (Fiorito et al., 2016). The treated cats had significantly improved clinical signs and decreased viral detection by PCR compared with a placebo group (Fiorito et al., 2016).

L-Lysine

The amino acid L-lysine has been shown to interfere with viral replication, presumptively through antagonism of L-arginine, an essential component of replication (Griffith et al., 1981; Maggs et al., 2000; Tankersley, 1964). *In vitro* support for this is evidenced by a study in which, after inoculation with FHV-1, CRFK cell cultures showed a significant (approximately 80% relative to control) reduction in virus titer when incubated with 200 or 300 μg/mL of lysine, provided that arginine levels were restricted to 0 or 2.5 μg/mL (Maggs et al., 2000). When higher, more physiologic arginine concentrations were tested *in vitro*, L-lysine did not inhibit the replication of FHV-1 (Cave et al., 2014).

In vivo, administration of 500 mg L-lysine orally twice daily to a group of random-source cats, beginning 6 hours prior to experimental inoculation with FHV-1 and continuing for the subsequent 3 weeks, significantly lessened but did not eliminate clinical signs of disease relative to untreated control cats (Stiles et al., 2002). Other studies reveal conflicting evidence regarding the efficacy of L-lysine supplementation, however (Drazenovich et al., 2009; Maggs et al., 2003, 2007; Rees & Lubinski, 2008). In an experimental setting, primary FHV-1 infection was induced in 14 SPF cats via viral inoculation, after which infection subsided and cats seroconverted to a latently infected status (Maggs et al., 2003). Treated cats then received 400 mg L-lysine orally once daily for 30 days, with recrudescent FHV-1 infection induced via methylprednisolone administration on day 15 of therapy. Although L-lysine was associated with reduced viral shedding in cats prior to corticosteroid challenge, it was not associated with a reduction in clinical signs throughout the 30-day time period (Maggs et al., 2003). Additionally, oral L-lysine supplemented at 51 g lysine/kg diet (vs. 11 g lysine/kg diet unsupplemented) to a colony of cats with enzootic upper respiratory disease was associated with increased clinical disease scores and viral shedding in supplemented cats. However, behavioral stresses or confounding pathogens may have been involved (Maggs et al., 2007). Finally, administration of 250–500 mg orally once daily to cats without signs of an upper respiratory infection when surrendered to a shelter did not decrease development of such clinical signs relative to an untreated control group (Rees & Lubinski, 2008), whereas a diet of 57 g lysine/kg diet versus 19 g lysine/kg diet was associated with increased occurrence of moderate to severe signs of upper respiratory tract infections and increased isolation of FHV-1 DNA in a separate group of shelter cats (Drazenovich et al., 2009). Regardless of its clinical efficacy, oral supplementation with L-lysine did not produce significant deficiencies in plasma arginine concentrations (Drazenovich et al., 2009; Fascetti et al., 2004; Maggs et al., 2003, 2007; Stiles et al., 2002), nor clinical signs associated with arginine deficiency (Fascetti et al., 2004; Maggs et al., 2003; Rees & Lubinski, 2008; Stiles et al., 2002) in any of the reports.

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8.3

Clinical Pharmacology and Therapeutics

Part 3: Anti-Inflammatory and Immunosuppressant Drugs

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Ocular Inflammation

Ocular inflammatory responses are mediated by several compounds including prostaglandins, leukotrienes, platelet-activating factor, neuropeptides (like calcitonin gene-related peptide and substance P), interleukins, and bradykinin (Millichamp & Dziezyc, 1991a; Regnier et al., 1986). Endogenous prostaglandins play an important role in the initiation and maintenance of intraocular inflammation. In response to mechanical or chemical stimuli, arachidonic acid is released from cell membranes by the enzymatic action of phospholipase A_2. Arachidonic acid is metabolized by two main pathways, the cyclooxygenase and the lipoxygenase pathways. Products of the lipoxygenase pathway include hydroxyl-eicosatetraenoic acids and leukotrienes. Cyclooxygenase converts arachidonic acid to prostaglandins (PGE_2, PGD_2, $PGF_{2\alpha}$, and PGI_2) and thromboxane A_2. Prostaglandins comprise a group of oxygenated fatty acids with a wide range of biological activity. They have been found in almost all mammalian tissues and have been shown to be involved in normal physiological as well as pathological processes. There are three isoenzymes of cyclooxygenase, COX-1, COX-2, and COX-3 which is a variant of COX-1. Unlike COX-1 and COX-2, COX-3 is unlikely to be involved in inflammation in human patients (Botting, 2003; Chandrasekharan et al., 2002). The COX-1 isoform is expressed constitutively in many cells and is generally considered responsible for production of baseline concentrations of prostaglandins involved in normal tissue homeostasis including gastrointestinal mucosal integrity, platelet aggregation, and regulation of renal perfusion. In contrast, the COX-2 isoform is inducible in reaction to noxious stimuli as well as being expressed in normal and neoplastic cells. Both COX-1 and COX-2 have been identified in normal rabbit iris and ciliary body which suggests that both enzymes have a role in maintaining the physiology of the eye (Damm et al., 2001). Prostaglandins have several effects in the eye including miosis, an initial increase and then a decrease in intraocular pressure (IOP), disruption of the blood–aqueous barrier, vasodilation, iris neovascularization, and possibly corneal neovascularization (Millichamp & Dziezyc, 1991a). Intracameral injections of prostaglandins have been shown to cause disruption of the blood–aqueous barrier and increase anterior chamber protein concentration (Beitch & Eakins, 1969; Stjernschantz, 1984; Unger et al., 1975). Prostaglandins can be produced in almost all ocular tissues with the exception of the lens, and they have been shown to be synthesized in the iris and ciliary body (Kulkari & Srinivasan, 1989; Stjernschantz, 1984). Prostaglandin receptors have been detected in the iris and ciliary body of several mammals, including rabbits, cats, cows, and humans (Bhattacherjee et al., 1993, 1997; Bhattacherjee & Paterson, 1994).

Anti-Inflammatory Agents

Corticosteroids

Mechanism of Action

Corticosteroids bind to specific receptors in the cytoplasm of cells in the conjunctiva, cornea, iris, retina, choroid, and sclera (Hernandez et al., 1981; Tchernitchin et al., 1980). The effectiveness of corticosteroids is mediated through their impact on both the cyclooxygenase and lipoxygenase pathways. Corticosteroids inhibit phospholipase A_2 activity on phospholipids, which prevents biosynthesis of arachidonic acid and subsequent formation of prostacylin, thromboxane A, prostaglandins, and leukotrienes (Flower, 1988; Schleimer, 1985). Glucocorticoids have also been shown to decrease prostaglandin synthesis at the level of the COX pathway (Goppelt-Struebe et al., 1989), and they may induce local expression of somatostatin, which has anti-inflammatory properties (Karalis et al., 1995). Lysosomal membrane stabilization is a well-known, yet not clearly defined, subcellular action of glucocorticoids. This effect blocks degranulation of neutrophils, mast cells, and

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basophils, and prevents release of proinflammatory substances such as proteases, histamine, and bradykinin.

Routes of Administration

Topical Ocular Administration

Topical administration of corticosteroids is indicated to treat anterior segment disease because of ease of application and decreased systemic side effects. Selection of a particular topical steroid and the frequency of administration varies with the severity and location of the inflammation. Topical steroid therapy should be continued at a reduced frequency for several days to weeks after resolution of signs of ocular inflammation, because prematurely discontinuing the medication can lead to a relapse of the inflammation (Leibowitz & Kupferman, 1980a; Leopold, 1967).

Several factors limit the therapeutic effect of a topical corticosteroid ophthalmic preparation, including corneal permeability, degree of steroid receptor binding, extent of ocular metabolism of the drug, and the effect of the drug on the target cell. The greatest barrier to intraocular penetration of topical corticosteroids is the lipophilic corneal epithelium. Therefore, lipophilic acetate and alcohol corticosteroid preparations penetrate the cornea more readily than sodium salts of the steroid phosphate (McGee et al., 1990; Musson et al., 1992). The water-soluble salts are generally formulated as solutions, and the more lipid-soluble derivatives are available as suspensions and ointments. Even though 0.1% dexamethasone sodium phosphate and 0.1% betamethasone sodium phosphate have five to seven times the anti-inflammatory effect of prednisolone, they are both poorly absorbed from the cornea (McGee, 1992). Due to their poor corneal penetration, they are not the drugs of choice when treating inflammation in the anterior segment of the eye. Prednisolone acetate 1% or dexamethasone alcohol 0.1% have superior intraocular penetration and are generally recommended as therapy for anterior segment inflammation.

Subconjunctival Injection

Subconjunctival injections of corticosteroids can be used as a supplement to topical and systemic administration of steroids in cases of severe inflammation and in uncooperative patients. Subconjunctival injections of corticosteroids are effective in achieving high drug concentrations in the anterior segment of the eye. Corticosteroids injected into the subconjunctival space should be well tolerated in the subconjunctival space as well as on the ocular surface because a portion of the injected material will flow back through the conjunctival hole and mix with the preocular tear film. Table 8.3.1 lists the corticosteroid solutions intended for parenteral injection which may be administered subconjunctivally. In general, ophthalmic preparations of corticosteroids should not be injected into the subconjunctival space because the preservatives in these compounds may be locally irritating. Phosphate esters are water soluble and are rapidly absorbed from the injection site and have a shorter duration of action, compared with acetate and diacetate esters that are poorly water soluble and have a longer duration of action. Dexamethasone's duration of effect is approximately 1–2 days whereas triamcinolone and betamethasone act as repositol preparations and have duration of effect up to 2–3 weeks.

Table 8.3.1 Commercially available corticosteroid agents for subconjunctival injection.

Drug	Suggested dose
Betamethasone	1–3 mg
Dexamethasone	0.5–1 mg
Methylprednisolone acetate	4–8 mg
Triamcinolone acetonide	4–12 mg

Intravitreal Injection

Intravitreal injections of corticosteroids are used in human patients to treat chronic uveitis, macular edema, and proliferative diabetic retinopathy (Degenring & Jonas, 2003; Jonas 2007; Googe et al., 2011; Penha et al., 2012). In veterinary medicine, intravitreal injections of corticosteroids are not commonly used. In a pilot study, there was no evidence of overt toxicity from intravitreal vehicle-free triamcinolone acetonide injections of 10, 20, or 40 mg in normal equine eyes, and there were sustained drug ocular concentrations for at least 3 weeks after the injection (Yi et al., 2008). There was transient ventral corneal edema in eyes injected with triamcinolone acetonide which resolved within 7 days. However, in that same study (Yi et al., 2008), bacterial contamination occurred in 33% of the horses either because of the intravitreal injection (placebo or triamcinolone acetonide) or during the aqueocentesis procedures that were performed, highlighting the importance of taking precautions to prevent bacterial contamination. Intravitreal injections of corticosteroids should be used with caution in equine patients living in geographic areas where fungal keratitis is prevalent. There have been reports of vision loss and sterile endophthalmitis in humans after intravitreal triamcinolone injection that contained benzyl alcohol as a preservative (Stepien et al., 2009). In the rabbit eye, benzyl alcohol injected intravitreally at concentrations modestly higher than what is available in commercial products was found to be toxic (Morrison et al., 2006). Decanting the supernatant, using other methods to remove the benzyl alcohol, or choosing a preservative-free formulation of the corticosteroid should be considered for intravitreal injections.

Systemic Administration

Inflammation of the adnexa, posterior segment, optic nerve, or orbit usually requires systemic administration of corticosteroids in veterinary medicine once an infectious etiology

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has been ruled out. Systemic corticosteroids may also be used to treat anterior uveitis in conjunction with topical corticosteroid therapy. Because adverse systemic effects are more likely to occur with systemically administered corticosteroids than topically applied medications, the lowest effective dose should be prescribed.

Indications for Ocular Disease

Corticosteroids are beneficial in treating various inflammatory disorders of the adnexa and globe. For treatment of superficial external ocular inflammatory conditions such as blepharitis, conjunctivitis, episcleritis, and nonulcerative keratitis, formulations of topical medications that do not penetrate the cornea well may be preferred such as topical dexamethasone sodium phosphate 0.1%, prednisolone sodium phosphate 1%, or hydrocortisone. Corticosteroids inhibit the formation of fibroblasts and limbal blood vessels (Boneham & Collin, 1995), and they are topically administered for treatment of nonulcerative keratitis in an attempt to preserve the transparency of the cornea. When treating intraocular inflammation, preparations that easily penetrate the cornea are preferred, such as topical prednisolone acetate 1% or dexamethasone alcohol 0.1%. The frequency of medication application is dictated by the severity of the disease condition being treated. Severe uveitis can be treated up to hourly, but generally six to eight times daily is sufficient, and the frequency is slowly tapered based on clinical improvement. Abrupt discontinuation of corticosteroid therapy can lead to a rebound phenomenon; therefore, gradual tapering of topical medications is recommended (Leibowitz et al., 1980a).

Subconjunctival corticosteroid injections may be used for the treatment of noninfectious keratoconjunctivitis, anterior episcleritis or scleritis, and anterior uveitis. A potential complication of injection of repository corticosteroids, such as methylprednisolone acetate and triamcinolone, is the formation of a granuloma that may necessitate surgical removal (Fischer, 1979; Hakanson et al., 1991).

Systemic corticosteroid administration may be combined with either topical or subconjunctival corticosteroids for the therapy of anterior uveitis or used alone for the treatment of blepharitis, chorioretinitis, optic neuritis, extraocular polymyositis, or noninfectious orbital inflammation. There are several systemic conditions that preclude the concurrent use of systemic corticosteroids, such as generalized infections, thrombophlebitis, osteoporosis, diabetes mellitus, pancreatitis, renal failure, and pregnancy.

Ophthalmic Corticosteroids

Prednisolone

Prednisolone is an effective anti-inflammatory agent in patients with external as well as intraocular inflammatory conditions. Due to the lipophilic nature of the acetate preparation, it is able to penetrate the intact corneal epithelium better than the water-soluble phosphate solution. In a study where topical steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs) were used to compare the efficacy of preventing paracentesis-induced blood–aqueous barrier disruption using fluorophotometry in dogs, it was found that pretreatment with topical prednisolone acetate 1% and flurbiprofen 0.03% were more effective than dexamethasone sodium phosphate 0.1% (Ward et al., 1992b). In a study in cats using laser flaremetry to assess intraocular inflammation after anterior chamber paracentesis, topical prednisolone acetate 1% significantly reduced intraocular inflammation (Rankin et al., 2011), although other studies comparing the effects of topical prednisolone acetate with flurbiprofen and a dual cyclooxygenase/lipoxygenase inhibitor failed to demonstrate significant anti-inflammatory effects of prednisolone acetate (Dziezyc et al., 1992, 1995). Compared with other topical ocular steroids, prednisolone acetate 1% is generally considered the most effective anti-inflammatory agent for anterior segment inflammation (Leibowitz & Kupferman, 1975).

Dexamethasone

Dexamethasone has been reported to be 10-fold more potent than prednisolone (Havener, 1984). The difference in potency between dexamethasone and prednisolone is somewhat obviated by the commercial formulations of these medications. Dexamethasone sodium phosphate was found in a study to be the least effective at stabilizing the canine blood–aqueous barrier compared with flurbiprofen 0.03% and prednisolone acetate 1% (Ward et al., 1992b). However, it is known that dexamethasone sodium phosphate has poor corneal penetration, and this could account for its poor efficacy in that study. Topical application of dexamethasone beloxil inhibited endotoxin-induced leukocyte influx in both rodent and feline models of uveitis (Bhattacherjee et al., 2003). Following a single application of topical dexamethasone ointment or suspension in normal cat eyes, detectable levels of dexamethasone were found in the third eyelid, cornea, aqueous humor, and iris at 3 and 6 hours (Bessonova, 2011). In that same study, at 6 hours after application there was a substantially higher level of dexamethasone in the eyes treated with dexamethasone ointment compared with the suspension (Bessonova, 2011).

Hydrocortisone

Hydrocortisone is available in combination with neomycin/polymyxin B/bacitracin ophthalmic ointment. It does not penetrate the cornea well and should not be used for treatment of intraocular inflammation, but may be appropriate for treatment of mild ocular surface inflammatory conditions.

Fluorometholone, Rimexolone, and Loteprednol

A number of glucocorticoids (fluorometholone, rimexolone, and loteprednol) have been developed and marketed which

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have a lower propensity to increase IOP than prednisolone and dexamethasone in human patients (Bartlett et al., 1993; Kass et al., 1986; Leibowitz et al., 1996; Mindel et al., 1980). Unfortunately, although they do not increase the IOP, they lack the anti-inflammatory efficacy of prednisone and dexamethasone. There are no reports of the efficacy of these medications in veterinary species.

Side Effects of Ophthalmic Corticosteroids

Effect on Ocular Infection

Corticosteroids decrease leukocyte migration and depress macrophage phagocytosis of microbes. Depression of the ingestive ability of monocytes and macrophages may result from changes in the number of receptors on their cell membranes and from a decreased activation of macrophages by lymphokines and nitric oxide synthase (Dannenberg, 1979; Moncada & Plamer, 1991). As a result, corticosteroids can potentially activate or exacerbate ocular bacterial, viral, or fungal infections and are generally considered contraindicated in most ocular infections. The administration of subconjunctival betamethasone has been shown to cause stromal keratitis in cats that have been experimentally infected with feline herpesvirus 1 (Nasisse et al., 1989). Although there are no reports in the literature citing the activation of latent feline herpesvirus infection after topical corticosteroid therapy, topical corticosteroids should be used cautiously in cats with suspected feline herpesvirus latent infection. In an experimental model of bacterial keratitis in rabbits, the use of a topical corticosteroid did not enhance bacterial replication when administered concurrently with an effective bactericidal antibiotic (Leibowitz & Kupferman, 1980b). If corticosteroids are considered in a clinical setting, they should be used only after the causative agent has been identified and is currently being treated. In horses with fungal keratitis or stromal abscesses, the use of topical corticosteroids is generally contraindicated (Hendrix et al., 1995; Nasisse & Nelms, 1992). Long-term topical use of corticosteroids is believed to predispose to keratomycosis in horses by interfering with local host immune defenses. Previous corticosteroid use was identified in 76% of 53 equine eyes with fungal keratitis (Gaarder et al., 1998). Topical application of corticosteroid–antibiotic combinations for 2 weeks in normal horses had no detrimental effects on the normal ocular flora (Gemensky-Metzler et al., 2005), suggesting that the role of glucocorticoids in infectious keratitis is probably not related to a direct increase in the prevalence of pathogens. In small animals, systemic glucocorticoids may be used cautiously in conjunction with specific antifungal therapy in cases of intraocular fungal infection (blastomycosis, histoplasmosis, etc.) in an attempt to decrease posterior segment inflammation and preserve vision.

Effects on Corneal Wound Healing

In vitro studies demonstrate that corticosteroids increase the lytic action of corneal collagenase, which can lead to rapid stromal melting of corneal ulcers (Brown et al., 1970). Therefore, topical corticosteroids are generally considered contraindicated in the presence of corneal ulceration. However, systemic corticosteroids have little effect on the corneal healing processes and may be used in patients with an active corneal ulcer. Topical corticosteroids are routinely used after intraocular surgery to reduce postoperative inflammation. Experimental data suggest that topical corticosteroids may delay corneal healing by affecting corneal epithelial healing rates (Petroutsos et al., 1983), stromal keratocyte proliferation, and collagen deposition (Phillips et al., 1983). *In vitro*, dexamethasone manifested less cytopathic effects than prednisolone on cultured canine epithelial cells, and dexamethasone may be the drug of choice when a corticosteroid is indicated in a dog with a corneal epithelial defect (Hendrix et al., 2002). However, in cultured human corneal keratocytes, dexamethasone induced proliferation and apoptosis of keratocytes (Bourcier et al., 1999).

Cataract Formation

Steroid-induced cataract formation, although not well documented in small animals, has been produced experimentally in cats by topical administration of dexamethasone or prednisolone. Subcapsular cataracts occurred after at least 40 days of corticosteroid therapy (Zhan et al., 1992). The mechanisms responsible for the cataractous changes are unknown, partly because of the difficulties in developing suitable *in vivo* and *in vitro* models for steroid-induced cataract formation (Jobling & Augusteyn, 2002). Decrease in lens enzymes, alteration in lens hydration by modulation of the Na^+, K^+-adenosine triphosphatase, and alterations in the systems involved in protection of the lens from oxidative stress may be involved in the pathogenesis of glucocorticoid-induced cataracts (Jobling & Augusteyn, 2002). Posterior subcapsular cataract formation, rise in IOP, and accumulation of subretinal fluid at the posterior pole of the fundus (central serous chorioretinopathy) have also been reported in human patients in response to systemically administered glucocorticoids (Bouzas et al., 2002; Carnahan & Goldstein, 2000).

Ocular Hypertension

Corticosteroids have been documented to produce an increase in IOP in healthy human subjects and in patients with glaucoma (Armaly, 1963a, 1963b; Becker & Mills, 1963; Linner, 1959). Human corticosteroid-induced ocular hypertension appears to have a genetic basis and is related to a decrease in outflow facility resulting from an accumulation of extracellular material, resembling basement membranes, in the trabecular meshwork (Johnson et al., 1997). Increased expression of laminin and myocilin has been identified in the trabecular meshwork cells in the presence of glucocorticoids and might play a pathogenic role in the accumulation of extracellular matrix material in the trabecular meshwork (Clark et al., 2001; Dickerson et al., 1998). The hypertensive

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effect of corticosteroids has recently been documented in Beagles with primary open-angle glaucoma and in normal cats and cattle. In Beagles with primary open-angle glaucoma, IOP increased by a mean of 5 mmHg in treated eyes within 2 weeks of topical application of dexamethasone 0.1% and returned to normal when the treatment was discontinued (Gelatt & Mackay, 1998). A recent study showed that topical corticosteroid administration (prednisolone acetate 1% and dexamethasone sodium phosphate 0.1%) to normal cats did not result in a clinically significant increase in IOP (Gosling et al., 2016). In that same study, eight of 11 cats with primary feline congenital glaucoma that were treated with a topical ophthalmic corticosteroid had an increase in IOP compared with the untreated contralateral eye (maximum discrepancy of 56 mmHg) (Gosling et al., 2016). In other studies, healthy cats treated with topical dexamethasone 0.1% or prednisolone acetate 1%, as well as normal cows receiving topical prednisolone acetate 1%, manifested a significant increase in IOP within 2–3 weeks of treatment (Bhattacherjee et al., 1999; Gerometta et al., 2004; Zhan et al. 1992). An increase in IOP was not observed in healthy dogs administered oral hydrocortisone at a dose of 3.3 mg/kg every 8 hours for 5 weeks (Herring et al., 2004). A recent study found that topical application of prednisolone acetate 1% did not alter topical 0.005% latanoprost's miotic and hypotensive effects in normal dogs (Kahane, et al., 2016), although in previous studies topical prednisolone acetate 1% (Pirie et al., 2006) and dexamethasone sodium phosphate 0.1% (Gilmour and Lehenbauer, 2009a) did reduce the hypotensive effect of latanoprost 0.005% in normal dogs.

Systemic Effects

After topical application of an ophthalmic medication, a portion of the medication will be absorbed systemically through the conjunctiva and/or nasal or oral mucosa after the medication passes through the nasolacrimal system. Although systemic absorption of topically applied medications is incomplete, even low serum levels can have demonstrable systemic side effects. Suppression of the hypothalamic–hypophyseal–adrenal axis has been noted in dogs after application of topical prednisolone acetate 1% four times daily for 2 weeks (Eichenbaum et al., 1988; Roberts et al., 1984). Topical application of dexamethasone suspension 0.1% four times daily to both eyes in Beagles (average dose of 0.03 mg/kg of body weight/day) also resulted in adrenal suppression as well as histopathologic changes in the liver (Glaze et al., 1988). Subconjunctival administration of two doses of 10 mg of methylprednisolone acetate at an interval of 21 days caused suppression of ACTH-stimulated cortisol (Regnier, 1982). Iatrogenic Cushing's syndrome has been documented in a dog that was receiving chronic topical ophthalmic steroid therapy (Murphy et al., 1990). Topical application of ophthalmic dexamethasone has been shown to increase blood glucose levels significantly in diabetic human patients undergoing cataract surgery (Bahar et al., 2007). Although it has been suggested that topical steroids may cause insulin antagonism and interfere with glycemic control in diabetic dogs (Feldman & Nelson, 2004), a recent study showed that there was no significant effect on diabetic regulation in dogs that were treated with topical prednisolone acetate 1% relative to diclofenac 0.1% four times daily for 4 weeks based on fructosamine concentrations, body weight, and clinical scores (Rankin, 2019). Administration of topical dexamethasone 0.1% ophthalmic ointment four times daily to one eye of adult horses resulted in detectable levels of corticosteroids in the urine and serum (Spiess et al., 1999). Another example of possible systemic side effects is late gestation abortions in llamas caused by topical dexamethasone ointment therapy (Graham et al., 2002).

Other Side Effects

In humans and horses, calcific band keratopathy has been associated with the use of topical ophthalmic corticosteroids (Berryhill, 2017; Brooks, 2012; Taravella et al., 1994) Although this condition is not reported in the veterinary literature, lipid keratopathy is a clinically recognized condition in small animal patients treated with topical corticosteroids. The lipid keratopathy does not resolve after cessation of the topical steroids.

In calves receiving parenteral administration of dexamethasone (30 mg/kg subcutaneously twice daily), bilateral exophthalmos was observed after approximately 28 days of treatment (Townsend et al., 2003). Protrusion of the globes was the result of adipose tissue deposition in the retrobulbar area. Excess body fat was not detected elsewhere in the body, and the mechanism by which dexamethasone induced this side effect was not determined (Townsend et al., 2003).

Nonsteroidal Anti-Inflammatory Drugs

Mechanism of Action

NSAIDs have been widely used for their analgesic, antipyretic, and anti-inflammatory properties in human and veterinary patients. NSAIDs inhibit prostaglandin synthesis by inhibiting the cyclooxygenase enzyme which converts arachidonic acid to prostaglandins (PGE_2, PGD_2, $PGF_{2\alpha}$, and PGI_2) and thromboxane A_2 (Vane & Botting, 1995). Two main isoforms of COX (COX-1 and COX-2) have been identified and are normally present in tissues at fairly constant concentrations. In general, COX-1 is responsible for production of prostaglandins that are required for normal tissue homeostasis, such as gastric cytoprotection, regulation of renal flow, and platelet function. Constitutive expression of COX-1 enzymes occurs on the endoplasmic reticulum of all cells, including gastrointestinal mucosa, renal medullary ducts, platelets, vascular endothelium, and pulmonary, hepatic, and splenic sites (Gaynes & Fiscella, 2002). In contrast, COX-2 produces prostaglandins primarily at sites of

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inflammation by cells that have been stimulated by cytokines and other inflammatory mediators, although it can be found in low amounts in physiologically normal tissues. Constitutive expression of COX-2 is found in the kidney, central nervous system, vascular endothelium, and gastrointestinal tract (Ito et al., 2001; Tomlinson & Blikslager, 2003; Wooten et al., 2008, 2009). The toxic effects of NSAIDs are thought to result primarily from inhibition of COX-1. Aspirin, indomethacin, flurbiprofen, and possibly flunixin meglumine cause irreversible inactivation of the enzyme, whereas interaction with ibuprofen is reversible (Smith et al., 1990). Classification of NSAIDs is according to their ability to preferentially inhibit one isoform versus the other. Cyclooxygenase selectivity is typically expressed as a ratio of the concentrations at which a specific drug inhibits each isoenzyme by 50%. Many common NSAIDs, such as aspirin, indomethacin, diclofenac, flurbiprofen, ketorolac, and ibuprofen are considered to be nonselective COX inhibitors, which mean they inhibit both COX-1 and COX-2. NSAIDs have been classified based on their selectivity for COX-1 and COX-2 on the assumption that greater selectivity for COX-2 would result in fewer adverse effects but still provide anti-inflammatory and analgesic effects. However, both COX-1 and COX-2 have been localized in normal rabbit iris and ciliary body tissues (Damm et al., 2001). This pattern of distribution in normal rabbit eyes suggests a role for both enzymes in maintaining the normal physiologic status of the eye and the development of inflammation. Meloxicam is considered to be a preferential COX-2 inhibitor *in vitro* because it inhibits COX-2 more readily than COX-1 (Kay-Mugford et al., 2000; Streppa et al., 2002). *In vitro* studies (Kay-Mugford et al., 2000; McCann et al., 2004) have revealed that meloxicam inhibits COX-2 activity 10–12 times as effectively as it inhibits COX-1 activity. Deracoxib, firocoxib, robenacoxicib, etodolac, and carprofen are classified as selective COX-2 inhibitors (Clark, 2006; Sessions et al., 2005; Sharp et al., 2016). Although these NSAIDs are selective for inhibition of COX-2, most have varying degrees of inhibitory activity against COX-1. Tepoxalin is COX-1 preferential and is currently not commercially available in the United States.

Indications for Ocular Disease

Topical NSAIDs have been developed to improve the ocular bioavailability of these compounds and to decrease their systemic side effects. In humans, topical NSAIDs are used for the management of postoperative ocular inflammation and the prevention of cystoid macular edema after cataract surgery. They are also used to prevent intraoperative miosis during cataract surgery, for the relief of the symptoms of allergic conjunctivitis, and to alleviate ocular discomfort after refractive surgery. Several studies have also shown the analgesic effects of topical NSAIDs in humans (Appiotti et al., 1998; Epstein & Laurence, 1995; Fry, 1995; Gwon et al., 1994). Topical NSAIDs are not used commonly in veterinary medicine to reduce corneal pain, but in one study (Chen et al., 1997) topical indomethacin, diclofenac, and flurbiprofen, as well as the calcium antagonist diltiazem, diminished the responsiveness of feline corneal polymodal nociceptors to chemical stimuli. The mechanism by which the responsiveness of the nocioceptors was diminished appears to be caused by the direct effect of the drugs on the excitability of the nerve endings and also by inhibition of the formation of cyclooxygenase products such as prostaglandins (Chen et al., 1997). In a recent study of normal, nonbrachycephalic dogs after multiple drops or twice-daily dosing for 30 days, topical diclofenac and flurbiprofen did not have an effect on corneal sensitivity (Dorbandt et al., 2017). In contrast, in humans, topical diclofenac decreased corneal sensitivity (Acosta et al., 2005; Aragona et al., 2000). In veterinary medicine, topical NSAIDs are most commonly used to decrease intraocular inflammation and to prevent intraoperative miosis during cataract surgery. Topical NSAIDs are often used in combination with topical corticosteroids to reduce intraocular inflammation, and they may allow less frequent application of topical steroids. Although topical NSAIDs may be potent inhibitors of corneal neovascularization (Cooper et al., 1980), they are not routinely used in veterinary medicine for treatment of keratitis. Although subconjunctival injection of flunixin meglumine was found to inhibit local prostacyclin accumulation in a model of intraocular inflammation in horses (Cooley et al., 1984), this route of administration is not recommended because it causes severe inflammation at the injection site (Krohne & Vestre, 1989).

Ophthalmic NSAIDs

Topical ophthalmic NSAIDs include bromfenac 0.07%, 0.075%, and 0.09%, diclofenac 0.1%, flurbiprofen 0.03%, ketorolac 0.4%, 0.045%, and 0.5%, and nepafenac 0.1% and 0.3%. Topical formulations of indomethacin are commercially available only outside the United States. Several studies (Dziezyc et al., 1995; Krohne et al., 1998b; Millichamp & Dziezyc, 1991b; Regnier et al., 1995; Ward, 1996; Ward et al., 1992a, 1992b) have shown the ability of topical prostaglandin-inhibiting drugs to decrease the disruption of the blood–aqueous barrier in dogs. By use of fluorophotometry, topical pretreatment for 48 hours with flurbiprofen 0.03% was shown to more effectively decrease fluorescein leakage into the anterior chamber than pretreatment with prednisolone 1% when a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser was used to create an anterior capsulotomy in dogs (Dziezyc et al., 1995). In that same study (Dziezyc et al., 1995), flurbiprofen was much more effective at maintaining mydriasis than was prednisolone acetate, and there were no significant differences in IOP between the groups. In another study (Millichamp & Dziezyc, 1991b) in which a Nd:YAG laser anterior capsulotomy-induced inflammation was used,

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topical flurbiprofen was found to be as effective as flunixin meglumine administered IV at maintaining mydriasis, compared with untreated controls. In a study (Ward, 1996) comparing the efficacies of topical NSAIDs at preventing paracentesis-induced blood–aqueous barrier breakdown in dogs, 1% diclofenac suspension was superior to 1% suspensions of flurbiprofen, suprofen, and tolmetin. In that study (Ward, 1996), flurbiprofen and suprofen were also effective at preventing blood–aqueous barrier disruption. Two formulations of indomethacin (0.1% solution and 1% suspension) were compared using anterior chamber paracentesis-induced inflammation in dogs (Regnier et al., 1995). Miosis and aqueous humor protein concentrations were significantly reduced in the indomethacin-pretreated eyes compared with controls; however, there was no significant difference between the two formulations (Regnier et al., 1995). Topical diclofenac significantly reduced intraocular inflammation in cats with paracentesis-induced intraocular inflammation (Rankin et al., 2011).

Flurbiprofen is not ocularly metabolized, and approximately 10% of the dose enters the anterior chamber when topically applied (Tang-Liu et al., 1984). Following topical administration of flurbiprofen to rabbits, a large portion (74%) of the dose entered the systemic circulation (Tang-Liu et al., 1984). Ocular pharmacokinetic data in human patients indicate that after topical application, aqueous humor levels of flurbiprofen and diclofenac are similar and reach a maximum in about 2 hours, and that diclofenac remains in the anterior chamber longer than flurbiprofen (7.4 hours vs. 3.7 hours) (Ellis et al., 1994). Following application of one drop of diclofenac 0.1% to both eyes in rabbits, diclofenac was detected in the plasma at a peak concentration of 72.7 ng/mL 15 minutes after diclofenac administration, and it was still detectable at 240 minutes at a concentration of 2.6 ng/mL (Gonzalez-Penas et al., 1998). After topical application of diclofenac, high drug levels are reached in the normal as well as inflamed corneas, but diffusion into the aqueous humor is poor when the cornea is inflamed (Palmero et al., 1999). In a recent study both flurbiprofen and diclofenac were detected in the plasma of healthy cats treated topically four times daily for 14 days and flurbiprofen reached higher plasma concentrations compared with diclofenac (Lanuza et al., 2016). In another study topical application of diclofenac to healthy cats resulted in detectable systemic concentrations after 7 days of four times a day treatment (Hsu et al., 2015). A study evaluating the efficacy of COX-2 inhibitors in controlling inflammation and the development of posterior capsular opacification after cataract surgery in dogs found that celecoxib-IOL (lenses incubated for 24 hours with celecoxib and dimethyl sulfoxide) and prednisolone-acetate treated eyes had less posterior capsular opacification in the short term, and bromfenac-treated eyes had better long-term control of capsular opacification (Brookshire et al., 2015).

Side Effects of Ophthalmic Nonsteroidal Anti-Inflammatory Drugs

The most common adverse effect with topical ophthalmic NSAIDs is transient ocular irritation after administration of the medication. This is generally characterized by epiphora, blepharospasm, and conjunctival hyperemia.

Effects on Ocular Infection

Topical NSAIDs should not be considered as ideal substitutes for topical corticosteroids in cases of infectious keratitis because of their potential negative effects on ocular infection. For example, flurbiprofen is comparable to dexamethasone in its ability to worsen experimental herpetic keratitis in rabbits (Trousdale et al., 1980). Experimental studies have found that in some forms of uveitis, leukocyte infiltration of the inflamed areas is potentiated by NSAID treatment (Rao et al., 1987). This implies that NSAIDs may be detrimental in treating some forms of ocular inflammation, such as granulomatous uveitis. It has been suggested that selective inhibition of the COX pathway may shift more arachidonic acid toward the lipoxygenase pathway and thereby increase the synthesis of leukotrienes (Rao et al., 1987).

Effects on the Cornea

Corneal complications after topical NSAIDs use are relatively uncommon. In human patients, superficial punctate keratitis, corneal infiltrates, and epithelial defects have been reported after use of these agents (Gills, 1994; Probst & Machatt, 1996; Sher et al., 1994; Shimazaki et al., 1995). The effect of topical NSAIDs on corneal wound healing has been investigated in rabbits. Re-epithelialization was significantly retarded with diclofenac and flurbiprofen as compared with placebo, but there was no effect on corneal stromal healing (Hersh et al., 1990). Results of an *in vitro* study on canine corneal epithelial cells suggest that topical suprofen may cause a concentration-dependent decrease in the rate of healing of epithelial defects if administered frequently and therefore should be used judiciously in the presence of a corneal ulcer (Hendrix et al., 2002). Although not reported in veterinary species, corneal ulceration with stromal melting, and in some cases corneal perforation, has been associated with topical diclofenac (Flach, 2001; Gaynes & Fiscella, 2002; Guidera et al., 2001; Lin et al., 2000) and ketorolac (Guidera et al., 2001) use in human patients. Mechanisms of corneal ulceration and stromal melting include the relationship between NSAIDs and corneal matrix metalloproteinase and direct toxicity caused by cytotoxic agents such as surfactants, solubilizers, and preservatives found in these ophthalmic preparations (Gaynes & Fiscella, 2002; Hargrave et al., 2002). Corneal epithelial cells have been shown to be capable of secreting MMP-1 and 8 and may participate in the stromal degradation and repair process of the ulcerative

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keratolysis associated with topical NSAIDs use in the perioperative period (O'Brien et al., 2001).

Ocular Hypertension

Topical NSAIDs have not been reported to increase IOP in human patients; however, in veterinary species, they have been shown to increase IOP in both dogs (Krohne et al., 1998b; Millichamp et al., 1991a) and cats (Rankin et al., 2011). The increased IOP associated with the use of topical NSAIDs may be caused by a reduction of aqueous outflow. In dogs, topical flurbiprofen caused a decrease in aqueous outflow that was more pronounced in eyes with intraocular inflammation (Millichamp et al., 1991a). In a recent study, treatment with topical flurbiprofen and bromfenac caused elevated postoperative IOPs in dogs after cataract surgery (Lu et al., 2017). Treatment with topical bromfenac was more likely to generate postoperative ocular hypertension that required intervention than in dogs treated with topical flurbiprofen after cataract surgery (Lu et al., 2017). Concurrent administration of flurbiprofen and latanoprost to normal dogs resulted in a 20.41% reduction in the ocular hypotensive effect compared with latanoprost therapy alone (Pirie et al., 2011). Therefore, these medications should be used with caution in patients with a history of ocular hypertension. In a recent study there was no significant difference in the IOP of normal horses treated topically with either latanoprost once daily or latanoprost and diclofenac once daily (Toffelmire et al., 2017). In that same study, the clinical signs of ocular discomfort associated with latanoprost administration were mitigated by diclofenac (Toffelmire et al., 2017).

Systemic Effects

Reported systemic effects associated with the use of topical ophthalmic NSAIDs are rare. However, systemic absorption of topical ophthalmic NSAIDs has been documented to exacerbate bronchial asthma in human patients (Sharir, 1997). In a recent study, there were no clinically significant abnormalities in serum blood urea nitrogen, creatinine, or urine specific gravity of healthy cats treated with topical flurbiprofen or diclofenac four times daily for 14 days (Lanuza, 2016). In another study topical application of diclofenac was associated with reduced glomerular filtration rate in volume-contracted cats (Hsu et al., 2015). In normal chickens, topical diclofenac administered twice daily for 1 week resulted in detectable plasma levels of diclofenac and minor biochemical alterations (Griggs et al., 2017).

Systemic Nonsteroidal Anti-Inflammatory Drugs

Systemically administered NSAIDs are used commonly in veterinary medicine to pretreat cataract patients to inhibit intraoperative inflammation, as well as for other causes of ocular and periocular inflammation. Orally administered NSAIDs are often used postoperatively for their analgesic and anti-inflammatory properties after intraocular surgery. Currently, FDA-approved drugs for use in dogs include deracoxib, carprofen, firocoxib, and meloxicam. Recently the FDA has approved galliprant, a PGE_2 receptor antagonist NSAID, for the use in dogs. In cats, only meloxicam as a single subcutaneous injection and robenacoxib administered once daily for up to three consecutive days are approved for use in the United States.

Several studies have evaluated the efficacy of systemic anti-inflammatory agents in dogs (Brightman et al., 1981; Gilmour & Lehenbauer, 2009b; Krohne & Vestre, 1987; Krohne et al., 1998a; Millichamp & Dziezyc, 1991b; Millichamp et al., 1991b; Pinard, 2011; Regnier et al., 1986; Spiess et al., 1991; Ward et al., 1992a). Tepoxalin was more effective than carprofen or meloxicam for controlling the production of PGE_2 in dogs with experimentally induced intraocular inflammation (Gilmour & Lehenbauer, 2009b). Combined administration of parenteral flunixin meglumine and dexamethasone has an additive effect at reducing the blood–aqueous barrier breakdown in dogs (Krohne & Vestre, 1987). In a study using paracentesis-induced blood–aqueous barrier disruption in dogs, systemically administered flunixin meglumine was the most effective, aspirin was moderately effective, and sulindac was no more effective than the placebo at suppressing the blood–aqueous barrier disruption (Ward et al., 1992a). In that study, both flunixin and aspirin caused gastrointestinal bleeding (Ward et al., 1992a). In another study, inflammation was induced by disruption of the anterior lens capsule using a Nd:YAG laser. In this study, mydriasis was maintained and the aqueous humor PGE_2 levels were reduced in dogs that were pretreated with either intravenous flunixin meglumine or topical flurbiprofen (Millichamp et al., 1991b). Using a topical pilocarpine irritative model of inflammation, dogs that were pretreated with oral carprofen had a 68% inhibition of flare quantified by the laser flare cell meter (Krohne et al., 1998a). Tolfenamic acid has been shown to limit the synthesis of PGE_2 in the aqueous humor and reduce signs of ocular inflammation induced by corneal surgery (Roze et al., 1996).

Side effects of systemic NSAIDs administration include renal disease (Clive & Stoff, 1984), gastrointestinal irritation and ulceration (Bjorkman, 1996), and inhibition of platelet function (Rackear et al., 1988). In human patients, there has been an increased incidence of myocardial infarction and other adverse cardiovascular events associated with the use of COX-2 selective NSAIDs (Bresalier et al., 2005; Schjerning Olsen et al., 2011). To our knowledge, there have been no reports of cardiovascular complications associated with NSAID use in veterinary species. Both COX-1 and COX-2 enzymes appear to be important in maintaining normal renal function, but their relative importance and physiological role may differ between species. For example, greater COX-2 expression was found in the kidneys of dogs with chronic renal disease than in cats (Yabuki et al., 2007).

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This suggests that the ability of NSAIDs to affect renal function may vary between species. Under conditions of decreased renal blood flow, such as general anesthesia and hypovolemia, prostaglandins become crucial in maintaining renal function and glomerular filtration rate. Short-term meloxicam administration did not measurably alter the glomerular filtration rate as assessed by plasma clearance of iohexol in healthy adult cats (Goddman et al., 2009). Several canine studies have shown that COX inhibition caused by NSAID administration significantly lowers renal blood flow in dogs under specific conditions, for example, anesthetized dogs (Terragno et al., 1977), or dogs that are salt-depleted (Blasingham et al., 1980). The mechanisms by which NSAIDs cause gastric damage are not completely understood, though it is generally accepted that it is due in part to decreased production of gastroprotective prostaglandins as well as mucosal injury by the acidic properties of the NSAIDs (Wolfe et al., 1999). Oral administration of etodolac in dogs has been associated with the development of severe keratoconjunctivitis sicca (Klauss et al., 2007), and the mechanism by which this occurs is not understood.

In cats, systemic NSAIDs have been associated with gastrointestinal ulceration, bone marrow suppression, acute renal failure, hemorrhage, vomiting, and diarrhea. Cats have an increased risk of complications associated with the use of systemic NSAIDs because they have a reduced ability for glucuronide metabolism that results in prolonged action of many drugs.

Immunosuppressant Drugs

Cyclosporine, tacrolimus, pimecrolimus, and rapamycin (sirolimus) are immunosuppressant drugs that inhibit specific signal transduction pathways that lead to T-lymphocyte activation. Cyclosporine, a 1.2-kDa cyclic polypeptide, was isolated from the fungus *Tolypocladium inflatum* in 1972. Tacrolimus and rapamycin are macrolide antibiotics isolated from *Streptomyces tsukubacusis* and *Streptomyces hygroscopicus*, respectively (Baumann, 1992). The effects of these compounds on T-cell signaling are dependent on their interactions with two different cytoplasmic receptors, termed immunophilins: cyclophilin, which binds cyclosporine, and FK-binding protein which binds both tacrolimus and rapamycin (Fischer et al., 1989; Handschumacker et al., 1984; Harding et al., 1989; Schreiber, 1991; Siekierka et al., 1989; Takahashi et al., 1989). Over the last several years, there is increasing evidence that the intracellular target of these complexes is calcineurin (Klee et al., 1979, 1988), a calcium-calmodulin-dependent phosphatase, which is inhibited by these immunophilin–ligand complexes. Cyclosporine and tacrolimus prevent T-cell proliferation by inhibiting a Ca-dependent event required for induction of interleukin-2 transcription (O'Keefe et al., 1992). Although rapamycin is similar in structure to tacrolimus and cyclosporine, it is not a calcineurin inhibitor. The rapamycin-FK binding protein complex leads to the suppression of T-lymphocyte activation and proliferation through inhibition of cell cycle progression (Sehgal, 1998).

Cyclosporine is currently available as a commercial 0.2% ophthalmic ointment or compounded oil or aqueous solution (1 or 2%) for topical use. In human patients, a 0.05% ophthalmic emulsion, Restasis® (Allergan, Irvine, CA, USA), has been approved for the treatment of chronic dry eye (Stonecipher et al., 2005). Episcleral and suprachoroidal (deep scleral lamellar) cyclosporine implants have been evaluated for use in veterinary species (Gilger et al., 2006, 2010; Kim et al., 2005; Lee et al., 2007).

The most common use of cyclosporine in veterinary medicine is for the treatment of canine keratoconjunctivitis sicca (KCS), which is a presumed immune-mediated disease of the lacrimal glands. Cyclosporine typically increases tear production within 2–3 weeks of therapy, and after its discontinuation, tear production can decrease within 12–24 hours (Kaswan et al., 1989). Topical application of 1% or 2% cyclosporine solution as well 0.2% ophthalmic ointment increases tear production in approximately 80% of canine KCS cases (Christmas, 1995; Kaswan et al., 1989; Morgan & Abrams, 1991; Olivero et al., 1991; Salisbury et al., 1990; Sansom et al., 1995). However, in severe cases (initial Schirmer tear test [STT] between 0 and 2 mm/min), the rate of success is reported to be 60% (Morgan & Abrams, 1991). Improved lacrimation is characterized by an increase of at least 5 mm of the STT and is apparent within the first month of treatment in most cases. Some dogs may require 2–3 months of therapy before improvement of STT values are observed (Morgan & Abrams, 1991).

Most dogs require continuous twice daily application of cyclosporine to maintain adequate tear production, but for some dogs with posttreatment STT values ≥20 mm/min, it is possible to reduce the frequency of medication to once daily or every other day without a significant decrease in tear production (Morgan & Abrams, 1991). The most common side effect of topical cyclosporine is a mild local irritation (blepharospasm, conjunctival hyperemia), and it may be related to the formulation of cyclosporine. Periocular irritation can be found in 2%–10% of dogs who receive oral cyclosporine diluted in an oil vehicle (Kaswan & Salisbury, 1990).

Topical or systemic administration of cyclosporine has been shown to decrease corneal angiogenesis (Benelli et al., 1997; Lipman et al., 1992). The exact mechanism by which cyclosporine inhibits angiogenesis is unknown, but it may involve inhibition of lymphokines particularly interleukin-2 (Benelli et al., 1997; Lipman et al., 1992). Improvement in corneal pigmentation has been reported in dogs treated with topical cyclosporine. Partial to complete clearing of the cornea was achieved in 67%–100% of cases (Morgan & Abrams, 1991; Salisbury et al., 1990). Reduction of corneal

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vascularization and pigmentation may take several months to become apparent. Improvement in corneal pigmentation and vascularization has been reported to occur in dogs without increased lacrimation (Morgan & Abrams, 1991; Salisbury et al., 1990).

Topical cyclosporine therapy may lead to regeneration of atrophied lacrimal acinar lobules in the gland of the nictitating membrane in dogs with KCS (Bounous et al., 1995). Cyclosporine therapy has been shown to increase mucin production in dogs with KCS independent of lacrimogenic effects (Moore et al., 2001). The increase in mucin production with cyclosporine therapy may contribute to the overall therapeutic effect in its use for treatment of KCS.

When applied topically, cyclosporine achieves high levels of the drug in the cornea, conjunctiva, sclera, and lacrimal tissues but not in the aqueous humor, uveal tissues, or vitreous humor. Systemic absorption of cyclosporine after topical application has been reported in rabbits (Bellot et al., 1992) and dogs (Gilger et al., 1996). In the dog, the blood concentration of cyclosporine observed after long-term topical administration of the 2% solution is high enough to suppress cellular immunity as measured by lymphocyte proliferation assays and $CD4^+/CD8^+$ lymphocyte subset analysis (Gilger et al., 1995, 1996). The adverse effects or clinical significance of this level of immunosuppression is undetermined. Another study was unable to demonstrate any change in lymphocyte stimulation index or significant blood levels of cyclosporine after administration of either 0.2% or 2% cyclosporine, although it was unclear how often the dogs in that study were treated (Williams, 2010).

The use of cyclosporine has been extended to treatment of other immune-mediated ophthalmic diseases. Cyclosporine has proved useful in controlling chronic superficial keratitis in dogs (Jackson et al., 1991), and response to therapy monitored over a 6-week period showed that topical 0.2% cyclosporine ointment was as effective as 0.1% dexamethasone eye drops (Williams et al., 1995). The efficacy of topical cyclosporine for treating nictitans plasmacytic conjunctivitis has also been shown (Read, 1995). Topical cyclosporine may be an alternative to glucocorticoid therapy in poorly responsive cases of eosinophilic keratoconjunctivitis, episcleritis, scleritis, and superficial punctate keratitis (Read et al., 1995). Some forms of equine keratitis and keratouveitis have been reported to respond favorably to topical cyclosporine (Gratzek et al., 1995; Read et al., 1995). Devices for sustained release of cyclosporine into intraocular tissues have been developed for long-term control of equine recurrent uveitis (ERU). A polyvinyl alcohol/silicone-coated intravitreal cyclosporine implant, releasing 4 μg/day of cyclosporine, was first evaluated (Gilger et al., 2001). Although intravitreal implantation of this device was reported as a successful treatment for ERU, complications in the immediate as well as long-term postsurgical period (i.e., intraocular hemorrhage, progressing cataract, and retinal detachment) were encountered with its use (Gilger et al., 2000). A new cyclosporine slow-release device has been developed that is implanted into the suprachoroidal space allowing constant release of cyclosporine to the uveal tissue (Gilger et al., 2006, 2010).

A review of 133 horses (151 eyes) that had cyclosporine devices implanted for ERU showed that horses with implants had significantly fewer episodes of inflammation after surgery (mean 0.09 flares/month) (Gilger et al., 2010) compared with the frequency rate of uveitis episodes reported prior to surgery (0.54 uveitis episodes/month) (Gilger et al., 2006). In that study (Gilger et al., 2010) 78.8% were visual at the time of the last follow-up examination (13–85 months after surgery). It takes 30–45 days after implantation of the cyclosporine device to obtain adequate ocular drug levels, and the duration of medication delivery is approximately 36 months (Gilger & Deeg, 2011).

The pharmacokinetics of an episcleral cyclosporine implant has been evaluated in rabbits and dogs (Lee et al., 2007). In that study, the corneal cyclosporine concentrations were 0.09 ± 0.05 μg/mg at the 3-hour time point and remained in the inhibitory range for both T-cell activation and vascular endothelial cell proliferation for a minimum of 1 year (Lee et al., 2007). Another study showed that episcleral cyclosporine implants were safe and delivered potentially therapeutic cyclosporine levels to the lacrimal gland. Pharmacodynamic studies have shown that an episcleral cyclosporine implant in dogs was safe, and it produced lacrimal gland drug levels 1–2 log units higher than those reported with a variety of topical cyclosporine formulations (Kim et al., 2005). In that same study, the episcleral implant showed efficacy in a model of canine KCS (Kim et al., 2005). The episcleral implant is placed into a subconjunctival pocket, and fibrous encapsulation adequately secures the implant to the episclera. In normal dogs, a subconjunctival sustained-release cyclosporine implant showed no signs of toxicity over a 6-month period based on clinical exams, electroretinography, and histopathology (Beale et al., 2004). Episcleral silicone matrix cyclosporine implants are well tolerated and associated with treatment success with superficial and endothelial immune-mediated keratitis in horses, especially if placed early in the course of the disease (Gilger et al., 2014). A sustained release subconjunctival cyclosporine implant has also been successfully used to successfully treat KCS in a red wolf (Acton et al., 2006) and in dogs with KCS (Barachetti, 2015).

Administration of oral cyclosporine can also be considered in the treatment of immune-mediated conditions such as episcleritis, blepharitis, and extraocular polymyositis. Oral cyclosporine is administered at a dose of 5 mg/kg twice daily for 3 weeks, and if there is clinical improvement, the dose is tapered to 5 mg/kg once daily for 4 weeks, then every third day for one month, and then once weekly for another month. Cyclosporine can be administered concurrently with

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oral prednisone during the early course of treatment. An association between systemic administration of corticosteroids and/or cyclosporine and the development of acute bullous keratopathy in cats has been suggested (Pierce, 2016).

Tacrolimus can be compounded into a 0.02% or 0.03% oil or aqueous solution or as an ointment. A 0.03% tacrolimus solution in olive oil applied twice daily for 14 days was safe in healthy dogs and gave clinical results similar to those observed with topical 2% cyclosporine in KCS-affected dogs (Adkins et al., 2003). Twice daily application of 0.02% tacrolimus aqueous suspension effectively increased tear production in dogs with KCS (Berdoulay et al., 2005). In that study (Berdoulay et al., 2005), 83% of eyes with a very low initial STT value (≤2 mm/min) increased ≥5 mm/min after tacrolimus therapy. Topical tacrolimus may be a promising alternative to cyclosporine for treatment of presumed autoimmune-mediated canine KCS and may be beneficial in patients that do not respond adequately to topical cyclosporine.

Superficial corneal squamous cell carcinoma has been described in 26 dogs with chronic keratitis (Dreyfus et al., 2011). In that report, 16 out of the 21 dogs whose drug history was known had a history of treatment with either cyclosporine or tacrolimus at the time of diagnosis (Dreyfus et al., 2011). The authors concluded that there may be a potential association between chronic corneal inflammation and topical immunosuppressive therapy in the development of corneal squamous cell carcinomas in dogs.

Topical pimecrolimus was evaluated in a pilot study with 14 dogs with either KCS or chronic superficial keratitis (Nell et al., 2005). Topical treatment with 1% pimecrolimus was effective in 10/14 dogs in that study. Larger controlled studies are warranted to determine the role of pimecrolimus in the treatment of immune-mediated ocular diseases in veterinary species.

Systemic rapamycin has proved effective for the treatment of uveitis in human patients (Shanmuganathan et al., 2005). Intravitreal injection of rapamycin in normal horses showed no signs of toxicity, and rapamycin was detected in both the aqueous and vitreous humor (Douglas et al., 2008). Further study is needed to determine the efficacy of intravitreal rapamycin injections in horses affected with ERU.

An aqueous calcineurin inhibitor, SCY-641, which is a semisynthetic derivative of cyclosporine is well tolerated in dogs with naturally occurring KCS when applied topically twice daily (Gilger et al., 2013). A significant increase in STT values occurred in dogs treated topically with SCY-641 compared with dogs treated with a placebo (Gilger et al., 2013).

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8.4

Clinical Pharmacology and Therapeutics

Part 4: Mydriatics/Cycloplegics, Anesthetics, and Tear Substitutes and Stimulators

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Mydriatics/Cycloplegics

Pharmacological agents used to achieve pupillary dilation and/or relieve ciliary spasm have a variety of ophthalmic diagnostic and therapeutic applications. The agent of choice for any given situation is dictated by a number of factors, most notably the desired duration of mydriasis and whether or not cycloplegia is required. In the diagnostic setting, mydriasis is commonly warranted to facilitate visual examination of the posterior segment of the eye, in which case a short-acting agent with or without significant cycloplegic effect is appropriate. While cycloplegia is important to refraction in human and nonhuman primates, refraction by retinoscopy is reportedly unaffected by cycloplegia in dogs or horses (Groth et al., 2013; McMullen et al., 2014; Murphy et al., 1992; Nowak & Neumann, 1987). In the management of iridocyclitis, longer mydriasis and significant cycloplegia are often desired. In such cases, mydriasis will help prevent posterior synechia whereas relaxation of the ciliary body will relieve some of the discomfort associated with uveitis. Mydriasis is also required for cataract extraction surgery and surgeries of the posterior segment.

Mydriatic agents achieve pupillary dilation by either paralysis of the pupillary sphincter (e.g. cholinergic antagonists) or stimulation of the iris dilator muscle (e.g. sympathomimetics). Generally speaking, drugs that induce pupillary sphincter paralysis also provide a variable degree of cycloplegia, whereas those that stimulate the iris dilator musculature do not. Although mydriatic and cycloplegic medications are generally applied topically, intracameral application of mydriatics during phacoemulsification is also employed (Behndig & Eriksson, 2004; Lundberg & Behndig, 2003; Mori et al., 2011).

With regard to speed of onset, completeness of effect, and duration of action, the effects of the available mydriatic/cycloplegic medications vary by species. In addition, ophthalmic disease states (e.g. uveitis) may affect these parameters. A summary of the reported mydriatic effects of some commonly utilized mydriatic/cycloplegics in dogs, cats, and horses is provided in Table 8.4.1 (Rubin & Wolfes, 1962; Gelatt et al., 1973; Gelatt et al., 1995b).

Cholinergic Antagonists

Mechanism of Action

Cholinergic antagonists act through a reversible blockade of cholinergic receptors in smooth muscle and secretory glands.

Clinical Indications

Cholinergic antagonists are used clinically to facilitate lens and posterior segment visualization during ophthalmic examination and intraocular surgery. They also have therapeutic indications in the management of iridocyclitis.

Side Effects/Contraindications

Mydriatic agents should be avoided in glaucoma cases, where pupillary dilation may cause a severe rise in intraocular pressure (IOP). Statistically significant IOP elevations have been documented in cats after topical anticholinergic application (Stadtbaumer et al., 2006; Stadtbaumer et al., 2002). Studies in dogs and horses have reported variable IOP effects related to topical mydriatic application (Hacker & Farver, 1988; Herring et al., 2000; Mughannam et al., 1999; Taylor et al., 2007; Wallin-Hakanson & Wallin-Hakanson, 2001). Dilation of the pupil may also allow an unstable lens to migrate anteriorly, potentially resulting in pupillary block glaucoma. Topical application of some anticholinergic agents can occasionally induce a substantial reduction in aqueous tear production (Hollingsworth et al., 1992; Margadant et al., 2003; Selk Ghaffari et al., 2009). Salivation is seen frequently and vomiting occasionally after topical administration of anticholinergics, particularly in cats, presumably because of their bitter taste (Gelatt et al., 1973; Lynch & Rubin, 1965; Rubin & Wolfes, 1962). This can be partially ameliorated by utilization of ointment instead of drops, where available. Systemic side effects of topically

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Table 8.4.1 A summary of the reported mydriatic effects of some commonly utilized mydriatic/cycloplegics in dogs, cats, and horses.

Drug	Species	Time Until Maximal Dilation (Hours)	Duration of Action (Hours)	Extent of Dilation
1% tropicamide	Dog	0.5	12	Maximal
	Cat	0.75	8–9	Maximal
	Horse	5	12	Maximal
1% atropine	Dog	1	96–120	Maximal
	Cat	1	60	Maximal
	Horse	10–48	132	Maximal
2% homatropine	Dog	0.75	48	Moderate
	Cat	0.75	7	Moderate
	Horse	3	8	Moderate
1% cyclopentolate	Dog	0.75	60	Maximal
	Cat	0.5	66	Maximal
	Horse	12	96	Maximal
0.25% scopalamine	Dog	0.75	96–120	Maximal
	Cat	NA[a]	NA	NA
	Horse	4	108	Maximal
10% phenylephrine	Dog	2	12–18	Maximal
	Cat	–[b]	–	–
	Horse	––	–	–

[a] Information not available.
[b] – Indicates no significant effect.

applied anticholinergics are a particular concern in horses because of their potential for inducing colic. Decreases in gastrointestinal myoelectric activity, decreased borborygmi, and abdominal pain have been documented after topical and subconjunctival administration of atropine in this species (Williams et al., 2000; Zekas & Lester, 1998). However, in a recent study, six horses were treated with atropine topically every 6 hours for the first 24 hours, then every 12 hours for four additional days, with no subjective or objective evidence of colic or ileus over the study period (Wehrman et al., 2017). Small but statistically significant increases in heart rate may occur in dogs after topical ophthalmic application of atropine (Greenberg et al., 2015).

Tropicamide

Tropicamide is available as a 0.5% and 1.0% solution. Due to its rapid onset, completeness of mydriasis, and relatively short duration of action, it is well suited for diagnostic mydriasis. In the dog, complete mydriasis is produced within 30 minutes and effects may begin to wane as soon as 2 hours after application (Rubin & Wolfes, 1962). In cats, mydriasis from a single application of 0.5% tropicamide begins within 15 minutes, becomes maximal within 1–2 hours and begins to decline within 4 hours (Gelatt et al., 1973; Stadtbaumer et al., 2006). In the horse, 0.5%–1% tropicamide has a similar rapid onset, with reasonably complete mydriasis occurring within 15–30 minutes, maximal mydriasis within 1–5 hours and effects lasting 5–12 hours (Gelatt et al., 1995b). Tropicamide is also the most appropriate mydriatic for diagnostic mydriasis in goats, with onset within 15 minutes, maximal effect at 2 hours and duration of effect of 6 hours (Whelan et al., 2011). Tropicamide is useful for inducing mydriasis prior to cataract extraction surgery, where multiple doses are commonly applied in the hours preceding the procedure. In this setting, the relatively short duration of action of tropicamide may make it less likely to exacerbate postoperative ocular hypertension than a longer acting agent, such as atropine.

While excellent mydriasis can be achieved with tropicamide, its cycloplegic effect is not as pronounced as that of atropine, homatropine, or cyclopentolate, thus limiting its usefulness in the treatment of discomfort associated with uveitis (Egashira et al., 1993; Gettes & Bellmont,1961; Hiatt & Jerkins, 1983; Lovasik, 1986). However, tropicamide has been shown to reduce blood–aqueous barrier permeability (Mori et al., 1992; Petternel et al., 2000). With regard to effects on aqueous tear production, a single application of tropicamide does not cause a reduction in Schirmer tear test (STT) values in normal dogs but may cause a transient STT decline in cats and horses (Margadant et al., 2003; Selk Ghaffari et al., 2009). In cats with primary congenital glaucoma, topical ophthalmic application of tropicamide causes a clinically significant rise in IOP (Gomes et al., 2011). Rise

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in IOP is also induced in ophthalmically normal cats, an effect that seems more pronounced in younger cats (Gomes et al., 2011; Stadtbaumer et al., 2002).

Atropine

Atropine sulfate is available as a 0.5%–2.0% solution and a 1% ointment. Due to its potent mydriatic and cycloplegic effects and long duration of action, atropine is generally the cycloplegic agent of choice in cases of iridocyclitis.

Onset and duration of action varies somewhat by species. Maximal pupillary dilation occurs in 30–60 minutes in normal dogs, cats and cattle (Gelatt et al., 1973; Gelatt et al., 1995a; Rubin & Wolfes, 1962). In dogs, using 1% solution, maximum mydriasis is noted in 1 hour and mydriasis lasts 96–120 hours (Rubin & Wolfes, 1962), whereas in cats mydriasis occurs in 30–45 minutes and persists for 60 hours (Gelatt et al., 1973). In the horse, 1% atropine sulfate begins to take effect within approximately 45 minutes, but mydriasis does not become maximal until 10–48 hours postadministration (Davis et al., 2003; Gelatt et al., 1995b). Duration of action in horses may extend beyond 14 days, with females and Arabian breeds being potentially more sensitive to the mydriatic effects of the drug (Davis et al., 2003). Iridal melanin binding of atropine is well documented in humans and rabbits (McGregor, 1994; Salazar & Patil, 1976; Salazar et al., 1976) where it subsequently acts as a slow-release depot, thereby extending atropine's duration of action in eyes with heavily pigmented irides. In normal dogs, topically applied atropine is able to partially counteract the miotic effect of latanoprost without negating its ocular hypotensive effect (Kahane et al., 2016).

Side effects of topical atropine in dogs and cats are common and include profuse salivation and occasional vomiting (Gelatt et al., 1973; Rubin & Wolfes, 1962). These side effects are likely related to the bitter taste of the drug, which is ingested after exiting the nasolacrimal duct and can be minimized to some degree by the use of ointment instead of solution. Contact allergic periocular dermatitis associated with ophthalmic atropine has been documented in human patients and the author of this chapter has occasionally noted this in animals. It is important to recognize this potential problem so that it is not confused with exacerbation of the disease under treatment. Delirium has been reported after topical atropine administration in human patients (Summers & Reich, 1979) and is also noted occasionally in older dogs, where it is usually manifest as compulsive circling and resolves when the drug is discontinued (Ward, 1999).

Homatropine

In dogs and cats, homatropine acts more slowly than atropine and does not achieve complete mydriasis (Gelatt et al., 1973; Rubin & Wolfes, 1962). Mydriasis generally subsides within 10 hours in cats (Gelatt et al., 1973) and 24 hours in dogs (Rubin & Wolfes, 1962). In horses, homatropine is a less effective mydriatic with a shorter duration of action than atropine, but somewhat longer than tropicamide (Gelatt et al., 1995b).

Scopolamine

Scopolamine is a potent mydriatic with a rapid onset of action and long duration in dogs, horses, and cattle (Gelatt et al., 1995a, 1995b; Rubin & Wolfes, 1962).

Cyclopentolate

Cyclopentolate is an effective mydriatic/cycloplegic with a duration of action comparable to that of atropine in dogs, cats, horses, and cattle (Gelatt et al., 1973; Gelatt et al., 1995a, 1995b; Rubin & Wolfes, 1962). Maximal pupillary dilation occurs at 12 hours in dogs, returning to pretreatment diameter after 72 hours (Costa et al., 2016). Similarly, mydriasis lasts for over 60 hours in cats (Gelatt et al., 1973). Conjunctival edema has been reported as a common side effect of topical cyclopentolate application in dogs (Rubin & Wolfes, 1962), but not cats (Gelatt et al., 1973). A recent report documented no significant effect of 1% cyclopentolate on IOP or tear production in healthy dogs (Costa et al., 2016). Intracameral administration of cyclopentolate, in combination with lidocaine and phenylephrine, is a safe and effective method of achieving mydriasis during phacoemulsification in human patients (Behndig & Eriksson, 2004; Lundberg & Behndig, 2003).

Sympathomimetics

Mechanism of Action

Sympathomimetic effects on the iris include direct stimulation of alpha-adrenergic receptors in the iris dilator musculature.

Clinical Indications

Sympathomimetics are useful in potentiating the effects of other mydriatic medications in some species and to provide adjunct mydriasis and vasoconstriction during ocular surgery. Adrenergic agents are also useful in the diagnosis and lesion localization of ocular sympathetic denervation (Horner's syndrome) (Boydell, 1999).

Side Effects/Contraindications

Side effects after ophthalmic application of sympathomimetic medications are rare. Arterial hypertension and cardiac arrhythmia have been described in clinical cases of dogs and cats receiving topical ophthalmic 10% phenylephrine in preparation for ocular surgery (Franci et al., 2011; Pascoe et al., 1994). Topical administration of 10% phenylephrine in

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research dogs elicits a dose-dependent arterial hypertensive response and associated bradycardia (Herring et al., 2004). Although unlikely to cause clinical complications in routine clinical use, it is advisable to use caution when considering ophthalmic administration of sympathomimetics in animals with known or suspected arterial hypertension. Due to myocardial sensitization to epinephrine induced by halothane anesthesia and the attendant risk of inducing cardiac arrhythmias, it would be prudent to avoid intracameral epinephrine in animals undergoing halothane anesthesia (Katz et al., 1962; Rubin 1968; Zink et al., 1975) or receiving thiobarbiturates (Atlee & Malkinson, 1982; Bednarski et al., 1985; Bednarski & Muir, 1983; Muir et al., 1975). Similar concerns may be valid when using propofol anesthesia (Kamibayashi et al., 1991).

Phenylephrine

Ophthalmic phenylephrine hydrochloride is available in 2.5% and 10% solutions. A direct-acting alpha-1 adrenergic agonist, phenylephrine causes local ocular effects of mydriasis and conjunctival vasoconstriction after topical ophthalmic administration. It is commonly used in conjunction with other medications to maximize pupillary dilation for diagnostic and therapeutic purposes, and alone to help localize the site of sympathetic denervation in Horner's syndrome (Boydell, 1999). Due to the absence of cycloplegic effects from phenylephrine, its usefulness in treatment of iridocyclitis is limited to helping achieve mydriasis when posterior synechia is present. Although it does achieve complete pupillary dilation in the dog, the time to complete mydriasis is too long (approximately 2 hours) for the drug to be practical as the sole agent in achieving diagnostic mydriasis (Kovalcuka et al., 2017; Rubin & Wolfes, 1962). It is ineffective as a sole mydriatic agent in the cat but may prolong the action of parasympatholytics (Gelatt et al., 1973; Stadtbaumer et al., 2006). Similarly, 10% phenylephrine has no significant mydriatic effect in horses when applied alone or in combination with tropicamide (Gelatt et al., 1995b; Hacker et al., 1987) and may actually shorten the duration of mydriasis achieved by atropine (Gelatt et al., 1995b). Phenylephrine also appears ineffective as a mydriatic in sheep (Ribeiro et al., 2014). Because phenylephrine appears to potentiate the mydriatic effect of other medications in some species, it is often considered a useful adjunct medication to facilitate mydriasis in preparation for intraocular surgery.

Epinephrine

Applied topically, 0.1% epinephrine is an ineffective mydriatic (Rubin & Wolfes, 1962), but at 1%–2% concentrations incomplete mydriasis of short duration occurs (Gwin et al., 1978). Topical 2% epinephrine is an ineffective mydriatic in the cat (Gelatt et al., 1973). Intracameral epinephrine is commonly used to help achieve maximal pupillary dilation during intraocular surgery, where it is instilled alone as a dilute solution (1:10,000), or added to irrigating fluids (1:1,000,000). Several clinical trials have confirmed the efficacy of this latter approach (Corbett & Richards, 1994; Elliott & Carter, 1989; Liou & Yang, 1998). Intracameral epinephrine may also help provide intraocular hemostasis through its vasoconstrictive properties. It is imperative that epinephrine introduced into the anterior chamber be preservative-free and bisulfite-free, because of endothelial toxicity associated with these additives (Edelhauser et al., 1982; Slack et al., 1990).

Indirect-Acting Sympathomimetics

Cocaine and hydroxyamphetamine are indirect-acting sympathomimetic agents with clinical utility predominantly related to the localization of nerve lesions causing ocular sympathetic denervation (Horner's syndrome). Cocaine exerts sympathomimetic activity by preventing norepinephrine reuptake at the nerve terminus, resulting in buildup of norepinephrine at the synapse. In humans, cocaine is an effective mydriatic in the normal eye and can be used to confirm (but not localize) Horner's syndrome by virtue of the fact that an iris with sympathetic denervation will not dilate. In normal dogs, 4% cocaine exerts no mydriatic effect (Rubin & Wolfes, 1962). However, it has been suggested that 6% cocaine applied topically may be useful in confirming Horner's syndrome in dogs and cats (Scagliotti, 1999), as it is in human patients. Hydroxyamphetamine elicits release of norepinephrine from sympathetic nerve endings. When applied topically in animals with Horner's syndrome, it will cause pupillary dilation in animals with preganglionic sympathetic disruption, but not those with postganglionic lesions (Scagliotti, 1999).

Local Anesthetics

As outlined below, the applications of local anesthetic agents in veterinary ophthalmology are numerous. Pertinent routes of administration include topical application and intracameral, intravenous, and regional administration.

All local anesthetics act by temporarily impeding sodium ion entrance to the axon interior, thereby preventing nerve depolarization (Strichartz, 1976). Local anesthetics share a common general structure, which consists of a hydrophilic amino group (a secondary or tertiary amine) linked by an amide or ester linkage to a lipid soluble aromatic residue. Many of the pharmacological differences between the various local anesthetics are determined by the nature of this amide/ester linkage (Catterall & Mackie, 2001).

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Topical

Topical ophthalmic anesthetics facilitate many veterinary ophthalmic diagnostic and therapeutic procedures including tonometry, corneal and conjunctival scrapings, corneal suture and foreign body removal, nasolacrimal canalicular manipulations, and intracameral injection or centesis. Topical anesthetics are sometimes employed in a modification of the STT (i.e. STT II) to investigate basal tear production, wherein the anesthetic causes a substantial reduction in STT values (Gelatt et al., 1975; Hamor et al., 2000). Topical ophthalmic anesthetics can also be used intraoperatively to increase corneal analgesia and may thereby allow maintenance of a lower plane of general anesthesia. However, because of their toxic effects on corneal epithelium, repeated application of such agents may be injurious (Behrendt 1956; Gunderson & Liebman, 1944). The effects of topical anesthetics on precorneal tear film stability have been evaluated with variable results. Reportedly, topical oxybuprocaine has no effect on precorneal tear film stability (Mengher et al., 1986), whereas topical proparacaine destabilizes the tear film (Lemp & Hamill, 1973).

Due to their toxic effects on corneal epithelium, topical anesthetics should never be used as therapeutic agents (Behrendt 1956; Gunderson & Liebman, 1944). Numerous reports in the human ophthalmic literature highlight the potentially devastating ocular consequences of topical anesthetic abuse. It should also be kept in mind that topical anesthetics have demonstrated antimicrobial activity, so, where possible, corneoconjunctival cultures should be obtained prior to applying these agents (Badenoch & Coster, 1982; Mullin & Rubinfeld, 1997).

Cocaine was the first drug utilized for corneal anesthesia (Koller, 1934), but deleterious effects on the corneal epithelium as well as unnecessary sympathomimetic pupillary effects have rendered it a historical footnote in this application. Currently, the two compounds most commonly used for topical ophthalmic anesthesia in veterinary ophthalmology are proparacaine and tetracaine.

Proparacaine

Available as a 0.5% solution, proparacaine hydrochloride is a well-tolerated and effective topical ophthalmic anesthetic. In human patients, proparacaine reportedly causes less discomfort and exerts a longer anesthetic effect than tetracaine after ophthalmic instillation (Bartfield et al., 1994; Boozan & Cohen, 1953; Shafi & Koay, 1998). In dogs, using Cochet-Bonnet aesthesiometry as a measurement tool, a single application of topical proparacaine results in a significant anesthetic effect lasting 45 minutes, with maximal effect lasting approximately 15 minutes (Herring et al., 2005). Application of a second drop extended the detectable duration of effect to 55 minutes (Herring et al., 2005). In cats and horses, the duration of measurable corneal anesthesia induced by topical ophthalmic proparacaine is approximately 25 minutes (Binder & Herring, 2006; Kalf et al., 2008). Reports of anesthetic effect in the horse, as assessed by Cochet-Bonnet aesthesiometry, are somewhat conflicting with regard to achieved depth of corneal anesthesia in this species, with one study demonstrating only moderate anesthetic effect (Kalf et al., 2008) and another reporting near complete corneal anesthesia (Pucket et al., 2013). Both of these studies documented duration of anesthetic effect to be shorter than that in the dog and cat (Kalf et al., 2008; Pucket et al., 2013). In all species that have been studied, recovery of corneal sensation follows a steep curve as topical anesthetic effects begin to wane.

Tetracaine

Tetracaine is an effective topical ophthalmic anesthetic and is available as an aqueous or viscous solution and as an ointment. In human patients, discomfort upon instillation of tetracaine is significantly more pronounced and prolonged than that experienced with proparacaine (Bartfield et al., 1994; Shafi & Koay, 1998) and duration of corneal anesthesia is slightly shorter (Bartfield et al., 1994). However, a recent report in dogs demonstrated topical viscous 0.5% tetracaine to provide a longer duration of anesthesia (approximately 34 minutes) than either 0.5% proparacaine or 3.5% lidocaine gel (Venturi et al., 2016). Ocular sensitivity manifest by symptoms of acute conjunctival hyperemia, chemosis, and nictitans protrusion occurs in dogs after topical application (Koch & Rubin, 1969) and is more commonly manifest with tetracaine than other topical anesthetics (Venturi et al., 2016). Nevertheless, topical ophthalmic tetracaine is well tolerated in horses (Monclin et al., 2011a; Sharrow-Reabe & Townsend, 2012). In the horse, maximal anesthetic effect and total duration of action of tetracaine after a single application of 0.5% solution have been reported as 5.5 minutes and 30 minutes, respectively (Monclin et al., 2011b, 2011a). Duration of effect was prolonged after multiple instillations of 0.5% solution (maximal effect of 16 minutes and total duration of 60 minutes) or use of a 1% solution (maximal effect of 15 minutes and total duration of 50 minutes) (Monclin et al., 2011b). In a separate equine study, duration of maximal effect for aqueous 0.5% tetracaine was 20 minutes which was similar to 0.5% aqueous proparacaine, whereas viscous 0.5% tetracaine provided a duration of maximal effect of 30 minutes (Sharrow-Reabe & Townsend, 2012). Additionally, tetracaine appears to exert an overall more profound corneal anesthetic effect in the horse than topical proparacaine, suggesting that it may be a preferred topical anesthetic in this species (Kalf et al., 2008; Monclin et al., 2011b; Sharrow-Reabe & Townsend, 2012).

Oxybuprocaine

Less commonly available than proparacaine and tetracaine, anesthetic effects of 0.4% oxybuprocaine have recently been

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studied in a variety of companion animal species. In the dog, effects of oxybuprocaine are similar to 0.5% proparacaine, with maximal corneal anesthesia being achieved within 1 minute of application and lasting for at least 15 minutes (Douet et al., 2013). Total duration of effect varies widely by individual, ranging from 27 to 70 minutes (mean of 52 minutes) (Douet et al., 2013). Similar effects are documented in cats, with maximal corneal anesthesia occurring within 1 minute and lasting for 5–30 minutes (mean of 21 minutes) (Giudici et al., 2015), findings similar to those for 0.5% proparacaine in this species (Binder & Herring, 2006). A study evaluating 0.4% oxybuprocaine in horses and cattle found that it was well tolerated and achieved corneal anesthesia within 1 minute and lasted at least 75 minutes, but total duration of efficacy was not described (Little et al., 2016a, 2016b).

Intracameral

Intracameral anesthetics are commonly employed as an adjunct method of pain control in human patients undergoing cataract extraction surgery, with the additional benefit of provision of mydriasis. Studies have shown preservative-free lidocaine at concentrations ≤1% to be safe with regard to short-term endothelial toxicity (Carino et al., 1998; Heuermann et al., 2002; Kadonosono et al., 1998). In dogs, intracameral administration of 0.1 mL 1% and 2% preservative-free lidocaine caused no clinically detectable adverse effects on corneal endothelial density or morphology, corneal thickness, or IOP (Gerding et al., 2004). A study in research Beagles demonstrated that sufficient mydriasis (pupil diameter 10 mm) is achieved with both 1% and 2% intracameral lidocaine, with the onset and duration of mydriasis being volume and concentration dependent (Park et al., 2009a). A separate study by the same group demonstrated a significant analgesic effect from intracameral administration of 0.3 mL 2% lidocaine preceding phacoemulsification, which significantly reduced both intraoperative isoflurane requirements and the proportion of dogs requiring supplemental analgesia in the first 3 hours postoperative (Park et al., 2010).

Regional Administration

Local anesthetic agents are often applied by injection to achieve eyelid akinesia (via auriculopalpebral nerve block), local analgesia through local infiltration/line blocks, or globe akinesia and analgesia via peribulbar/retrobulbar injection. Additional local administration routes include splash blocks and use of anesthetic-infused absorbable sponges. The local anesthetic agents most commonly employed in such manners are lidocaine and bupivacaine. Lidocaine, an intermediate-acting local anesthetic, has a rapid onset of action and provides approximately 45 minutes to 1 hour of clinical effect (Craig, 1994). Bupivacaine is approximately four times more toxic than lidocaine, but is also four times more potent and thereby provides significantly longer anesthetic effect, lasting approximately 5–10 hours when used as a 0.5% solution (Laaka et al., 1972).

Lidocaine 2% appears to be the most popular local anesthetic used for auriculopalpebral nerve block in animals. Although numerous local anesthetics and combinations have been used for retrobulbar or peribulbar injection in human ophthalmic practice, a combination of lidocaine/bupivacaine is perhaps most popular, with lidocaine providing rapid onset and bupivacaine providing prolonged duration of effect (Wong, 1993). The duration of effect of certain local anesthetics, particularly lidocaine, can be prolonged with the addition of epinephrine (5 μg/mL) to the injection (Catterall & Mackie, 2001). The addition of hyaluronidase to peribulbar/retrobulbar anesthetic injection is reported to improve the speed and quality of the block (Dempsey et al., 1997; Kallio et al., 2000).

Utilizing regional periocular anesthetic injection in conjunction with sedation or general anesthesia can provide substantial benefit in a variety of ophthalmic adnexal surgical procedures (Giuliano, 2008; Park et al., 2009b). In such applications, regional anesthesia is a useful intraoperative adjunct and also provides a degree of analgesia in the immediate postoperative period.

In domestic animal species retrobulbar anesthetic block techniques have been described in cattle, horses, dogs, and cats (Accola et al., 2006; Gilger & Stoppini, 2011; Peterson, 1951; Raffe et al., 1986; Shilo-Benjamini et al., 2013). Retrobulbar and peribulbar injection of local anesthetic can be a useful adjunct to general anesthesia during ophthalmic surgery in animals (Raffe et al., 1986). In addition to providing akinesia and analgesia, reported benefits include abolishing the oculocardiac reflex (Kirsch et al., 1957; Mendelblatt et al., 1962; Oel et al., 2014). A clinical study on dogs undergoing enucleation confirmed significant postoperative analgesic effect from retrobulbar bupivacaine injection, supporting the clinical effectiveness of this approach (Myrna et al., 2010). More recent studies have demonstrated equal efficacy of preoperative retrobulbar anesthetic injection, intraoperative splash block, and application of anesthetic-infused absorbable gelatin hemostatic sponge in achieving postoperative pain control (Chow et al., 2015; Ploog et al., 2014). A recent pilot study comparing peribulbar and retrobulbar administration of bupivacaine in cats found that peribulbar injection more commonly resulted in intraconal drug deposition than the retrobulbar technique, with presumably less associated procedural risk (Shilo-Benjamini et al., 2014). Retrobulbar lidocaine injection has also been reported as an alternative to systemic neuromuscular blockade to achieve central eye positioning for phacoemulsification in dogs (Ahn et al., 2013a; Hazra et al., 2008).

Complications of retrobulbar nerve block are uncommonly reported in companion animals. One source reports

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lidocaine hypersensitivity as the most common complication in horses (Gilger & Stoppini, 2011). Significant complications of peribulbar/retrobulbar injections in human patients include globe perforation (Mount & Seward, 1993; Ramsay & Knobloch, 1978), anesthetic myotoxicity (Han et al., 2004; Rainin & Carlson, 1985; Salama et al., 2000), and brain stem anesthesia (Javitt et al., 1987). Numerous less significant complications, such as orbital hemorrhage and chemosis, may also occur (Cionni & Osher, 1991). In human patients, central nervous system complications of retrobulbar anesthesia are rare but well documented (Hamilton, 1992; Javitt et al., 1987; Nicoll et al., 1987). This complication is most commonly believed related to penetration of the optic nerve sheath and subarachnoid injection of the anesthetic agent (Javitt et al., 1987; Nicoll et al., 1987). With an increasing amount of anesthetic agent placed in the retrobulbar space, risk of respiratory arrest increases via mechanisms not related to direct central nervous system or vascular injection (Wittpenn et al., 1986). Though poorly documented in animals, the author of this chapter has witnessed sudden death in a calf during a Peterson block.

Subconjunctival administration of 0.2 mL of local anesthetic was reported recently to achieve corneal analgesia of 1.5–2 hours duration in horses (Jinks et al., 2018). All three agents studied (lidocaine, bupivacaine, and mepivacaine) achieved similar clinical effects, which were somewhat less profound than the previously reported effects of topical ophthalmic anesthetic agents in this species (Jinks et al., 2018).

Sub-Tenon's (episcleral) anesthesia has long been regarded as a safe and effective method of achieving eyelid and globe akinesia and analgesia in human ophthalmic surgery (Briggs et al., 1997; Ripart et al., 2000). In dogs, sub-Tenon's lidocaine has been demonstrated to be effective and comparable to systemic neuromuscular blockade and retrobulbar anesthesia for achieving globe akinesia and mydriasis (Ahn et al., 2013a, 2013b).

Intravenous

Intravenous lidocaine has been examined as an adjunct to general anesthesia for veterinary ophthalmic application, where systemic lidocaine infusion has been shown to be as effective as morphine in provision of intraoperative analgesia during phacoemulsification in dogs (Smith et al., 2004).

Tear Substitutes and Stimulators

Tear Substitutes

Tear replacement solutions and ointments are widely used in the management of quantitative and qualitative tear film disorders in animals, the most common of these being canine immune-mediated keratoconjunctivitis sicca (KCS). Tear substitutes serve a host of purposes in these conditions, the most important being provision of lubrication, thereby improving corneal health and improving comfort levels in affected animals. Additionally, optical aberrations induced by poor tear film quality (Tutt et al., 2000) are reduced with artificial tear supplementation, resulting in improved vision (Liu & Pflugfelder, 1999; Montes-Mico et al., 2004). A wide array of products of varying compositions are commercially available, some of which contain preservatives whereas others are preservative free. The recommended frequency of application depends upon the agent used and severity of disease. Due to corneal epithelial toxicity associated with preservatives, particularly benzalkonium chloride, the long-term use of preservative-free medications is often advocated for people with severe KCS where frequent application of solutions is indicated (Berdy et al., 1992; Gobbels & Spitznas, 1992; Lopez Bernal & Ubels, 1991; Palmer & Kaufman, 1995). Clinical trials to assess for deleterious effects of artificial tears with preservatives have not been performed in companion animals. Preservative-free tear substitutes are provided in single-dose packaging and are generally considerably more costly than multidose products containing preservatives.

Primary limitations to the effectiveness of tear substitutes include intermittent application providing only transient effects and the inability of tear substitutes to replicate the specific molecular composition and trilaminar nature of the normal tear film. In order to improve tear substitute efficacy, improved corneal adhesion and prolonged corneal contact are desirable. Common tear replacement solution agents include polyvinyl alcohol, cellulose polymers (e.g. methylcellulose, carboxymethylcellulose, hydroxypropyl methylcellulose), polyethylene glycol, dextran, polyvinylpyrrolidone, and hyaluronate. With their prolonged action relative to solutions, artificial tear ointments are also commonly utilized in the management of KCS. Due to the hypertonic nature of the tear film in KCS, most appropriate tear replacement products are hypotonic or isotonic. Studies have not been reported for companion animals, and human studies conflict somewhat on the ideal tonicity of artificial tears in the management of dry eye. It has been reported that isotonic and hypotonic tear replacement solutions are equally beneficial in human patients with mild KCS (Papa et al., 2001), whereas hypotonic solutions are a more effective treatment in people with severe KCS, where it results in improved tear film stability, corneal fluorescein staining, and conjunctival cytology findings compared with isotonic solutions (Aragona et al., 2002).

As implied above, the ideal tear replacement solution has yet to be identified. Solutions containing sodium hyaluronate appear to pose a number of therapeutic advantages as tear replacement agents. Their relatively high viscosities lead to prolonged ocular retention and pseudoplasticity of hyaluronate provides reduced viscosity under

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the shear stress of eyelid closure, thus facilitating natural blinking. Sodium hyaluronate has been shown to suppress breakup of the tear film in human patients (Hamano et al., 1996; Johnson et al., 2006). Specifically, tear film stability is prolonged with hyaluronate at concentrations ≥0.1% (Hamano et al., 1996). Controlled studies comparing 0.1% hyaluronate with 1.4% polyvinyl alcohol and 0.9% NaCl solution in KCS human patients showed significant benefits from hyaluronate with regard to clinical symptoms and reduction in rose bengal staining (Condon et al., 1999; McDonald et al., 2002). Sodium hyaluronate has also been demonstrated to exert a positive influence on corneal epithelial migration *in vitro* and *in vivo* (Miyauchi et al., 1990; Nishida et al., 1991; Sugiyama et al., 1991), which may provide an additional benefit in patients with KCS because of the common occurrence of corneal ulceration in this population. However, a recent study investigating the effect of topical 0.2% hyaluronic acid-containing eye drops on corneal wound healing in dogs did not find a beneficial effect (Gronkiewicz et al., 2017).

Studies evaluating efficacy of tear replacement solutions in companion animals are very limited, but recent studies in KCS-affected dogs have demonstrated greater ameliorative effects of hyaluronic acid-containing tear replacement solution compared with carbomer-based gel (Williams et al., 2012), and greater effects of crosslinked hyaluronic-acid based hydrogel compared with standard hyaluronate containing tear replacement solution (Williams & Mann, 2014).

Autologous Serum

The composition of tears and serum closely resemble each other in a number of respects, with some exceptions, including serum containing more vitamin A, lysozyme, fibronectin, and TGF-B1, and less IgA, epidermal growth factor, and vitamin C than tears (Tsubota & Higuchi, 2000). Individual studies have documented improvement in tear film break up times, corneal vital staining, pain scores, and impression cytology in human KCS patients treated with topical autologous serum (Fox et al., 1984; Kojima et al., 2005; Kojima et al., 2008; Noble et al., 2004; Tsubota et al., 1999), although clinical efficacy remains in question, awaiting more rigorous controlled studies (Pan et al., 2017). Topical ophthalmic application of serum is commonly utilized in the management of corneal disease in veterinary patients; however, no reports exist regarding its use in the management of tear film disorders.

Tear Stimulators

Calcineurin Inhibitors: Cyclosporine, Tacrolimus, Pimecrolimus

Cyclosporine A (CsA), a naturally occurring fungal metabolite, exhibits immunosuppressive mechanisms related to the binding of nuclear proteins required for initiation of T-cell activation, preventing T-cell production of specific inflammatory cytokines such as interleukin (IL)-2 and IL-4, and thereby disrupting immune-mediated processes (Hess, 1993). Because of its highly specific inhibition of T-cell activation, CsA has been used to treat a number of immune-mediated ocular disorders in animals, including KCS.

In early studies using a 1%–2% solution of CsA in an oil base, 75%–82% of idiopathic canine KCS cases showed significant improvement in aqueous tear production and clinical signs, although positive responses sometimes required 2–3 months of treatment (Kaswan et al., 1989; Morgan & Abrams, 1991; Olivero et al., 1991; Salisbury et al., 1990). A 0.2% ointment product was subsequently shown to be similarly efficacious (Sansom et al., 1995). Increased aqueous tear production is more likely to result in dogs with initial STT values >2 mm/min than dogs with STT values of 0–2 mm/min, presumably because of more extensive and irreversible lacrimal acinar destruction in the latter group (Kaswan et al., 1989; Sansom et al., 1995). Tear production in dogs with neurogenic KCS is not likely to improve with CsA treatment (Kaswan et al., 1989). Beyond improvements in tear production, other clinical benefits of CsA therapy in KCS-affected animals include reduction of corneal vascularization and pigmentation (Kaswan et al., 1984; Kaswan & Salisbury, 1990). This improvement in keratitis occurs even in dogs whose tear production does not increase (Kaswan et al., 1989; Sansom et al., 1995). In the treatment of KCS, twice daily treatment is generally recommended for control of the disease, although once daily administration appears clinically adequate in some dogs. However, whether or not low-grade lacrimal adenitis persists during low frequency administration of CsA in KCS-affected dogs is unknown.

Multiple mechanisms of action are likely responsible for the therapeutic efficacy of CsA. T-cell suppression by CsA undoubtedly plays a major role in restoring tear production in dogs affected with immune-mediated lacrimal adenitis, where lymphocytic infiltration of lacrimal gland acini and ducts has been documented as a hallmark of the disease (Kaswan et al., 1984). Improvement in conjunctival mucin stores in KCS affected dogs has also been documented with CsA treatment, which may contribute to its therapeutic effect in this disease (Moore et al., 2001). In dogs with spontaneous chronic idiopathic KCS, topical CsA suppresses lacrimal acinar and conjunctival epithelial cell apoptosis and facilitates lymphocytic apoptosis, leading to reestablishment of the normal apoptotic balance in affected dogs (Gao et al., 1998). Considering the reversible increase in lacrimation that occurs in normal dogs treated with topical CsA, a direct lacrimal stimulant effect is also likely (Kaswan et al., 1989). Some of its effects may also be related to stimulation of neurotransmitter release (Yoshida et al., 1999), which appears to be impaired in KCS-affected animals (Zoukhri & Kublin, 2001).

While the route of application of CsA for KCS management has traditionally been topical, surgical placement of

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episcleral CsA implants has recently been described (Barachetti et al., 2015; Mackenzie et al., 2017). Reports are limited, but this approach would appear to be a viable alternative to topical therapy, potentially useful in cases that either do not tolerate or are medically refractory to topical treatment (Barachetti et al., 2015). A primary limitation to this approach would appear to be the finite pharmacologically effective lifespan of the implant.

Topical CsA has the longest history of use in the management of immune-mediated KCS, but other calcineurin inhibitors have also been investigated and employed clinically for this condition (Berdoulay et al., 2005; Gilger et al., 2013; Nell et al., 2005; Ofri et al., 2009). Topical 0.02% tacrolimus has been shown to increase tear production significantly and improve clinical signs in dogs with naturally occurring KCS (Berdoulay et al., 2005; Hendrix et al., 2011; Radziejewski & Balicki, 2016), including some animals that were nonresponsive to topical CsA treatment (Berdoulay et al., 2005). While clinical use of pimecrolimus does not appear to be as widespread as that of tacrolimus as a CsA alternative, two studies evaluating it for the treatment of canine KCS have been reported. One demonstrated improvement in STT values and clinical signs in eight KCS affected dogs treated with pimecrolimus (Nell et al., 2005), whereas a subsequent study comparing 1% pimecrolimus with a commercial 0.2% CsA ointment revealed pimecrolimus-treated dogs to have significantly improved STT values and clinical scores compared with the CsA-treated group (Ofri et al., 2009).

Topical calcineurin inhibitors are indispensable in the management of canine KCS and other corneal diseases, but the potential for adverse effects of these medications exists. The primary documented side effect of topical CsA is ocular irritation, which occurs in a proportion of dogs, but often improves with continued treatment and resolution of disease (Morgan & Abrams, 1991; Sansom et al., 1995). In this author's experience, ocular irritation appears to be more common with compounded oil-based preparations than the commercially available ointment-based product. However, dogs will, on occasion, also not tolerate the latter. Reduction in blood lymphocyte counts and suppression of lymphocyte proliferation has been demonstrated in dogs receiving topical ophthalmic CsA (Gilger et al., 1995, 1996; Izci et al., 2002), although another investigation failed to detect such effects (Williams, 2010). In any case, adverse clinical sequelae related to systemic effects of topical ophthalmic cyclosporine application have not been reported. Concerns regarding the carcinogenic potential of calcineurin inhibitors, stem largely from a 2005 Food and Drug Administration "black box warning" concerning tacrolimus and pimecrolimus (Food and Drug Administration, 2005; Niwa et al., 2003). However, there remains considerable debate regarding the actual risk of malignancy with topical use (Czarnecka-Operacz & Jenerowicz, 2012; Siegfried et al., 2016; Thaci & Salgo, 2010). Although the pathogenic role of the medications, if any, cannot be determined, it was reported in a case series of 26 dogs with corneal squamous cell carcinoma that 16/21 dogs with a known treatment history were receiving topical ophthalmic cyclosporine or tacrolimus prior to tumor diagnosis (Dreyfus et al., 2011). Finally, in a case series of five dogs with chronic ocular surface disease and being treated with cyclosporine or tacrolimus, ocular surface protozoal infections were reported, raising the potential that long-term local immunosuppression may have played a role in pathogenesis (Beckwith-Cohen et al., 2016). Considered in the context of their widespread use and documented efficacy in the management of ocular surface disease in veterinary patients, combined with the rare reports of potential adverse effects, it would appear that the therapeutic benefits of calcineurin inhibitors far outweigh their potential risks.

Sirolimus (Rapamycin)

Also known as rapamycin, sirolimus is a macrolide compound with several known biologic effects, including immunosuppression, which shows promise as an alternative treatment option for idiopathic/immune-mediated KCS. An experimental study employing subconjunctival administration of a liposomal sirolimus formulation in dogs with naturally occurring KCS demonstrated improved tear production in treated animals (Linares-Alba et al., 2016). In a recently reported clinical trial, topically applied 0.02% sirolimus aqueous suspension was shown to be both well tolerated and similarly efficacious to 0.02% tacrolimus in its lacrimostimulant properties in KCS-affected dogs (Spatola et al., 2017).

Pilocarpine

Topical and oral pilocarpine, a muscarinic cholinergic agonist, have long been recommended for the management of KCS (Rubin & Aguirre, 1967; Severin, 1973), but controlled studies involving KCS-affected animals are lacking. Applied topically, pilocarpine produces no detectable effect on tear production in normal dogs (Smith et al., 1994). Oral pilocarpine has been described as efficacious in a case series of normal and KCS-affected animals, but signs of systemic toxicity (e.g. salivation, vomiting, inappropriate defecation, or diarrhea) are common with this route of administration (Rubin & Aguirre, 1967). While largely supplanted in the treatment of KCS by drugs such as CsA, pilocarpine remains a viable treatment in dogs with neurogenic KCS wherein loss of parasympathetic innervation is the presumed cause of impaired lacrimal secretion (Matheis et al., 2012). The efficacy in such cases, however, remains undetermined.

Other Potential Lacrimostimulants

In a study of three English Bulldogs with KCS induced by surgical removal of the gland of the nictitans, treatment with topical nerve growth factor resulted in significant improvements in STT, conjunctival goblet cell density, tear mucous,

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corneal haze, corneal sensitivity, and impression cytology (Coassin et al., 2005). Based upon these findings, further investigation of this treatment would appear warranted.

An open label clinical trial evaluating the efficacy of oral alpha-interferon in dogs with chronic KCS found a favorable response in STT values in 55% of dogs (Gilger et al., 1999). The increase in STT values was modest, but posttreatment STT values in responders were significantly greater than their pretreatment STT values (Gilger et al., 1999). The exact role of these treatments as primary or adjunctive therapeutic measures in the management of KCS remains to be determined.

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8.5

Clinical Pharmacology and Therapeutics

Part 5: Medical Therapy for Glaucoma

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The primary risk factor and clinical sign of glaucoma that is the most common target of therapy is elevated intraocular pressure (IOP). Control of elevated IOP may be achieved through medical or surgical means. However, a combination of both approaches is often the most successful. Medical treatment of glaucoma is generally directed at lowering the existing IOP to what is considered a "safe" or target level. Topical or systemic pharmacologic agents are grouped into three categories on the basis of their IOP lowering effect: (1) those that reduce the rate of aqueous humor production; (2) those that increase aqueous humor outflow without affecting its formation; and (3) those that affect both aqueous humor outflow and formation. A variety of pharmacologic agents that work through different mechanisms are available, including parasympathomimetic and adrenergic agents, carbonic anhydrase inhibitors (CAIs), prostaglandin analogues, calcium channel blockers (CCBs), and osmotic diuretics. These drugs may be used as monotherapy or in combination to decrease IOP in order to prevent the progressive loss of vision associated with the pathophysiology of glaucoma (Miller et al., 2000; Willis 2004; Willis et al., 2002). Most pharmacologic agents employed for the treatment of glaucoma are administered through the topical route in order to target affected tissues and minimize exposure of the rest of the body to a drug that may be associated with adverse effects.

Typically, topical solutions or suspensions are used. However, there are increasing numbers of studies that use drug-laden contact lenses or biodegradable drug-laden subconjunctival or intraocular implants to deliver antiglaucoma medications more consistently and reliably than pulse drop therapy (Jung et al., 2013; Peng et al., 2012a, 2012b). Contact lenses laden with β-adrenergic antagonists, CAIs, or prostaglandin analogues have all been shown to be effective at lowering IOP in glaucomatous Beagles (Jung et al., 2013; Peng et al., 2012a, 2012b). Hopefully, soon these will be available for the treatment of glaucoma in humans and companion animals. While IOP remains the target of mainstay treatment of glaucoma, alternative therapies aimed at preventing disease or pressure-induced damage to the retinal ganglion cells, optic nerve, and outflow pathways are increasingly being developed and employed (Danesh-Meyer, 2011).

Cholinergic Agonists (Miotics)

Also known as parasympathomimetics or cholinomimetics because they produce biologic responses similar to those of acetylcholine, these agents are classified according to their mechanism of action as either direct or indirect. Direct agents stimulate cholinergic receptors, whereas indirect agents inhibit acetylcholinesterase, permitting acetylcholine to accumulate at the cholinoreceptive sites (Bartlett et al., 2008).

Mechanism of Action

Topical application of a parasympathomimetic compound on the eye results in miosis and lowering of IOP. In human and nonhuman primate eyes, contraction of the longitudinal fibers of the ciliary muscle with widening of the scleral spur to decrease resistance of aqueous humor passage through the outflow pathway is the likely mechanism through which these drugs act (Kaufman & Gabelt, 1997). Additionally, an increase in the number of giant vacuoles in the endothelium of Schlemm's canal may also participate in improved aqueous outflow in these species (Kaufman & Gabeth, 1997). In small animals, the contribution that contraction of ciliary muscle makes on aqueous removal has not been determined and thus the mechanism by which parasympathomimetics lower the IOP is not established. Nevertheless, a cholinergic activity has been identified in the ciliary body musculature of the canine eye, indicating that there is the potential for modulation of outflow facility by the cholinergic nervous system (Gwin et al., 1979). Further evidence supporting

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such a hypothesis were observations that either intracameral injection of pilocarpine or N-demethylated carbachol (Chiou et al., 1980), as well as topical application of pilocarpine in canine eyes (Gum et al., 1993b), induce a substantial increase in the conventional outflow facility.

Direct-Acting Parasympathomimetics

Pilocarpine is a natural alkaloid obtained from the leaves of South African shrubs of the genus *Pilocarpus*. The drug is used as a nitrate or a hydrochloride and is available in concentrations of 0.5%–8% in methylcellulose or polyvinyl alcohol vehicles. Most commercial pilocarpine eye drops are in solutions with a pH range of 4.5–5.5 to preserve the drug from hydrolysis, which can be highly irritating. Pilocarpine hydrochloride 4% in a high-viscosity acrylic gel has been introduced to prolong drug-eye contact time (Kaufman & Gabelt, 1997). Studies in glaucomatous (open-angle) and normotensive Beagles indicate that a single instillation of 0.5%–8.0% pilocarpine hydrochloride solution reduces IOP by 30%–40% for at least 6 hours (Gwin et al., 1977; Whitley et al., 1980), whereas the gel formulation reduces IOP by 25%–30% for at least 24 hours in glaucomatous canine eyes (Carrier & Gum, 1989). In these animals, a single drop instillation of pilocarpine (1%, 2%, or 4%) increased the coefficient of tonographic outflow facility from 0.33 μL/min/mmHg prior to treatment up to 0.61 μL/min/mmHg after treatment in normal eyes and from 0.15 μL/min/mmHg prior to treatment up to 0.38 μL/min/mmHg after treatment in glaucomatous eyes (Gum et al., 1993b). Glaucomatous Beagles responded with a greater reduction of IOP than normotensive dogs and no significant difference in the hypotensive response was found among the different concentrations. Miosis occurred within 10–15 minutes and lasted for 6–8 hours (Gwin et al., 1977). Therapeutic additivity of pilocarpine with adrenergic agents or CAIs has been shown in human eyes (Kaufman & Gabelt, 1997). The combination of 1% epinephrine and pilocarpine hydrochloride (1%, 2%, 3%, 4%, and 6%) produced a significant IOP-lowering effect in glaucomatous (open-angle) and normotensive beagles. Following a single instillation of these combinations, the drop in IOP lasted for at least 8 hours and was not dose related (Gelatt et al., 1983). Surprisingly, combined administration of 1% epinephrine with either 1%, 2%, or 4% pilocarpine did not increase tonographic outflow facility in these eyes in comparison to pilocarpine 4% used alone (Gum et al., 1993b). While in research settings pilocarpine has been shown to reliably decrease IOP in both normotensive and glaucomatous animals, its clinical utility is limited because it does not typically lower IOP to a level that either supports vision retention or comfort and its administration is generally very irritating given its low pH.

In normotensive mares, once-daily or twice-daily topical application of 2% pilocarpine hydrochloride was not associated with significant decrease in both IOP and vertical pupil size (van der Woerdt et al., 1998). The lack of pharmacologic effect of pilocarpine on IOP was attributed most likely by a decrease in uveoscleral outflow resulting from ciliary muscle contraction. Dilution of the drug in the large equine tear volume leading to a subtherapeutic concentration penetrating the eye might also contribute to low availability of the drug (van der Woerdt et al., 1998).

Indirect-Acting Parasympathomimetics

Carbachol is the carbamyl ester of choline. Because the drug is not lipid-soluble at any pH and penetrates the intact corneal epithelium poorly, it must be combined with a surfactant, such as benzalkonium chloride, to facilitate its penetration through the corneal epithelium (Kaufman & Gabelt, 1997). Carbachol is stable in solution and is available for topical use in concentrations of 0.75%–3%. A 0.01% solution is used for intracameral administration at completion of intraocular surgery to induce rapid miosis and inhibit postoperative ocular hypertension (Kaufman & Gabelt, 1997). At concentrations of 0.75%, 1.5%, 2.25%, and 3%, carbachol reduced IOP in normotensive and early glaucomatous (open-angle) Beagles. The reduction in IOP was clearly evident within 1 hour and peaked 2–7 hours after instillation (Gelatt et al., 1984). A minimum concentration of 0.75% carbachol was recommended in the management of open-angle glaucoma in the Beagle (Gelatt et al., 1984). In an initial report, 0.01% solution injected into the anterior chamber of dogs at the end of cataract surgery was found to prevent the postoperative increase in IOP associated with phacoemulsification (Stuhr et al., 1998). This preventive effect on the development of acute postoperative hypertension (POH) was not evident in a different study in which dogs were treated with intracameral administration of 0.3 mL of 0.01% carbachol immediately after phacoemulsification. These dogs had significantly higher IOP than the controls (no treatment) 2 hours after administration and had a number of POH peaks not significantly different from that observed in the controls (Crasta et al., 2010). A more recent study suggests that intracameral carbachol does decrease the incidence of POH in most breeds but may exacerbate POH in the Labrador Retriever (Moeller et al., 2011).

The anticholinesterases are divided into the carbamate inhibitors, which bind to the acetylcholinesterase in a reversible manner, and the organophosphorus inhibitors which irreversibly inhibit the enzyme by forming a stable complex.

Demecarium bromide is a potent carbamate inhibitor, no longer commercially available, but which can be compounded in 0.125% and 0.25% solutions for veterinary use. The drug remains stable for extended periods and does not require refrigeration (Kaufman & Gabelt, 1997). A single drop of demecarium bromide in a human eye provided a significant reduction of IOP starting a few hours after instillation and lasting for more than 3 days (Shihab, 1987).

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The accompanying miosis lasted for up to 10 days (Shihab, 1987). Investigations using single-drop application of either 0.125% or 0.25% topical demecarium bromide and conducted in normotensive and glaucomatous (open-angle) Beagles revealed that both formulations induce long-term miosis (up to 77 hours) and an IOP-lowering effect that lasts up to 55 hours (Gum et al., 1993a). The mean decrease in IOP is about the same magnitude as that observed with pilocarpine solution and gel as well as with carbachol solution, but is more prolonged (Gum et al., 1993a). This drug is rarely used singly unless it is used as prophylactic therapy for the normotensive fellow eye of a dog previously diagnosed with glaucoma in the contralateral eye, but more often in combination therapy with drugs from other classes when used in a hypertensive globe (Dees et al., 2014).

Echothiophate iodide (or phospholine iodide) is another long-acting organophosphorus compound, which, although no longer commercially available, may be compounded in 0.03%, 0.125%, and 0.25% solutions (Ellis, 1997). The refrigerated solution remains stable for at least 1 month after reconstitution. Instillation of one drop echothiophate iodide 0.125% or 0.25% results in decrease in IOP of about 10 mmHg and about 1 mmHg in normotensive and glaucomatous (open-angle) Beagle eyes, respectively (Gum et al., 1993a). Reduction in IOP persists for 25–53 hours. Associated miosis becomes maximal within 1–3 hours and persists for 49–55 hours (Gum et al., 1993a).

Clinical Use

The major use of parasympathomimetic drugs has been the long-term treatment of open-angle glaucoma in the dog. Use of these agents in combination with adrenergic drugs or CAIs would also be of help for initial therapy in most early glaucomas. However, once glaucoma is advanced, parasympathomimetic therapy has little beneficial effect because the filtration angle is usually obliterated by extensive peripheral anterior synechiae (Gaarder, 2000). Parasympathomimetic agents should be avoided in secondary glaucoma associated with iridocyclitis and used with caution in dogs with subluxated or luxated lens, because miosis may predispose to synechia formation and lens dislocation may induce a pupillary block. Pilocarpine solution should be prescribed three to four times daily (Gaarder, 2000), whereas pilocarpine gel is applied once daily. Although demecarium bromide is a long-acting hypotensive ocular agent, its instillation has been recommended in the dog on a twice-daily basis to regulate IOP and avoid occasional peaks that may be destructive for the glaucomatous eye (Gum et al., 1993a). In order to determine the ability of prophylactic antiglaucoma treatment to prevent or delay onset of glaucoma in the second eye of dogs with unilateral closed-angle glaucoma, a combination of 0.25% demecarium bromide (DB) and a topical corticosteroid gentamicin/betamethasone (GB) (DB/GB) was compared with topical 0.5% betaxolol in a multicenter clinical trial (Miller et al., 2000). Untreated control eyes developed glaucoma significantly sooner (median 8 months) than eyes treated either with betaxolol (median 30.7 months) or DB/GB (median 31 months). Although both treatment protocols similarly delayed the onset of glaucoma in the fellow eye, DB/GB would be preferable to betaxolol in preventing closed-angle glaucoma because of less frequent dosing (Miller et al., 2000). A recent study comparing the efficacy and time to medical failure of a variety of antiglaucoma medications with or without concurrent anti-inflammatory medication suggests that patients receiving demecarium bromide 0.125% had the longest estimated median time to medical failure at 330.0 days, followed by latanoprost 0.005%, dorzolamide hydrochloride 2.0%, and demecarium bromide 0.25% at 284.0 days, 272.5 days, and 143.0 days, respectively (Dees et al., 2014). The estimated median time to medical failure for patients receiving topical antiglaucoma and anti-inflammatory medication was 324.0 days versus 195.0 days in patients receiving antiglaucoma medication alone, although the results were not statistically significant (Dees et al., 2014). Pilocarpine is also used topically or orally (well mixed with food) in small animal ophthalmology to stimulate tear production in patients with keratoconjunctivitis sicca, and to improve the ocular and digestive signs of feline dysautonomia.

Adverse Effects

Because of the low pH (4.5–5.5) of its ophthalmic solutions, pilocarpine may cause local irritation manifested by blepharospasm, prolapsed nictitans, epiphora, and conjunctival hyperemia which are observed within the first 15 minutes and may last for up to 6 hours (Martin & Wyman 1978; Whitley et al., 1980). These signs are most prominent for the first 72 hours of treatment. Use of a special droptainer with a buffer system in its tip to adjust the pH of the pilocarpine solution to a level close to the physiological pH was evaluated in glaucomatous Beagles (Gelatt et al., 1997). One and two percent pilocarpine solutions instilled by buffer-tip droptainer (pH 7) showed excellent pharmacological effects determined by miosis and ocular hypotension and were well tolerated (Gelatt et al., 1997). Topical application of pilocarpine transiently increases the permeability of the blood–aqueous barrier (BAB), but does not result in short- or long-term changes (Krohne, 1994). In the dog, systemic side effects are unlikely after topical administration of pilocarpine 0.5%–8% solution or 4% gel (Carrier & Gum 1989; Whitley et al., 1980).

Ocular and systemic side effects may occur with topical application of indirect-acting parasympathomimetics. Since they potentiate the action of acetylcholine on muscles, they produce more severe ciliary and iridal spasms than does pilocarpine. Decreased vision resulting from miosis and induced myopia is the most adverse reaction reported in

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human patients (Kaufman & Gabelt, 1997). A transient increase in BAB permeability, resulting in increase in aqueous humor flare, occurs in the canine eye after topical application of pilocarpine and demecarium bromide, and may represent a potentially adverse effect in dogs with glaucoma (Krohne, 1994). An experimental investigation in dogs showed that miosis and increased flare caused by topical pilocarpine were inhibited by both proparacaine and nonsteroidal anti-inflammatory drugs (NSAIDs), such as flurbiprofen, suprofen, and diclofenac, whereas IOP was decreased only in proparacaine-treated eyes and increased in NSAID-treated eyes (Krohne et al., 1998). In light of these observations, the investigators concluded that miosis and increased aqueous flare caused by pilocarpine are prostaglandin-mediated events probably secondary to neuropeptide release in aqueous humor (i.e., substance P or calcitonin gene-related peptide) from antidromic stimulation (Krohne et al., 1998). In addition, the pilocarpine IOP-lowering effect observed in the eyes additionally treated with proparacaine was of a comparable amount to that previously reported for eyes treated only with pilocarpine, indicating that this pharmacologic effect is not affected by BAB breakdown (Krohne, 1994; Krohne et al., 1998). Another relevant conclusion of this investigation was that NSAID should not be used in glaucomatous dogs because it interferes with pilocarpine-induced decrease in IOP (Krohne et al., 1998). Systemic toxicity may develop with any cholinesterase inhibitor and may include salivation, vomiting, diarrhea, and abdominal cramps. In order to minimize the risk of toxicity, indirect-acting parasympathomimetics should be avoided in subjects treated with flea preparations containing organophosphates (Gum et al., 1993a). When signs are severe, atropine (0.2 mg/kg IV or IM) and pralidoxime chloride (20 mg/kg IV) are administered to block the action of acetylcholine. In human patients, their long-term use may result in cataract formation, disruption of the BAB, retinal detachment and, in children, development of iris cysts (Ellis, 1997; Kaufman & Gabelt 1997).

Drugs Acting on Adrenoceptors

Drugs that stimulate or block the activity of the ocular sympathetic nervous system may be used to lower IOP. Pharmacologically, their mechanisms of action are still unresolved and continue to be the subject of study and debate.

Epinephrine and Dipivefrin

Epinephrine, or adrenaline, is classified as a nonspecific adrenergic agonist which stimulates both α- and β-membrane receptors. Dipivefrin, or dipivalyl epinephrine, is an epinephrine prodrug produced by the addition of two pivalic acid groups to the parent compound. The lipophilic prodrug penetrates the corneal epithelium barrier, where it is converted by esterases (acetylcholinesterase, cholinesterase, and arylesterase) to its parent drug, epinephrine, which is absorbed in the anterior segment (Nakamura et al., 1993; Wei et al., 1978). Epinephrine has been used for many years to treat glaucoma in human patients but knowledge of its mechanism of action is still incomplete. Currently, it is believed that its ability to lower IOP is manifested both by reduction in formation of aqueous humor and increase in aqueous outflow. Investigations in human and nonhuman primates indicate that epinephrine and dipivefrin reduce aqueous humor formation most likely by decreasing blood flow in the ciliary body because of their vasoconstrictive action upon the vasculature of the ciliary body (Alm, 1980; Michelson & Groh, 1994). Improvement in conventional aqueous outflow facility by adrenergic drugs has also been clearly identified in nonhuman primate and human eyes (Erickson et al., 1978; Erickson-Lamy & Nathanson, 1992; Neufeld, 1984). In the human eye, an increase in aqueous outflow is mediated by β_2-adrenergic receptors and is correlated with increased cyclic adenosine monophosphate (cAMP) production by the trabecular meshwork (Erickson et al., 1978; Erickson-Lamy & Nathanson, 1992).

Concentrations of 1% and 2% topical epinephrine were effective in reducing IOP in glaucomatous (open-angle) and normotensive Beagles (Gwin et al., 1978). In these animals, the 0.5% solution of dipivefrin manifested hypotensive and mydriatic effects similar to those of the 2% solution of epinephrine (Gwin et al., 1978). Topical epinephrine or dipivefrin, alone or in combination with other antiglaucomatous drugs such as direct-acting parasympathomimetics, β-blockers, and CAIs, has its main indication in the management of open-angle glaucoma. Various local and systemic side effects have been reported in human patients with the ocular instillation of epinephrine and dipivefrin (Fang & Kass, 1997). The most common side effects include local intolerance, formation of adrenochrome deposits in the conjunctiva and cornea, loss of eyelashes, and macular edema in aphakic eyes (Fang & Kass, 1997). Incidence of conjunctival and corneal staining in veterinary patients is unknown. Local irritation consisting of mild conjunctivitis and tearing has been reported in the dog with the 0.5% solution of dipivefrin (Gwin et al., 1978). Since some of the corneal esterases that convert dipivefrin to epinephrine are inhibited by anticholinesterase drugs, combined use of indirect parasympathomimetics (demercarium, echothiophate, or phospholine iodide) and dipivefrin is contraindicated (Abramovsky & Mindel, 1997).

Alpha2-Adrenergic Agonists

The mechanism by which α_2-adrenergic agonists lower IOP is not fully understood. Studies in human eyes have clearly shown that these drugs decrease aqueous formation, but

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gave conflicting results as regards their effect on outflow facility (Lee et al., 1984a). From different investigations, it appears that α_2-adrenergic agonists most likely decrease aqueous humor formation by interfering with presynaptic (nerves) and postsynaptic (nonpigmented epithelial cells) α_2-adrenoceptors at the sympathetic nerve–ciliary body junction (Lee et al., 1984a; Ogidigben et al., 1994; Toris et al., 1995b). Activation of the presynaptic α_2-receptors inhibits norepinephrine release, thereby blocking the tonic adrenergic stimulation of the secretory ciliary epithelium by endogenous norepinephrine. Activation of the postsynaptic ciliary body α_2-receptors, coupled to a G_i protein, suppresses the activity of adenylate cyclase and reduces the intracellular concentration of cAMP in the ciliary body epithelium. The net effect is a decrease in aqueous humor formation (Ogidigben et al., 1994).

Apraclonidine (p-aminoclonidine), a derivative of clonidine with comparable IOP lowering effect and minimal cardiovascular effects, has been developed for use in human patients (Toris et al., 1995b). It is available as a topical 0.5% solution. The IOP lowering ability of apraclonidine has been evaluated in normal dogs and cats. Single topical administration of 0.5% apraclonidine in canine eyes resulted in a 3.0 mmHg (16%) IOP decrease 8 hours after treatment (Miller 1996a). In the cat, apraclonidine-treated eyes showed mean IOP decrease of 4.8 mmHg (24%) 6 hours after treatment (Miller et al., 1996). The topical application of apraclonidine resulted in ocular and nonocular side effects both in dogs and cats. Mydriasis occurred in 29% of the treated canine eyes and miosis, with a reduction in pupillary diameter of 46%, occurred in treated feline eyes (Miller et al., 1996b). Reduction in heart rate was more marked in cats than in dogs and undesirable gastrointestinal effects, such as salivation and vomiting, occurred in most cats (Miller et al., 1996a, 1996b). Thus, it appears that apraclonidine is not a first-line antiglaucoma agent in the dog and is too toxic to be used in the cat. Nonocular side effects most likely result from systemic absorption of the topical drug. This is consistent with the finding that the conjunctival/scleral route is the main pathway for apraclonidine absorption after topical application (Chien et al., 1990).

Brimonidine tartrate, a highly selective α_2-agonist, has been introduced for treating acute and chronic elevations of IOP in human patients (Walters, 1996). Its hypotensive effect in human glaucoma patients was found to be similar to that of timolol maleate, a β-adrenergic antagonist, and was not associated with any systemic side effects (Katz, 1999). Current data indicate that brimonidine reduces IOP in human eyes by a dual mechanism, decreasing aqueous inflow and increasing uveoscleral outflow (Toris et al., 1995a). Ocular effects of single and multiple doses of topical 0.2% brimonidine has been evaluated in glaucomatous beagles (Gelatt et al., 2002a). After application, a trend to reduction in IOP was observed but not at statistical significance. As a result, the authors advised to use brimonidine as additive therapy and not as monotherapy in glaucomatous dogs. Side effects observed with brimonidine treatment in dogs included miosis and bradycardia (Gelatt et al., 2002a). A survey conducted in a poison control center documented the clinical signs associated with ingestion of brimonidine ophthalmic solution by dogs (Welch & Richardson, 2002). Severe dose-dependent cardiovascular effects (hypotension, bradycardia) and central nervous system depression can ensue after the ingestion of brimonidine. Supportive care, as well as systemic administration of an α_2-antagonist, such as yohimbine or atipamezole, is helpful to reverse the signs of toxicosis (Welch & Richardson, 2002).

Beta-Adrenergic Antagonists (Beta-Blockers)

Topical β-blockers have become the most widely used medications for the control of ocular hypertension in human patients. In 1967, it was observed that propranolol caused a reduction in IOP after intravenous or topical administration. A number of other β-blockers used for cardiovascular disease (i.e., practolol, oxprenolol, and atenolol) were then investigated as antiglaucoma agents, but adverse side effects limited their ocular use. In 1977, timolol was found to be a safe and effective agent for lowering IOP in human glaucoma patients. Since the drug was first marketed in 1978, levobunolol, betaxolol, metipranolol, carteolol, and nipradilol have also been released as antiglaucoma medications. Additional agents are currently being investigated and developed for ophthalmic use including nebivolol and carvedilol (Szumny & Szelag, 2014). All but betaxolol are nonspecific β-blocking agents which block both β_1- and β_2-receptors. Betaxolol is a β_1-selective ophthalmic β-blocker. Carteolol is the only compound which possesses intrinsic sympathetic activity when bound to the β-adrenergic receptors (Frishman et al., 1994; Juzych & Zimmerman, 1997; Zimmerman, 1993). Many investigations have convincingly shown that topical β-blockers reduce IOP by decreasing formation of aqueous humor (Coakes & Brubaker, 1978; Helal et al., 1979; Liu et al., 1980; Vogh et al., 1989). A single drop of 0.5% timolol solution suppresses aqueous formation in the range of 13%–48% in normal human eyes (Coakes & Brubaker, 1978). In cat eyes, the rate of aqueous humor formation is reduced 28%, 56%, and 71% by 0.005%, 0.025%, and 0.15% intracamerally injected timolol solution, respectively (Liu et al., 1980).

Topical 0.5% timolol given to normal rabbit eyes decreases aqueous flow by 35% as measured by sulfacetamide clearance from aqueous humor (Vogh et al., 1989). However, their mechanism of action is still uncertain, and three possibilities have been suggested: (1) they may block β-receptors in the ciliary body processes; (2) they may inhibit active transport and ultrafiltration related to Na^+-K^+-adenosine triphosphatase (ATPase); or (3) they may act through a vasoactive mechanism. According to the classic view, β-blocking

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agents lower aqueous humor flow by altering the adrenergic neuronal control of aqueous humor formation by blockade of the β-receptors in the ciliary body processes (Frishman et al., 1994). β_2-adrenergic receptors seem to predominate in the ciliary body processes (Nathanson, 1981; Trope & Clark, 1982), and experimental findings indicate that β-adrenergic receptors mediating pressure changes in the anterior segment of the cat eye are predominantly β_2 (Colasanti & Trotter, 1981). It has been postulated that occupation of the β-adrenoceptors of the ciliary body epithelium inhibits the tonic influence of norepinephrine released by the sympathetic nerves, thereby inducing a decrease of cAMP levels in the ciliary body epithelium and hence a reduction of the secretory function of the ciliary body epithelium (Juzych & Zimmerman, 1997). However, *in vivo* and *in vitro* findings indicated that the correlation between aqueous humor formation and ciliary body epithelial cAMP content was unclear and that β-blocking drugs might act through mechanisms unrelated to β-adrenergic blockade in the ciliary body epithelium (Boas et al., 1981; Shahidullah et al., 1995). Since plasma membrane ATPases of the ciliary body epithelium are involved in aqueous humor formation, the potential relationship between inhibition of ciliary ATPases and the IOP-lowering effect of the β-blockers has been investigated. *In vitro* and *in vivo* studies support a mechanism for β-adrenergic antagonist inhibition of ciliary Na^+-K^+-ATPase activity (Rittenhouse & Pollack, 1999; Whikehart et al., 1992). However, other studies in rabbits showed that neither Na^+-K^+-ATPase nor Mg^{++}-ATPase was inhibited by timolol, and showed that the IOP-lowering effect of the drug was related to a significant reduction of blood flow in the iris root-ciliary body, related to a significant reduction in dopamine concentrations in this tissue (Watanabe & Chiou, 1983). β-blockers have no effect on aqueous outflow (Juzych & Zimmerman, 1997).

Topical timolol is available as a 0.25% and 0.50% solution of the maleate salt. In the United States, the drug is also supplied as a 0.25% and 0.50% hemihydrate salt, which has an ocular hypotensive effect similar to that of the maleate salt in human patients (Bartlett et al., 2008). In 1993, timolol maleate also became available in an anionic heteropolysaccaride gellan gum (Gelrite), which gels in contact with the cations in the tear fluid. This *in situ* gel-forming formulation allows increased bioavailability and is administered once daily. Diverging results have been obtained in normotensive dogs after single and repeated instillation of 0.5% timolol maleate. In an early investigation, a mean reduction in IOP of 2.5 mmHg (16%) was observed within 2–4 hours postdosing (Wilkie & Latimer, 1991a), whereas in two other reports the 0.25% and 0.5% timolol formulations were found ineffective at reducing IOP in normotensive dogs (Gum et al., 1991b; Smith et al., 2010). In clinically healthy cats, a single application of 0.5% solution induced a mean reduction in IOP of 4.1 mmHg (22%), with the maximum IOP reduction occurring within 6–12 hours after instillation (Wilkie & Latimer, 1991b). A contralateral decrease in IOP also occurred in nontreated eyes, both in dogs and cats (Wilkie & Latimer, 1991a, 1991b). A dose–response study of timolol maleate employing single- and multiple-drop instillations in glaucomatous (open-angle) Beagles found that 0.25% and 0.5% timolol lowered IOP by approximately 4–5 mmHg (Gum et al., 1991b). A dose-related reduction in IOP was observed in normotensive dogs, with concentrations of 2%–8% (Gelatt & MacKay, 1995). In eyes with open-angle glaucoma, decrease in IOP ranging from 8 to 14 mmHg was observed for up to 6 hours after administration of 4%, 6%, and 8% concentrations (Gelatt & MacKay, 1995). Once-daily instillation of timolol maleate 0.5% gel-forming ophthalmic solution in healthy Beagles was found to induce a mean reduction in IOP of 5.4 mmHg (Takiyama et al., 2006). The hypotensive effect persisted for 24 hours after the instillation (Takiyama et al., 2006). A gel formulation of 0.5 % timolol maleate had an inconsistent effect on IOP when dosed once daily in both normal and glaucomatous cats, with maximum IOP-lowering effect (mean = 5.6 mmHg, 17.4%) observed 6 hours posttreatment in glaucomatous individuals (Kiland et al., 2016). The drug caused significant miosis from 4 to 8 hours posttreatment, but had no effect on heart rate (Kiland et al., 2016). As β_2-receptors predominate in the feline anterior segment, β_1-selective blockers, such as betaxolol, may have lower efficacy in cats (Colasanti & Trotter, 1981). Due to lower sympathetic tone, β-blockers also are ineffective at lowering IOP during sleep, which may reduce their efficacy in felines that nap frequently during the day and exhibit peak IOP during the nocturnal phase (McLellan & Miller, 2011). The effect of topical application of timolol on IOP has been evaluated in mares with normotensive eyes (van der Woerdt et al., 2000). A significant mean decrease of approximately 4–5 mmHg was observed 8 hours after single-dose application, and the pressure-lowering effect was present throughout the 5-day multiple-dose study with a maximum reduction in IOP of 27% (van der Woerdt et al., 2000). No ocular side effects were noted with the exception of 11% reduction in the pupil size. These results indicate that timolol could be of benefit in the management of glaucoma in horses (van der Woerdt et al., 2000).

In people, carteolol, metipranolol, and levobunolol have similar potency to that of timolol for decreasing IOP (approximately 20%–30%) (Zimmerman, 1993). In rabbits, most of the topical β-blockers, including nebivolol and carvedilol, lower IOP to a comparable effect (Szumny & Szelag, 2014). Studies in dogs have looked at timolol, betaxolol, levobunolol, and nipradilol, which seem to lower IOP similarly, but may differ in their local and systemic side effects or in their IOP lowering effects when used in combination with drugs from other classes. The IOP-lowering effect of β-blockers, although significant, is generally not large (2–6 mmHg) which limits the utility of these drugs for monotherapy of

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overt glaucoma. However, they may be very helpful for lowering IOP when used in combination with drugs from other classes. Typically, such combinations provide an additive effect by using two drugs that work through different mechanisms, usually affecting both aqueous production and outflow. For instance, pilocarpine is often used in combination with β-blockers. In glaucomatous beagles (open-angle), the response to either 4% or 6% timolol was enhanced by combination with 2% pilocarpine (Gelatt et al., 1995). Topical 0.5% timolol when used in combination with the topical CAI dorzolamide decreases IOP to a greater extent than does either drug alone in glaucomatous beagles, suggesting a synergistic effect, the underlying mechanism behind which remains unknown (Plummer et al., 2006). Topical instillation of levobunolol 0.5% combined with dorzolamide in normotensive dogs produces a stronger hypotensive effect than the combination of timolol and dorzolamide (Scardillo et al., 2010). Timolol in combination with the prostaglandin analogue latanoprost lowers IOP to a greater extent than does either drug alone (Smith et al., 2010). When two topical antiglaucoma medications are combined during the same dosing episode, at least 5 minutes should pass between applying the two formulations because coadministration reduces their ocular bioavailability. Pharmacokinetics data in rabbits show that when timolol is coadministered with either pilocarpine or epinephrine, its ocular absorption is reduced by 20%–70% (Lee et al., 1991).

Another clinical utility for topical β-blockers is in the prophylactic treatment of a normotensive fellow eye in an animal in which the contralateral eye has been diagnosed with overt glaucoma. Although the IOP lowering effects of monotherapy of these drugs is modest, it is sufficient in many instances to prolong the onset of overt glaucoma (Miller et al., 2000). As mentioned previously, topical 0.5% betaxolol is an alternative to demecarium bromide to prevent or delay the onset of hypertension in canine eyes predisposed to primary closed-angle glaucoma (PCAG) (Miller et al., 2000).

The most common ocular side effect of topical β-blocking agents is local intolerance (i.e. stinging, burning) on ocular instillation (Juzych & Zimmerman, 1997). Photophobia, ptosis, blepharoconjunctivitis, and superficial keratitis are other potential ocular side effects of these drugs (Juzych & Zimmerman, 1997). Changes of the ocular surface observed during treatment with timolol have been associated with a significant reduction in tear production and turnover (Shimazaki et al., 2000). It seems that carteolol has better ocular tolerability than the other compounds (Zimmerman, 1993). In human patients, topical timolol has minimal effect on pupillary diameter. On the contrary, significant reduction in the pupil size is observed in the canine and feline-treated eyes (Gelatt et al., 1995; Wilkie & Latimer, 1991a, 1991b). Reduction of pupillary diameter is more marked in cats than in dogs with a maximum duration of persistence 1 week after treatment is discontinued (Wilkie & Latimer, 1991a, 1991b). Timolol has been shown to be more toxic to regenerating corneal epithelium than levobunolol and betaxolol in rabbit eyes (Trope et al., 1988), and therefore may not be the drug of choice in animals with both glaucoma and corneal epithelial defects. Topical β-blockers are contraindicated in human patients with severe heart failure and bronchial asthma because of their potential cardiopulmonary adverse effects resulting from systemic absorption. It is possible that the partial agonist activity of carteolol may reduce its cardiovascular and bronchopulmonary adverse effects by lessening systemic β-blockade effect (Frishman et al., 1994; Zimmerman, 1993). Significant decrease in pulse rate was observed in normotensive and glaucomatous Beagles treated with topical timolol at concentrations ranging from 0.5% to 8% (Gelatt et al., 1995; Gum et al., 1991b; Plummer et al., 2006) and with topical levobunolol (Scardillo et al., 2010). A contralateral effect on IOP and pupillary diameter was also identified in the nontreated eyes when timolol was topically given to dogs and cats (Wilkie & Latimer, 1991a, 1991b). These effects likely result from systemic uptake via transconjunctival route and nasolacrimal duct pathway. Systemic activity of topically applied timolol has been shown in an experimental dog model (Svec & Strosberg, 1986). To prevent occurrence of deleterious cardiovascular effects secondary to systemic absorption, suggestion of using 0.25% timolol in cats as well as dogs weighing less than 10 kg, and 0.5% timolol in dogs with body weight above 10 kg, is given in the literature (Willis, 2004). Use of timolol in cats with asthma is probably contraindicated. The reduction of IOP by 0.25% nipradilol is similar to that of 0.5% timolol maleate, but nipradilol was associated with fewer systemic side effects in dogs, so it may be a useful alternative (Maehar et al., 2004).

Carbonic Anhydrase Inhibitors

CAIs that belong to the class of nonbacteriostatic sulfonamide-related compounds were used in ophthalmology as early as 1954 with the introduction of acetazolamide. Methazolamide and dichlorphenamide were released subsequently. These agents have been widely used ever since, but because their clinical usefulness is limited by various systemic side effects, topical CAIs have virtually replaced them for the treatment of glaucoma.

Mechanism of Action

The ciliary body process epithelium contains enzyme systems, such as Na^+-K^+-ATPase and carbonic anhydrase, which are involved in aqueous humor formation. Carbonic anhydrase (CA) is a ubiquitous enzyme for which seven isoenzymes have been identified. CA I, CA II and CA III are located in the cytosol, CA IV is membrane bound, CA V is present in mitochondria, and CA VI and CA VII are only

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found in salivary glands (Jampel et al., 1997). Only CA II, CA III, and CA IV are present in significant amounts in pigmented and nonpigmented ciliary body epithelial cells to catalyze the reversible hydration of carbon dioxide (Jampel et al., 1997). Aqueous humor formation depends on the production of bicarbonate (HCO_3^-) from CA II, the isoenzyme found in the nonpigmented ciliary body epithelium. Chemically, the enzymatic effect of CA is to catalyze carbon dioxide (CO_2) hydration to carbonic acid (H_2CO_3) which dissociates spontaneously into protons and bicarbonate ions according to the equation: $H_2O + CO_2 \leftrightarrow HCO_3^- + H^+$. Newly formed bicarbonate ions are neutralized by sodium and other cations and transferred to the intercellular channels and the posterior chamber (Fig. 8.5.1). Water is then osmotically attracted from the vessels of the ciliary stroma to form aqueous humor (Derick, 1994).

The common feature of CAIs is a sulfonamide group (-So_2NH_2) attached to an aromatic ring. Competition of the sulfonamide group with carbonic acid for its site on carbonic anhydrase, to make it inactive, is the basis of the pharmacological action of these drugs (Higginbotham, 1989). It is known that 98% inhibition of CA II must be achieved in ciliary body epithelium by systemic or topical inhibitors for full IOP reduction (Brechue & Maren, 1993). In parallel to the decreased appearance of bicarbonate into the posterior chamber, the rate of sodium transport is decreased by an equimolar amount, and entry of water into the posterior chamber is reduced. Accordingly, aqueous humor formation is suppressed by 40%–60% (Friedland & Maren, 1984). In the dog, carbonic anhydrase inhibition by acetazolamide lowers aqueous flow from 9 μL/min prior to treatment to 6.4 μL/min after treatment (Friedland & Maren, 1984). In general, sulphonamide CAIs inhibit the enzyme with high specificity, meaning that they have no inhibitory activity against other enzymes, and in a noncompetitive and reversible manner.

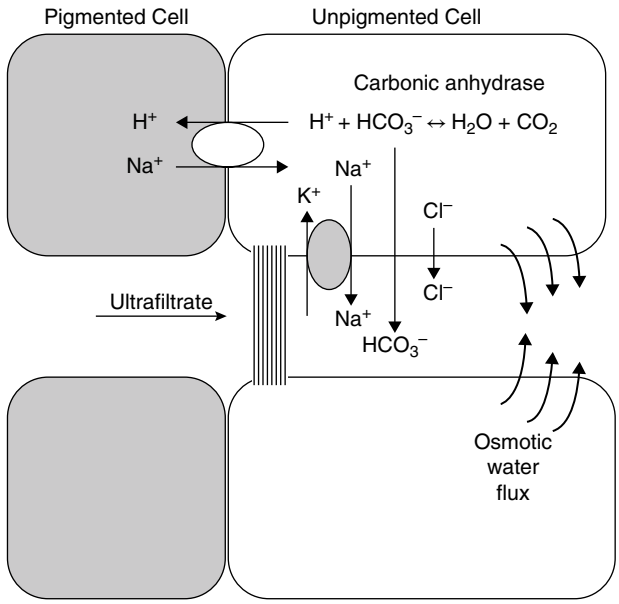


Figure 8.5.1 Contribution of carbonic anhydrase to aqueous humor formation in the pigmented and non-pigmented ciliary body epithelium.

Although systemic CAIs are diuretics, it is currently believed that their ocular hypotensive effect does not depend on diuresis. There is, however, some indication that the systemic acidosis induced by these agents also inhibits aqueous humor formation and enhances their pressure-lowering effect (Friedland & Maren, 1984). In addition to their IOP-lowering effect, CAIs have also been shown to affect the ocular circulation. Carbon dioxide is a potent vasodilator involved in autoregulation of blood flow in the eye and elsewhere in the body. Blockade of CA in local tissues results in increased levels of CO_2 and/or lower tissue pH that can act on blood vessels and produce vascular dilation and increased blood flow (Rassam et al., 1993; Taki et al., 1999). However, the recent observation that the vasodilation induced by these drugs on retinal arterioles is increased by the perivascular retinal tissue, by acidosis, but not by hypercapnia, suggest that mechanisms other than carbonic anhydrase inhibition might also be involved in the vasodilating effect of CAIs, although a contributing action of the enzyme cannot be excluded (Torring et al., 2009). According to the authors, alternative mechanisms of action could include an effect through voltage-gated K^+ channels or an effect mediated by nitric oxide (NO) (Torring et al., 2009). An increase in ocular blood flow in the retinal circulation has been shown in human eyes after application of topical CAIs, and is expected to be beneficial to patients with glaucoma (Siesky et al., 2009). In rabbits, topical dorzolamide vasodilates the ciliary body circulation, increasing ciliary blood flow by 18%, but does not alter the choroidal hemodynamics (Reitsamer et al., 2009). This mechanism is in contrast with those of drugs that decrease aqueous formation indirectly by constricting the ciliary body circulation (i.e., epinephrine, β-blockers) (Reitsamer et al., 2009).

Systemic Carbonic Anhydrase Inhibitors

Acetazolamide, the first drug in this group to be synthesized, can be administered either orally or intravenously. It is supplied in tablets of 125 and 500 mg as well as in time-release capsules of 500 mg. A single oral administration of a dose ranging from 10 to 75 mg/kg significantly lowers IOP in normotensive and glaucomatous Beagles for at least 8 hours (Gelatt et al., 1979). A dosage of 4–8 mg/kg two to three times daily is usually recommended for treatment of canine glaucoma (Gaarder, 2000). In the cat, doses ranging from 10 to 25 mg/kg are effective in lowering the IOP in glaucomatous animals. The hypotensive effect lasts about 5 hours in this species (Othman & Samy, 1987). Acetazolamide is also available for intravenous injection as a lyophilized

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powder (500 mg/vial). Intravenous acetazolamide at a dose of 5–10 mg/kg is useful as adjunctive therapy in the management of acute glaucoma. Topical antiglaucoma drugs should be employed concurrently and diligently continued thereafter for continued effect.

Dichlorphenamide is no longer in routine use for the treatment of glaucoma, but it has been recently returned to the market for the treatment of other systemic condition, so although available, it is expensive. The oral dose rate in the dog ranges from 2 to 4 mg/kg, two to three times daily (Gaarder, 2000). In glaucomatous Beagles, the maximal effect occurs at a dose of 10 mg/kg, 3 hours after administration (Gelatt et al., 1979). Single oral administration of dichlorphenamide in the cat in doses ranging from 0.5 to 2 mg/kg significantly reduced IOP for 4 hours (Othman & Samy, 1987).

Methazolamide is supplied in 50 mg tablets. After oral administration of 25 mg or 50 mg methazolamide to healthy Beagle dogs, a significant dose-dependent decrease in IOP of 18%–21% was observed 3–6 hours after administration. Nevertheless, IOP increased to levels above the control baseline values thereafter (Skorobohach et al., 2003). The lowering effect on IOP occurred because of a mean reduction in aqueous humor formation of 28% (Skorobohach et al., 2003). The rebound effect was ascribed to a possible upregulation of CA after treatment ceased, and it should be kept in mind in a clinical setting when administration of methazolamide is discontinued (Skorobohach et al., 2003). In a study of the systemic CAIs in normal and glaucomatous dogs, results suggested that methazolamide decreases IOP at dosage levels lower than acetazolamide, dichlorphenamide, and ethoxzolamide (Gelatt et al., 1979). In glaucomatous dogs, the IOP decreasing effect of oral metazolamide (5 mg/kg twice daily) was comparable to that achieved with topical dorzolamide instilled twice or three times daily (Gelatt & MacKay 2001b). When coadministered, the drugs did not produce an additional reduction in IOP (Gelatt & MacKay, 2001b).

Topical Carbonic Anhydrase Inhibitors

Systemic complications associated with chronic use of oral CAIs in human patients inspired the development of topical formulations of CAIs with the goal of fewer systemic adverse effects. Dorzolamide was the first of these drugs to be marketed in 1995, followed by brinzolamide a few years later. The history of the design and development of the topical CAIs has been extensively reviewed (De Santis, 2000; Higginbotham, 1989). In 1991 MK-927, another Merck topical CAI, lowered IOP in glaucomatous Beagles; its maximum effect occurred after 5 days of dosing, suggesting a possible drug loading effect (King et al., 1991).

Dorzolamide and brinzolamide are most potent against CA II, with less activity against CA IV (De Santis, 2000; Maren, 1997). Experimental data in rabbits indicate that topical dorzolamide and brinzolamide readily penetrate the eye by both the corneal and scleral routes (Maren, 1997; De Santis, 2000). After topical application onto canine eyes, dorzolamide concentrations achieved in the ciliary body are much higher than those reached in the aqueous humor, suggesting that in the dog, the cornea/scleral route has also a role in the intraocular penetration of the drug (Cawrse et al., 2001). In healthy dogs, administration of a single dose of 2% dorzolamide was associated with a mean reduction in IOP of 3.1 mmHg (18%) from 30 minutes to 6 hours after treatment (Cawrse et al., 2001). Mean aqueous flow rate decreased 43% in treated eyes (Cawrse et al., 2001). In a short-term study in normotensive dogs, a maximum decrease in IOP of about 6 mmHg was reached after 5 days of treatment at 8-hour intervals (Kennard & Whelan, 2001). In glaucomatous dogs, 2% dorzolamide decreased IOP to an even greater extent, with a mean reduction of 30% (Plummer et al., 2006).

Topical dorzolamide was also found to lower IOP when applied to normotensive feline eyes every 8 or 12 hours (Rainbow & Dziezyc, 2003; Rankin et al., 2012). The amplitude of IOP decrease observed in cats after twice daily applications of dorzolamide was almost the same as that observed previously in dogs with three times daily applications (Cawrse et al., 2001; Rainbow & Dziezyc, 2003). In cats with primary glaucoma, topical dorzolamide decreases IOP by nearly 46% when administered three times daily (Sigle et al., 2011).

Topical dorzolamide seems to influence IOP in horses less than it does in small animals, because its twice daily application to normotensive equine eyes only reduced IOP by an average of 2 mmHg (Willis et al., 2001b). In the light of these findings, the authors' suggestion was that topical dorzolamide can only be recommended as adjunctive therapy in glaucomatous horses. Anecdotally, many clinicians report a much greater response to topical 2% dorzolamide in glaucomatous equine eyes.

The effect of topical administration of 1% brinzolamide on the IOP has been evaluated in small and large animals. In a preliminary study in healthy dogs, 1% brinzolamide instilled twice daily significantly reduced IOP with the peak effect observed between 5 and 6 hours postmedication. The amplitude of the IOP reduction was similar to that induced by topical dorzolamide, but lower than that resulting from oral administration of 5 mg/kg of methazolamide (Whelan et al., 1997). Mean IOP returned to baseline value about 10–11 hours after treatment, indicating that administration every 8 hours would be more appropriate than every 12 hours for optimal pharmacologic effect (Whelan et al., 1997). Contrary to dorzolamide, brinzolamide topically applied every 12 hours was unable to significantly influence IOP of normotensive feline eyes (Gray et al., 2003), but did significantly reduce IOP when administered every 8 hours, albeit to a lesser extent that dorzolamide (McLellan et al., 2009). In horses, topical application of 1% brinzolamide was well

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tolerated, and the mean IOP reduction achieved with once- and twice-daily administration was 3.1 mmHg and 5.0 mmHg, respectively (Germann et al., 2008), which represents a higher IOP-lowering effect than that previously reported with dorzolamide in equine patients (Willis et al., 2001b). This finding seems to indicate that monotherapy or adjunctive therapy with 1% brinzolamide may represent a valuable option for the treatment of equine glaucoma (Germann et al., 2008).

Clinical Use

Because they diminish aqueous humor formation, CAIs can be employed in the treatment of practically all types of glaucoma. Short-term administration of systemic or topical CAIs may be effective in the management of acute increases in IOP resulting from primary or secondary glaucoma. On the basis of findings in normal and glaucomatous dogs, combined administration of topical and systemic CAI has no additional IOP-decreasing effects over dorzolamide or brinzolamide alone that would warrant its use in dogs with acute glaucoma (Gelatt et al., 2001a; Whelan et al., 1997). Topical CAIs also represent a valuable substitute for oral methazolamide in the long-term treatment of chronic glaucoma in dogs because their effects on IOP are comparable and systemic side effects are less likely (Gelatt & MacKay 2001b; Whelan et al., 1997). Theoretically, CAIs can be used in combination with other antiglaucoma agents because their effect is usually additive, reducing IOP more than any single agent. In the dog, the combined use of dorzolamide and latanoprost may be appropriate for the management of chronic glaucoma because dorzolamide given every 8 hours and latanoprost instilled once in the morning were shown to have an additive effect on decreasing IOP (Kennard & Whelan, 2001). The additivity of topical CAIs to topical β-blockers regarding the decrease in aqueous humor outflow has also been documented in normotensive human eyes. In healthy eyes, 18% and 47% reduction in aqueous flow is observed after topical treatment with dorzolamide alone or in combination with timolol, respectively. Topical administration of an unfixed combination of both drugs leads to an incremental 55% decrease in flow (Wayman et al., 1997). A fixed combination of dorzolamide 2% and timolol 0.5% is currently available. Its administration twice daily in glaucomatous human patients has an IOP-lowering effect similar to that obtained with dorzolamide alone instilled three times daily (Hutzelmann et al., 1998). In glaucomatous beagles, the combination product has been compared with monotherapy with either timolol 0.5% or dorzolamide 2% three times daily. After 4 days of treatment, the mean reduction in IOP was 7.50 mmHg, 3.75 mmHg, and 8.40 mmHg for the dorzolamide, timolol, and combination product, respectively (Plummer et al., 2006). Thus, the fixed combination of dorzolamide–timolol seems more effective at decreasing the IOP in dogs with glaucoma than is either dorzolamide or timolol alone (Plummer et al., 2006). By contrast, data indicate that in horses this combination may not have additional IOP-lowering effects over dorzolamide alone (Willis et al., 2001b). However, a recent study showed that the application of a fixed combination of dorzolamide 2% and timolol 0.5% every 12 hours onto normotensive equine eyes led to a mean IOP reduction of 13% (approximately 3.5 mmHg), which is 1.5–1.75 times greater than the reported reduction of IOP in response to dorzolamide alone (Tofflemire et al., 2015b; Willis et al., 2001b). No significant additive ocular hypotensive effect was observed in normal cats treated with a combination of the CAI, dorzolamide 2%, and timolol 0.5%, relative to the effect of treatment with dorzolamide 2% alone (Dietrich et al., 2007).

Adverse Effects

No ocular side effects have been described in relation to the systemic administration of CAIs, but acute overdosage or long-term therapy may result in a variety of clinical and biochemical disorders. The side effects of the various agents of this class are similar, with dichlorphenamide appearing to cause the fewest and being considered the drug of choice for prolonged treatment in small animals (Gaarder, 2000). Common transient side effects associated with oral or parenteral CAIs include increased diuresis, gastrointestinal disturbances (anorexia, vomiting, diarrhea), and increased respiratory rate secondary to metabolic acidosis. Cats appear to be more susceptible to these drugs and should be observed very closely. The dose should be decreased or therapy discontinued if signs of toxicity are observed. Except for acetazolamide, little is known about either the short- or long-term effects of the other CAIs on blood chemistry in the dog. In this species, the intravenous and oral administrations of acetazolamide were found to cause significant metabolic acidosis that achieved a steady state after 1–5 days of treatment (Haskins et al., 1981; Rose & Carter, 1979). This effect, attributed to increased bicarbonaturia, was associated with an increase in PO_2, and a decrease in PCO_2, indicative of compensatory hyperventilation. All dogs given acetazolamide had an increase in plasma chloride. A decrease in plasma potassium also develops, reaching its maximum between the second and fifth day of treatment, presumably as a result of increased kaliuresis. Normal food intake usually obviates any serious potassium depletion, but care must be taken in patients with anorexia or preexisting hypokalemia (Haskins et al., 1981; Rose & Carter, 1979). When acetazolamide administration is discontinued, complete recovery of acid-base and blood electrolyte disorders occurs within 36 hours, because of the short half-life of the drug (Haskins et al., 1981).

The ophthalmic formulation of 2% dorzolamide has a pH of 5.6, and its instillation may be associated with symptoms

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of ocular discomfort (i.e., burning, stinging) on instillation in people (Strahlman et al., 1996). By comparison, 1% brinzolamide is formulated as an ocular suspension with a pH of 7.5 which compares favorably to the pH of the tear fluid and is better tolerated by human patients (Silver & the Brinzolamide Comfort Study Group 2000). In short-term studies of topical CAIs in the dog, cat, and horse, no local or systemic side effects were reported (Cawrse et al., 2001; Rainbow & Dziezyc, 2003; Willis et al., 2001b). However, since those controlled studies were performed several reports of adverse reactions have been made. Topical administration of 2% dorzolamide in dogs in the clinical setting has occasionally been associated with blepharitis which resolves after discontinuation of the drug (Willis et al., 2002). There is a report of keratitis in six dogs that was unresponsive to topical anti-inflammatory therapy but resolved after discontinuation of topical dorzolamide (Beckwith-Cohen et al., 2015). Hypokalemia and suspected renal tubular acidosis associated with topical dorzolamide therapy has been reported in a cat (Thiessen et al., 2016). Despite these sporadic adverse events, the topical CAIs have the advantage over parasympathomimetics and prostaglandin analogs of not causing miosis, and they have the advantage over β-blockers to be less problematic for animals with cardiac or pulmonary disease.

Prostaglandin Analogues

History and Chemistry

The prostaglandins (PGs) are a family of biologically active lipids with a wide spectrum of possible pharmacologic activity. Since early studies showed that low doses of $PGF_{2\alpha}$ can decrease IOP, it has been established that most of the naturally occurring PGs, as well as some of their analogues and esters, are potent ocular hypotensive agents in both animals and humans (Alm, 1998; Bito, 1984). The ocular hypotensive effects in healthy dogs and glaucomatous Beagles was first reported in 1991 using topical prostaglandins PGA_2, PGA_2 isopropyl ester, and $PGF_{2\alpha}$ isopropyl ester. The reduction in both IOP and pupil size were remarkable (Gum et al., 1991a)

The PG derivatives currently approved for the reduction of IOP in human and animal glaucoma patients were all developed through chemical modification of $PGF_{2\alpha}$. Latanoprost and isopropyl unoprostone first emerged as a result of active screening programs. Unosprostone was available in Japan in 1994 and was marketed in 2000 in the United States. It is presently seldom used because it has limited efficacy compared with the other PG analogues (Bean & Camras, 2008; Gelatt et al., 2004). Latanoprost was marketed in 1996, and then two other PG analogues, travoprost and bimatoprost, were approved for use in 2001 (Bean & Camras, 2008; Bito, 1984, 1986). Other agents in this important drug class, such as tafluprost, continue to be developed and explored (Kwak et al., 2017). Because the naturally occurring PGs are hydrophilic molecules, their carboxylic acid moiety and several hydroxyl groups mean that they penetrate the membranes poorly. Therefore, all commercially available PG analogues used for their IOP-lowering activity are esterified prodrugs of the $PGF_{2\alpha}$, more lipophilic, and designed to facilitate penetration through the ocular membranes (Bean & Camras, 2008). Latanoprost is the right-handed epimer of a phenyl-substituted analogue of $PGF_{2\alpha}$, whereas unoprostone is an isopropyl ester of the 20-ethyl derivative of $PGF_{2\alpha}$. Travoprost and bimatoprost are structurally similar to other $PGF_{2\alpha}$ analogues (Fig. 8.5.2) (Eisenberg et al., 2002). After topical application, the prodrug is enzymatically hydrolyzed during its passage through the corneal epithelium to release the active molecule (the carboxylic acid) which is then delivered to the anterior segment of the eye (Bito 1986; Bito & Baroody, 1987). The major intraocular metabolite that is expected to act on target tissues is 17-phenyl-$PGF_{2\alpha}$ for latanoprost, bimatoprost, and travoprost (Bito &Baroody, 1987; Davies et al., 2003), and a free acid of isopropyl unoprostone for unoprostone (Numaga et al., 2005). It has been established that human and canine ocular tissues have a similar profile of $PGF_{2\alpha}$ prodrug hydrolysis (Woodward et al., 1996).

Mechanism of Action

A common feature of the biologically active forms of latanoprost, bimatoprost, travoprost, and unoprostone is the high affinity and selectivity for the prostaglandin F (FP) receptor, and investigation revealed that the IOP-lowering action of these PG derivatives is mediated through the binding of their free acid (the active molecule) to FP receptors in humans (Anthony et al., 1996), monkeys (Lee et al., 1984b), and presumably in dogs (Gum et al., 1991a). Despite their differences in potency at the FP receptor, the free acids of latanoprost, travoprost, and bimatoprost fully activate the receptor relative to the naturally occurring $PGF_{2\alpha}$ (Bean & Camras, 2008). The pivotal role of FP receptors in the ocular hypotensive effects of the $PGF_{2\alpha}$ analogs has also been shown with the use of FP-receptor deficient (FPKO) mice (Ota et al., 2005). The IOP-lowering action of PGs in the feline species reportedly works through EP_1 receptors and not FP receptors (Bhattacherjee et al., 1999; Lee et al., 1984b). In the dog, prostaglandin E (EP) receptors mediating PGE_2 action also can alter aqueous humor dynamics as shown with a potent and selective EP4-PGE_2 agonist which was able to lower IOP by 5–7 mmHg in healthy Beagles when given topically (Aguirre et al., 2009). The mechanism by which this EP4-receptor agonist lowers IOP is currently unknown but may involve trabecular outflow and not uveoscleral outflow (Aguirre et al., 2009).

In humans and animal species studied so far, it has been well established that increase in uveoscleral outflow is the

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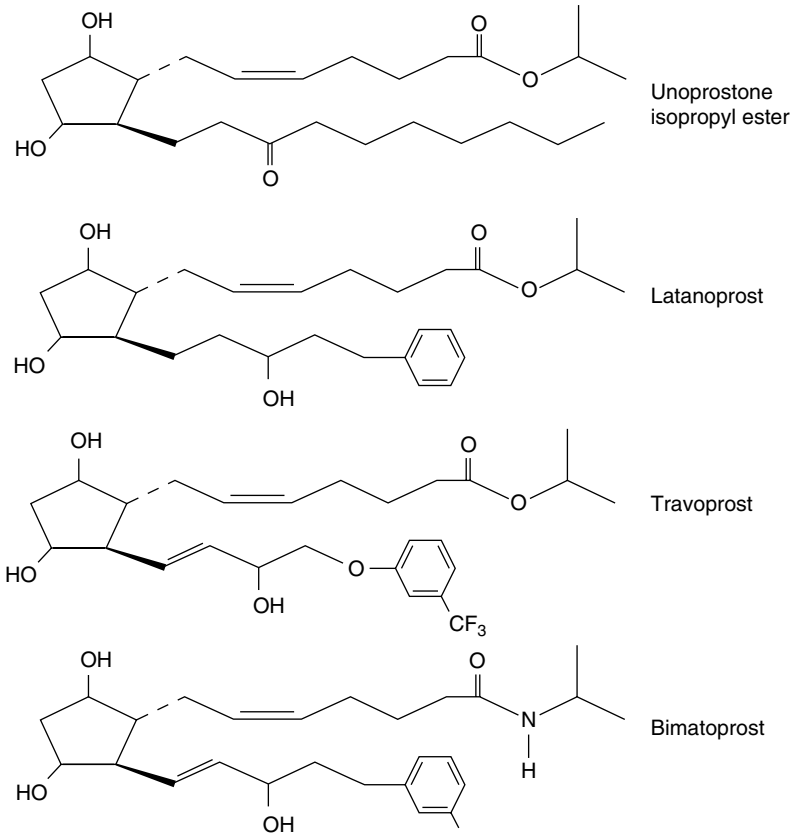


Figure 8.5.2 Chemical structures of the four commercially available prostaglandins in veterinary ophthalmology.

primary mechanism by which PGs reduce IOP (Hurwitz et al., 1991). Increased uveoscleral outflow has been reported in human and nonhuman primates, rabbits, and dogs treated with $PGF_{2\alpha}$ or its analogues (Gabelt & Kaufman, 1990; Gum et al., 1991a; Payer et al., 1992; Toris et al., 1993), and in cats treated with PGA_2 (Toris et al., 1995c). However, data in the current literature indicate that latanoprost, bimatoprost, and unoprostone also affect the pressure-dependent conventional outflow pathway (Richter et al., 2003; Taniguchi et al., 1998). The mechanisms by which activation of FP receptors lead to an increased uveoscleral outflow are still under investigation, but there is scientific evidence that matrix metalloproteinase (MMP)-mediated remodeling of the extracellular matrix (ECM) of the ciliary body muscle contribute to this pharmacological effect. This concept is based on *in vitro* and *in vivo* observations that after several days of treatment with $PGF_{2\alpha}$, the MMP-1, -2, and -3 are increased within uveoscleral outflow tissues (Gaton et al., 2001; Weinreb et al., 1997), whereas collagen types I, III, and IV are decreased (Sagara et al., 1999). In human ciliary body tissue, the transcription of the genes for MMP-3 and MMP-17 is increased after topical treatment with latanoprost (Oh et al., 2006). MMP-9 is also present and may contribute to the ECM changes, whereas tissue inhibitor of metalloproteinase 3 (TIMP-3) is upregulated and may compensate for the increase in MMPs (Oh et al., 2006). The amount of myocilin, an intra- and extracellular protein of the ciliary body muscle, which may contribute to outflow resistance, also is reduced after topical $PGF_{2\alpha}$ treatment (Lindsey et al., 2001, 2002). Ultrastructurally, remodeling of ECM components within uveoscleral outflow pathway was characterized as lysis of ECM between ciliary body muscle bundles and widening of the intermuscular spaces in monkey eyes treated with $PGF_{2\alpha}$ (Lütjen-Drecoll & Tam, 1988), latanoprost, or bimatoprost (Richter et al., 2003). In addition to the changes induced within the uveoscleral outflow pathway, various experimental data argue for an effect of PG analogs on alteration of aqueous outflow through the trabecular meshwork. Among these are the identification of FP receptors in human trabecular meshwork and increased expression of different MMPs and TIMPs by trabecular meshwork cell culture treated with latanoprost (Toris et al., 2008). Long-term treatment with latanoprost or bimatoprost also led to morphologic changes in the trabecular meshwork perhaps in agreement with increased conventional outflow facility (Richter et al., 2003). Increase in both uveoscleral and trabecular outflow has been observed in monkeys given topical tafluprost, a fluoroprostaglandin $F_{2\alpha}$ (Takagi et al., 2004). This drug has also shown to lower IOP in dogs (Kwak et al., 2017). If stimulated induction of MMPs within the ciliary body muscles is the most thoroughly understood effect of PG treatment, it also appears certain that endogenous PGs are released in iris and ciliary body

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muscles secondarily to topical administration of $PGF_{2\alpha}$ analogues and may contribute to the observed hypotensive effects (Yousufzai et al., 1996). Endogenous PGE_2, PGD_2, and $PGF_{2\alpha}$ are produced via phospholipase A2 stimulation and release of arachidonic acid for PG synthesis (Toris et al., 2008; Yousufzai et al., 1996). Inhibition of the latanoprost-induced reduction of IOP in human eyes by ophthalmic NSAID bromfenac (Chibac et al., 2006), and in dogs by topical prednisolone and flurbiprofen (Pirie et al., 2006, 2011), suggest that the IOP-lowering response to topical latanoprost is mediated in part through formation of endogenous PGs both in humans and dogs. In what manner the endogenous released PGs act to alter aqueous outflow is unclear. Widening of the connective tissue-filled spaces among the ciliary muscle bundles, caused by relaxation of the ciliary muscle, and with subsequent reduction in outflow resistance via the uveoscleral pathway, has been suggested as responsible for the reduction in IOP induced by PGE_2 (Poyer et al., 1995). Investigations showed that scleral permeability is enhanced with exposure to PGs or PG analogues, such as latanoprost (Aihara et al., 2001; Kim et al., 2001), and that these changes are associated with increased intrascleral MMP-1, MMP-2, and MMP-14 expression (Lindsey et al., 2007). Prostaglandin-induced changes in the sclera may also be important in the regulation of the uveoscleral outflow (Toris et al., 2008), and suggest that the prospect of increasing transscleral permeability by PG cotreatment might allow sufficient transscleral transport to provide delivery of high molecular weight substances to the posterior segment of the eye (Aihara et al., 2001; Kim et al., 2001).

Experiments in human and nonhuman primates and rabbits indicate that in addition to its IOP-reducing effect, latanoprost increases blood velocity in the optic nerve head (ONH) or dilates the vessels supplying the ONH because of its pharmacologic effect on the vessels (Ishii et al., 2001). Increased ONH perfusion may be important for preservation of visual function in glaucomatous eyes (Fig. 8.5.3).

Clinical Pharmacology

Experimental studies have shown that topical application of 0.005% latanoprost significantly reduces IOP in normotensive and glaucomatous canine eyes (Studer et al., 2000). In normotensive canine eyes, 0.005% latanoprost instilled in the evening, morning, as well as twice daily induced an average decline in IOP of about 25%, whereas in glaucomatous eyes, it produced a mean decline in IOP of about 50% (Gelatt & MacKay, 2001a; Studer et al., 2000). In glaucomatous dogs, a comparable IOP-lowering action was observed with once or twice daily application of 0.03% bimatoprost (Gelatt & MacKay, 2002b), and 0.004% travoprost (Gelatt & MacKay, 2004; MacKay et al., 2012). In normal dogs, the amplitude and duration of the IOP-lowering effect of a single application of 0.12% unoprostone isopropyl or continued once or twice daily administration were found to be similar with those observed after similar doses of 0.005% latanoprost (Gelatt & MacKay, 2001a; Gelatt & MacKay, 2004; Ofri et al., 2000).

Both drug concentration and dosing schedule can alter PG ocular effects. Using single doses of topical travoprost in glaucomatous Beagles, concentrations of 0.0001% produced only pupillary constrictions but no effect on IOP. Higher concentrations (0.0033% [similar to the 0.004% commercial preparation]; 0.001% and 0.00033%) of travoprost produced both significant IOP reductions and pupillary effects. These studies suggest the canine species is highly sensitive to topical PGs (MacKay et al., 2012).

Species differences in prostanoid receptor distribution within different ocular tissues have major implications for the effects and efficacy of topical prostaglandin analog therapy for glaucoma. In contrast to dogs, neither once daily application of 0.005% latanoprost (Studer et al., 2000) or 0.03% bimatoprost (Bartoe et al., 2005), nor twice daily applications of 0.03% bimatoprost (Regnier et al., 2006) or 0.12% unoprostone (Bartoe et al., 2005), which are all FP receptor agonists, significantly lowered the IOP of normal cats. These observations are in agreement with the fact that FP receptor signaling does not play a crucial role in the IOP response to PGs or PG analogues in cats (Bhattacherjee et al., 1999; Lee et al., 1984b). Topical application of PGs in cats does, however, produce intense miosis (Regnier et al., 2006; Studer et al., 2000). This is attributable to the presence of exquisitely well-coupled FP receptors in the iris sphincter muscle of cats, compared with humans (Bhattacherjee & Paterson, 1994, Sharif et al., 2008). Although FP receptors are largely responsible for the effects of prostaglandin analogs on the canine and human ciliary body, these receptors are lacking in the ciliary body of cats and EP receptors are predominantly responsible for relaxation of feline ciliary muscle (Bhattacherjee et al., 1999). Unfortunately, with the refinement of prostaglandin analogs to maximize their specificity for FP receptors on the human ciliary body, in order to minimize adverse effects such as ocular inflammation, commercially available prostaglandin analogs are less likely to have any ocular hypotensive effect in cats. A recent study (McDonald et al., 2016) indicates that latanoprost 0.005% transiently lowers IOP in glaucomatous cats after a single topical application, but this effect is diminished after 3 weeks of twice daily administration of the drug.

The potential of 0.005% latanoprost for lowering IOP has also been evaluated in normotensive equine eyes (Willis et al., 2001a). In clinically normal horses, a once daily application of 0.005% latanoprost resulted in a mean decrease in IOP of 1.03 mmHg or about 5% in males, and 3.01 mmHg or about 17% in females (Willis et al., 2001a). The reason for the gender effect in the response of the equine eye to topical 0.005% latanoprost has not been determined (Willis et al., 2001a). A more recent study showed a mean IOP reduction

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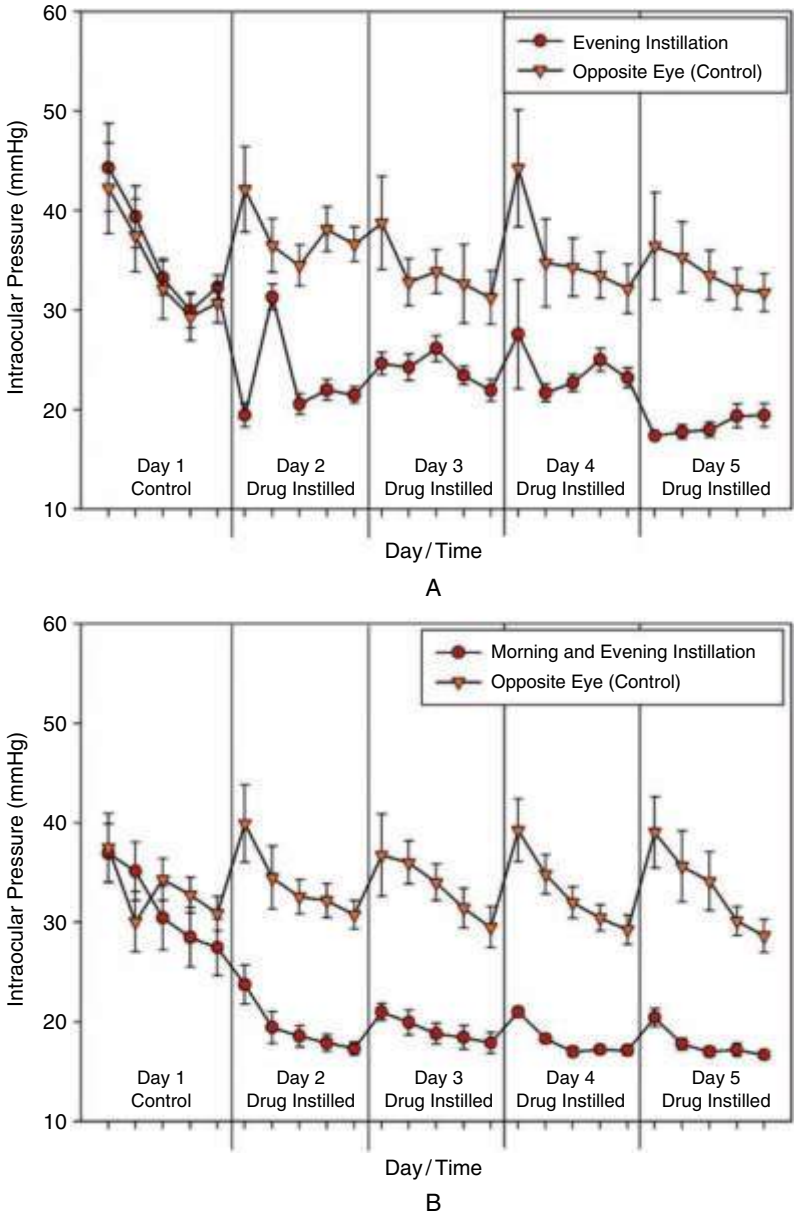


Figure 8.5.3 Effect on IOP of 0.005% latanoprost in the Beagle with primary open-angle glaucoma after evening (**A**) and q 12h dosing (**B**).

of 13.7% and 8% in normotensive equine eyes that were treated once daily with latanoprost or latanoprost and diclofenac, respectively. When latanoprost was given alone, the reduction in IOP was greater than when a combined treatment of latanoprost and diclofenac was given, although the difference was not statistically significant. However, latanoprost-induced discomfort was mitigated by concurrent application of diclofenac (Tofflemire et al., 2017).

Clinical Use

In a short time, PG derivatives have reached extensive clinical use in human patients with ocular hypertension and primary open-angle glaucoma (POAG) (Soltau, 2002). Several studies documented the IOP-lowering effect of PG derivatives in humans, but latanoprost has mostly been evaluated as either monotherapy or an adjunctive agent added to another antiglaucoma agent (Alm, 1998). In human patients with either ocular hypertension or POAG, latanoprost, bimatoprost, and travoprost administered once daily in the evening induce a higher reduction in IOP than 0.5% timolol applied twice daily (Alm & Stjernschantz, 1995; Mishima et al., 1996; Sherwood & Brandt, 2001). Latanoprost twice daily is less effective than once daily in human glaucoma patients (Lindén & Alm, 1998). This reduction of efficacy possibly may result either from desensitization or downregulation of the FP receptor with twice daily administrations (Lindén & Alm, 1998). In glaucomatous patients who are no

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longer regulated on one antiglaucoma drug alone, a combination of two drugs is common. In addition to their use as monotherapy, $PGF_{2\alpha}$-related drugs became first-line prescriptions as combination therapies in human patients because about half of the patients require more than one antiglaucoma agent for IOP reduction (Bean & Camras, 2008). Beta-blockers, topical CAIs, and alpha-adrenergic agonists are the most common antiglaucoma agents used in combination with PGs analogues in glaucomatous humans (Tabet et al., 2008). Three fixed combinations of timolol 0.5% with either latanoprost 0.005%, travoprost 0.004%, or bimatoprost 0.03% have been evaluated in human patients with primary glaucoma, and almost all published data indicate that each fixed combination has a greater IOP-lowering effect than monotherapy with either timolol or the PG analogue (Tabet et al., 2008). Used in unfixed combinations, latanoprost proved efficacious when added either to timolol or pilocarpine (Stewart et al., 2000; Toris et al., 2001). When added to β-blockers, latanoprost compared favorably in IOP-lowering efficacy and was similar in safety to brimonidine and dorzolamide (Stewart et al., 2000). In the dog, the PG derivatives are mostly indicated for the treatment of primary glaucoma and have effectively replaced mannitol and/or acetazolamide as first-line drugs in the emergency management of acute PCAG (Willis, 2004).

Investigations using high resolution imaging of the anterior segment of dogs with primary glaucoma suggested that latanoprost may rapidly lower IOP in PCAG by inducing miosis which breaks the pupillary block, and by opening the collapsed ciliary cleft in POAG (Miller et al., 2003; Tsai et al., 2012). Topically applied to normotensive canine eyes, the latanoprost 0.005%–timolol 0.5% fixed combination caused the IOP to decrease by 1–2 mmHg more than the decrease for latanoprost alone, whereas no ocular hypotensive effect was observed with 0.5% timolol alone (Smith et al., 2010). Although latanoprost, bimatoprost, and travoprost are instilled once daily in human patients, experimental data in glaucomatous dogs suggest that twice daily instillation of these drugs should be recommended in the dog to result in less daily IOP fluctuations (Gelatt & MacKay, 2001a, 2002b, 2004). Dosing three times a day with latanoprost in the dog may decrease IOP even further. However, this should be done with caution because this drug and the miosis it causes have the potential to narrow the iridocorneal angle and increase episcleral venous pressure significantly, which may impair conventional outflow (Tofflemire et al., 2015a; Tsai et al., 2013). Latanoprost instilled immediately after phacoemulsification in dogs was found to have no significant effect on the number of POH peaks compared with control untreated dogs (Crasta et al., 2010) in one study. However, in another study, there was a trend towards a decrease in POH with postoperative latanoprost use (Dees et al., 2017). Primary or secondary intraocular inflammation is often associated with glaucoma in dogs, and therefore ophthalmic anti-inflammatory drugs sometimes are administered concurrently to antiglaucoma agents. As mentioned in a previous section, topical prednisolone and flurbiprofen were shown to significantly inhibit the IOP-lowering effect of latanoprost in normotensive dog eyes (Pirie et al., 2006, 2011). However, another small study refutes this and showed that prednisolone acetate does not mitigate the IOP-lowering effect of latanoprost (Kahane et al., 2016a). This potential interaction should be taken into account when prescribing ophthalmic anti-inflammatory drugs to glaucomatous dogs treated with $PGF_{2\alpha}$-related agents.

Adverse Effects

Side effects most commonly encountered in glaucomatous human eyes treated with $PG_{2\alpha}$ analogues include conjunctival hyperemia, iris darkening, and eyelash changes (Alm et al., 2008). The secondary effects of elongation and thickening of the human eyelashes after latanoprost therapy has resulted in a new commercial use for this drug in man. Current evidence indicates that these represent only cosmetic concerns with no apparent consequences (Alm et al., 2008). Other potential and relatively rare complications of this therapy include cystoid macular edema, anterior uveitis, iris cysts, herpes simplex reactivation, periocular skin darkening, and headaches (Alm et al., 2008; Schumer et al., 2002). Several PG derivatives used for the treatment of glaucoma cause increased pigmentation of the iris in man, but most of the data have been obtained with latanoprost (Stjernschantz et al., 2002). Increased iris pigmentation was observed in about 5% of the patients during 2 years of treatment with latanoprost, and it appeared that individuals with hazel or heterochromic eye color were at risk of developing this side effect (Stjernschantz et al., 2002). As $PGF_{2\alpha}$ analogues are selective agonists of FP receptors, it is likely that FP receptor activation is involved in this phenomenon. Results of different studies suggested that latanoprost can stimulate tyrosinase gene transcription in the iris (Lindsey et al., 2001), and that latanoprost-induced melanogenesis most likely results from stimulation of iridal melanogenesis rather than melanocyte proliferation (Alm & Stjernschantz, 1995; Stjernschantz et al., 2002). Endogenous PGE_2 produced by iridal melanocytes exposed to latanoprost might also contribute to the increased melanogenesis (Bergh et al., 2002). Iris darkening in human subjects has raised concerns about the possibility of development of precancerous lesions or pigmentary glaucoma in some individuals, but presently no evidence of harmful consequences of this phenomenon has been reported (Grierson et al., 2002; Stjernschantz et al., 2002). In addition, a recent study showed that there are no histopathological features suggesting premalignant changes in human latanoprost-treated darkened irides (Albert et al., 2008). Darkening of the latanoprost-treated irides is associated with a thickening of the

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anterior border layer, and an increased amount of melanin in this layer and within the stromal keratocytes (Albert et al., 2008). As reported in humans, conjunctival hyperemia has been observed in dogs treated with latanoprost (Studer et al., 2000), which also induced epiphora, blepharospasm, blepharedema, conjunctival hyperemia, and transient corneal edema in some horses, when instilled in equine eyes (Willis et al. 2001a; Tofflemire et al., 2017). These clinical signs where alleviated when diclofenac was concurrently applied (Tofflemire et al., 2017). The mechanism behind the vasodilation of the conjunctival vessels predominantly seems to involve NO release (Alm et al., 2008). Decreased stromal collagen density has been identified by histopathologic evaluation in latanoprost-treated conjunctival specimens (Terai et al., 2008). This reduction in the ECM of the conjunctival stroma might result from marked upregulation of MMP-2, MMP-3, and MMP-9 along with a decrease in TIMP-1 in this tissue after treatment with latanoprost (Honda et al., 2010; Terai et al., 2008). This MMP enhancement observed in the conjunctival matrix and at the ocular surface was said potentially to have a favorable effect on the outcome of glaucoma-filtering surgery by decreasing the risk of local fibrosis (Terai et al., 2008), but on the contrary, it also may contribute to lysis of the corneal stroma (Honda et al., 2010). For the latter reason, use of topical latanoprost is not recommended in human patients with keratoconus or after laser-assisted *in situ* keratomileusis (Honda et al., 2010), and by extension should be used with great care in glaucomatous dogs with corneal defects.

A moderate to marked miosis is usually present in dogs treated with the $PGF_{2\alpha}$ derivatives (Gelatt & Mackay, 2001a, 2002b, 2004; Studer et al., 2000). The pupillary constriction is more limited when the drug is instilled only in the evening (Gelatt & MacKay, 2001a, 2002b, 2004). The occurrence of miosis reflects the sensitivity of the canine iridal sphincter muscle to the $PGF_{2\alpha}$ which appears to act directly rather than through the release of adrenergic neurotransmitters (Yoshitomi & Ito, 1988). Reports have also described miosis in cats and horses receiving latanoprost (Studer et al., 2000; Tofflemire et al., 2017; Willis et al., 2001a), as well as in cats treated with bimatoprost (Regnier et al., 2006). The miotic effect of PG derivatives in companion animals may make their use contraindicated in cases of glaucoma secondary to subluxation or anterior luxation of the lens, because of the potential pupillary block that may result from vitreous entrapment (Willis, 2004). The miotic effect may be countered with concurrent administration of either tropicamide or atropine if the pupil must be dilated for diagnostic or surgical purposes (Kahane et al., 2016b). A study in normal dogs revealed that parasympatholytic agents were able to dilate the pupil in the face of latanoprost. However, further study is needed in the instances of disease and chronic administration of PG (Kahane et al., 2016b).

Prostaglandins at high concentrations were first identified for their ability to induce breakdown of the BAB (Alm et al., 2008). Although PG analogues developed for glaucoma treatment are used at very low concentrations, they retain the potency to induce or enhance BAB breakdown. An experimental study with topical latanoprost showed a significant disruption in the BAB of healthy dogs, compared with topical treatment with a fixed 0.5% timolol-2% dorzolamide combination (Johnstone-McLean et al., 2008). For this reason, PG derivatives should be used cautiously in glaucomatous dogs with intraocular inflammation (Seki et al., 2005), and also in aphake or pseudophake patients because they may increase the existing BAB breakdown in these subjects (Arcieri et al., 2005). Although anterior uveitis is a rare but real potential side effect in human patients treated with topical PG analogues (Alm et al., 2008), recent clinical data observed in human patients with uveitis indicate that there is no significant difference in the frequency of anterior uveitis between the patients treated with PG analogues and those treated with non-PG agents (Chang et al., 2008). Nevertheless, because most horses with secondary glaucoma develop the condition because of preexisting chronic uveitis and PG analogues have the potential to exacerbate the inflammatory process, they should be used with caution in these animals (Willis et al., 2001a).

Calcium Channel Blockers

Calcium channel blockers (CCBs) such as verapamil, diltiazem, nifedipine, and flunarizine, have been long and widely used to treat essential hypertension and certain types of cardiac diseases such as angina pectoris, and they have been shown in experimental models of cerebral ischemia to have neuroprotective effects. Their use in ophthalmology is not yet widespread but given their potential for not only neuroprotection but for IOP lowering effects, they may be a promising adjunctive therapy in the future for ocular disorders including glaucoma (Siegner et al., 2000).

Mechanism of Action

CCBs alter the intracellular calcium concentration by modifying calcium flux across cell membranes and affect various intracellular signaling processes. Lipid soluble CCBs act at the central nervous system level, whereas water soluble CCBs act mainly on the cornea and optic nerve. It is also known that calcium influx is the terminal step in axonal death in the glutamate pathway (Brooks et al., 1997). The ability to block calcium influx can, therefore, produce a neuroprotective benefit. Furthermore, CCBs can improve ocular blood flow through inhibition of endothelin-1. Despite this, the effect of CCBs on IOP remains controversial (Araie & Mayama, 2011). Calcium influx could have

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several effects on aqueous humor dynamics, including a hydrostatic component caused by an effect on arterial blood pressure and ciliary body perfusion, and an osmotic component caused by an effect on the active secretion of sodium, calcium, and other ions by ciliary epithelium (Araie & Mayama, 2011). Ocular effects of various CCBs have been studied in selected species, such as rats, rabbits, cats, dogs, and human and nonhuman primates (Segarra et al., 1993; Tamaki et al., 2003). In addition to their direct neuroprotective effects on retinal ganglion cells, CCBs can also increase ocular blood flow and help to prevent retinal ischemia (Saito et al., 2005; Takahashi et al., 1992). Several mechanisms have been discussed for the IOP-decreasing effect of CCBs, including a decrease in production of aqueous humor by inhibition of calcium-dependent cation transport in the nonpigmented ciliary epithelium and an increase in outflow facilitated by relaxation of trabecular meshwork cells (Mito et al., 1993; Erickson et al., 1995).

Clinical Use

CCBs can increase or decrease IOP, depending upon the specific compound and the species. Experiments in rabbits have indicated that topical application of CCBs, especially verapamil, caused significant IOP reductions, whereas ocular hypotensive effects in humans were not substantial (Segarra et al., 1993). Flunarizine, a difluorinated piperazine derivative, is a mixed L- and T-type CCB with additional antagonistic effects on sodium channels and mixed agonist-antagonist action on opioid receptors (Holmes et al., 1984). In a number of reports, investigators indicated that topical application of the CCB flunarizine lowers the IOP in clinically normal monkeys, rabbits, and dogs (Campana et al., 2002; Greller et al., 2008; Siegner et al., 2000). A significant bilateral decrease in IOP up to 2.6 mmHg in clinically normal dogs was evident after 2 days of twice-daily unilateral treatment with topically applied 0.5% flunarizine solution in one study (Greller et al., 2008). Throughout the study, there were no significant differences in IOP between treated and untreated eyes, which suggested a systemic effect of flunarizine on the untreated eye in addition to the local effect on the treated eye. A decrease in the IOP of the untreated contralateral eye has also been reported in rabbits, monkeys, and human patients treated topically with CCBs (Segarra et al., 1993; Siegner et al., 2000; Tamaki et al., 2003). This systemic effect was supported by the detection of flunarizine in serum samples obtained following drug application in normal dogs (Greller et al., 2008). Dogs experienced mild irritation and conjunctival hyperemia while flunarizine was administered (Greller et al., 2008). Some ophthalmic β-adrenoceptor antagonists, especially betaxolol, interact with L-type calcium channels and show CCB activity, which may be partly responsible for the neuroprotective effects of these drugs (Wood et al., 2001). CCBs may deserve future study to evaluate their use for additive or synergistic ocular hypotensive effects that would complement their neuroprotective potential.

Osmotic Agents

Osmotic agents are a group of antiglaucoma drugs most commonly employed on an emergent basis to lower IOP quickly in cases of acute congestive glaucoma. They are generally only indicated for short-term use and are almost always used in combination with other drugs that take over and are continued for maintenance therapy.

Mechanism of Action

After oral or intravenous administration, osmotic agents (also called hyperosmotic agents) are distributed in the extracellular fluids (primarily plasma), thereby contributing to a substantial increase in their osmolality. This increase creates an osmotic gradient in which the extracellular fluids are hypertonic to intraocular fluids (i.e., aqueous and vitreous humors), from which they are separated by semipermeable membranes (i.e., blood–aqueous and blood–vitreous barriers). This osmotic gradient favors the diffusion of water from the intraocular fluids back into the plasma (Craig 1994; Dugan et al., 1989). This fluid shift has two effects on the eye. First, it inhibits the ultrafiltration process that contributes to aqueous humor formation, and second, it reduces the volume of the vitreous body. Shrinkage of the vitreous displaces the iris-lens diaphragm posteriorly and subsequently opens the iridocorneal angle, allowing for better drainage through the conventional outflow passage (Gwin, 1980). As a final result, IOP is reduced. For the pharmacologic effects of osmotic agents to occur, they should not cross the blood–aqueous and blood–vitreous barriers. If for any reason the integrity of either barrier is compromised, as in ocular inflammation, the osmotic agent may leak in the intraocular fluids, and the extent of osmosis as well as that of ocular hypotension will be reduced (Brooks, 1990). Because of its large molecular weight, mannitol penetrates in the eye less than other osmotic agents in the presence of ocular inflammation (Singh & Krupin, 1997). Other factors important in the establishment of an adequate osmotic gradient between plasma and intraocular fluids include the dosage of the drug, its molecular weight, and its systemic bioavailability (rate of absorption for oral route and rate of elimination). Water deprivation for up to 4 hours after the use of an osmotic agent will reduce the extracellular fluid volume and will enhance the increase in blood osmolality and the resulting hypotensive ocular effect (Craig, 1994).

Products Available

Mannitol, a six-carbon sugar, is poorly absorbed from the gastrointestinal tract and must, therefore, be administered

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intravenously. It is available in concentrations of 5%–25%, but the 20% solution is most often used in ophthalmology (Craig, 1994). The dose for the lowering of IOP in dogs ranges from 1 to 2 g/kg, infused over a period of 20–30 minutes (Gwin, 1980; Lorimer et al., 1989). To increase the effectiveness of the drug, one fifth of the total dose can be administered rapidly over the first 2–5 minutes (Gwin, 1980).

Following intravenous administration of 1.5 g/kg mannitol, IOP of normal canine eyes decreases from baseline values between 0.25 to 5.5 hours postadministration. A mean maximal depression of 9 mmHg occurs 1.5 hours after administration (Lorimer et al., 1989). In patients with acute glaucoma, mannitol is an effective hyperosmotic agent, reducing IOP within 0.5–1 hour, with the effect lasting for some 6–10 hours (Bedford, 1980). Mannitol is not metabolized but is filtered across the glomerulus and excreted in the urine without reabsorption by the renal tubules, causing a marked diuresis. If mannitol is infused during surgery, bladder catheterization is advisable to prevent uncontrolled urination during the recovery period.

Saline hypertonic hydroxyethyl starch (HES), used in human patients for the treatment of hemorrhagic shock and intracranial pressure, has been evaluated for its effects on IOP in dogs (Volopich et al., 2006). In healthy normotensive dogs, the IOP-lowering effect of 4 mL/kg intravenous HES (7.5%/6%) was comparable to that of mannitol 20% but was shorter in duration. Used in a small series of dogs with acute primary glaucoma, intravenous hypertonic HES induced an average maximum decrease in IOP of 24% from baseline values in most subject dogs (Volopich et al., 2006). Major potential side effects of HES include hypernatremia and hypokalemia, particularly in patients with preexisting dehydration.

Glycerin, or glycerol, is a trihydric alcohol that is rapidly absorbed from the gastrointestinal tract after oral administration. The drug is marketed as flavored commercial preparations of 50% and 75% glycerin. Glycerin USP, which contains approximately 1.25 g of glycerin per milliliter, may also be used and mixed in milk or syrup to improve palatability (Singh & Krupin, 1997). Administrations of 1.44 g/kg glycerin in healthy dogs led to a significant ocular hypotensive effect, occurring within 1 hour and lasting about 10 hours (Lorimer et al., 1989). Another study revealed a 17% decrease in IOP from baseline after oral administration of 1.5 g/kg glycerin within 30 minutes which persisted for only 2 hours (Wasserman et al., 2013). Although rarely used for maintenance therapy of glaucoma, glycerin may be administered per os or in food in a daily dose of 1–2 g/kg (Gwin, 1980). It is most often dispensed for emergency treatment of a hypertensive crisis by the pet owner prior to presentation to the veterinarian. Occasionally, animals may experience nausea or vomiting after ingestion of the drug. The incidence of vomiting appears to be dose-dependent, occurring most frequently with doses higher than 2 g/kg (Gwin, 1980; Lorimer et al., 1989). Glycerin is metabolized into glucose, so hyperglycemia and glycosuria may ensue (Dugan et al., 1989; Wasserman et al., 2013), and therefore it should be used with caution in diabetic patients. Weight gain may be another consequence of glycerin metabolism if the drug is administered for a prolonged period. As this agent is readily metabolized, it induces less diuresis than mannitol.

Isosorbide is a dihydric alcohol that resembles mannitol in chemical structure and can be given orally. It has been shown to decrease IOP with similar efficacy as glycerol in humans, rabbits, and normal dogs. Unlike glycerin, it is not metabolized after systemic absorption and is excreted unchanged in the urine. Therefore, it does not affect glucose homeostasis, which may allow for its use in diabetic patients. Another potential benefit of isosorbide is that its side effects, which include nausea and vomiting, occur less frequently when compared with glycerol. It is available as a 45% flavored solution (Singh & Krupin, 1997). In humans, a dose of 1.5–2.0 g/kg induces an ocular hypotensive effect similar to that of 1–1.5 g/kg glycerin (Craig, 1994). A daily dose of 1.5 g/kg is recommended in the dog (Dugan et al., 1989; Wasserman et al., 2013). In normal dogs, this dose resulted in a 13.5% decrease in IOP which was sustained for 90 minutes (Wasserman et al., 2013). Although this was not statistically different from control, it is likely that the magnitude of the decrease would be more significant in glaucomatous individuals.

Clinical Use

Osmotic agents are used mainly in the emergency treatment of acute glaucoma (Brooks, 1990; Gaarder, 2000; Gwin, 1980). These compounds are employed for short-term control of IOP because they are not practical for prolonged therapy (Singh & Krupin, 1997). More rapid reduction of IOP is usually achieved with mannitol rather than with glycerin. Both drugs, however, can be used in combination for maintenance of normal IOP. Mannitol is infused first; 6–8 hours later, glycerin can be administered and repeated as necessary to maintain the lowered IOP (Brooks, 1990). More commonly, once an osmotic agent has been administered and IOP has normalized, topical therapy is employed to sustain the IOP within the target range. Osmotic agents are also indicated to reduce IOP in patients with hyphema, but their value in facilitating the resorption of anterior chamber hemorrhage has not been clearly established. Mannitol may be employed preoperatively or intraoperatively to lower IOP and reduce vitreous volume (Singh & Krupin, 1997). This drug may also be used both before and during surgical procedures on the lens (i.e., cataract surgery, removal of a luxated or subluxated lens, manual reduction of an anteriorly luxated lens), because shrinkage of the vitreous body reduces the incidence and severity of vitreous prolapse. Finally, osmotic agents may be indicated after intraocular surgery to relieve ciliary body block glaucoma (Singh & Krupin, 1997).

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Adverse Effects and Contraindications

The major potential toxicity of intravenous osmotic agents is related to their effect on the volume and distribution of body fluids. Mannitol may quickly expand extracellular fluid volume and subsequently overload the cardiovascular system (Craig, 1994; Dugan et al., 1989; Singh & Krupin, 1997). This acute expansion of extracellular fluid volume may precipitate pulmonary edema in patients with cardiac failure or who are under general anesthesia. Deaths caused by pulmonary edema occurred in a few dogs and cats that underwent ophthalmic surgery and were given mannitol while anesthetized with methoxyflurane in oxygen (Brock & Thurmon, 1979). Subsequent studies have shown that infusion of 2.2 g/kg of 20% mannitol in healthy dogs, under the same anesthetic regimen of methoxyflurane with oxygen maintenance, increases central venous pressure enough to produce pulmonary perivascular and interstitial edema (Brock et al., 1985). Infusion of a lower dose (0.25 g/kg) of 25% mannitol in dogs anesthetized with halothane does not induce significant changes in cardiovascular variables, but has no effect on IOP (Gilroy, 1986). Mannitol does not cross the blood–brain barrier and thus extracts water from cerebral fluid and tissue. Cerebral dehydration induced during the phase of maximal plasma hyperosmolization has been found in association with side effects such as nausea, vomiting, and altered consciousness. Shrinking of the brain could also promote subdural hematoma formation (Craig, 1994). Mannitol should be avoided in patients with renal failure. Glycerin should be avoided in patients with diabetes mellitus because the drug is converted to glucose (Singh & Krupin, 1997).

New Directions

Pharmacologic treatment for glaucoma is directed towards lowering IOP to slow disease progression and tissue damage and delay vision loss. The currently available medical treatment options discussed above can be effective, particularly if treatment is initiated early in the disease process. However, they do not stop disease progression and there remains enormous need for improvements and advancements in the medical treatment of glaucoma in both human and veterinary patients. Issues with existing drugs include failure to achieve target IOP with monotherapy, drug-related side effects, and low patient compliance with multiple daily administration of eye drops. In recent years, the scientific and medical community has seen encouraging development of novel classes of drugs for glaucoma, the majority of which lower IOP by targeting the trabecular meshwork outflow pathway to increase aqueous humor outflow. Among the most promising new pharmacologic candidates are rho kinase inhibitor, adenosine receptor agonists, and modified prostaglandin analogs (Liebmann & Lee 2017; Lu et al., 2017). Hopefully, these agents and others will be readily available soon and will improve our abilities to control this frustrating disease.

Rho-associated protein kinase (ROCK) inhibits IOP by increasing aqueous outflow through the trabecular meshwork. They disrupt actin stress fibers and focal adhesions in trabecular meshwork cells (Lin et al., 2018). IOP-lowering ophthalmic solutions that inhibit ROCK and norepinephrine transporters (Net) are currently under clinical evaluation. Netarsudil, the most well-investigated topical ROCK inhibitor to date, produces large reductions in IOP in rabbits and monkeys that are sustained for at least 24 h after once daily dosing, with transient, mild hyperemia observed as the only adverse effect (Lin et al., 2108; Sturdivant et al., 2016). Netarsudil, also known as AR-13324, reduces IOP in normotensive monkey eyes by 53% within 6 hours of administration (Wang et al., 2015). Tonographic studies indicate that a dual mechanism of action, an increase in tonographic outflow facility, and a decrease of aqueous humor flow rates, accounts for this IOP reduction (Wang et al., 2015). Not only do topical ROCK/Net inhibitors lower IOP, they have been observed to promote retinal ganglion cell survival and regeneration after optic nerve crush injuries (Shaw et al., 2017). Coordinated IOP lowering and neuroprotective or regenerative effects may be advantageous in the treatment of patients with glaucoma.

The adenosine receptor agonist, trabodenosine, and similar compounds are showing promise for the treatment of glaucoma in humans. Twice-daily topical ocular doses of trabodenoson, from 50 µg to 500 µg, were well tolerated and showed a dose-related decrease in IOP that was statistically significant and clinically relevant in patients with ocular hypertension or primary open angle glaucoma (Myers et al., 2016). No studies on companion animals are currently available.

The role of latanoprost in increasing uveoscleral outflow of aqueous humor is well established. This drug and other FP prostaglandin analogues are the leading mode of therapy at present for human and animal glaucoma. Given the success these drugs have had, it follows naturally that modifications of these agents and discoveries of related compounds would occur. A variety of promising E_2 prostaglandin analogues are currently in development and study (Prasanna et al., 2009). More exciting, however, is a new strategy that involves modulating physiologic mediators such as NO in concert with the actions of latanoprost. Impacting these mediators is being evaluated as a novel way to impact disease progression by both lowering IOP and improving ONH perfusion. Latanoprostene bunod (LBN) is a topical ophthalmic therapeutic for the reduction of IOP in patients with glaucoma. LBN is composed of latanoprost acid linked to an NO-donating moiety. It has shown promise in clinical trials and is the first NO-releasing prostaglandin analogue to be submitted for marketing authorization in the United States. NO released from LBN elicits trabecular meshwork cell

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relaxation by reducing myosin light chain phosphorylation, inducing cytoskeletal rearrangement, and decreasing resistance to current flow (Cavet & DeCory, 2018). As an NO-donating prostaglandin F2-alpha receptor agonist, LBN has been proven to effectively, and with good tolerability, reduce IOP in glaucoma patients. The drug capitalizes on NO's ability to modulate the conventional aqueous humor outflow system, directly improving outflow through the trabecular meshwork, Schlemm's canal and distal scleral vessels (Aliancy et al., 2017; Cavet & De Cory, 2018). Importantly, targeting the conventional outflow tissues with NO-donating drugs represents an opportunity to restore outflow function. This will most likely have the beneficial consequence of additional IOP-lowering effects by dampening diurnal and other IOP fluctuations, which occurs naturally in the healthy trabecular meshwork (Aliancy et al., 2017). A recent study compared the ocular hypotensive activity of LBN, to that of latanoprost in monkeys with laser-induced ocular hypertension, dogs with naturally occurring glaucoma, and rabbits with saline-induced ocular hypertension (Borghi et al., 2010). In primates, a maximum decrease in IOP of 31% and 35% relative to baseline was achieved with LBN at doses of 0.036% and 0.12%, respectively. In comparison, latanoprost elicited a greater response than vehicle only at 0.1% (much higher than commercially available preparations) with a peak effect of 26%. In glaucomatous dogs, IOP decreased from baseline by 44% and 27% after LBN and latanoprost, respectively (Borghi et al., 2010; Impagnatiello et al., 2011). Intravitreal injection of hypertonic saline in rabbits increased IOP transiently. Latanoprost did not modulate this response, whereas LBN significantly blunted the hypertensive phase. LBN lowered IOP more effectively than latanoprost presumably as a consequence of a contribution by NO in addition to its prostaglandin activity (Borghi et al., 2010; Krauss et al., 2011). The same effects have been noted in a clinical trial of human glaucoma patients. In these patients, LBN 0.024% dosed once daily shows significantly greater IOP lowering and comparable side effects relative to latanoprost 0.005% (Weinreb et al., 2015). Once daily LBN ophthalmic solution 0.024% was safe and well tolerated in human patients with glaucoma when used for up to 1 year and provides sustained IOP reduction (Kawase et al., 2016). These data indicate that LBN has a dual mechanism of action, increasing aqueous humor outflow through both the uveoscleral (using latanoprost acid) and trabecular meshwork/ Schlemm's canal (using NO) pathways (Cavet & DeCory, 2018).

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9

Veterinary Ophthalmic Pathology

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Introduction and Principles

Few would argue that understanding disease processes on a cellular and subcellular level greatly facilitates clinical management of any disease. With that in mind, one can envision that a thorough understanding of ocular pathology is essential for the practicing veterinary ophthalmologist. The objectives of this chapter are to facilitate understanding by providing an overview of ocular pathology that compliments with minimal duplication the material that is covered in the other chapters of this book. The gross, subgross, and light microscopic descriptions of the common ocular disorders of animals are emphasized.

Current clinical examination techniques provide the veterinary ophthalmologist with enhanced views of most of the intraocular structures allowing observation of gross and subgross pathology in ocular tissues with resolution that approaches that of the light microscope. Clinical findings and results of histopathology unify clinical and pathologic disciplines.

This chapter is organized as follows: methods of fixation and processing; general principles of ocular pathology; congenital conditions; acquired and inherited disorders, and review of the neoplasms that affect ocular tissues.

Fixation and Processing of Ocular Tissues

Ocular tissues are submitted to the pathologist as whole globes with attached orbital tissues, globes without orbital tissues, eviscerated specimens, excisional or incisional biopsies, cytology of exfoliative preparations, or aspirates. Each type of sample has unique fixation and preparation requirements to optimize the pathologist's examination. Globes should be fixed promptly after removal to ensure rapid fixation of the intraocular structures to minimize autolytic changes.

The preferred fixative for intact globes is Davidson's fixative, which penetrates the globe rapidly to fix the retina and retinal pigment epithelium (RPE) and maintains these tissues in anatomic apposition. However, the most common method of fixation is immersion in 10% buffered formaldehyde, which is adequate. Bouin's fluid, among others (Table 9.1), is occasionally used, notably for research.

Tissues are immersed in a one part tissue to 10 parts 10% buffered formalin solution and placed on a rotary mixer for approximately 24 hours (this step is less common in today's fast-paced laboratories). In addition, globes should also receive an intravitreous formaldehyde injection (0.5–1 mL) via a 25 gauge needle inserted immediately adjacent to the optic nerve prior to immersion to compensate for limited penetration through the sclera. Globes can be hardened by immersion into graduated concentrations of 60–80% alcohol for 24–48 hours; the resultant dehydration facilitates sectioning.

Exenterations are performed as a surgical therapy for orbital neoplasia. It is important that the surgeon clearly identify any margins that they want examined in detail. The volume of tissue removed by an exenteration is large and the orbital tissues should be incised every 2 cm through to the sclera to allow fixation penetration (Fig. 9.1A), or preferably the periocular tissues of interest would be trimmed and identified with a marker or sutures to facilitate sectioning.

Once the globe is trimmed, the pathologist will measure and record the dimensions of cornea, globe, and attached optic nerve. Some prefer to section the optic nerve at this time across its base as it leaves the sclera to provide a cross section for histologic examination that compliments the longitudinal section that will accompany the globe **(**Fig. 9.1B, C**)**.

The globe can be transilluminated to locate intraocular masses or foreign bodies before orienting and sectioning. Enucleated globes from most species are oriented by

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Table 9.1 Ocular fixatives and their advantages and disadvantages.

	Formaldehyde	Bouin's fluid	Gluteraldehyde	Triple fixatives paraformaldehyde, glutaraldehyde formaldehyde, and osmium	Zenker's fluid	Davidson's fixative
Maintenance of tissue relationships (neurosensory retina-RPE)	Marginal	Good	Poor by immersion. Globes must be sectioned and then small pieces immersed	Excellent; however, globes are typically opened	Good	Excellent
Preservation of membranes for ultrastructure	Poor	Poor	Excellent	Excellent	Good	Very good
Immuno compatibility	Good	Good; however, different epitope retrieval is required	Good	Good; however, different epitope retrieval is required	Good; however, different epitope retrieval is required	Good
Advantages and disadvantages	Cost, availability	Better penetration of globe	Excellent fixation of small tissue sections or small globes with thin sclera (mice, rats) destined for electron microscopy	Uncommonly used except in research, osmium is toxic and expensive	Uncommonly used related to toxicity of mercury	Very good immersion fixative

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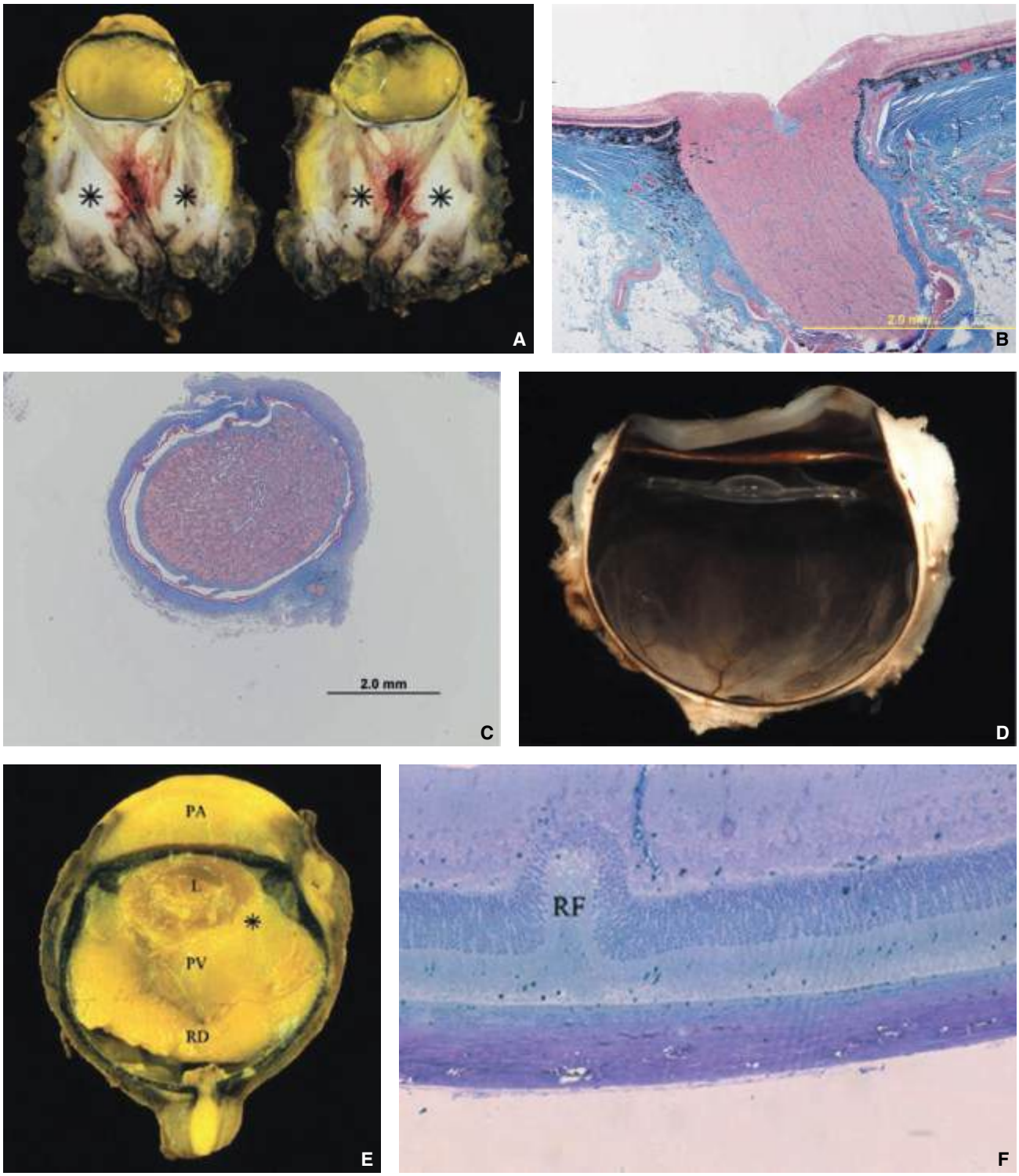


Figure 9.1 **A.** An exenterated bovine eye that was immersion fixed in Bouin's fluid for 72 hours and sectioned. Note the incomplete fixation of the orbital and ocular tissues (*). To ensure adequate fixation of globes that are exenterated or removed by transpalpebral enucleation, the orbital tissues should be trimmed and labels attached prior to immersion in fixatives, or multiple incisions placed circumferentially to the level of the episclera at 0.5–1 cm intervals. **B, C.** Optic nerves may be sectioned sagittally and in cross section to facilitate thorough examination of the axons and meninges. In the bovine specimen above the thickened pia septae and enlarged subdural space are hallmarks of optic atrophy (Masson's trichrome stain). **D**. Gross examination with photographic documentation in this canine globe reveals pseudophakia which would not be obvious on histologic section. **E.** A Bouin's fluid fixed globe from a dog that was diagnosed with a chronic lens rupture that was enucleated via a transconjunctival approach. Note the lack of extraocular tissues and adequate fixation. The lens (L) is encased by the plasmoid aqueous (PA) and vitreous (PV), and the lens capsule rupture is evident (*). An exudative retinal detachment (RD) is also present. These gross findings are synonymous with the diagnoses endophthalmitis and phacoclastic uveitis which were confirmed with light microscopy. **F.** This is a section of the posterior segment from a Sprague Dawley rat with a retinal fold (RF). Note the excellent fixation and minimal artifacts present in this epon-embedded tissue. This globe was triple fixed, plastic embedded, and sectioned. (Original magnification 40×; Toluidine blue stain.)

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identification of the shape of the cornea, extraocular muscle insertions, and location of the vortex veins, ciliary arteries, and optic nerve. This allows the pathologist to bisect the eye in a vertical plane from dorsal to ventral to include both the tapetal and non-tapetal fundus. Globes from animals with maculae are sectioned horizontally to allow histologic examination of the macula and fovea. Unused brain, razor, or histosectioning blades are utilized for sectioning the globe. Examination with a dissecting microscope and documentation of findings is performed with the globe under fluid (Fig. 9.1D).

Once the pathologist has determined a preferred hemisphere, a cap is removed to permit wax to penetrate the entire globe. Then the collotte is placed in an embedding chamber of appropriate size and labelled. An alternative to hemisection (which can dislocate the lens) is the removal of the cap, cutting from just inside the limbus to adjacent to the optic disc on the same side, followed by subgross intraocular examination and making a parallel cut to the first to end up with a central section and two calottes.

Rodent and other small globes are fixed by immersion, then oriented appropriately with embedding, and processed whole. Multiple sections are taken until the appropriate area in the eye is examined. Fetal rodents have very small globes that are difficult to remove intact. Fixation of the whole body in Bouin's fluid and then serial sections of the skull horizontally to view both globes is the method of choice for light microscopy. Photographs of the gross sections may facilitate histologic examination (Fig. 9.1D, E).

The commonly preferred stains for light microscopic examination of ocular tissues are hematoxylin and eosin (H&E), periodic acid Schiff (PAS), and Luxol fast blue (for myelin) and Bodian stain (for axons). These stains allow for a thorough examination of the cellular morphology, basement membranes, and optic nerve. Additional histochemical stains for evaluating ocular tissues and infectious organisms are provided in Table 9.2 and Table 9.3.

Biopsies of eyelid skin, conjunctiva, and adnexa are also common submissions. The clinician should identify the surfaces with India ink, sutures, or other labels and provide drawings on the acquisition forms to facilitate orientation and margin evaluation.

Paraffin embedding is performed routinely for all globes and biopsies. Some histotechnologists prefer sectioning luxated lenses in a separate block to improve the quality of the subgross section, whereas others replace these within the posterior segment for sectioning with the globe.

Fine needle aspirates or exfoliative cytology of intraocular, orbital, and eyelid tumors, and exudates are occasionally submitted. Usually these aspirates are submitted as smears on glass slides and are stained routinely with Wright's Giemsa, or they are submitted as a small liquid aspirate in an ethylenediaminetetraacetic acid (EDTA) tube and submitted for cytospin analysis.

Transmission and occasionally scanning electron microscopy are useful to identify cells of origin of poorly differentiated neoplasms, specific infectious agents, and as research tools. Specimens destined for electron microscopy have specific fixation, embedding, sectioning, and staining requirements to obtain optimal electron microscopic evaluation. Small biopsies of eyelid skin, conjunctiva, sclera, or cornea are adequately fixed by immersion in glutaraldehyde. Although biopsies of intraocular tissues from globes that are routinely immersion-fixed can be prepared for epon embedding and sectioning for electron microscopy, the subcellular details will be limited related to autolysis. Several fixation techniques are available. Most often these globes are immersed in cold fixative immediately after enucleation for several minutes, removed, and opened with a pars plana incision to enhance exposure of the intraocular tissues to other fixatives and buffers. For optimal outer segment and RPE fixation, osmium is often added to these protocols. These protocols provide excellent fixation and detail of the outer and inner retinal segments **(**Fig. 9.1F).

Occasionally, methodologies such as histochemistry for lipids and immunohistochemistry require fresh tissue or special fixation and snap freezing. Preoperative communication between the clinician and pathologist to identify and address issues that surround specific projects is encouraged.

Fundamental Pathology

The eye is a relatively closed system and injury to one ocular tissue often induces bystander injury to adjacent tissues. Many of the ocular tissues are postmitotic which limits the capacity for pristine repair. Most ocular tissues must adapt to injury in relatively limited ways, and many of these adaptations are sequential. The adaptation and related responses of ocular tissues occur from development to maturity and include hypoplasia, atrophy, aplasia, dysplasia, hypertrophy, hyperplasia, metaplasia, necrosis, apoptosis, degeneration and calcification, and neoplasia.

Hypoplasia is defined as diminished cell proliferation caused by inadequate cytokine stimulation, lack of progenitor cells or specific cellular receptors, or yet undiscovered processes. Hypoplasia is most commonly associated with restricted development of an ocular tissue. The most common example occurs in subalbinotic animals where the uvea is hypoplastic. These blue-eyed animals have less pigment and less blood supply throughout their entire uvea, and this is consistently present in dogs with Collie eye anomaly. Uveal hypoplasia is a consistent anomaly in some forms of anterior segment dysgenesis (ASD), especially those associated with glaucoma (Fig. 9.2).

Aplasia is a lack of development of a tissue and reflects a complete lack of cellular development. Aplasia is usually

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Table 9.2 Common histochemical stains used in ophthalmic pathology.

Target	Stain	Result
General purpose	Hematoxylin and eosin	Proteins – pink
		Nucleic acid – purplish blue
		Calcium – blue
Basement membranes (mucopolysaccharides and glycoproteins)	Periodic acid-Schiff (PAS)	Dark pink
Collagen/muscle	Masson's trichrome	Collagen – blue
		Muscle – red
Acid mucopolysaccharides	Alcian blue	Blue
	Colloidal iron	Blue
Mucin	Mucicarmine	Pink to red
Iron	Perl's Prussian blue	Blue
Calcium	Von Kossa	Black
	Alizarin red	Red
Myelin	Luxol fast blue	Aqua to blue
Axons	Bodian	Black
Lipid (fresh frozen tissue only)	Oil red-O	Red
	Sudan black	Black
Amyloid	Congo red	Red (yellow green birefringence with polarization)
	Thioflavin T	Fluorescent white
	Crystal violet	Violet to purple
Elastic tissue	Verhoeff-Van Gieson	Black
Melanin	Fontana-Masson	Black
Fungi and basement membranes	PAS	Purple-pink
Fungi	Gomori methenamine silver	Black
Acid-fast organisms	Ziehl-Neelsen	Red
	Fite-Faraco	Red
Acanthomoeba	Calcaflour white	Fluorescent white
	Acridine orange	Fluorescent orange
Chlamydia	Giemsa	Pink inclusions
Mast cell granules	Duffy's stain	Blue granules

focal in ocular tissues. Absence of tissue creates a defect called a coloboma. Colobomas are only occasionally examined with light microscopy, because most of these do not affect ocular function and are incidental findings in globes submitted for other disorders (Fig. 9.3).

Dysplasia by definition is atypical growth of a developing tissue. Dysplasia manifests as a morphologic abnormality in cell shape and organization. There are many examples of dysplasia in veterinary ophthalmology including photoreceptor, RPE, and retinal dysplasias (Fig. 9.4) (Rodarte-Ahmeida et al., 2016). However, retinal dysplasia is occasionally an adaptational response to a virus, a toxin, or nutritional deficiency which can induce necrosis or degeneration and inflammation of the affected tissues during development (Dombroski et al., 2016).

Dystrophy is an abnormality that is initiated by faulty metabolism within mature cells. Several examples are inherited mutations in specific breeds of dogs. The most common example is corneal dystrophy (Fig. 9.5).

Atrophy is a reduction of tissue mass after the cells are mature. Etiologies are diverse and include ischemia, denervation, inadequate nutrition, aging, and prolonged elevations of intraocular pressure. These conditions often induce degeneration, necrosis, or apoptosis and subsequently loss

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Table 9.3 Common immunohistochemical and histochemical markers used in ophthalmic pathology. (Tagging the antibody with a red marker instead of the common brown marker enhances the examiner's ability to identify positive labeling in the often heavily pigmented ocular tissues).

Tissue	Antibody
Melanocytes	S-100, melanin A, tyrosinase, HMSA 45
Glial cells	Glial fibrillary acidic protein (GFAP)
Vascular endothelium	Factor VII
Epithelial cells	Cytokeratin
Smooth muscle cells	Actin
Hematopoietic cells	Leucocyte common antigen
Mast cells and eosinophils	Duffy's stain
B lymphocytes	CD79
T lymphocytes	CD3
Histiocytes	CD18

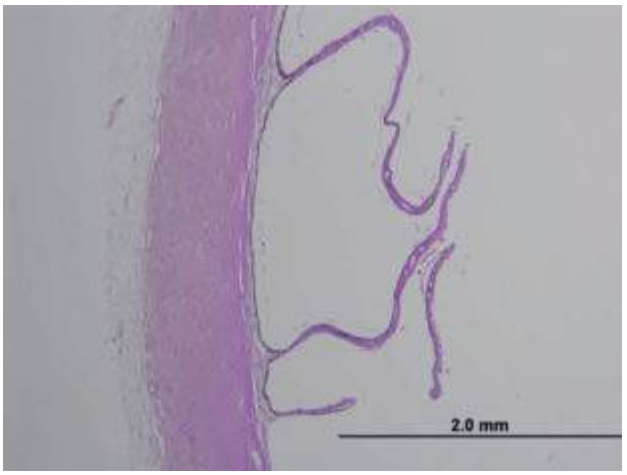


Figure 9.2 Ciliary hypoplasia and elongated ciliary processes are common and consistent features in globes from animals with glaucoma associated with ASD. (Hematoxylin and eosin stain.)

of tissue. Common examples include senile iris atrophy, glaucomatous uveal, retinal and optic nerve atrophy, and outer segment atrophy associated with retinal detachment (Fig. 9.6).

Hypertrophy is an increase in cell size and therefore cellular mass. A few ocular tissues adapt to varied conditions with hypertrophy, which is often a prelude to hyperplasia. A common example is RPE hypertrophy and subsequent hyperplasia that develops in response to retinal detachment (Fig. 9.7).

Hyperplasia is an increase in the number of cells and this adaptational response develops secondary to multiple stressors. Hyperplasia is an efficient adaptation response within ocular tissues that are capable of mitotic replication including retinal pigment, lens, and corneal epithelia, and uveal melanocytes (Fig. 9.7C).

Metaplasia is an adaptational response to stress where a mature tissue changes or transforms into another. This is an important response in the eye, and examples include fibrous or even osseous metaplasia within corneal, lens, uveal, and RPE tissues (Fig. 9.8). Perhaps the most spectacular example of metaplasia exists in birds where lens fibers occasionally develop within the retina.

These adaptational and other cellular responses leave a footprint that is often unique in its appearance. These cellular responses facilitate the diagnosis by the ophthalmologist and confirmation of such by the pathologist. When the ocular cells or tissues can no longer adapt to the insult, cell death occurs by at least two basic mechanisms; necrosis or apoptosis.

Necrosis is characterized with light microscopy by increased cellular cytoplasmic eosinophilia and nuclear

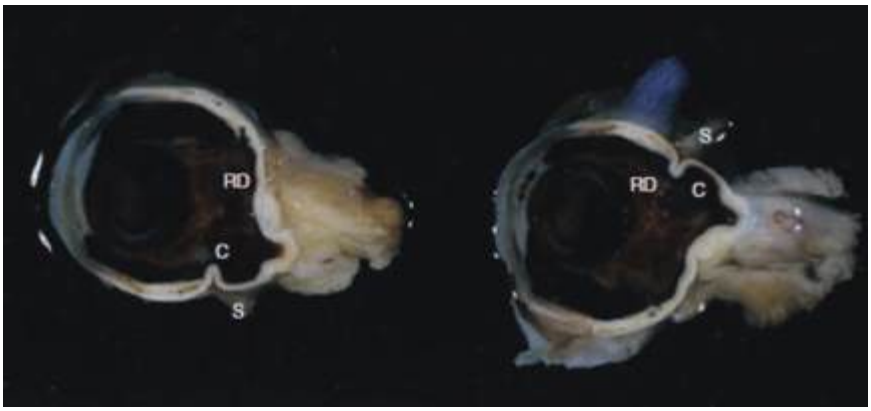


Figure 9.3 A gross section of a formalin-fixed eye from a blind Collie puppy. Note the peripapillary coloboma (C), staphyloma (S), and retinal detachment (RD).

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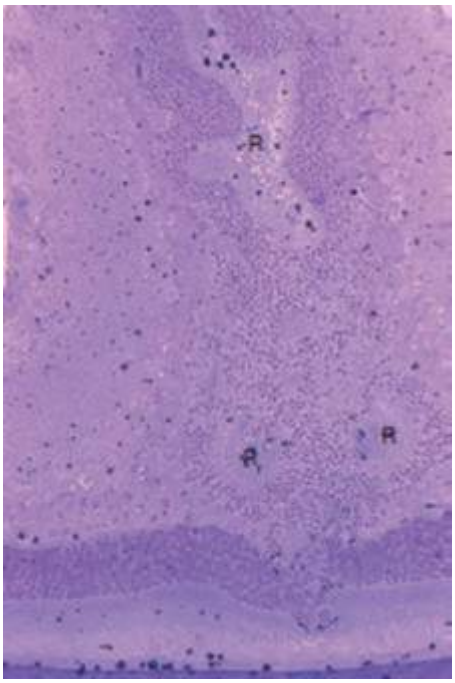


Figure 9.4 A section of retina from a Miniature Schnauzer with inherited retinal dysplasia. Note the prominent rosettes (R). The external limiting membrane was discontinuous centrally where the outer nuclear nuclei are displaced into the layer of inner segments of the photoreceptors. (Original magnification 60×. Toluidine blue stain.)

changes of pyknosis, karyolysis, and karyorrhexis. Different types of necrosis are recognized. With coagulative necrosis, the cell morphology is retained somewhat. Liquefactive necrosis occurs when enzymes destroy the cellular architecture (Fig. 9.9A). Necrosis is usually accompanied by an inflammatory infiltrate.



Figure 9.5 Inherited corneal dystrophy in an Alaskan Malamute. Note the opalescent circular ring in the cornea.

In contrast, apoptosis is programmed cell death that often affects individual cells. Type I apoptosis is characterized by histomorphological clues including cell shrinkage, detachment from neighboring cells, development of cell surface blebs, and frequently phagocytosis of the affected cell **(**Fig. 9.9B**)**. Type II apoptosis is similar but is characterized by autophagy. Autophagy involves intracytoplasmic degeneration by cellular lysosomes. Both types I and II are recognized as efficient methods of cell removal and remodeling of ocular tissues during development. Apoptosis is also a recognized part of both developmental ocular disorders (photoreceptor dysplasias) and acquired ocular disorders, including sudden acquired retinal degeneration, indolent corneal ulceration, and many neoplasms. An inflammatory infiltrate does not usually accompany apoptosis, in contrast to necrosis where inflammation is often present.

In contrast to cell death and loss, neoplasia is uncontrolled persistent abnormal cellular proliferation. Neoplasms are

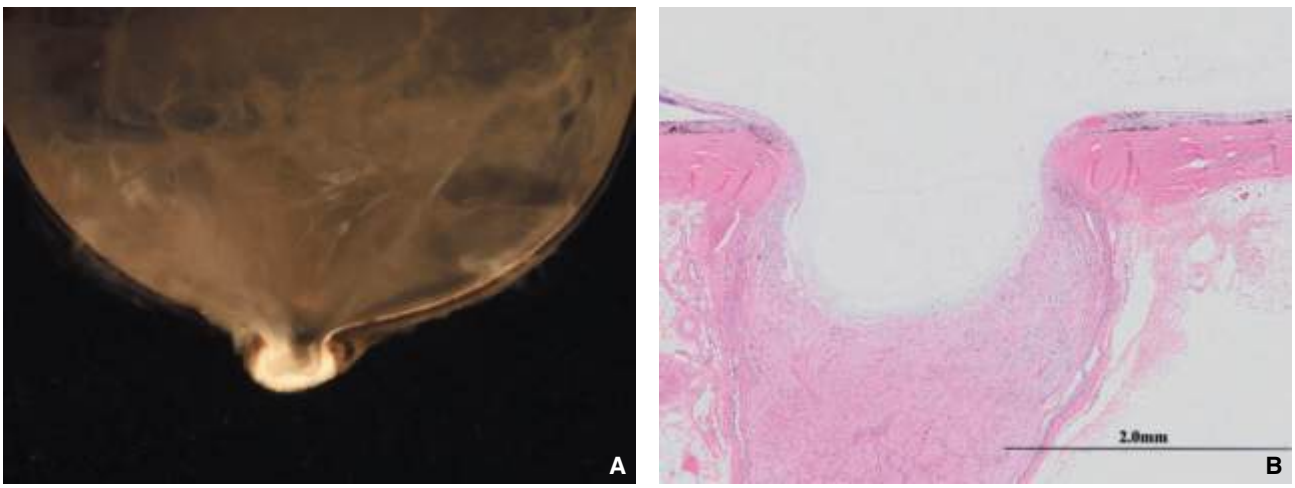
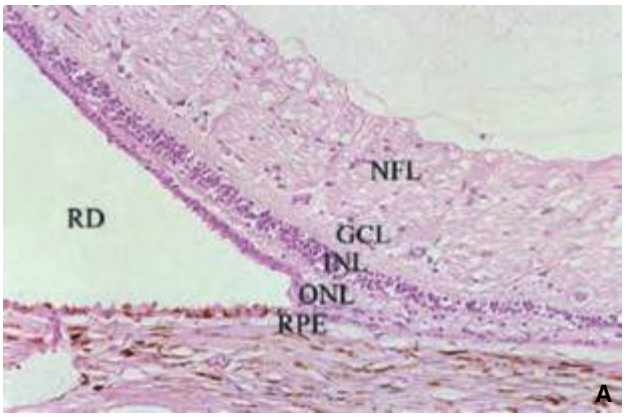


Figure 9.6 Optic nerve atrophy is a common lesion that develops secondary to glaucoma. Note the cavitation of the optic nerve in the gross (**A**), and histologic (**B**) section of a dog with chronic glaucoma.

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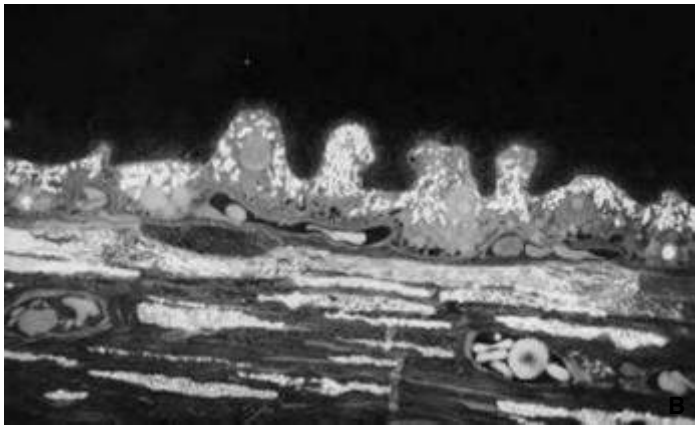




Figure 9.7 **A.** A histologic section of a chronically detached retina. Note the retinal detachment (RD), outer nuclear layer (ONL) is atrophied, and the retinal pigment epithelium (RPE) is hypertrophied and pigmented. The inner nuclear layer (INL) and ganglion cell layer (GCL) and nerve fiber layer (NFL) are relatively normal in this peripapillary section. (Original magnification 60×. Hematoxylin and eosin.) **B.** RPE hypertrophy is common and represents an acute adaptational response to retinal detachment in domestic animals. (Original magnification 100×. Toluidine blue stain, epon embedded.) **C**. A scanning electron micrograph of the RPE under a detached retina. The retina has been removed. Note the RPE hypertrophy and hyperplasia in a dog. (Bars = 0.1 mm.)



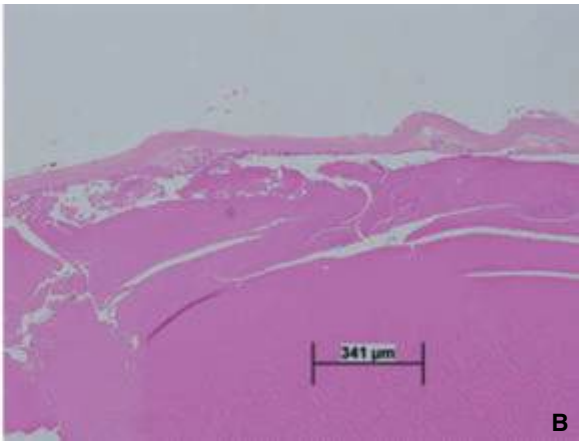


Figure 9.8 **A**. Osseous metaplasia (OM) of the anterior segment of a Guinea pig eye. (Original magnification 100×. Hematoxylin and eosin.) **B.** Posterior lens of a dog with a hypermature cataract. Note the wrinkled posterior lens capsule secondary to loss of lens cortical material and fibrous metaplasia and migration of lens epithelium under the posterior lens capsule. (Hematoxylin and eosin.).

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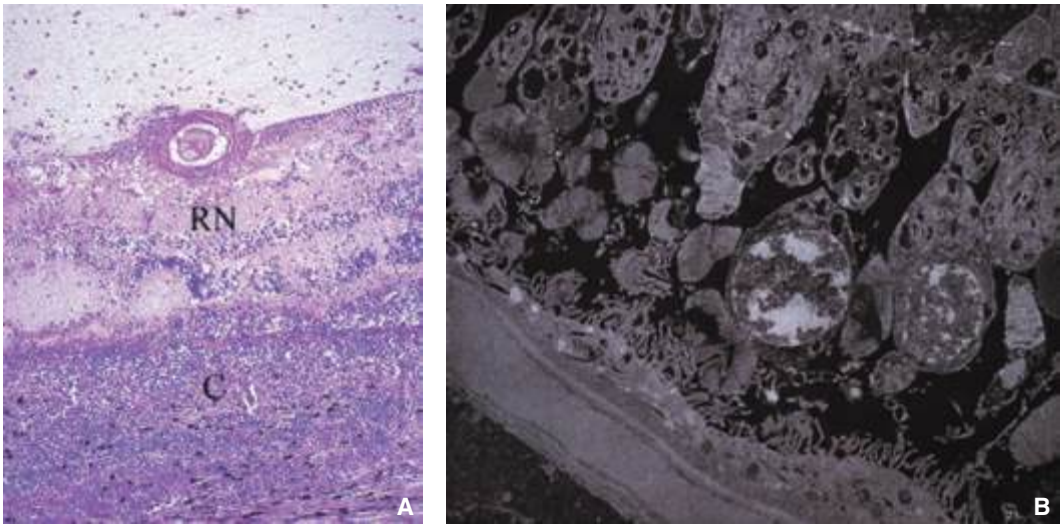


Figure 9.9 **A.** Choroiditis (C) and retinal necrosis (RN) in a septic bovine calf. The inflammatory infiltrate in these tissues is predominately neutrophilic. Note the thrombus present in the retinal blood vessel. (Original magnification 20×. Hematoxylin and eosin.) **B.** A transmitting electron micrograph of the outer segments of the photoreceptors of a middle-aged Collie with progressive retinal atrophy. Note the organelle swelling and shrinking cone nuclei exhibiting apoptotic change. (Magnification 3600×.)

benign or malignant. Benign ocular neoplasms contain well differentiated cells (Fig. 9.10A, B). Benign neoplasms are generally termed by adding the suffix "oma" to the cell of origin, i.e., melanocytoma, tarsal gland adenoma, etc. Benign neoplasms are slowly expansile, are usually encapsulated, and induce damage by compression of adjacent tissues.

Malignant neoplasms are signified by attaching sarcoma or carcinoma to the tissue of origin, i.e., intraocular sarcoma or squamous cell carcinoma. Malignant ocular neoplasms are categorized into four groups: carcinomas, sarcomas, melanomas, and lymphoreticular (round cell) neoplasms. These neoplasms range from poorly to well-differentiated and are characterized best by their invasion of tissues. Histologic features of malignant neoplasms include cellular pleomorphism, increased nucleocytoplasmic ratio, high mitotic index, atypical mitotic figures, necrosis, and destruction and invasion of cellular architecture **(**Fig. 9.10C**)**.

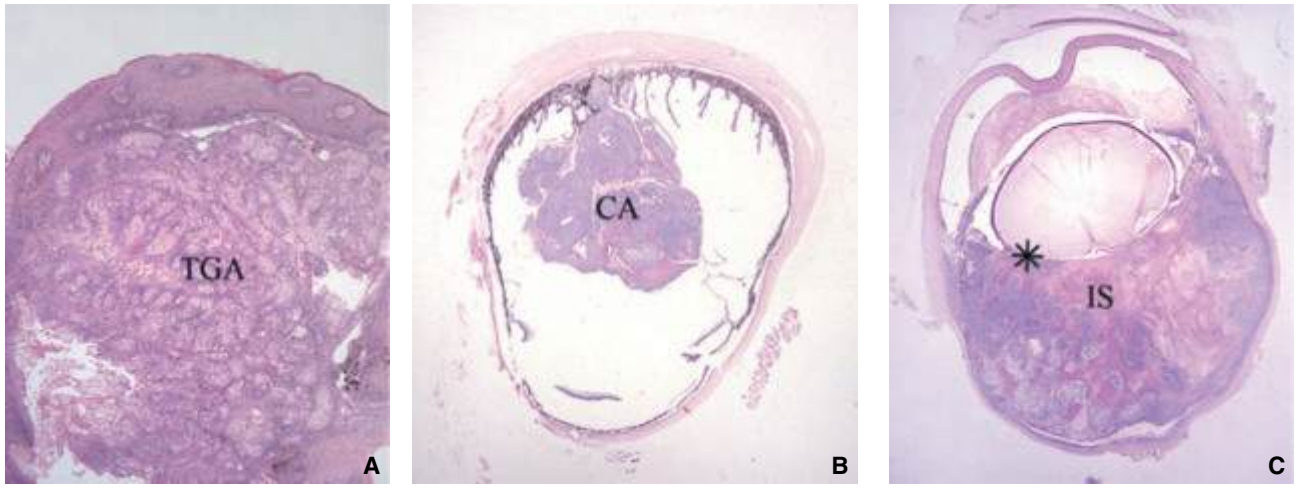


Figure 9.10 **A.** Tarsal gland adenomas (TGA) are common benign eyelid neoplasms of dogs. Note the location on the eyelid margin and well-differentiated glandular structure on histologic section. (Original magnification 10×. Hematoxylin and eosin.). **B.** A well-differentiated ciliary adenoma (CA) within the posterior segment of a cat. Notice the characteristic endophytic growth and lack of ocular tissue invasion of this benign neoplasm. (Magnification 2×. Periodic acid-Schiff.). **C.** A subgross view of a malignant posttraumatic intraocular sarcoma (IS) in a cat. Note the complete invasion of the vitreous, choroid, ciliary body, and iris. Note the incomplete lens capsule (*), and the invasion of the uvea by this tumor. (Original magnification 2×. Periodic acid-Schiff.)

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Ocular Inflammation

Ocular inflammation is the result of a variety of insults including accidental or surgical trauma, exposure to toxic substances, infectious agents, noninfectious immunogenic stimuli, physical agents, and neoplasia. The clinician dedicates significant resources to temper ocular inflammation. The unique anatomic and physiologic properties of the eye render it exquisitely sensitive to inflammation and its sequelae. These properties include ocular functional dependence on transparency and precise intertissue physical relationships. Inflammation resolves with fibrosis, and scars are not transparent and distort tissue relationships as they mature and contract. Likewise, the eye is largely composed of voluminous extracellular fluid compartments (anterior and posterior chambers and vitreous) which allow chemical mediators and products of inflammation to exert an exaggerated and prolonged effect. Elsewhere in the body, products of inflammation are metabolized, diluted, and carried away by the vasculature in a more efficient manner.

The eye is an immunologically privileged site related to the isolation and avascularity of many of its component tissues and the absence of lymphatics. The conjunctiva does have lymphatics, and their presence in the orbit is somewhat controversial. These features largely dictate how a particular ocular tissue responds to inflammatory stimuli. Anterior chamber-associated immune deviation (ACAID) has implications for the modulation of the ocular inflammatory response (see Chapter 6). Ocular inflammation should be regarded as a series of events occurring over time; the pathologist is thus limited to viewing a single frame. Inflammation is primarily regulated by a vast array of chemical mediators. Most are endogenous, but some are exogenous in origin, including venoms and microbial products. Acute inflammation is of rapid onset and of short duration, in terms of days. The initial events are vascular and exudative, mediated by plasma factors (kinin, clotting, and complement systems) and tissue factors (vasoactive amines, prostaglandins, lysosomal, and lymphocyte products). Vascular changes include dilation with congestion and increased vascular permeability with disruption of the blood–ocular barriers and subsequent egress of intravascular fluid and protein into adjacent ocular tissues. Fibrin, the smallest of the plasma proteins, is the primary proteinaceous component. Fibrinous inflammation is commonly associated with bacterial infection, septicemia, or surgical or accidental trauma. Clinically, these changes manifest as conjunctival and uveal edema, aqueous flare, and plasmoid vitreous. If these mediators compromise the RPE barrier, serous or exudative retinal detachment often develops. If the tight intercellular junctions of the ciliary epithelium remain intact, edema of the ciliary processes develops. This is a common and sensitive indicator of uveitis. Subsequent events are defined by the attraction and recruitment of inflammatory

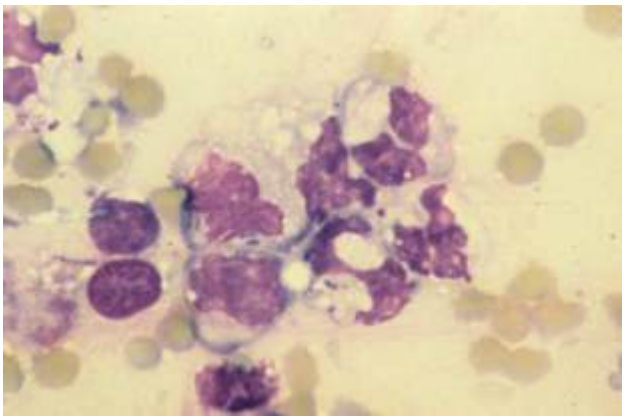


Figure 9.11 Fine needle aspirate from the vitreous of a dog with septic endophthalmitis. Note the cluster of toxic neutrophils in the center of this field. They contain intracytoplasmic bacteria, and there are accompanying red blood cells and mononuclear cells. (Magnification 100×.Wrights Giemsa stain.)

cells. Neutrophils are the hallmark of acute inflammation (Fig. 9.11); note that this is the pathologists' definition of acute, which may differ from that of the clinician.

Neutrophils are produced in the bone marrow, are rapidly mobilized in response to injury, and have a short life span of 1–2 days in tissues. They are phagocytic cells whose granules contain substances that degrade nonviable substances. Neutrophils possess direct antimicrobial capacity. External degranulation can contribute to tissue damage. This is the case with the type III hypersensitivity reaction to canine adenovirus, type I, where the antigen-antibody complexes that form within the corneal endothelium subsequently fix complement which is a neutrophil chemotaxin. If infiltration is accompanied by liquefactive necrosis, the inflammation is described as purulent and suppurative. In the anterior chamber, neutrophils gravitate inferiorly and are seen as hypopyon.

Inflammation becomes chronic with persistence of the original stimulus, significant and prolonged tissue destruction, a foreign body, or an altered blood supply. Chronic inflammation is often exudative and proliferative, occurs over weeks, and is superimposed on the repair process. Lymphocyte and plasma cell infiltrates are the hallmark of chronic disease, with implications of an immune-mediated process (Fig. 9.12).

Lymphocytes are either thymus- (T-lymphocytes) or non-thymus-derived lymphocytes (B-lymphocytes). The former are involved with cell-mediated immune responses and include subpopulations that are specifically cytotoxic, secretors of lymphokines, immunomodulatory, and carriers of immune memory. B-lymphocytes are capable of transforming into plasma cells, which secrete class-specific antibodies to a specific antigen. Inspissation of plasma cells leads to the evolution of plasmacytoid and Russell body cells. Some lymphocytes lack both T and B characteristics

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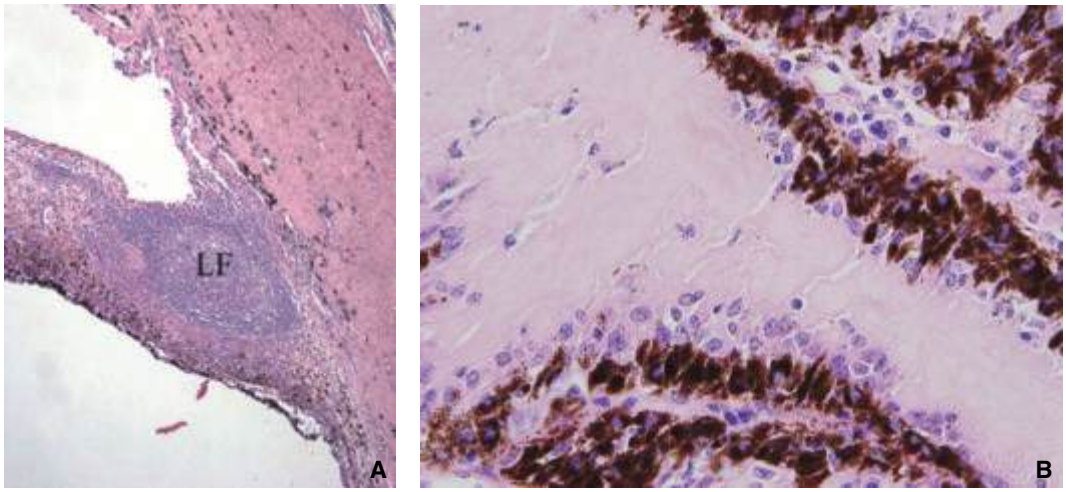


Figure 9.12 **A.** This is a section of a part of the anterior segment of a cat's eye with idiopathic lymphocytic plasmacytic uveitis. Note the diffuse infiltration of lymphocytes and the lymphoid follicle (LF) at the anterior base of the iris. (Original magnification 200×. Hematoxylin and eosin.) **B**. Lymphocytes, recognizable by their small size and scant cytoplasm and plasma cells with their pink cytoplasmic perinuclear halos are common inflammatory cells in uveitis, and these are both present within the ciliary processes of this horse with equine recurrent uveitis. (Magnification 60×. Hematoxylin and eosin.)

and are referred to as null cells and have cytotoxic capabilities. In the anterior chamber, lymphocytes and plasma cells will adhere to the iris and corneal endothelium as fine granular precipitates. Lymphoplasmacytic inflammation is a common histopathologic diagnosis. Many infectious and immune-mediated diseases present with such an infiltrate and additional diagnostic modalities (serology, culture, immunofluorescence assay, polymerase chain reaction) are often indicated.

Eosinophils are produced in the bone marrow and are present in both acute and chronic inflammation (Fig. 9.13); their granules contain arginine-rich basic protein, peroxidase, arylsulfatase, and phospholipase. They are attracted by antibody-antigen complexes, modulate the inflammatory response by inhibiting mast cell products, and show a killer function toward parasites, and thus are associated with allergic reactions and parasitic infestation. Mast cell granules contain heparin, histamine, and serotonin, among other factors (Fig. 9.14), are found in abundance in the conjunctiva and uvea, and play an initiating role in hypersensitivity responses. Cytoplasmic metachromatic granules, not seen on routinely stained preparations, are readily evident when stained with toluidine blue.

The presence of a resistant or replicating stimulus leads to activation of the macrophage system, which is referred to as granulomatous inflammation and is always chronic. Seldom does the response contain only macrophages because neutrophils are often present. When their numbers are significant, the inflammation is pyogranulomatous. Often diffuse or follicular collections of lymphocytes and plasma cells are also present. Granulomatous uveitis develops secondary to specific organisms, immunologic

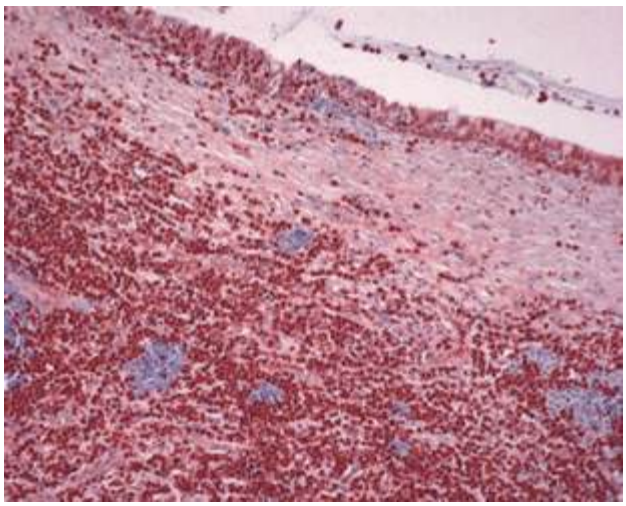


Figure 9.13 Eosinophils and mast cells are readily identified by several histochemical stains including Duffy's stain. Note the blue-stained mast cells and red stained eosinophils in this palpebral conjunctival biopsy from a cat with eosinophilic conjunctivitis. (Original magnification 200×. Duffy's stain.)

reactions, or foreign bodies. Its hallmark is the epithelioid cell, a specialized histiocyte characterized by abundant cytoplasm and a large pale nucleus (with an appearance reminiscent of a squamous epithelial cell). Fusion of epithelioid cells forms multinucleated giant cells. Foreign body giant cells possess multiple nuclei dispersed throughout the cytoplasm. The nuclei of Langhans giant cells array around the periphery of the cell and are usually associated with infectious granulomas. Touton giant cells are encountered in xanthomatous and lipogranulomatous

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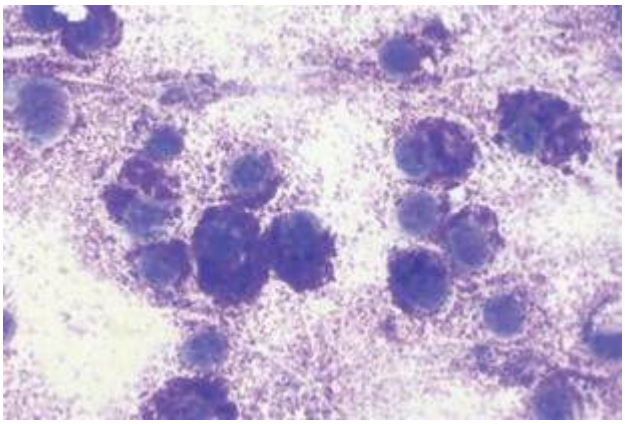


Figure 9.14 Mast cells are normal inhabitants of the conjunctival and episcleral tissues, and their prominent granules contain heparin, histamine, and serotonin. This cytological specimen was a fine needle aspirate from an episcleral lesion from a dog with a conjunctival mast cell tumor. (Magnification 400×. Toluidine blue stain.)

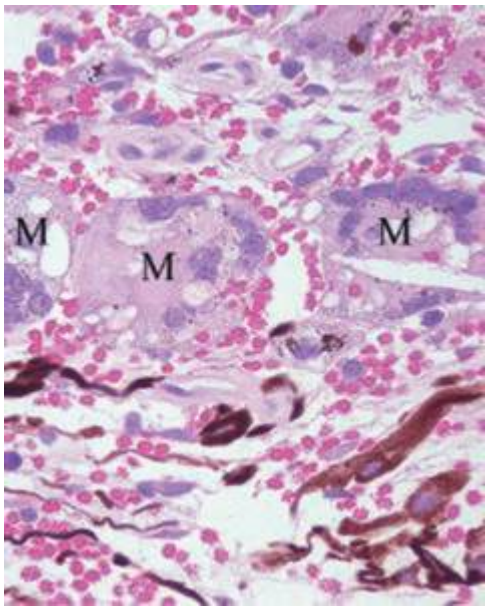


Figure 9.15 Multiple coalescing epithelioid macrophages (M) within a fibrovascular membrane on the iris of a dog with chronic retinal detachment and uveitis. Some of these giant cells have peripheral nuclei typical of Langerhans giant cells. It is unusual to have a granulomatous cellular infiltrate with retinal detachments, and special stains should be applied to rule out specific bacterial and fungal organisms. (Original magnification 400×. Hematoxylin and eosin.)

disease with cytoplasmic lipid vacuoles and the nuclei concentrically arranged in the mid-periphery (Fig. 9.15).

Granulomatous inflammation is described as discrete, zonal, or diffuse, dependent upon the organization of the macrophages. In the discrete form, distinct compact granulomas develop; there may or may not be central necrosis. Discrete granulomas can form in virtually any of the ocular tissues and require distinction both clinically and histopathologically from nodular or follicular lymphoplasmacytic infiltrates. In zonal granulomatous inflammation, the epithelioid cells surround the stimulus; chalazion, phacoclastic uveitis (in some species), and scleritis exemplify, with sebaceous secretion, lens protein, and collagen, the respective stimuli (Alleaume et al., 2017). Epithelioid cells intermixed with lymphocytes and plasma cells are broadly distributed in diffuse granulomatous inflammation, with uveodermatologic syndrome providing a prototypic example. In the anterior chamber, macrophages will congregate and adhere to the corneal endothelial surface as large "mutton-fat" precipitates.

Regardless, the pathologist attempts to identify what the cells are phagocytizing to arrive at an etiologic diagnosis, and stains for fungi, mycobacteria, and spirochetes (silver stains) are useful in this regard (see Table 9.2).

Granulomatous inflammation can have an acute neutrophilic component typical of mycotic infections (Fig. 9.16). Pyogranulomatous blepharitis (presumed an immune-mediated disease) and the pyogranulomatous uveitis that accompanies feline coronavirus infection are additional examples. Note that the terminology is not precise in that there is not necessarily necrosis and suppuration in these processes.

Inflammation can be described as acute or chronic, as nongranulomatous or granulomatous, or suppurative or lymphocytic/plasmacytic based upon the nature of the cellular infiltrate. Ocular inflammation can also be classified by the extent of involvement of the ocular tissues. Involvement of isolated or adjacent tissues is described with the suffix "itis"; if two or more tissues are involved, that which is most directly or primarily involved comes first in the terminology. If there is significant involvement of one of the large extra-

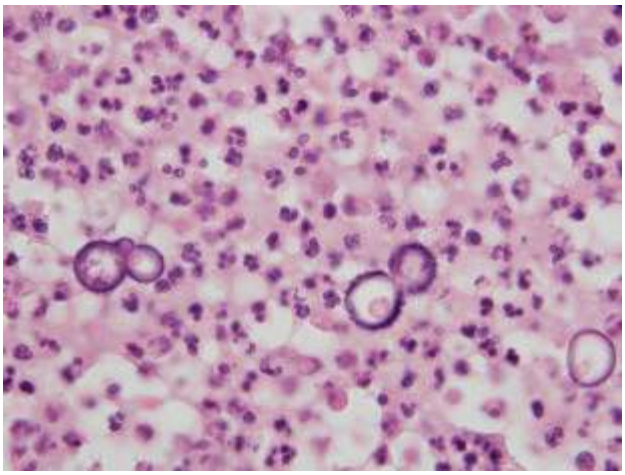


Figure 9.16 Pyogranulomatous inflammation commonly accompanies fungal endophthalmitis such as noted in this dog with blastomycosis. (Magnification 400×. Hematoxylin and eosin.)

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cellular fluid compartments – the anterior and posterior chambers or the vitreous – then endophthalmitis is the appropriate descriptor. Panophthalmitis implies extensive intraocular involvement as well as involvement of the fibrous coats – cornea and/or sclera – with extension to adjacent orbit and adnexa.

Repair of Ocular Tissues

The principles of tissue healing and repair are the same within the eye as other tissues and are discussed in detail in the introduction to this chapter. However, in addition to the interdependence of the ocular tissues and the function of transparency, the limited mitotic potential of critical tissues (the corneal endothelium in most species and retinal neurons) as well as the proliferative and metaplastic capabilities of the lens and neuroectodermal epithelium, dictate that functional repair is the exception rather than the rule.

Sequelae of Ocular inflammation

In general, the sequelae and consequences of intraocular inflammation are proportional to its severity and duration. Fibrinous exudation develops acutely and subsequently forms the scaffolds for fibrous ingrowth, organization into fibrous adhesions, and membranogenesis. Adhesions can form between iris and cornea (anterior synechiae) and iris and lens (posterior synechiae) (Fig. 9.17A). Adhesions between iris root and peripheral cornea (peripheral anterior synechiae) result in iridocorneal angle closure.

Ocular membranogenesis is an important sequelae to inflammation. Cyclitic membranes are membranes that organize around the lens and use the iris as a scaffold and induce pupillary occlusion or grow across a condensation of vitreous and incorporate the ciliary processes (Fig. 9.17B, C). They can be devastating by virtue of ciliary and retinal traction with resultant ciliary detachment, hypotony, tractional retinal detachment, and often phthisis bulbi or buphthalmos secondary to chronic glaucoma. Vitreal and periretinal membranes, although less common in animal eyes compared with humans, also result in retinal detachment as they mature and contract. Although these membranes may be referred to as retrolental membranes, pupillary membranes, cyclitic membranes, and the like, they typically extend as an anatomic continuum along the surfaces of the anterior and posterior segment. Photographs of gross sections reveal their extent better than clinical examinations and histologic sections in the acute and chronic stages (Fig. 9.17D–F).

These membranes can be caused by fibrous ingrowth through a corneal or scleral wound, organization of fibrinous exudation or hemorrhage, granulation responses by the uveal tissue, or arise from metaplastic epithelium. Phacoclastic uveitis, which occurs after breach of the lens capsule, is largely the result of the proliferation of metaplastic lens epithelium.

The formation of fibrovascular membranes on the anterior iris (Fig. 9.17G), retina, or optic disc as a consequence of the effects of soluble vasogenic proteins (predominantly vascular endothelial growth factor) is common in domestic animals. They often occur as a result of chronic retinal detachment, retinal ischemia from glaucoma or hypertension, chronic uveitis, and intraocular tumors. The source of the proteins could be retinal neurons, inflammatory cells, or neoplastic cells. In domestic animals, the iris is more commonly affected than the posterior segment tissues. Although clinically the process is described as rubeosis iridis, or "red iris", in human eyes, clinical manifestations are more difficult to detect in animals and the term "pre-iridal fibrovascular membranes (PIFMs)" is preferred (Peiffer et al., 1990; Treadwell et al., 2015). These membranes often proliferate over the pectinate ligaments and lead to iridocorneal angle closure or obstructive glaucoma, bleed as a common cause of spontaneous hyphema, and extend as pupillary, retroiridal, or anterior lens capsular membranes.

Secondary cataracts occur because of the effects on lens metabolism by the products of inflammation. The lens epithelial cells respond with anterior subscapular fibrous plaques, and metaplastic epithelium can migrate along the posterior lens capsule. Bladder cell and Morgagnian globule formation are common. Membranes can adhere to the anterior lens capsule causing focal cataracts. Inflammatory cells and products can weaken the zonules with resultant lens dislocation.

Secondary glaucoma occurs commonly as a sequela of inflammation (Johnstone McLean et al., 2008). Extensive peripheral anterior synechiae with angle closure occurs with or without iris bombé or pupillary membranes. As mentioned above, iridocorneal angle obstruction and/or closure can occur as a result of PIFMs or other anterior chamber membranes. In phacolytic glaucoma, lens protein escaping through the intact lens capsule is ingested by macrophages that are of significant dimension to physically obstruct the trabecular meshwork. In chronic lymphoplasmacytic uveitis, notably in cats, accumulations of inflammatory cells within the ciliary cleft can block access to the trabecular meshwork. Lastly, the chemical by-products of chronic inflammation might have a deleterious effect on trabecular endothelial cells.

Retinal detachment often occurs as the result of exudation from the choroid as the RPE barrier is compromised **(**Fig. 9.18A**)**, or as a result of traction by cyclitic, vitreal, or perilenticular membranes that induce retinal tears **(**Fig. 9.18B).

Atrophy is a postinflammatory sequelae to cell and tissue loss and occurs in uvea, retina, and optic nerve **(**Fig. 9.6 and Fig. 9.19**)**. Less significant uveal changes include a

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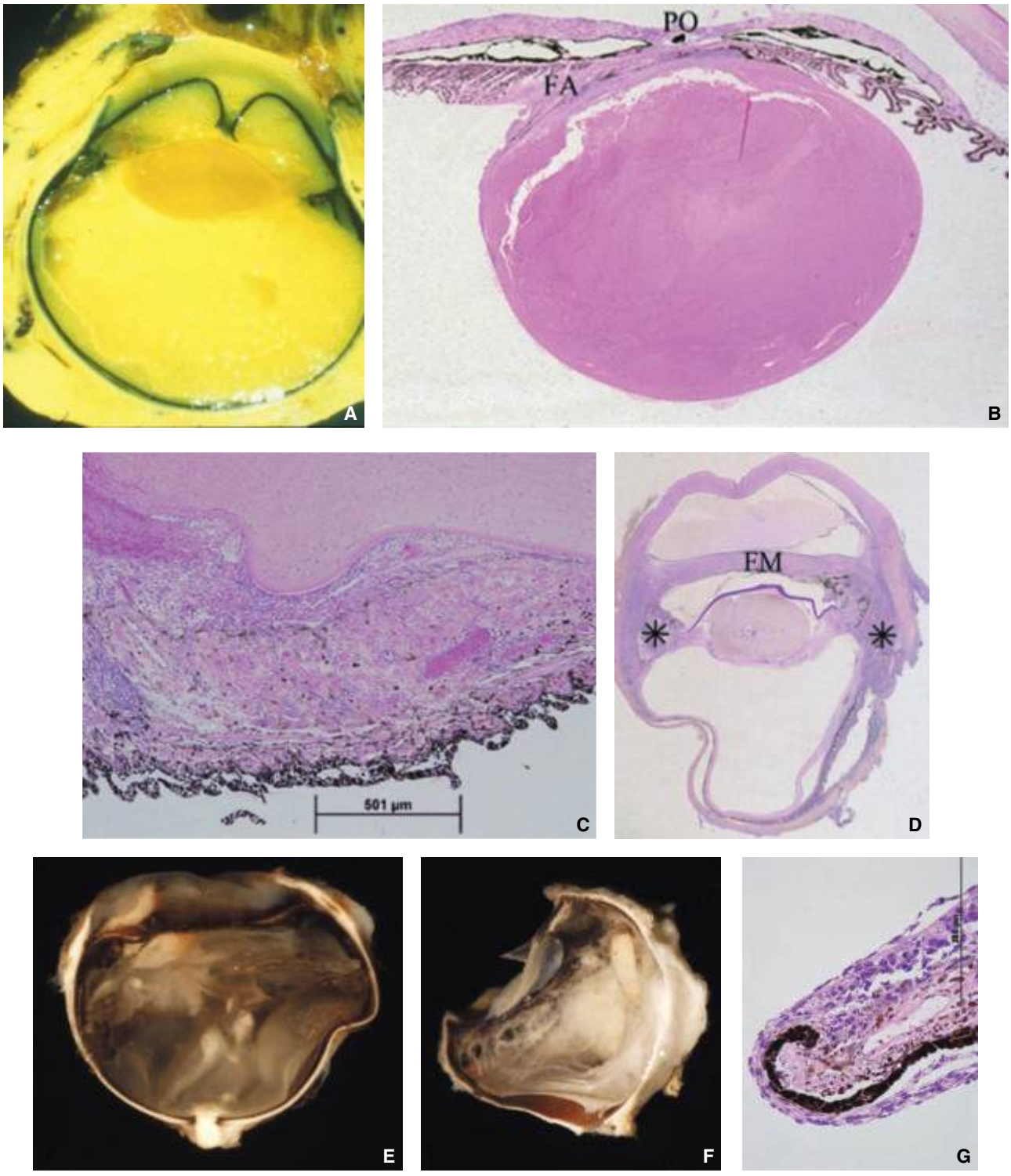


Figure 9.17 **A**. This Bouin's fixed canine globe has panophthalmitis with plasmoid material in the vitreous, posterior and anterior chambers, and in the subretinal space as portions of the retina have detached. Iris bombé is evident and developed secondary to the anterior and posterior synechiae. **B.** Pupillary occlusion (PO) due to posterior synechiae. Note the fibrous adhesion (FA) of the iris leaflets and ciliary processes to the anterior lens capsule in this domestic chicken. (Original magnification 40×. Hematoxylin and eosin.) **C.** This is a section of the anterior chamber of a dog diagnosed clinically with uveitis. Note the fibrovascular adhesion of this iris leaflet and the cornea and the lymphocytic–plasmacytic inflammation. (Magnification 200×. Hematoxylin and eosin.) **D.** A ruptured feline lens capsule with perilenticular fibrous membranes also known as cyclitic membranes, or perilenticular membranes. FM, fibrous membrane. Asterisk, thickened iris and ciliary body. (Original magnification 2×. Periodic acid-Schiff.) **E.** In the early stages of endophthalmitis, fibrin and neutrophils collect within anterior and posterior segments and form a scaffold for fibrous membranes to grow upon. In this gross section the lens implant is visible and significant purulent debris is collecting around the lens capsule and within the anterior vitreous of this dog. **F.** With time the fibrous membranes stretch across the intraocular tissues and occlude the pupil and encircle the lens which is ruptured in this dog. These fibrous membranes are also lifting and tearing the retina in this globe. **G**. Ectropion uveae in a dog due to a preiridal fibrovascular membrane that envelops the iris leaflet and contracts with outward deviation of the sphincter muscle and iris margin. (Magnification 400×. Hematoxylin and eosin.)

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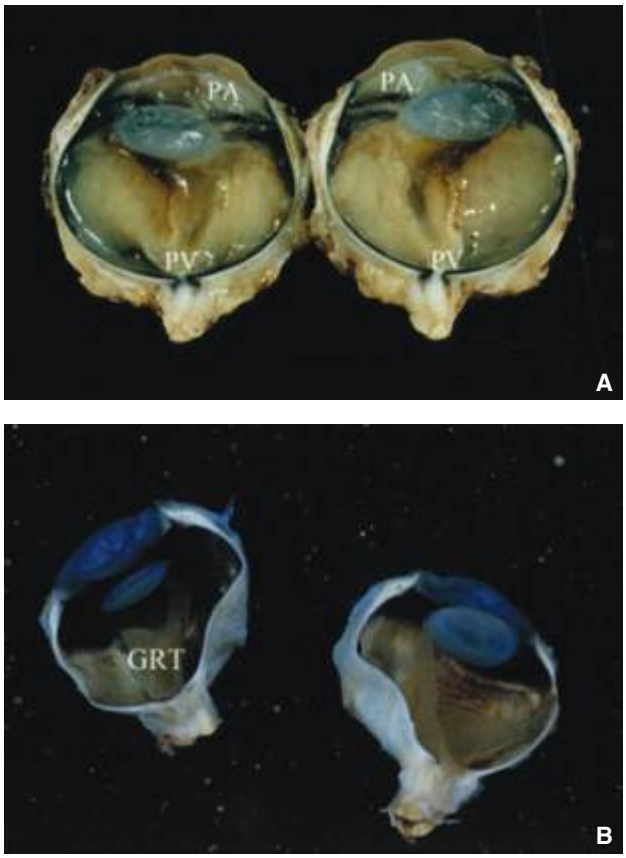


Figure 9.18 **A**. Gross section of canine eye with septic endophthalmitis. Note the opaque plasmoid aqueous (PA) and vitreous (PV), and exudative retinal detachment. **B**. Gross section of a formalin-fixed dog's eye with a rhegmatogenous retinal detachment. Note the giant tears in the peripheral retina, and the retinal scrolling. Focal vitreous traction bands induced the scrolling and contraction of the retina. GRT, giant retinal tear.

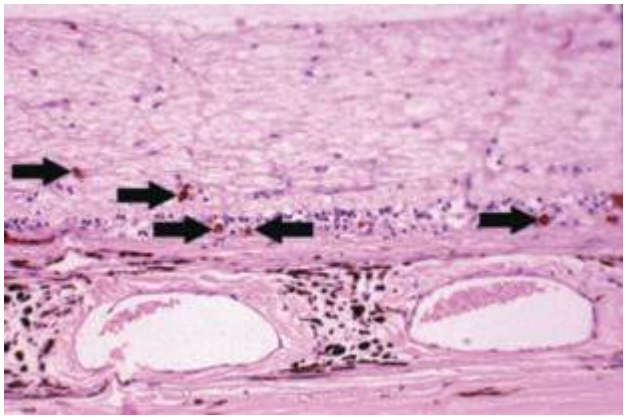


Figure 9.19 Retinal and choroidal degeneration with intraretinal migration of retinal pigment epithelium cells (arrows). (Original magnification 300×. Hematoxylin and eosin.)

melanocytic hyperplasia with resultant hyperpigmentation and the formation of inflammatory iridociliary cysts. Phthisis bulbi occurs when severe inflammation and its sequelae result in cessation of aqueous production (Fig. 9.20). The clinical appearance of this end-stage process is a shrunken eye. Histologically, the hallmarks are an atrophic and disorganized globe characterized by cyclitic membranes, folds in Descemet's membrane and the cornea, a thickened sclera, loss of the anterior and posterior chambers and vitreous cavity, and variable degrees of chronic inflammation. Fibrous or osseous metaplasia of the ocular epithelium is common and necessitates decalcification prior to processing the globe.

Pathology of Congenital Disorders

Congenital disorders manifest at birth or shortly thereafter. Although the etiologies are diverse and often unknown or idiopathic, they include genetic mutation(s) or exposure of the embryo to nutritional deficiencies, toxins, or infectious agents. Anomalies have been categorized as those that occur during organogenesis and those disorders of tissue differentiation that develop subsequent to organogenesis and target specific ocular tissues (surface ectoderm, mesoderm, neural crest, and neuroectoderm). Normal embryologic ocular development is not reviewed here and readers are encouraged to review Chapter 1 of this text.

Defective Organogenesis

Anophthalmos is a total absence of ocular tissue that occurs because of failure of the primary optical vesicle to develop or because of complete regression of the optic vesicle (Fulton et al., 1977; Rothenburger et al., 2017). The few reported natural cases are bilateral. Vitamin A deficiency is also associated with anophthalmos and concurrent anomalies of skeletal and central nervous systems anomalies in swine (Bendixen, 1944; Hale, 1935; Leipold & Huston, 1968). Far more common is the clinical perception of anophthalmos with histologic evidence of a microphthalmic globe or other ocular primordial element.

Cystic eyes are very rare and consist of spherical structures lined by a single layer of undifferentiated neuroectoderm. The ocular development arrested at the optic vesicle stage with failure of invagination to form the optic cup and failure of lens development and invagination of the neuroectodermal tissues.

Microphthalmia is a small globe that usually has multiple ocular anomalies including cataract, microphakia, uveal hypoplasia, and varied colobomas (Fig. 9.21) (Da Silva et al., 2015). When a small globe is otherwise normal and the entire globe is symmetrical, the term nanophthalmia is appropriate. Phthisis bulbi is the major differential diagnosis, and the

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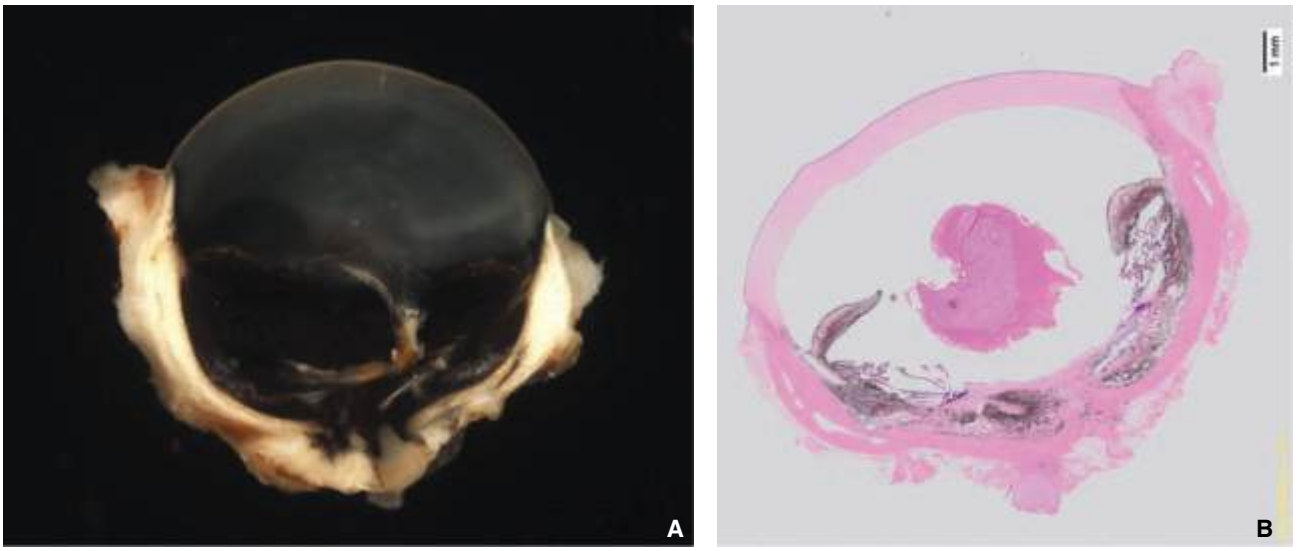


Figure 9.20 Gross (**A**) and subgross (**B**) sections. Phthisis bulbi develops secondary to unrelenting endophthalmitis. The hallmarks are a shrunken globe with multiple folds in the fibrous tunic and signs of chronic inflammation as present in this canine globe with chronic phacoclastic uveitis. (Magnification 2×. Hematoxylin and eosin.).

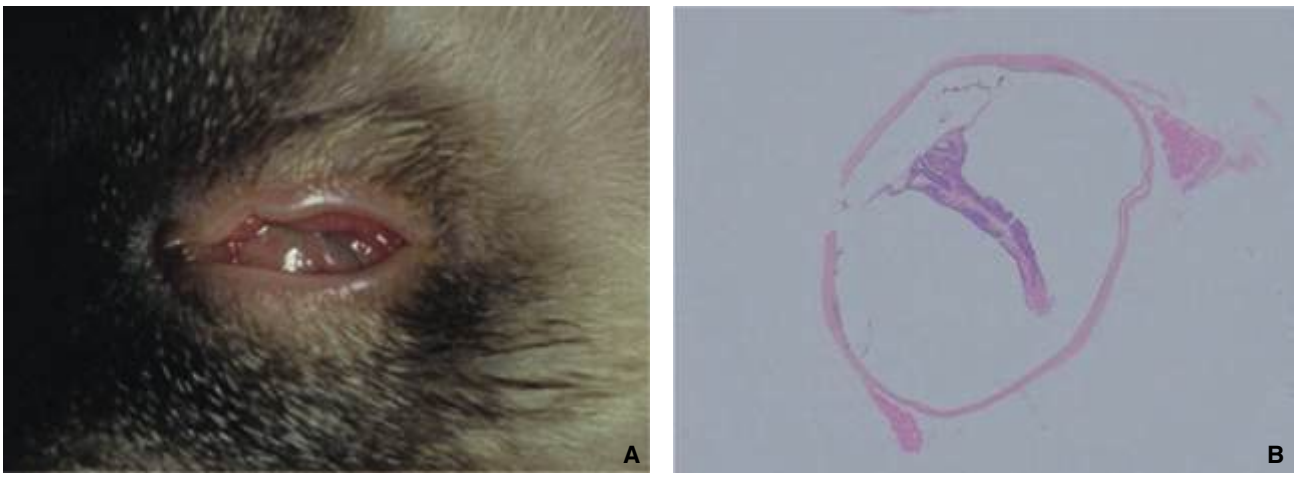


Figure 9.21 **A.** Microphthalmia in a Siamese kitten. Lack of support by a normal globe allows passive prolapse of the third eyelid. **B.** This microphthalmic eye is from a puppy. Absence of cornea and lens indicates ASD, hypoplastic uveal-like tissue lines the entire fibrous tunic (sclera), and the retina is dysplastic and nonattached. (Magnification 2×. Hematoxylin and eosin.)

histologic footprints of inflammation and thickened sclera facilitate distinction.

True cyclopia is an exceedingly rare congenital anomaly in domestic animals that manifests as single orbit and globe located centrally in the forehead (Fig. 9.22A). More typically, a midline anomaly represents fusion of the developing globes with partial or complete duplication of intraocular structures and is properly referred to as synophthalmos (Fig. 9.22B). Both conditions are usually accompanied by multiple midline anomalies including cleft palate, hydrancephaly, microcephaly, median proboscis, and cranioschisis. Cyclopia has been induced by feeding ewes *Veratum californica* (Binns et al., 1959, 1965). This plant contains steroid alkaloids that damage the neural groove of the fetal lamb exposed at gestational days 14 and 15. Similarly, synophthalmia has been induced in mice by exposure of pregnant dams to ochratoxin (Robinson et al., 1993). Griseofulvin toxicity induces cyclopia, anophthalmia, and aplastic optic nerves in kittens from medicated queens (Scott et al., 1974).

Coloboma is an absence of ocular tissue. Colobomas are classified as typical (orientated along the embryonic fissure) and atypical (those that are orientated along all other planes). Typical colobomas develop because of incomplete fusion of the embryonic fissure whereas atypical colobomas develop because of a lack induction or impaired proliferation of the

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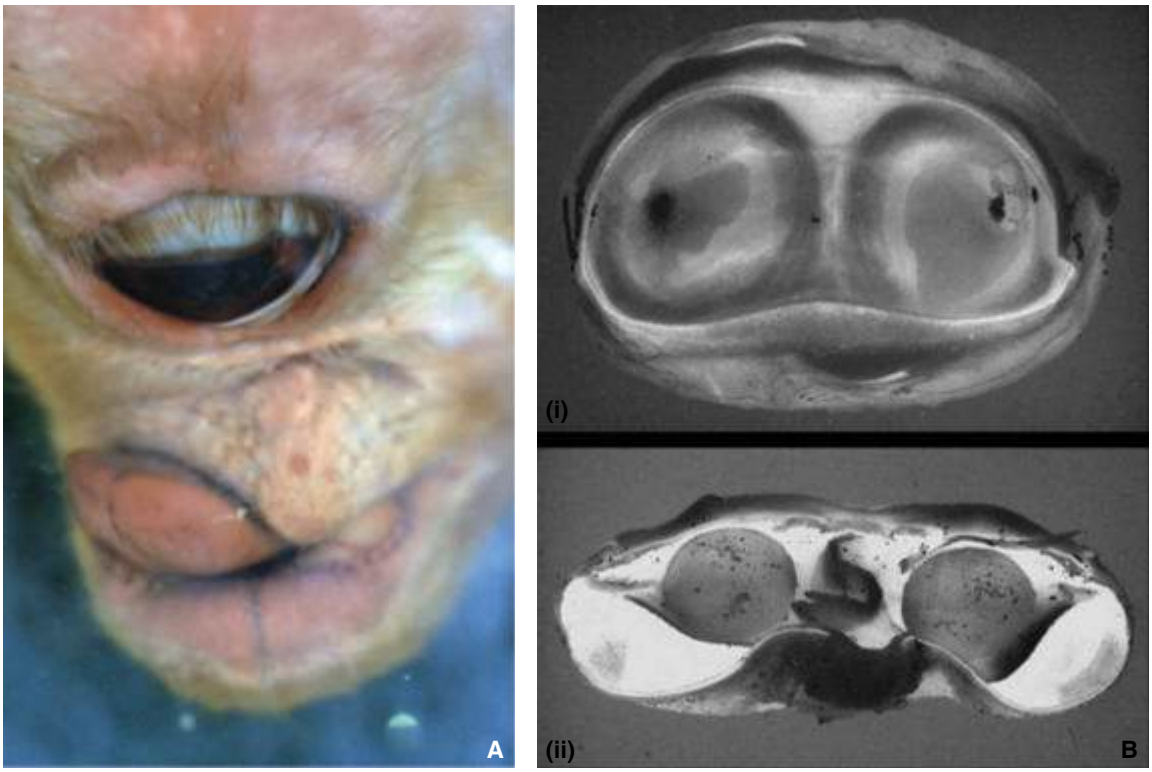


Figure 9.22 **A.** A bovine cyclops with a single central eye and lack of nasal and maxillary development. **B.** (i) Synophthalmos in a newborn kid. (ii) Sagittal section reveals paired lens, partial separation of the anterior segments, and sharing of a posterior segment. (Courtesy of Brian Wilcock.)

affected tissues. Colobomas can affect most ocular tissues; so-called lens colobomas are misnamed, and they are a deformity manifesting as a consequence of ciliary body and zonular colobomas.

Extensive scleral colobomas lead to thinning (ectasia) with outpouching of the uvea and retina (staphyloma). Scleral colobomas can give rise to orbital cysts, which are lined by anomalous neural crest and neuroectodermal tissues (Greenberg et al., 2016). Inherited choroidal and optic nerve colobomas are common in dogs with Collie eye anomaly (Fig. 9.3 and Fig. 9.23), and in Charlais cattle (Brown et al., 1979; Roberts, 1960; Roberts et al., 1966).

Defective Tissue Differentiation

After the optic cup is formed, ocular development continues with differentiation of neuroectoderm into retina, ciliary, and iridal epithelia. Neural crest tissues migrate and develop into the uvea, whereas mesenchymal differentiation proceeds into the vascular and fibrous tunics of the eye. Surface ectoderm differentiates into the lens, corneal and conjunctival epithelium, and lacrimal, eyelid and conjunctival glands. The congenital anomalies that develop during tissue differentiation are reviewed by the originating tissue.

Defective Neuroectoderm Differentiation

Retinal Dysplasia

Retinal dysplasia reflects disorganization of the neuronal lamellae. The quintessential histologic lesion of retinal dysplasia is the rosette (Fig. 9.24).

Rosettes consist of a central lumen containing dysplastic photoreceptor inner and outer segments surrounded by multiple layers of neuroblasts and axons and a discontinuous external limiting membrane. The pathogenesis of retinal dysplasia is complex and largely unknown (Silverstein et al., 1971).

Retinal dysplasia has multiple etiologies, the most common being genetic mutations. The mode of inheritance has been confirmed in multiple dog breeds, and multiple organ system involvement is occasionally reported (Carrig et al., 1988; Grahn et al., 2004; Meyers et al., 1983; Whiteley, 1991).

Retinal dysplasia can be induced by *in utero* virus infections in cattle, dogs, cats, and sheep. These lesions are characterized by cellular necrosis and scarring with rosettes. Incriminated agents include bovine virus diarrhea, feline panleukopenia, feline leukemia, canine herpes, and bovine blue tongue viruses (Albert et al., 1976; Bistner et al., 1970). The acute lesions are a nonsuppurative endophthalmitis with multifocal chorioretinal necrosis. Chronic lesions

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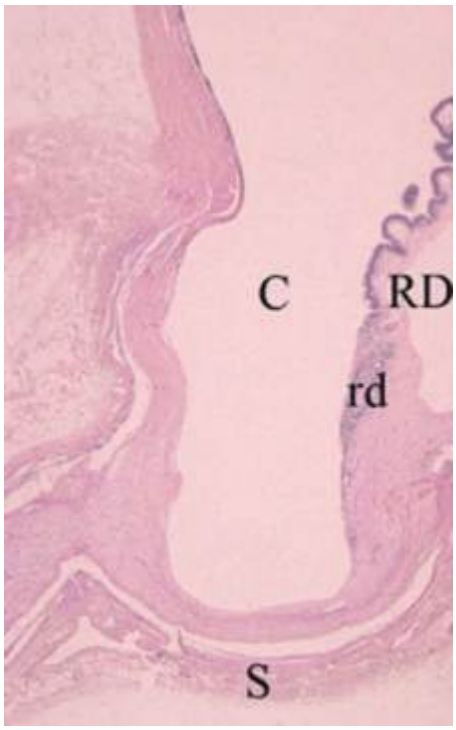


Figure 9.23 A peripapillary coloboma (C), staphyloma (S), retinal detachment (RD), and retinal dysplasia (rd) in a Collie puppy with collie eye anomaly. (Original magnification 100×. Hematoxylin and eosin.)

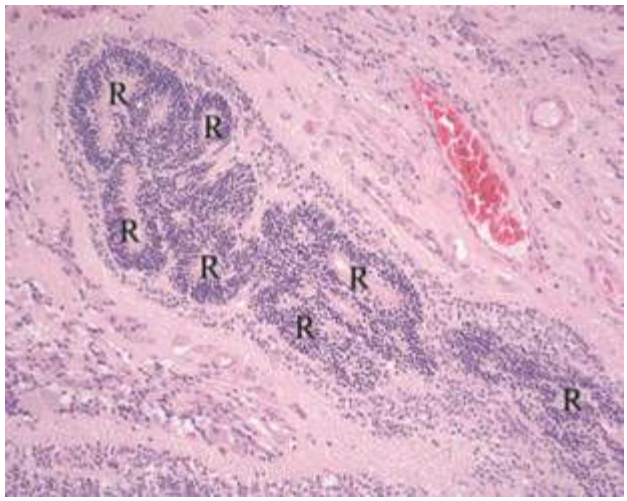


Figure 9.24 Retinal dysplasia in a dog. Note the outer nuclear rosettes (R) and complete disorganization of the retina. (Original magnification 300×. Hematoxylin and eosin.)

include multifocal chorioretinal scarring, atrophy, and retinal rosettes. The RPE is commonly affected with multifocal hyperplasia and degeneration. It is commonly accompanied by cerebellar atrophy, hydrocephalus, and hydrancephaly. Retinal dysplasia also occurs secondary to maternal toxin exposure (Percy & Danylchuk, 1977) and nutritional deficiencies (vitamin A, zinc, taurine) (Barnett & Grimes, 1974; Bendixen, 1944; Paterson et al., 1999).

Retinal folds represent uncoordinated growth of retina and the outer coats such that excess retina is present (Fig. 9.1F). Although folds can be encountered as a component of retinal dysplasia as a secondary consequence of altered growth rate, they are distinct in terms of pathogenesis and significance. The antithesis is a developing retina that grows less than normal with resultant stretching, peripheral tearing, and congenital nonattachment.

Optic Nerve Hypoplasia and Ganglion Cell Hypoplasia

Optic nerve hypoplasia develops secondary to ganglion cell hypoplasia as the axons of these ganglion cells form the optic nerve. The clinical diagnosis of optic nerve hypoplasia is limited to morphologic estimation **(**Fig. 9.25**)**. These conditions are likely inherited, and they all involve ganglion cell hypoplasia (Barnett & Grimes, 1974; da Silva et al., 2008; Ernest, 1976; Gelatt & Leipold, 1971; Kern & Riis, 1981).

In utero optic nerve atrophy is difficult to distinguish from hypoplasia both clinically and histologically; the former is distinguished by gliosis. Optic nerve and ganglion cell atrophy are induced in young cattle by vitamin A deficiency. The pathogenesis includes failed remodeling of the optic foramen resulting in stenosis and optic nerve compression and atrophy (Hayes et al., 1968). Vitamin A deficiency induces optic nerve hypoplasia, retinal dysplasia, and systemic anomalies in piglets (Bendixen, 1944; Hale, 1935) Griseofulvin toxicity induces cyclopia, anophthalmia, and aplastic optic nerves in kittens from medicated queens (Scott et al., 1974).

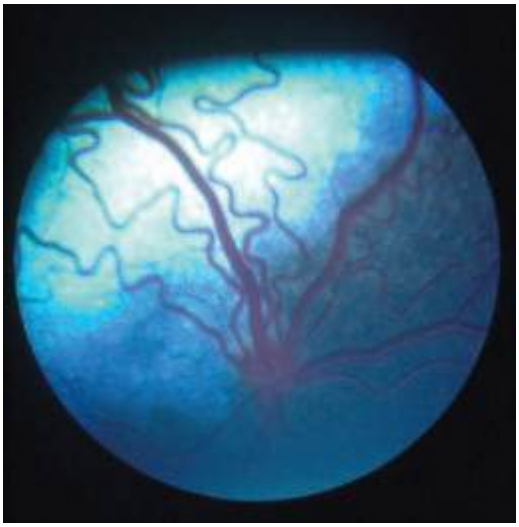


Figure 9.25 Optic nerve hypoplasia manifests as a small optic nerve; the affected animal may have abnormal pupillary light reflexes and visual impairment.

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Defective Neurocrest and Mesenchymal Differentiation

After the optic cup is formed and the lens vesicle separates from the surface ectoderm, the periocular mesenchyme and neural crest cells undergo a series of migrations, differentiations, and atrophies, and perturbations give rise most notably to ASD. ASD includes multiple anomalies of the cornea, lens, and anterior uvea. Affected globes often have microcornea, corneal edema and scarring, adhesion of lens to cornea, microphakia, spherophakia, and cataract. The anterior uvea and filtration angle are usually hypoplastic and congenital glaucoma can result (Fig. 9.26A, B; Helanda et al., 1997). Often marked angle recession precludes filtration angle assessment. ASD is caused by a primary lack of induction and differentiation of neural crest tissues or surface ectoderm or physical obstruction to migration by delayed separation of lens from surface ectoderm (Fig. 9.26C, D).

There is considerable confusion surrounding congenital and perinatal glaucoma associated with ASD and primary glaucoma of dogs. Briefly, these are completely different syndromes. Congenital glaucoma and glaucoma associated with ASD are confirmed by documenting a bupthalmic globe with microphakia and a hypoplastic uvea from birth to approximately three years of age. The intraocular pressures

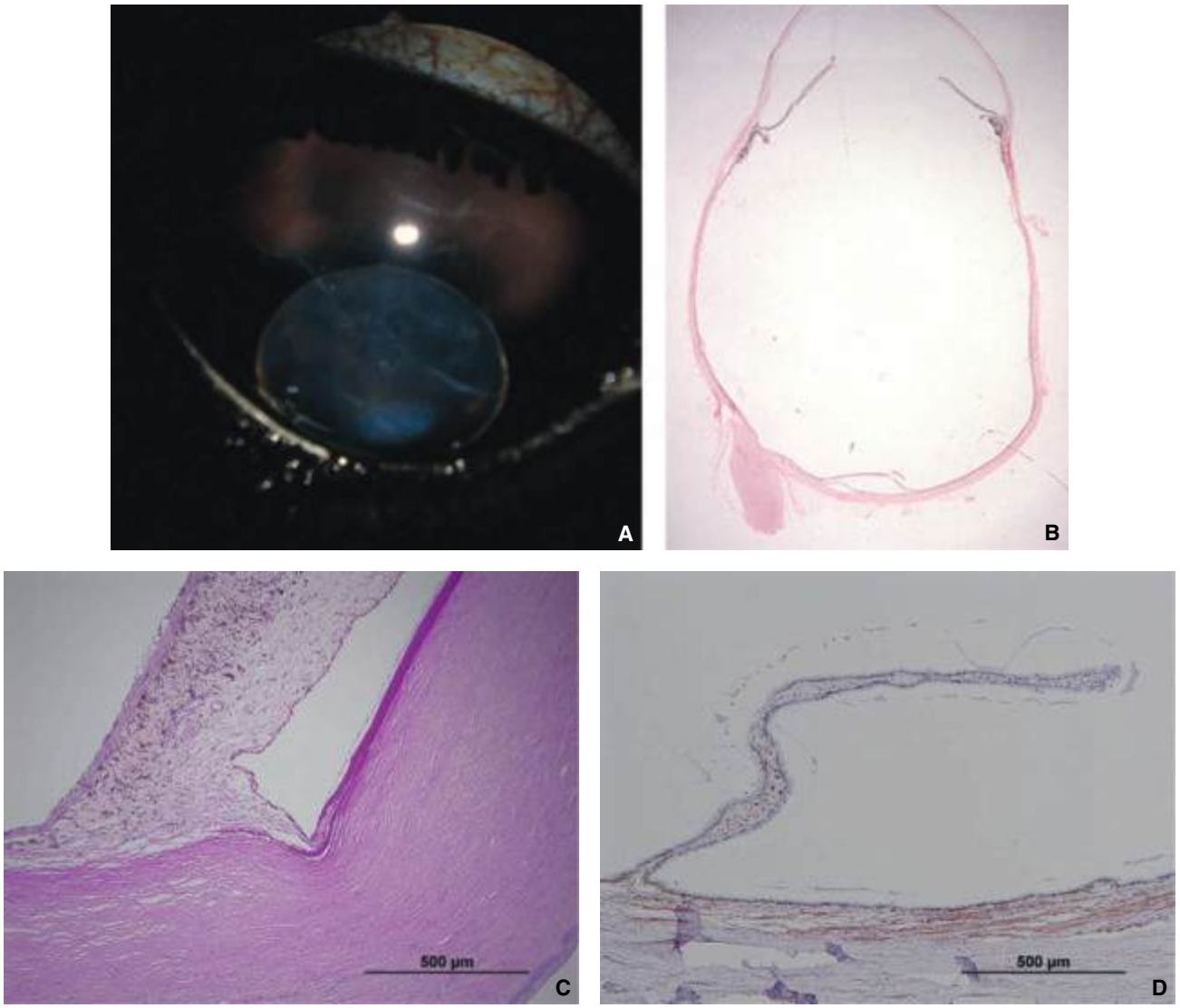


Figure 9.26 **A.** Congenital glaucoma in a llama (*Llama glama*) characterized by microphakia, corneal striae, and a dilated pupil. (Reprinted with permission, Cullen, C.L. & Grahn, B.H. (1997). Congenital glaucoma in a llama *(Llama glama*). *Veterinary and Comparative Ophthalmology*, **7**, 253–257.) **B.** Subgross section of the llama eye in **A** demonstrates buphthalmia, uveal hypoplasia, and mild optic disc cupping. The microphakic lens was removed from the anterior chamber during sectioning. (Original magnification 2×. Periodic acid-Schiff.) **C.** Filtration angle hypoplasia is a common anomaly associated with glaucoma associated with ASD. (Periodic acid-Schiff.). **D.** Ciliary hypoplasia is a consistent anomaly in dogs and cats with glaucoma that is associated with ASD. (Smooth muscle actin label.)

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in these globes are variable. In contrast, primary glaucoma associated with goniodysgenesis or open angles are developmental anomalies that usually manifest much later in life. Although the outflow pathway in ASD might be described as goniodysgenesis, distinction is made from the other changes associated with primary glaucoma.

Uveal hypoplasia is a common anomaly. All animals with poorly pigmented uvea have a hypoplastic vascular tunic. The extreme of this hypoplasia is albinism where uveal and neuroectodermal pigment are absent. The tapetum is usually poorly developed or absent in animals with hypoplastic uvea. Blue-eyed animals lack iris stromal pigment whereas the neuroectodermal pigment remains. It has been assumed the lack of neurocrest (melanocytic) cells are a significant factor that results in the thin uvea in this condition; however, research is lacking.

Collie eye anomaly is a congenital condition in Collie and Collie-related dogs. The basic defect is focal choroidal hypoplasia located temporal to the optic disc and is inherited as an autosomal recessive trait. The genetic mutation is a homozygous deletion of 7.8 kb from the *NHEJI* gene, an intronic deletion in a conserved binding domain that binds several developmentally important proteins (Parker et al., 2007). This syndrome is also reported in Border Collies, Shetland Sheepdogs, Australian Shepherd dogs, and Nova Scotia Duck Tolling dogs.

Ophthalmic and gross examination reveals a variety of ocular anomalies including microphthalmia, choroidal hypoplasia that is focal and located temporal to the optic disc, optic disc and peripapillary colobomas and scleral ectasia, and retinal detachment (Fig. 9.3). Light microscopic examination confirms the focal choroidal hypoplasia manifesting with thinning and hypopigmentation and other lesions.

Persistent pupillary membranes, persistent hyperplastic primary vitreous (PHPV), persistent hyperplastic tunica vasculosa lentis (PHTVL) and patent hyaloid artery have been categorized within the classification of retention of primitive embryonic vasculature (PEV) (Fig. 9.27).

Persistent (or dysplastic) pupillary membranes represent incomplete atrophy of the perilenticular vasculature. These remain as pigmented strands that arise and insert on the iris collarette and usually span the pupil. If the membrane inserts on the lens or cornea, not only is it persistent but also dysplastic because in normal development such relationships do not occur. This condition is common and in some breeds of dogs is an inherited congenital condition (Rubin, 1989). Iris to iris persistent pupillary membranes are present in most if not all horses.

PHPV, PHTVL, and patent hyaloid artery are disorders that involve persistence of the posterior segment vascular supply to the lens. During ocular development the hyaloid artery extends from the optic disc to the lens and anastomoses with a capillary net from the anterior uvea (tunica vasculosa lentis). During normal development in domestic animals these vessels atrophy and only focal remnants commonly remain (Bergmeister's papilla, Mittendorf's dot, anterior lens capsule pigment). Retention of these vascular nets are often incidental idiopathic congenital conditions (Boillot et al., 2015), although PHPV and PHTVL are inherited congenital conditions in Doberman dogs, Staffordshire Terriers, Bloodhounds, and Miniature Schnauzer dogs (Grahn et al., 2004; Leon et al., 1986; Rensburg et al., 1992; van der Linde-Sipman et al., 1983; Venter et al., 1996). The light microscopic features of PHPV (a misnomer because the tissue is actually metaplastic as well) include retention of multiple blood vessels and primitive perilenticular mesoderm and neurocrest cells in a core that extends from the optic disc to the posterior lens capsule. Occasionally, choriostomatous cartilaginous or adipose tissues are encountered. The lens is often cataractous, and the posterior lens capsule is usually thickened with spindle cells and melanocytes. The posterior lens capsule is occasionally incomplete, and vessels and fibrous and pigmented tissues extend into the posterior lens cortex. The light microscopic findings with patent hyaloid arteries are similar; however, they are milder and include only a patent blood vessel that extends from the optic disc to the posterior lens capsule. The light microscopic findings of PHTVL are somewhat similar; however, the majority of vessels, pigmented neurocrest, and mesodermal tissues extend from the iris around the lens and anastomose with the retained primary vitreous cone and extend to the optic disc.

Congenital anomalies of extraocular muscles are documented occasionally in dogs (brachycephalic breeds) and cattle (Holsteins), but the extraocular muscles have not been examined histologically. The clinical manifestations are often a bilateral strabismus (usually exotropia). The neurologic system is usually normal. There is speculation that the affected extraocular muscles are either hypoplastic or have displaced scleral insertions.

Defective Surface Ectoderm Differentiation

The corneal epithelium, lens, eyelids, and adnexal tissues are derived predominantly from surface ectoderm, although neurocrest and mesenchymal tissues might also contribute to some of the associated anomalies. Congenital anomalies, although not rare clinically, are seldom examined by the pathologist. Eyelid colobomas, micropalpebrae, and macropalpebrae are examples of such, and they might accompany other ocular anomalies including microphthalmia, entropion, and ectropion. Colobomas and micropalpebrae are examples of defective ectodermal induction and differentiation.

Similarly, anomalies involving the cilia and tarsal glands of dogs are common but only occasionally examined histologically. Ectopic cilia and distichiasis develop because of dysplasia of the tarsal glands (Fig. 9.28). They are inherited

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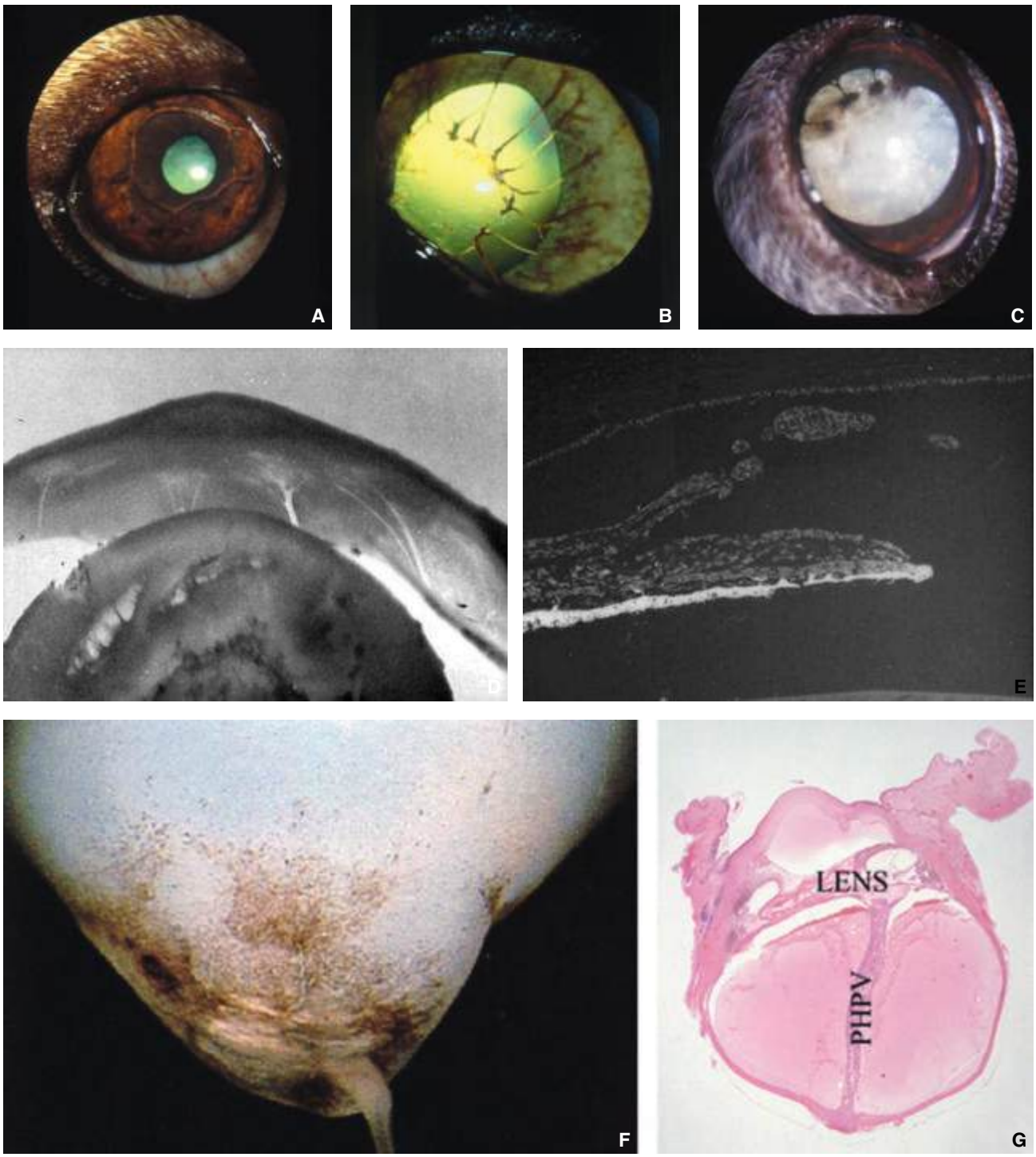


Figure 9.27 Persistent and dysplastic pupillary membranes occur in three variants: iris to iris (**A**), iris to cornea (**B**), and iris to lens (**C**). The gross and light microscopic findings include pigmented uveal tissue that envelops small often nonpatent embryonic blood vessels that originate from the iris (**D, E**). **F.** Spherophakia and persistent hyperplastic primary vitreous in a dog. Note the pigment patches on the protruding posterior lens capsule and the vascularized stalk that adheres to the posterior lenticonus. **G.** Persistent hyperplastic primary vitreous (PHPV) in a dog. Note the shrunken lens (LENS) and lens capsule folds. The posterior lens capsule is incomplete. (Original magnification 2×. Hematoxylin and eosin.) (Courtesy of Brian Wilcock.)

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Figure 9.28 Multiple dysplastic eyelid tarsal glands with ectopic cilia in a dog. Multiple ectopic cilia are present on the palpebral conjunctival surface. The yellow distended and impacted tarsal glands are the chalazia.

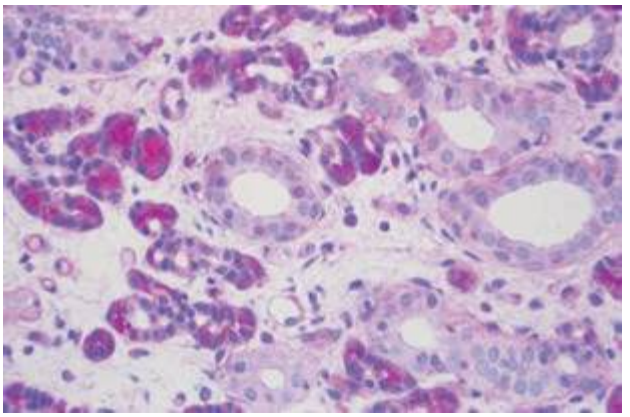


Figure 9.29 Dacryops in a dog. Note the primarily double layered cuboidal epithelium with submucosal fibrosis and a clear lumen (Hematoxylin and eosin.) (Courtesy of Diane Hendrix.)

in some dogs. Trichiasis and trichomegaly are similar congenital anomalies of the eyelids that occur because of misdirected normal hair follicles and excessively large cilia, respectively.

Lacrimal gland and duct aplasia or hypoplasia are potential etiologies for congenital keratoconjunctivitis sicca. Ipsilateral micropalpebral fissure is commonly associated. Congenital lacrimal gland disorders probably develop because of a lack of induction of the gland or secondary to duct atresia.

Punctal, canalicular, and nasolacrimal duct atresia occur in dogs, camelids, cattle, and horses, but histologic examination of these tissues is not reported. The etiology is atresia. Occasionally, ectopic and supernumerary nasolacrimal duct openings are reported. The etiology is usually unknown and the pathogenesis is thought to be a lack of development of the surface ectoderm into a patent duct.

Dacryops, canaliculops, and orbital cysts are uncommon congenital anomalies of dogs, cats, and horses (Dawson et al., 2016; Gerding, 1991; Grahn & Mason, 1995; Sritrakoon et al., 2016). These arise from abnormal development of the lacrimal glands, glands of the third eyelid, nasolacrimal drainage ducts, and canaliculi. The clinical manifestations include a cystic mass in the periocular tissue in the first months of life. Light microscopic findings include a monolayer of cuboidal epithelium with or without an outer layer of spindle-shaped myofibroblasts surrounding a serous to hemorrhagic fluid (Fig. 9.29).

Dermoids are congenital lesions of the superficial cornea, conjunctiva, and eyelid skin. Dermoids are choriostomas which are misplaced normal tissues **(**Fig. 9.30A**)**. They most likely develop because of defective induction or differentiation of surface ectoderm. Histologic examination reveals stratified squamous epithelium that is keratinized and variably pigmented. The associated dermis contains sebaceous and sweat glands, adipose tissue, and hair follicles (Fig. 9.30B). Occasionally cartilage and bone are encountered. The edges of the dermoid blend into the corneal and conjunctival epithelium and stroma.

Microcornea and macrocornea are uncommon and have no apparent histologic abnormality. The etiology is likely defective induction of neurocrest and or surface ectoderm. Congenital corneal opacities are frequently diagnosed in domestic animals; however, they are seldom examined histologically. Those that involve the endothelium and are white or pigmented are often remnants of the embryonic vasculature (see persistent pupillary membranes).

Congenital anomalies of the lens include cataracts, aphakia, microphakia, spherophakia, lenticonus, incomplete or delayed separation from the cornea, and lenticular coloboma (Fig. 9.31 and Fig. 9.32). These disorders might be isolated; however, they are commonly associated with ASD, congenital glaucoma, and PEV. Most of these anomalies develop secondary to defective induction and differentiation of surface ectoderm with some contributions of neurocrest and mesenchymal tissues during development.

Cataracts are the most common congenital lenticular anomaly. The light microscopic manifestations are nonspecific and include lens fiber protein alteration, fiber cell membranolysis, and lens epithelial cell dysplasia, hypertrophy, and posterior migration, and occasionally mineralization. Congenital cataracts are unilateral or bilateral and solitary or associated with microphakia, lenticonus, spherophakia, and ASD.

Aphakia is complete absence of a lens and is rare (Peiffer, 1982). The failure of differentiation of a lens from surface ectoderm does occur and dysplastic lens remnants can be found embedded within or adherent to the cornea **(**Fig. 9.32C, D**)**. Microphakia and aphakia are common accompaniments in cases of congenital glaucoma. Microphakia manifests as a primary congenital anomaly and

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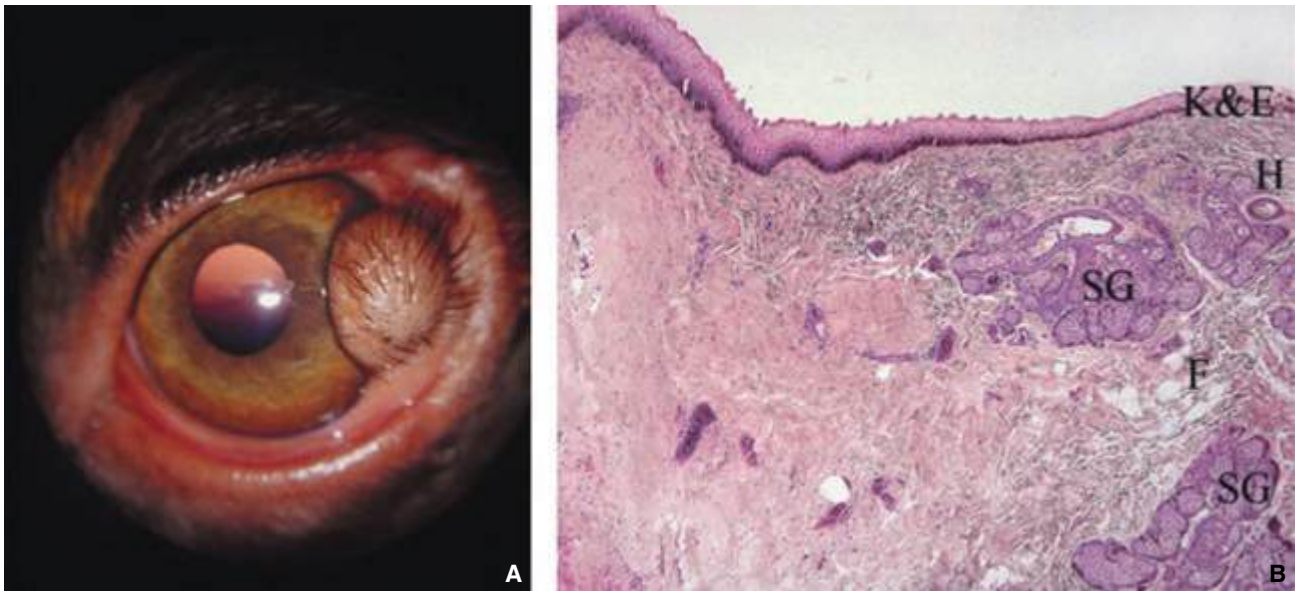


Figure 9.30 **A.** A corneal dermoid in a puppy. **B.** Histologic section of a corneal dermoid of the dog in **A** after keratectomy. The dermal components include hair follicles (H), sebaceous glands (SG), adipose tissue (F), keratinized pigmented epithelium (K&E). (Original magnification 200×. Hematoxylin and eosin.)

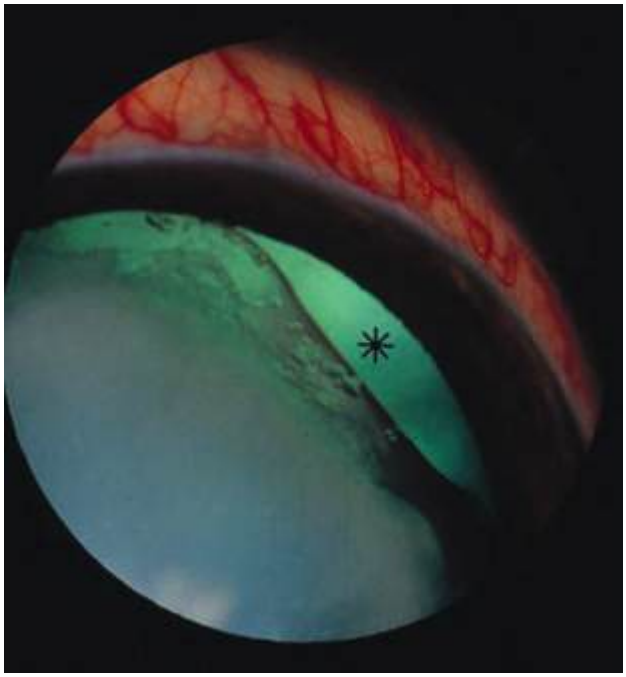


Figure 9.31 Congenital cataract and lenticular pseudocoloboma (*) in a dog. The equator is flattened and zonules absent. Generalized nuclear and focal cortical cataracts are present.

is usually associated with cataracts or ASD. Many breeds of dog with microphakia also have microphthalmia, and the condition is bilateral and often inherited.

Spherophakia and microphakia are indicative of cessation of lens growth prior to the formation of secondary lens fibers. Lenticonus describes a misshapen lens with a posterior or more rarely an anterior protuberance that results from dysplastic basement membrane production by the primary lens fibers. Posterior lenticonus (Fig. 9.32A, B) is commonly associated with PEV and posterior lens capsule dysplasia. Anterior lenticonus is most often associated with ASD and occasionally congenital glaucoma and reflects delayed separation of the lens vesicle from surface ectoderm (Fig. 9.32C, D**)**. Light microscopy reveals lens capsule distortion in either an anterior or posterior direction and subcapsular cataract. When the condition is associated with developmental anomalies of the vitreous, a posterior retrolental fibovascular membrane is often present; often the posterior lens capsule is incomplete and these abnormal tissues extend into the lens cortex.

Certain breeds of dog (notably terriers) have a heritable condition in which the zonules appear normal initially but are of reduced tensile strength and rupture easily (Farlas et al., 2010; Foster et al., 1986). Light microscopic examination of terriers and Shar Pei dogs with zonular dysplasia reveals distinctive lamellar and crosshatched zonular patterns with positive PAS and Mason's trichrome and negative elastin staining (Morris & Dubielzig, 2005).

Lens colobomas are actually pseudocolobomas that occur secondary to zonular aplasia. These are rare anomalies which manifest as an equatorial lens flattening where the zonules are absent (Fig. 9.31). Other than the misshapen equator, lens morphology is normal. If multiple colobomas are present around the lens equator, lens subluxation can result because of lack of zonular support. The light microscopic findings with this disorder include focal zonular

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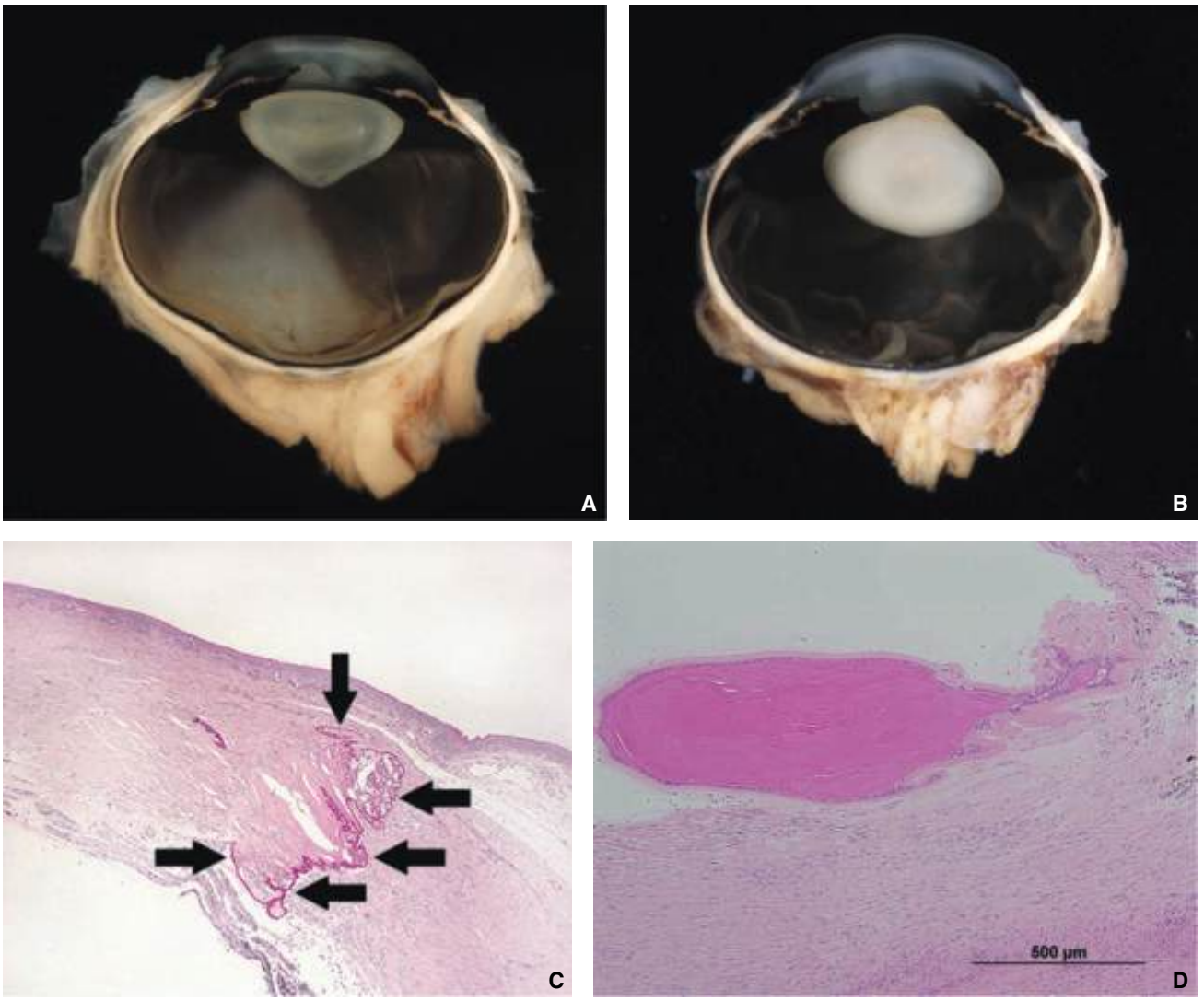


Figure 9.32 **A.** Posterior lenticonus in a calf. This is a congenital protrusion of posterior lens cortex, and the lens capsule might be incomplete in this area. **B**. Anterior lenticonus in a bovine. **C.** Histologic section of a cornea of a puppy with ASD with congenital glaucoma, aphakia, and other ocular anomalies. A periodic acid-Schiff positive basement membrane of varied thickness is embedded in peripheral cornea (arrows). The epithelial cells within the membrane resemble lens epithelium, but misplaced corneal endothelium with Descemet's membrane is also a consideration. (Original magnification 20×. Periodic acid-Schiff.) **D**. This microphakic lens has not separated from the cornea in this dog with ASD. (Magnification 40×. Hematoxylin and eosin.).

aplasia associated with ciliary body colobomas or focal ciliary hypoplasia.

Acquired Ocular Disorders

The pathology of acquired ocular disorders is diverse. The following information has been organized so that each ocular tissue (orbita, conjunctiva, cornea, sclera, uvea, vitreous and retina, optic nerve, and glaucoma) is discussed individually within the broad topics of noninfectious ocular disorders, infectious ocular diseases, degenerative disorders, and conditions presumed to be inherited. Then metabolic and infectious diseases that commonly affect ocular tissues will be summarized, and then finally ocular neoplasia is reviewed.

The topics covered in the degenerative sections have some nebulous overlap with the earlier sections on congenital and inherited developmental diseases. In this section "degeneration" is defined broadly to include: those diseases associated with a nutritional or metabolic basis; toxic conditions; aging changes; changes that occur associated with systemic disease; and those diseases of unknown etiology that are suspected to have a genetic basis but remain somewhat equivocal in regard to cause. Inherited ocular disorders can be congenital or developmental and manifest later in life. This inconsistency in age of initial presentation makes

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classification of inherited congenital, inherited, or breed specific developmental disorders, and some acquired ocular conditions somewhat problematic. Accurate diagnosis of an inherited developmental disorder requires knowledge of breed predispositions, ages of onset, clinical manifestations and appreciation of the primary lesions, and changes that occur secondary to the primary lesion. Confirmation requires test breeding and a pedigree analysis to determine the mode of inheritance. Finally, examination of DNA, RNA, and proteins at a molecular level are required to document the mutation inducing the anomaly. Ophthalmologists categorize many disorders as inherited based on breed predisposition and pedigree analysis because the basic research is often lacking. The descriptions here have been limited to a few disorders that have a unique breed predisposition, a consistent bilateral clinical manifestation, and histologic examination findings that are most consistent with a developmental disorder.

Noninfectious Inflammatory Ocular Disease

Ocular Trauma

Traumatic disease is almost always accompanied by inflammation (Moore et al., 2017; Welihozkiy et al., 2011); the importance of the post-traumatic inflammation varies tremendously. Mechanical trauma includes: accidental perforating and penetrating wounds of the globe, with or without the introduction of microbes and foreign bodies; contusion injuries; and surgical trauma. Physical trauma includes chemical and thermal burns and those changes induced by electromagnetic radiation.

A penetrating wound is one that extends only partway through the tissue of reference; a perforating wound has both an entrance and exit site in the tissue of reference (Fig. 9.33). Thus, a perforating injury to the cornea may be either a penetrating wound of the globe or perforating if the injury extends through the cornea and sclera. With either, the sudden decompression of the globe leads to breakdown of the blood–ocular barrier and protein exudation (Fig. 9.33B). Uveal tissue is drawn into the defect, which it might effectively seal; if not, extrusion of lens, vitreous, and retina can follow. Shearing of the ciliary vessels as they pass from sclera to choroid can occur leading to expulsive subchoroidal hemorrhage that hastens the extrusion of globe contents.

Although small hemorrhages usually resorb without significant sequelae, large and recurrent hemorrhages can stimulate synechiae and membranogenesis as they organize (Fig. 9.33D), lead to hemoglobin-staining of the cornea in the presence of endothelial compromise and elevated intraocular pressure (IOP), and leave behind hemosiderin and cholesterol residues.

The specific lesions that are related to trauma are listed in Table 9.4.

Table 9.4 Ocular lesions associated with accidental or surgical trauma.

Orbit	Edema, hemorrhage
	Orbital bone fractures
Adnexa	Edema, hemorrhage
	Laceration
Globe	Corneoscleral perforation
	Epithelial or fibrous ingrowth (late)
Conjunctiva	Erythema, chemosis, and hemorrhage
	Laceration
Cornea	Epithelial erosion
	Blood staining (with hyphema, endothelial damage, elevated intraocular pressure)
	Penetration/perforation
Anterior uvea	Hyphema
	Trabecular fracture
	Iris sphincter muscle rupture
	Iridodialysis
	Iridoschisis (separation of pigmented epithelium)
	Postcontusion angle deformity
	Cyclodialysis
Lens	Capsular rupture
	Luxation/subluxation with zonular disinsertion
	Cataract
Vitreous	Detachment
	Prolapse (if zonules ruptured)
	Hemorrhage (from retinal vessels)
Retina	Edema
	Hemorrhage
	Necrosis
	Tear/peripheral dialysis/detachment
Optic nerve	Avulsion

Acquired Orbital Disorders

Idiopathic Orbital Inflammatory Syndrome

Historically described in the human ophthalmic pathology literature as "pseudotumor," this process occurs rarely in animal species. By definition, it is a benign nongranulomatous, noninfectious inflammatory process characterized by a diffuse lymphocytic plasmacytic orbital cellulitis and fibrosis with chronicity.

Cases previously reported as orbital pseudotumor in cats would now most likely be diagnosed as feline restrictive orbital myofibroblastic sarcoma (Bell et al., 2011; Billson et al., 2006; Miller et al., 2000). Histologic examination reveals orbital fibrosis and lymphocytic/plasmacytic orbital inflammation. This condition is progressive and manifests

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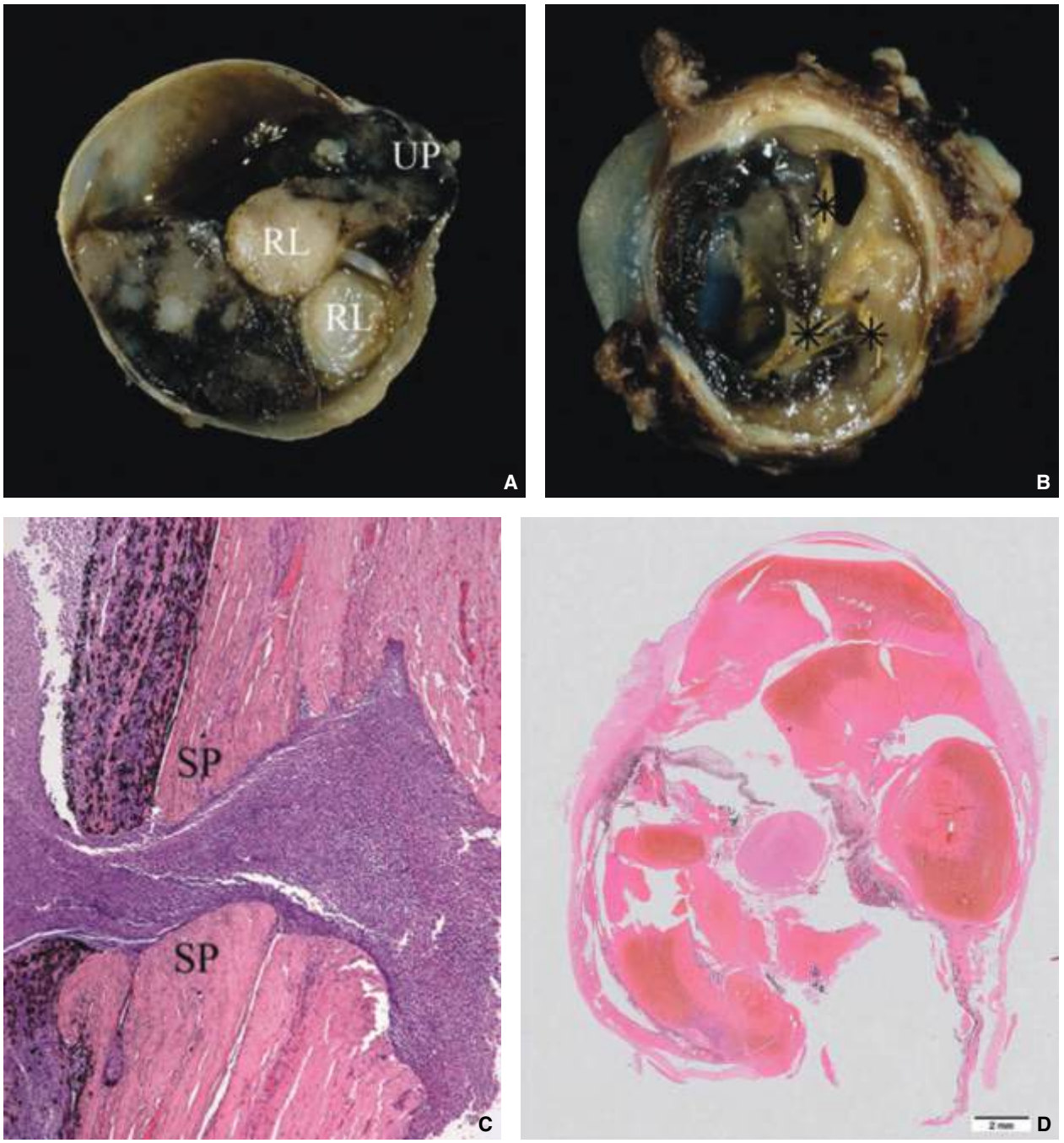


Figure 9.33 **A.** This cat eye sustained penetrating and perforating trauma. Note the thin discontinuous sclera with the uveal plug (UP), the ruptured lens (RL), and major disruption of the intraocular contents. **B**. Plant foreign bodies within the vitreous of this dog's eye. Spear grass seeds (asterisks) will occasionally penetrate and then perforate the sclera and induce a fulminant endophthalmitis. **C**. Endophthalmitis and scleral perforation (SP) in a dog with penetrating trauma and septic endophthalmitis. Note the streaming of inflammatory exudates through the choroidal and scleral perforation. (Original magnification 200×. Hematoxylin and eosin.). **D**. Blunt ocular trauma often induces significant intraocular hemorrhage with disruption of most ocular tissues like this canine globe.

histologically with a diffuse spindle cell infiltration with variable collagen accumulation around the episcleral tissues.

Orbital Cellulitis/Abscess

Orbital cellulitis/abscess is a suppurative process with multiple causes including: sharp foreign bodies that penetrate the oral cavity behind the upper last molars, the eyelids, or conjunctiva; foreign body migration (porcupine quills) (Grahn et al., 1995b); self-inflicted wounds (hedgehogs) (Wheler et al., 2002); cat bite wounds; hematogenous seeding of bacteremia; or extension of diseased adjacent tissues (Grahn et al., 1995a). Although clinical signs and imaging

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are usually definitive, fine needle aspirates and orbital biopsies can be used to confirm the diagnosis. Acutely, this condition is largely neutrophilic; with time, the infiltrate will become mixed, with macrophages, lymphocytes, and plasma cells predominating.

Masticatory Myositis

Masticatory and extraocular myositis occurs in large breeds of dogs (Allgoewer et al., 2000; Carpenter et al., 1989). Initially, exophthalmos is related to compression of the orbital contents by the inflamed muscles of mastication, and chronically enophthalmos results from atrophy of both muscle and orbital tissues. Histopathology reveals that the orbital tissues are edematous and infiltrated diffusely with lymphocytes, plasma cells, and eosinophils secondary to the masticatory myositis (Fig. 9.34). Muscle degeneration and inflammation predominate initially, with muscle atrophy a sequela in chronic cases.

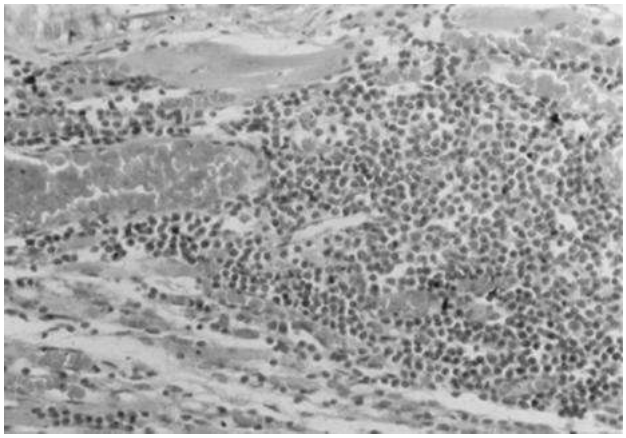


Figure 9.34 Extraocular myositis in a young Golden Retriever. There are dense infiltrations of lymphocytes and plasma cells within the rectus muscles. (Original magnification 100×. Hematoxylin and eosin.)

Orbital Cysts and Mucoceles

Orbital and periorbital cysts occur in young animals and most commonly arise from dysplastic lacrimal tissue (Grahn & Mason, 1995; Martin et al., 1987). Light microscopic examination reveals thin-walled cysts lined by a bilayered epithelium containing serous fluid (Fig. 9.35). Zygomatic mucoceles are identified by nonencapsulated mucinous secretions dissecting through the orbit and periorbital soft tissues.

Degenerative Orbit Disorders

Enophthalmos secondary to atrophy of periorbital muscles/adipose tissue is a common sequel to chronic extraocular myositis and orbital cellulitis, and also occurs with aging. Histopathologic alterations include atrophy and fibrosis of the orbital tissues including the extraocular muscles; sequelae to cases caused by myositis or cellulitis often have an inflammatory footprint.

Presumed Inherited Orbital Conditions

Proptosed globes induce significant orbital cellulitis and extraocular myositis and most commonly occur in brachycephalic dogs with shallow orbits and large eyelid fissures. This most likely has a multifactorial inheritance. Similarly, extraocular myositis of Golden Retrievers, eosinophilic masticatory myositis of German Shepherd dogs and Weimaraners, and craniomandibular osteopathy of West Highland and Scottish Terriers are bilateral immune-mediated predominantly breed-specific conditions which most likely have a genetic etiology or predisposition. Diagnoses of eosinophilic myositis and extraocular myositis are confirmed by biopsy and light microscopic examination

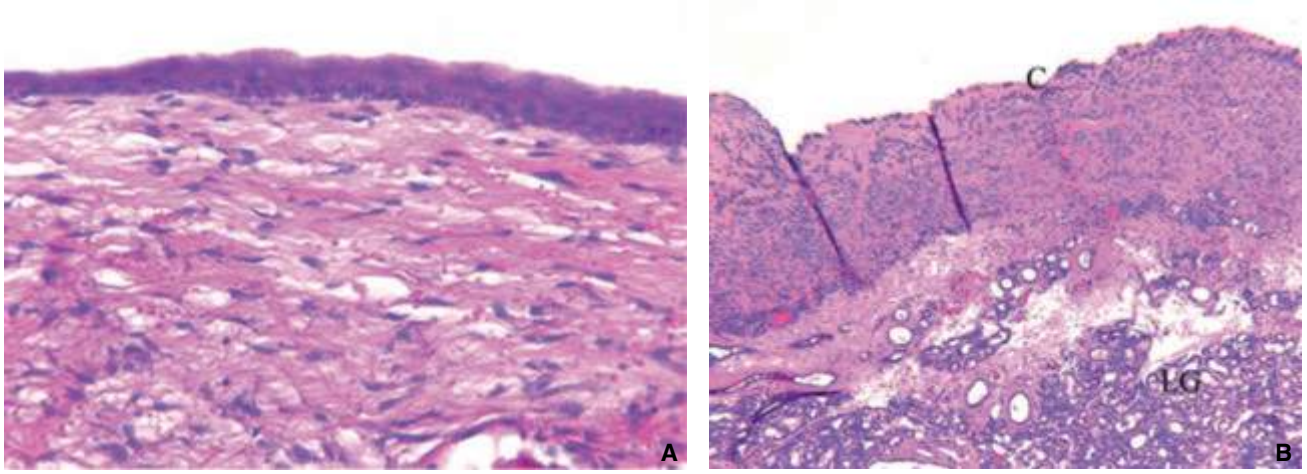


Figure 9.35 **A.** Lacrimal gland cyst with a bilayered lining of cuboidal epithelial cells and fusiform myoeithelium. (Original magnification 200×. Hematoxylin and eosin.) **B.** Lacrimal gland cyst lining (C) that is fibrotic and infiltrated with numerous lymphocytes adjacent to the lacrimal gland (LG) from a dog. (Original magnification 200×. Hematoxylin and eosin.)

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which reveals eosinophilic and lymphocytic plasmacytic myositis, respectively, acutely. When the myositis is chronic, nonspecific fibrosis and atrophy of the affected muscles can be found. The pathogenesis of both disorders is largely unknown; antibodies against 2M muscle fibers have been detected.

Acquired Lacrimal Gland Disease

Degenerative Lacrimal Gland Disorders

Lacrimal gland degeneration develops most commonly secondary to immune-mediated or inflammatory adenitis, and less frequently from toxicities and denervation (Fig. 9.36A). Immune-mediated adenitis is lymphoplasmacytic, with extension of neutrophils (Fig. 9.36B). Chronically, gland atrophy and fibrosis with smatterings of residual inflammatory cells and keratoconjunctivitis sicca result (Kaswan et al., 1984, 1985; Kern et al., 1988; Martin et al., 1988).

Acquired Conjunctival Disorders

Conjunctivitis

The conjunctiva serves as a mediator of inflammation of the anterior segment. A resident small population of lymphocytes and plasma cells and the occasional mast cell is commonly present. A diagnosis of "conjunctivitis" requires appreciation of other anterior segment changes to determine if the conjunctiva is primarily involved or simply reacting to what is happening with adjacent tissue. Conjunctivitis is characterized acutely by vascular dilation, edema, cellular infiltration, and exudation, which manifests as ocular discharge (Fig. 9.37A). Rarely, pseudomembranes form and are composed of necrotic cells, protein, and fibrin. True membranes result from epithelial necrosis, and removal results in an ulcerative, frequently hemorrhagic lesion. With chronicity, lymphoid follicles often form on the surface (Fig. 9.37B). Although there are diverse etiologies for conjunctivitis, light microscopic changes are generally nonspecific. However, conjunctival biopsies are readily harvested and are potentially useful. Eosinophilia is suggestive of a parasitic disease. In concert with cytology, infectious organisms such as mycoplasma and chlamydia may be identified.

Eosinophilic Keratoconjunctivitis

Eosinophilic keratoconjunctivitis is an idiopathic chronic ocular condition of cats (Fig. 9.13) (Allgoewer et al., 2001) and horses (Lassaline-Utter et al., 2014). The clinical manifestations include conjunctival hyperemia and nonulcerative vascular keratitis with multifocal white to yellow surface granules. The diagnosis is confirmed with light microscopic examination of cytologic specimens or biopsy which reveals a mixed inflammatory infiltrate with variable but prominent numbers of eosinophils accompanied by lymphocytes, plasma cells, and mast cells. The surface granules are thought to represent concretions of mast cell products. A similar condition with identical histologic features can be found in horses.

Lipogranulomatous Conjunctivitis

Multifocal gray to yellow nodules have been reported on the palpebral conjunctiva of cats (Kerlin & Dubielzig, 1997; Read & Lucas, 2001). These have light microscopic features of lipogranulomas with packets of free lipid delineated by pillars of giant cells, macrophages, and a sparse number of neutrophils and lymphocytes. The pathogenesis is not

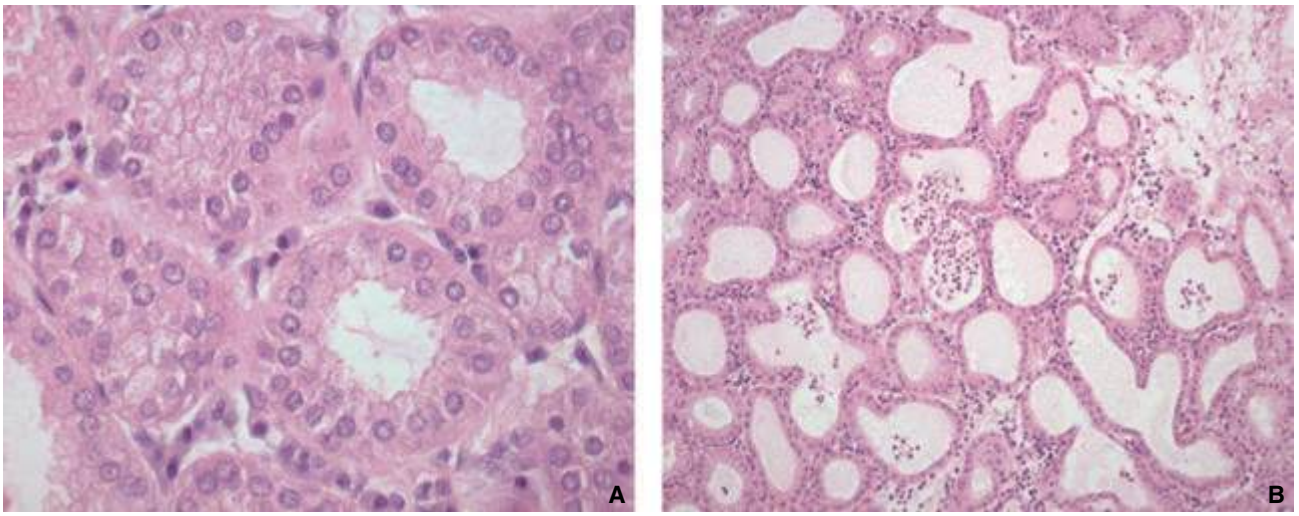


Figure 9.36 **A.** Normal canine lacrimal gland. Note the acinar structure and occasional periacinar lymphocytes and plasma cells. (Original magnification 60×. Hematoxylin and eosin.) **B.** Lacrimal gland adenitis with neutrophil infiltration. (Original magnification 20×. Hematoxylin and eosin.)

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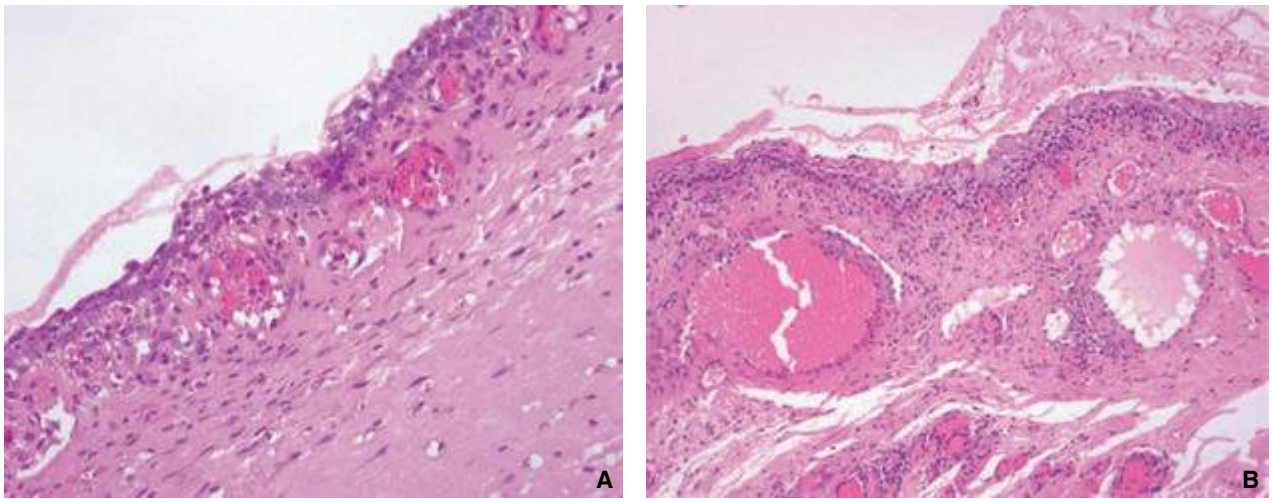


Figure 9.37 **A.** Acute conjunctivitis in a dog. Note the vasodilation congestion and neutrophilic infiltration. (Original magnification 200×. Hematoxylin and eosin.) **B.** Chronic conjunctivitis in a dog. Note the proteinaceous surface exudate, vasodilation, and diffuse mononuclear cell infiltrate (Original magnification 200×. Hematoxylin and eosin.)

known but speculated to be related to meibomian gland dysfunction and ultraviolet radiation.

Miscellaneous Conjunctival Disorders Including Goblet Cell Atrophy, Conjunctival Overgrowth, and Conjunctival Sequestrae

Deficiency of tear film mucin has been reported in both dogs and cats (Cullen et al., 1999; Grahn et al., 2005; Moore et al., 1987). The clinical manifestations include conjunctivitis and keratitis. The light microscopic examination of bulbar conjunctival biopsies typically reveals reduced numbers of goblet cells in all quadrants and a mild nonspecific lymphocytic plasmacytic conjunctivitis (Fig. 9.38). PAS sections facilitate goblet cell assessment, and normal ratios of goblet cells to basal epithelial cells by quadrant have been reported (Cullen et al., 1999; Grahn et al., 2005).

Conjunctival overgrowth is an unusual idiopathic condition of rabbits that manifests clinically with a fold of redundant conjunctiva that develops circumferentially around the peripheral cornea (Fig. 9.39A). Light microscopic findings include a fold of conjunctiva that originates from the limbus and extends axially across the cornea. The epithelium on the leading edges of the overgrowth and the cornea is occasionally noted to be hyperplastic (Fig. 9.39B). A mild lymphocytic plasmacytic cell infiltrate is often present but not considered significant.

Sequestrae of the conjunctiva (including the third eyelid and conjunctival grafts) occur in cats and are similar

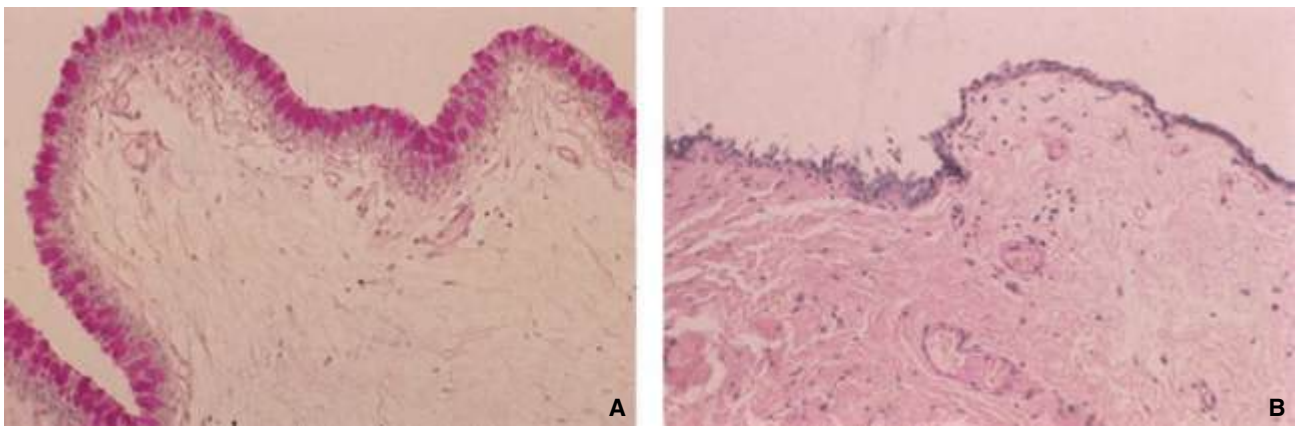


Figure 9.38 **A.** A conjunctival biopsy from the conjunctival fornix of a normal cat. (Original magnification 50×. Periodic acid-Schiff.) **B.** A conjunctival biopsy from a cat with goblet cell atrophy. Compare this photo with an age-matched control cat in **A**. (Original magnification 50×. Periodic acid-Schiff.) (*Source:* Reprinted with permission from Cullen, C.L., Njaa, B.L. & Grahn, B.H. (1999) Ulcerative keratitis associated with qualitative tear film abnormalities in cats. *Veterinary Ophthalmology*, **2**, 197–204.)

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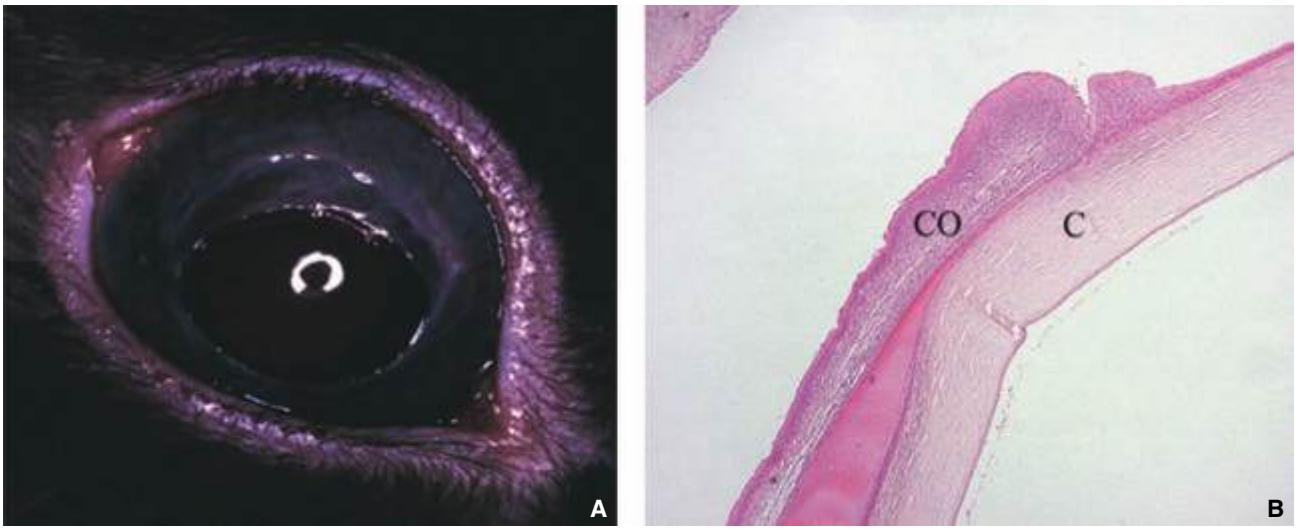


Figure 9.39 **A.** Conjunctival overgrowth in rabbit. **B.** Histologic appearance of conjunctival overgrowth (CO) in the rabbit noted in **A**. Note the plicated conjunctiva overlying the cornea (C) and hyperplastic corneal epithelium at the leading edge. (Original magnification 100×. Hematoxylin and eosin.)

histologically to corneal sequestrum; the reader is referred to the section on Corneal Sequestrae for a more complete description.

Conjunctival Disorders That Are Presumed Inherited

Ligneous conjunctivitis is a manifestation of a suspected inherited disease of Doberman Pinscher dogs and Golden Retrievers (McLean et al., 2008; Ramsey et al., 1996). The clinical presentation is dramatic with thickening of the conjunctiva with yellow-gray membranes. Ulcerative lesions of other mucous membranes and proteinuria often occur concurrently. The surface of the conjunctiva is often encased in purulent debris and fibrin (Fig. 9.40) with an amorphous hyaline membrane in the substantia propria and diffuse lymphocyte infiltration. The condition is related to a plasminogen deficiency, and the prognosis is poor (McLean et al., 2008).



Figure 9.40 Ligneous conjunctivitis in a Doberman Pinscher. Note the hyperemic conjunctivitis and fibrinous conjunctival discharge. (Courtesy of Lynne Sandmeyer.)

Acquired Conditions of the Cornea

Keratitis

Inflammatory disease of the cornea is meaningfully classified as either ulcerative or nonulcerative and superficial or deep (stromal).

Nonulcerative Keratitis

Acute inflammation is characterized by edema associated with loss of epithelial integrity and/or compromise of the limbal blood vessels. Neutrophilic infiltrate gains access from the conjunctiva via the tear film or migration from limbal vessels. With chronicity, the nature of the infiltrate changes, neovascularization from limbal blood vessels occurs, and scarring and epithelial pigmentation often develop (Fig. 9.41).

Ulcerative Keratitis

Ulcerative keratitis can be classified as simple, indolent, and complex. As simple ulcers are superficial, they are seldom examined histologically unless they are incidental to another globe-threatening disorder. The histologic findings include absence of epithelium with associated edema and sparse neutrophilic infiltrate. Indolent, or slow or nonhealing corneal ulcers (superficial chronic corneal epithelial defects) are best categorized as primary (idiopathic) or secondary to

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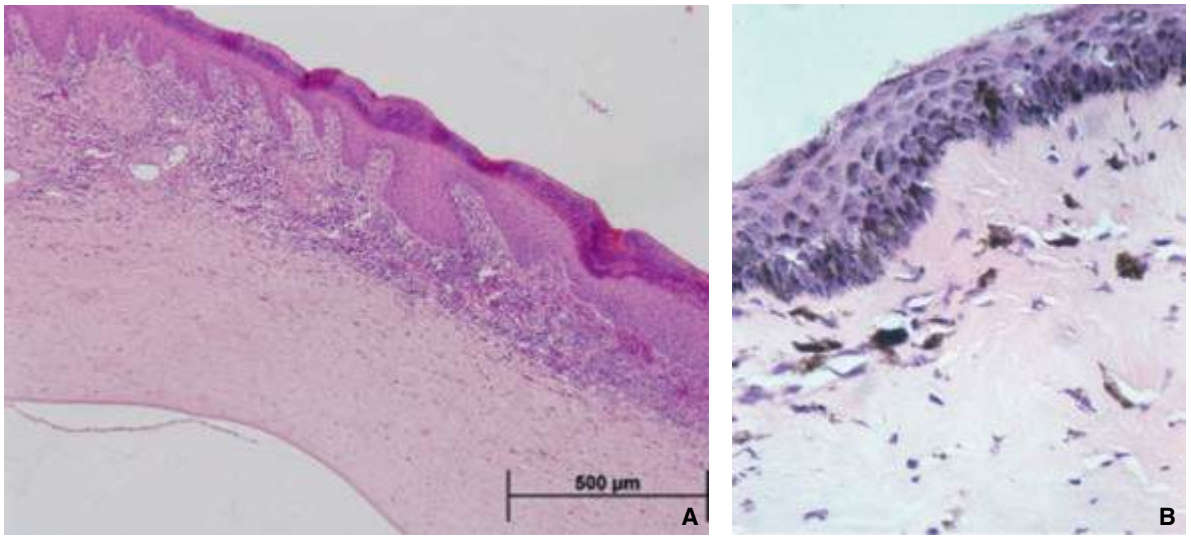


Figure 9.41 **A.** Chronic keratitis in any species can induce chronic changes in the cornea to the extent that the cornea begins to resemble skin, or epidermalization. The epithelium thickens and rete peg projections develop. Dyskeratosis can occur. The underlying stroma demonstrates fibrovascular ingrowth, and there is a zonal lymphocytic and plasmacytic infiltrate. (Original magnification 100×. Hematoxylin and eosin.). **B.** Pigmentary keratitis that develops in a medial to temporal progression is common in brachycephalic dogs with shallow orbits and an enlarged palpebral fissure. Light microscopy reveals epithelial and subepithelial melanocyte hypertrophy and hyperplasia and subepithelial scarring and vascularization. (Original magnification 400×. Hematoxylin and eosin.)

a known cause, that is, tear film abnormality, conjunctival or eyelid foreign body or cilia, or breed associated (notably Boxer dogs). The epithelium at the margins is elevated off the stroma; cellular disorganization is manifested by loss of polarity and epithelial cellular eddies. The basement membrane is often absent or thickened. An acellular zone is usually present on the denuded corneal surface (Fig. 9.42). Although the ulcer is focal (usually) the entire cornea is involved in the underlying condition. The pathogenesis is unknown, with possible origins including defects in epithelial cell hemidesmosomes, basement membrane, or underlying stroma (Bentley et al 2001; Gelatt & Samuelson, 1982; Hempstead et al., 2014; Jegou & Tromeur, 2015; Kirschner et al., 1989; La Croix et al., 2001). Complex corneal ulcers typically involve loss of stroma, can have a robust neutrophilic infiltration, and exhibit variable collagenolysis (Fig. 9.43); infectious agents are often identified with special stains. Progression to perforation and associated complications is a frequent finding in enucleated globes.

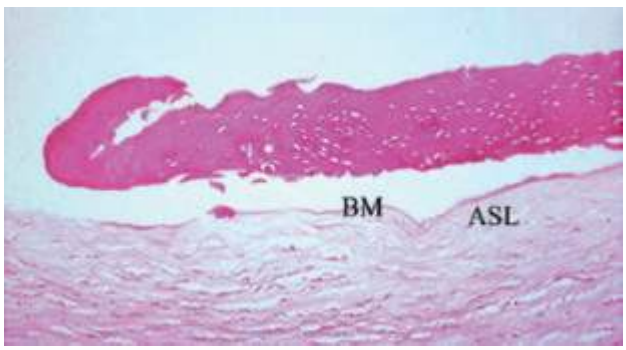


Figure 9.42 An indolent corneal ulcer in a Boxer dog. Note the epithelial nonadherence, irregular thickened basement membrane (BM), corneal edema, and the relatively acellular subepithelial stromal layer (ASL). (Original magnification 100×. Hematoxylin and eosin.)

Corneal Inclusion Cysts

Occasionally, corneal epithelium becomes displaced by trauma into the corneal or conjunctival stroma and rarely into the eye (Fig. 9.44). The epithelium then proliferates, resulting in an inclusion cyst. These cysts have a yellow-gray appearance clinically and contain desquamated epithelial cells and are lined by corneal epithelium. The diagnosis is confirmed by light microscopic confirmation of an epithelial-lined cyst within the cornea or the presence of epithelium growing across intraocular surfaces.

Degenerative Corneal Disorders

Degenerative corneal disease includes pigmentary keratitis (Fig. 9.41B), calcific degeneration (Fig. 9.45A), and lipid degeneration (Fig. 9.45B) and occurs in dogs, horses, and cats (Berryhill et al., 2017). The majority of corneal degenerations are the product of chronic keratitis (including that seen with exposure keratopathy or keratoconjunctivitis sicca), and the primary etiology might not be evident histopathologically.

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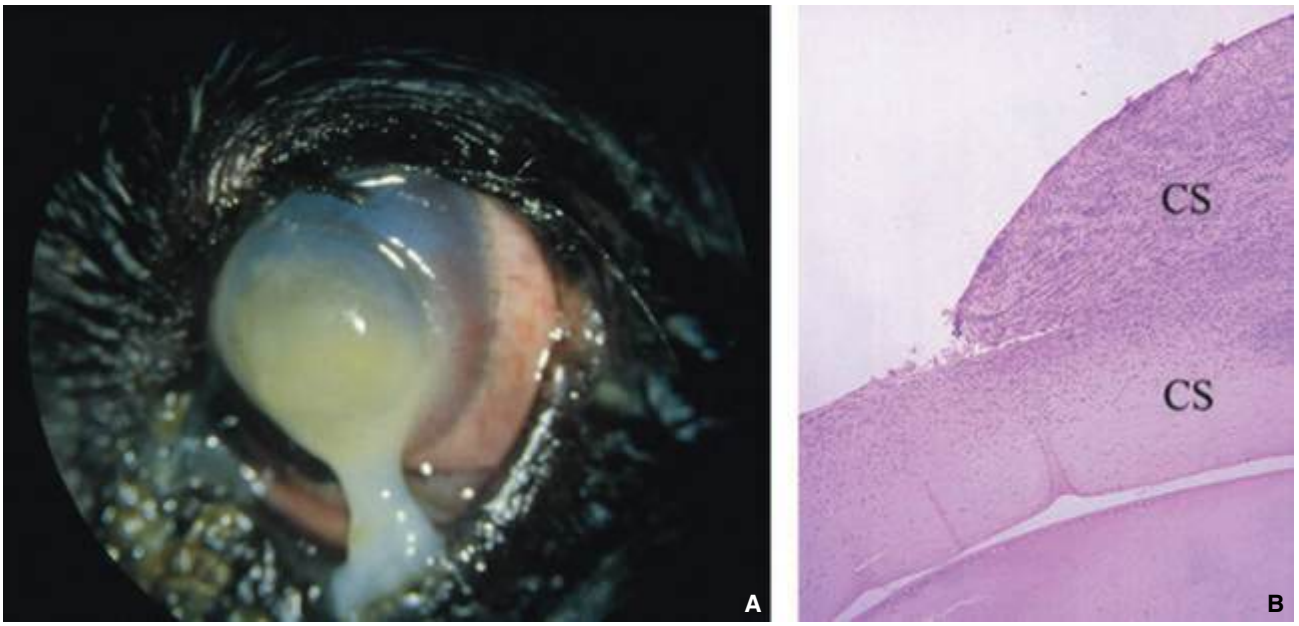


Figure 9.43 **A.** Collagenolysis of the cornea in dog. A large deep ulcer is present with a mucopurulent stream of liquefied collagen extending off the inferior edge. **B.** Histopathology of a melting cornea shows absence of corneal epithelium, neutrophilic infiltration throughout the corneal stroma, loss of corneal stroma (CS) secondary to collagenolysis, and plasmoid aqueous. (Original magnification 250×. Hematoxylin and eosin.)

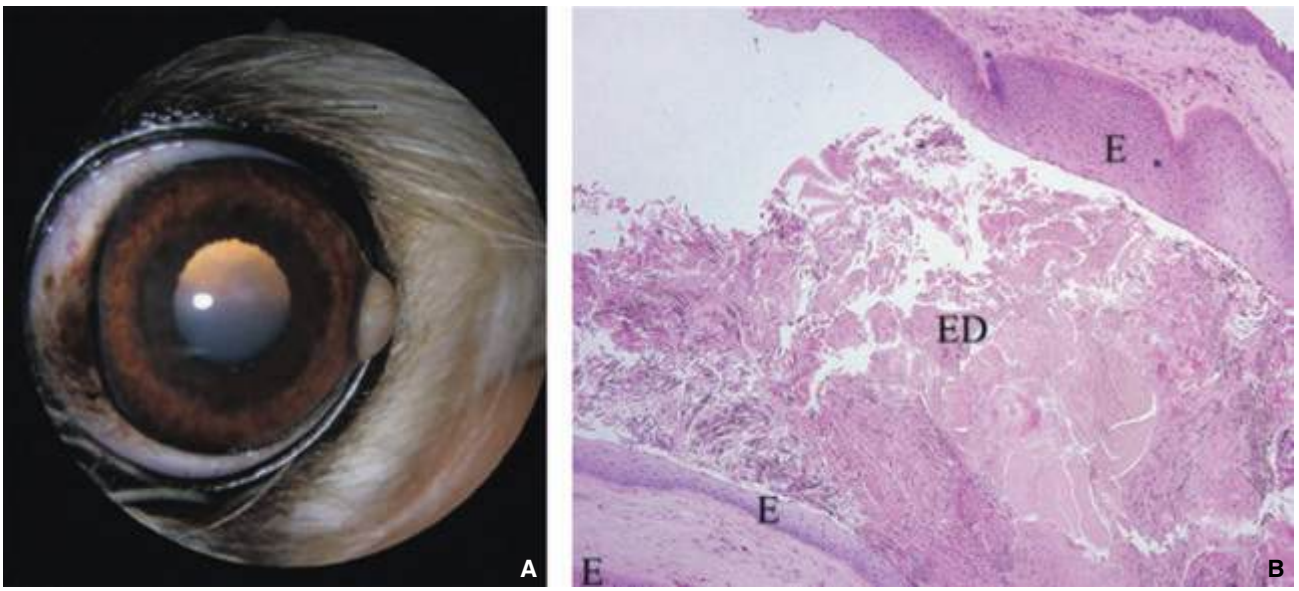


Figure 9.44 **A.** A corneal epithelial inclusion cyst in a Miniature Poodle. **B.** Histologic section of corneal epithelial inclusion cyst noted in **A**. Epithelial inclusion cysts are lined by a nonkeratinized epithelium (E) and contain desquamated epithelial debris (ED). (Original magnification 100×. Hematoxylin and eosin.)

Corneal Sequestrae

Corneal sequestrae are common in cats. Variant lesions have rarely been described in horses and dogs. In cats, sequestrae manifest as a golden to dark brown discoloration of the corneal stroma. Etiology is unknown; association with feline herpesvirus-1 infection and corneal ulceration has been hypothesized, and Persians and Himalayans are predisposed. Histologic features include a loss of keratocytes with stromal hyalinization and an amber pink coloration on hematoxylin and eosin-stained sections (Fig. 9.46). The corneal lesion commonly involves the anterior stroma, but full-thickness lesions including Descemet's membrane occur. PAS stains

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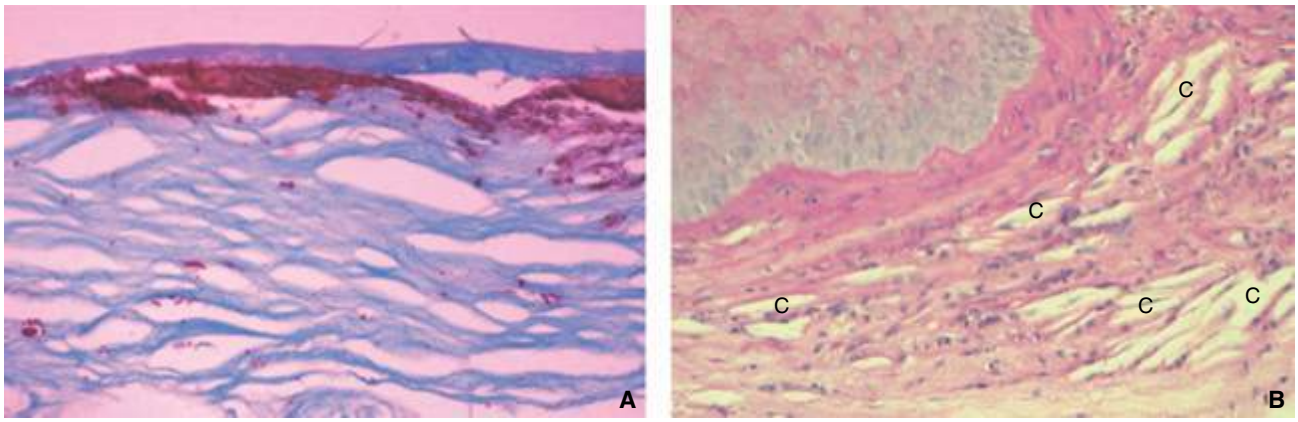


Figure 9.45 **A.** Calcific corneal degeneration in a dog. Calcium appears as a red granular supbepithelial deposit. (Original magnification 250×. Alizarin red stain.) **B.** Lipid corneal degeneration in a dog. Note stromal clefts (C) where lipid was present before processing and the diffuse infiltration of lymphocytes and plasma cells and neutrophils. (Original magnification 250×. Periodic acid-Schiff.)

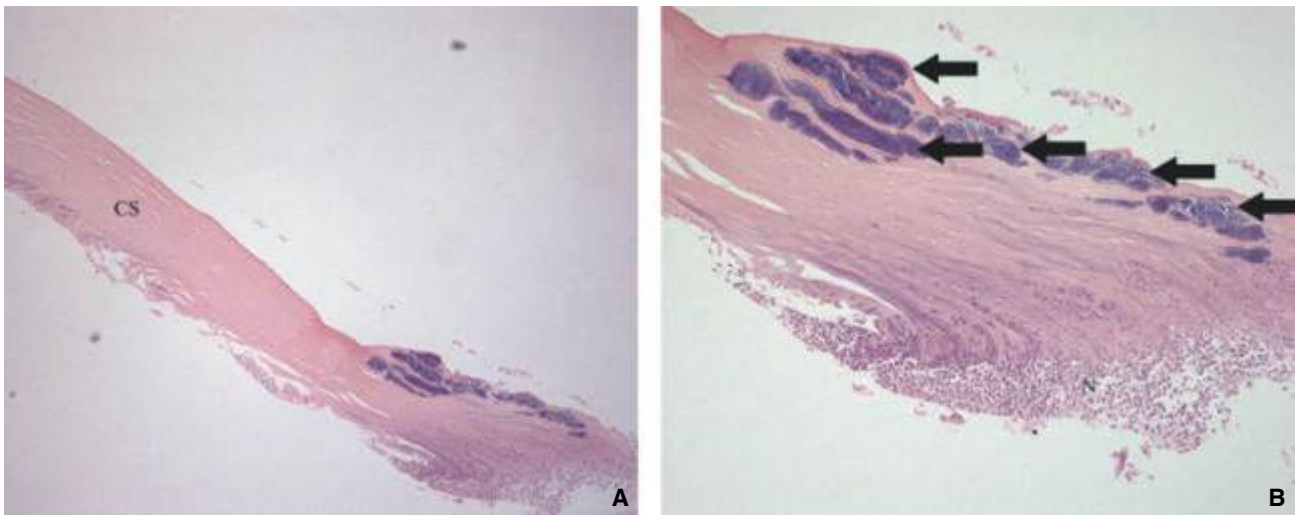


Figure 9.46 **A.** A feline corneal sequestrum (CS) with characteristic amber color and stromal acellularity and compaction. (Original magnification 50×. Hematoxylin and eosin.) **B.** The edge of the sequestrum in **A** with numerous degenerating neutrophils (N) invading the edge of and colonies of bacteria (arrows) present near the surface of this sequestrum. (Hematoxylin and eosin. Original magnification 200×.)

identify granules in the degenerate keratocytes and suggest an autolytic process. The source of the discoloration is not known (Featherstone et al., 2004; Newkirk et al., 2011). With chronicity, stromal vascularization and inflammatory infiltrates encompass the sequestrum (Fig. 9.46B).

Bullous Keratopathy in Cats

An idiopathic condition characterized by uni- or bilateral formation of large corneal stromal bullae occurs in cats. Histologically, stromal fibers are separated by clear fluid and the endothelium appears normal. Mild inflammatory infiltrates are present with neutrophils the most common.

Inherited Corneal Disorders

Corneal dystrophy occurs in many species. For example, corneal dystrophy in rabbits and rodents likely has a genetic basis; incidence varies depending on strain. Histologic features include calcification of the basal lamina and an overlying epitheliopathy. The following discussion will focus on dogs.

Corneal Stromal Dystrophies

Corneal stromal dystrophies are inherited stromal metabolic defects that result in the accumulation of extracellular and intracellular lipid in many breeds of dogs (Ekins et al., 1980;

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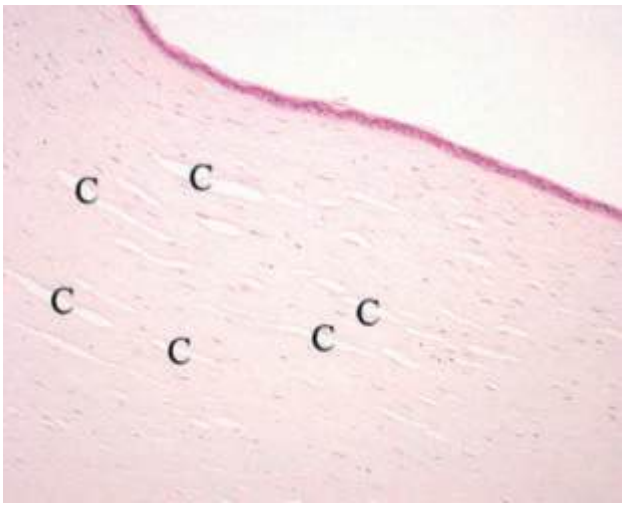


Figure 9.47 Inherited corneal dystrophy in a young American Cocker Spaniel. A band of subepithelial clefts (C) are present where lipid that was dissolved during processing was present. This lesion is easily mistaken as stromal artifact; however, the lesion was bilaterally symmetric and the clefts larger than the artefactual separations of fixation. (Original magnification 50×. Periodic acid-Schiff.)

MacMillan et al., 1979; Martin & Dice, 1982; Morrin et al., 1982; Rubin, 1989; Spangler et al., 1982; Waring et al., 1986). The light microscopic findings are subtle with spherical to elliptical clefts situated between the collagen fibers in the superficial and mid stroma and less commonly in the deep stroma (Fig. 9.47). Stromal keratocytes in affected corneas appear degenerate, necrotic, or normal. Frozen sections of affected cornea stained with lipid stains, including oil red O, reveals extracellular and intracellular lipid. Differentiation from the morphologically similar lipid degeneration that occurs secondary to chronic keratitis, episcleritis, or at the corneal margin of a limbal melanocytoma is facilitated by identification of an initiating factor.

Corneal Endothelial Dystrophy

Corneal endothelial dystrophy manifests as corneal edema. Predisposed breeds of dogs include the Boston Terrier, Poodle, Chihuahua, Dachshund, and Shih Tzu (Gwin, 1982; Rubin, 1989). Clinically, stromal and epithelial edema with bullae and ulceration, vascularization, and pigmentation are evident. The pathogenesis appears to involve endothelial apoptosis that allows the pressure gradient of IOP to overwhelm the remaining endothelial pump function, and corneal decompensation and edema develop. The edema often begins in the paracentral or temporal areas and progresses across the entire cornea. The histologic features include extensive corneal edema detected by the presence of intra- and intercellular edema and subepithelial bullae, thickening of the corneal stroma with dampening of tinctorial quality and notable decreases in common artefactual fixation-induced intercollagenous clefts, thickening of Descemet's membrane by a retrocorneal membrane, and depletion and fibrous metaplasia of endothelial cells (Fig. 9.48).

Corneal Subepithelial Dystrophy

Corneal subepithelial dystrophy is also known as epithelial erosion syndrome and superficial punctate keratopathy. This condition is likely inherited in Shetland Sheepdogs and

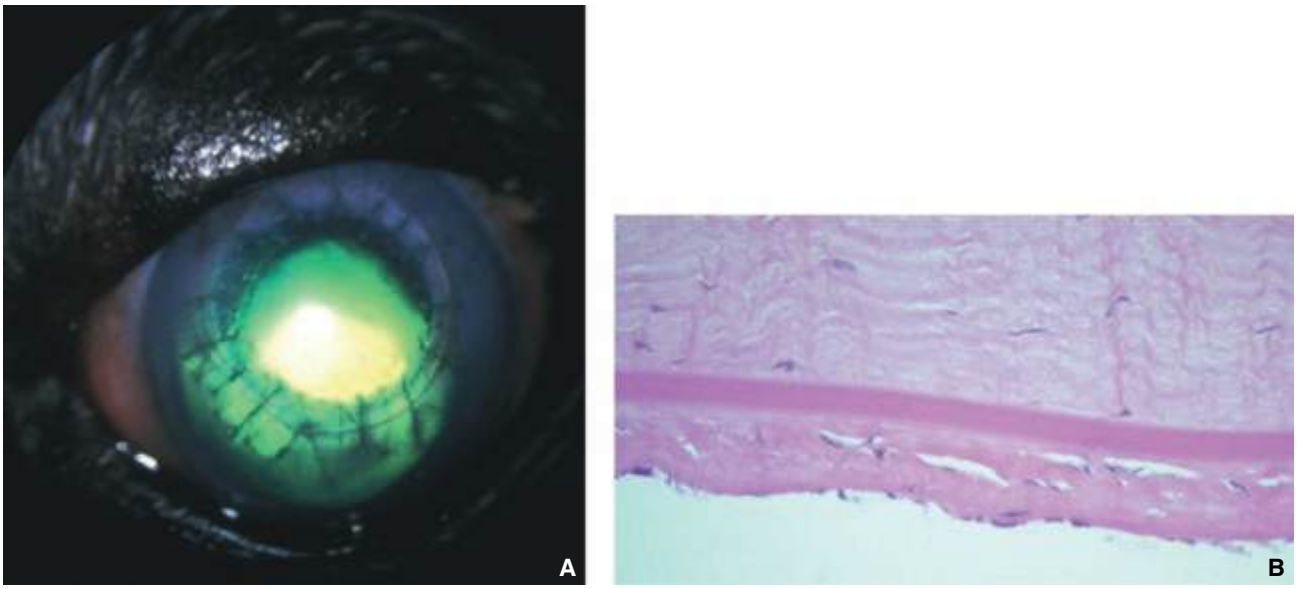


Figure 9.48 **A.** A Boston Terrier with endothelial dystrophy following corneal transplantation contrasting the central clear button with peripheral diffuse corneal edema. **B.** The diseased cornea of the dog in **A** was characterized by a depletion of endothelial cells. Fibrous metaplasia has formed a fibrous retrocorneal membrane. (Original magnification 300×. Hematoxylin and eosin.)

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Dachshunds (Rubin, 1989). The pathogenesis might involve a metabolic defect that induces multifocal punctate lipid deposits around and beneath the epithelial cells. This condition manifests with focal corneal rings and spots with white to yellow margins. The histologic manifestations have not been reported but likely include subepithelial lipid and mineral infiltrates.

Chronic Superficial Keratitis (Pannus)

Chronic superficial keratitis (pannus) is a bilateral symmetrical immune-mediated nonulcerative keratitis that may have a genetic component and manifests primarily in the German Shepherd dog, Greyhound, and several other large breed dogs (Rubin, 1989). In those rare instances when the cornea is examined histologically, there is edema, vascularization, pigmentation, and mineralization (Fig. 9.49). The inflammatory cell infiltrate is mixed and includes lymphocytes and plasma cells that array along the epithelial basement membrane.

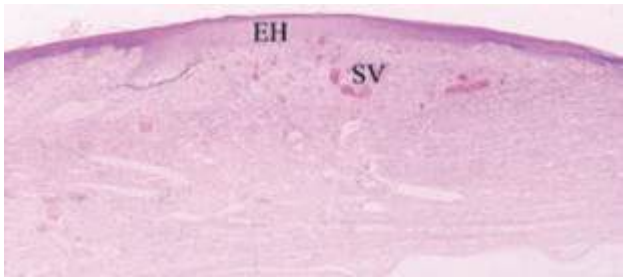


Figure 9.49 Chronic superficial keratitis in a dog. Note the nonspecific epithelial hyperplasia (EH), pigmentation, and undulating epithelial basement membrane, and stromal vascularization (SV) and scarring. (Original magnification 100×. Hematoxylin and eosin.)

Acquired Disorders of the Sclera

Episcleritis and Scleritis

Inflammation of the sclera and episclera is classified by location (anterior vs. posterior), as diffuse or nodular, as granulomatous or nongranulomatous, and as necrotizing or non-necrotizing (Fig. 9.50).

Scleritis typically is characterized by macrophages palisading about degenerating collagen fibrils and may be accompanied by discrete uveal granulomas or extend to involve adjacent uvea in a diffuse inflammatory process (Breaux et al., 2007; Day et al., 2008; Denk et al., 2012; Williams et al., 2005). Scleral necrosis (degeneration is a more appropriate term) and malacia with perforation can occur and is considered pathognomonic for necrotic scleritis (Fig. 9.51). The majority of primary scleritis cases are immune-mediated processes localized to the eye.

Presumed Inherited Episcleral Disorders

Nodular episclerokeratitis (which may involve the conjunctiva as well) is a bilateral inflammatory disorder that is unique to the Collie dog (Deykin et al., 1997; Paulsen et al., 1987). The clinical manifestations include bilateral nodular pink masses that commonly develop near the temporal limbus, cornea, or third eyelid (Fig. 9.50A). Excisional biopsies reveal a diffuse mixed inflammatory infiltrate with lymphocytes, plasma cells, macrophages, and fibroblasts (Fig. 9.50B). The pathogenesis is assumed to be immune-mediated based on the response to immunomodulators.

Bilateral episcleritis is diagnosed commonly in American Cocker Spaniels. Light microscopy reveals a diffuse mixed inflammatory cell infiltrate that targets the episcleral tissues similar to nodular episclerokeratitis in Collies. It is assumed

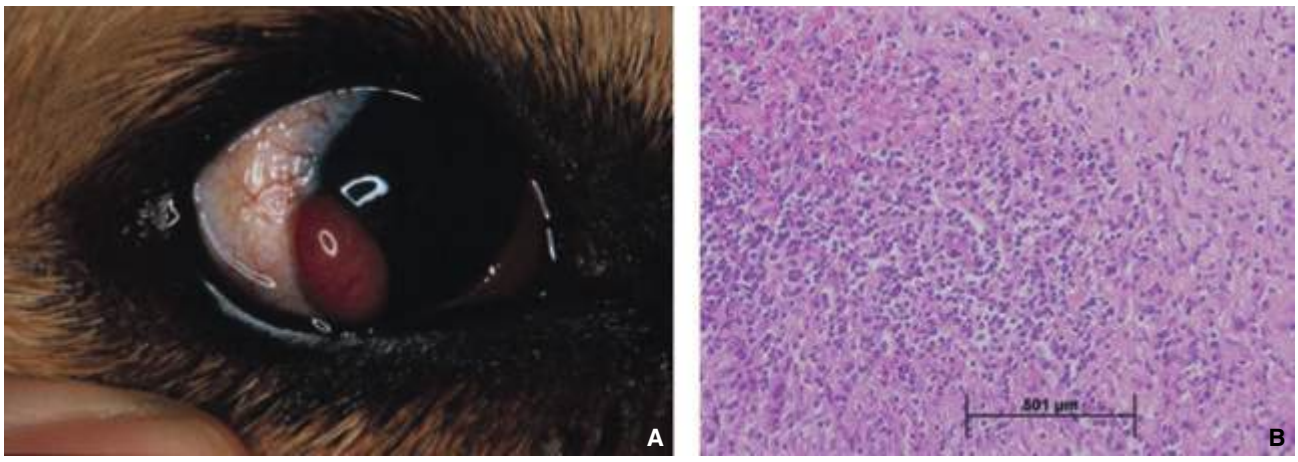


Figure 9.50 **A.** Nodular episclerokeratitis in a Collie. **B.** The light microscopic manifestations are nonspecific and consistent with all forms of episcleritis and include a mixture of lymphocytes, plasma cells, macrophages, fibroblasts, and occasional neutrophils. (Magnification 200×. Hematoxylin and eosin.)

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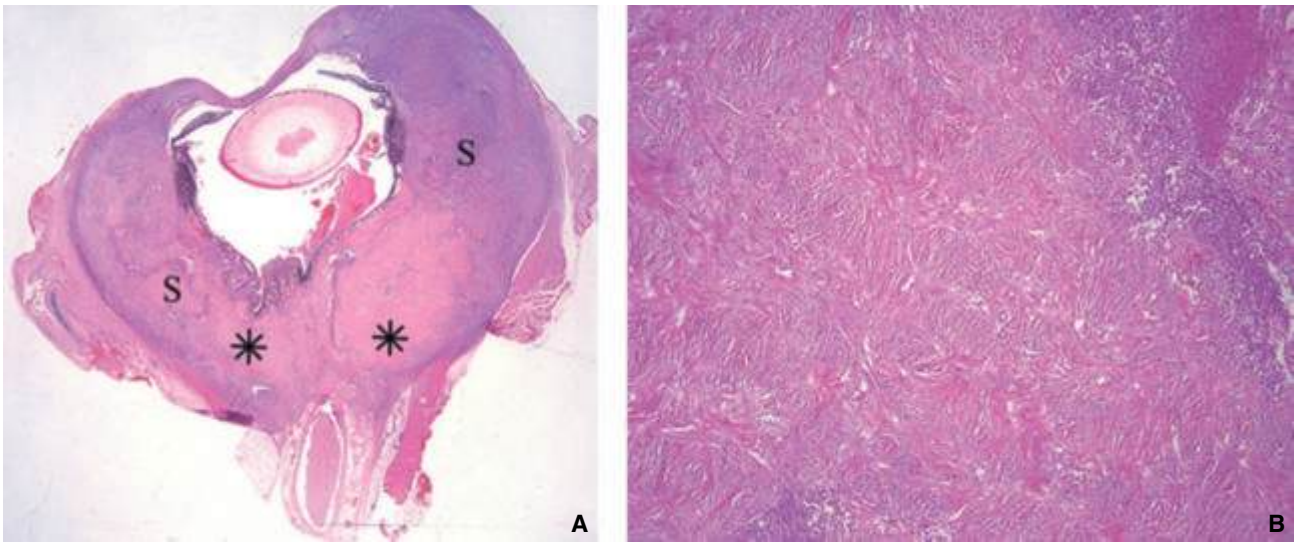


Figure 9.51 **A.** Canine globe with necrotic scleritis. Note the extensive thickened sclera (S) and eosin-stained patches characteristic of collagen degeneration (*). (Original magnification 2×. Hematoxylin and eosin.) (Courtesy of Brian Wilcock.) **B.** Collagen degeneration in necrotic scleritis which is a nonspecific finding as it is also found in non-necrotizing scleritis cases. Note the eosinophilic staining of the scleral collagen fibers, the lack of sclera cells, and the bands of dark blue inflammatory cells near the edges. Examination at higher magnification revealed lymphocytes, plasma cells and macrophages, and occasional neutrophils. (Original magnification 100×. Hematoxylin and eosin.)

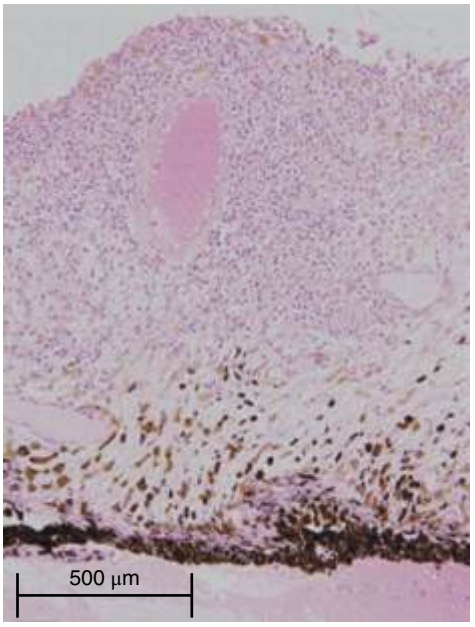


Figure 9.52 Lymphoplasmacytic uveitis in a cat diagnosed with secondary glaucoma. Note the perivascular cellular infiltrate in the iris that extended into the trabecular meshwork. (Original magnification 200×. Hematoxylin and eosin.)

to be immune-mediated based upon histology and response to immunosuppression.

Acquired Inflammatory Uveal Disorders

Lymphoplasmacytic uveitis is a common nonspecific histologic diagnosis in animals (Bergstrom et al., 2017; Jinks et al., 2016). The classic histologic features include diffuse or nodular infiltrates of lymphocytes and plasma cells in the anterior (Fig. 9.52) and occasionally the posterior uvea (choroid). Granulomatous uveitis occurs infrequently (see Fig. 9.69A, B). Several accompanying ocular disorders include glaucoma, ulcerative and nonulcerative keratitis, hyalitis, vitreous degeneration, and cataract.

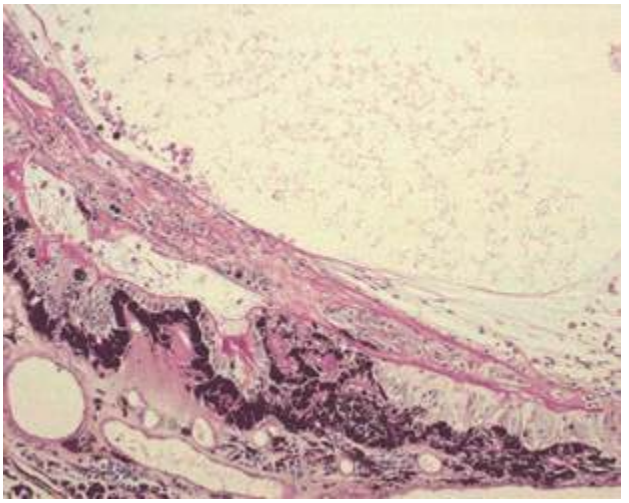


Figure 9.53 Equine recurrent uveitis. A fibrovascular membrane incorporates the ciliary processes and neutrophils and lymphocytes extend from the ciliary body into the vitreous which contains fibrin as well. (Original magnification 200×. Periodic acid-Schiff.)

Equine recurrent uveitis and feline lymphocytic uveitis are common idiopathic conditions characterized by lymphoplasmacytic uveitis (Fig. 9.53). Equine recurrent uveitis in its acute form manifests histologically as a predominantly

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lymphocytic anterior uveal and peripapillary choroidal infiltrate with exudation into the aqueous and vitreous. With chronicity and recurrence, crystalline protein inclusions might be seen ultrastructurally within the ciliary epithelium, and the basal layer of the inverted nonpigmented ciliary epithelial cells are enveloped by amyloid. An accompanying mononuclear perivascular infiltrate will be evident in uvea, retina, and optic nerve (Cooley et al., 1990; Dubielzig et al., 1997).

Heterochromic iridocyclitis has been reported in horses (Pinto et al., 2015), and it is characterized histologically as a lymphocytic uveitis with iridal pigment loss and endotheliitis and keratitis.

In feline lymphoplasmacytic uveitis, two variants, one with and the other without anterior uveal lymphoid nodules, exist (Davidson et al., 1991; Peiffer & Wilcock, 1991). These nodules are largely lymphocytic without follicular differentiation. Many cases will show a granulomatous component with "mutton fat" keratic precipitates that with chronicity can lead to endothelial damage and bullous keratopathy. Secondary glaucoma is common. Inflammatory cells and proteinaceous globules can localize retrolentally and within the peripheral anterior vitreous in a "snow banking" effect caused by cells migrating from the retina where mononuclear perivascular infiltrates are common. The condition has been associated with feline immunodeficiency virus, feline herpesvirus-1, feline leukemia virus, toxoplasmosis, and bartonellosis, but many cases remain idiopathic and are presumed immune mediated in spite of exhaustive diagnostics.

Bovine malignant catarrhal fever is characterized by the accumulation of lymphocytes and lymphoblasts within the subendothelial and adventitial regions of blood vessels. Arterial, arteriolar, and venular necrosis and hemorrhage are also seen (Fig. 9.54). The lymphoid cells often have frequent mitoses. Conjunctiva, uvea, retina, and optic nerve meninges can be involved. The inflammation has been classified as a type IV hypersensitivity reaction.

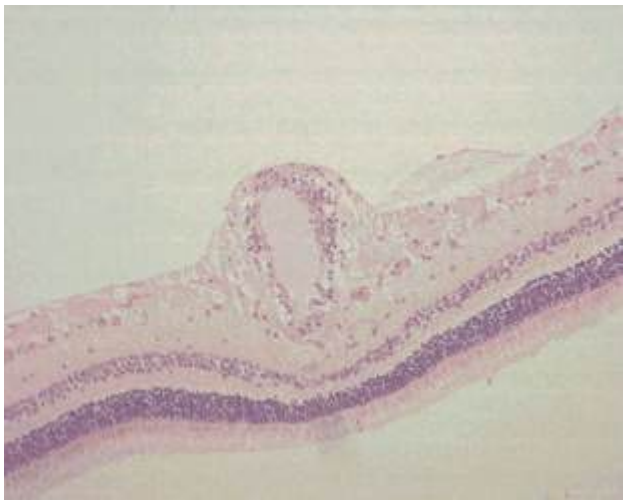


Figure 9.54 Vasculitis in the retina of a cow with malignant catarrhal fever. Note the inflammatory infiltrate within the retinal arterial wall. (Original magnification 250×. Hematoxylin and eosin.)

Lens-Induced Uveitis

Lens-induced uveitis manifests in two forms, phacolytic and phacoclastic in all species. *Phacolytic uveitis* also has two variants: a mild lymphoplasmacytic uveitis and a severe granulomatous anterior uveitis (Fig. 9.55) (van Der Woerdt et al., 1992; Wilcock & Peiffer, 1987). The pathogenesis of both is thought to be caused by liquefied cataractous lens proteins leaking through an intact capsule and initiating the inflammatory response. The light microscopic findings of the mild form include minimal anterior uvea lymphocytic plasmacytic infiltrate and a cataract. The granulomatous version also includes a cataractous lens; however, the uveitis is more severe, and the inflammatory infiltrate includes macrophages, lymphocytes, and neutrophils. The reason for the difference is unknown; the granulomatous variant occurs most commonly in diabetic cataracts with a predisposition for Miniature Schnauzers.

Phacoclastic uveitis presents most often as a granulomatous lens-induced uveitis that follows rupture of the lens capsule with resultant exposure of large amounts of lens protein (Fig. 9.56) (Wilcock & Peiffer, 1987). The capsular rupture occurs after blunt or penetrating (including surgical) trauma, spontaneously with an intumescent cataract (usually diabetic), or associated with infectious agents (*Encepalitizoon caniculi*). The nature of the response is dependent upon species, age, amount and nature of the lens protein exposed, the presence of concurrent microbial endophthalmitis, and duration. The resulting lesion represents a combination of the effects of the initial insult, the immunologic response to the released lens protein, a



Figure 9.55 Severe phacolytic uveitis in a dog. Note the keratic precipitates and hypopyon.

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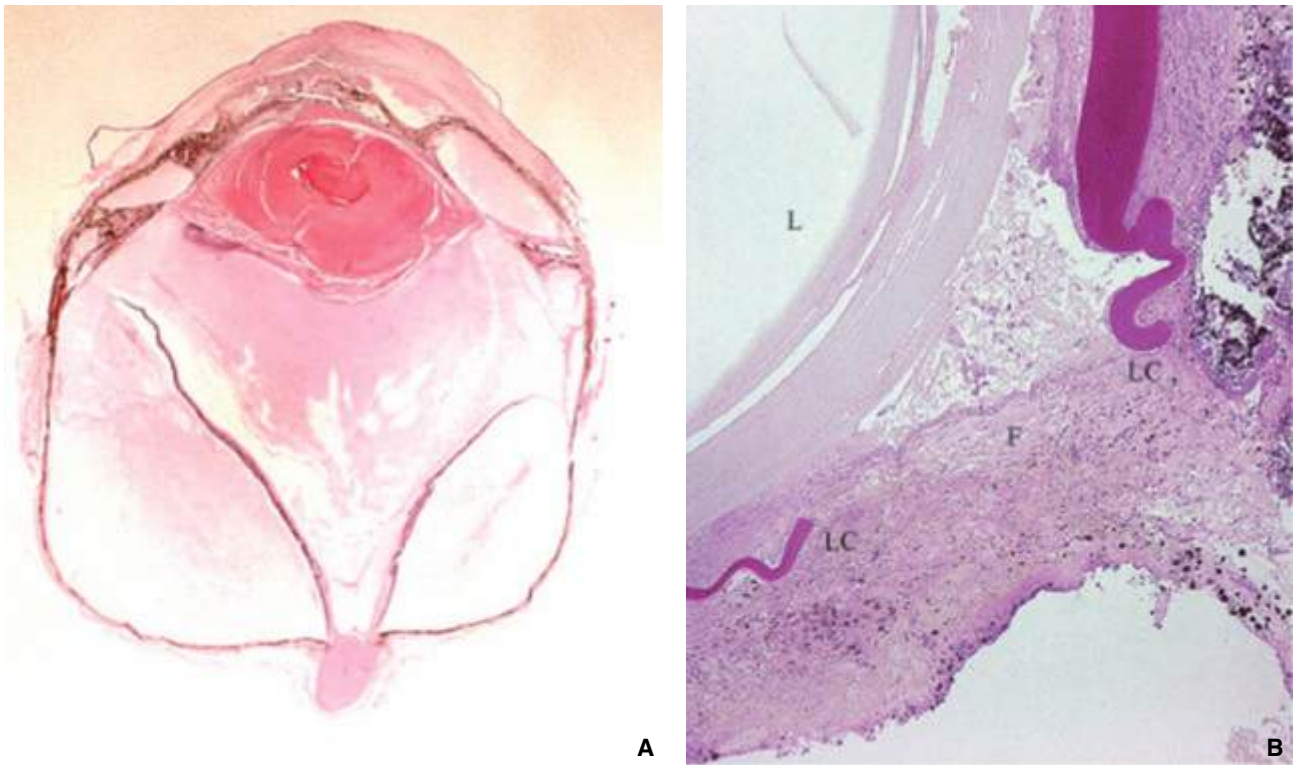


Figure 9.56 **A.** Phacoclastic uveitis in a dog. Note the discontinuous lens capsule, keratitis, posterior and anterior synechiae, retinal detachment, and plasmoid aqueous and vitreous. These gross findings are usually synonymous with penetrating ocular trauma. (Original magnification 2×. Hematoxylin and eosin.) (Courtesy of Brian Wilcock.) **B.** An equatorial lens capsule rupture in a dog. Note the discontinuous and coiled lens capsule (LC), fibrous tissue (F), and inflammatory cells that span the capsular tear and envelop the lens (L). (Original magnification 250×. Periodic acid-Schiff.)

reparative fibrometaplastic proliferation of the lens epithelium, membranogenesis of proximal tissues, sepsis, and not infrequently, secondary glaucoma. The inflammatory response is zonal, being most severe at the site of capsular rupture; the edges of the ruptured capsule are fimbriated, retracted, and/or coiled. Response in the dog eye is intense with a prominent neutrophil component acutely; the inflammation can extend throughout the eye. The response of the rabbit eye to capsular rupture is localized, measured, and largely granulomatous, with the cat eye somewhere between. Spontaneous and small traumatic lens capsule ruptures in young animals of any species often occur with minimal inflammatory response.

Degenerative Uveal Conditions

Uveal Atrophy and Cysts

Uveal atrophy is nonspecific and occurs secondary to chronic glaucoma, uveitis, and aging. The iris, ciliary body, and choroid decrease in thickness secondary to a loss of pigment, smooth muscle, and vascular tissues, and all of these are readily discernable on histologic examination.

Anterior uveal epithelial cysts are common accompaniments to many chronic degenerative ocular conditions. These likely develop secondary to epithelial alterations induced by the ocular disorder. Incidental anterior uveal cysts and iris atrophy are nonspecific findings and only need to be differentiated from inherited pigmentary/cystic glaucoma of Golden Retrievers.

Inherited Uveal Conditions

Melanocytosis of Dogs, Pigmentary/Cystic Glaucoma of Golden Retrievers, Uveal Cysts, and Uveodermatologic Syndrome

Melanocytosis, also known as pigmentary glaucoma and melanosis, is an inherited, intraocular melanocytic proliferation disorder of the Cairn Terrier (Gearhart et al., 2008; Petersen-Jones, 1991; Petersen-Jones et al., 2007, 2008). This syndrome has also been reported in Boxers and Golden Retrievers (van de Sandt et al., 2003). Melanocytosis induces secondary glaucoma by the accumulation of pigment, melanocytes, and pigment-laden macrophages in the filtration angle and anterior uvea. Light microscopy reveals a diffusely

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thickened uvea with an infiltrate primarily consisting of atypical polyhedral melanin-laden melanocytes (Fig. 9.57). Remarkably similar cellular populations (melanocytoma cells) are encountered in limbal melanocytomas and uveal melanocytomas. These cells accumulate throughout the filtration angle, uvea, anterior and posterior chambers, vitreous, and around the episcleral collecting veins and within the episcleral tissues. Secondary ocular pathology is consistent with sustained glaucoma. The etiology and pathogenesis are unknown.

Pigmentary/cystic glaucoma in Golden Retrievers is an inherited slowly progressive disorder that manifests clinically with multiple ciliary and iridal cysts that rupture and disperse pigment over the lens, iris, and cornea (Holly et al., 2016; Sapienza et al., 2000). This condition is suspected to have an autosomal dominant mode of inheritance with partial penetrance. The light microscopic findings are limited to minimal lymphocytic plasmacytic anterior uveal accumulations, large thin-walled asymmetrical epithelial cysts, and ocular changes consistent with secondary glaucoma.

Uveal cysts are sporadically identified in many species. They manifest clinically as a round black to brown cyst that is either floating free in the anterior chamber or attached to any of the anterior chamber tissues. Light microscopic examination reveals variably pigmented fluid filled, epithelial lined cysts (Spiess et al., 1998). They might have a genetic etiology, but some cysts appear to develop secondary to uveitis (Corcoran & Koch, 1993).

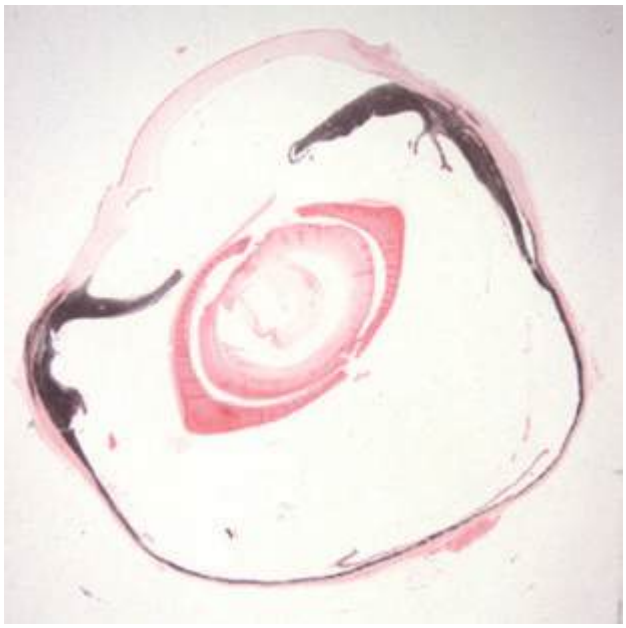


Figure 9.57 Ocular melanocytosis in a Cairn terrier. Note the heavily pigmented irides and ciliary body with extension of pigment into the episcleral tissues around the aqueous collecting veins and choroid. Glaucoma is indicated by the thin sclera and was confirmed with light microscopic examination of the retina and optic nerve. (Original magnification 2×. Hematoxylin and eosin.)

Uveodermatologic syndrome is an immune-mediated condition of young dogs. Clinical signs include severe and relentless granulomatous panuveitis and depigmentation of the hair coat (poliosis), and skin (vitiligo), and/or mucus membrane ulceration. The skin lesions typically develop later than the panuveitis (Kern et al., 1985; Lindley et al., 1990). Akitas, Siberian Huskies, and Samoyeds appear predisposed. Dispersion and phagocytosis of melanin is a histologic feature of both dermal and ocular lesions, and if skin lesions are present, biopsy can confirm the ocular diagnosis. Extensive diffuse granulomatous panuveitis and exudative retinal detachment are frequent presenting features, and glaucoma is a common blinding sequela (Fig. 9.58).

Acquired Retinal Disorders

Retinal Detachment

The lateral junctions of the RPE (along with the tight endothelial junctions of the retinal vascular endothelium) form the posterior blood–aqueous barrier. When compromised by inflammation or ischemia, the choroidal blood vessels leak serous to protein-rich fluid that collects in the potential space between the retina and RPE with resultant neurosensory retinal detachment (see Fig. 9.3, Fig. 9.7A, Fig. 9.17A, Fig. 9.18A, B, and 9.58A). Separated from the nutrition of the choriocapillaris and the metabolic support of the RPE, the outer segments will atrophy initially with the photoreceptors following. Exudative retinal detachment is a nonspecific response to infectious or noninfectious inflammatory diseases or ischemia of the RPE, as encountered in systemic hypertension. The neurosensory retina remains attached at the ora ciliaris retinae and the optic disc, with the fluid in the subretinal space varying from serous to protein-rich to hemorrhagic, and with or without inflammatory infiltrates dependent upon the causes of the primary disease process.

Rhegmatogenous retinal detachments develop secondary to retinal holes or tears. Retinal tears develop secondary to trauma or vitreous traction. These detachments are often focal initially and then expand with time.

Tractional retinal detachments occur secondary to contractile disease processes within the vitreous.

Sudden Acquired Retinal Degeneration Syndrome

Sudden acquired retinal degeneration syndrome (SARDS) is a retinal disorder in dogs characterized clinically by its acute onset, permanent blindness, and predisposition for middle-aged often overweight dogs (Komaromy et al., 2016; Leis et al., 2017b; Miller et al., 1998; van Der Woerdt et al., 1991). The light microscopic findings in SARDS are generalized photoreceptor apoptosis, with minimal inflam-

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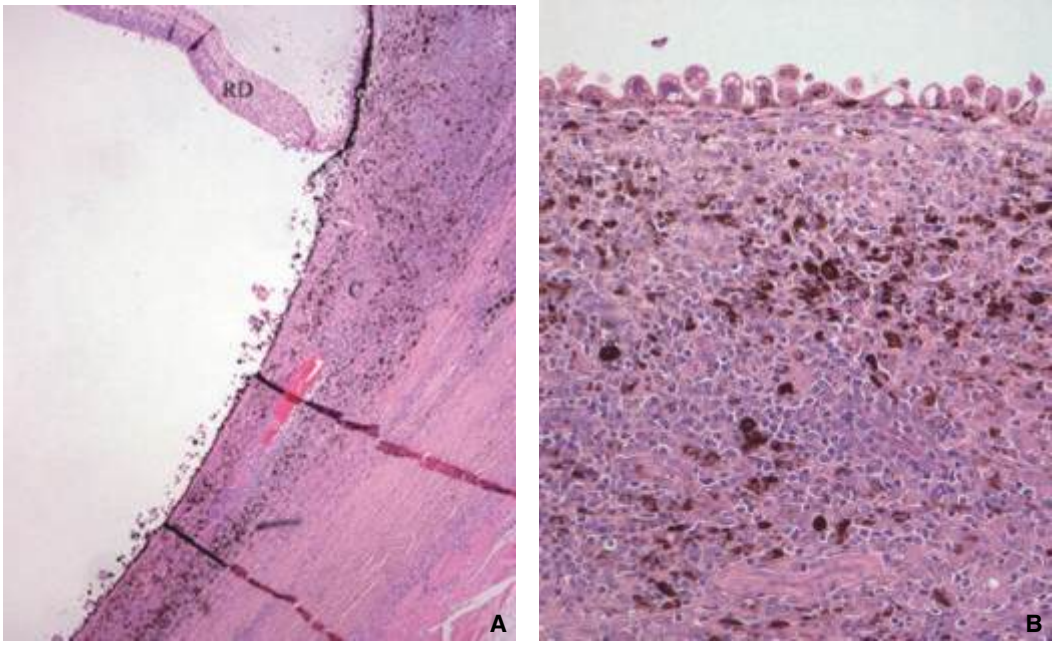


Figure 9.58 **A.** Exudative retinal detachment (RD) in a dog with uveodermatologic syndrome. Note the diffuse inflammatory infiltrate in the choroid (C) and pars plana and the detached retina and retinal pigment epithelium (RPE) hypertrophy. (Original magnification 400×. Hematoxylin and eosin.) **B.** Uveodermatologic syndrome in a dog. Note the granulomatous choroiditis with macrophages that are targeting the choroidal melanocytes. The retina was detached and the RPE is hypertrophied. (Original magnification 400×. Hematoxylin and eosin.)

mation except a few macrophages that engulf the photoreceptor debris. The etiology and pathogenesis remain unknown. There is evidence that ongoing photoreceptor apoptosis occurs after blindness (Braus et al., 2008; Miller et al., 1998).

Inherited Conditions of the Retina and Vitreous

Inherited retinopathies are common in dogs, cats, and rodents, and are uncommon in other species. This discussion will be limited to those of the dog and cat because the gross, light, and electron microscopic changes are similar across species.

Progressive Retinal Atrophy in Dogs

Progressive retinal atrophy (PRA) is a collective term for the multiple inherited retinopathies that occur in the dog and cat that manifest clinically in a similar fashion. Specific genetic mutations have been found in many breeds. Clinical diagnosis is often made with a history of nyctalopia, findings of diffuse retinal degeneration, and scotopic and photopic electroretinography.

Light microscopic examination of affected eyes reveals outer and inner segment degeneration prior to maturation of these tissues at 8 weeks of age in the photoreceptor dysplasias and later in life for photoreceptor degenerations (see Fig. 9.9B). The photoreceptor atrophy is accompanied by apoptosis of the outer nuclear and outer plexiform layers, and eventually the inner nuclear and inner plexiform layers. Several variations include rod dysplasia, rod cone dysplasia, and cone dysplasia. Despite variations in the photoreceptor affected, light microscopic findings are similar, and with time, the retina is reduced to a glial scar. The RPE, which is responsible for phagocytosis of degenerating photoreceptors and neurons, is secondarily involved with hypertrophy, hyperplasia, and metaplasia. With time, retrograde changes occur, including vitreous liquefaction (syneresis) with clumped collagen strands suspended in the dependent posterior segment. Cataracts develop, initially posterior subcapsular, presumably related to the release of photosensitizing ketones that are released by degenerating photoreceptors and diffuse across the vitreous. Rarely, zonular degeneration leads to lens luxation. PIFMs are also occasionally noted in globes affected with chronic photoreceptor dysplasia. The histologic confirmation of chronic PRA is difficult because the diffuse panretinal degeneration is nonspecific. The histopathologic differential diagnoses that warrant consideration include nutritional deficiencies (taurine, vitamin E, vitamin A), toxins (numerous drugs including fluoroquinolones and aminoglycosides), plant toxicoses including bracken fern *Pterdium* sp. and locoweed (*Astragulus* sp.), phototoxicity, radiation, and SARDS (see acquired retinal diseases) (Buyukmichi, 1981; Jamieson et al., 1991; Kuwabora & Gorn, 1968; Lanum, 1978; Miller et al., 1998; Peiffer et al.,

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1981; Roberts et al., 1987; Sadda et al., 1994; van der Woerdt et al., 1991).

Progressive Retinal Atrophy in Cats

Three early onset photoreceptor degenerations have been reported in cats: mixed breed retinal degeneration (West-Hyde & Buyukmichi, 1982); Persian retinal degeneration (Rubin & Lipton, 1973); and Abyssinian retinal dysplasia (Barnett & Curtis, 1985; Leon & Curtis, 1990). The Persian retinal degeneration is an autosomal recessive condition (Narfstrom & Nilsson, 1986), whereas the other two are autosomal dominant (Barnett & Curtis, 1985; West-Hyde & Buyukmichi, 1982). These three rod cone degenerations all manifest with clinical signs of retinal thinning with tapetal hyperreflectivity and retinal vascular attenuation, within a few months of age (Narfstrom & Ekesten, 1999). Light microscopic examination confirms both rod and cone degeneration that extends from the outer segment to the inner segment and gradually throughout all the layers of the retina. Abyssinian cats with photoreceptor dysplasia fail to develop rod and cone outer segments, and there is incomplete synaptogenesis; degeneration begins near the central retina and progresses to the periphery by about 7 months. Eventually, the RPE, choriocapillaris, and tapetum also atrophy.

A late-onset autosomal recessive photoreceptor degeneration is also reported in Abyssinian cats (Narfstrom & Nilsson, 1986, 1989). Light microscopic examination reveals initial disorientation of the rod outer segments with subsequent degeneration of the outer segment by approximately 6 months of age. Over the next year, the rods, their axons and associated nuclei, and axons in the outer plexiform, inner nuclear, and inner plexiform layers degenerate (Fig. 9.59). The cones remain normal until the affected cats are 2–3 years of age.

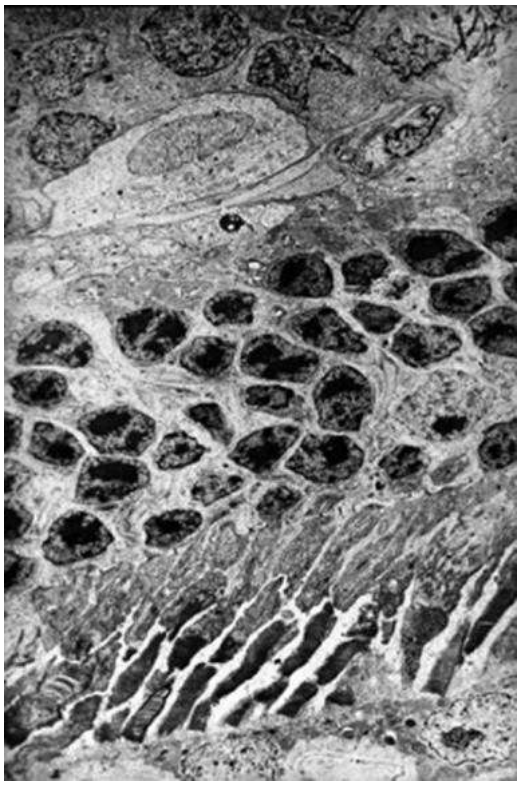


Figure 9.59 Transmission electron micrograph of the retina of a 6-month-old Abyssinian cat with progressive retinal degeneration characterized by degenerating photoreceptor outer and inner segments. (Magnification 4000×.) (Courtesy of K. Narfstrom.)

Retinal Pigment Epithelial Disorders

At least two inherited retinal degenerations of dogs are associated with primary disease of the RPE: congenital stationary night blindness in Briard dogs and retinal pigment epithelial dystrophy as reported in several breeds of dog (Aguirre & Laties, 1976; Aguirre et al., 1998; Bedford, 1984). In addition, multifocal retinopathies are inherited in Great Pyrenees, Coton de Tulear, and Mastiff dogs and are directly related to mutations that alter RPE function.

Congenital Stationary Night Blindness in Briard Dogs

Congenital stationary night blindness has been reported in the Briard dog. This disorder is a slowly progressive blinding disorder that is caused by a mutation in the *RPE 65* gene (Aguirre et al., 1998). The gross manifestations include retinal atrophy. Light microscopic abnormalities include RPE vacuoles and hyperpigmentation with apoptosis and degeneration of the photoreceptors and a progressive loss of the nuclear and plexiform layers (Narfstrom, 1999; Narfstrom et al., 1989, 1994).

Retinal Pigment Epithelial Dystrophy

Retinal pigment epithelial dystrophy (RPED) (also referred to as central PRA) is a rare disorder of dogs in North America, and multiple etiologies have been reported, including genetic mutations and nutritional deficiency of vitamin E (Barnett, 1967; Davidson et al., 1998; McLellan et al., 2002; Riis et al., 1981; Watson & Bedford, 1992). Some dog breeds manifest with central PRA because of mutations that alter vitamin E metabolism (Davidson et al., 1998). The hallmark histologic finding is lipofuscin accumulation within the RPE and degeneration of the outer and inner segments. If chronic, the outer and inner nuclear and associated plexiform layers will also be degenerate. Unlike PRA and photoreceptor dysplasia, secondary intraocular diseases such as cataracts and vitreous degeneration are uncommon.

Multifocal Retinopathies in Dogs

Multifocal retinopathies develop most likely secondary to retinal pigment epithelial dysplasia that affects RPE function. These disorders are inherited in the Great Pyrenees,

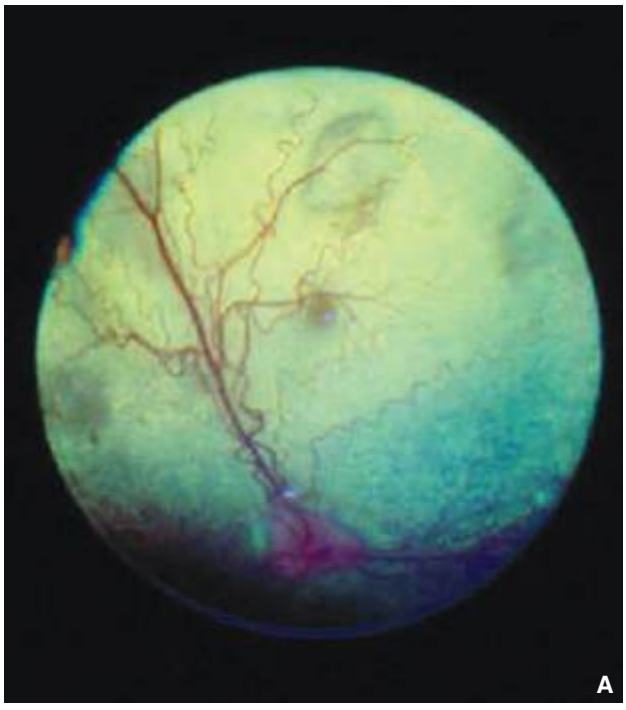
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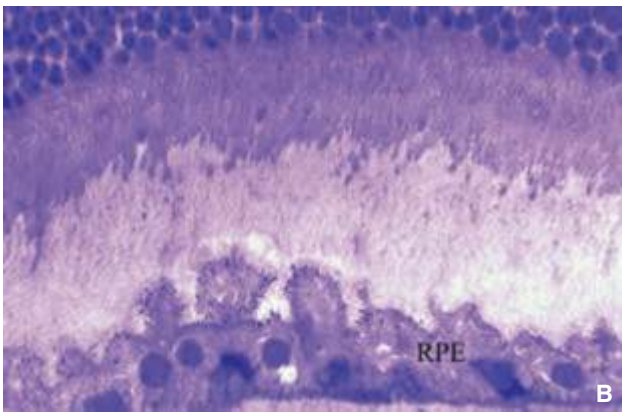
Coton de Tulear, and Bullmastiff dogs. They manifest as bullous retinal detachments at approximately 11–17 weeks (Fig. 9.60A). There is progressive enlargement of focal retinal and RPE detachments and development of new lesions until approximately 6–10 months of age. Light microscopic examinations confirm multifocal bullous retinal detachments with associated RPE hypertrophy, hyperplasia, and hyperpigmentation (Grahn et al., 1998, 1999, 2008) (Fig. 9.60B). In addition, there are focal areas of degeneration of the outer nuclear and plexiform layers associated with each detachment. The RPE also develops focal detachments from Bruch's membrane in affected Great Pyrenees dogs (Fig. 9.60C). The mutations responsible for these multifocal retinopathies have been reported in the Bestrophin gene, and the pathogenesis relates to altered RPE fluid transfer (Grahn & Cullen, 2001; Guziewicz et al., 2007).

Acquired Vitreous Disorders

Although vitreous syneresis (liquefaction) and detachment are considered consequences of normal aging, they also occur as a result of pathologic processes, including inflammation and glaucoma that cause depolymerization of vitreous hyaluronic acid and induce collagenolysis (Fig. 9.61A). Clinical diagnosis of either condition can be problematic; however, it is facilitated by posterior segment biomicroscopic examination. Syneresis is generally regarded as innocuous. Posterior vitreous detachment can be diagnosed in paraffin-embedded sections with optimal processing, with protein condensation delineating the posterior hyaloid membrane. Syneresis is a gross pathologic diagnosis made upon qualitative evaluation of vitreous viscosity upon opening the globe.

Asteroid hyalosis is the formation of 0.01–0.1 mm of roughly spherical bodies suspended within formed vitreous. Their nature is thought to be a calcium and phosphorous-containing lipid, and they could arise from degenerated vitreous collagen fibrils (Fig. 9.61B). Asteroid bodies are weakly basophilic with H&E and have the suggestion of a lamellar arrangement. They stain positively for lipid, although they resist fat solvents. They are mucopolysaccharide positive and hyaluronidase resistant. With polarized light, one





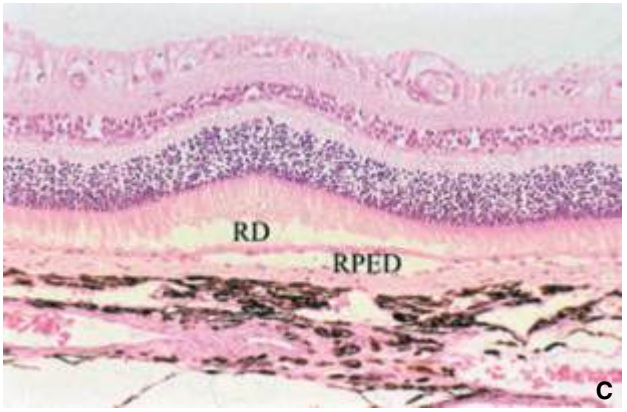


Figure 9.60 **A.** Inherited multifocal retinopathy of Great Pyrenees dogs. **B.** Retinal pigment epithelium hypertrophy, vacuolation, and pigmentation that developed near the edge of a focal inherited retinal detachment in a Great Pyrenees dog. (Original magnification 300×. Toluidine blue stain) **C.** Histologic section of the retina of a 4-month-old Great Pyrenees dog with inherited multifocal retinopathy. Note the focal retinal detachment (RD) and retinal pigment epithelial detachments (RPED). (Original magnification 200×. Hematoxylin and eosin.) (*Source:* Reprinted with permission from Grahn, B.H., Philibert, H., Cullen, C.L., Houston, D.M. & Schmutz, S. (1999) Multifocal retinopathy of Great Pyrenees. *Veterinary Ophthalmology*, **1**, 211–221.)

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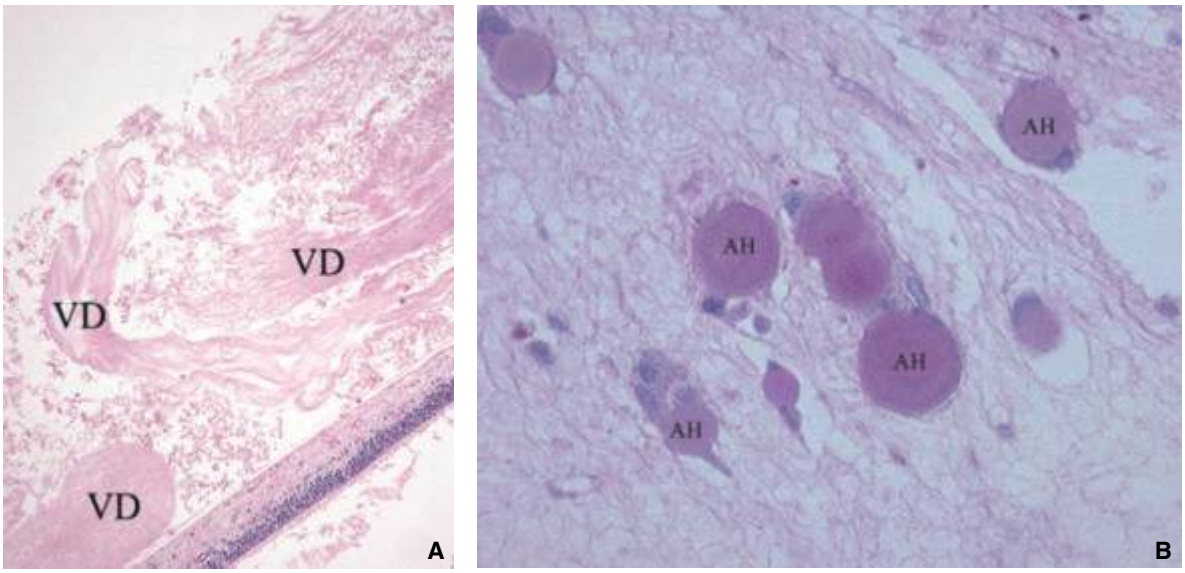


Figure 9.61 **A.** Vitreous degeneration (VD) in dog with secondary glaucoma and retinal detachment. The vitreous strands are congealed and therefore appear thickened and bunched together, and they are apposed to the inner limiting membrane in some areas of the ventral non-tapetal retina. Plasma proteins are also present around the thickened vitreous tendrils. Note the characteristic retinal degeneration of the inner retina (glaucoma) and loss of photoreceptors and outer nuclear layer (retinal detachment). (Original magnification 200×. Periodic acid-Schiff.) **B.** Asteroid hyalosis (AH) in a dog. Note the amorphous pink granular bodies associated with dark small hyalocyte nuclei. (Original magnification 400×. Periodic acid-Schiff.)

observes birefringent spicules. Asteroid hyalosis is not an uncommon finding in older dogs and has not been reported in cats or other domestic animals. It is unilateral or bilateral, and even in its densest presentation, does not seem to affect vision appreciably.

Cholesterolosis bulbi is an uncommon condition that results from incomplete resolution of intraocular hemorrhage and syneresis. The refractile cholesterol crystals settle to the bottom of the vitreous chamber (and/or the anterior chamber in aphakic eyes) when the eye is at rest. Other significant ocular lesions usually accompany the condition. In paraffin-embedded sections, the cholesterol esters have been dissolved in processing. Their location can be identified as slit-like spaces, occasionally with an associated granulomatous inflammatory response, and hemosiderosis can be present and is shown nicely with stains for iron.

Inherited Choroidal and Vitreous Anomalies

Tapetal Degeneration in Dogs and Cats

Inherited tapetal degeneration in Beagles is an autosomal recessive condition where the number of tapetal cells is normal at birth. The clinical manifestations include loss of the normal reflective tapetum caused by progressive degeneration which begins at approximately 2 months of age; by about 3 months, the tapetal cells have lost all their rodlets and are packed with membranous inclusions (Bellhorn et al., 1975; Wen et al., 1982a).

A similar disorder occurs in Siamese cats with Chediak–Higashi syndrome. The tapetum in these cats is likewise normal at birth and is completely degenerate by 2 months of age. Macrophages are absent in both of these disorders (Collier et al., 1985; Wen et al., 1982b).

Borzoi Chorioretinopathy

Multifocal choroidal retinal lesions have been reported in Borzoi dogs (Fig. 9.62A) (Chaudieu, 1995; MacMillan & Scagliotti, 1977; Rubin, 1989; Storey et al., 2005). The mode of inheritance is unknown. PRA has been excluded as part of this disorder by electroretinographic and light microscopic examinations (Storey et al., 2005). The light microscopic findings of Borzoi retinopathy include focal choroidal atrophy, loss of choriocapillaris, focal hypertrophy and pigmentation of the RPE, and focal degeneration of associated photoreceptors (Fig. 9.62B).

Inherited Vitreous Degeneration

Vitreous degeneration is suspected to be an inherited condition in Whippets and Italian Greyhounds given the development of syneresis and prolapse of tendrils of degenerate vitreous into the anterior chamber in young dogs (from 6 months to 4 years of age). Light microscopic diagnosis of vitreous degeneration is nonspecific in regard to etiology, and the lesions are subtle. Thorough light microscopic examination of the vitreous reveals condensed vitreous

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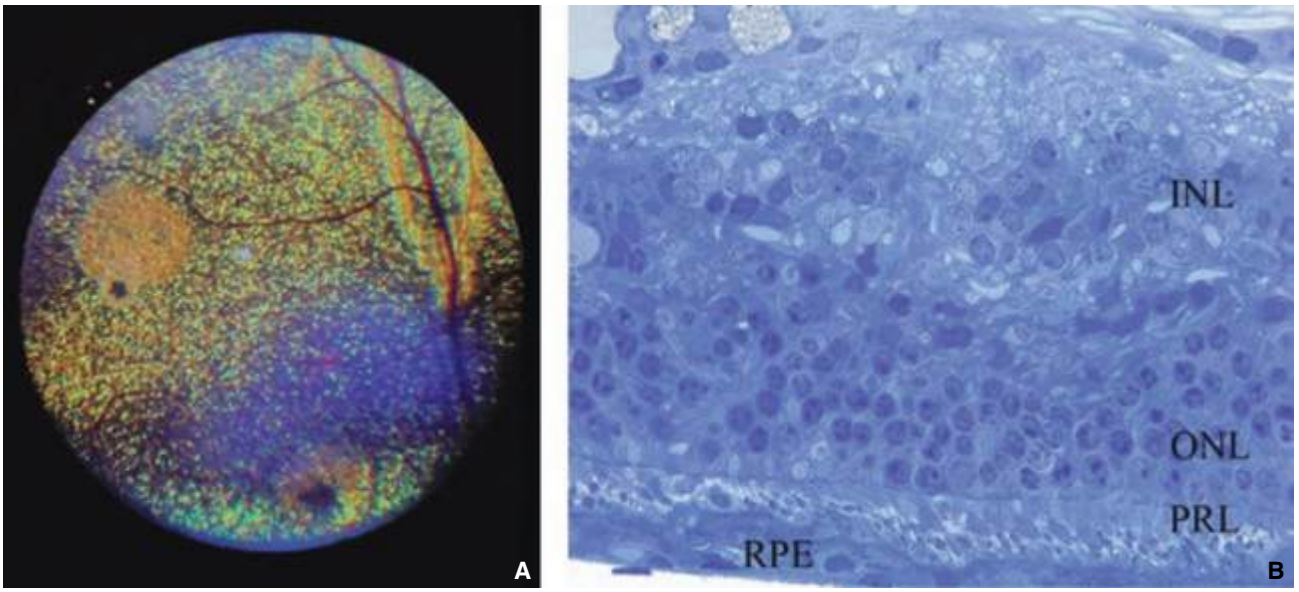


Figure 9.62 **A.** A mature male Borzoi dog with Borzoi chorioretinopathy. Note the focal hyperreflective lesions with hyperpigmented foci located ventrally and dorsally in this fundic photograph. **B.** Histologic lesions include retinal pigment epithelium (RPE) hypertrophy, hyperplasia and pigmentation, and the outer nuclear layer (ONL) and inner segment photoreceptor (PRL) degeneration and loss of outer nuclear, outer plexiform, and inner nuclear (INL) layers. Occasional mononuclear cells are present within this focal lesion. The retina on either side of this lesion was normal morphologically. (Original magnification 400×. Toluidine blue stain.)

fibers and a lack of fine fibrillary vitreous collagen and detachment of these condensed fibers from the inner limiting membrane.

Inherited Storage Disorders, Amino Acid, and Lipid Peroxidation Disorders

Metabolic storage diseases are uncommon in animals. However, several have been investigated thoroughly in the research laboratory as models for similar human disorders. These storage disorders result from genetic defects in metabolism and are generally the result of a deficient degradory pathway. These metabolic defects result in accumulation of complex lipids, glycoproteins, or polysaccharides within specific types of cells within the eye and other organs. These cells include keratocytes, ganglion cells, or RPE. Histopathologic signs are subtle when the sole diagnostic examination is light microscopy; these systemic metabolic conditions are best defined by histochemistry and transmission electron microscopy. The typical clinical presentation is that of a young animal with neurologic and frequently ocular signs. Only the histologic findings found in the eyes are described here. Clinical findings and references can be found in respective chapters. *Lysosomal storage diseases* include gangliosidosis (G_{m1} and G_{m2}) and mucopolysaccharidoses (MPSI VI, VII) and cause the accumulation of glycosaminoglycans and glycoproteins within membranous inclusions in the corneal stromal keratocytes and endothelium. These inclusions are identifiable by light and electron microscopy. Similarly, these metabolic by-products accumulate in the retina and RPE and affect their function and can cause blindness. *Fucosidosis* has been reported in English Springer Spaniels with alpha-L-fucosidase deficiency and manifests histopathologically as vacuolated ganglion cells, astrocytes, and RPE. *Ornithinuria,* a deficiency of ornithinuria transferase, causes generalized histopathologic lesions including retinal, RPE, choriocapillaris, and choroidal atrophy. Choroidal vascular atrophy is the unique histologic finding with this disorder. The diagnosis is confirmed by documenting elevated levels of ornithine in the urine or plasma. *Lipid peroxidation defects* include neuronal ceroid lipofuscinoses which is caused by decreased peroxidase activity and is associated with the intracellular accumulation of ceroid lipofuscin. Stacked membranous inclusions in RPE (Fig. 9.63) and ganglion cells are noted with light and electron microscopy and are accompanied by ophthalmoscopic lesions and visual dysfunction.

Degenerative Lenticular Disorders

A basic discussion of cataractogenesis should reference the biochemical and metabolic changes that precede or accompany the morphologic changes. Alterations in nutrition, metabolism, and osmotic balance can lead to alterations in cell membranes and/or proteins that define cataracts. The lens consists predominantly of water and protein, with

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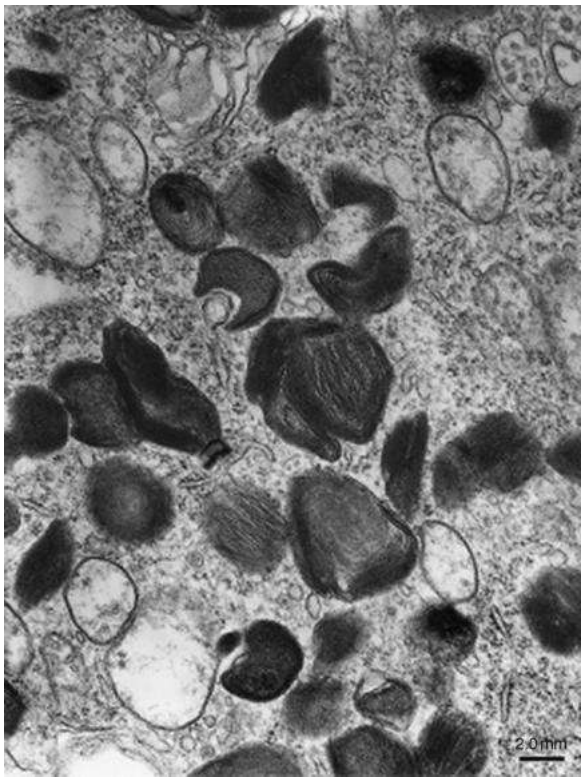


Figure 9.63 The inclusions that are characteristic of neuronal ceroid lipofuscinosis. (Courtesy of K. Narfstrom.)

minute amounts of inorganic ions, organic phosphates, nucleic acid, and lipid. The proteins include the soluble crystalline, insoluble albuminoids, mucoproteins, and nucleoproteins. Differentiation of lens epithelial cells into lens fiber cells is a life-long process that occurs at the equator; these cells mediate transcapsular transport, provided by a Na^+, K^+-ATPase-dependent pump. Oxygen needs are minimal, and anaerobic glycolysis, which converts glucose to lactic acid, provides most of the energy required. Glucose enters the lens by both diffusion and facilitated transport; transport mechanisms play a role in cation and amino acid influx as well. Alterations in substrate or enzymatic activity can alter the homeostatic equilibrium of the lens with increased hydration and associated protein alterations. Cataractogenesis is also associated with increases in lens glutathione, insoluble proteins, and hydrolytic enzymes. There is increasing evidence that oxidative damage is a common final pathway for a variety of cataracts.

Although the pathologist strives for an etiologic diagnosis, the nonspecificity of cataract morphology frequently limits diagnosis to morphologic description. Histopathologically, cataractogenesis is manifested by a limited number of morphological alterations in the lens capsule, epithelial cells, and/or lens fiber cells. These alterations represent the common end stage of a spectrum of insults, be they genetic, traumatic, toxic, or secondary to ocular or systemic disease (Thoresen et al. 2002). The histopathologist can readily classify these changes by location and morphology but in the absence of other clues may be hard pressed to determine etiology (Fig. 9.64).

Distinction between artifact and real change can be challenging, especially in regard to cortical and nuclear alterations. The lens is dense and sequestered within the globe; thus, fixatives penetrate poorly, and shattering and fragmentation under the microtome blade occurs frequently. Both fixative and osmotic factors can distort size and shape and contribute to the appearance of vacuoles that can mimic pathologic alterations.

Anterior capsular changes of delamination as seen with heat and/or infrared exposure and pseudoexfoliation have not been described in animal eyes; however, anterior capsular thickness might increase in response to excess basement membrane production by stressed lens epithelial cells. Capsular opacification associated with persistence of the fetal vasculature and spontaneous congenital capsular rupture have been discussed in the section Pathology of Congenital Disorders, and the features of traumatic or spontaneous acquired capsular rupture in the paragraph on Phacoclastic Uveitis.

Lesions affecting the lens epithelium involve the anterior or equatorial epithelial cells. These cells degenerate, develop fibrous metaplasia, migrate along the posterior lens capsule, hypertrophy, and/or become hyperplastic in response to disease. Epithelial cells can transform from cuboidal to flattened fusiform cells, frequently forming a multilayered plaque; although fibrous in appearance by light microscopy, ultrastructurally these cells maintain intercellular macula adherents and are surrounded by basement membrane, maintaining characteristics of epithelial cells. When epithelial cells migrate posteriorly, they follow the capsule where they undergo metaplasia or migrate into the posterior cortex where they hypertrophy, perhaps as an abortive attempt at repair, with production of lens proteins. These spherical cells maintain their nuclei and are known as bladder cells.

Cortical cataracts are characterized by changes in cell membranes, lens proteins, or both (Taylor et al., 1997). Intercellular fluid accumulation manifests as vacuoles, clefts, and fissures between cells. Intracytoplasmic swelling imparts enlarged profiles and a granular cytoplasm; as lens proteins denature, they become more eosinophilic and homogeneous. Fiber cell membranolysis results in extracellular pools or distinct spherules of altered protein; the latter is referred to as Morgagni globules. Increased fluid intake leads to swelling of the lens with stretching of the capsule (spontaneous rupture, usually of the posterior capsule, can occur). As the osmotic pressure with the aqueous humor equalizes across the lens capsule because of altered metabolism and loss of transcapsular transport mechanisms, soluble proteins will diffuse from the lens, with resultant

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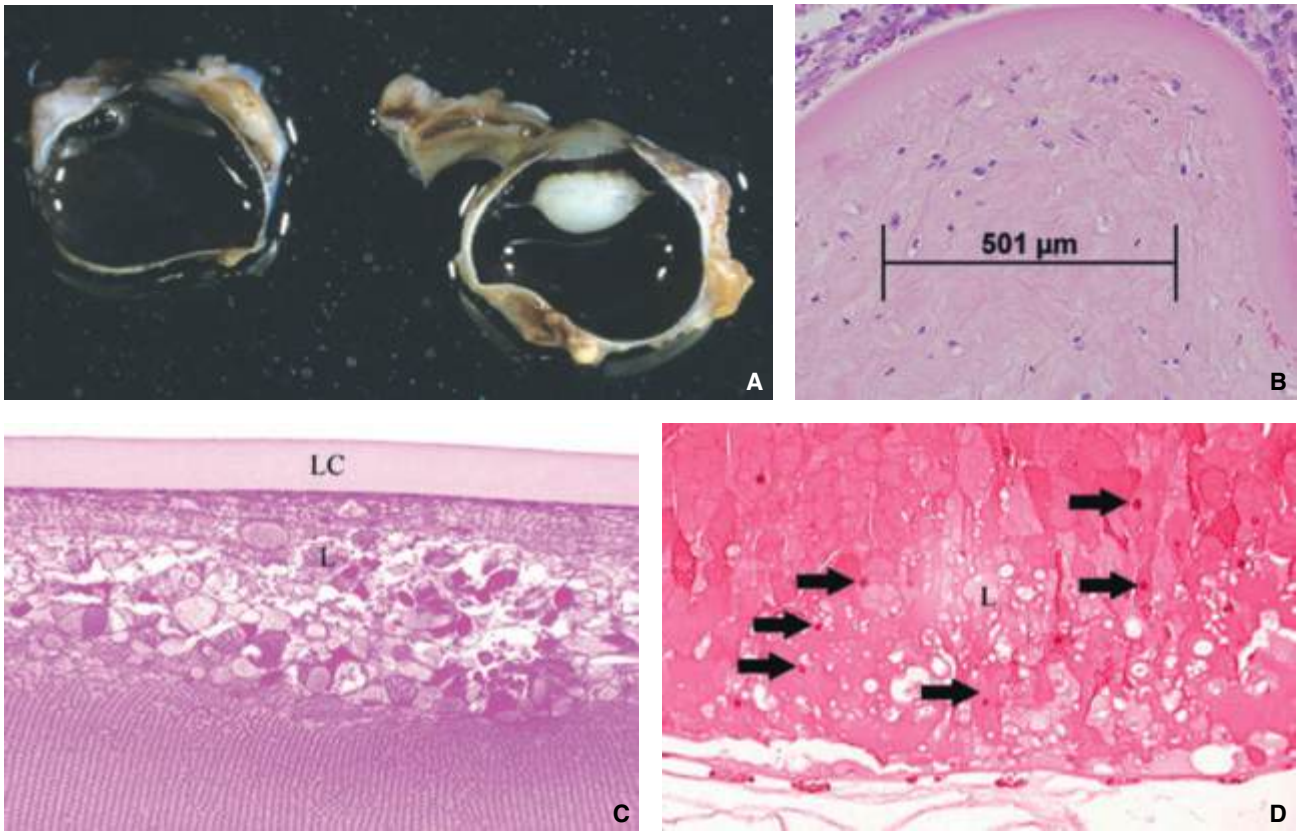


Figure 9.64 **A.** A mature cataract is present in this gross section of this dog's eye. **B.** Fibrous metaplasia of lens epithelium under a folded anterior lens capsule of a dog. Note the capsular fold and lens epithelial cells that are scattered among collagen fibers. (Original magnification 250×. Hematoxylin and eosin.) **C.** Cortical liquefaction (L) is present under the anterior lens capsule (LC) of this dog. (Original magnification 200×. Hematoxylin and eosin.) **D.** Cortical liquefaction (L) is present under the posterior lens capsule in this dog. Arrows, posterior migration of lens epithelial cells. (Original magnification 200×. Hematoxylin and eosin.)

shrinkage and capsular wrinkling. Cholesterol deposits or dystrophic calcification can occur.

The role of altered carbohydrate metabolism, in particular glucose and galactose, has been studied extensively. In diabetes mellitus, excessive levels of glucose enter the lens, the rate-limiting enzymes of the Embden-Meyerhoff pathway are saturated, and the sorbitol pathway and aldose reductase are activated, with the sugar being metabolized to polyalcohols with resultant osmotic imbalance and water influx (Beam et al., 1999). Elevation of galactose levels related to excessive dietary intake or genetic enzymatic defects follows a similar pattern (Sato et al., 1991; Wyman et al., 1988); neonatal marsupials supplemented with cow's milk, which is high in galactose that these animals are unable to properly metabolize, will develop cataracts. Low glucose levels can also lead to cataract formation and further reveals the pivotal role that glucose plays in lens metabolism.

Hypocalcemia can cause cataracts in dogs and cats, and numerous toxins, chemicals, and pharmaceutical agents have been shown to cause both experimental and spontaneous disease. Glucocorticoids administered both topically and systemically in humans can result in posterior subcapsular cataracts that continue to progress after treatment is discontinued; domestic species appear to be relatively resistant to steroid cataracts. Heavy metals including lead and silver can induce cataracts. A cholinesterase inhibitor used to control sea lice in Atlantic salmon has been implicated in cataractogenesis. Dinitrophenol in dogs and hygromycin B in swine have also been shown to be cataractogenic (Bunce et al., 1990; Glaze & Blanchard, 1983; Martin, 1975; Martin & Chambreau, 1982).

Radiant energy can cause cataractogenesis; light energy might be cataractogenic in fish. The lens is quite sensitive to radiation, which results in increases in membrane permeability and alters protein synthesis and metabolism. Younger animals are more susceptible; birds are remarkably resistant. A period of latency follows exposure with vacuoles forming at the posterior pole and progressing to cortical involvement (Brightman et al., 1984; Brown et al., 1972; Jamieson et al., 1991; Lipman et al., 1988; Peiffer et al., 1981; Roberts et al., 1987).

Nutritional factors other than carbohydrates may be cataractogenic, including amino acid deficiencies of tryptophan,

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phenylalanine, valine, and histidine. Arginine deficiency causes cataracts in wolf pups (Anderson et al., 1988; Hughes et al., 1981; Ketola, 1979; Poston & Rusey, 1983; Poston et al., 1977; Vainisi et al., 1981).

Other diseases such as uveitis, glaucoma, and retinal degeneration cause cataracts by altering the ocular milieu and thus lens nutrition. Turkeys and chickens with avian encephalomyelitis and Marek's disease develop cataracts. In fish, phacotropism is demonstrated by trematode (diplostomum) larvae with associated cataract, and encephalitizoon has been associated with cataract and lens capsule rupture primarily in rabbits (Shariff et al., 1980; Wolfer et al., 1993).

In many cases, including cataracts in pinnepeds, etiologies remain undefined; various dietary, environmental, genetic, and traumatic factors have been postulated. Likewise, the cellular and subcellular mechanism of inherited cataracts in domestic animals is largely unknown.

Acquired Lens Luxation

The lens is anchored by the zonular fibers which blend with the anterior and posterior lens capsule and extend to the ciliary body. Disruption usually occurs at the site of capsular insertion, with resultant subluxation or luxation (Fig. 9.65). Congenital abnormalities in zonular insertion and/or physical properties in connective tissue disorders predispose to dislocation, and bilateral lens luxation has been described in a dog with Ehlers–Danlos syndrome. Heritable conditions in certain dog breeds (notably terriers) (Curtis, 1983; Curtis & Barnett, 1983; Gwin et al., 1982; Kuchtey et al., 2011; Lazarus et al., 1998) exist in which the zonules have reduced tensile strength and rupture easily and are discussed in the section on Inherited Developmental Disorders. Chronic inflammation will also result in zonulysis and lens luxation in both dogs and, more notably, cats and horses (Martin, 1978). Physical trauma to the globe of sufficient magnitude can dislodge the lens and, as described later, chronic glaucoma with globe enlargement and zonular stretching to rupture is a common finding.

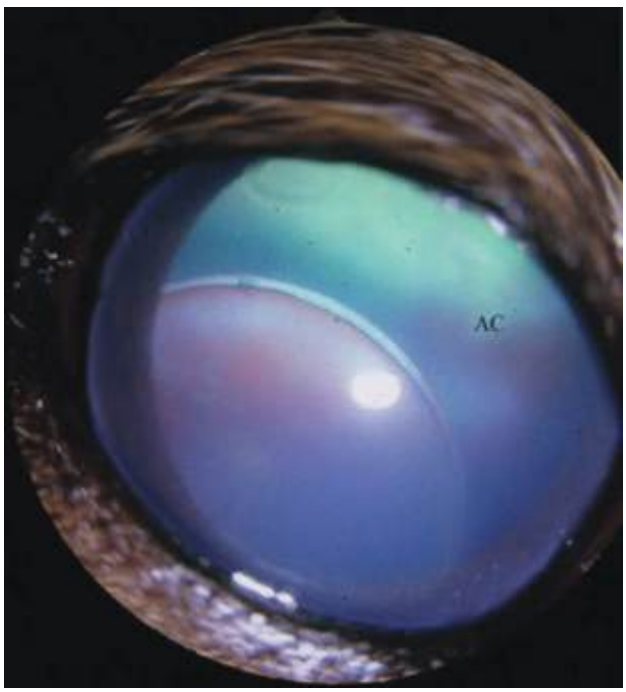


Figure 9.65 A clinical photograph of an inherited posterior lens luxation in a Jack Russell Terrier. Note the prominent aphakic crescent (AC) and the equator of the inferiorly and posteriorly luxated lens.

Posterior subluxation may be associated with elevated IOP if formed vitreous moves anteriorly to obstruct the pupil or outflow pathway; similar events can occur with posterior luxations, as well as perilenticular membranogenesis with resultant retinal traction. Anterior luxations in the dog are accompanied by glaucoma as the lens and/or adherent vitreous obstruct the pupil and outflow pathway. Regardless of species, physical contact between lens and corneal endothelium often compromises the latter.

Acquired Glaucoma

Glaucoma is a generic term used to describe a variety of pathophysiological processes in which the IOP reaches a level sufficient to cause damage to the eye. In humans, glaucoma can occur in individuals whose IOP falls in or close to normal range (normotensive glaucoma); alternatively, a population is recognized with IOP above normal values but without evidence of glaucomatous damage (ocular hypertension). Neither of these conditions has been unequivocally reported to occur in eyes of other animal species. Pathologic elevation of the IOP is the consequence of obstruction or misdirection of aqueous flow or outflow anywhere along its course.

In terms of classification, glaucoma should foremost be classified as being primary or secondary. The former is a genetic and bilateral (although not usually concurrently so) condition that occurs in the absence of antecedent ocular disease. The latter, in contrast, occurs as a direct result of antecedent or concurrent ocular disease that results in impaired aqueous circulation or outflow. Glaucoma that manifests at birth or shortly thereafter is best labeled "congenital," and the reader is referred to section on Pathology of Congenital Disorders. This scheme is somewhat ambiguous; for example, the primary glaucoma most commonly encountered in the dog is associated with congenital goniodysgenesis, but manifests much later in life.

Because of the unique morphology of the subprimate outflow pathway, a morphologic classification of glaucoma in animals should consider those changes that occur within the ciliary cleft (CC) distinct and separate from those that occur at the iridocorneal angle (ICA). With an open ICA,

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normal anatomic relationships exist between iris root, pectinate ligament, and the inner surface of the peripheral cornea. An ICA can be open but dysplastic, with abnormalities of the pectinate ligament (to be elaborated upon shortly). An ICA can be open but obstructed, for instance by the proliferation of a fibrovascular membrane from the iris root across the face of the pectinate ligament. The ICA is closed when the anterior surface of the iris root is displaced anteriorly to come in contact with the anterior surface of the pectinate ligament and peripheral cornea, with resultant obstruction of aqueous access to the trabecular meshwork (TM) and the CC. The CC may be open, narrowed, or collapsed. It is quite possible to have an open ICA with a collapsed CC; in fact, this is the most common manifestation associated with both primary glaucoma and glaucoma associated with lens luxation in the dog. As the cleft collapses, access of the aqueous fluid to the CC and TM is likewise impaired; outflow decreases, and the IOP increases and the anterior chamber becomes more shallow or deepens depending on the type of glaucoma. Because of the anatomic relationships, angle closure is always associated with narrowing and collapse of the CC. Collapse of the CC could be the key event that leads to acute elevation of IOP in the majority of animal glaucoma cases; unfortunately, the mechanism(s) that maintain and control CC width have yet to be defined. Although determining shallowing of the anterior chamber related to anterior displacement of the iris leaflet can be problematic for the pathologist, both the status of the ICA and the width of the cleft can be assessed with reasonable accuracy in histopathologic sections.

Gonioscopic appearance can readily be correlated with the above morphologic classification scheme; if the ICA is open, but the cleft collapsed, the iris root will be in direct apposition with the outer pigment band; the pectinate ligament and cleft will not be observable. With angle closure, the iris root is displaced anteriorly to obscure visualization of the outer pigmented band.

Species Characteristics of Acquired Glaucoma

Canine Acquired Glaucoma

In the dog, secondary glaucoma occurs two to three times as frequently as primary glaucoma. Congenital glaucoma occurs rarely, and when it does, it is usually associated with ASD (see the section on Pathology of Congenital Disorders). A recessively inherited primary open angle glaucoma in the Beagle dog has been investigated as a model for primary glaucoma in humans (Gelatt et al., 1977; Gelatt & Gum, 1981; Gum et al., 1993; Samuelson et al., 1989b). There is no evidence of goniodysgenesis at the time of insidious elevation of IOP, which first is noted at about a year of age, and the ICA and CC are open at this stage. With chronicity, the cleft closes. The most common primary glaucoma seen in dogs is an inherited condition associated with goniodysgenesis. Goniodysgenesis is a broad term that implies abnormal development of the pectinate ligament, CC, and/or TM.

Primary Glaucoma and Goniodysgenesis in Purebred Dogs

Primary glaucoma associated with goniodysgenesis is reported in American Cocker Spaniels, Bouviers des Flanders, Siberian Huskies, Bassett Hounds, Shar Peis, and many other breeds of dogs, and is most likely inherited in all breeds (Gelatt & Mackay, 2004). This form of glaucoma is challenging to treat effectively, and to alleviate pain and discomfort many eyes are enucleated or eviscerated because of blindness and lack of response to most therapies.

There has been confusion regarding the classification of open and closed angles in veterinary medicine. To clarify this, the ICA is closed when the base of the iris is displaced anterior to overlie the pectinate ligament and the peripheral cornea. This occurs most commonly with peripheral anterior synechiae and with expansive iridal and ciliary neoplasms, and these changes are accompanied by narrowing or closure of the CC. Goniodysgenesis includes failure of development of the pectinate ligament, CC, and/or TM. Rarefaction of the primitive uveal neurocrest tissues to form the filtration angle occurs shortly after birth, but fails to do so in eyes affected with goniodysgenesis. The histologic features of goniodysgenesis include nodular thickening of the termination of Descemet's membrane, thickened and shortened pectinate ligaments with infrequent flow holes, and hypoplasia of the CC; it is difficult for the histopathologist to distinguish hypoplasia of the cleft from collapse. In dogs with primary glaucoma, PAS-positive basement membrane material is identified within the TM (Fig. 9.66A) and is hypothesized to reflect dysplastic trabecular cells. Progressive deposition of this material can lead to physical obstruction of the TM and explains why the disease does not manifest until later in life. Pectinate ligament dysplasia is the only manifestation of goniodysgenesis readily evident to the clinical ophthalmologist, and although in itself it does not play a role in the pathogenesis of primary glaucoma, it rather serves as a marker for the CC and trabecular changes in the aforementioned dog breeds. Pectinate ligament dysplasia by itself has little predictive value; many dogs will fail to develop glaucoma despite the smallest of flow holes in the dysplastic filtration angle.

Light microscopic examination of eyes with primary glaucoma and goniodysgenesis reveals a spectrum of intraocular pathology depending on the duration and severity of the glaucoma. Acute (<11 days) histologic lesions include corneal edema, a mild and variable mixed inflammatory response with predominant neutrophil infiltrations in the TM, pigment dispersion within the anterior segment, and some retinal and optic nerve degeneration. This includes loss of ganglion cells, nerve fiber layer, and focal full thickness retinal necrosis (Reilly et al., 2005; Smedes

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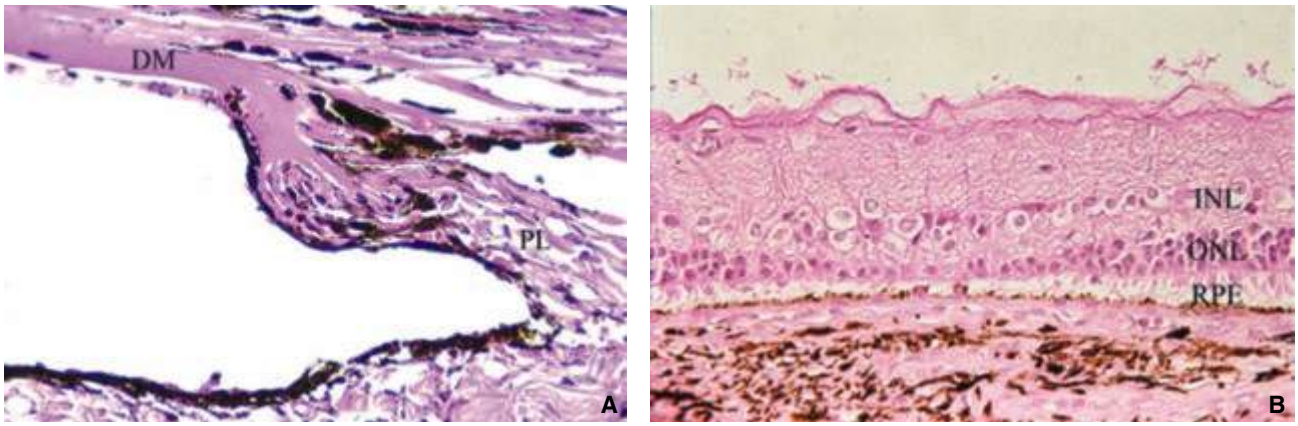


Figure 9.66 **A.** Goniodysgenesis in an American Cocker Spaniel. The pectinate ligament (PL) is shortened and thickened, and the termination of Descemet's membrane (DM) is fimbriated. (Original magnification 200×. Hematoxylin and eosin.) **B.** Retinal degeneration associated with chronic glaucoma. Note the loss of nerve fiber, ganglion cell, and inner plexiform layers. In addition, the inner nuclear layer (INL) and outer plexiform layers are reduced, and centrally, there is a focal full thickness retinal degeneration with reduction of the outer nuclear layer (ONL), and two hyperplastic retinal pigment epithelium (RPE) cells are present centrally. (Hematoxylin and eosin. Original magnification 300×.)

& Dubielzig, 1994). Chronic primary glaucoma associated with goniodysgenesis is manifested histologically by buphthalmos and scleral thinning, corneal striae and exposure keratitis, uveal atrophy, PIFMs, lens luxation, cataract formation, optic nerve atrophy, and the retina may be reduced to a glial scar (Fig. 9.66B). It is important to stress that the histologic diagnosis of goniodysgenesis is made very difficult by the chronic ravages of the high IOPs and their effect on the filtration angle, and a masked histologic study has reported that goniodysgenesis is a clinical diagnosis not a histologic one (Bauer et al., 2016).

Primary Glaucoma in Rabbits

The New Zealand White rabbit is subject to a recessively inherited goniodysgenesis that early in life manifests as buphthalmos, a result of the elasticity of the thin lapine corneosclera. Interestingly, because the rabbit lacks a lamina cribrosa, it is a good model to compare and contrast mechanisms of posterior segment changes associated with elevated IOP.

Acquired Glaucoma of Cats

Most glaucomas in cats are secondary to chronic lymphoplasmacytic uveitis or diffuse iris melanoma, with occasional congenital cases associated with ASD. Narrow-angle glaucoma occurs in middle-aged domestic cats that present a shallow anterior chamber and moderate elevation of IOP. Ciliovitreal block occurs for undefined reasons and results in posterior misdirection of aqueous flow, which in turn causes anterior displacement of the lens–iris diaphragm. IOP elevation likely occurs because of increased resistance to aqueous circulation at both the pupil and the narrowed ICA. By light microscopy, the TM and lens appear normal (Blocker & Van Der Woerdt, 2001; Czederpiltz et al., 2005; Ridgway & Brightman, 1989; Wilcock et al., 1990).

Acquired Glaucoma of Horses

The majority of equine glaucoma cases occur secondary to chronic uveitis; the prominence of uveoscleral outflow in this species may render these beasts somewhat resistant to IOP elevation because of conventional pathway alterations (Brooks et al., 1995; Curto et al., 2014; Cullen & Grahn, 2000; Henriksen et al., 2017; Miller et al., 1995; Samuelson et al., 1989a; Wilcock et al., 1991). Histopathologically, PIFMs are frequent findings.

Pathogenesis of Secondary Glaucoma

Secondary glaucoma occurs because of obstruction of the circulation of aqueous at the ciliary process diaphragm, the pupil, the ICA, the CC, or the TM. Ciliovitreal block has been described earlier as a primary mechanism in the cat and might play a role in the IOP elevation that occurs with anteriorly luxated lenses or after lens extraction and partial vitrectomy. In all of these situations, anterior displacement of vitreous prevents flow of aqueous through the pupil and results in posterior segment aqueous accumulation.

Obstruction of aqueous flow through the pupil can occur as an intumescent cataract swells anteriorly to increase resistance at the lens–iris diaphragm (phacomorphic glaucoma) or by an anteriorly luxated lens and adherent vitreous acting as a cork to obstruct the pupil. Phacolytic glaucoma describes an IOP elevation related to obstruction by macrophages filled with ingested lens protein, and hemolytic glaucoma is caused by macrophages filled with ingested erythrocytes or their breakdown products. With a ruptured lens capsule, denatured lens proteins can be seen obstructing the CC; this condition is labeled lens particle glaucoma. In addition, the CC can be obliterated by primary or secondary intraocular neoplasia, most commonly melanocytomas or iridociliary adenocarcinomas. Secondary glaucoma also occurs as a

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result of damage to the TM itself by blunt or penetrating trauma.

Effects of Elevated IOP

The changes that occur secondary to elevated IOP can be attributed to one of four mechanisms: direct or indirect physical effects of the elevated pressure on cells and tissues; vascular effects as the IOP exceeds the luminal pressure of the capillary beds, creating a state of hypoxia; stagnation of aqueous flow; and neuroexcitatory toxicity.

In glaucoma, the avascular tissues that are dependent on aqueous circulation (cornea, lens, and vitreous) are deprived of both nutrition and metabolic waste removal. Although the mechanism(s) that stimulates release of neuroexcitotoxins is not well understood, these substances (notably glutamate), likely contribute to posterior segment changes (Table 9.5).

Enlargement of the globe occurs as a result of direct pressure on the collagen of the cornea and sclera and is species and age dependent and related to the elasticity of the connective tissue. In general, young animals have a greater tendency for enlargement of the globe than older animals. In the cat, the anterior segment enlarges in greater proportion than the posterior segment. The intercalary sclera is thinner than that posterior to the equator and is a common location for localized ectasia and staphyloma formation as well as posterior displacement of the ICA relative to the limbus.

As the globe enlarges, exposure keratitis often occurs and manifests with a spectrum of possible changes from ulceration to epidermidalization. Diffuse corneal edema results as a consequence of endothelial dysfunction related to direct pressure effects and aqueous stagnation. Descemet's membrane is less elastic than the stroma and with stretching can fracture (Fig. 9.67A) to produce striae which represent focal scarring (Fig. 9.67B). Acutely, hypoxia to iris endothelial cells might result in the leakage of protein into the aqueous, and iris musculature hypoxia contributes to a fixed moderate pupil. With chronicity, uveal atrophy develops. Stagnation of aqueous predisposes to cataract formation. As the globe enlarges, the zonules stretch and rupture, leading to secondary lens dislocation, and vitreous syneresis occurs.

Table 9.5 Pathophysiology of ocular changes in glaucoma.

Tissue	Effect	Result
Globe	Direct pressure	Globe enlargement
		Scleral ectasia/staphyloma
		Exposure keratitis
Conjunctiva/episclera	Indirect pressure (compression of vasculature with resultant increased venous pressure and decreased return)	Vascular injection/hyperemia
Corneal endothelium	Aqueous stagnation	Corneal edema
Uvea	Tissue hypoxia	Aqueous flare
		Muscle dysfunction
		Atrophy
Lens	Aqueous stagnation	Cataract
	Indirect pressure (zonular stretching with globe enlargement)	Subluxation/luxation
Vitreous	Direct pressure	Syneresis
Retina and optic nerve	Indirect pressure	Retinal atrophy and optic nerve atrophy +/− cupping, liquefactive necrosis (Schnabel's cavernous atrophy)
	Tissue hypoxia	
	Neuroexcitotoxicity	
	Direct pressure	
	Indirect pressure (compression of ganglion cell axons at lamina cribrosa with disruption of axoplasmic flow)	
	Hypoxia	

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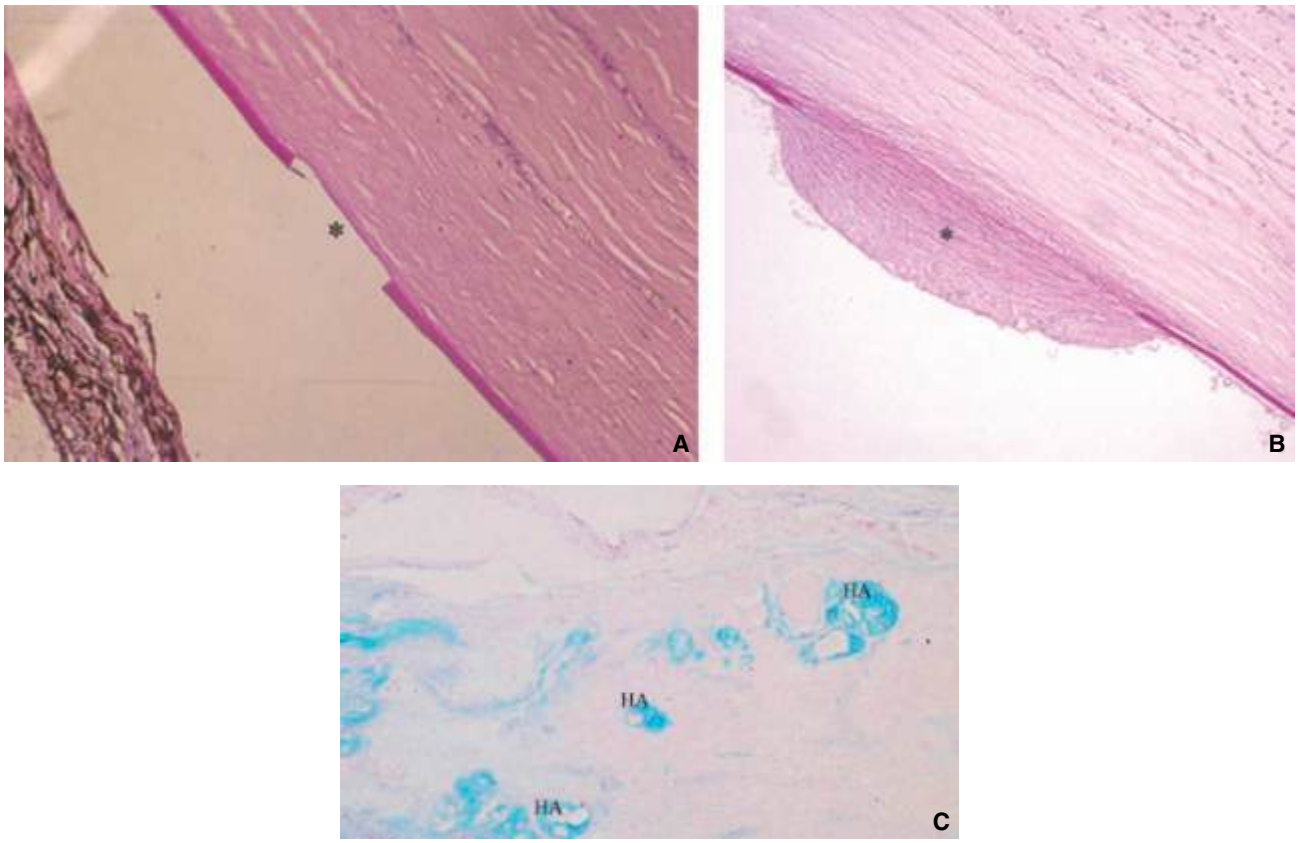


Figure 9.67 **A.** A light microscopic section of a corneal stria that developed secondary to buphthalmos and corneal stretching. Note the break in Descemet's membrane (*) and the corneal vascularization. Light microscopic examination of the retina confirmed glaucoma. (Original magnification 300×. Periodic acid-Schiff.) **B.** With time, striae will change in histologic appearance as corneal endothelial cells slide to cover the defect with subsequent elaboration of a new Descemet's membrane. Reduplication to form multiple thin layers of basement membrane (*) and fibrous metaplasia can occur. (Original magnification 200×. Periodic acid-Schiff.) **C.** Liquefactive necrosis of the optic nerve will occasionally develop in glaucoma, and hyaluronic acid (HA)-positive material that is presumed to be vitreous will be displaced into the optic nerve (Original magnification 200×. Alcian blue.)

The most critical changes involve the neurosensory retina and optic nerve. Fascinating and somewhat enigmatic species differences in susceptibility to and patterns of posterior segment changes exist. A variety of factors are at play in the pathogenesis of these changes. The first is a direct pressure effect on the cells of the retina. The second is a vascular effect on both the retinal and choroidal circulation with hypoxia. Thirdly, there is an indirect physical effect as the ganglion cell axons are compressed at the level of the lamina cribrosa with resultant disruption of axoplasmic flow. Lastly, affected retinal neurons may release neuroexcitotoxins that adversely affect neighboring neurons. In human eyes, classical glaucomatous degeneration is limited to the inner retina (ganglion cell and nerve fiber layers), and the cat eye largely follows this pattern. In the dog, degenerative changes frequently involve all of the retinal layers, and there is a geographic sensitivity whereby the superior retina is somewhat more resistant to IOP-mediated degenerative change. Cat and horse retinas experience less severe effects when compared to dogs with equivalent extent and duration of elevated IOP.

Optic nerve changes include atrophy with or without cupping of the optic disc and associated posterior bowing of the lamina cribrosa. Cupping occurs in approximately 50% of glaucomatous canine eyes as a result of the physical effects of elevated IOP on this relatively weak area of sclera, as well as the loss of axons and glial cells from the optic disc (Fig. 9.6). Large diameter ganglion cells and their axons are more susceptible to glaucomatous injury. Postlaminar liquefactive necrosis, or cavernous atrophy with vitreous implantation, can be found occasionally in glaucomatous canine eyes (Fig. 9.67C).

Optic Nerve Degeneration

Optic nerve degeneration or atrophy is a common pathologic diagnosis. The etiologies include optic nerve trauma, glaucoma, optic nerve neoplasia, optic neuritis, retinal degenerative processes, and retinal detachment. The gross clinical

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signs include a small dark optic disc (the result of demyelination) with or without cavitation. Histologic findings include decreased axons, gliosis, and fibrosis (Fig. 9.6).

Metabolic Diseases That Affect the Eye

Diabetes Mellitus

The ocular manifestations of diabetes mellitus other than cataracts have not been systematically studied in animal species. In human eyes, manifestations include: glycogenic vacuolization of the iris pigmented epithelium; thickening of the ciliary body basement membrane; and ischemic retinopathy with retinal and optic disc neovascularization. Secondary ramifications include vitreous hemorrhage, tractional retinal detachment, rubeosis iridis, and neovascular glaucoma. The canine and feline posterior segments are generally spared the vasoproliferative disease, perhaps simply as a consequence of disease duration. Diabetic cataracts in dogs are osmotic in nature, related to polyalcohol accumulation, and are rapid in onset, accompanied by intumescence, and are frequently associated with lens-induced uveitis.

Systemic Hypertension

The ophthalmic pathology of systemic hypertension in the dog and cat includes: vascular lesions including fibrinoid necrosis and occlusion of choroidal and retinal arterioles with nonperfusion of the choriocapillaris and ischemic atrophy of the RPE and retinal detachment; retinal ischemia with exudation, hemorrhage, and necrosis; and papilledema (Fig. 9.68).

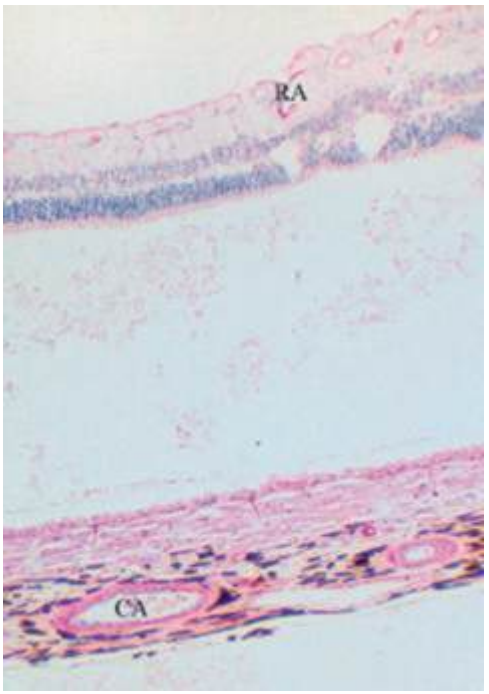


Figure 9.68 Systemic hypertension will induce significant intraocular disease including retinal detachment, retinal edema and hemorrhage, and fibrinoid necrosis of retina (RA) and choroidal (CA) arterioles. (Original magnification 250×. Periodic acid-Schiff.)

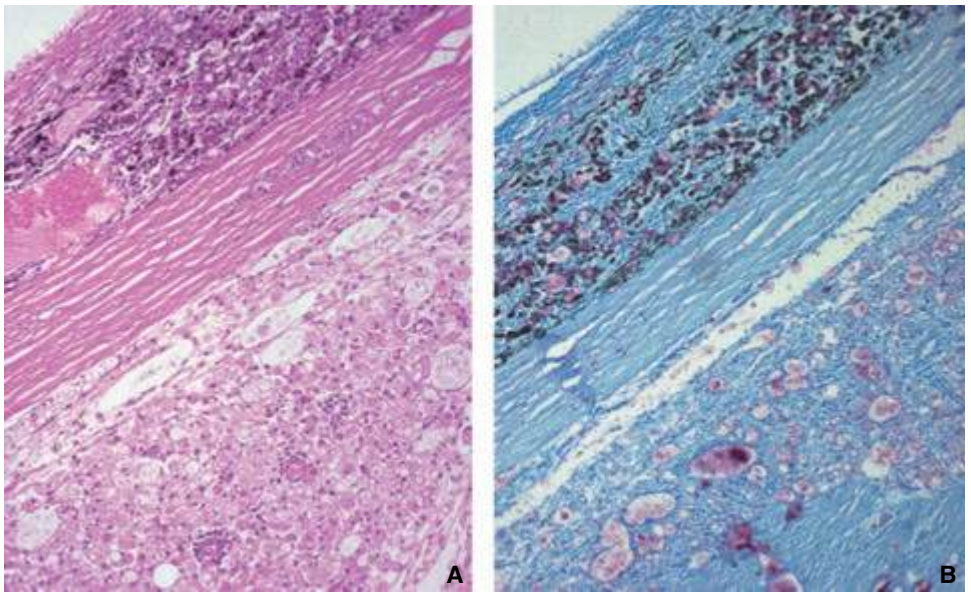


Figure 9.69 **A**. Granulomatous uveitis in a cat. Note the predominance of large foamy macrophages in the episcleral tissues and within the choroid and scattered lymphocytes and plasma cells around episcleral and scleral vessels and within the choroid. (Original magnification 300×. Hematoxylin and eosin.) **B.** Confirmation of acid-fast bacilli (ocular tuberculosis) in a cat noted in **A**. Note the filamentous pink bacilli within the macrophages. (Original magnification 300×. Fites stain.).

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Infectious Diseases That Commonly Affect Ocular Tissues

A myriad of infectious agents affect the orbital, adnexa, or ocular tissues, either as a result of vascular seeding or direct extension of endogenous infectious disease from adjacent tissues, or as a consequence of inoculation of endogenous agents as a result of trauma. The visibility of the eye, the importance of vision as a cognitive sense, and anatomic, physiologic, and immunologic factors contribute to the fact that ocular signs are frequently the reason for presentation of systemic infectious disease. Infectious agents, their morphology, and common features are summarized in Table 9.6.

Ocular Neoplasia

The discussion of neoplasia of the globe, orbit, and adnexa is organized by the tissue involved (orbit, adnexa, conjunctiva, cornea, uvea, retina, and optic nerve). Ocular neoplasms are either primary, metastatic, or the neoplasm invades the orbit and then the globe by extension or invasion from adjacent tissue. Most primary intraocular neoplasms are benign in behavior, despite frequent histologic evidence of the ocular tumor to the contrary. However, their expansive growth induces significant alterations that often necessitate enucleation.

Virtually any malignant neoplasm can metastasize to the eye. Indeed, the rich vascularity of the uvea and the eyes' suppressed interaction with the immune system might mark it as a favored site for metastatic disease. Malignant neoplasms extend into or from the eye via the uveal circulation because there is no intraocular lymph system. Based on the incidence of uveal metastasis in humans with extensive systemic neoplasia, there are likely more metastatic uveal neoplasms in animals than our current veterinary pathology archives indicate. As medical and radiation therapy prolongs life of companion animals, we anticipate an increased prevalence of metastatic ocular neoplasia. More clinical information about these tumors in specific ocular tissues can be found in the respective chapters.

Table 9.6 Common endogenous infectious causes of ocular inflammatory disease with key histopathologic features.

Organism/disease	Morphologic features of organism	Classification of inflammation
Feline immunodeficiency virus	—	Lymphoplasmacytic uveitis Retinal perivasculitis
Feline corona virus	—	Pyogranulomatous inflammation and lymphoplasmacytic vasculitis/endophthalmitis with prominent exudation
Feline herpes virus	Intranuclear inclusions	Lymphoplasmacytic keratoconjunctivitis/uveitis
Bovine malignant catarrhal fever	—	Lymphoblastic perivascular and intramural accumulation with vascular necrosis, +/− hemorrhage
Canine distemper virus	Inclusions in glial, other cells	Nongranulomatous lacrimal adenitis, chorioretinitis, optic neuritis
Canine adenovirus-1	Inclusions in corneal endothelial cells	Nongranulomatous anterior uveitis, neutrophilic endothelialitis
Rickettsia	—	Mononuclear perivasculitis Hemorrhagic uveitis
Borrelia burgdorferi		Nongranulomatous uveitis
Equine recurrent uveitis	Silver positive spirochetes, Onchocerca microfilaria (both rarely identified)	Lymphoplasmacytic uveitis Amyloid envelopment of ciliary processes (Fig. 9.12B, Fig. 9.53)
Histoplasma capsulatum	Intracytoplasmic (macrophage) 2–4 µm PAS+ yeasts with central density and a clear capsule	Diffuse granulomatous to pyogranulomatous uveitis
Cryptococcus neoformans	Focal-multifocal ellipsoidal yeasts 4–40 µm in diameter, thin-walled PAS+ yeasts, thick mucicarmine+ capsule	Minimal pyogranulomatous host reaction, neurotrophic
Coccidioides immitis	Large coalescing pyogranulomas with PAS+ endospore-containing spherules	Discrete pyogranulomatous uveitis
Blastomyces dermatitidis	5–20 µm PAS+ thick-walled, broad-based budding organisms	Diffuse pyogranulomatous inflammation (Fig. 9.16)

(Continued)

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Table 9.6 (Continued)

Organism/disease	Morphologic features of organism	Classification of inflammation
Aspergillus	PAS and silver+ septated hyphae within vitreous, oriented perpendicular to retinal surface	Pyogranulomatous endophthalmitis +/− necrosis
Prototheca (*P. zopfii* most common)	2–20 µm refractile, PAS+, argyrophilic wall. Unicellular or multiple daughter cells within a single parent cell (Shank et al., 2015)	Lymphoplasmacytic to diffuse granulomatous endophthalmitis with retinal detachment
Nocardia asteroides	Branching, filamentous gm+ bacteria, vitreous predisposition	Pyogranulomatous endophthalmitis +/− necrosis
Tuberculosis	Acid-fast organisms within macrophages	Discrete granulomatous uveitis/ panophthalmitis (Fig. 9.69)
Leishmaniasis	Protozoa within macrophages	Granulomatous uveitis/panophthalmitis
Toxoplasmosis	Rare merozoites or cysts	Lymphoplasmacytic uveitis distant from organism +/− focal necrotizing retinitis
Hepatozoon canis	Protozoan – intracytoplasmic gametes or schizonts in tissue (muscle biopsy)	Orbital cellulitis
Toxocara canis, *Baylisascaris procyonis*	+/− nematode fragments	Zonal eosinophilic granulomatous endophthalmitis
Bartonella	Gram-negative bacteria	Lymphoplasmacytic uveitis, conjunctivitis
Candida albicans	PAS positive yeast	Lymphoplasmacytic uveitis (Fig. 9.70)

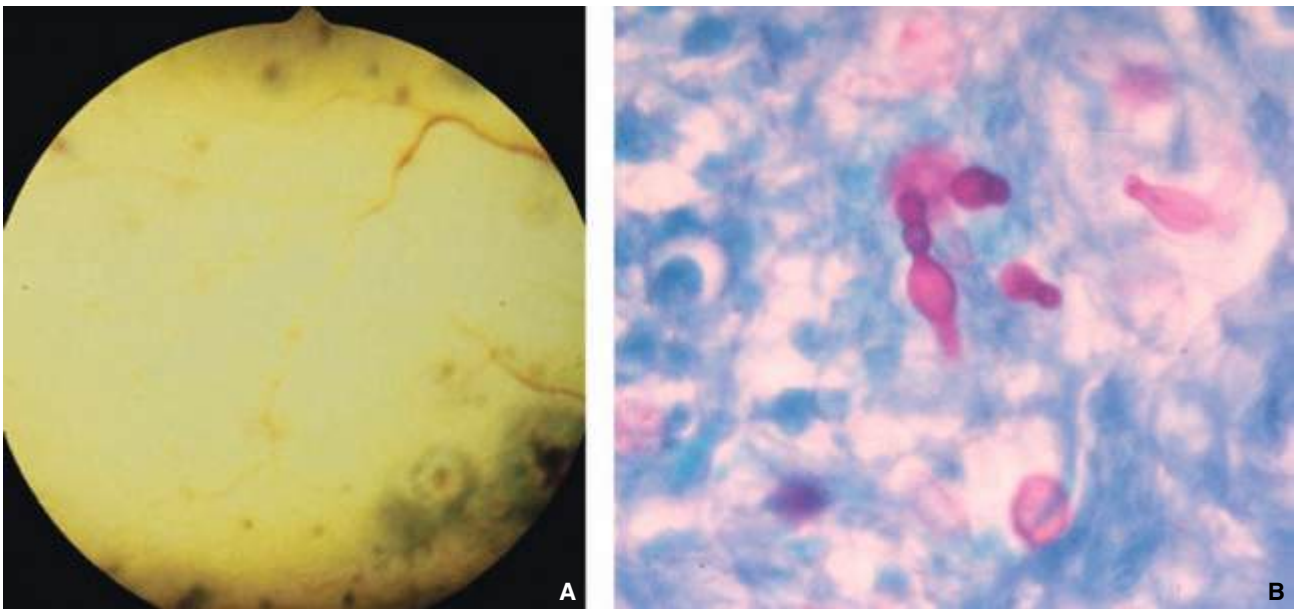


Figure 9.70 **A.** A fundus photograph of a cat with systemic candidiasis. **B.** Histologic appearance of *Candida albicans*. (Original magnification 400×. Periodic acid-Schiff.)

Orbital Neoplasia

Orbital neoplasia is uncommon in domestic animals. It is reported that over 56% are primary and arise from orbital tissues (Attali-Soussay et al., 2001; Gilger et al., 1992; Hendrix & Gelatt, 2000; Kern, 1985). Most of the secondary tumors are either lymphosarcomas or extensions from adjacent tissues (nasal carcinomas or sinus squamous cell carcinomas). The majority of orbital neoplasms are malignant and encompass a spectrum of tissues (Fig. 9.71A, B**)** (Attali-Soussay et al., 2001; Basher et al., 1997; Gilger et al., 1992; Goodhead et al., 1997; Hendrix & Gelatt, 2000; Kern, 1985; Mauldin et al., 2000; O'Brien et al., 1996; Pletcher et al., 1979; Rebhun, 1982;

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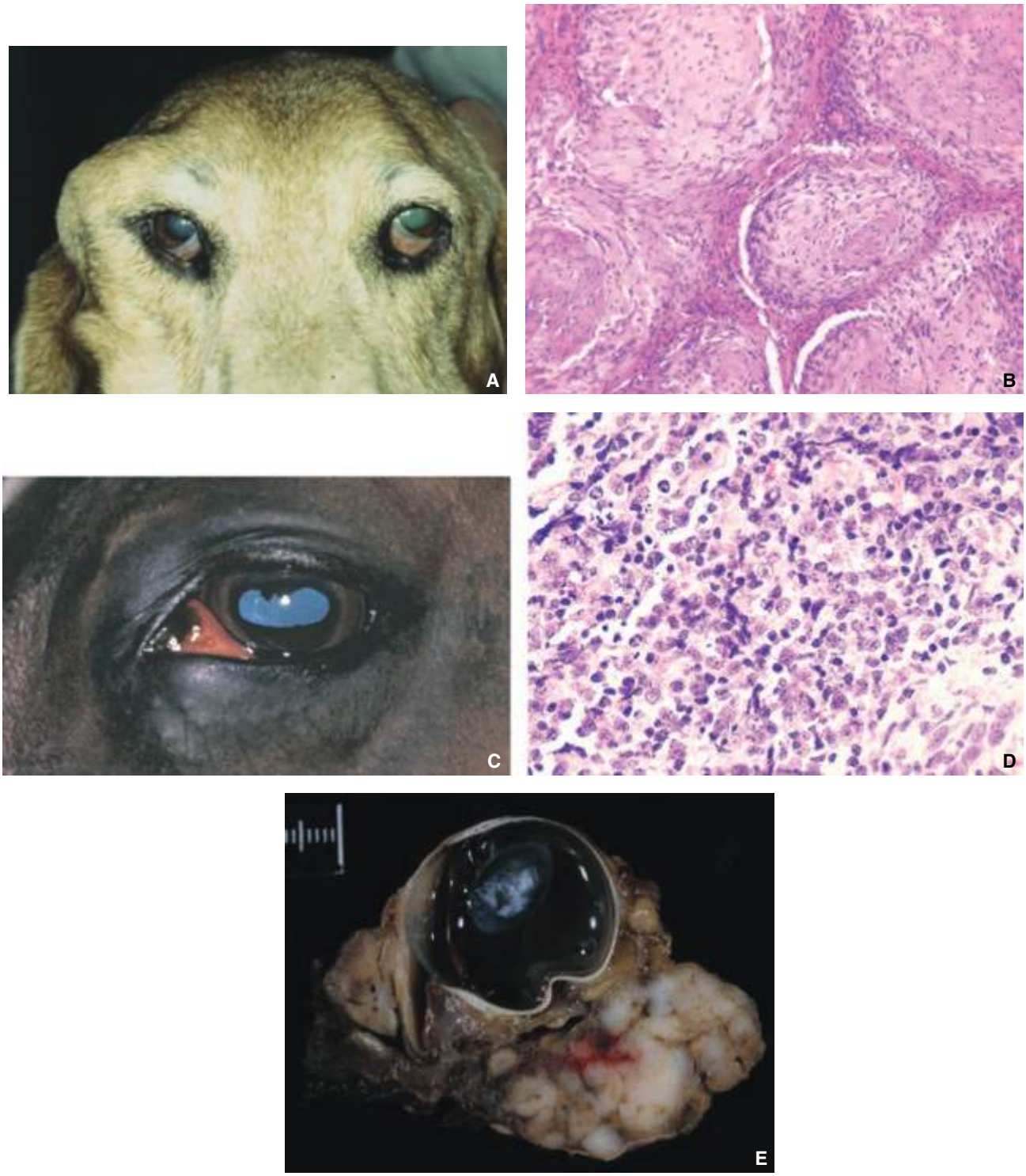


Figure 9.71 **A.** A firm mass is present arising from the zygomatic arch in this elderly dog. **B.** Flat bone osteosarcoma was confirmed after orbital biopsy of the dog in **A**. (Original magnification 2500×. Hematoxylin and eosin.) **C.** Note the medial canthal tumor that is inducing third eyelid prolapse in this horse. **D.** Histology confirmed orbital lymphosarcoma after an orbital biopsy was completed on the horse in **C**. (Original magnification 300×. Hematoxylin and eosin.) **E.** Note the glandular mass ventral to this exenterated canine globe. Light microscopic examination confirmed the diagnosis of zygomatic adenocarcinoma.

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Rebhun & Edwards, 1977; Scott et al 2016). As a rule, these are aggressive malignancies that carry a guarded prognosis.

Reported metastatic and invasive neoplasms include nasal adenocarcinoma, lymphosarcoma (Fig. 9.71C, D), squamous cell carcinoma (SCC) (Attali-Soussay et al., 2001; Cullen et al., 2000; Gilger et al., 1992; Kern, 1985; Rebhun, 1982; Rebhun & Del Piero, 1998; van Maanen et al., 1996; Wolfer & Grahn, 1995), peripheral nerve sheath tumors (Curto et al., 2016), and others.

Contemporary imaging has greatly enhanced the clinical management of orbital disease, allowing localization, characterization, and guided needle and excisional biopsies. The histories that accompany the biopsies of these metastatic orbital neoplasms are valuable to the pathologist in identifying the potential tissues of origin of anaplastic neoplasms. Histologic features of primary and metastatic orbital neoplasms are presented in Table 9.7 and Table 9.8.

Immunohistochemical staining patterns and electron microscopic ultrastructure are often required to confirm a tissue-specific diagnosis with anaplastic orbital neoplasia. Cytokeratin markers help identify epithelial neoplasms; vimentin is expressed on most neoplasms that arise from neurocrest tissues; synatophysin and neurospecific enolase help identify most neoplasms that are neuroectoderm in origin; actin is expressed on some mesenchymal neoplasms; and S100, tyrosinase, and melanin A are useful in identifying poorly pigmented melanomas.

Eyelid and Conjunctival Neoplasms

Eyelid and conjunctival neoplasms arise from a variety of dermato-, mesenchymal, and mucous membrane tissues. There are common tumors in dogs (tarsal gland adenomas), cattle (SCC), and horses (sarcoids and SCC). The characteristics of the common eyelid neoplasms of dogs are presented in Table 9.9. Most canine eyelid neoplasms are behaviorally benign even if histologic features of malignancy exist. Meibomian or tarsal gland adenomas account for approximately 40% of the reported eyelid tumors in

Table 9.7 Gross and histologic characteristics of primary orbital neoplasms.

Neoplasm	Gross features	Histologic features
Osteoma and osteosarcoma	Firm, white, and gritty on cross section	Trabecular bone with fibrous tissue and cartilage
Chondrosarcoma	Translucent grey	Cartilage and poorly differentiated mesenchymal cells
Rhabdomyosarcoma	Grey to red in color and nodular	Ribbon and strap cells with cross striations
Neurofibrosarcoma	Grey to white and firm	Bundles and fascicles of spindle cells
Lacrimal gland adenomas and adenocarcinomas	Pink, friable, lobulated mass located in dorsolateral orbital quadrant	Sheets of epithelial cells with variable gland and duct formation
Zygomatic gland adenomas and adenocarcinomas	Pink, friable, lobulated mass located in ventral orbit	Sheets of epithelial cells with variable gland and duct formation
Third eyelid adenomas and adenocarcinomas	Pink, friable, lobulated mass located in ventral medial orbital quadrant	Sheets of epithelial cells with variable gland and duct formation
Mast cell neoplasms	Edematous, red, friable mass without distinct borders	Diffuse round cell neoplasm with granules and eosinophils
Melanoma	Usually pigmented and arising from conjunctiva	Variable spindle to plump cells with pigment (usually)
Meningioma	White to grey and often round or oval	Multiple nests and whorls of spindle-shaped cells with osseous metaplasia

Table 9.8 Gross and histologic features of common metastatic and locally invasive orbital neoplasms of animals.

Neoplasm	Gross features	Histologic features
Nasal or sinus adenocarcinoma	Grey, friable, well vascularized, may have mucin, and will extend into orbit from the nasal cavity or sinus	Basal epithelial cells with variable adenomatous development
Squamous cell carcinoma	Salmon pink, friable mass that extends into orbit from the conjunctiva	Sheets of epithelial cells with tight junctions and variable keratin production
Lymphosarcoma	Grey, friable mass that lacks distinct borders	Diffuse round cell tumor with a large nuclei and minimal cytoplasm

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Table 9.9 Common eyelid and conjunctival neoplasms.

Neoplasm	Species most commonly affected	Gross characteristics	Histologic features
Tarsal gland adenoma	Dogs	Variably pigmented, friable nodular mass associated with the tarsal glands (Fig. 9.72A)	Multilobular arrangement with large vacuolated epithelial cells or basal cells usually arranged in distinctive glandular pattern with variable pigment and often with chalazion and associated foamy macrophages and lymphocytes (Fig. 9.72B, C)
Squamous cell carcinoma	Cattle, horses, cats	Pale, salmon pink, friable, flat eyelid skin or conjunctival mass	Large, pale, pink-staining epithelial cells with intercellular bridges, abundant cytoplasm, keratin pearls, and hyperplastic projections into the substantia propria (Fig. 9.72D–H)
Papillomas	Dogs, horses, and cattle	Pedunculated roughened, friable, cauliflower-like, often pigmented eyelid mass of younger animals (Fig. 9.73A)	Hyperplastic squamous epithelial fronds with central fibrovascular cores (Fig. 9.73B)
Histiocytic tumors	Dogs and cats	Firm, nodular, pale masses (Fig. 9.74A)	Large, pale macrophage-like cells (Fig. 9.74B).
Lymphosarcoma	Any species	Infiltrative eyelid mass that is firm (Fig. 9.75A).	Round, cells with large nuclei and sparse dark cytoplasm (Fig. 9.75B)
Eyelid melanocytomas	Dogs and horses	Pigmented, often pedunculated masses on the eyelid skin (Fig. 9.76A)	Variable mix of spindle to plump more epithelial-like cells with prominent nucleoli, and they are usually pigmented (Fig. 9.76B)
Conjunctival melanoma	Dogs, cats	Flat, variably pigmented conjunctival masses, commonly occur on the third eyelid (Fig. 9.77A)	Variable pigmentation with a mix of plump spindle cells with prominent nucleoli and noted junctional activity (Fig. 9.77B)
Sarcoid	Horses	Firm, pale, pedunculated, or intradermal masses	Spindle to spiral cells that form interlacing bundles with overlying hyperplastic epithelium with extensive rete pegs (Fig. 9.78)
Mast cell tumors	Dogs and cats	Edematous and hyperemic diffuse eyelid masses	Large, round cells with cytoplasmic granules
Peripheral nerve sheath neoplasms	Cats and horses	Firm, pink eyelid mass	Sheets and fascicles of spindle cells
Hemangioma, hemangiosarcoma	Dogs, horses	Vascular mass that originates in the conjunctiva and may extend into the cornea (Fig. 9.79A)	Vascular mass with dilated thin-walled vascular channels (hemangioma); hemangiosarcomas are more cellular with evidence of invasion (Fig. 9.79B, C)
Feline hidrocystoma	Cats	Cystic, multifocal, pigmented eyelid mass	Epithelial-lined cysts that likely arise from sweat glands

dogs, with melanomas and papillomas accounting for 20% and 17% respectively (Gelatt, 1980; Krehbiel & Langham, 1975; Roberts & Severin, 1986). In contrast, in the cat and cow, SCC is the most common eyelid and conjunctival neoplasm (Anderson et al., 1957; Kaps et al., 2005; Monlux et al., 1957; Williams et al., 1981).

Tarsal gland adenomas are sebaceous gland neoplasms that develop most commonly in older dogs (>10 years) (Fig. 9.72A). In any given tarsal gland neoplasm, either basal cells with very little sebaceous differentiation predominate (tarsal gland epithelioma) or fully differentiated glandular cells predominate (tarsal gland adenoma) (Fig. 9.72B, C). In the older literature, ductal adenomas were confused with basal cell carcinomas (Gelatt, 1971), which are rarely encountered in domestic animals. Histologically, hemorrhage, necrosis, pigmentation, and chalazion are commonly noted within these tumors. The lipid secretion is often extruded from the tarsal gland during progressive neoplastic expansion and induces a significant granulomatous response. Rarely hyperchromatism and increased mitotic activity give rise to concerns; however, excision or ablation is curative.

SCC is a common eyelid and conjunctival neoplasm of horses, cattle, and cats. Poorly pigmented eyelids, actinic exposure, and papilloma virus play a role in pathogenesis and predispose to precancerous changes including plaques, papillomas, keratin horns (Fig. 9.72D), and carcinoma *in situ* (Fig. 9.72E). These preneoplastic lesions are erythematous,

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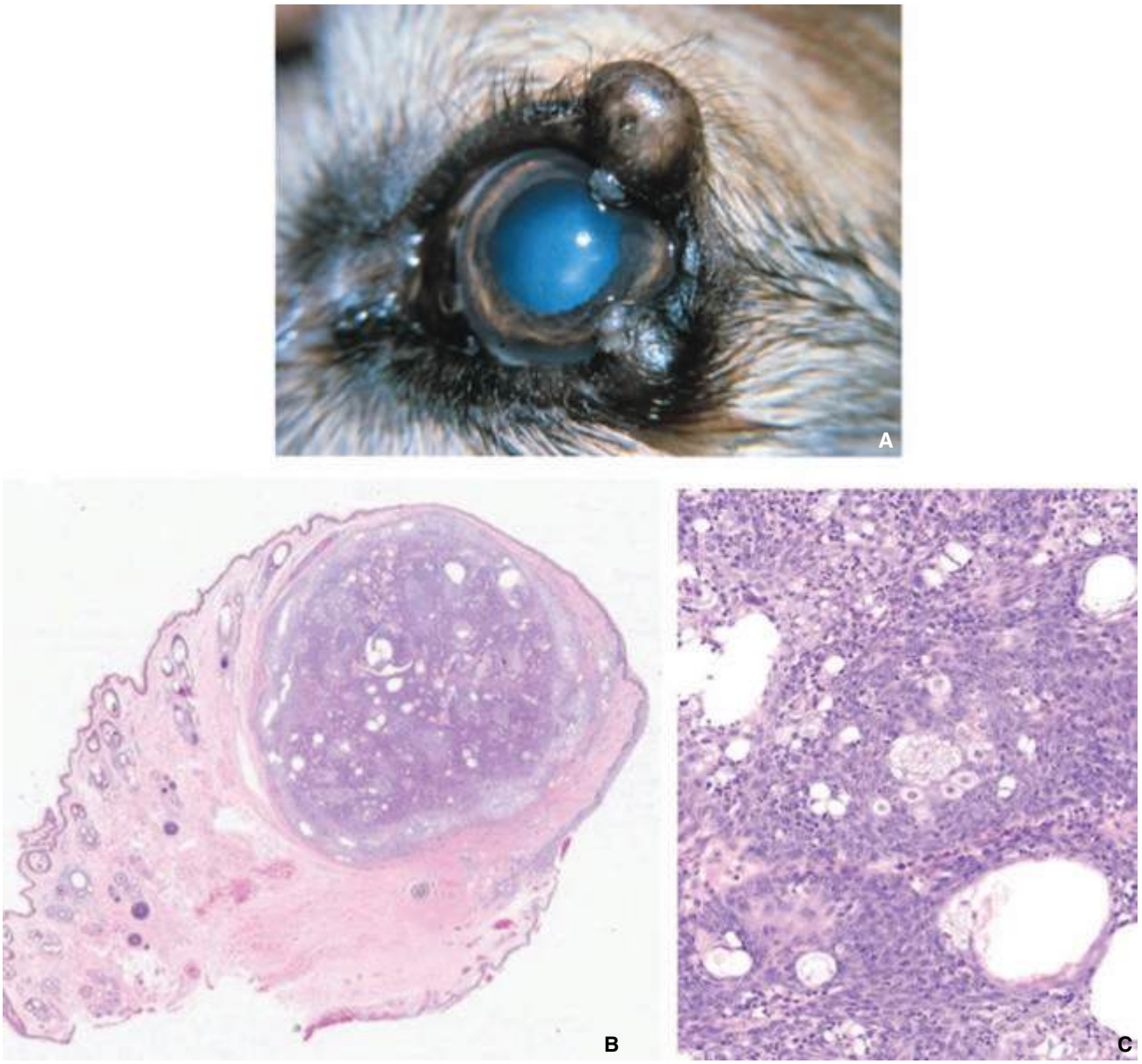


Figure 9.72 **A.** Multiple tarsal gland adenomas on the eyelid margin of an aged American Cocker Spaniel. **B.** Subgross appearance of one tarsal gland adenoma depicts the marginal location with displacement of the eyelid skin and palpebral conjunctiva over the basophilic adenoidal tumor. (Original magnification 2×. Hematoxylin and eosin.). **C.** Histologic features of a tarsal gland adenoma include basophilic staining basal cells with focal sebaceous differentiation and a mild diffuse neutrophil and macrophage infiltration. This inflammatory cell infiltration is a common response to the lipid extrusion (clear vacuoles). (Original magnification 300×.Hematoxylin and eosin.) **D.** A keratin horn that was removed from the cornea near the temporal limbus of a Hereford bull. (Original magnification 200×. Hematoxylin and eosin.) **E.** Bovine squamous cell carcinoma (SCC) *in situ* in the perilimbal corneal epithelium. Tumor cells are confined to the epithelium and have not breached the basement membrane to invade the stroma. The surface is keratinized and contains a focal keratin pearl. (Original magnification 300×. Hematoxylin and eosin.) **F.** A well-differentiated SCC from the conjunctiva of a Hereford bull invades the subconjunctival tissues. Multiple keratin pearls are present. (Original magnification 300×. Hematoxylin and eosin.) **G.** Orbital biopsy with keratin pearls and diverse epithelial morphology confirms an invasive SCC in a horse. **H.** Histologic section of invasive SCC has replaced most of this bovine cornea in this cow. (Original magnification 300×. Hematoxylin and eosin.)

scaly, crusty, or even hornlike, and they can regress spontaneously or slowly develop into SCC. In horses, cattle, and cats, SCC manifests as a friable salmon pink placoid often-ulcerated lesion. Incisional biopsy is used to confirm the increased mitotic figures. Broder's classification can be utilized to establish the prognosis; grade I SCCs are well differentiated with large round epithelial cells with prominent intercellular bridges, abundant pink cytoplasm, homogenous

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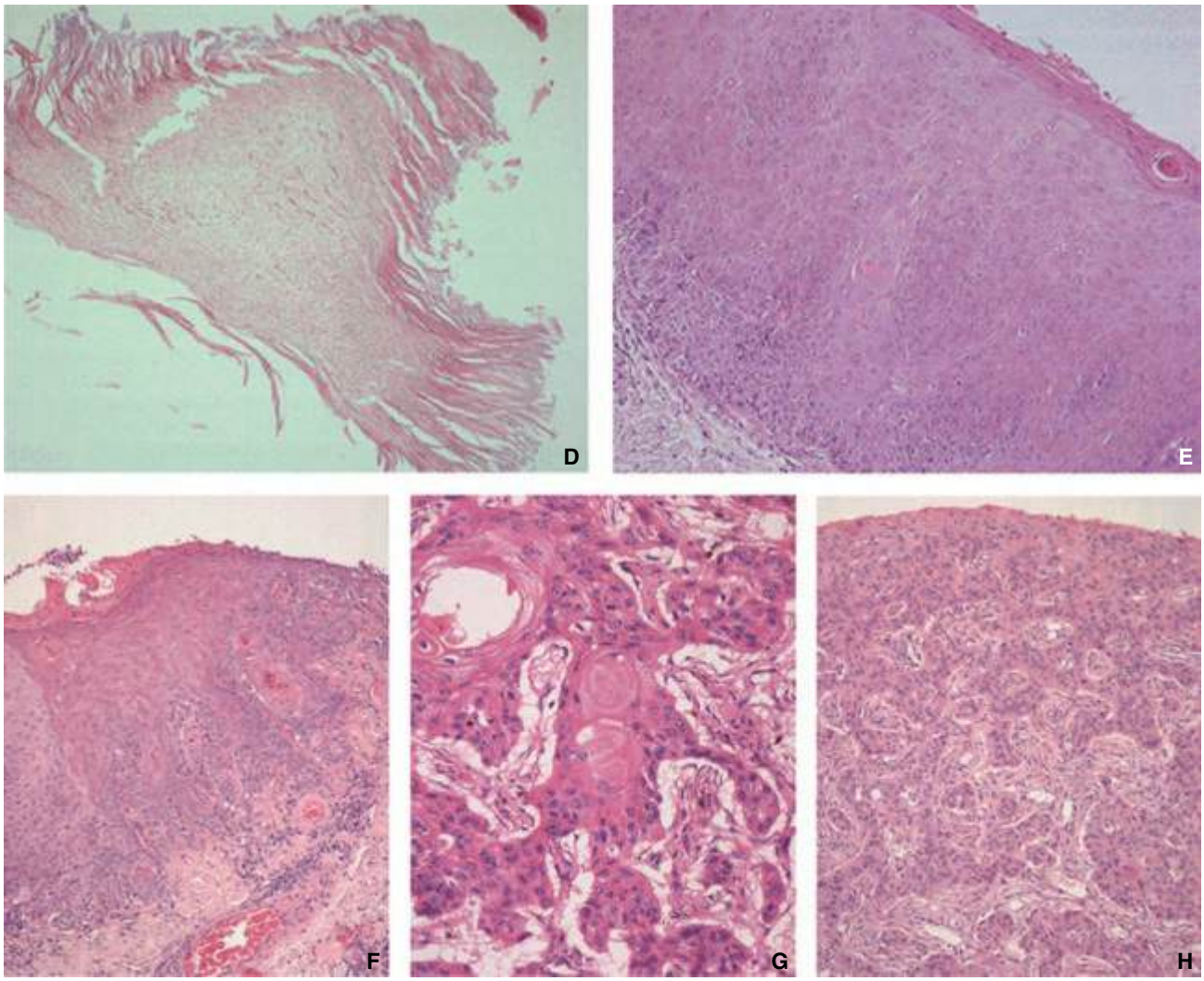


Figure 9.72 (Continued)

nuclear patterns, and only a few mitotic figures. Keratin pearls are prominent features as are neutrophils within these well-differentiated neoplasms (Fig. 9.72F). Grade II SCCs are similar; however, the mitotic index is higher. Grade III SCCs have fewer keratin pearls and there is evidence of tissue invasion which creates multiple neoplastic islands (Fig. 9.72G). Grade IV tumors are poorly differentiated carcinomas with absence of keratin pearls and amphophilic cytoplasm with pleomorphic and hyperchromatic nuclei. The mitotic index is high, and tissue invasion is prominent (Fig. 9.72H). Metastatic potential increases with each grade of SCC, and although uncommon, these tumors can spread via the lymphatics to the regional lymph nodes (mandibular, retropharyngeal, and mediastinal). Papilloma virus plays a role in the development of some SCCs. Papillomas of the eyelids are common in dogs, horses, and ruminants (Fig. 9.73A, B**)**. Papillomas are induced by papilloma viruses and manifest as multiple lesions in young animals (<1 year of age). Grossly, papillomas are often pedunculated, with a corrugated surface. Light microscopic examination reveals hyperplastic squamous epithelium that envelops a fibrovascular core, and the viral-induced papillomas manifest with koilocytes and keratohyaline deposits. Papillomatoid variations of SCCs are similar in appearance but more invasive.

Histiocytomas are benign and similar to viral-induced papillomas and occur in young animals. They are round and smooth and manifest as sessile smooth pink tumors on eyelid skin. Often, the center of the tumor is depressed and may be ulcerated. Light microscopic features include a mass of large round to polyhedral histiocytes that extend through the epidermis and into the dermis (Fig. 9.74). These neoplasms resolve spontaneously, usually over a few months.

Mast cell neoplasms occasionally arise in the eyelids and conjunctiva (Grahn et al., 1994; Hallstrom 1970; Johnson et al., 1988) and occasionally invade the cornea (Halse et al., 2014), and metastasis to the uvea has been reported (Boostrom et al., 2014). Although often nodular proliferative lesions, eyelid mast cell tumors can be diffuse and infiltrative,

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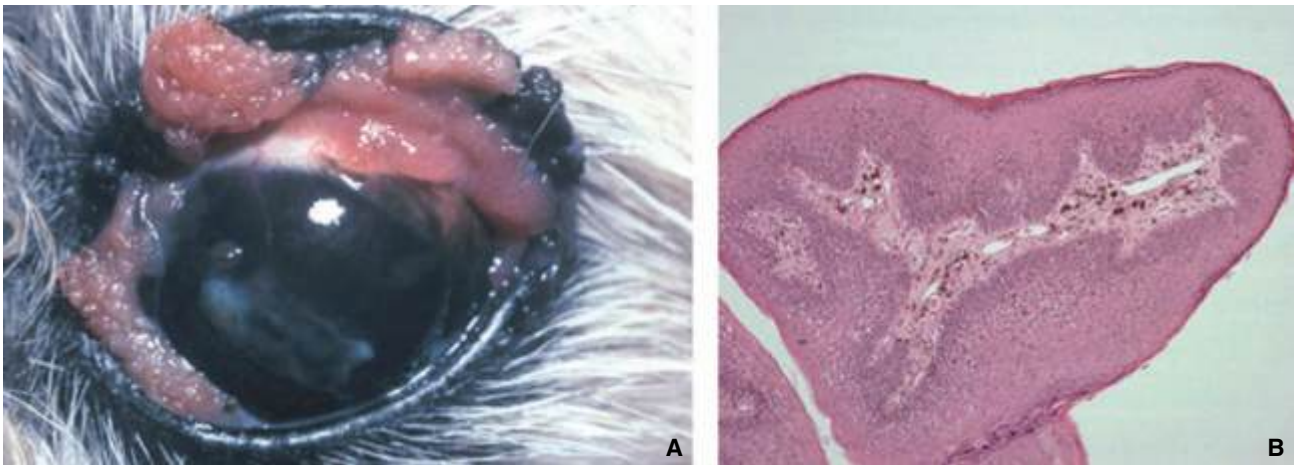


Figure 9.73 **A.** Conjunctival papillomatosis in dog with pigmentary keratitis. Note the characteristic corrugated surface. **B.** Histological section of a conjunctival papilloma with an acanthotic hyperkeratotic epithelium enveloping a fibrovascular core. (Original magnification 200×. Hematoxylin and eosin.)

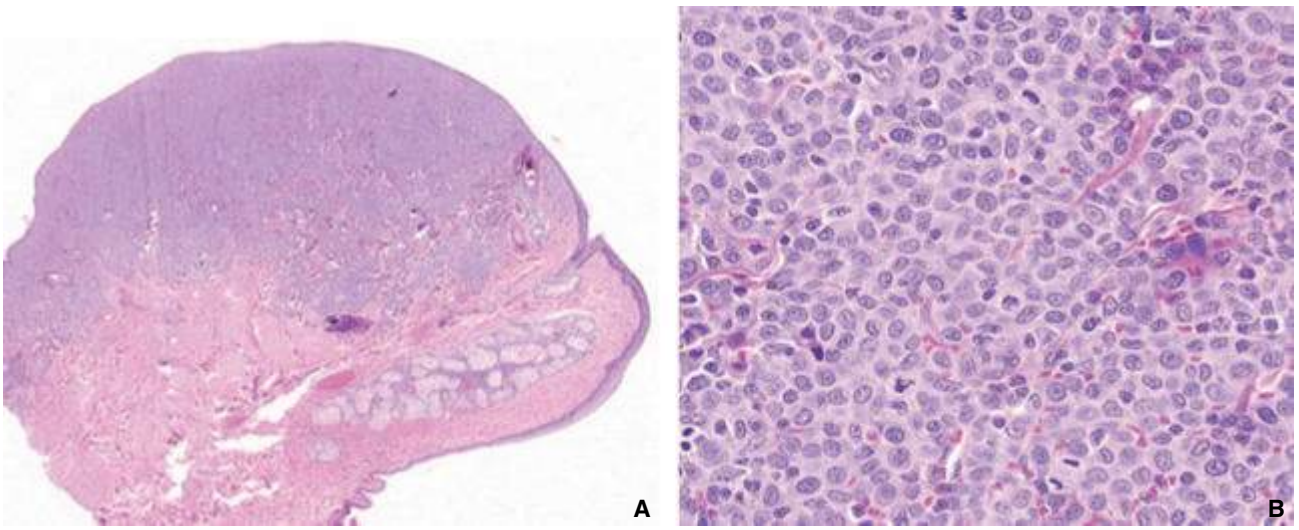


Figure 9.74 **A.** Button-like profile of a histiocytoma in a young dog. (Original magnification 50×. Hematoxylin and eosin.) **B.** Large polyhedral cells with bland nuclei and abundant pale cytoplasm are characteristic of histiocytomas. (Original magnification 300×. Hematoxylin and eosin.)

presenting with hyperemia, edema, and swelling. Histopathology reveals a diffuse population of round cells with basophilic granular cytoplasm (see Fig. 9.14). When a mast cell neoplasm is confirmed histologically, it should be staged by aspirating the draining lymph nodes and the primary source of the neoplasm determined. Mast cell neoplasms are graded by differentiation of the cells, mitotic activity, nuclear and nucleolar size, and tissue invasion. Eosinophils and collagen degeneration are common accompaniments in mast cell neoplasms. Fortunately, most periocular mast cell neoplasms are predictable, and they behave as benign neoplasms in most species.

Eyelid and conjunctival lymphosarcoma (Fig. 9.75) present as diffuse or focal tumors with or without inflammation (Blodi & Ramsey, 1967; Krohne et al., 1994, McCowan et al., 2014). Most, if not all, are a manifestation of systemic disease. Morphology is that of a round cell tumor with either follicular or diffuse architecture. Diffuse lymphosarcomas are categorized by nuclear size (small, mixed, and large). Follicular lymphosarcomas are categorized into floral, mantle cell, marginal cell, and large cell variants. Immunohistochemistry is useful in diagnosing T cell, B cell, and leukemic variants of lymphosarcoma.

Peripheral nerve sheath neoplasms (schwannoma) of the eyelids are reported in cats and horses (Hoffman et al., 2005; Strubbe, 2001). These are locally aggressive neoplasms that are firm on palpation. Histologic characteristics include interlacing fascicles of spindle cells with Antoni A patterns

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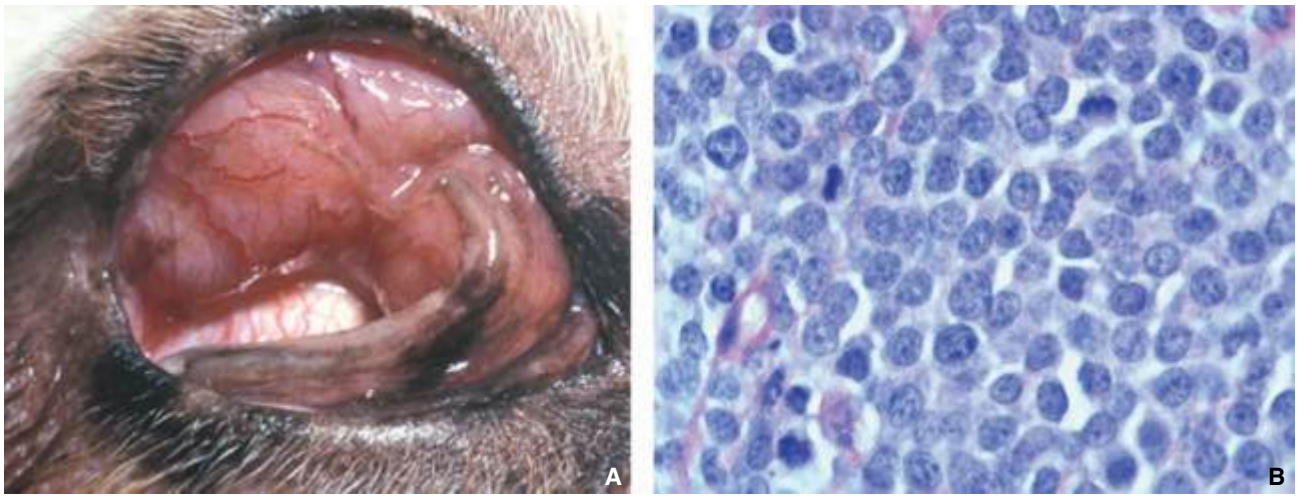


Figure 9.75 **A.** Conjunctival lymphosarcoma in a Golden Retriever that presented with bilateral conjunctival swelling. A diffuse lymphadenopathy was also present. **B.** Conjunctival biopsy of the lesions depicted in **A** revealed a homogeneous population of round cells with scant cytoplasm and anisokaryosis that are characteristic of lymphosarcoma. (Original magnification 400×. Hematoxylin and eosin.)

with elongated plump nuclei arranged in rows and palisades and Antoni B patterns where the spindle cells are arranged in a loose interlacing pattern with smaller nuclei.

Eyelid melanocytomas are round to oval black to brown tumors that involve eyelid skin of older animals (Fig. 9.76A). Light microscopic features include variable pigmented round- to spindle-shaped melanocytes with prominent nucleoli (Fig. 9.76B). Eyelid melanocytomas are benign. Occasionally, eyelid melanomas are diagnosed and are malignant with a morphology of pleomorphic cells with a mitotic index greater than 2 per high power field with evidence of invasive growth into the dermis and subcutaneous tissues. Malignant melanomas are often accompanied by ulceration and inflammation. Poorly pigmented melanomas can be difficult to diagnose based on morphology, and immunohistochemical stains including S-100, tyrosinase, HMSA5, and melanin A are often useful in rendering a diagnosis.

Conjunctival melanoma is usually malignant, invasive, and prone to metastasize (Collins et al., 1993; Cook et al., 1985; Croxatto, 1992; Levene, 1973). Gross examination

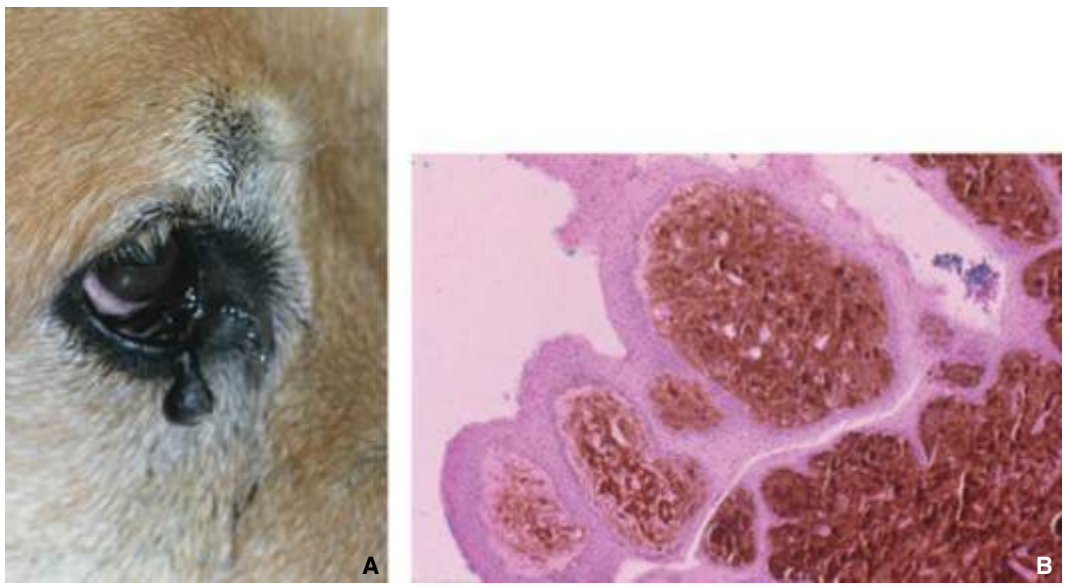


Figure 9.76 **A.** Darkly pigmented and pedunculated eyelid melanoma in a Golden Retriever. **B.** Plump pigment-laden noncohesive melanocytes within hyperplastic epithelium characterize eyelid dermal melanocytomas. These are benign and excisional biopsies are curative. (Original magnification 300×. Hematoxylin and eosin.)

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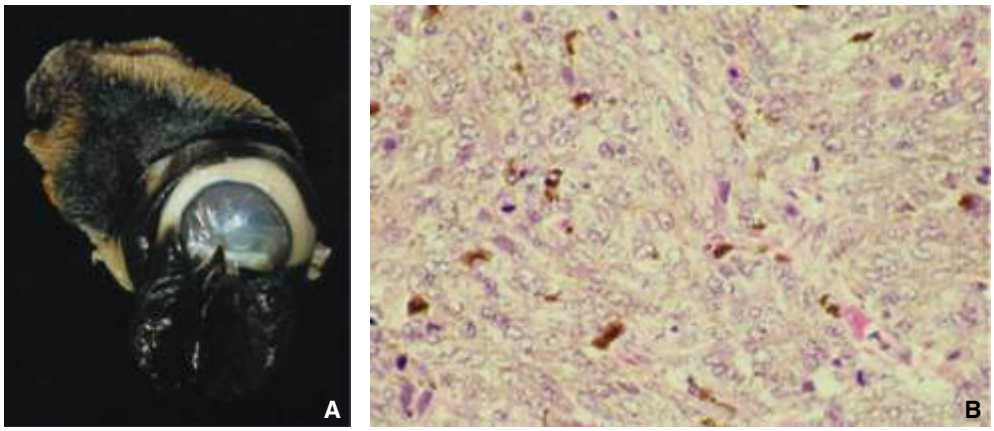


Figure 9.77 **A.** Conjunctival melanoma when ignored will invade and metastasize. Involvement of the conjunctiva, third eyelid, and cornea are evident in this canine exenteration specimen. **B.** Lightly pigmented conjunctival malignant melanoma from a dog with anisocytosis, anisokaryosis, and a high mitotic index. Malignant conjunctival melanomas will grow in tendrils to beyond the apparent edges of the tumor which makes complete surgical excision problematic. (Original magnification 300×. Hematoxylin and eosin.)

reveals a black to brown, flat to nodular mass with indistinct margins (Fig. 9.77A). The bulbar surface of the third eyelid is the most common site of origin. Light microscopic examination of biopsies or enucleation or exenteration specimens will show variably pigmented pleomorphic cells that appear as plump spindle or epithelioid cells (Fig. 9.77B). These tumors arise from the basal epithelium and a distinguishing feature is junctional activity where nests of neoplastic melanocytes extend out from the basal layer to invade the substantia propria. Exenteration might be lifesaving in extensive cases.

Sarcoids are common tumors of the eyelids of horses (Knottenbelt & Kelly, 2000; Piscopo, 1999; Tarwid et al., 1985). Thoroughbred horses appear to be predisposed and younger horses are commonly affected with these benign fibroblastic tumors. Light microscopic examination reveals a monotonous population of fascicles of spindle cells that are woven together (Fig. 9.78). These spindle cells extend through the dermis, and the overlying epithelium extends deep into the sarcoid as rete pegs. These benign fibromas induced by bovine papilloma virus and a type C retrovirus respond to several therapies (Cheevers et al., 1982; Nasir & Reid, 1999; Trenfield et al., 1985).

Conjunctival hemangiomas and hemangiosarcomas occur in dogs, horses, and other domestic animals (Buyukmichi, 1981; Crawley et al., 1987; Hacker et al., 1986; Moore et al., 1986; Mughannam et al., 1997; Murphy et al., 1989; Summer, 1990; Vestre et al., 1982). Clinical features include a vascular tumor that often develops in the bulbar conjunctiva and might extend into adjacent cornea (Fig. 9.79). Hemangiomas are benign and composed of well-differentiated capillaries, pleomorphic hyperchromatic spindle cells, and prominent hyalinized collagen beams. Hemangiosarcomas consist of poorly differentiated endothelial cells, lack well-developed capillaries, and are invasive. Factor VIII immunochemical

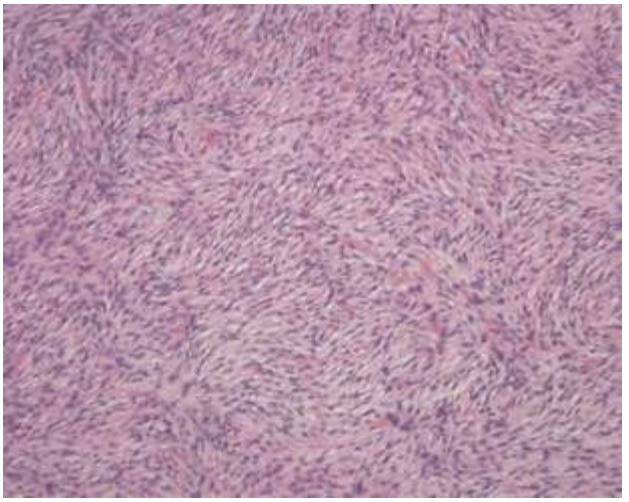


Figure 9.78 Equine eyelid sarcoid with prominent interlacing spindle cells and a storiform pattern. (Original magnification 300×. Hematoxylin and eosin.)

positivity is of value in poorly differentiated tumors. Recurrence at the original site and metastasis, especially in horses, are reported. Subconjunctival hibernomas are reported in dogs. These brown fat tumors are composed of sheets of polygonal cells that can be labelled with uncoupling protein-1 (Stuckey et al., 2015).

Leiomyoma has been reported to develop in the third eyelid of the dog. Histologically, spindle to polygonal cells with eosin staining cytoplasm were seen. They stained positively with Masson's trichrome and labelled positively with smooth muscle actin (Mathes et al., 2016). Adenocarcinomas are the most common neoplasm of the third eyelid lacrimal gland (Dees et al., 2016).

Avian ocular neoplasia is generally similar to mammals (Fernandez & Dubielzig, 2015). Ocular and conjunctival

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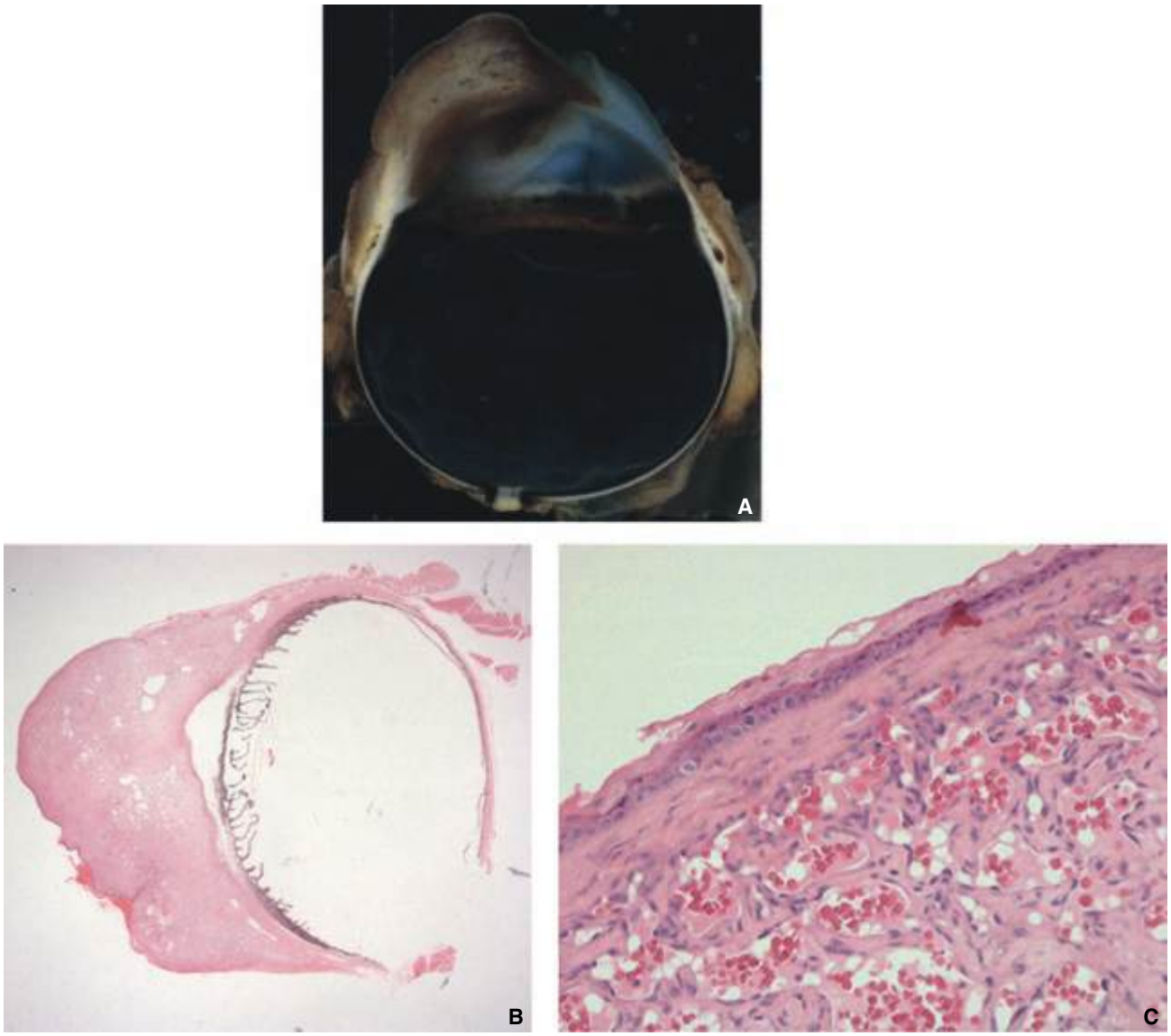


Figure 9.79 **A.** Gross section of a canine eye with a vascularized corneal and scleral tumor. **B.** Subgross section of this tumor suggests corneal and scleral invasion and multiple vascular channels within the neoplasm. **C.** The conjunctival hemangiosarcoma is composed of variable sized vascular channels that invaded the cornea and sclera. (Original magnification 350×. Hematoxylin and eosin.)

mucinous adenocarcinomas have recently been reported in an Ostrich (*Struthio camelus)* (Perrin et al., 2017).

Neoplasms of the Cornea and Limbus

Although the cornea can be invaded by conjunctival malignancies, primary neoplasms of the cornea and limbus are limited to limbal melanocytoma (Diters et al., 1983; Harling et al., 1986; Martin, 1981; Ryan & Diter, 1984) with isolated reports of SCC (Bernays et al., 1999; Lassaline et al., 2015; Latimer et al., 1987), nerve sheath tumors (Leis et al., 2017a), hemangiomas/hemangiosarcomas, fibrosarcomas (Strong et al., 2016), and corneal melanoma (Bauer et al., 2015). Scleral neoplasms have not been reported, although several primary eyelid, conjunctival, orbital, and intraocular neoplasms invade the sclera.

Limbal melanocytoma is a relatively common primary neoplasm of the cornea and sclera of the dog and occurs less frequently in cats (Harling et al., 1986). Limbal melanocytomas are benign and arise from the band of melanocytes that delineate the limbus. Gross appearance is that of a curvilinear rainbow-shaped band of darkly pigmented neoplastic cells that extend from the limbus into the deep corneal stroma just above Descemet's membrane as well as outward into the deep sclera and episclera, Tenon's capsule, superficial cornea, and conjunctiva (Fig. 9.80A). A zone of lipid degeneration often precedes the advancing edge of the

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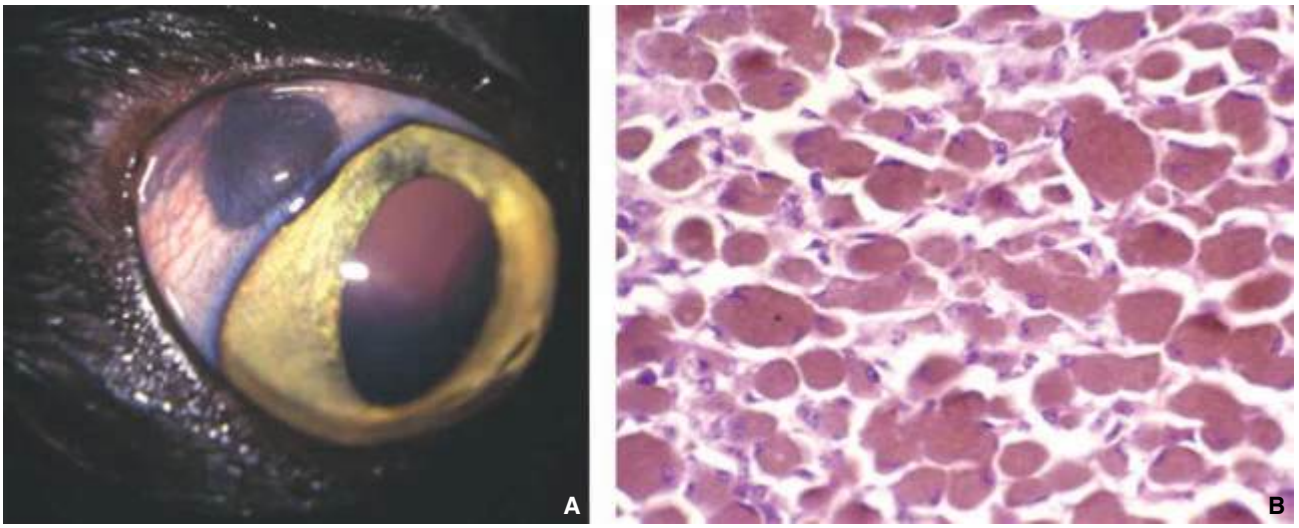


Figure 9.80 **A.** Limbal melanocytoma in a cat. Note the small fan-shaped deep corneal extension and the more obvious extension under the conjunctiva. This growth pattern is pathognomonic for limbal melanoma. **B.** Histologic section of a limbal melanoma in a cat. The predominate cells are plump melanocytes, although pigmented spindle cells are present within this benign neoplasm. (Original magnification 3000×. Hematoxylin and eosin.)

neoplasm as it expands into cornea. Light microscopy reveals a population of pigment-laden melanocytes that require bleaching for appreciation of cellular morphology (Fig. 9.80B). Two cell types are present, a spindle cell and a large noncohesive melanin-laden cell, with the intracytoplasmic pigment displacing the nucleus to the cell periphery. Nuclei are bland with mild anisocytosis, single nucleoli, and rare mitotic figures. Growth is by expansion rather than invasion.

Limbal melanocytomas occur in two age groups of dogs: in young animals, growth tends to be relatively rapid compared with animals older than 8 years of age where slow growth may dictate less aggressive intervention. Intraocular extension rarely if ever occurs. In cats, these tumors tend to be slow-growing, and gross and histologic manifestations mirror the canine limbal melanocytoma.

Primary corneal SCC is uncommon (Bernays et al., 1999; Latimer et al., 1987). Gross manifestations include a friable pink corneal tumor that is not contiguous to the limbus. In dogs, pigmentary keratitis and topical immunosuppression are assumed to be predisposing factors; chronic corneal exposure may likewise contribute to the pathogenesis (Colitz et al., 2007; Dreyfus et al., 2011; Latimer et al., 1987). The light microscopic findings are similar to those described for conjunctival SCC and include epithelial atypia, hyperchromasia, mitoses, anaplasia, and invasion of the stroma. Squamous eddies and keratin pearls are commonly encountered. The differential diagnoses of corneal SCC include extension from a primary conjunctival site, corneal carcinoma *in situ* (where the neoplasm is confined to the epithelium and does not extend through the basement membrane), corneal papilloma, and corneal inclusion cysts.

Intraocular Neoplasia

Intraocular neoplasia arises from the globe (primary) or is metastatic to the eye from a distant site. The clinical and histologic features of common primary and metastatic intraocular neoplasms are listed in Table 9.10. Statistically, the majority of primary neoplasms are benign; however, their expansive growth and associated complications of glaucoma, uveitis, and intraocular hemorrhage can lead to blind and painful eyes. Additional information about each tumor type can be found in the respective clinical chapters.

Uveal Neoplasia: Uveal Melanocytomas and Melanomas

Uveal melanocytomas and melanomas are the most common intraocular neoplasm of dogs. The differential diagnoses that should be considered during the clinical examination include iridal nevi and freckles, and uveal cysts. The former can be differentiated clinically from uveal melanomas by their flat appearance and static behavior. Histologically, the freckles and the nevi are benign collections of spindloid melanocytes. Uveal cysts are round to oval and fluid-filled smooth-margined lesions. They have distinctive clinical features, including transillumination (neoplasms are solid and will not transilluminate), or when required related to posterior chamber locations, ultrasound will identify the fluid-filled round cystic structures.

Anterior uveal melanocytomas and melanomas manifest clinically in either nodular or diffuse forms and arise from iris, ciliary body, or choroid (Bussanich et al., 1987; Friedman et al., 1989; Giuliano et al., 1999; O'Toole & Murphy, 1983; Ryan & Diter, 1984; Truska et al., 1985; Wilcock & Peiffer, 1986). In dogs and horses, the nodular

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Table 9.10 Clinical and histologic characteristics of some primary and metastatic intraocular neoplasms.

Neoplasm	Species and clinical behavior of the neoplasm	Gross appearance	Histologic characteristics
Uveal melanocytoma	Dog, horse, cat; benign clinical course is expected	Nodular variably pigmented iridal tumor or ciliary mass (Fig. 9.81A, B); rare involvement of choroid	Variably pigmented spindle to ovoid cells with small, round, or slightly elongated nuclei, and large round heavily pigmented cells (Fig. 9.81C)
Uveal melanoma	Dog, horse, cat	Nodular or diffuse anterior uveal tumor with rare choroidal involvement	Plump spindle and epithelioid cells with anisokaryosis and a high mitotic index (Fig. 9.81D)
Choroidal melanoma	Dog, occasionally in cats; this neoplasm is benign, and if it is extensive and exits the globe around the optic nerve, care should be taken to ensure clean margins around the optic nerve	Brown choroidal mass (Fig. 9.82A)	Choroidal location is key to diagnosis, variably pigmented spindle to polyhedral cells with eccentric nuclei and single nucleoli, will invade the sclera often extending into the orbit around the optic nerve (Fig. 9.82B, C)
Diffuse iris melanoma	Cat, occasionally seen in dogs; generally considered benign provided the globe is enucleated prior to extension of the neoplasm out of the filtration angle	Diffuse brown iridal thickening (Fig. 9.83A)	Iris is thickened by spindle to oval often lightly pigmented cells with prominent nucleoli; usually mitotic figures are rare, extend out through sclera around the aqueous collecting veins (Fig. 9.83B)
Feline intraocular sarcomas	Reports primarily limited to cats; this is a general exception to most intraocular neoplasms because it is considered malignant and commonly extends out of the globe and metastases occur	Yellow-tan-white rapidly growing intraocular mass (Fig. 9.84A)	Cell types are variable and include plump spindle cells to round cells, to giant cells (Fig. 9.84B–D)
Ciliary adenoma	Dog, cat; this is a benign posterior segment neoplasm	Pink to light brown mass that grows into the vitreous behind the lens or into the posterior chamber and through the pupil or into the anterior chamber through the iris (Fig. 9.85A)	Tumor is composed of sheets and cords of pale staining cuboidal or columnar cells with eosinophilic cytoplasm that may contain a few melanin granules and distinct basement membranes (Fig. 9.85B, C)
Ciliary adenocarcinoma	Cat, dog, occasionally other species; generally, the prognosis for life is good provided the globe is enucleated promptly	Ciliary, iridal to anterior choroidal tumors often accompanied with inflammation; commonly present as pink lesions extending through the iris root	Solid sheets of epithelial cells with less differentiation and prominent mitotic figures, pleomorphism, and invasion of the ciliary body, choroid, and iris (Fig. 9.86)
Intraocular nerve tumors	Rare, in dog, cat; these neoplasms are potentially malignant	Pale grey iridal or ciliary tumors (Fig. 9.87)	Interlacing bundles of spindle cells
Hemangiomas of the iris and ciliary body	Rare in any species, and a primary versus metastatic hemangiosarcoma should be considered; prognosis is guarded	Vascularized mass in iris or ciliary body	Vascular cords and sinuses with plump endothelial-like cells
Intraocular leiomyosarcoma	Rare, dog; these neoplasms are clinically benign	Grey, iridal, anterior or posterior tumor	Spindle cells resembling smooth muscle
Medulloepithelioma	Dog, cat, occasionally other species; this uncommon neoplasm is benign	Young animal with leukocoria, hyphema, or a white mass arising from the ciliary body and extending into the vitreous (Fig. 9.88A)	Nonteratoid – contain cells that resemble RPE and ciliary epithelium and neuroglia Teratoid – contain hyaline cartilage, bone rhabdomyoblasts, neuroglia, and mesenchymal cells (Fig. 9.88b)
Retinoblastoma	Dog, Llama (single reports), rare in any species	Retinal – choroidal mass in a young animal	Small neuroblastic cells with hyperchromatic nuclei and scant cytoplasm with rosettes and pseudorosettes (Fig. 9.88c)

(Continued)

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Table 9.10 (Continued)

Neoplasm	Species and clinical behavior of the neoplasm	Gross appearance	Histologic characteristics
Optic nerve neoplasms	Gliomas, astrocytomas, etc.; rare in all species and considered benign	Grey optic nerve mass	Small, round cells with prominent nuclei (Fig. 9.89)
Optic nerve meningioma	Most common optic nerve neoplasm in any species, and provided clean margins are achieved, the prognosis is excellent	Pale grey mass that extends from the orbit into the optic disc uncommonly (most induce exophthalmos) (Fig. 9.90A)	Whorls and nests of spindle cells that arise from the meninges, calcification is common (Fig. 9.90B)
Extraskeletal intraocular osteosarcoma	Rare (single report in dog); prognosis is guarded	Uveitis	Pleomorphic spindle cells with osteoid production
Metastatic intraocular neoplasms	May occur in all species with chronic systemic metastatic neoplasia	Uveitis (hyphema, aqueous and vitreous flare), retinal detachment, secondary glaucoma, cataract	Variable depending on the primary neoplasms (mesenchymal, Fig. 9.91A, B) (round cell, Fig. 9.91C), and (epithelial Fig. 9.91D) most invade the ciliary body and choroid

anterior uveal melanocytomas are most common and manifest as brown to black tumors that extend into the anterior or posterior chambers or the vitreous (Fig. 9.81A). With continued growth, they extend outward to the sclera and grow along the emmisaria (Fig. 9.81B, C) to extend beyond the globe at the limbus or the posterior pole. Anterior uveal melanomas vary in pigmentation, and poorly pigmented and amelanotic types may be misdiagnosed clinically as ciliary epithelial neoplasms or spindle cell neoplasms of the iris. Both uveal melanocytomas and melanomas induce inflammation and PIFMs. Malignant variants do occur; however, enucleation before the melanoma extends beyond the globe is usually curative. Uveal melanocytomas are morphologically identical to limbal melanocytomas, with two cell types observed: type 1, the more common plump overdistended pigmented melanocytic cell that represents an end-stage postmitotic cell, and type 2, a germinal melanocytic cell which is less pigmented and is fusiform in shape with a prominent central nucleus (Fig. 9.81D). Uveal melanomas may arise *de novo* or from uveal melanocytomas and are composed of pleomorphic plump spindle and epithelioid cells with variable histologic features of malignancy, notably a high mitotic index. Within this group of neoplasms metastatic potential is low with an incidence of less than 5% (Bussanich et al., 1987; Diters et al., 1983; Giuliano et al., 1999; Minami & Patnaik, 1992; Render et al., 1997; Roperto et al., 1993; Rovesti et al., 2001; Truska et al., 1985).

Choroidal melanocytomas and melanomas are much less common in domestic animals compared with humans (Fig. 9.82A) and have similar morphology and behavior as their anterior uveal counterparts (Aguirre et al., 1984; Bourguet et al., 2015; Collinson & Peiffer, 1993; Dubielzig et al., 1985; Hyman et al., 2002; Morgan & Patton, 1993; Schoster et al., 1993; Weisse et al., 1985). They are typically diagnosed later in their course of disease because of their hidden location and manifest grossly as a heavily pigmented choroidal tumor or spontaneous vitreous hemorrhage. If they extend through the basement membrane of the RPE, they will proliferate under the retina, induce retinal detachment, and extend into the vitreous (Fig. 9.82B). Choroidal melanocytomas also grow slowly and follow the path of least resistance and usually extend out of the globe through the scleral emmisaria; translaminar invasion of the optic nerve can occur with malignant variants. Poorly pigmented choroidal melanocytomas are uncommon. Heavily pigmented choroidal melanomas must be bleached to allow for evaluation at the cellular detail. The histologic appearance is typical of most uveal melanocytomas and includes pigment-laden round to polyhedral cells which vary from plump cells with pyknotic nuclei to plump or slender spindle cells or even small epithelioid cells (Fig. 9.82C). Mitotic figures will vary from none to significant numbers. Only occasional malignant versions of these choroidal melanomas will metastasize.

Diffuse iris melanomas occur in cats as unilateral variably brown pigmented neoplasms that originate on the anterior iridal border. As these neoplastic cells proliferate, they invade iris stroma, and efface the filtration angle with access to the aqueous veins. Glaucoma is a frequent end stage complication (Fig. 9.83A) (Acland et al., 1980; Bellhorn & Henkind, 1970; Bertroy et al., 1988; Bjerkas et al., 1997; Cordy, 1977; Duncan & Peiffer, 1991; Harris & Dubielzig, 1999; Kalishman et al., 1998; Patnaik & Mooney, 1988; Peiffer et al., 1977; Schwink & Betts, 1988; Souri, 1978; Wiggans et al., 2016). Most diffuse iris melanomas are pigmented and are occasionally considered amelanotic (actually these are usually very poorly pigmented forms). There is a very rare form known as a balloon cell variant with clear

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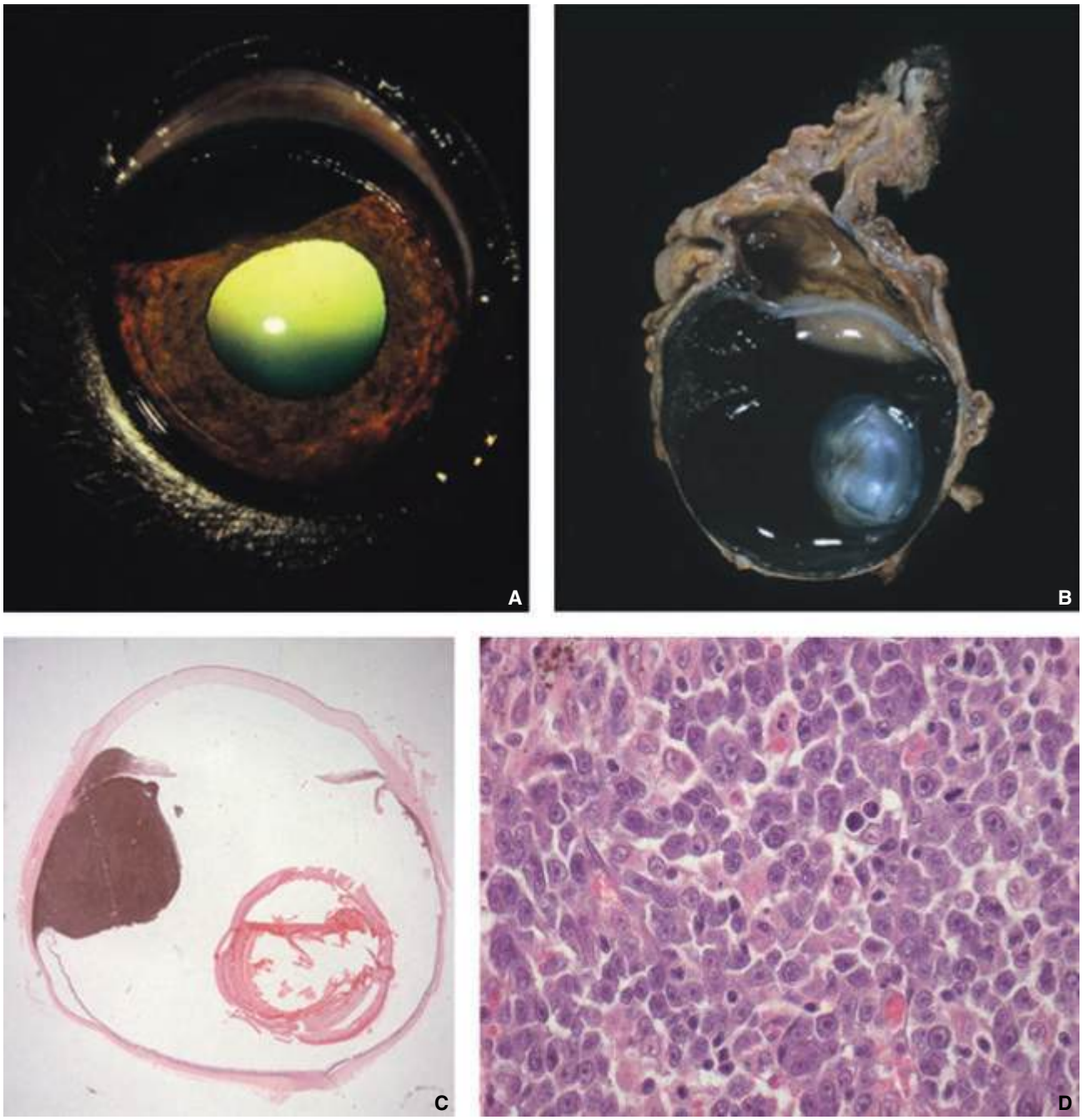


Figure 9.81 **A.** Clinical appearance of an anterior uveal melanoma in a dog. Almost always the neoplasm will be more densely pigmented than adjacent uvea. **B.** A black nodular lesion effaces the iris and ciliary body in an enucleated canine eye. **C.** Subgross section of the anterior uveal melanoma noted in **B**. (Original magnification 2×. Hematoxylin and eosin.) **D.** Histologic section an epithelioid anterior uveal melanoma. Note the anisocytosis, anisokaryosis, prominent distinctive nucleoli, and cytoplasm with occasional pigment granules. (Original magnification 400×. Hematoxylin and eosin.)

cytoplasm. Regardless of the form, the cells are noncohesive and can be within the aqueous, on the anterior lens capsule, and seeding the outflow pathway. Although the progenitor cells on the iris surface are bland and angulated, two morphologies are encountered: a pleomorphic population of oval to round epithelioid cells with large nuclei and cytoplasmic pseudoinclusions, and a plump spindle cell (Fig. 9.83B). The intracytoplasmic pigmentation is variable and amelanotic forms are not uncommon. Incidence of metastasis is unknown, but compilation of published data suggests that it may approach 20%, and the identification of tumor cells within the aqueous collecting veins warrants a poor

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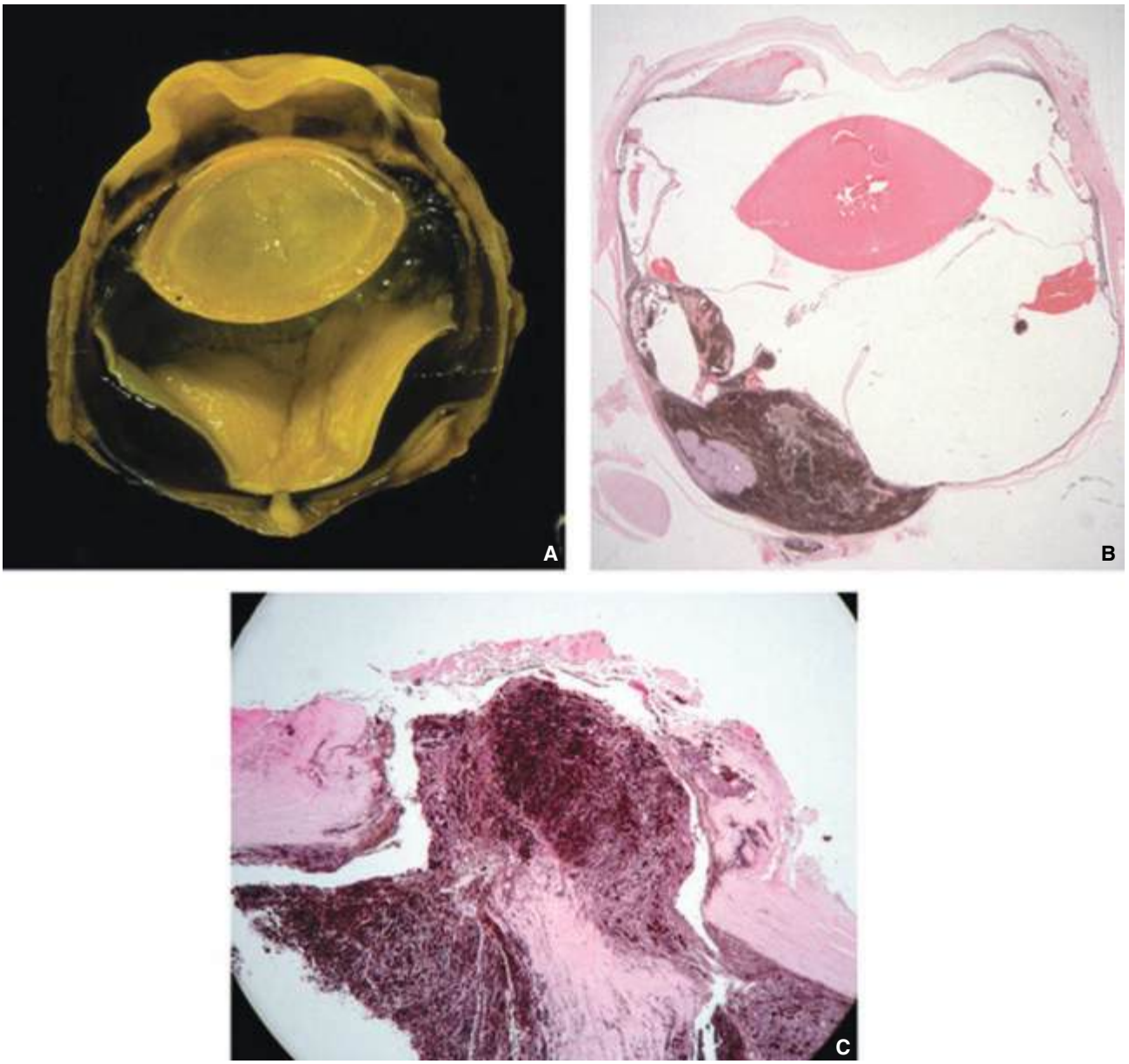


Figure 9.82 **A.** This is a section of a Bouin's fixed eye from a dog with a brown choroidal tumor. Note the extension into the sclera and through the choroid. **B.** Subgross appearance of a choroidal melanoma in a dog with orbital invasion and a prominent preiridal fibrovascular membrane. (Original magnification 2×. Hematoxylin and eosin.) **C.** The light microscopic features of choroidal melanoma are similar to anterior uveal melanomas. They will commonly exit the globe along a path of least resistance through the peripapillary emmisaria as noted in this specimen. (Original magnification 100×. Hematoxylin and eosin.)

prognosis. Clinical manifestations of metastatic disease can have a long latency (up to 1–2 years).

An experimental animal model has been created with intracameral feline sarcoma virus injections (Albert et al., 1981; Niederkorn et al., 1982); the presence of these viral particles in spontaneous clinical cases is unknown. However, polymerase chain reaction for this virus in two studies of a few naturally occurring feline diffuse iris melanomas has been inconclusive (Cullen et al., 2002; Stiles et al., 1999).

Primary intraocular spindle cell neoplasms are uncommon in all animals, and reports are limited to a few miscellaneous spindle cell neoplasms of the uvea of dogs (Billson et al., 2003; Heath et al., 2003; Sato et al., 2005) and posttraumatic sarcomas of cats (Barrett et al., 1995; Cullen et al., 1998; Dubielzig, 1984; Dubielzig et al., 1990, 1994; Grahn et al., 2006; Hakanson et al., 1990; Miller & Boosinger, 1987; Peiffer et al., 1988; Stoltz et al., 1994; Zeiss et al., 2003).

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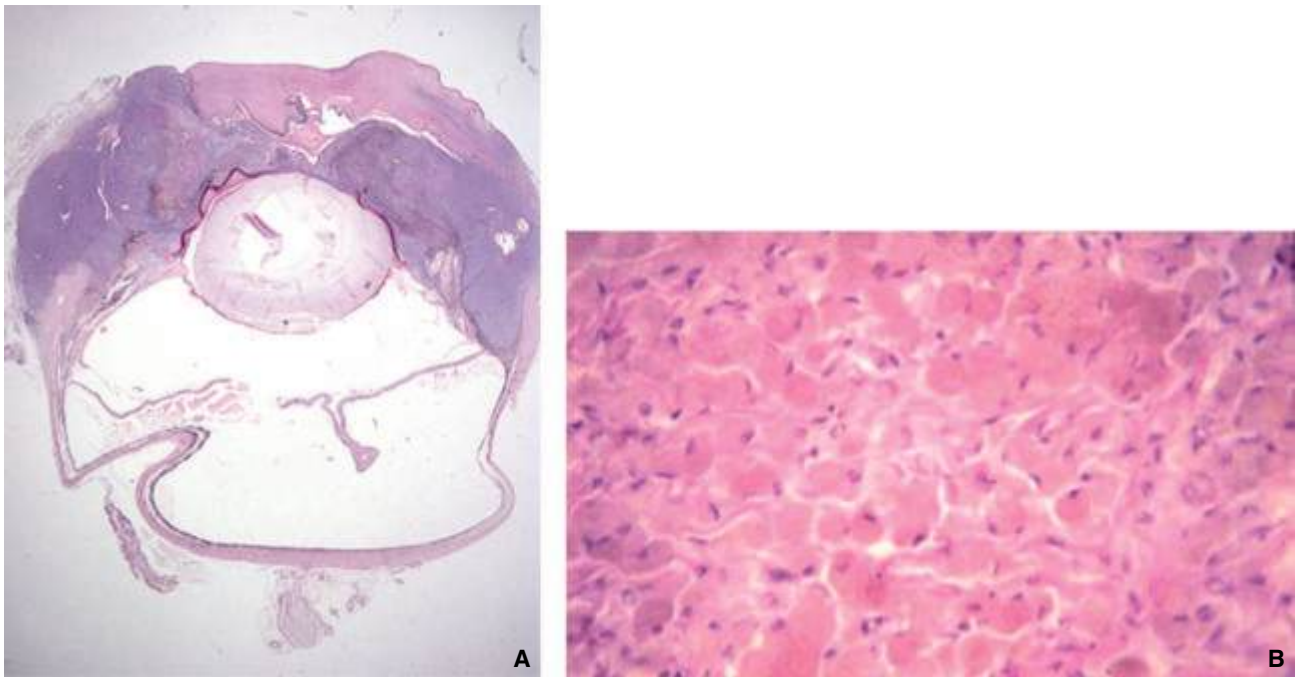


Figure 9.83 **A.** The subgross characteristics of a malignant feline diffuse iridal melanoma. Note the thickened heavily pigmented iris and extension through the sclera around the aqueous collecting veins. Note the unusual findings in this eye that included a lens capsule rupture and detached retina. (Original magnification 2×. Periodic acid-Schiff.) **B.** The histologic characteristics of diffuse iris melanoma in cats are varied; however, most of the neoplastic melanocytes are a bland-appearing population of plump cells with a displaced peripheral nucleus and limited numbers of spindle cells. Mitotic figures are usually uncommon and nucleoli are often inconspicuous in cats. (Original magnification 250×. Hematoxylin and eosin.)

Feline intraocular sarcomas are aggressive malignancies. Most or perhaps all of these spindle cell sarcomas are associated with prior trauma (frequently with a latency of several years) and a ruptured lens (Barrett et al., 1995; Dubielzig, 1984; Grahn et al., 2006; Hakanson et al., 1990; Miller & Boosinger, 1987; Peiffer et al., 1988; Zeiss et al., 2003). The clinical manifestations include leukocoria and evidence of a rapidly growing white mass, frequently in a circumferential pattern internal to the sclera. These neoplasms can invade the sclera and commonly exit the globe into the orbit around the optic nerve and at the filtration angle. Evidence suggests that these sarcomas are presumed to arise from neoplastic transformation in metaplastic lens epithelium sometimes years after a lens capsule rupture. Light microscopy reveals a spindle cell neoplasm with many phenotypes which include osteosarcoma, fibrosarcoma, chrondrosarcoma, and a giant and round cell variant supporting the argument of a pluripotential origin (Fig. 9.84). These neoplasms can mimic other primary or metastatic intraocular neoplasms, and immunohistochemical staining is warranted in some cases (Grahn et al., 2006). When these spindle cells exit the globe, they might extend into the orbit and cranial vault, invade the optic nerve, and metastasize to the lung, liver, and other organs. Prognosis in most cases is bleak.

Iridal tumors of blue-eyed dogs are unique, uncommon, low-grade spindle cell neoplasms that develop notably in the Siberian Husky. These neoplasms manifest clinically as a flat or nodular vascularized iridal mass that can extend into the anterior chamber and ciliary body (Fig. 9.87). Light microscopic features include a pleomorphic spindle cell population that most likely originates from iridal nerves. Metastasis of these neoplasms has been reported. Other reported spindle cell uveal neoplasms include osteosarcoma (Heath et al., 2003), peripheral nerve sheath neoplasms (Sato et al., 2005), and smooth muscle leiomyomas (Billson et al., 2003). The prognoses for these rare neoplasms are unknown.

Ocular Neuroectodermal Neoplasms

Neoplasia of neuroectodermal origin other than iris and ciliary adenomas and ciliary adenocarcinomas is rare and includes medulloepitheliomas, retinoblastomas, astrocytomas, and gliomas. With the rare exception of the occasional ciliary body adenocarcinoma, these neoplasms exhibit benign behavior and metastasis is uncommon.

Ciliary adenomas represent over 90% of these neuroectodermally derived neoplasms (Barron & Saunders, 1959; Clerc, 1996; Dubielzig et al., 1998; Lavach, 1984; Peiffer, 1983; Whittemore et al., 2004). Adenocarcinomas are uncommon,

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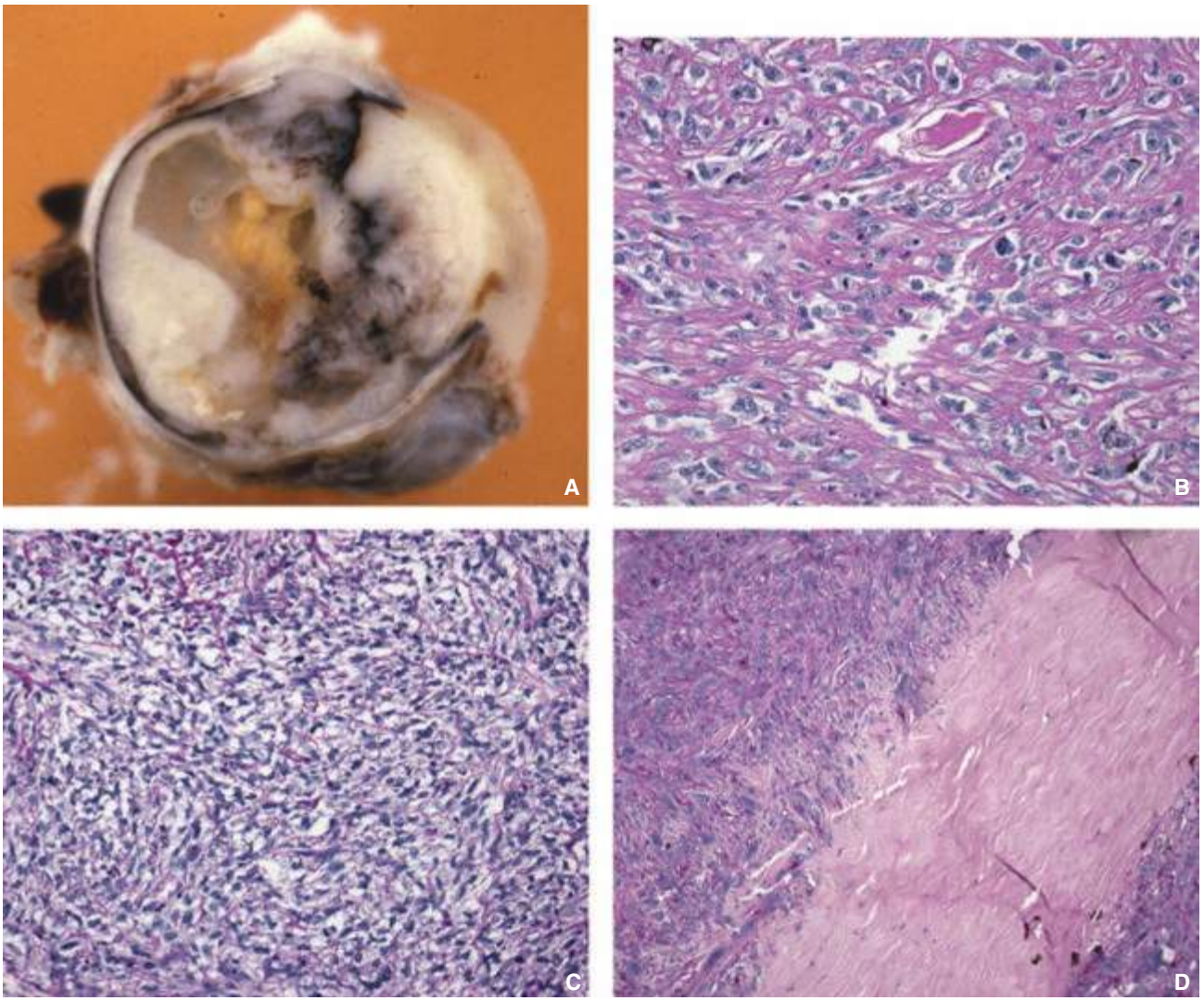


Figure 9.84 **A.** Feline intraocular sarcomas are aggressive neoplasms that will often encircle the inner sclera as noted in this gross specimen. These neoplasms will often obliterate the anterior and posterior segment and extend through the sclera. **B.** Spindle cell type of feline intraocular sarcoma exhibiting basement membrane production and marked anisocytosis and anisokaryosis. (Original magnification 300×. Periodic acid-Schiff.) **C.** Foamy spindle cell variant of feline intraocular sarcoma. (Original magnification 300×. Periodic acid-Schiff.) **D.** Feline intraocular sarcomas are invasive and transscleral extension is common. Note the neoplastic cell population on both sides of the sclera in this cat. (Original magnification 250×. Periodic acid-Schiff)

and even more rarely the posterior iridal pigmented adenoma is diagnosed. Clinical manifestations of the ciliary adenoma include a variably pigmented, usually pink to white endophytic tumor that grows into the posterior chamber in front of the lens with anterior bowing of the iris, around the lens, and/or into the vitreous posterior (Fig. 9.85A). Signs of uveitis, including hyphema and aqueous flare, can occur, and PIFMs often develop in response to tumor-elaborated vasogenic factors. Light microscopic examination reveals a variably pigmented papillary or solid tumor composed of neuroectoderm that is very similar in appearance to ciliary epithelium (Fig. 9.85B, C). Well-differentiated ducts and chords of variably pigmented cuboidal to columnar cells supported by a prominent basement membrane and minimal fibrovascular stroma are noted histologically. The ducts can be dilated with proteinaceous fluid. Neoplastic cells have variably distinct cell borders, moderate amounts of granular eosinophilic to clear cytoplasm, and round to oval, usually hyperchromatic nuclei with a variably distinct nucleolus.

In contrast, ciliary adenocarcinomas tend to invade anteriorly and posteriorly into the iris and choroid. They typically present clinically as nonpigmented nodules emerging from the anterior iris root. The tumors lack the adenoidal differentiation of ciliary body adenomas and light microscopy reveals sheets of epithelial cells with numerous mitotic figures, anisocytosis, and anisokaryosis with invasion of adjacent tissues (Fig. 9.86). Histochemical and immunohistochemical stains can be helpful to differentiate them from intraocular

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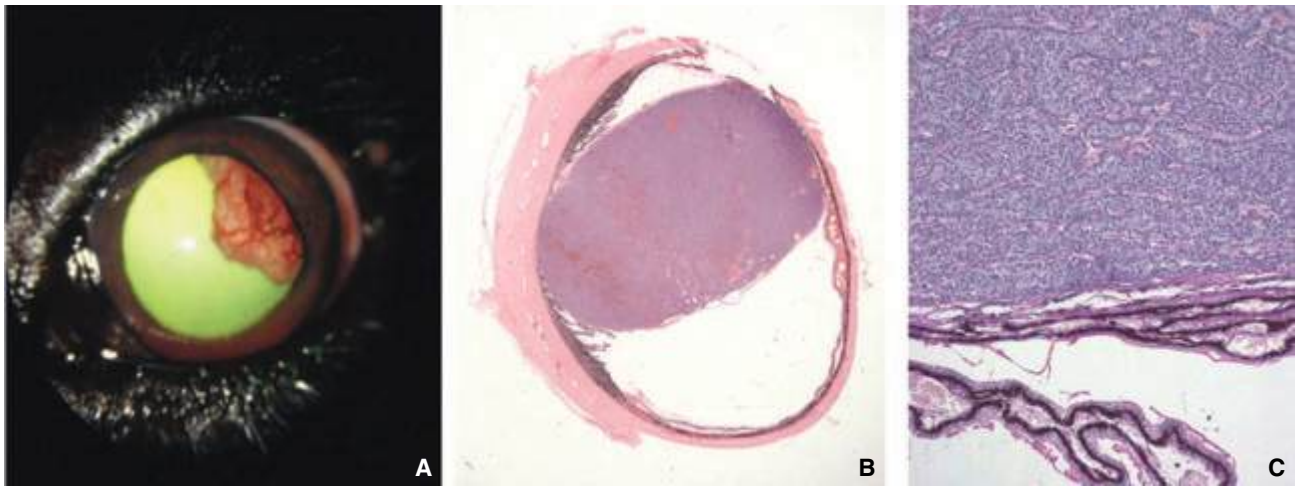


Figure 9.85 **A.** Ciliary adenomas are usually pink-colored masses that grow from one or two ciliary processes into the posterior chamber to envelop the equatorial lens as demonstrated in this American Cocker Spaniel. **B.** A ciliary body adenoma in a cat eye has grown posteriorly into the vitreous. **C.** The ciliary body tumor noted in **B** exhibits adenoidal features with cords of epithelial cells with pale blue cytoplasm and prominent basement membranes. Note the many cellular similarities to the normal nonpigmented ciliary epithelium of the ciliary process at the bottom of the photo. (Original magnification 300×. Periodic acid-Schiff.)

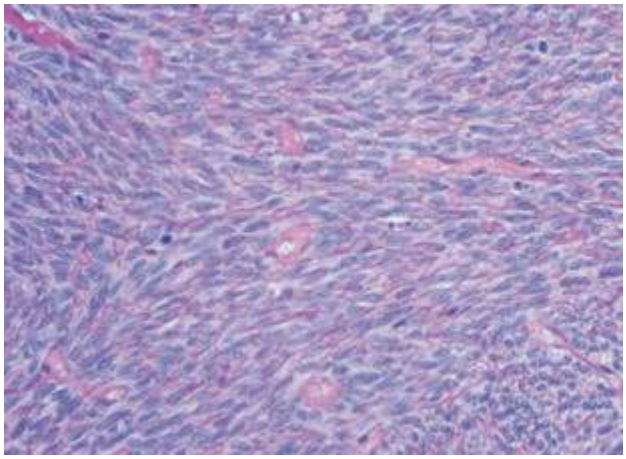


Figure 9.86 Ciliary body adenocarcinomas can resemble intraocular sarcomas or medulloepitheliomas. They produce prominent basement membranes and grow in sheets. They usually have some of the characteristics of ciliary epithelium including the round to oval nucleus as noted in this section from a feline globe. (Original magnification 400×. Periodic acid-Schiff.)

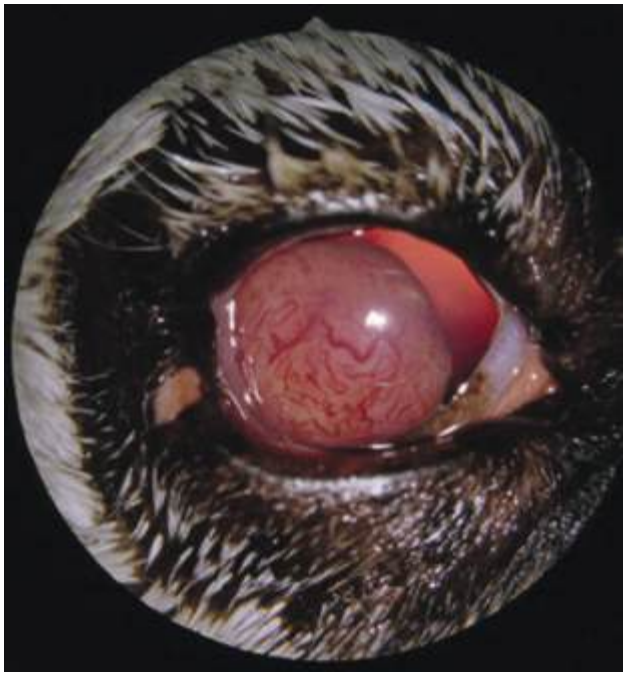


Figure 9.87 This well-vascularized iridal tumor was confirmed as a spindle cell neoplasm of a blue-eyed Siberian Husky.

sarcomas, metastatic carcinomas, lymphosarcoma, and melanomas. Differentiating stains include positive staining with PAS, Alcian blue, or colloidal iron (hyaluronidase positive), neurospecific enolase, vimentin, and absence of staining with cytokeratin and melanocytic and lymphosarcoma markers (Grahn et al., 2006). Ciliary body neoplasms are unique in their propensity to secrete hyaluronic acid. Asteroid hyalosis and PIFMs are commonly associated with both benign and malignant iris and ciliary neoplasia.

Medulloepitheliomas are primitive neuroectodermal neoplasms that are congenital, although they do not typically manifest clinically until the affected animal is several months to years old. They have been reported in various species (Aleksandersen et al., 2004; Bistner, 1974; Bras et al., 2005; Eagle et al., 1978; Hendrix et al., 2000; Lahav & Albert, 1978; Lahav et al., 1976; Langloss et al., 1976; Leiva et al., 2013; Monk et al., 2017; Riis et al., 1990; Wilcock & Williams, 1976; Symanski, 1987). The clinical manifestations include leukocoria caused by a pink to white endophytic pupillary mass that extends into the vitreous or less commonly the posterior chamber (Fig. 9.88A, B). These neoplasms develop

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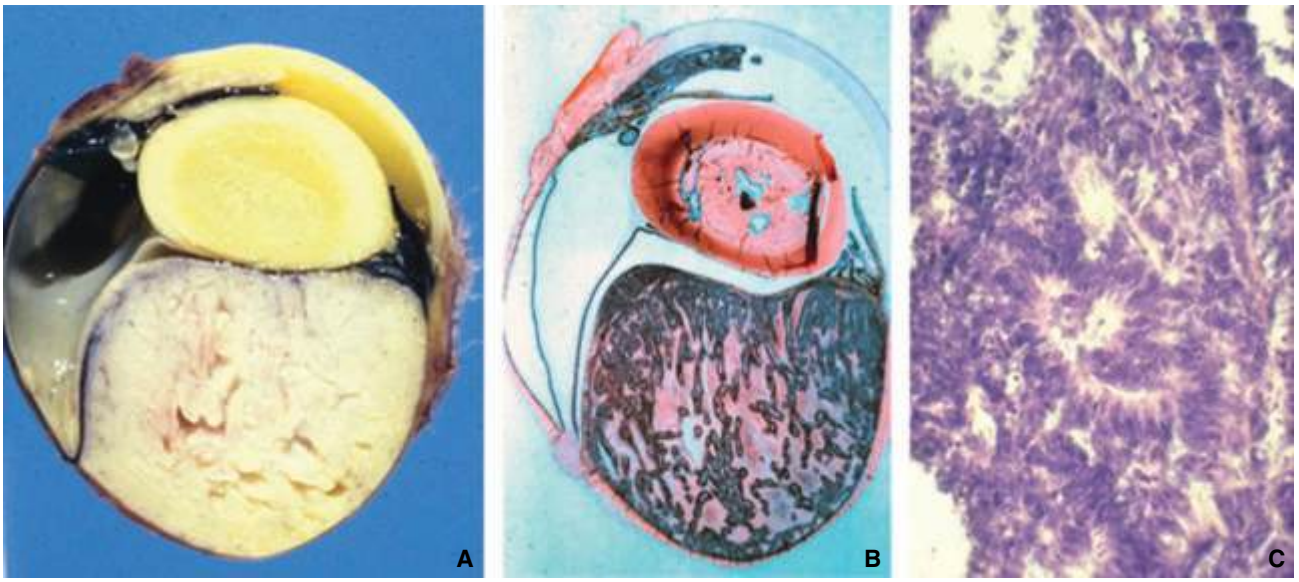


Figure 9.88 **A.** This medulloepithelioma appears as a pale frond-like tumor that is growing through the vitreous of a cat. **B.** Subgross of the tumor noted in the gross section in **A**. The cellular characteristics are consistent with the diagnosis of medulloepithelioma. These neoplasms originate from the immature ciliary epithelium, and they extend into the vitreous and under the retina and through the iris. (Original magnification 2×. Periodic acid-Schiff.) **C.** Neoplastic retinal rosettes are one of the characteristics of retinoblastomas and some medulloepitheliomas. (Original magnification 300×. Hematoxylin and eosin.)

from primitive pluripotential neuroectoderm destined to become iridociliary epithelium. Light microscopic examination reveals sheets and rosettes of primitive elongated neuroblasts with prominent basement membranes. These neoplasms often contain islands of muscle, cartilage, bone, and primitive vitreous and neurogenic tissue and are labeled teratoid medulloepithelioma. Medulloepitheliomas are easily mistaken for retinoblastoma, which is not surprising given the origin of both from neuroectoderm that lines the primitive optic cup.

Retinoblastomas are very rare in domestic animals (Fugaro et al., 2005; Regan et al., 2013; Syed et al., 1997), although it is a more common primary intraocular neoplasm in humans. The clinical manifestation is leukocoria caused by an endophytic vitreous tumor that is variably pigmented. Histologic features include rosettes and fluerettes of primitive neuroblast cells that were destined to become retina (Fig. 9.88C).

Primary neoplasia of the neuroectoderm of the optic nerve is uncommon and includes gliomas and astrocytomas. These neoplasms are rare, and the clinical manifestations and light microscopic descriptions and features are limited to a few reports (Barnett & Grimes, 1972; Brooks & Patton, 1991; Caswell et al., 1999; Ehrhart et al., 2005; Jensen et al., 2003; Spiess & Wilcock, 1987; Stone et al., 2005). Clinical manifestations of gliomas of the optic nerve and retina include pale grey tumors that extend from the optic nerve into the vitreous. Light microscopy reveals glial cells with subtypes of astrocytoma (Fig. 9.89),

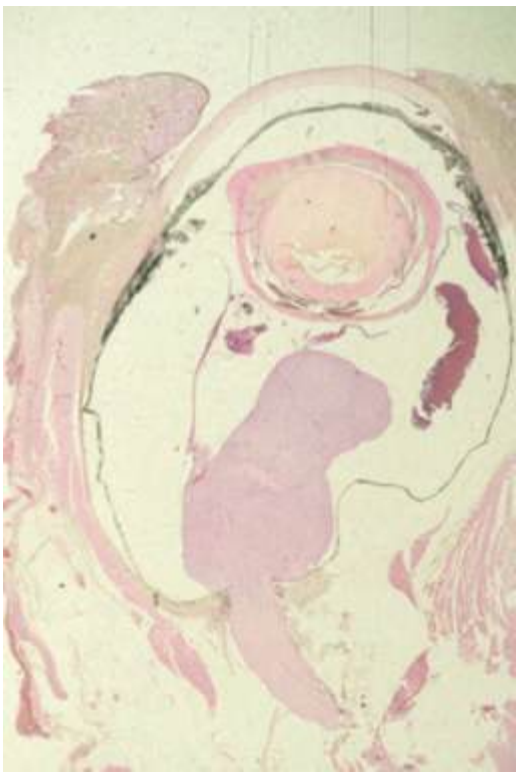


Figure 9.89 Canine eye with an optic nerve astrocytoma. Note the neoplasm extends from the optic disc into the vitreous cavity. (Original magnification 2×. Hematoxylin and eosin.)

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oligodendroglioma, and ependymoma. Immunohistochemistry is required for differentiation (Ehrhart et al., 2005; Stone et al., 2005). The prognosis for these rare neuroectodermal neoplasms is undetermined.

Neoplasia of the Neural Crest Tissues of the Optic Nerve

Meningiomas arise from the meninges that envelop the optic nerve and brain (Andrews, 1973; Dugan et al., 1993; Lawson et al., 1984; Nafe, 1979; Patnaik & Kay, 1986; Paulsen et al., 1989). When meningiomas extend into the orbit (Fig. 9.90A) or the eye, the clinical presentation is that of exophthalmos and third eyelid prolapse. Histologic features are dominated by epithelioid cells arranged in nests (Fig. 9.90B). Cellular variations include primitive mesenchymal cells with prominent cytoplasm and foci of osseous or cartilaginous metaplasia that account for the calcification noted on imaging studies of these neoplasms. Although metastasis has been reported (Dugan et al., 1993; Jensen et al., 2003), the majority are slow growing and relatively benign neoplasms.

Metastatic Ocular Neoplasia

Metastatic neoplasia to the eye does occur, and because radiation therapy and chemotherapy extend life expectancy, an increased number of metastatic ocular neoplasms might be expected. All malignant neoplasms could metastasize to the ocular tissues given the prominent vascular supply to and the immunologically privileged nature of the eye and orbit.

The clinical manifestations of metastatic ocular disease are nonspecific and include exophthalmos if the metastases involve the orbit or uveitis when the ocular tissues are invaded. This description will be limited to general histologic features of metastatic intraocular neoplasms. Access is achieved via the uveal vasculature with subsequent invasion of adjacent tissues. Most intraocular metastatic neoplasms manifest clinically as anterior uveal or choroidal tumors with or without retinal detachment. Tumor necrosis and compromise of resident tissues manifests as uveitis, with aqueous flare and hyphema. The cellular characteristics of mesenchymal (Fig. 9.91A, B), round (Fig. 9.91C) and epithelial cell (Fig. 9.91D) types will assist the pathologist in the selection of appropriate histochemical and immunohistochemical differentiating labels. These metastatic neoplasms are often anaplastic and challenging to distinguish from anaplastic primary intraocular neoplasms. Lymphosarcomas are the most common metastatic intraocular tumors across species, as well as the most common metastatic neoplasm to the orbit and adnexa (Malmberg et al., 2017; Ota-Kuroki et al., 2014). They have occasionally been reported as possible primary intraocular neoplasms (Gerding et al., 2015; Trope et al., 2014; Wiggans et al., 2014). They are round cell tumors readily identified by common lymphocytic markers. Metastatic renal, respiratory, mammary, and gastrointestinal

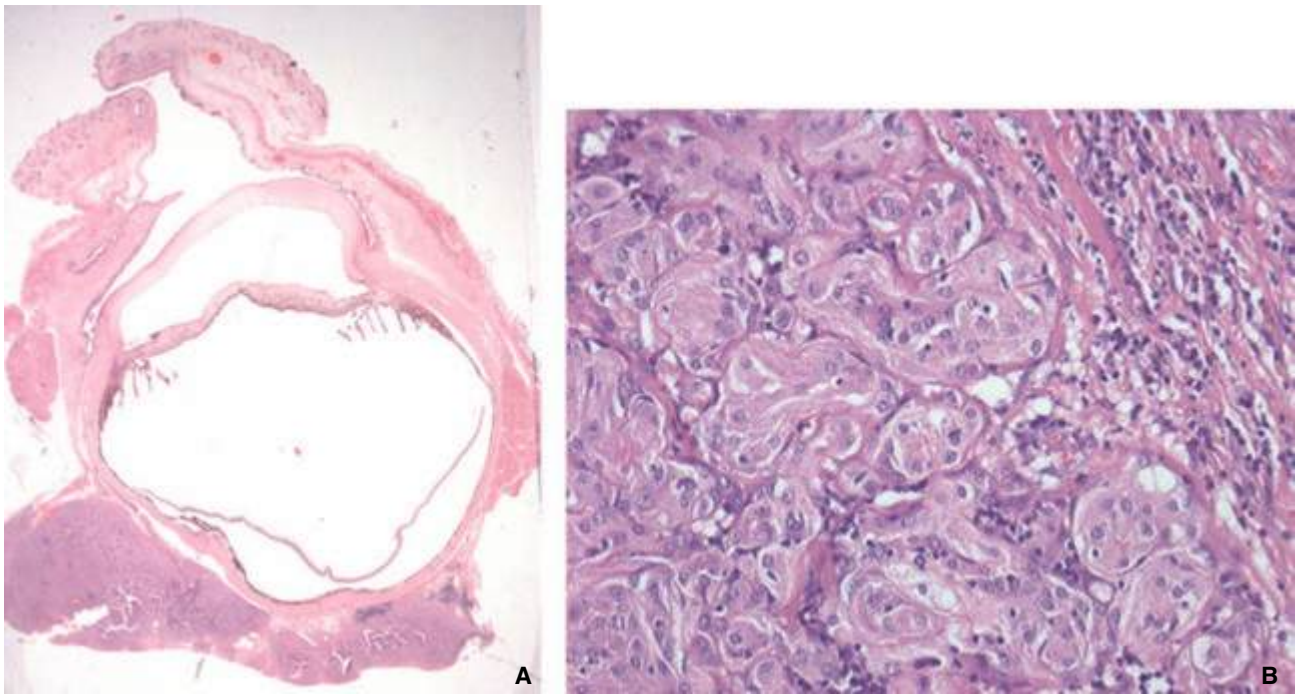


Figure 9.90 **A.** Canine exenteration specimen with an orbital meningioma that invades the orbital tissues. (Original magnification 2×. Hematoxylin and eosin.) **B.** The orbital neoplasm noted in **A** was composed of epithelial cells with pale pink cytoplasm, small, dark-staining nuclei organized into nests. (Original magnification 400×. Hematoxylin and eosin.)

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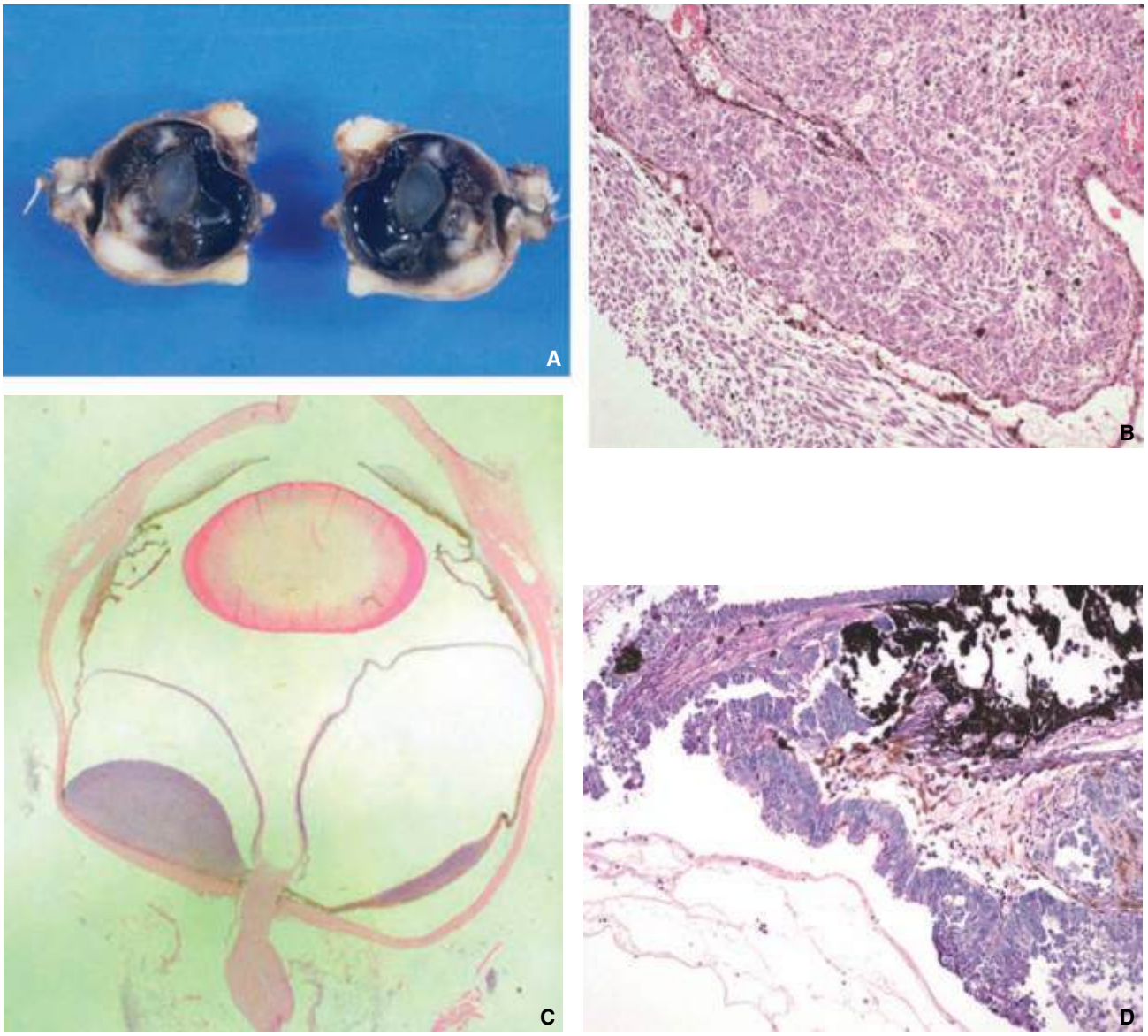


Figure 9.91 **A.** Canine globe that contains a metastatic neoplasm that has invaded the ciliary body and choroid. **B.** A poorly differentiated metastatic spindle cell neoplasm distends a ciliary process and extends into the vitreous in a canine eye. (Original magnification 400×. Hematoxylin and eosin.) **C.** A metastatic choroidal lymphosarcoma with overlying serous retinal detachment in a cat. (Original magnification 2×. Hematoxylin and eosin.) **D.** Note the sheets of epithelial neoplasia that extend over the ciliary process in this cat's eye. This growth pattern of columnar epithelial cells lining is consistent with the diagnosis of a metastatic carcinoma. (Original magnification 300×. Periodic acid-Schiff.)

carcinomas are often so anaplastic that the original tissue of origin is not discernable. These carcinomas often proliferate in sheets across the surfaces of intraocular tissues. They also produce prominent basement membranes and most will stain readily with cytokeratin markers (Grahn et al., 2006).

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10.1

Ophthalmic Examination and Diagnostics

Part 1: The Eye Examination and Diagnostic Procedures

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An ophthalmic diagnosis can often be made at the time of the examination, more than in most body systems, because most ocular structures can be visualized either directly or indirectly. Furthermore, the eye lends itself to numerous simple and efficient diagnostic procedures, many of which can be performed during a routine examination. This chapter describes examination techniques and diagnostic procedures available to veterinarians interested in ophthalmology and, in particular, to veterinary ophthalmologists.

I: OPHTHALMIC EXAMINATION

History

A thorough history, when combined with clinical findings, will support appropriate case management. In taking a history, the same considerations apply as to other body systems and include signalment, use of the animal, environment, diet, characterization of the primary complaint (onset, initial clinical signs, progression, duration), treatment (response and current treatment), and nonophthalmic disease (previous and concurrent). Additional information that may be helpful includes travel history, vaccination and deworming history, and whether other animals in the vicinity are similarly affected. More specific information pertaining to the eye includes the owner's interpretation of vision, pain, and whether one or both eyes are involved. Further information may be required depending on the primary presenting problem.

Signalment can provide an important clue to the cause of many ophthalmic conditions. For example, some conditions are specific to a particular species (e.g., corneal sequestrum in the cat), whereas others are associated with a particular coat color (e.g., multiple ocular anomalies in the homozygous merle dog). Many conditions have strong breed predispositions (e.g., keratoconjunctivitis sicca [KCS] in the West Highland White Terrier) and others are known to be hereditary (e.g., cataract in the Morgan horse).

Primary complaints from the owner usually include ocular discharge, change in appearance of the eye (size, color, pupil), or reduced vision or blindness. The role of concurrent disease or secondary complaints should not be underestimated, because many ophthalmic diseases are manifestations of systemic disease (e.g., diabetic cataract, mycotic chorioretinitis, hypertensive retinopathy, and others). Concurrent systemic disease may also affect treatment; for example, timolol, a topical beta blocker, should be avoided in cats with glaucoma and concurrent asthma. Existing medical therapy can influence the ophthalmic findings; for example, topical atropine can induce mydriasis for up to 14 days in the horse (Davis et al., 2003). This type of situation is more likely if the owner, or a relative or friend, has medical knowledge and access to drugs. Although owners usually find it difficult to provide accurate information regarding their animal's vision, their opinion is invaluable given that they spend much more time with their pet than the veterinarian. Questions should be directed toward vision in different situations: photopic (light) and scotopic (dark) conditions – that is, hemeralopia (day blindness) versus nyctalopia (night blindness); and stationary and moving objects – that is, central versus peripheral retinal disease. Owners are often poor judges of ocular pain. They may notice classic signs of ophthalmic pain, such as watery discharge (increased lacrimation), closed or small eye (blepharospasm), and photophobia, but not interpret them as such.

General Ocular Examination

As with the examination of any body system, ocular examination should proceed in a logical and systematic manner. The general order of steps is listed in Table 10.1.1, but the method will vary according to personal preference, available

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Table 10.1.1 Diagnostic sequence for the basic eye examination.

1) History: signalment, primary complaint, concurrent disease, and treatment

2) Examination in ambient lighting
   i) Distance examination
      - Observation of animal's demeanor and movement within its environment
      - Symmetry, ocular discharge
      - Globe (position, size, movement)
   ii) "Hands-on" examination
      - Neuro-ophthalmic testing: menace response, dazzle reflex, pupillary light reflex, corneal reflex, vestibulo-ocular reflex
      - Tear tests, corneal esthesiometry
   iii) Close examination of adnexa and globe

3) Examination after topical anesthesia
   iv) Tonometry
   v) Gonioscopy
   vi) Posterior third eyelid

4) Mydriasis
   vii) Anterior segment after pupil dilation (lens)
   viii) Posterior segment after pupil dilation (vitreous humor and fundoscopy)

5) Additional diagnostic tests: corneoconjunctival culture and cytology, ophthalmic dyes, nasolacrimal flush, conjunctival biopsy, aqueous and vitreous paracentesis, imaging modalities, photography, and electroretinography

equipment, and the individual case. However, certain diagnostic tests and observations must precede others to avoid interference with results and interpretation. Important examples include measurement of aqueous tear production (e.g., by Schirmer tear test, STT) before the topical application of any agent, and evaluation of pupillary light reflexes (PLRs) and tonometry before the administration of mydriatic agents.

The range of normal variation is vast, not only between species but between individuals. Good equipment and a standard routine will minimize the risk of lesions being missed, but familiarity with the range of normal appearances is paramount. This expertise will develop simply by experience and will ultimately be more important than the equipment or protocol used.

The variety of animals that present for ocular examination necessitates a variety of examination facilities. Regardless of the species, it is essential to have a well-lit area for the initial examination and the option to darken the environment for subsequent steps. The examination area should also be quiet and away from major distractions. An appropriate examination area minimizes animal and examiner stress, which in turn maximizes cooperation levels and helps to reduce examination time.

Small animals can usually be examined on a table in a closed room. Conversely, large animals require more specialized facilities, for example stocks or stalls for horses and chutes or stanchions for cattle. A thorough examination always requires some method of restraint and, usually, topical anesthesia. Sedation and regional nerve blocks are also often required, particularly in the horse.

Restraint

The best method of restraint for any given situation varies with the species involved, the patient's temperament, and the desired effect. Generally, however, the best restraint for the ophthalmic examination is the least amount possible. Methods of restraint include manual, mechanical, and chemical. The health of the animal, extent and duration of the ophthalmic examination, and needs of the client must be considered before a method is chosen, and the client should be informed of any potential risk, especially if sedation or general anesthesia is necessary for completion of the ocular examination.

Most dogs and cats require only gentle manual restraint for an ophthalmic examination. Fractious animals may, however, require additional restraint. Muzzles can be employed with aggressive or fearful dogs, but their use is limited in brachycephalic breeds. The use of a large towel or blanket to "wrap up" a fractious cat is a minimally invasive way to avoid claw injuries to the examiner or owner; specifically designed "cat bags" are also commercially available for the same purpose. If, however, the safety of the examiner, staff, and owner cannot be guaranteed or if the patient cannot be kept still with the above-described measures, chemical restraint may be necessary to allow a detailed ophthalmic examination. If sedation or general anesthesia is necessary, it is important to consider the effects of pharmacologic agents on the ocular examination (Collins et al., 1995; Hofmeister et al., 2006a, 2006b, 2008, 2009). Many anesthetic agents and sedatives decrease tear production (Arnett et al., 1984; Biricik et al., 2004; Brightman et al., 1983; Dodam et al., 1998; Ghaffari et al., 2010a; Grundon et al., 2011; Herring et al., 2000; Sanchez et al., 2006) or alter intraocular pressure (IOP; Hofmeister et al., 2006a, 2006b, 2008, 2009; McClure et al., 1976; van der Woerdt et al., 1995). In most dogs, sedation and general anesthesia frequently make the ophthalmic examination more difficult because the eyes tend to roll downward (infraversion) and the nictitating membrane tends to protrude. Ketamine with or without diazepam in combination for brief sedation of cats results in a loss of the blink reflex, which can lead to corneal drying, and mydriasis, which alters the PLRs (Arnett et al., 1984). Ketamine can cause nystagmus and, in some species, will elevate IOP (Hofmeister et al., 2006a). Opioids may alter pupil size, reactivity, and IOP (Douet et al., 2018). Specifically, opioids tend to produce mydriasis in those species that exhibit central nervous system (CNS) excitation, and miosis in those that become sedated after opioid administration. Acepromazine may cause nictitans protrusion, which obscures the globe during evaluation. In small animals, protrusion of the nictitating membrane presents a frequent

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challenge to a thorough ophthalmic examination. This problem can be averted by keeping the animal alert with movements or interesting noises, moving the patient's head in different directions, positioning the animal over the edge of a table, and limiting the length of time and intensity of the light to which the patient's eye is exposed. Experienced clinicians can complete most examinations quickly by using these maneuvers. Practice of the essential components of the ophthalmic examination facilitates its completion even in uncooperative patients.

Chemical restraint greatly facilitates a complete ophthalmic examination of the horse. Detomidine hydrochloride (0.02–0.04 mg/kg intravenously [IV]) is the chemical agent of choice, as it provides rapid-onset tranquilization without an excitatory phase and a steady and low head position without movement (Gilger & Stoppini, 2011). However, the examiner must be aware that horses undergoing sedation with alpha2-agonists may still be able to kick or bite while appearing sedated otherwise. Xylazine (0.5–1.0 mg/kg IV) has also been recommended to facilitate equine ocular examination; it may be necessary to add butorphanol (0.01–0.02 mg/kg IV) or acepromazine (0.02–0.04 mg/kg IV) for painful procedures or additional restraint (Cooley, 1992; Muir & Hubbel, 1991). Alpha2-agonists and butorphanol can be used as constant-rate infusions to prolong the sedative period, particularly when more complicated procedures are being performed, including surgery. Fine head tremors may occur during sedation with xylazine or butorphanol and are specifically undesirable for slit-lamp biomicroscope examination and during corneal surgery. Difficult horses should be restrained in stocks, and a twitch may be used in conjunction with chemical restraint during the examination. As with small animals, the use of restraint and sedation in the horse depends on the animal's temperament, the experience of the handlers and examiner, and the facilities. In addition, a limited choice of drugs might be licensed for use in horses in countries where the horse is considered a food-producing animal.

Dairy cattle can usually be adequately restrained in a stanchion, with the head pulled laterally by an assistant using a nose lead. Beef cattle may be more difficult to restrain, and squeeze chutes with special head restraints may be necessary. Sheep and goats can usually be restrained manually with the help of an assistant. Goats can be examined standing, and sheep can be examined seated on their rumps to avoid excessive movements. Llamas and alpacas may need to be supported in a chute or a sling.

Rodents, rabbits, birds, and small exotic species can usually be restrained manually. Mice and rats are sometimes challenging to examine because of their small size and inherently fast and agile movements. Restraint of rodents is best achieved by grasping the animal in the palm of the hand, with the heel of the hand gently tucked under the trunk and tail, and then gently stabilizing the head by holding the base of the skull between the thumb and the forefinger (Beaumont, 2002). Alternatively, an open syringe case or other thin, rigid tube may be utilized so that the rodent's head, protruding from one end, is stabilized, again with the thumb, while the tail is gently grasped from the other end of the tube (Beaumont, 2002). Rabbits are usually adequately restrained on a table, with a handler's hands supporting the hind limbs with one hand and the back or neck with the other. Difficult rabbits may be restrained in special box devices, and medetomidine (0.1–0.5 mg/kg intramuscularly [IM] or subcutaneously [SC]) produces mild to profound sedation, which can be antagonized with atipamezole at the conclusion of the examination (Longley, 2008). Nonhuman primates can be similarly restrained in special devices or seats, and ketamine (5–40 mg/kg IM) may be used for additional restraint (Marx & Roston, 1996). Most small to medium-sized birds can be examined safely when properly restrained with a hand about the neck and feet, with wings tucked in or wrapped within a towel. Leather working gloves facilitate handling of raptors and other large birds. Ferrets are usually simply and sufficiently restrained by suspension from the neck scruff with legs dangling free.

Fish present a different challenge, because their removal from water must be for an extremely limited period (no more than 3–5 minutes). Most require heavy sedation or anesthesia, which is usually accomplished by adding a species-specific dose of tricaine methanesulfonate (MS 222) to a small container of clean water and placing the fish in this bath (Jurk, 2002). However, MS 222, which is the only Food and Drug Administration (FDA)–approved drug to anesthetize fish in the United States, has been shown to cause reversible retinal defects and is a suspected carcinogen, and a 21-day withdrawal period for the drug exists prior to consumption or release into the wild (Mylniczenko et al., 2007). The fish should be immobilized within 5 minutes and then can be very carefully removed from the water and either restrained manually or placed gently on a smooth, padded, plastic surface. The fish should be kept moist and handled only with powder-free latex gloves, because its skin is very easily injured (Jurk, 2002). Whenever an exotic species is to be examined, the clinician should have a strong working knowledge of the species-specific sedation and anesthetic protocols and their potential risks; otherwise, the clinician should defer to an experienced exotic animal specialist. Many wild species require sedation or anesthesia for the ocular examination in order to secure the safety of the examiner and any handlers and to minimize stress for the patient.

The examiner is always urged to be aware that chemical restraint, if used to facilitate the examination of painful eyes or potentially painful procedures, must be combined with appropriate analgesic measures, for example topical anesthetic agents, local nerve blocks, or systemic analgesic agents.

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Akinesia

The orbicularis oculi muscle closes the eyelids and thus can impair or even prevent ocular examination, especially in large animals. Akinesia of this muscle is routine in the horse, occasionally required in cattle, and only rarely performed in small animals. Eyelid akinesia may be performed for routine eye examination, diagnostic procedures (e.g., corneal cytology, electroretinography [ERG]), treatment (e.g., subconjunctival injection), and to augment anesthesia during surgery (Gilger & Stoppini, 2011; Hewes et al., 2007; Komáromy et al., 2003; Park et al., 2009; Pollock et al., 2008; Robertson, 2004; Wilkie, 1991). Most horses require an auriculopalpebral nerve block for a thorough ocular examination, especially if the eye is painful or if the structural integrity of the globe (usually the cornea) is compromised (Gilger & Stoppini, 2011; Ollivier et al., 2007).

The palpebral nerve, which arises from the auriculopalpebral branch of the facial nerve (cranial nerve VII), innervates the orbicularis oculi muscle. These motor fibers may be blocked at any point between the origin of the auriculopalpebral nerve and the palpebral nerve branch. There are three main points at which the auriculopalpebral or palpebral nerves can be blocked in the horse (Fig. 10.1.1). The first point is just anterior to the base of the ear, where the auriculopalpebral nerve emerges from beneath the parotid salivary gland and becomes subcutaneous on the lateral aspect of the coronoid process. Here, local anesthetic may be injected into the depression just caudal to the ramus of the mandible, at the ventral edge of the temporal portion of the zygomatic arch (Gilger & Stoppini, 2011; Rubin, 1964; Skarda & Tranquilli, 2007c). The rostral auricular artery and vein should be avoided. The second point is just lateral to the highest point of the caudal zygomatic arch, where the palpebral nerve can be "strummed" under the skin over the dorsal border of the bone (Gilger & Stoppini, 2011; Manning & St. Clair, 1976). The third point is where the palpebral nerve lies on the zygomatic arch, caudal to the bony process of the frontal bone (Gilger & Stoppini, 2011). Considering the branching of the motor fibers, more proximal blocks are generally preferred because they affect more of the orbicularis oculi muscle (see Fig. 10.1.1; Ollivier et al., 2007). A 25-gauge, 5/8 in. needle is used to inject 1–2 mL of anesthetic agent subfascially adjacent to the nerve; the injection site is then massaged to facilitate drug diffusion around the nerve (Gilger & Stoppini, 2011; Manning & St. Clair, 1976; Rubin, 1964). Lidocaine or mepivicaine is most often employed for this procedure because of its rapid onset and reasonably long duration; procaine, bupivacaine, and ropivicaine can also be used (Skarda & Tranquilli, 2007c). Both lidocaine hydrochloride 2% and mepivacaine 2% have a rapid onset of action (3–5 minutes) and an intermediate duration of action (1–2 hours), whereas bupivacaine and ropivicaine have a longer duration (3–6 hours; Gilger & Stoppini, 2011; Skarda & Tranquilli, 2007c). The duration and quality of the anesthetic block can be improved with the addition of epinephrine (5 µg/mL) to the anesthetic solution (Skarda & Tranquilli, 2007c). With effective akinesia, ptosis, narrowing of the palpebral fissure, and occasionally lower ectropion result. A hospitalized horse receiving repeated auriculopalpebral nerve blocks occasionally becomes resistant, thereby taking longer to achieve akinesia and sometimes requiring higher doses of anesthetic (Ollivier et al., 2007). Following completion of the ocular examination, lubrication of the ocular surface should be carried out every 30 minutes until a full blink has returned, to prevent exposure-induced corneal desiccation and ulceration.

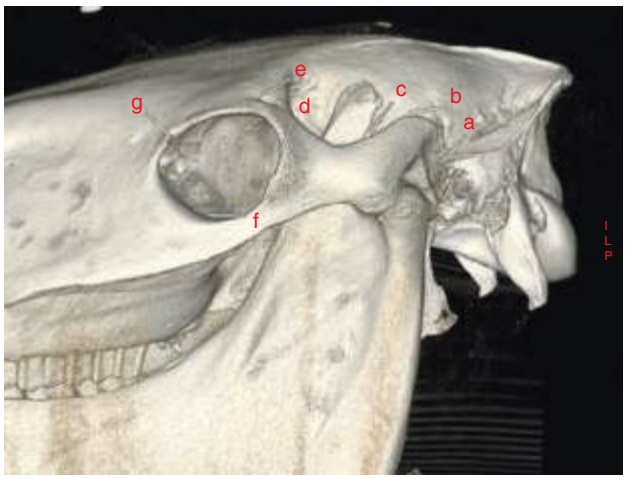


Figure 10.1.1 Three-dimensional computed tomography reconstruction of a horse's head depicting hypodermic needles at the appropriate sites for the auriulopalpebral (a and b); palpebral (c); lacrimal (d); frontal/supraorbital (e); zygomatic (f); and infratrochlear (g) nerve blocks.

Akinesia can be achieved in a similar fashion in cattle. The auriculopalpebral nerve can sometimes be palpated as it passes over a palpable notch in the zygomatic arch at the level of the temporomandibular joint (Skarda, 1996; Skarda & Tranquilli, 2007b). If the nerve cannot be palpated, anesthetic may be injected subcutaneously along the zygomatic arch, starting at the supraorbital process and continuing approximately 3.75 cm caudally (Welker, 1995). The needle is directed caudally, dorsally, and medially until it contacts the zygomatic arch. The needle is then advanced over the dorsal border of the zygomatic arch, and the area is infiltrated with 5–10 mL of anesthetic agent.

In the dog, the auriculopalpebral nerve can be located and blocked along the most lateral part of the zygomatic arch, at the midpoint of the caudal third of the bone (Ollivier et al., 2007). Alternatively, terminal palpebral nerve fibers may be

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blocked as they pass over the orbital rim. In the latter, the orbital rim is palpated, and a small-gauge, 5/8 or 1 in. needle is inserted 2 cm lateral to the lateral canthus. The needle is directed medially along the dorsal orbital rim, and the procedure is repeated along the ventral orbital rim, injecting a total of 1–3 mL of anesthetic agent throughout the region (Ollivier et al., 2007). This more distal block can also provide some anesthesia by blocking local sensory as well as motor nerves.

Regional Anesthesia/Analgesia

The most commonly applied form of anesthesia for the eye is the application of topical anesthetic to the cornea, which is routinely used during ocular examination, specifically to facilitate the assessment of painful eyes, measuring of IOP with the Tono-Pen® (Reichert Technologies, Buffalo, NY, USA), and for obtaining laboratory samples. The effect of proxymetacaine (proparacaine) has been investigated in different species (Binder & Herring, 2006; Herring et al., 2005; Kalf et al., 2008). In the dog, the application of a single drop of 0.5% proxymetacaine results in the loss of sensation for 55 minutes, with a maximal effect of 15 minutes, while the application of a second drop of the drug increased the maximal duration of corneal sensation loss to 25 minutes (Herring et al., 2005). The use of a 1% tetracaine and 0.4% oxybuprocaine preparation showed a fast onset of maximum corneal anesthesia within 1 minute and a significant loss of sensation for a duration of 45 minutes. However, tetracaine was not as well tolerated and resulted in conjunctival irritation in some dogs (Douet et al., 2013). More recently, both 2% lidocaine and 1% ropivicaine preparations were also shown to produce short-acting but fast-onset corneal anesthesia in dogs without significant side effects (Costa et al., 2014). In the cat, a single application of 0.5% proxymetacaine resulted in loss of sensation for 25 minutes with a maximal effect during the first 5 minutes (Binder & Herring, 2006). Equally, a single application of a drop of 0.4% oxybuprocaine resulted in complete loss of corneal sensation within 1 minute in all treated individuals, with a significant reduction in sensation from baseline over 45 minutes (Giudici et al., 2015). In the horse, maximal corneal sensation loss is noted 5 minutes following the application of a single drop of 0.5% proxymetacaine and the duration is approximately 25 minutes; however, full loss of corneal sensation is not achieved with proxymetacaine (Kalf et al., 2008). A 0.4% oxybuprocaine drop preparation showed similar effects when applied to the eyes of horses and donkeys (Little et al., 2016a). In contrast, tetracaine in a 0.5% aqueous solution showed an increased loss of sensation compared to proxymetacaine, while the application of a 0.5% viscous tetracaine preparation resulted in full loss of corneal sensation in some individuals (Sharrow-Reabe & Townsend, 2012). In cattle, both 0.4% oxybuprocaine and 0.5% proparacaine have been shown to produce maximal corneal anesthesia within 1 minute, with significant reduction in corneal sensitivity from baseline for 75 minutes (Little et al., 2016b).

Sensation to the eyelids is provided by the ophthalmic and maxillary divisions of the trigeminal nerve (i.e., cranial nerve V). In most domestic animals, the frontal, lacrimal, and infratrochlear nerves arise from the ophthalmic division of cranial nerve V, and the zygomatic nerve arises from the maxillary division (Dyce et al., 2009; Evans, 1993). In the horse, cow, and dog, the frontal nerve innervates most of the central upper lid, the lacrimal nerve innervates the lateral upper lid, the zygomatic nerve innervates most of the lateral lower lid, and the infratrochlear nerve innervates the medial canthus (Gilger & Stoppini, 2011; Manning & St. Clair, 1976; Skarda & Tranquilli, 2007b, 2007c; Wilkie, 1991). Anesthesia of these nerves is indicated for eyelid and conjunctival biopsies and for subpalpebral lavage placement, especially in the horse (Gilger & Stoppini, 2011). In small animals, any diagnostic or surgical procedure that requires blocking eyelid sensation is performed under general anesthesia; sensory blocks of the face are thus less commonly performed in these patients. However, local anesthetic techniques are applicable for patients under general anesthesia to lower the dose of anesthetic agent and to provide additional peri- and postoperative analgesia (Giuliano, 2008; Skarda & Tranquilli, 2007a). Given the risk of general anesthesia and the option of accurate regional nerve blocks with adjunctive sedation in large animals, these sensory blocks are very useful in large animal practice (Bettschart & Johnston, 2012; Hewes et al., 2007; Pollock et al., 2008; Robertson, 2004; Welker, 1995; Wilkie, 1991).

Several different sensory blocks may be employed in large animals depending on the location of the eyelid lesion to be addressed. The anesthetic agents used are the same as described above for the induction of eyelid akinesia. The central two-thirds of the upper eyelid are innervated by the frontal or supraorbital nerve, which is blocked by injecting 2 mL of 2% lidocaine under the skin immediately above the supraorbital foramen (Gilger & Stoppini, 2011). Techniques are also described to inject the anesthetic directly into the foramen itself (Skarda & Tranquilli, 2007c). However, this is not required to achieve an effective supraorbital nerve block, and injection of local anesthetic directly into the supraorbital foramen poses a risk of iatrogenic damage to the supraorbital artery and vein, and may cause discomfort if the periosteum in the canal is touched by the advancing needle (Gilger & Stoppini, 2011). The supraorbital foramen can be identified as a small depression in the supraorbital process of the frontal bone, medial to its most narrow aspect (Fig. 10.1.2). To palpate the foramen, the examiner places the thumb below the dorsal orbital rim, the middle finger in the supraorbital fossa, and the index finger midway between thumb and middle finger (Gilger & Stoppini, 2011; Skarda & Tranquilli, 2007c). The supraorbital nerve block may also provide some eyelid akinesia, most likely by having an effect

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Figure 10.1.2 The supraorbital nerve in the horse is blocked at the level of the supraorbital foramen. To locate the correct position, the examiner places the thumb against the orbital rim and the middle finger into the supraorbital fissure. The index finger is then placed halfway in between, where the supraorbital foramen can be palpated.

on branches of the palpebral nerve, and as such is often used to augment the effect of the auriculopalpebral nerve block. The lateral upper eyelid and lateral canthus are innervated by the lacrimal nerve and can be blocked either by injecting 1 mL of local anesthetic agent adjacent to the lacrimal notch (a depression that can be palpated on the dorsolateral bony orbital rim), or with a line block along the lateral third of the dorsal orbital rim (Gilger & Stoppini, 2011). A block of the zygomatic nerve will anesthetize the lateral lower lid and is achieved with a line block along the ventrolateral orbital rim. The medial canthal region is innervated by the infratrochlear nerve and is desensitized by injecting anesthetic agent through the bony trochlear notch on the dorsal rim of the orbit near the medial canthus (Gilger & Stoppini, 2011; Skarda & Tranquilli, 2007c; Wilkie, 1991).

Retrobulbar anesthesia aims to block cranial nerves III, IV, V, and VI and the ciliary ganglion, and therefore provides loss of sensation to the globe and eyelids as well as extraocular muscle akinesis (Accola et al., 2006). In the horse, retrobulbar blocks are commonly used to allow surgical manipulation of the eye and adnexa in order to avoid general anesthesia (Robertson, 2004; Welker, 1995; Wilkie, 1991). The use of combined sedation and retrobulbar block is well established for enucleation in the standing horse (Hewes et al., 2007; Pollock et al., 2008; Robertson, 2004; Welker, 1995; Wilkie, 1991). The retrobulbar block has been shown to prevent heart rate decrease associated with the oculocardiac reflex during enucleation (Oel et al., 2014). Retrobulbar blocks are also used in equine patients undergoing general anesthesia to provide extraocular muscle akinesia during cataract surgery, thereby reducing the need for nondepolarizing neuromuscular blocking agents (NMBA) and ventilation (McMullen & Utter, 2010). In small animals, retrobulbar injections are most commonly used to augment analgesia for enucleation procedures, and to replace the need for NMBA to provide immobilization and optimal exposure during intraocular surgery (Hazra et al., 2008; Myrna et al., 2010).

Three different techniques have been described to deliver the retrobulbar block in the dog: the inferior-temporal (ventrolateral) palpebral (ITP) technique, the perimandibular approach, and the combined superior–inferior peribulbar (dorsal–ventral) approach (Accola et al., 2006). In the ITP technique, an approximate 20 degree angle is created by bending a 2-gauge, 1.5 in. spinal needle at its midpoint. The needle is then positioned at the ventral orbital rim and inserted through the lower lid at the junction of its middle and lateral thirds. The needle is advanced until a slight "popping" sensation is detected, indicating that the orbital fascia has been pierced. The needle is then directed slightly dorsally and medially toward the apex of the orbit and advanced approximately 1–2 cm (Accola et al., 2006; Fig. 10.1.3). Then 1–2 mL of a suitable local anesthetic (for example lidocaine, bupivacaine, mepivacaine, or ropivicaine) is injected after gentle aspiration to check for blood to avoid intravascular injection. Increased resistance encountered on injection of the local anesthetic agent might indicate that the needle has been placed into the optic nerve sheath. In this case, the needle must be redirected to avoid intrathecal injection, which can cause respiratory arrest by infiltration of the subarachnoid space and the CNS (Oliver & Bradbrook, 2013; Skarda & Tranquilli, 2007a). Care must be taken not to exceed the toxic dose of the anesthetic agent, as systemic absorption from the retrobulbar space is significant.

In the cat, a dorsomedial approach for retrobulbar anesthesia has been shown to be more reliable than the inferotemporal approach recommended for dogs (Shilo-Benjamini et al., 2013). In cats the available retrobulbar space for an



Figure 10.1.3 Correct position of the needle in the inferotemporal approach for retrobulbar blockade in the dog. (Reproduced with permission from Accola, P.J., Bentley, E., Smith, L.J., et al. (2006) Development of a retrobulbar injection technique for ocular surgery and analgesia in dogs. *Journal of the American Veterinary Medical Association*, **229**, 220–225.)

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intraorbital injection is very limited. With the cat in sternal recumbency, a 1.5 in. (38 mm) spinal needle is bent at the midpoint to achieve an angle of approximately 20 degrees. The needle is then inserted through the superior eyelid at the medial region of the orbit (at the junction between the medial and middle third of the eyelid) and advanced approximately three-quarters of its length (30 mm) toward the caudal pole of the globe, but in close proximity to the orbital wall. Intraconal placement of the needle can be confirmed by ultrasound guidance with a 5–8 MHz transducer in a transpalpebral approach (Shilo-Benjamini et al., 2014). Having the cat in dorsal recumbency may result in a better distribution of injectate (Shilo-Benjamini et al., 2013).

In the horse, several methods are described: the four-point block, the modified Peterson block, and direct injection into the orbital cone above or below the zygomatic arch (Ollivier et al., 2007). The latter method, above the zygomatic arch and caudal to the temporal process of the malar bone, requires only a single injection, which is near neither the globe nor the optic nerve and is relatively safe. In this technique, a 22-gauge, 2.5 in. spinal needle is directed through the skin, perpendicular to the skull and into the orbital fossa, just posterior to the posterior aspect of the dorsal orbital rim. When the needle is advanced, the eye will show a slight dorsal movement as the needle passes through the fascia of the dorsal retrobulbar cone into the retrobulbar space (Gilger & Stoppini, 2017). The needle is advanced until it enters the cone, evidenced by the slight "popping" sensation as the eye is released into its normal position (Ollivier et al., 2007). After aspiration, 10–12 mL of 2% lidocaine, mepivicaine, or bupivicaine are injected into the space so that the globe is pushed forward. The onset of anesthesia usually occurs within 5-10 minutes and lasts 1–2 hours.

The four-point block is a local muscle block in which 5–10 mL of anesthetic agent is placed in each of four sites (dorsal, lateral, ventral, and medial) with a 20-gauge, 3 in. spinal needle through either skin or bulbar conjunctiva, following the curve of the globe posteriorly into the extraocular muscles and orbit. The ventral injection should be directed slightly nasally to avoid the optic nerve (Ollivier et al., 2007). If a curved needle is used to place the anesthetic agent into the retrobulbar space, as in small animals, it is often possible to need one or two, rather than four, injections (usually laterally and medially). This technique should not be used when intraocular surgery is to be performed because it may place pressure on the globe.

The Peterson nerve block is performed by placing an 18-gauge, 6 in. needle through the notch formed by the supraorbital process cranially and the zygomatic arch ventrally. It is advanced horizontally and slightly caudally until it hits the coronoid process of the mandible. It is then walked off the rostral border and advanced to a final depth of approximately 8 cm into the pterygopalatine fossa, where 7–15 mL of 2% lidocaine is injected (Pearce et al., 2003; Peterson, 1951).

In ruminants, retrobulbar anesthesia can be accomplished by retrobulbar injection or the Peterson nerve block and its modifications. A modified retrobulbar injection method has been shown to deliver the anesthetic agent more reliably to the target nerves than the complicated Peterson method, and thus may be the simpler and preferred choice for the practitioner (Pearce et al., 2003). With retrobulbar injection in cows or small ruminants, the slightly bent needle (approximately 5-degree curvature) is either placed laterally and medially at the canthi or dorsally and ventrally through the eyelids or conjunctival fornices, and directed along the orbital walls and advanced to a depth of 8–9 cm into the orbit (Pearce et al., 2003; Skarda & Tranquilli, 2007b; Welker, 1995). In cattle, 10–15 mL of 2% lidocaine is injected through an 18-gauge, 6 in. needle. In small ruminants, a smaller volume is injected through a 22-gauge, 3 in. needle (Skarda & Tranquilli, 2007b; Welker, 1995). Many practitioners find that a single injection (as opposed to the paired injections) is sufficient to achieve the desired result of relative exophthalmos, analgesia, and immobilization.

More recently, alternatives to retrobulbar anesthesia, including peribulbar injection and sub-Tenon's methods, have been explored for veterinary patients, as they might present less risk of inadvertent globe perforation or intrathecal injection (Ahn et al., 2013a, 2013b, 2013c; Shilo-Benjamini et al., 2013, 2014, 2017; Stadler et al., 2017). In peribulbar anesthesia, the needle is introduced into the extraconal space (i.e., outside the extraocular muscle cone), thereby limiting risk of injury to intraconal structures, especially the optic nerve and major blood vessels supplying the globe. The injectate spreads throughout much of the orbit, including the intraconal space. Peribulbar local anesthetic injection techniques have been described for dogs and been shown to be more reliable than retrobulbar anesthesia in the cat (Giuliano, 2008; Shilo-Benjamini et al., 2013, 2017; Wagatsuma et al., 2014). Classically, peribulbar anesthesia involves two (dorsomedial and ventrolateral) or even four injections (dorsal, medial, ventral, and lateral), but more recently the use of a single injection dorsomedially has been shown to be superior to two injections in the cat (Giuliano, 2008; Shilo-Benjamini et al., 2013). For peribulbar anesthesia in the cat, a 25-gauge, 5/8 in. needle is inserted through the superior eyelid at the medial region of the orbit and advanced to its full length in close proximity to the wall of the orbit. A volume of 3 mL of injectate (containing 1.5 mL bupivicaine 0.4%) has been recommended, but care must be taken that the toxic dose of local anesthetic agent is not exceeded given the low bodyweight of most feline patients. It may therefore be necessary to extend the amount of local anesthetic solution with sterile saline to achieve an adequate but safe amount of injectate to be delivered. Slight pressure was applied to the needle during injection to ensure that it remained in the desired location. A significant increase in IOP has been demonstrated with peribulbar anesthesia in

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the cat, which limits the usefulness of this procedure in eyes with deep corneal lesions or glaucoma (Shilo-Benjamini et al., 2014).

In the dog, sub-Tenon's injection has been shown to provide excellent akinesia and mydriasis with the injection of 2 mL of 2% lidocaine (Ahn et al., 2013a, 2013b, 2013c). Sub-Tenon's anesthesia in the dog and horse is described via the mediodorsal area of the bulbar conjunctiva, which is incised with ophthalmic scissors 5 mm from the limbus. Closed scissors are introduced through the created aperture and the sclera is exposed by blunt dissection through Tenon's capsule. A human, curved, blunt 19-gauge, 25 mm sub-Tenon's cannula is inserted along the equator of the globe until it reaches the posterior sub-Tenon's space, where the local anesthetic is infused (Ahn et al., 2013b, 2013c; Stadler et al., 2017). After injection, digital ocular compression is recommended to be applied for 1 minute to minimize reflux and maximize distribution of the injectate.



Figure 10.1.4 An aerial view highlights unilateral exophthalmos affecting the right eye in an adult Weimaraner. (Reproduced with permission from Featherstone, H., & Holt, E. (2011) *Small Animal Ophthalmology: What's Your Diagnosis?* Chichester: Wiley-Blackwell, Fig. 1.3b, p. 13.)

Ophthalmic Examination in Ambient Lighting

Initial examination is performed in ambient lighting and without instruments. This is an important stage because it can be very informative. Examination is started from a distance, before handling the animal, and is followed by close examination.

Distant Examination

The animal's attitude, general body condition, and ability to navigate in an unfamiliar environment are carefully evaluated to provide some information about its general health and vision. Conformation of the orbit and periocular region and the size, position, and movement of the eyes should be assessed, with particular note of asymmetry. Abnormalities in globe size (e.g., microphthalmia, buphthalmos), globe position (e.g., enophthalmos, exophthalmos), and any type of ocular discharge should be noted. Distant examination is the best time to assess for signs of pain by observation of the blink rate, size of the palpebral fissure (reduced with blepharospasm and enophthalmos), and photophobia. In the horse, it is especially helpful to assess the angle of the upper eyelashes; any change from the normal position (perpendicular to the cornea) is suggestive of discomfort, abnormal globe size or position, or ptosis. Closer observation of the eyelids, still without touching the animal, is made to assess the resting eyelid position and conformation and the position of the third eyelid (TEL). The general assessment of symmetry should, if possible, be performed from above as well as from a position facing the animal (Fig. 10.1.4); this helps the examiner detect subtle differences in globe size and position.

Vision Assessment and Neuro-ophthalmic Examination

The cranial nerve examination is an inherent and essential part of any thorough ocular examination. Specifically, cranial nerves II, III, IV, V, VI, VII, and VIII are assessed via the menace response, dazzle reflex, PLR, palpebral reflex, corneal reflex, and vestibulo-ocular reflex (VOR). These tests are described in the context of a routine ophthalmic examination, and more extensively, in Chapter 36.

Vision Assessment Vision can be assessed by the menace response, tracking reflex (cotton ball test), visual placing reflex (for small animals), and maze test (in photopic and scotopic conditions). The menace response is part of a routine ophthalmic examination.

The menace response is a learned protective response in which a menacing movement toward the eye results in closure of the ipsilateral eyelids, and possibly globe retraction or an avoidance head movement. The afferent arm of the menace response is the retina and cranial nerve II, and the efferent arm is the palpebral branch of cranial nerve VII, which innervates the orbicularis oculi muscle. Globe retraction, if it occurs, is mediated by cranial nerve VI. While making the menacing gesture with a finger or hand, care must be taken to avoid touching the vibrissae or creating excessive air currents that could be detected in a blind eye (i.e., false-positive result). The menacing gesture should be directed toward different visual fields to gather information about partial visual deficits. It is important to cover the contralateral eye in animals with frontally placed eyes (e.g., carnivores) so that each eye is assessed on its own.

The menace response takes longer to develop than the relatively simple PLR. The menace response is an *acquired* cortical response, which was highlighted by a study in calves: calves reared in isolation developed the response more slowly than those reared in a group setting (Raoofi et al., 2009). It should be present in puppies and kittens by approximately 12 weeks of age, although 3–4 weeks of age has been described (Lavely, 2006). In foals, the majority of studies concur that a

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menace response develops at 14–16 days after birth (Adams & Mayhew, 1984; Carastro, 2004; Leiva et al., 2011; Mayhew, 1995), and later in foals with postnatal problems (Enzerink, 1998). Other reports have described a positive menace response between 5 days and 19.5 weeks (Latimer & Wyman, 1985) and by 9 days (Enzerink, 1998). In lambs and kids, the menace response should be acquired by 8 and 14 days, respectively (Raoofi et al., 2011). The menace response is absent in rabbits, and is inconsistent in cats and birds and some exotic species. Inconsistent or false-negative results may occur in stoic, depressed, or frightened animals and are likely with repeated attempts. Lightly tapping the lateral or medial canthus before performing the menace response helps to heighten the animal's awareness. A visual eye may give a negative menace response if there is concurrent ipsilateral facial nerve paralysis. The menace response should be performed before sedation or eyelid akinesia; this applies in particular to the horse, for which these procedures are frequently performed.

Pupillary Light Reflex The resting pupil size should first be observed in normal light and then in a darkened room. Pupil size and asymmetry can be accurately assessed by distant direct or indirect ophthalmoscopy. By directing an ophthalmoscope light toward the center of the animal's head, from a distance of 3–5 ft for small animals and 6–8 ft for large animals, the tapetal reflection (tapetal reflex, fundic reflex) from each eye is easily detected simultaneously. This simple technique will usually detect subtle anisocoria (Fig. 10.1.5). Comparison of the degree of anisocoria in light and dark conditions helps in the diagnosis of Horner's syndrome. In an animal with unilateral Horner's syndrome, the anisocoria is most pronounced in the dark because the normal pupil dilates, whereas the abnormal pupil remains small because of the interruption to the sympathetic supply to the iris dilator muscle.

The PLR, tested by shining a bright focal light source at the eye, results in constriction of the ipsilateral pupil (direct PLR) and, in some species, constriction of the contralateral pupil (indirect or consensual PLR). The PLR evaluates the retina, cranial nerve II, midbrain, and cranial nerve III (parasympathetic fibers). An animal with cortical blindness can have a normal PLR because the pupillomotor fibers branch from the optic tract before the visual fibers. The PLR is present but sluggish when the eyelids open (10–16 days postnatally in puppies, 5–14 days in kittens). The PLR is similar to that of the adult dog when the retina is mature (28 days postnatally; Lavely, 2006). Lambs and kids have a PLR within 20 hours of birth (Raoofi et al., 2011). In foals, the PLR is present immediately after birth (Adams & Mayhew, 1984), but is sluggish and incomplete for several days (Leiva et al., 2011). The adult equine PLR is biphasic; that is, an initial brisk but small reaction followed by a slower complete constriction (Mayhew, 1995). The direct PLR is difficult to assess in birds, because intermittent dynamic anisocoria can be a normal feature; this results from (presumptive) voluntary control of the striated component of the iris musculature and the bird's emotional state (Kern, 2007).

The indirect PLR is only present in species with partial decussation of the optic nerve fibers at the optic chiasm (e.g., 33% in the cat, 75% in the dog, 85% in the horse; Shamir & Ofri, 2007). In species with more than 50% decussation, the indirect PLR is weaker than the direct PLR, because more efferent pupillomotor fibers return to the ipsilateral side of the brain (dynamic contraction anisocoria; Samuelson, 2007; Shamir & Ofri, 2007). It is more difficult to perform the

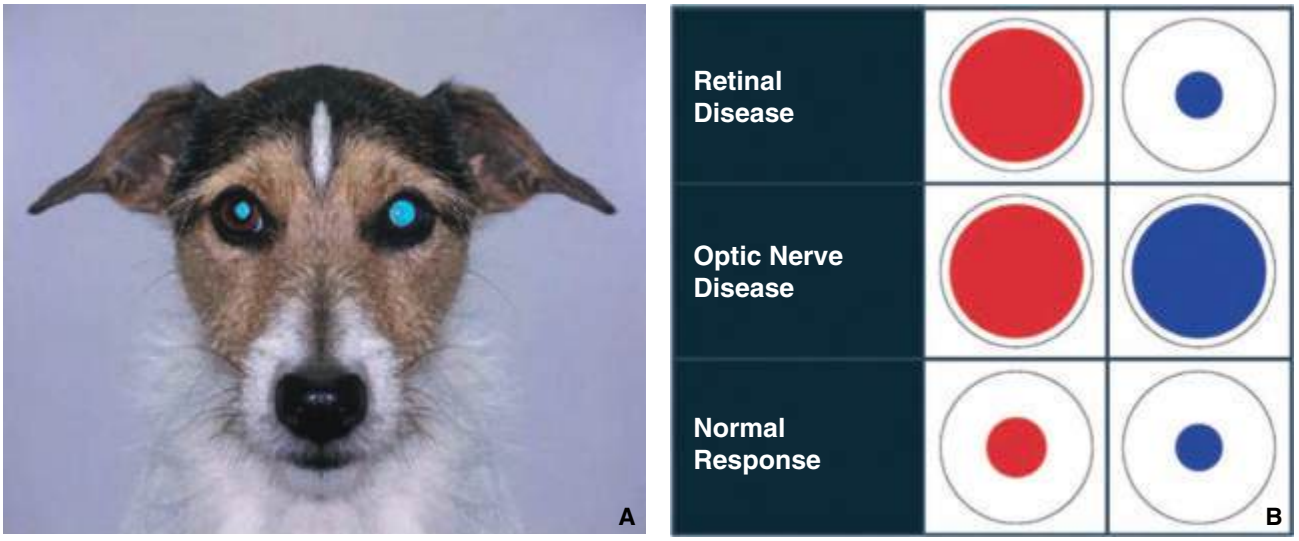


Figure 10.1.5 A. Anisocoria (left mydriasis) in an adult Terrier is recognized by comparison of the tapetal reflection from each eye with either distant direct or indirect ophthalmoscopy. (Reproduced with permission from Featherstone, H., & Holt, E. (2011) *Small Animal Ophthalmology: What's Your Diagnosis?* Chichester: Wiley-Blackwell, Fig. 11.4a, p. 211.) **B**. Schematic of canine chromatic pupillary light reflex testing. (Courtesy of Sinisa Grozdanic.)

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indirect PLR in species with laterally placed eyes (e.g., horse, rabbit), and an assistant is helpful. It is unnecessary to evaluate the indirect PLR if both eyes are visual and have a direct PLR. Nonmammalian vertebrates have 100% decussation of fibers and only have a direct PLR (Millichamp, 2002). A pseudo-indirect PLR may, however, occur in some bird species because the thin interorbital septum may allow light from one eye to illuminate the contralateral retina (Samuelson, 2007). Factors that may cause the PLR to be reduced include fear, low-intensity light source, iris atrophy, posterior synechiae, and prior topical administration of a mydriatic agent; even extensive cataract does not have a significant effect on the PLR.

The "swinging flashlight test" is a modification of the PLR. A focal light source is passed repeatedly from one eye to the other, causing the pupil under direct illumination to constrict slightly more than the contralateral pupil. A unilateral prechiasmal lesion (i.e., involving the retina and/or optic nerve) will result in a pupil that constricts when the fellow eye is illuminated, but subsequently dilates under direct illumination (a Marcus Gunn pupil). It is important to note, however, that pupillary escape, a *slight* dilation that follows constriction under direct light stimulation, is normal in many species (Scagliotti, 1999). A protocol for objective quantification of the PLR in the dog has been described (Whiting et al., 2013).

Chromatic PLR testing in dogs has been developed over the last decade and offers a practical diagnostic tool for assessment of the PLR and visual pathways in dogs. It differentiates PLR parameters elicited by activation of rods, cones, and intrinsically photosensitive retinal ganglion cells (ipRGCs) that contain a novel class of opsins: melanopsin (Grozdanic et al., 2007, 2013; Terakado et al., 2013; Whiting et al, 2013; Yeh et al., 2013, 2017). A handheld device (Melan-100®, Eickemeyer, Tuttlingen, Germany; cPLR Tester, Vision Biomedical Solutions, Apatin, Serbia) works on the principle that bright red light primarily stimulates the cone photoreceptors (200 kcd/m^2, 630 nm), and bright blue light corresponds to the peak spectral activity of melanopsin (200 kcd/m^2, 480 nm), but also activates cone and rod receptors. Computerized devices have been developed for more advanced studies for research (Whiting et al, 2013; Yeh et al., 2017). In simple terms, a PLR is elicited by red and blue light in healthy dogs (Figure 10.1.5B). Eyes with retinal pathology have a reduced or absent PLR when illuminated with high-intensity red light because of rod and cone damage, and a positive PLR when illuminated with high-intensity blue light because of activation of melanopsin in the ipRGCs, which are usually preserved even with advanced retinal changes (Grozdanic et al., 2007, 2013; Terakado et al., 2013; Whiting et al, 2013; Yeh et al., 2013, 2017). Dogs affected with optic nerve pathway disease have an absent PLR irrespective of the color of the light stimulus (Grozdanic et al., 2013).

Dazzle Reflex The dazzle reflex (photic blink reflex) is a subcortical reflex in which a bright focal light source shone quickly into the eye results in closure of the ipsilateral and, to a lesser extent, contralateral eyelids. The complete anatomic pathway for the dazzle reflex is unknown, but the retina, cranial nerve II, rostral colliculus, and/or supraoptic nuclei of the hypothalamus and cranial nerve VII (innervating the orbicularis oculi) are involved. Being a subcortical reflex, in contrast to the cortical learned menace response, the dazzle reflex is present from birth or soon after, for instance 1–2 days postnatally in puppies and kittens (Lavely, 2006). Sufficient brightness of the light source is crucial for this test to be performed reliably. Heat from the light source, if it is held too close to the cornea, can give a false-positive result and care should be taken to avoid this. The dazzle reflex is especially helpful to evaluate retina and optic nerve function when the PLR cannot be assessed, for example in hyphema and severe corneal edema.

Palpebral Reflex The palpebral reflex (blink reflex), tested by lightly touching the lateral and medial canthi, results in eyelid closure. The afferent arm is via the ophthalmic and maxillary branches of cranial nerve V, for medial and lateral stimulation, respectively. The efferent arm is cranial nerve VII. The palpebral reflex is present at 2–4 days postnatally in the puppy, 1–3 days in the kitten (Lavely, 2006), and immediately after birth in the foal (Adams & Mayhew, 1984). Physical reasons may reduce or prevent eyelid closure, for example buphthalmos and exophthalmos. Incomplete eyelid closure (lagophthalmos) is common in brachycephalic breeds of dog and cat. Although a slow incomplete palpebral reflex, associated with lagophthalmos, has been described in foals, a later study showed a normal PLR in 1-day-old healthy foals (Leiva et al., 2011). Eyelid closure is the endpoint for several routine neuro-ophthalmic tests, for example menace response and dazzle reflex, and so the palpebral reflex should ideally be performed early on in the cranial nerve assessment to avoid false-negative results. As for the menace response, the palpebral reflex should be performed before sedation or eyelid akinesia.

Corneal Reflex The corneal reflex is one of the most sensitive reflexes in the body and its purpose is to protect the eye. The corneal reflex is assessed by touching the peripheral cornea, to avoid a menace response, with a noninjurious object, such as a wisp of cotton wool, swab tip, or fiber from an esthesiometer. The expected result is retraction of the globe, protraction of the nictitating membrane, and closure of the eyelids (Fig. 10.1.6). The afferent arm of the corneal reflex is the ophthalmic branch of cranial nerve V, and the efferent arm is mediated by cranial nerves VI (globe retraction) and VII (eyelid closure). Corneal sensitivity is described later in further detail (see "Corneal Esthesiometry").

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Figure 10.1.6 Corneal reflex. Corneal sensation is tested by means of a wisp of cotton wool contacting the peripheral cornea.

Vestibulo-ocular Reflex (Oculocephalic Reflex) The VOR assesses eye movement in relation to changes within the vestibular apparatus. It thereby indirectly assesses the three cranial nerves (III, IV, and VI) that innervate the extraocular muscles, and cranial nerve VIII and the medial longitudinal fasciculus that coordinate movement. The animal's head is moved from side to side and up and down. During head movement, the eyes will attempt to maintain the last eye direction; that is, where the animal was looking at the start of the test. This results in a slow movement of the eyes away from the direction of head movement. As the head continues to be moved, the extraocular muscles, influenced by the vestibular system, move the eyes quickly in the same direction of head movement. The eyes should move in unison and should stop moving when head movement is stopped. This physiologic nystagmus will occur in blind animals, because it is caused by changes within the vestibular system rather than vision. Because it is often difficult to observe movement in eyes with dark irides (a common feature of most domestic species), retraction of the upper eyelid skin can be helpful to reveal the white of the sclera during eye movement. The VOR is more difficult to perform in large animals.

Tear Tests

At this point in the examination, or even before some of the neuro-ophthalmic tests, tear production should be measured. This is to avoid falsely high values from excessive manipulation of the eye and/or eyelids (inducing reflex tear production) and/or the administration of any topical agents (e.g., stains, anesthetic agents, mydriatic agents). Tear tests are described in a later section of this chapter ("Tear Tests").

Close Examination of Adnexa and Globe

Following initial distance examination, the animal can be handled gently, with minimal manipulation of adnexal tissues. The orbit should be examined by palpation of the bony orbital rim and indirectly by retropulsion of the globe through the closed upper eyelid. Forceful manipulation of the eyelids and retropulsion should not be performed if the structural integrity of the cornea or globe could be compromised. A more detailed assessment of the orbit includes manipulation of the mandible and oral examination (this can be deferred to minimize stress in the early stages). As the coronoid process of the vertical ramus of the mandible is closely associated with the floor of the orbit, jaw opening may cause pain or resistance if orbital disease is present. A careful examination of the oral cavity should follow, with particular attention paid to the region of the soft palate caudal to the ipsilateral last upper molar. Oral examination consists of direct observation, aided by a light source, and, in some species (e.g., the dog), light digital palpation (the latter is restricted to animals with a gentle disposition).

Eyelids should be examined in more detail in terms of position, mobility, and conformation, and skin lesions. In some animals, it is important to assess eyelid conformation with the head in different positions. This applies in particular to dog breeds with heavy skin folds on the head and/or face, for example Shar Pei, St. Bernard, and Basset Hound. Close inspection of the eyelid margins allows observation of the cilia (eyelashes) and meibomian gland openings. The eyelids differ greatly between species. The upper eyelid is more mobile in mammals, whereas the lower eyelid is more mobile in birds and many lower vertebrates. Larval amphibians and most fish lack eyelids and metamorphosed amphibians have poor eyelid development. Although most reptiles have mobile lower eyelids, crocodilians have well-developed upper eyelids with a bony tarsal plate. Birds have a tarsal plate in the lower eyelid and a well-developed, almost transparent TEL. Complete fusion of the upper and lower eyelid forms the spectacle in snakes and geckos.

The eyelids, conjunctiva, and TEL should be examined in one almost continuous movement: the upper eyelid is retracted to examine the dorsal bulbar conjunctiva; the eyelid margin is everted to examine the upper palpebral conjunctiva and the upper nasolacrimal punctum; the TEL is protruded by applying gentle pressure through the upper eyelid to retropulse the globe, to enable examination of the anterior surface, leading edge, and alignment of the TEL. Finally, the lower eyelid is retracted to aid visualization of the lower conjunctival fornix and nasolacrimal punctum. The leading edge of the TEL is usually pigmented. The TEL is a common site for squamous cell carcinoma in some species (e.g., horse, cattle), and effective protrusion of the TEL is essential for a thorough examination, followed by digital palpation if abnormalities are noted. The lacrimal caruncle lies just inside the medial canthus; it appears as a small mound covered with conjunctiva and, in some animals, fine hairs. It is more prominent in ungulates than in carnivores.

A preliminary assessment of the nasolacrimal system is made at this stage. Tear overflow (epiphora) is noted and can represent either increased tear production or decreased tear drainage. Increased tear production is typically caused by ocular surface irritation (e.g., ectopic cilia) or pain (e.g.,

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anterior uveitis) and can be objectively quantified by the STT (see the main section on "Tear Tests"). Tear drainage may be reduced or absent as a result of partial or complete obstruction of the nasolacrimal drainage system. The drainage apparatus is evaluated by examining the proximal upper and lower lacrimal puncta and the distal nasal punctum; the latter is only really practical in the horse, because it is large and easy to identify on the ventrolateral floor of the nasal vestibule. The lacrimal puncta are slit-like openings in most species, but are round in the cat. In the dog, the puncta are 1 mm long by 0.3 mm wide and are located 2–5 mm lateral to the medial canthus, on the palpebral conjunctiva, where the line of meibomian glands ends (Grahn & Sandmeyer, 2007). In the horse, the 2 mm slit-like puncta are located 8–9 mm lateral to the medial canthus (Latimer et al., 1984). The rabbit has a single lower lacrimal punctum and the pig has a single upper lacrimal punctum. The entire nasolacrimal system is absent in aquatic lower vertebrates, including fish, amphibians, and chelonians. In some animals, identification of the puncta is made easier by a small amount of surrounding pigment. Abnormalities in size, position, shape, and ocular discharge should be noted. The area ventral to the medial canthus should be evaluated for abnormalities (e.g., swelling) because of the underlying lacrimal sac. The lacrimal sac, the small dilation at the confluence of the upper and lower canaliculi, is a common site for foreign bodies. A more detailed assessment of the nasolacrimal system can be made with the application of fluorescein dye (Jones test), irrigation (see "Nasolacrimal Flush"), and imaging.

Gross examination of the ocular surface includes assessment of the tear film and cornea. The specular reflection of the cornea (Purkinje image) appears as a focal reflection of light from a window or artificial light in the examination area (Fig. 10.1.7). The specular reflection provides information about the optical smoothness of the ocular surface, and thereby the quality and quantity of the tear film and corneal regularity. The intensity of the corneal reflection can be quantitatively measured, a technique that has been used to monitor the response to treatment (Goto et al., 2011; Nankivil et al., 2014). In a study of human patients with dry eye, the intensity of the specular reflection was not only shown to be lower in dry eyes than in normal eyes as expected, but to

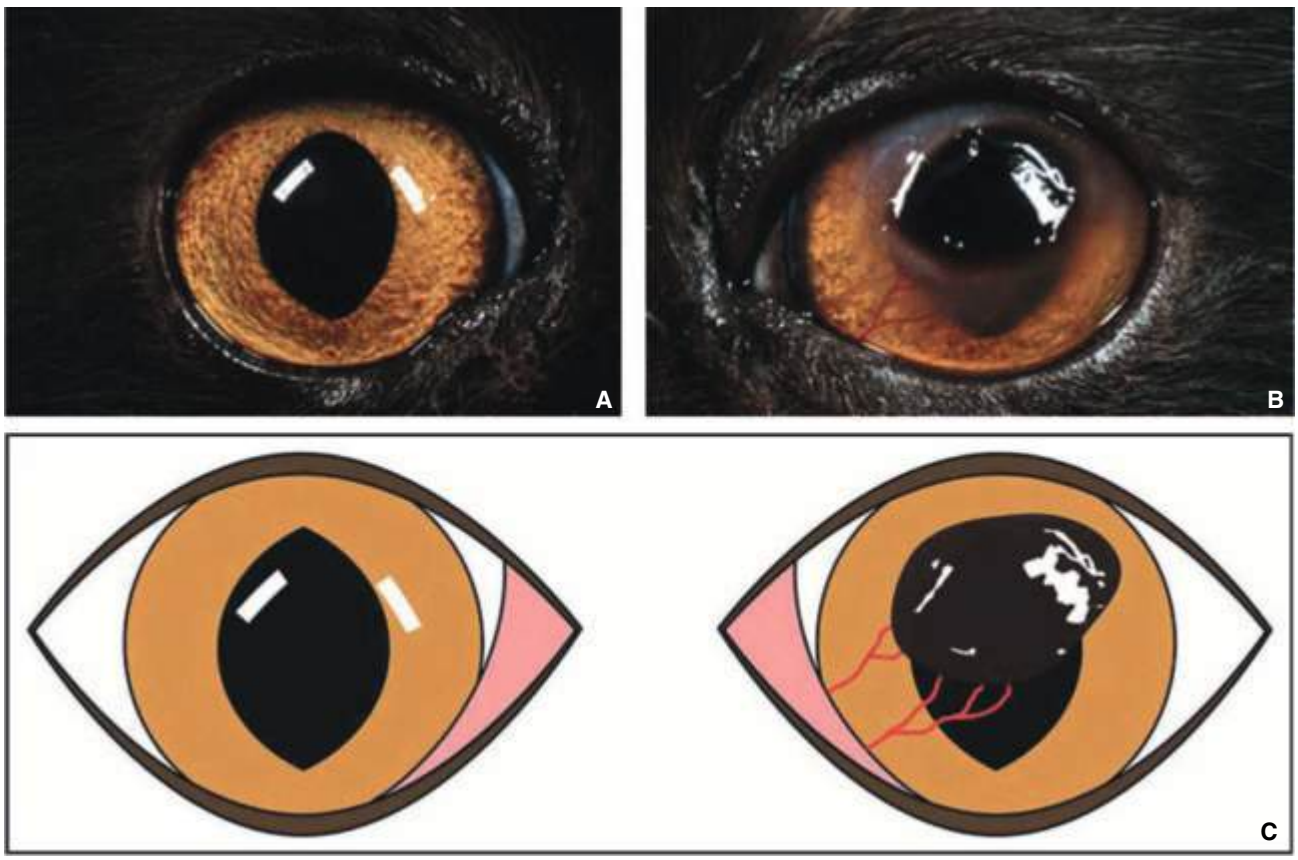


Figure 10.1.7 Specular reflection. **A**. The right eye of an adult Persian cat shows a normal corneal specular reflection (Purkinje image), which appears as two symmetric curved rectangular reflections from the overhead room lighting. **B**. In the left eye, the corneal specular reflection is severely disrupted by corneal pathology, comprising a large sequestrum with associated vascularization and edema. (Reproduced with permission from Featherstone, H., & Holt, E. (2011) *Small Animal Ophthalmology: What's Your Diagnosis?* Chichester: Wiley-Blackwell, Fig. 8.3b, p. 144.) **C**. Diagrammatic representation of the normal and abnormal corneal specular reflections shown in **A** and **B**. (Illustration by H. Featherstone and Simon Scurrell.)

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increase following treatment with lacrimal punctal plug placement (Goto et al., 2011). More detailed assessment of the tear film is described later (see "Tear Tests," "Slit-Lamp Biomicroscopy," and "External Ophthalmic Dyes").

Gross examination of the limbus, cornea, anterior chamber, anterior iris, pupil, and anterior lens is performed at this stage. The cornea is examined first, followed by evaluation of the pupil (resting size, shape, and mobility) and the appearance of the anterior chamber structures. In the horse, the insertion of the pectinate ligaments onto Descemet's membrane (i.e., "gray line") can be observed laterally and medially, enabling direct observation of the iridocorneal drainage angle. Direct observation of the drainage angle is also possible in the cat because of its deep anterior chamber and marked corneal curvature.

The cornea is examined next. Most mammalian corneas are oval, with a greater horizontal than vertical diameter. The normal cornea is a transparent, smooth, avascular, and nonpigmented convex structure. The presence of surface irregularities, blood vessels, pigment, or other opacities indicates disease. Corneal integrity is most readily evaluated with fluorescein dye. Fluorescein dye is hydrophilic and binds readily to exposed corneal stroma if an ulcer is present. The dye will not bind to intact healthy corneal epithelium or to Descemet's membrane and the endothelium.

Corneal sensation may be demonstrated by touching the cornea gently with a thin wisp of cotton while holding the eyelids open (Fig. 10.1.6). When touched from the periphery to avoid a menace response, the normal corneal reflex is retraction of the globe, with protraction of the nictitating membrane. This corneal reflex tests cranial nerves V, VI, and VII. The degree of corneal sensation can be semi-quantified in different areas of the cornea using an esthesiometer, which will be discussed later.

Slit-lamp biomicroscopy may be useful in characterizing the microscopic details and exact depth of corneal lesions. Specular microscopy may elucidate the cellular abnormalities and densities of the corneal endothelium. Additional tests for corneal disease include culture, cytology, tear tests, and other ophthalmic dyes, for example Rose Bengal.

The anterior chamber is observed for transparency and depth. Anterior chamber depth shows more variation in exotic species than in domestic animals, in part because of variation in the size and shape of the lens. In fish, the lens may appear to almost touch the cornea. The anterior chamber depth may decrease because of intumescent cataract, iris bombé, or a mass within or behind the iris. It may appear unusually deep in eyes without lens support in cases of aphakia or pseudophakia, resorbing cataract, or lens luxation. A slit beam, as may be found on many direct ophthalmoscopes and slit-lamp biomicroscopes, may be useful in evaluating the depth of the anterior chamber. The aqueous humor of the anterior chamber should be transparent and therefore free of blood (i.e., hyphema), protein (i.e., aqueous flare), cells, fibrin, cysts, parasites, tumors, and foreign material. Aqueous flare can be detected with a slit beam. In a dark room, a slit or tiny circular beam is focused on the cornea and viewed from an angle perpendicular to the beam. Containing only 10–50 mg/dL protein, the normal aqueous humor is clear (Blogg & Coles, 1970; Olin, 1977). With inflammation, however, this protein content can reach 5–7 g/dL, resulting in plasmoid aqueous (Hogan et al., 1973; Olin, 1977). Under these conditions, both protein and cells suspended in the aqueous humor reflect the focused beam, creating the Tyndall effect. An otoscope head or slit-lamp biomicroscope can provide magnification for characterizing microscopic debris such as keratic precipitates or aqueous "floaters."

If the anterior chamber cannot be visualized because of corneal opacification, B-scan ultrasonography may prove useful for evaluating chamber depth and consistency. Aqueous paracentesis, described in "Ophthalmic Diagnostic Procedures," may provide useful information via culture, serology, or cytology. Laser cell fluorophotometry or flaremetry can measure protein and cellular debris levels in the aqueous humor and is extensively used in pharmacologic testing (Krohne et al., 1995; Rankin et al., 2002; Rankin et al., 2011b).

Because of the presence of the scleral shelf, the canine iridocorneal angle (ICA) and ciliary cleft (CC) cannot be visualized without special lenses. The direct goniolens and indirect gonioprism allow observation of the entrance into the ICA for congenital defects, abnormal narrowing, peripheral anterior synechiae, extension of iris or limbal neoplasms, and foreign bodies. The gonioscopy instruments and techniques are described in detail later in this chapter. Ultrasonic biomicroscopy using probes from 40 to 60 MHz permits high-resolution imaging of the aqueous outflow pathways.

The iris is evaluated for color, apparent thickness, pupillary membrane strands, pupil size and shape, and stability. Multiple colors within an iris may occur congenitally, as with heterochromia iridis, or may be acquired, as with chronic inflammation or neoplasia. Blue irides occur in some lightly pigmented breeds, whereas albino animals have pink to white irides. Iris darkening or thickening (or both) may occur with chronic inflammation and neoplasia. Hypoplastic and atrophic irides are thin and usually transilluminate; focal holes may also be present, especially near the pupil margin.

The major arterial circle of the iris is often visible as an elevated, wavy line near the iris base. A similar but less obvious structure, the minor arterial circle of the iris, may occasionally be seen near the pupil margin. Strands of pigmented tissue on the iris collarette, which are occasionally seen extending to contact the lens, cornea, or other sites of the iris collarette, are abnormal remnants of the persistent pupillary membrane. Strands of iridal tissue arising from areas adjacent to the collarette and extending to the cornea and lens are called anterior and posterior synechia, respectively. Adhesions of the peripheral iris to the peripheral posterior cornea and across the opening of the CC are called peripheral anterior synechiae.

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The pupil may be abnormally dilated with iris atrophy, iris coloboma, glaucoma, retinal, or optic nerve disease, or it may be abnormally small in microphthalmic eyes with congenital hypoplasia of the iris sphincter, with Horner's syndrome, or anterior uveitis. Abnormalities of pupil shape may occur with lens luxation, anterior or posterior synechiae, iris neoplasia, trauma, or iris atrophy. With resorbing cataract, lens luxation and subluxation, and pseudophakia, the iris may be observed to tremor (i.e., iridodonesis) during eye movement, which is caused by the lack of lens support. The pupil is round in dogs, a vertical slit in cats, and a horizontal ellipse in horses and cattle. Most ungulate species have nodular extensions of the posterior pigmented epithelium of the iris (i.e., granula iridica or corpora nigra), which protrude along the dorsal and ventral pupillary margins. In alpacas and llamas, the dorsal iris is extended in "radial folds or pupillary ruffs" protruding above the pupil, similar to granula iridica in the horse (Gionfriddo, 2010). Similar structures are not typically seen in small animals. Focal iris elevations should be retroilluminated to determine whether they are hollow (i.e., cystic) or solid (i.e., neoplastic). Details of iris lesions may be seen through an otoscope head or, preferably, slit-lamp biomicroscope. A slit beam can be used to determine if an iris lesion is elevated or, less commonly, depressed. Further diagnostic procedures include gonioscopy, ultrasonography, cytology, and biopsy.

Intraocular Pressure Measurement and Pupil Dilation

The IOP should be assessed in all patients presented for ophthalmic examination. IOP may be measured with the Tono-Pen, the TonoVet (ICare, Espoo, Finland), the pneumatonograph, the Mackay–Marg tonometer (Biotronics, Redding, CA, USA), or, less preferably, the Schiøtz tonometer (Reister, Ambala, India). See "Tonometry" later in this chapter. Manual estimation of IOP (digital tonometry) is imprecise and should be avoided. IOP measurement should always be performed prior to the application of mydriatics.

In the absence of glaucoma and lens luxation, pupils are pharmacologically dilated. Tropicamide (1%) is preferred in most mammals because of its rapid onset (10–20 minutes) and relatively short duration (6–8 hours in dogs and 8–12 hours in horses; Davis et al., 2003; Klauss & Constantinescu, 2004; Munger, 2002). Topical mydriatics can increase the IOP in normal dogs in the treated eye (0.5% tropicamide, 1% atropine sulfate) and in both the treated and untreated eyes (10% phenylephrine hydrochloride; Kovalcuka et al., 2017). Care must be taken when applying tropicamide to the eyes of canine patients predisposed to glaucoma, as this can incite acute IOP increases (Grozdanic et al., 2010). IOP increases following the application of 0.5% tropicamide have been reported in both normotensive and glaucomatous cats, but reports give conflicting evidence as to whether increases occur only in the treated eye or in both eyes (Gomes et al., 2011; Stadtbaumer et al., 2002, 2006). Tubocurare derivatives such as vecuronium or rocuronium must be used in non-mammalian vertebrates, because of the presence of striated muscle fibers in the pupillary sphincter muscle (Barsotti et al., 2010a, 2010b; Loerzel et al., 2002). Atropine is usually not used for diagnostic purposes because of its slow onset of action and long duration of action, for example 3 days in dogs and 5–14 days in horses (Klauss & Constantinescu, 2004). Inflamed irides usually resist mydriasis and often require multiple doses of tropicamide (1%), atropine (1%), or the addition of phenylephrine (10%) and scopolamine (0.3%; Ollivier et al., 2007). Complete mydriasis is essential for thorough evaluation of the lens and the peripheral fundus, and for posterior segment photography.

Anterior Segment Examination after Pupil Dilation: Lens Examination

The lens is evaluated with both direct illumination and retroillumination for its position, size, shape, surface irregularities, and transparency. The size and shape of the lens in different species vary tremendously. A slit beam is often useful in characterizing cataracts. While directing the beam onto the lens and looking from an oblique angle, the examiner observes a cross-section of the lens. Cataracts should be classified both anatomically and by stage of maturity (for more detail, see Chapter 22). The presence of wrinkling of the anterior lens capsule and the visibility of a tapetal reflex can help with staging cataract maturity. Cataract appearance and location may give clues as to the cause – a nuclear cataract can be determined as congenital, while a posterior polar subcapsular cataract is recognized as an inherited condition in many gundog breeds.

Nuclear sclerosis, which is an aging change that leads to a hazy, gray-blue appearance in the center of the lens, must be distinguished from senile cataract. The lens may appear to be cataractous at a glance, but retroillumination and ophthalmoscopy demonstrate that nuclear sclerosis does not actually obstruct the passage of light or prevent visualization of the ocular fundus. Other methods of lens evaluation include both A- and B-scan ultrasonography.

Posterior Segment Examination

The normal vitreous is a clear and homogenous gel that fills the space between the posterior lens capsule and the retina. In prenatal animals, the hyaloid artery extends from the center of the optic disc to the axial posterior lens capsule. In very young animals, and especially ruminants, a persistent hyaloid artery may be visible postnatally for several weeks (Whitley & Moore, 1984). In cattle, a proximal remnant of this artery can be seen extending a short distance from the optic disc (i.e., Bergmeister's papilla). Visualization of a proximal hyaloid remnant requires either direct or indirect fundoscopy (see "Direct Ophthalmoscopy" and "Indirect Ophthalmoscopy"), or slit-lamp biomicroscopy using the Hruby and Goldmann lenses (Haag-Streit, Koeniz, Switzerland).

Abnormalities of the anterior vitreous may be observed with direct illumination and slit-lamp biomicroscopy. The vitreous should be examined for extensions of uveal or retinal

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hemorrhage, neoplasia, parasites, retinal detachment, infection, and inflammation. Degenerative changes appear as suspended crystalline formations (i.e., asteroid hyalosis), moving "snowflakes" (i.e., synchysis scintillans), or accumulations of collagen and cells (i.e., vitreal "floaters"). Ultrasonic examination of the vitreous may prove useful if direct visualization is impaired. Another diagnostic procedure, vitreous paracentesis (i.e., hyalocentesis), may be useful in chronic uveitis and suspected inflammatory lesions of the vitreous and is discussed in "Ophthalmic Diagnostic Procedures."

Successful examination of the ocular fundus requires intimate knowledge of the normal variations within each species. The fundus is a complicated structure that can suffer a variety of pathologic conditions, so it should be thoroughly examined in a systematic manner. Structures or areas to be evaluated include the optic nerve head (i.e., optic disc or optic papilla: shape, color, and topography), retinal vasculature (number, size, and pattern), tapetal fundus in species with a tapetum (e.g., reflectivity, pigmentation, depigmentation, hemorrhage, exudates), and nontapetal fundus (e.g., pigment loss, hemorrhages, exudates). Diagnostic procedures to evaluate the ocular fundus include both direct and indirect ophthalmoscopy, slit-lamp biomicroscopy with a condensing lens, fluorescein angiography, ERG, ultrasonography, biopsy, scanning laser tomography, and optical coherence tomography. Direct and indirect ophthalmoscopy are the primary means to visualize and evaluate the ocular fundus. Fluorescein angiography permits analysis of the retinal and choroidal blood vessels, their permeability, and the integrity of the retinal pigment epithelium. Flash ERG, discussed in Chapter 10.4, evaluates the function of the outer retinal layers and is most useful in the diagnosis and investigation of retinal degenerations. The pattern ERG is indicated for those diseases affecting the inner retinal layers (e.g., glaucoma). The newer imaging procedures, such as scanning laser tomography and optical coherence tomography, permit high-resolution topographic and full-thickness visualization of the retinal layers (see Chapter 10.2).

PART II: OPHTHALMIC DIAGNOSTIC PROCEDURES

Slit-Lamp Biomicroscopy

The slit-lamp biomicroscope is the most versatile diagnostic tool for the veterinary ophthalmologist, allowing magnified, three-dimensional examination of the adnexa, cornea, anterior chamber, lens, and vitreous. With the help of specifically designed condensing lenses, even the ocular fundus can be inspected with the slit-lamp biomicroscope (Berliner, 1943).

In 1911, Gullstrand developed the first slit-lamp biomicroscope, combining a corneal microscope with a slit-lamp biomicroscope that used a magnesium oxide light (Berliner, 1943; Schmidt, 1975). After years of refinement and modification (Berliner, 1943), the slit-lamp biomicroscope saw its first publications in veterinary medicine when Überreiter described its use in the evaluation of both normal and diseased animal eyes between 1953 and 1959 (Überreiter, 1954, 1956a, 1956b). Later, Martin published a series of papers on slit-lamp biomicroscopy of the normal dog eye (Martin, 1969b, 1969c, 1969d).

The slit-lamp biomicroscope is the combination of a binocular microscope with a highly versatile source of illumination. The microscope and light source are co-pivotal (i.e., they swing on the same axis), confocal (i.e., they focus on the same point), and isocentric (i.e., they center on the same plane; Fig. 10.1.8; Berliner, 1943). In the majority of slit-lamp biomicroscopes, it is the light source that pivots while the microscope is fixed; however, the alternative design with a microscope pivoting along the axis of the illuminator is also available. The strong white focal halogen, xenon, or light-emitting diode (LED) light can be modified by a series of diaphragms and filters that adjust the light shape (diffuse or focused beam), light intensity, and light beam width, length, orientation, and color (neutral density, cobalt blue, or red free). Returning light is focused through the objective lenses of the binocular microscope, and magnification can be adjusted from 5× to 40×, depending on the model. It is interesting to keep in mind the optic properties of the examined eye, as they add magnification to that provided by the optics of the biomicroscope. Therefore, the magnification of the biomicroscope remains unchanged at the surface of the cornea, but is multiplied by 1.1, 1.3, 1.5, and 1.7 inside of the cornea, at the anterior capsule, in the center of the



Figure 10.1.8 Keeler PSL®. Handheld lightweight (0.93 kg) slit-lamp model offering magnification of 10× or 16×, continuously adjustable levels of light-emitting diode (LED) illumination, slit-beam settings of 0.15, 0.5, 0.8, and 1.6 mm, as well as a round beam of 12 mm and a 1 × 1 mm square beam for the detection of aqueous flare.

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lens, and at the posterior lens capsule, respectively (numbers valid for humans; Berliner, 1943; Martin, 1969b, 1969c, 1969d; Überreiter, 1954, 1956a, 1956b).

Both table-mounted and portable slit-lamp biomicroscopes are available (Berliner, 1943; Martin, 1969b). Table-mounted models are more expensive and their use clearly presents logistical difficulties in the examination of many veterinary patients (Fig. 10.1.9). However, these static units do offer a wider range of magnification, greater variability of slit-beam width and orientation, as well as the option to decenter the light beam for additional illumination techniques. Most table-mounted slit-lamp biomicroscope models allow photographic documentation, and thus include a beam splitter, diffuse overall illuminator, and flash (Martonyi et al., 2007). With the progression of digital technology, photographic and video adapters have also become available for some of the handheld slit-lamp biomicroscope models, including smartphone adapters. Portable slit-lamp biomicroscopes are less expensive, can be used in any position, and are thus useful for both laboratory and companion animal patients (Fig. 10.1.10). These factors have made handheld slit-lamp biomicroscopes the models of choice among veterinary ophthalmologists. However, many of the more intricate ways to use complex lighting methods at high levels of magnification to allow visualization of even the most subtle pathologies will only be possible with table-mounted slit-lamp biomicroscopes (Table 10.1.2).

Theory and Principles of Slit-Lamp Biomicroscope Examination

The aim of slit-lamp biomicroscope examination is to serially examine the eye under magnification with as many forms of illumination as possible, to identify any pathology and to create a mental, complete composite of the eye, including both detail and context (Martonyi et al., 2007). The



Figure 10.1.9 Table-mounted slit-lamp models may provide superior optics and levels of magnification, but present logistical difficulties in the examination of veterinary patients.



Figure 10.1.10 Use of a handheld slit-lamp in a dog.

light beam used during the slit-lamp biomicroscopy can be diffuse or focal (Martin, 1969b, 1969c, 1969d; Martonyi et al., 2007). Diffuse forms of lighting are useful to examine a large area for gross abnormalities and to obtain an initial overview of the adnexa, cornea, anterior chamber, and iris (Fig. 10.1.11). However, to gain more detailed information and highlight subtle lesions, more focal forms of illumination are required. The concept of slit-lamp biomicroscopy with a focal light is the creation of an optical section of the transparent tissues of the eye (cornea, anterior chamber, and lens; Fig. 10.1.12). This is achieved by projecting a narrowly delineated, sharply focused, and bright slab of light onto the eye. The optical section of the structures visible to the examiner through the adjacent nonilluminated tissues can be likened to a histologic section. Portable slit-lamp biomicroscopes offer slit beam width options varying from 0.1 to 1.6 mm. With the use of a broad slit beam (> 0.5 mm), transparent ocular structures such as the cornea become visible as a parallel-piped "block of tissue" (Fig. 10.1.13).

Corneal examination with such a broad slit can be helpful to visualize many opacities, but is less efficient than the creation of an optical section with a thin beam (0.1–0.2 mm), as it creates a variable amount of overlap between anterior and posterior corneal surface (Martonyi et al., 2007). Abnormalities of the deeper structures may therefore best be seen in sections using a broad beam, when examining the "trailing edge" of the parallel-piped block (Fig. 10.1.14). In contrast, in the corneal section created with a thin beam of light, tear film, and epithelium, corneal stroma, and endothelium all become visible separately (Fig. 10.1.15). It is important that with the use of both broad and narrow beams, an appropriately wide angle between the slit-lamp microscope and illuminator (more than 45 degrees) is chosen, as the section collapses with too narrow an angle (Fig. 10.1.16; Martonyi et al., 2007). Examination with a slit beam will also help to provide topographic information, both about the tissues examined as well as the relationship of ocular structures to each other (Martonyi et al., 2007). The slit beam is deflected away from the examiner with a depression and toward the examiner by an elevation. This is well illustrated by the

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Table 10.1.2 Overview of characteristics of commonly available portable slit-lamp models.

Model	Magnification	Slit Options (mm width)	Light Source	Illumination Levels	Light Filters	Photo/Video Port	Weight (kg)	Extras
KOWA SL 17®	10×, 16×	1 × 1 0.1, 0.2, 0.8 5.0 and 12.0 circle	LED	Continuous	Blue, white	Video (via iPhone adapter)	0.79	
Keeler PSL classic®	10×, 16×	1 × 1; 0.15, 0.5, 0.8, 1.6, 12.0 circle	LED	Continuous	Red free, blue, neutral density, clear	Video (iPhone adapter)	0.93	
Hawkeye® (Dioptrix, Toulouse, France)	8×, 12.5×, 20×	1 × 1; 0.1, 0.2, 15.0	LED	Continuous	Green (red free), cobalt blue	Photo and video (6 MPX integrated digital camera)	1.5 (including camera)	Inbuilt holder for fundus exam lenses
Reichert PSL® (Depew, NY, USA)	10×, 16×	0.15–11.0	LED		Red free, blue color temperature conversion		0.68	

LED, light-emitting diode; MPX, megapixel.

example of corneal ulceration, where the slit on the surface of the cornea will be deflected away from the examiner (Fig. 10.1.17), and by the example of an iris tumor, where the slit beam overlying the iris lesion is deviated toward the examiner (Fig. 10.1.18).

The experienced examiner will also gain the ability to distinguish between normal thickness of ocular tissues and increased or decreased thickness of the tissues in their diseased state (see Fig. 10.1.13A, B; Fig. 10.1.17; and Fig. 10.1.18). With time, the experienced examiner is able to form a mental reference library of distances between ocular structures visible in the beam for the normal eye at any given angle, allowing for recognition and estimation of distances in the pathologic status. Typical examples are the shallow anterior chamber associated with lens intumescence, and the increased anterior chamber depth associated with largely resorbed hypermature cataract. The former is demonstrated on optical sectioning by a reduced distance between the slit image on the posterior corneal surface and the convex bright slit section on the anterior lens surface, while the latter is associated with an increase in the same distance, if examined at the same angle (Fig. 10.1.19).

The usually tall or long slit beam used for optical sectioning can be reduced to a minimum height or even a pinpoint (1–2 mm) to allow checking for the Tyndall effect, indicating any deviations of the composition of the normally optically clear aqueous (Fig. 10.1.20). The phenomenon of specular reflection is also utilized in the ocular slit-lamp biomicroscope examination, specifically during assessment of the integrity of the outer and inner corneal surfaces. A specular reflection is the creation of an image of the light source itself that can, according to Snellen's law, only be seen from the correct position – as the angle of incidence equals the angle of reflection. To visualize the corneal specular reflection, the examiner must therefore place both illuminator and microscope at angles approximately 25–30 degrees to the midline, and project the light onto the transparent ocular structure under scrutiny. The clarity and sharpness of the specular reflection depend on the smoothness and reflectivity of the surface on which it is created. With normal corneal surface health, the specular reflection will directly mirror the image of the light source (see Fig. 10.1.18A). Deficiencies of the precorneal tear film or epithelial irregularities will negatively affect the specular reflection from the corneal surface and result in a distorted and irregular image of the light source (see Fig. 10.1.6). The phenomenon of specular reflection can also be used to examine the integrity of the corneal endothelium. The surfaces of healthy corneal endothelial cells are usually smooth and highly reflective, whereas their borders are irregular, and thus highlighted by the absence of specular reflection, leading to the "honeycomb" appearance of the normal corneal endothelium on high-magnification examination, as described above (Fig. 10.1.21). Pathology of endothelial cells will lead to loss of the normal specular reflection, visible as a dark "fill defect" in the normal endothelial pattern. Individual endothelial cells can only be appreciated, however, with magnification settings of 25–40×, which exceeds the ability of handheld biomicroscopes. Specular reflection can also be used to examine irregularities in the epithelial cells lining the anterior lens capsule, but the same requirement for magnification exists here.

Both direct illumination and retroillumination are utilized during ocular slit-lamp biomicroscopy. With direct illumination, the structure to be examined is illuminated by the light source itself, while in retroillumination, the structure of interest is illuminated by light reflected from a neighboring tissue (Berliner, 1943; Martin, 1969b; Martonyi et al., 2007). The same opacity within the clear ocular media may appear bright in direct illumination and dark on indirect illumination (Fig. 10.1.22). For this purpose, corneal changes are mostly examined by retroillumination from the iris, while iris and lens

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Figure 10.1.11 Magnification during use of the slit lamp for examination of the anterior ocular segment with a broad beam. **A**. Anterior segment in chronic anterior uveitis in a Domestic Shorthair, 12× magnification. **B**. Same patient as **A**, but increased detail visible on 25× magnification. **C**. Follicular conjunctivitis on 25× magnification. **D**. Chronic blepharitis on 25× magnification. (Courtesy of AHT, Newmarket, UK.)

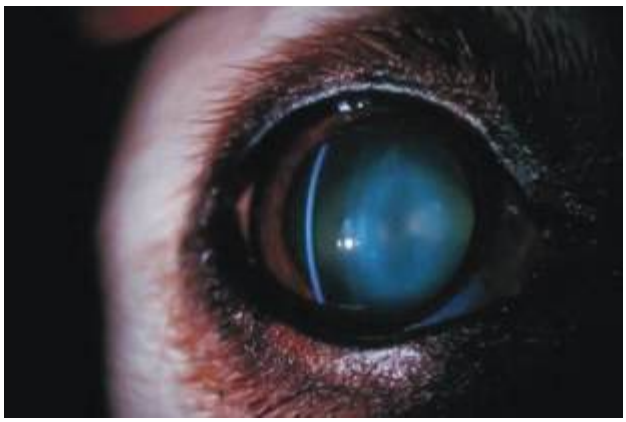


Figure 10.1.12 On a slit setting with high levels of illumination, the slit lamp functions to section the transparent tissue of the anterior segment with a slab of light. Slit-lamp image of an elderly Labrador Retriever with nuclear sclerosis, showing the reflection of the slit beam on the cornea and lens. (Courtesy of AHT, Newmarket, UK.)

changes are routinely examined with the help of light reflected from the fundus. Iris transillumination can be achieved when the fundus is illuminated through a small pupil only and will highlight defects in iris pigmentation or tissue (Martonyi et al., 2007). If mydriasis has been induced, fundic retroillumination can be created to allow corneal examination (Martonyi et al., 2007). To achieve optimal fundic retroillumination, the angle between the slit-lamp biomicroscope illuminator and the microscope should be as narrow as possible.

Retroillumination from the iris can be both direct and indirect (Fig. 10.1.23 and Fig. 10.1.24). With direct retroillumination, corneal anomalies are highlighted by light reflected from the iris immediately posterior to them (see Fig. 10.1.23 and Fig. 10.1.24). For this purpose, a moderately broad slit beam is placed onto the iris at an angle wide enough to avoid directly illuminating the area of cornea that is to be examined. Indirect retroillumination is created by scattering of light into areas of the cornea adjacent to those directly retroilluminated from the iris. Thus, the corneal area of interest is examined against a dark, nonilluminated iris background. Indirect retroillumination is used to highlight the most subtle changes within the cornea, whose degree of transparency only minimally deviates from that of the surrounding tissue and which would not be seen against an illuminated iris background (i.e., with direct retroillumination; see Fig. 10.1.23 and Fig. 10.1.24). To achieve optimal indirect retroillumination, the normally isocentric relationship between the slit-lamp biomicroscope illuminator and

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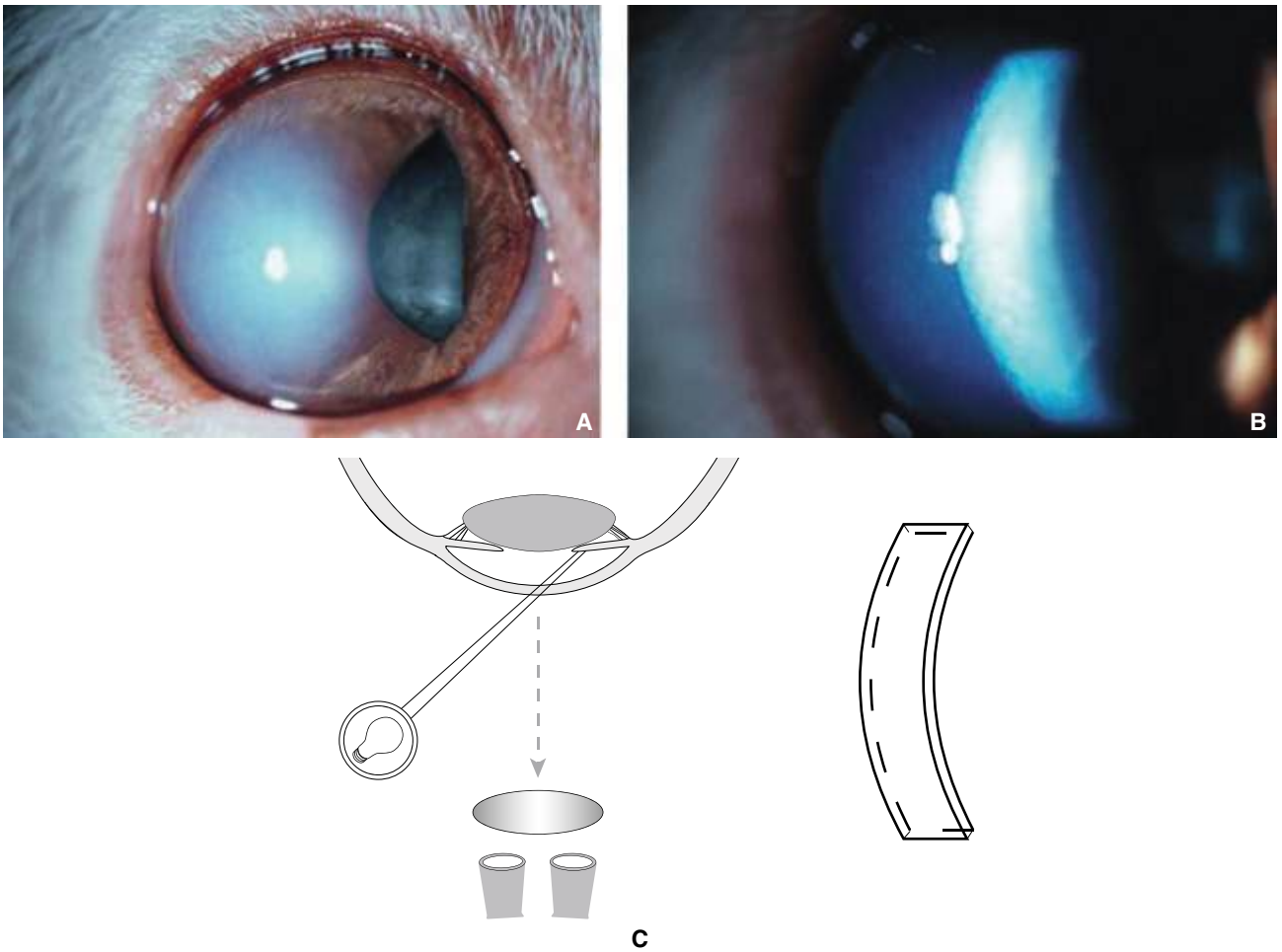


Figure 10.1.13 The use of a broad slit beam (> 0.5 cm) is demonstrated here on a patient with corneal edema. **A**. Corneal edema seen with the diffuse beam. **B**, **C**. The broad slit beam creates a parallel-piped corneal section, as seen in the same patient and depicted in the schematic diagram. (Courtesy of AHT, Newmarket, UK.)

the biomicroscope is uncoupled and the slit beam is placed tangentially to the axis of viewing (Martonyi et al., 2007). Unfortunately, many handheld slit-lamp biomicroscopes do not offer the option to decenter the light beam, and precise indirect retroillumination may be limited to the more sophisticated table-mounted slit-lamp biomicroscope models.

Using direct retroillumination, three basic types of lesions can be defined (Fig. 10.1.25): obstructive, translucent, and refractile (Berliner, 1943). Obstructive lesions block the reflected light and stand out dark against a bright background. Examples of obstructive lesions include active corneal blood vessels, corneal pigmentation, blood clots in the anterior chamber, dense cataract, and tissue masses. Translucent lesions allow the passage of some light on retroillumination, but detailed examination through the lesion is not possible. Corneal edema, keratic precipitates, iris cysts, fibrin, incipient cataract, and thin scars all are examples of refractive lesions. Refractile lesions allow the passage of light on retroillumination and will take on the color of their background. They will refract the light, but will still allow more posterior structures to be examined in detail. Examples of refractile lesions include lens vacuoles, lens capsular wrinkling, the distorted tear film, or interrupted epithelium and corneal bullae (Berliner, 1943).

Practical Application of Slit-Lamp Biomicroscope Examination

At the start of slit-lamp biomicroscopy, the oculars (eye pieces) should be adjusted to accommodate the interpupillary distance and to correct any refractive error of the examiner's eyes (Berliner, 1943; Blumenthal, 1995; Schmidt, 1975). This is done by focusing on a target rod (i.e., focusing bar) that attaches to the instrument at a fixed distance from the objective (i.e., the focal distance of the slit beam) or on small print or small parallel lines present in the periphery of the viewing field, as seen through the slit-lamp biomicroscope oculars (Blumenthal, 1995). The animal's head is restrained by an assistant or with the examiner's free hand (see Fig. 10.1.10). The light beam is angled at 20–45 degrees from the axis of the microscope, initially away from the muzzle, and the oculars are rested against the examiner's brow. During the course of the examination, however, the light

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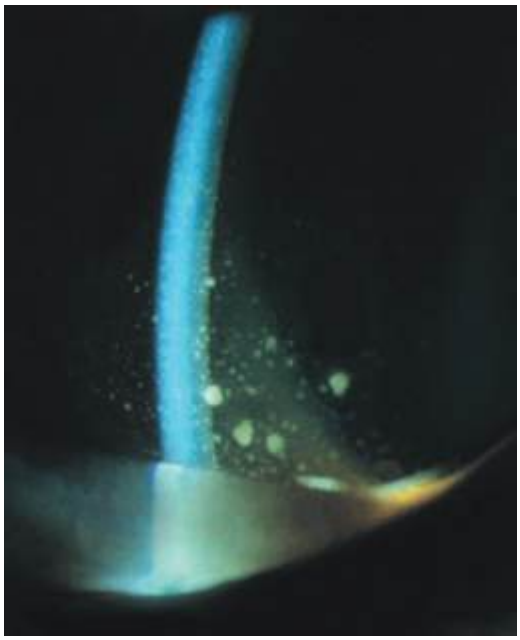


Figure 10.1.14 Keratic precipitates in a cat with chronic anterior uveitis. Due to the tissue overlap that occurs with the use of a broad beam, the deeper corneal structures are best examined at the trailing edge of the beam, allowing ideal location of the position of the precipitates to the corneal endothelium level. (Courtesy of N. Wallin Håkansson.)

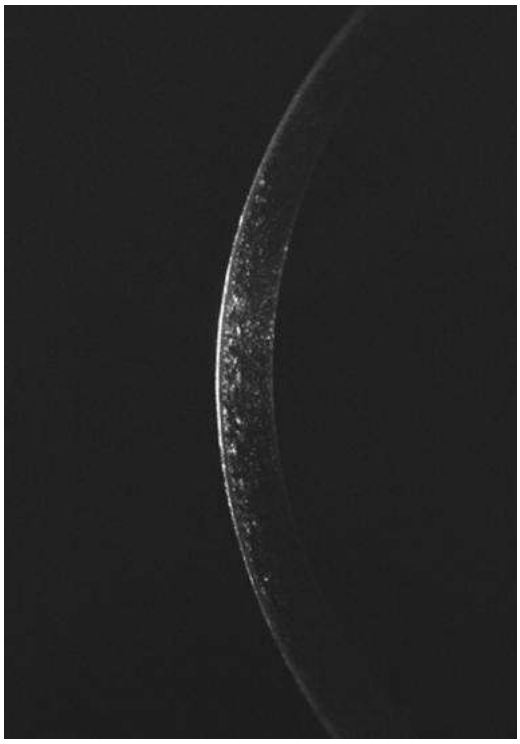


Figure 10.1.15 Human cornea on examination with a thin slit beam. In the corneal section created with a thin beam of light, tear film and epithelium, corneal stroma, and endothelium all become visible separately. (Reproduced with permission from Martonyi, C.L., Bahn, C.F., & Meyer, R.F. (2007) *Clinical Slit Lamp Biomicroscopy and Photo Slit Lamp Biomicrography*. Ann Arbor, MI: Time One Ink.)

beam should be alternated between sides to allow examination of the ocular structures with light reaching the eye at a variety of different angles. The focal distance of the instrument is 7–12 cm, at the intersection of the light beam axis with the microscope axis, and the fine focus is achieved by moving either toward or away from the eye within this range. The inexperienced examiner may at first find it difficult to orient him- or herself with respect to the position of the eye when looking through the oculars at the beginning of the examination. A helpful tip is for the examiner to approach the corneal surface with the slit-lamp biomicroscope turned "on" until the circle of light observed with the naked eye has a sharp outline on the cornea or eyelids, before applying his or her eyes to the oculars. This way, the slit-lamp biomicroscope is already at the correct focal position, avoiding an embarrassing "search for the eye." Initially, the entire ocular surface is screened with the slit-lamp biomicroscope using a diffuse, unfocused beam with a low intensity and low level of magnification. Some examiners also like to use focal illumination with a broad beam (> 0.8 mm) for this purpose, as the reduced light intensity might improve patient cooperation.

The adnexa are first examined and any abnormalities noted. Specifically, the lids are examined for aberrant lashes and the eyelid margin is everted to allow visualization of ectopic cilia. Meibomian gland orifices are assessed, and the glands themselves can also be visualized through the palpebral conjunctiva at the everted eyelid margin. The status of palpebral and bulbar conjunctiva as well as the appearance of the nictitating membrane are noted. The nasolacrimal puncta can be identified and their shape and patency assessed. Diffuse illumination is specifically suited to reveal gross corneal pathology, such as the presence of foreign bodies, ulceration, pigmentation, active vascularization, or edema, and serves to note areas of interest to be subsequently examined with more selective methods and higher magnification. The specular reflection of the corneal surface, which represents the integrity of the precorneal tear film and corneal epithelium, can also be observed under diffuse lighting on low magnification, with the slit-lamp biomicroscope illuminator and microscope positioned as described above.

The anterior chamber and iris are also screened with the diffuse beam for obvious changes such as hypopyon, fibrin, hyphema, cysts, pigmentary changes, pupillary distortion, or mass effects. The presence of iridodonesis or vitreal herniation is noted. Examination of the lens with the diffuse beam prior to induction of mydriasis will be limited to confirming its correct anatomic position, as well as the presence of obvious anterior capsular anomalies and cataract. In the next step, focal illumination with a broad beam (0.5–1.5 mm) is employed to create a parallel-piped section of the cornea, giving a three-dimensional view of a block of corneal tissue. Specific attention is paid to the trailing edge of the beam, as deeper structures are visible here without an overlay from more anterior tissues. Once the observer has scanned the

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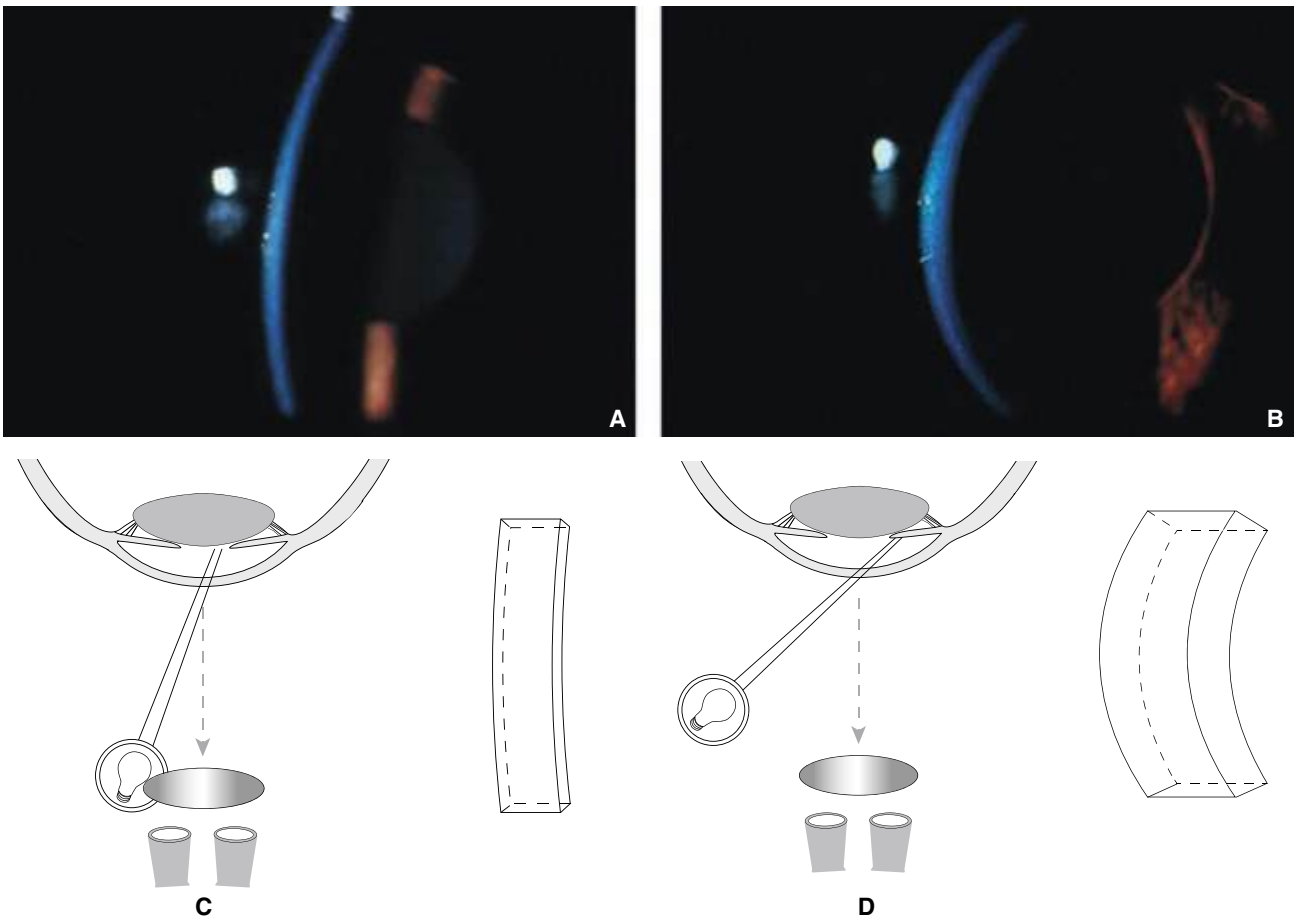


Figure 10.1.16 It is important that with both the use of broad and narrow beams, an appropriately wide angle between the slit-lamp microscope and illuminator (more than 45 degrees) is chosen, as the section collapses with too narrow an angle. **A**, **C**. Narrow angle between illuminator and biomicroscope. (Courtesy of AHT, Newmarket, UK.) **B**, **D**. Wide angle between illuminator and microscope.

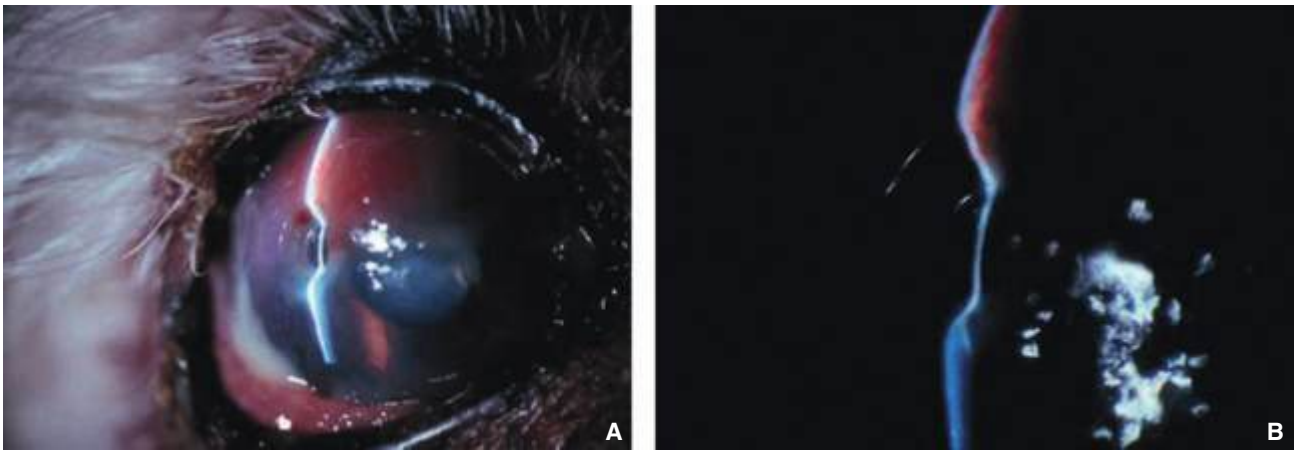


Figure 10.1.17 Descemetocoele in a West Highland White Terrier with keratoconjunctivitis sicca. **A**. The slit image on the corneal surface deviates away from the examiner, indicating the presence of a corneal defect. The steep decline of the slit on the surface into the depth of the ulcer confirms the lesion to be deep stromal. **B**. On higher magnification, the examiner can appreciate that the slit image on the floor of the ulcerated area is gently bowing toward the examiner again, indicating the presence of a descemetocoele. (Courtesy of AHT, Newmarket, UK.)

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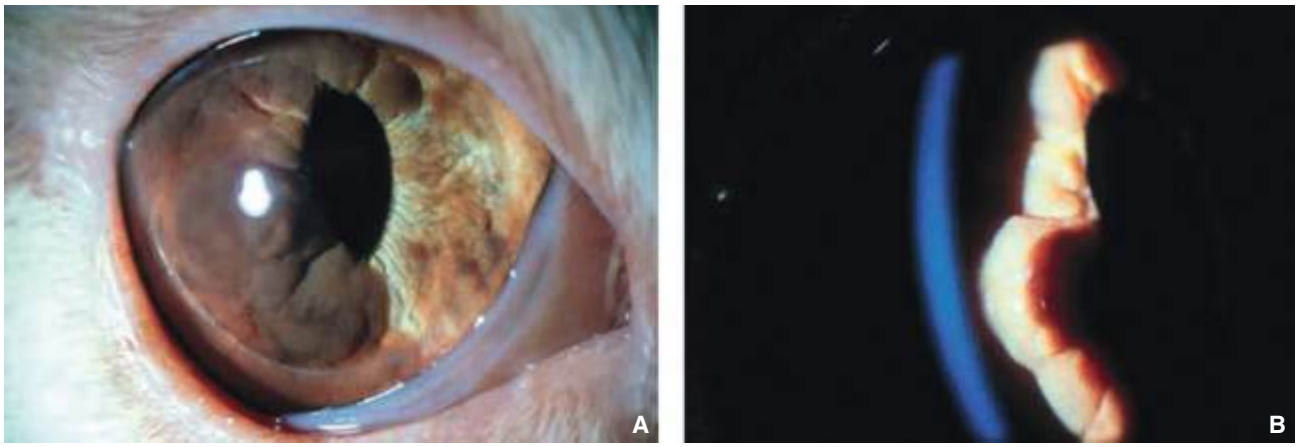


Figure 10.1.18 Diffuse iris melanoma in a cat. **A**. Appearance of a lesion on slit-lamp examination with a diffuse beam. **B**. On examination with a slit beam, the iris lesion is deviated toward the examiner, indicating that the iris surface is raised. (Courtesy of AHT, Newmarket, UK.)

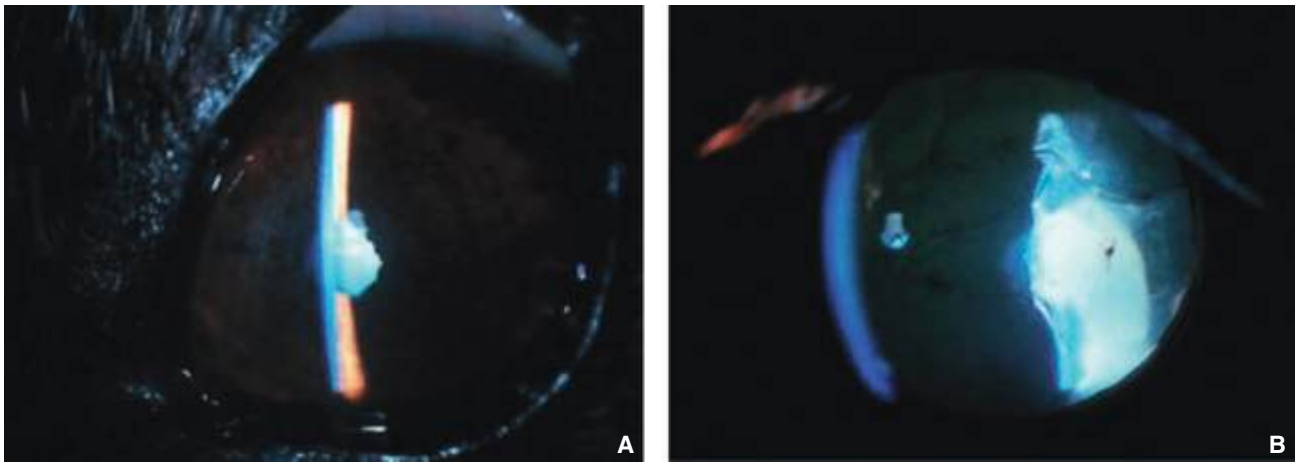


Figure 10.1.19 Distance estimation with the help of a slit beam. **A**. The close proximity of the slit beam image on cornea and iris surface indicates marked anterior chamber shallowing in this patient with diabetes with an intumescent cataract. **B**. The increased anterior chamber depth is made visible by the increased distance between the slit beam on the cornea and the wrinkled anterior lens capsule in this patient with a hypermature cataract. (Courtesy of AHT, Newmarket, UK.)

cornea with the broad slit for an overview, the beam is narrowed to allow optical sectioning of the transparent ocular media. For this purpose, a tall slit beam of approximately 0.1–0.2 mm diameter is focused onto the cornea, with an angle of at least 45 degrees between illuminator and microscope. The cornea is then sequentially sectioned as the slit beam is moved across its entirety.

In the optical section of the healthy cornea examined at high magnification (25–40×), the tear film is seen as a bright, sharp line, underlain immediately by a dark zone representing the corneal epithelium (see Fig. 10.1.15). On lower magnifications (8–16×), as provided by most handheld units, it will not be possible to distinguish between tear film and epithelium, and the anterior corneal surface will appear as a bright line of reflection only. The corneal stroma is visible as a diffusely gray zone, which is less intense toward the corneal endothelium, the latter standing out in the optical section as a gray line slightly less bright than that at the corneal surface (see Fig. 10.1.15). Loss of intensity and fragmentation of the usually bright leading line of reflection of the optical section of the cornea are typically seen in patients with tear film deficiencies, epithelial irregularities, or frank ulceration. Stromal lesions such as vascularization, ulceration and edema, deposition of aberrant metabolites, and tearing or disruption of Descemet's membrane will all distort the normal, orderly, and well-defined appearance of the corneal slit section.

To best appreciate changes in the posterior aspect of the corneal slit section, the specular reflection of this area is utilized. In order to visualize the specular reflection of the

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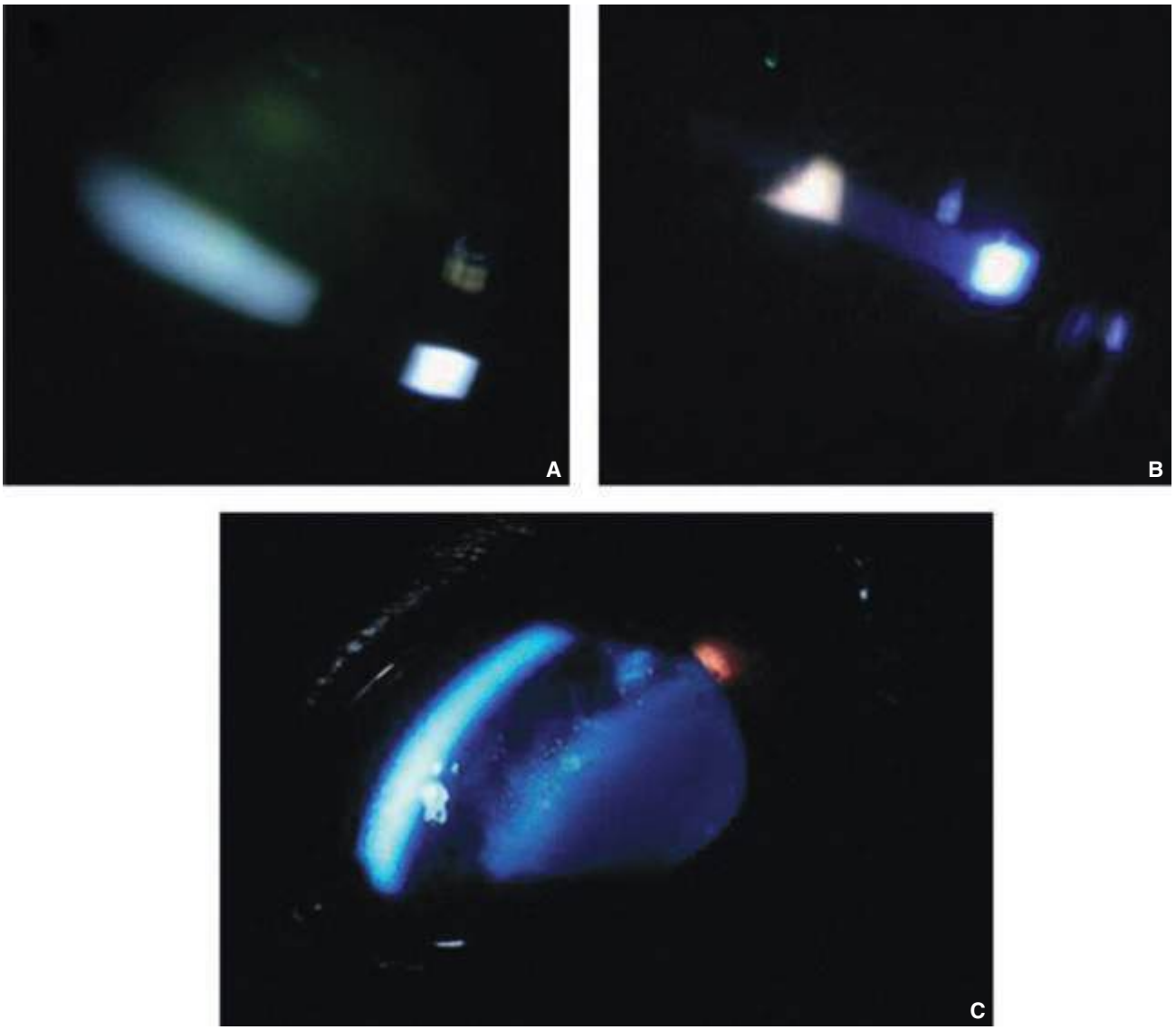


Figure 10.1.20 Examination of the anterior chamber for signs of aqueous flare. **A**. Absence of aqueous flare. **B**. Aqueous flare is visible as a faint haze in the light beam. **C**. Not only protein but also herniated vitreous and pigment can cause the Tyndall effect on examination with a slit beam, as seen here in an Italian Greyhound with vitreal degeneration. (Courtesy of AHT, Newmarket, UK.)

endothelial cells, the observer first centers and focuses on the brighter reflection of the corneal surface with a narrow beam and an angle of approximately 30 degrees between illuminator and microscope. At this point, the reflection from the corneal endothelium will become visible as a significantly less bright line. Once this is in sharp view, the examiner moves the focus onto the endothelial reflection by moving the slit-lamp biomicroscope forward minimally – by a distance approximating the thickness of the corneal stroma. Individual endothelial cells may be appreciated by the help of their specular reflection in the typical honeycomb pattern at magnifications from 25× to 40×. Even at lower magnification levels, endothelial defects characterized by cell loss may become visible, as dark zones and endothelial deposits such as keratic precipitates may be visible as highly reflective areas.

Optical sectioning is also utilized to estimate corneal thickness. In corneal ulceration, the distance between anterior and posterior slit image will be narrowed, and the most proximal slit image will be deflected away from the examiner. The remaining thickness of illuminated stroma allows precise gauging of the depth of ulceration (see Fig. 10.1.17A). A complex image of the leading slit beam is seen in the presence of a descemetocoele, where the peripheral part of the slit beam is deflected away from the examiner and the deepest, central part of the section is deviated toward the examiner, indicating an outward bowing of Descemet's membrane (see Fig. 10.1.17B). However, an increase in corneal thick-

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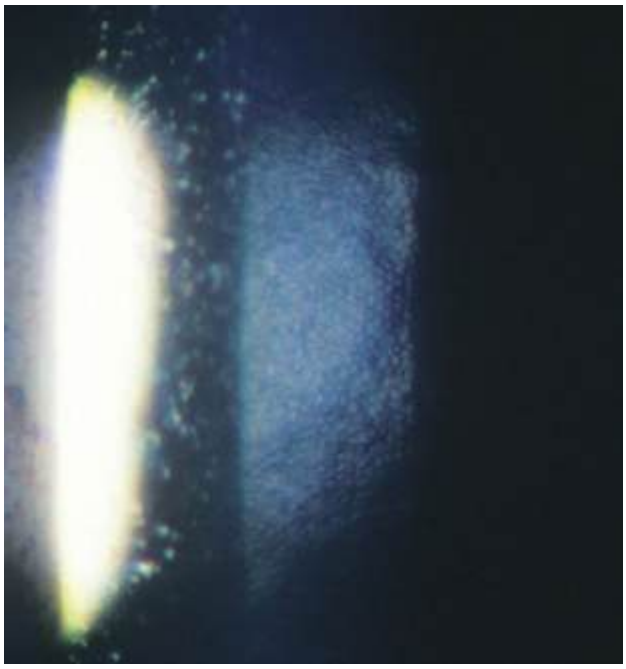


Figure 10.1.21 Appearance of the human corneal endothelium by examination of its specular reflection on slit-lamp examination. The surfaces of healthy corneal endothelial cells are usually smooth and highly reflective, whereas their borders are irregular and thus highlighted by the absence of specular reflection, leading to the "honeycomb" appearance of the normal corneal endothelium on high-magnification examination, as previously described. Pathology of endothelial cells will lead to loss of the normal specular reflection – visible as a dark "fill defect" in the normal endothelial pattern. To visualize individual endothelial cells, magnification levels of 25–40× are required, which exceeds the scope of most handheld slit-lamp models. (Reproduced with permission from Martonyi, C.L., Bahn, C.F., & Meyer, R.F. (2007) *Clinical Slit Lamp Biomicroscopy and Photo Slit Lamp Biomicrography*. Ann Arbor, MI: Time One Ink.)

ness, such as in corneal edema, will result in an increase of the thickness of the optical section compared with the normal cornea if the same angle between illuminator and microscope is chosen (see Fig. 10.1.13B). In bullous keratopathy associated with loss of endothelial cell function, areas of stromal fluid accumulation are seen as dark "fill defects" in the otherwise grayish stromal section, often accumulating subepithelially. In cases of tearing of Descemet's membrane, the normally bright posterior aspect of the corneal slit section is distorted, and associated stromal edema is visible as fill defects in the increased stromal aspect of the corneal section. The level of blood vessels and position of sequestra or foreign bodies with regard to their depth within the cornea can also be determined by optical sectioning: if a lesion is visible one-third within the optical section, it is positioned at one-third of corneal depth (Fig. 10.1.26).

The iris surface is also examined with a narrow slit beam and changes in surface texture and thickness are noted. The pupillary margin of the iris can be examined by retroillumination from the fundus, as can areas of iris hypoplasia. It must be remembered, however, that examination of the iris is two-dimensional because of its nontransparent nature, and an optical slit section cannot be obtained (Berliner, 1943). Areas of changes in iris pigmentation must be specifically and carefully examined across their surface, as any deviation of the slit beam toward the examiner could indicate the presence of an iridal mass (see Fig. 10.1.18A, B). A slit projected onto the iris surface would also be deflected toward the examiner if the iris was distorted forward by a mass or cysts within the posterior chamber. In equine iris hypoplasia, the forward-bowed iris would elicit a deflection of the slit toward the examiner, but the absence of a mass lesion in this case would be eliminated by the translucency of the thinned iris tissue. Iris cysts present freely in the anterior chamber or attached to

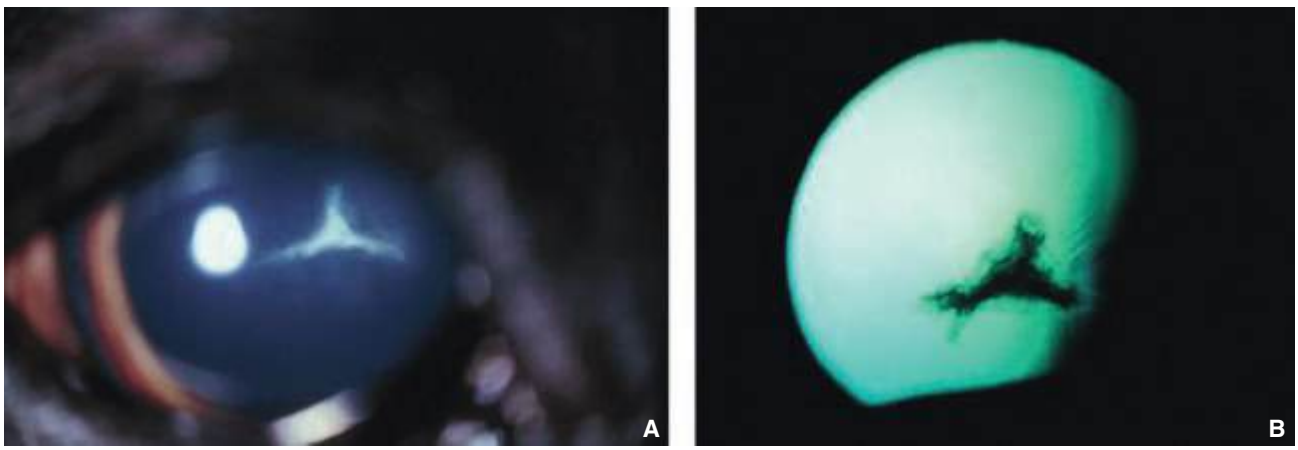


Figure 10.1.22 A posterior polar subcapsular cataract seen with the broad beam on direct illumination and on retroillumination, demonstrating that the form of illumination chosen will affect the appearance of an opacity in the visual pathways. **A**. On direct illumination, the cataract appears as a light-colored opacity. **B**. On retroillumination, the cataract stands out dark against the bright fundic reflex. (Courtesy of AHT, Newmarket, UK.)

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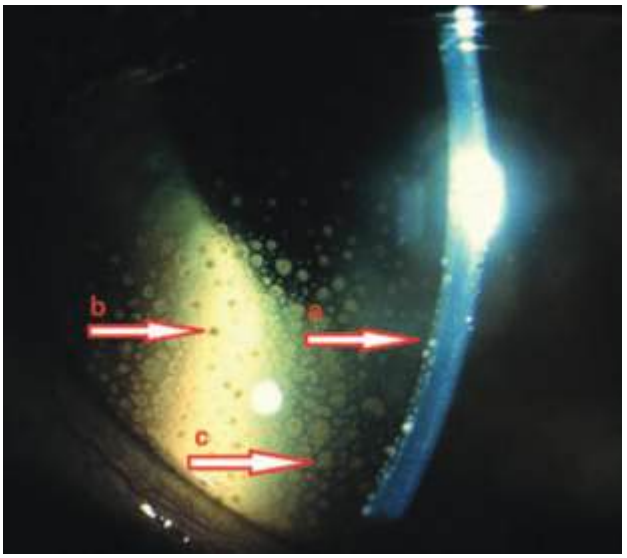


Figure 10.1.23 Subtle corneal changes are best examined with indirect methods of illumination. The photograph shows the appearance of keratic precipitates in direct illumination (a) and retroillumination from the iris (b, c). Retroillumination from the iris can be direct (b) and indirect (c), with the latter method being able to highlight even the most subtle corneal opacities by scattering of light against an otherwise dark background. (Courtesy of N. Wallin Håkansson.)

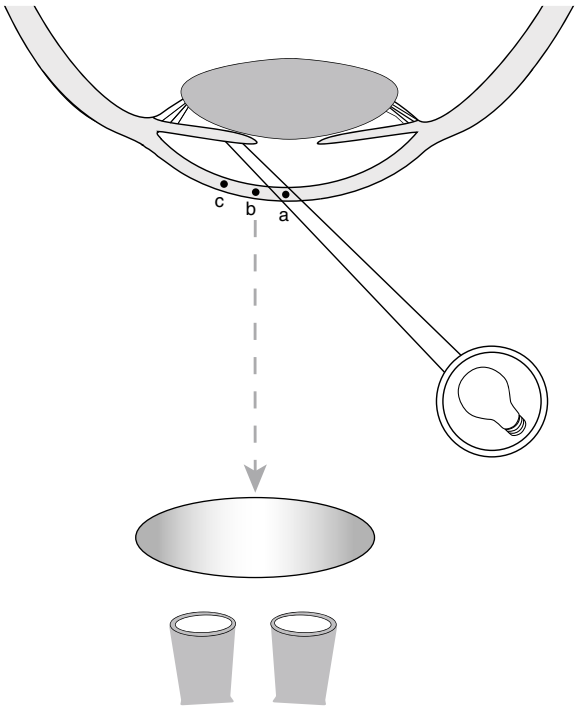


Figure 10.1.24 Illustration of the same changes as shown in Fig. 10.1.23.

the pupillary margin are distinguished from solid masses as they transilluminate when examined at an oblique angle with a bright and narrow light beam. In the next step, the anterior chamber is assessed for flare using a bright slit beam reduced to a minimal height (ideally pinpoint lighting). Protein, cells, or pigment dispersed within the anterior chamber are highlighted, as smoke would be if hit by a beam of light falling into an otherwise darkened room (see Fig. 10.1.20). The degree of aqueous flare observed should be noted and graded (Munger, 2002).

Following this first part of the biomicroscopic examination, mydriasis is induced to allow complete assessment of the lens and, if desired, the fundus (Gelatt et al., 1973, 1995a, 1995b; Munger, 2002; Rubin & Wolfes, 1962). Diffuse illumination of the lens may reveal lentodonesis (phacodonesis). On optical sectioning, the lens is visible with a convex bright line of illumination representing the anterior lens capsule; a concave, less bright line of illumination representing the posterior lens capsule; and a diffuse, gray zone in between. In cases of aphakia or lens luxation, the above reflections are absent; in lens subluxation, only the very peripheral part of the reflected slit-lamp biomicroscope beam on the lens may be missing, highlighting an aphakic crescent. Changes to the anterior lens capsule such as tears or wrinkling can be appreciated as distortions or loss of brightness of the anterior reflections. In adult dogs (at more than 1 year of age), it is possible to distinguish between two distant areas within the lens as cortex and nucleus, and with advancing age the distance from anterior lens capsule to nucleus will increase. Both anterior and posterior suture lines may be visible as thin white lines separated by a central dark line (Martin, 1969c, 1969d). Cataracts will be visible as bright opacities in the lens section and their position can be precisely identified and recorded (Fig. 10.1.27). Changes in lens volume will be reflected in the anterior chamber depth, as previously described. Changing focus to just behind the posterior lens capsule, the anterior vitreous can be examined on the slit section via a mydriatic pupil. The vitreo-hyaloid ligament insertion, a normal physiologic structure, is visible in the dog as a small round opacity just beside and below the posterior lens pole. In the center of this opacity, the Mittendorf's dot is visible as a small, white, pigtail-like structure protruding into the anterior vitreous for 1–2 mm (Martin, 1969c, 1969d). In vitreal disease, the Tyndall phenomenon may highlight vitreal condensations, cellular infiltrates, blood, or pigment.

With direct and indirect goniolenses, the slit-lamp biomicroscope allows for a magnified and stereoscopic view of the ICA and CC (Schmidt, 1975). Special contact and noncontact lenses are also available for use with the slit-lamp biomicroscope to allow visualization of the vitreous chamber, ciliary body, and fundus (Martonyi et al., 2007). Examples of such lenses are the Goldmann 3, Hruby, and Rosen lenses (Schmidt, 1975). Fundic examination of veterinary patients with handheld slit-lamp biomicroscope models is technically challenging in the clinical setting, as the examiner has to use both hands to hold the instrument and condensing

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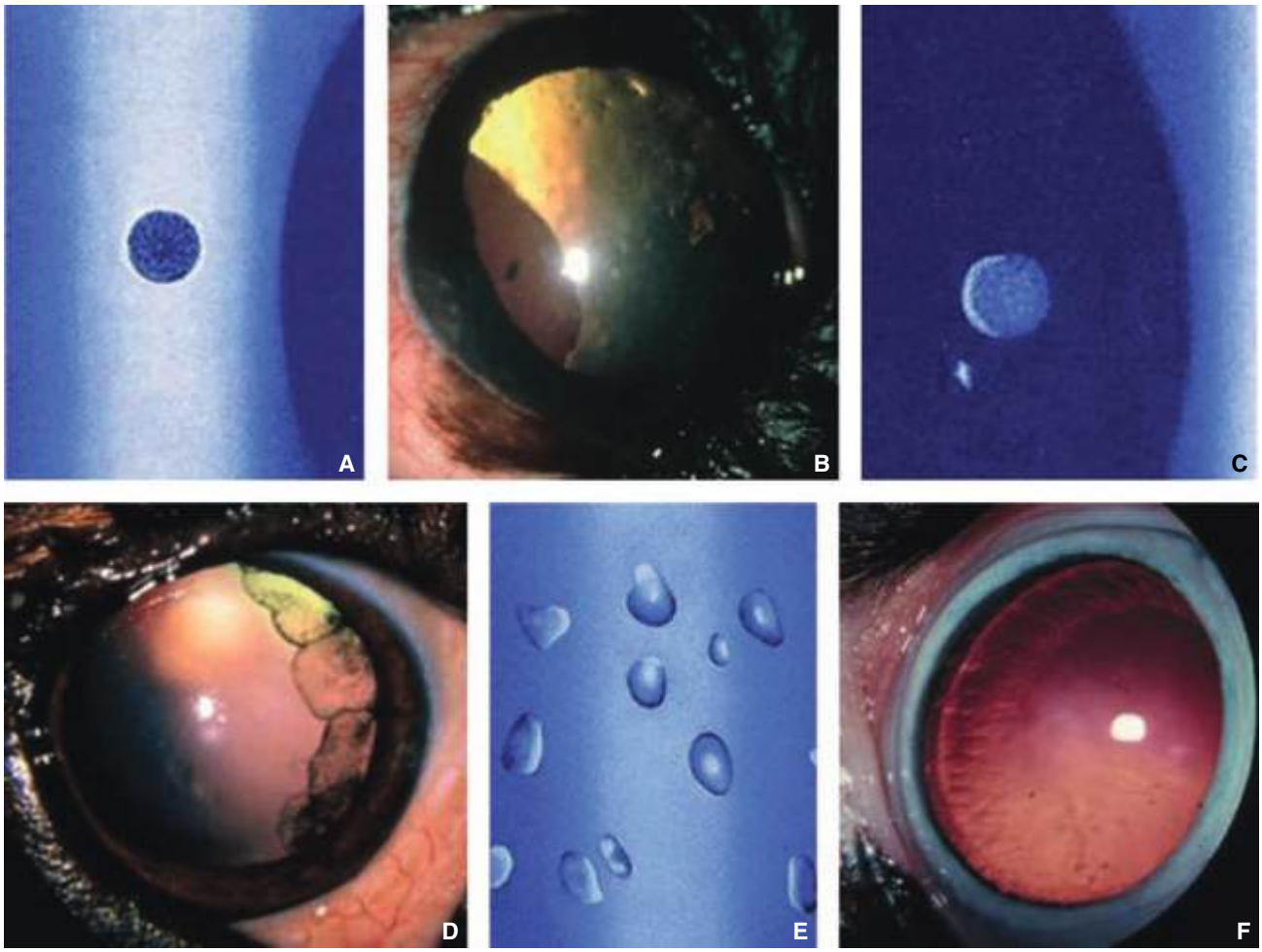


Figure 10.1.25 Types of lesions observed with the slit-lamp biomicroscope. Using the direct and retroillumination methods, three basic methods of lesion can be defined: obstructive lesions (**A**; i.e., they block the light) such as pigment, blood clot, dense scar, dense cataract, and tissue masses, including ciliary body tumor (**B**); translucent lesions (**C**; i.e., some light may pass through the lesion but is scattered), such as corneal edema, keratic precipitates, fibrin, mild cataract, thin scars, and cysts, including ciliary body cysts (**D**); and refractile lesions (**E**; i.e., light passes freely through the lesion but is refracted), such as the lens equator, lens vacuoles (**F**), lens wrinkles, distorted tear film, and corneal bullae.

lens, and will rely entirely on the assistant to restrain the patient's head and keep the eyelids open. Only few portable slit-lamp biomicroscope models have integrated holders for condensing lenses at the front of the instrument, making the use of the slit-lamp biomicroscope for fundic examination in veterinary patients a more viable option (see Table 10.1.2). The use of the slit-lamp biomicroscope has also been described for examination of the precorneal tear film using polarized light in healthy cats and dogs, as well as in dogs with KCS (Carrington et al., 1987a, 1987b, 1987c)

Given the significant cost of even the handheld slit-lamp biomicroscope units, several manufacturers have made efforts to produce cost-effective alternatives. For this purpose, manufacturers have developed either simplified handheld units or headpieces for the direct ophthalmoscope handle, which combine a bright light source that can be used both diffuse (approximately 3–5 mm circle) or on a slit setting (0.3–0.4 mm) with a magnifying lens of 6× magnification at a 25–35 degree fixed angle. These instruments have obvious limitations when compared with the more versatile handheld slit-lamp biomicroscopes previously described, but can still be useful to help with depth estimation of lesions in the anterior segment and lens, as well as with the detection of aqueous flare.

Direct Ophthalmoscopy

In 1704, Méry described direct visualization of the feline ocular fundus when the eye was immersed in water (Albert & Edwards, 1996; Enbaugh, 1958). De la Hire later explained this phenomenon, stating that the water neutralized the reflective and refractive effects of the corneal curvature. In 1846, William Cumming reported his findings of the fundus

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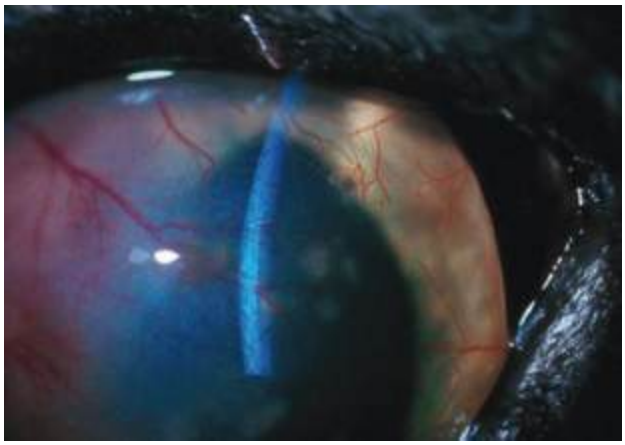


Figure 10.1.26 The level of blood vessels and position of sequestra or foreign bodies with regard to their depth within the cornea can also be determined by optical sectioning. In this patient with immune-mediated keratitis, blood vessels can be located to the midstroma on slit-lamp examination. (Courtesy of AHT, Newmarket, UK.)

reflex in humans. Charles Babbage subsequently developed the first ophthalmoscope, using a mirror with a hole in its center. This crude device reflected light at the eye, with the central hole allowing visualization of the fundus by the examiner. In 1854, Thomas Wharton Jones publicized Babbage's device, and Von Helmholtz reported his ophthalmoscope several years later (Albert & Edwards, 1996). Constructed out of pasteboard, cover glasses, and a lens, this device permitted visualization of an image of the patient's ocular fundus. Reynat is credited as being the first to use direct ophthalmoscopy for veterinary ophthalmology in 1858 (Rubin, 1974). Van Biervliet and van Rooy in Belgium and Guerineau in France subsequently reported equine ocular abnormalities observed by direct ophthalmoscopy in 1861. Three decades later, in 1892, Bayer of Vienna published the first atlas of comparative ophthalmoscopy.

Ophthalmoscopy is a technique that requires extensive practice until it becomes a valuable and rapid diagnostic tool for the clinician. This is not only because of the actual difficulty of performing the procedure, but because of the huge variation in fundic appearance both between and within different species. It is only with considerable practice that it is possible to accumulate the vast "memory reference library" of fundic images that will enable the clinician to instantaneously distinguish between normal variations and signs of pathology.

Direct ophthalmoscopy is the classic form of ophthalmoscopy with which most clinicians are familiar, because the direct ophthalmoscope is commonly available as part of a set with an otoscope. The direct ophthalmoscope consists of a power source and a halogen or LED coaxial optical system (Fig. 10.1.28). Light is directed via a mirror or prism into the patient's eye and is reflected back through a lens in the ophthalmoscope to the examiner (Fig. 10.1.29; Ollivier et al., 2007). Direct ophthalmoscopes take advantage of the refractive power of the patient's cornea and lens. Therefore, refractive errors in both the patient and the examiner affect the ability to focus on the ocular fundus. Refractive errors of most animals appear to be reasonably static, with the exceptions of the nonhuman primate and the cat, in which some accommodation may occur. Most fundi are in focus at 0–2 diopters (D) if the examiner is emmetropic (Ollivier et al., 2007). The resultant image is real, erect, and magnified several times, depending on the species being evaluated (Table 10.1.3). The size of the eye being examined, and

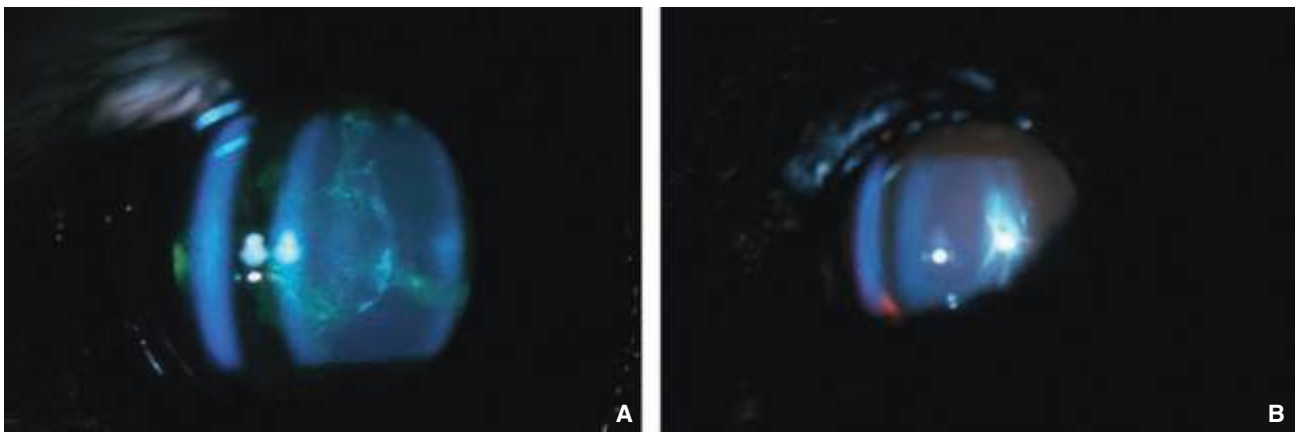


Figure 10.1.27 The position of a cataract can be located accurately on examination with the slit beam. **A**. Nuclear cataract with subtle cortical extensions in a Golden Retriever clearly visible on the slit section between slit image on anterior and posterior lens capsule. **B**. Posterior polar subcapsular cataract in a Labrador Retriever located just in front of the slit beam on the posterior lens capsule. (Courtesy of AHT, Newmarket, UK.)

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Figure 10.1.28 Direct ophthalmoscope head. **A**. Observer side with viewing aperture, lens dial, quick lens switch, and diopter indicator. **B**. Patient side with viewing hole and switches/dials allowing selection of beam size and shape as well as light filters.

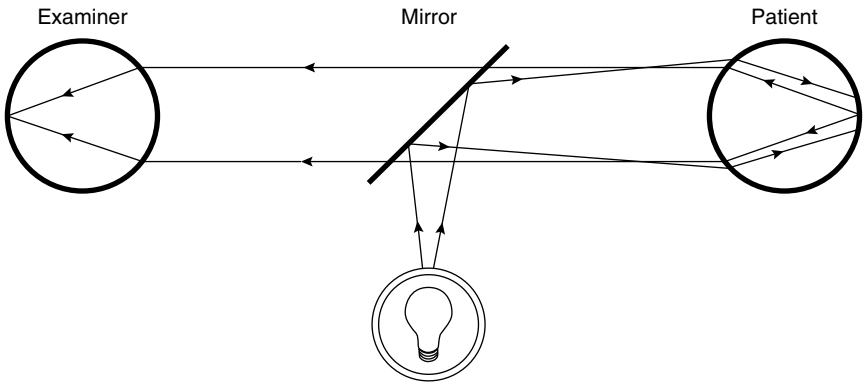


Figure 10.1.29 Optics of direct ophthalmoscopy. The direct ophthalmoscope allows alignment of the observer's visual axis with a light beam, which is reflected via a mirror to illuminate the patient's fundus. Light rays emanating from the patient's eye form a real image on the observer's retina.

therefore the working distance between the examiner and the lesion of interest, will affect magnification, so it is important to compare any lesion(s) with the size or diameter of the optic disc, rather than with any units of measurement.

In order for the clinician to perform direct ophthalmoscopy, animals must be either reasonably cooperative or adequately restrained. Most small animals can be gently restrained on the examination table by the owner or an assistant; some fractious animals or large animals require some form of sedation and/or an auriculopalpebral nerve block. Before examination, the pupils are usually dilated with a short-acting mydriatic such as 0.5%–1% tropicamide (Klauss & Constantinescu, 2004; Munger, 2002).

Eyes with dark-colored irides may require repeat application of the mydriatic agent compared with eyes with lighter colored irides, and frequently take longer to dilate (Ollivier et al., 2007). The fundi of large animals such as the horse can often be visualized without dilation, but mydriasis will ensure a thorough examination. Following induction of adequate mydriasis, the examiner rests the direct ophthalmoscope against his or her brow and identifies the patient's fundic reflex from approximately arm's length (Fig. 10.1.30).

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Table 10.1.3 Optical changes of direct ophthalmoscopy in animals: Change in millimeters with 1 D change in focus with the direct ophthalmoscope.

Species	Fundus Equivalent/ Diopter Change	Magnification (mm)
Dog	17.2	0.28
Cat	19.5	0.22
Horse	7.9	1.33
Cow	10.6	0.74
Sheep	13.9	0.43
Pig	15.2	0.36
Rabbit	25.3	0.13
Rat	77.2	0.01
Iguana	38.8	0.06
Great Horned Owl	9.6	0.90
Pigeon	31.6	0.08
Monkey	20.7	0.19
Human	14.7	0.39

Source: Modified from Murphy, C.J. & Howland, H.C. (1987) The optics of comparative ophthalmoscopy. *Vision Research*, **27**, 599.



Figure 10.1.30 Distant direct ophthalmoscopy. The patient's fundic reflex is picked up at arm's length and any opacities in the clear ocular media will stand out dark against the bright background. This test is also helpful to check for anisocoria if both fundic reflexes are compared.

Ideally, the examiner's right eye should be used to examine the patient's right eye and vice versa. This is especially important in patients with frontal eyes and long noses, because this position minimizes contact between the examiner's nose and the patient's muzzle.

Alternating eyes, however, does require practice, because most people have a dominant eye that they prefer to use.



Figure 10.1.31 Close direct ophthalmoscopy. The examiner must be as close as possible to obtain an optimal image with direct ophthalmoscopy. To achieve this, the examiner ideally should use the right eye to examine the patient's right eye and vice versa.

Once the fundic reflex is identified, the examiner moves toward the patient to a point approximately 2–3 cm from the eye. The closer the examiner is to the patient's eye, the wider the angle of view will be (Fig. 10.1.31). If the direct ophthalmoscope is positioned too far from the cornea, the entire fundus cannot be visualized, and even the slightest movement will cause most of the fundic image to be lost. The constant head and eye movements of veterinary patients will frequently cause the examiner to lose the image. If this happens, the quickest way to regain alignment is to step back, find the tapetal reflection again, and then move in close. Once the fundus is visualized, ophthalmoscopy should proceed in a timely and orderly fashion. It is important for each examiner to establish an order or pattern for the fundic examination to ensure that no features are missed. The optic nerve is typically identified and examined first. Afterward, the remainder of the fundus is thoroughly examined in quadrants, making sure that the tapetal regions of the fundus, the atapetal regions of the fundus, the fundic periphery, and the retinal vasculature are closely examined.

A circular dial on the direct ophthalmoscope holds a series of concave and convex lenses that can be rotated through the viewing aperture (see Fig. 10.1.28A; Barnett, 1967; Bistner, 1983; Bunce, 1955; Catcott, 1952). Green or black numbers on the circular dial represent convex or converging lenses (positive), while red numbers represent concave or diverging lenses (negative). A separate dial or switch adjusts the size, shape, and color of the light beam (see Fig. 10.1.28B). Possible options include large and small spots, slit, graticule, red-free filter (which appears green), and cobalt blue filter. The red-free light is used to evaluate retinal vessels and the nerve fiber layer. It is also useful for differentiating hemorrhage, which appears black, from normal pigment and pigmented lesions

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such as melanomas, which appear brown. The graticule consists of a grid (often of 16 squares) used to estimate the size of fundic lesions. This is most useful for ophthalmologists examining human eyes, which are of very similar size. The cobalt blue filter can also be used to examine the nerve fiber layer of the retina and to highlight the presence of fluorescein dye. The slit beam aids in detection of elevations or depressions in the ocular fundus. Distances between the normal retina and the surface of such abnormalities can be estimated by changing the dioptric power of the ophthalmoscope. For example, if the retina is in focus at 0 D, and the surface of a lesion is in focus at +3 D (green or black), the lesion is elevated. If, however, the surface of the lesion is in focus at −3 D (red), it is depressed. The diopter equivalent is the actual distance (in millimeters) that the focal plane moves anteriorly or posteriorly with each diopter, and it varies with the species examined (Table 10.1.4; Murphy & Howland, 1987). The size of the circular spot of white light should be adjusted to the patient's pupil size to minimize light reflections from the corneal surface. The intensity of the illuminating light is controlled by a rheostat and is generally adjusted as low as possible to allow a good view for the comfort of both the patient and the examiner. If for some reason the pupil is not dilated, it is best to have the illuminating light dim to minimize the pupillary constriction that will result when the light is directed on the eye. It is also important to perform fundic examination in a darkened room to optimize the conditions for a thorough and complete examination.

The direct ophthalmoscope can also be used to pick up any central opacities in the clear media anterior to the fundus by retroillumination. Once the fundic reflex is identified by the examiner looking through the ophthalmoscope at a distance ("distant direct ophthalmoscopy"; see Fig. 10.1.30), a dark spot detected against the fundus reflection indicates that an opacity is blocking the return of light to the observer. Ideally, the presence of this opacity is noted and its exact depth (whether it is in the cornea, anterior chamber, lens, or vitreous) will be determined subsequently with slit-lamp biomicroscope examination. However, in the absence of access to a slit-lamp biomicroscope, it is possible to determine whether

Table 10.1.4 Lateral and axial magnification in indirect ophthalmoscopy.

	Lateral Magnification				Axial Magnification			
Species	**14 D Lens**	**20 D Lens**	**30 D Lens**	**40 D Lens**	**14 D Lens**	**20 D Lens**	**30 D Lens**	**40 D Lens**
Dog	2.57	1.72	1.11	0.82	8.85	3.97	1.65	0.90
Cat	2.91	1.95	1.26	0.93	11.31	5.08	2.11	1.15
Horse	1.18	0.79	0.51	0.38	1.86	0.84	0.35	0.19
Cow	1.58	1.06	0.68	0.50	3.34	1.50	0.62	0.34
Sheep	2.07	1.39	0.90	0.66	5.74	2.58	1.07	0.58
Great Horned Owl	1.43	0.96	0.62	0.46	2.75	1.23	0.51	0.28
Tawny Owl	2.16	1.45	0.94	0.69	6.26	2.81	1.17	0.64
Pigeon	4.72	3.16	2.04	1.51	29.84	13.40	5.58	3.04
Pig	2.26	1.52	0.98	0.72	6.83	3.07	1.28	0.70
Human	2.19	1.47	0.95	0.70	6.39	2.87	1.19	0.65
Monkey	3.09	2.07	1.34	0.99	12.79	5.74	2.39	1.30
Rabbit	3.77	2.53	1.63	1.20	18.99	8.53	3.55	1.93
Gecko	4.19	2.81	1.81	1.34	23.48	10.54	4.39	2.39
Iguana	5.79	3.88	2.50	1.85	44.71	20.07	8.35	4.55
Flying Fox	5.38	3.60	2.32	1.72	38.62	17.34	7.22	3.93
Opossum	7.30	4.89	3.16	2.33	71.24	31.98	13.31	7.25
Frog	9.15	6.13	3.95	2.92	111.9	50.24	20.91	11.39
Rat	11.52	7.72	4.98	3.68	177.44	79.65	33.15	18.06
Bat	36.23	24.27	15.66	11.56	1753.33	787.07	327.60	178

Source: Murphy, C.J. & Howland, H.C. (1985). Optics of comparative ophthalmoscopy. *Transactions of the Sixteenth Annual Scientific Program of the College of Veterinary Ophthalmologists*, **1985**, 132–157.

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the identified opacity is anterior or posterior to the lens nucleus with the help of the phenomenon of parallax. Opacities located anterior to the lens nucleus will move *away* from the observer and light source, and those located posterior to the lens nucleus will move *with* the observer and light source during lateral motion of the observer.

The advantages of direct versus indirect ophthalmoscopy include greater magnification, availability of options such as the slit and grid, and ability to alter the dioptric power of the ophthalmoscope. Disadvantages include a small field of view that can result in lesions being missed, short working distance between examiner and patient, lack of stereopsis, difficulty in examining the peripheral fundus, and greater distortion when the visual axis is not completely transparent (Fig. 10.1.32).

Indirect Ophthalmoscopy

Ruete first conceived of the indirect ophthalmoscope in 1853 (Albert & Edwards, 1996). Despite several advantages over direct ophthalmoscopy, it did not gain wide acceptance in the United States until 1947, when Schepens and Bahn (1950) developed a high-intensity light that improved visualization of the fundus. In 1960, Rubin (Rubin, 1960) published the first study describing indirect ophthalmoscopy in dogs; this was closely followed by Vierheller's clinical experiences with the device (Vierheller, 1966). Indirect ophthalmoscopy has since become a routine part of the veterinary ophthalmic examination.

Indirect ophthalmoscopy, in contrast to direct ophthalmoscopy, allows the clinician to view a larger portion of the fundus (larger field of view) at one time and to do so from a greater and safer working distance from the patient (Fig. 10.1.33 and Fig. 10.1.34). The image generated with indirect ophthalmoscopy may initially be confusing to the novice examiner because it is inverted and reversed (upside down and backward), but once the technique is mastered, it is an indispensable tool for a thorough evaluation (see Fig. 10.1.32; Havener & O'Dair, 1963). Because there is much less magnification of the image perceived with indirect ophthalmoscopy than with direct ophthalmoscopy, a better overview of the

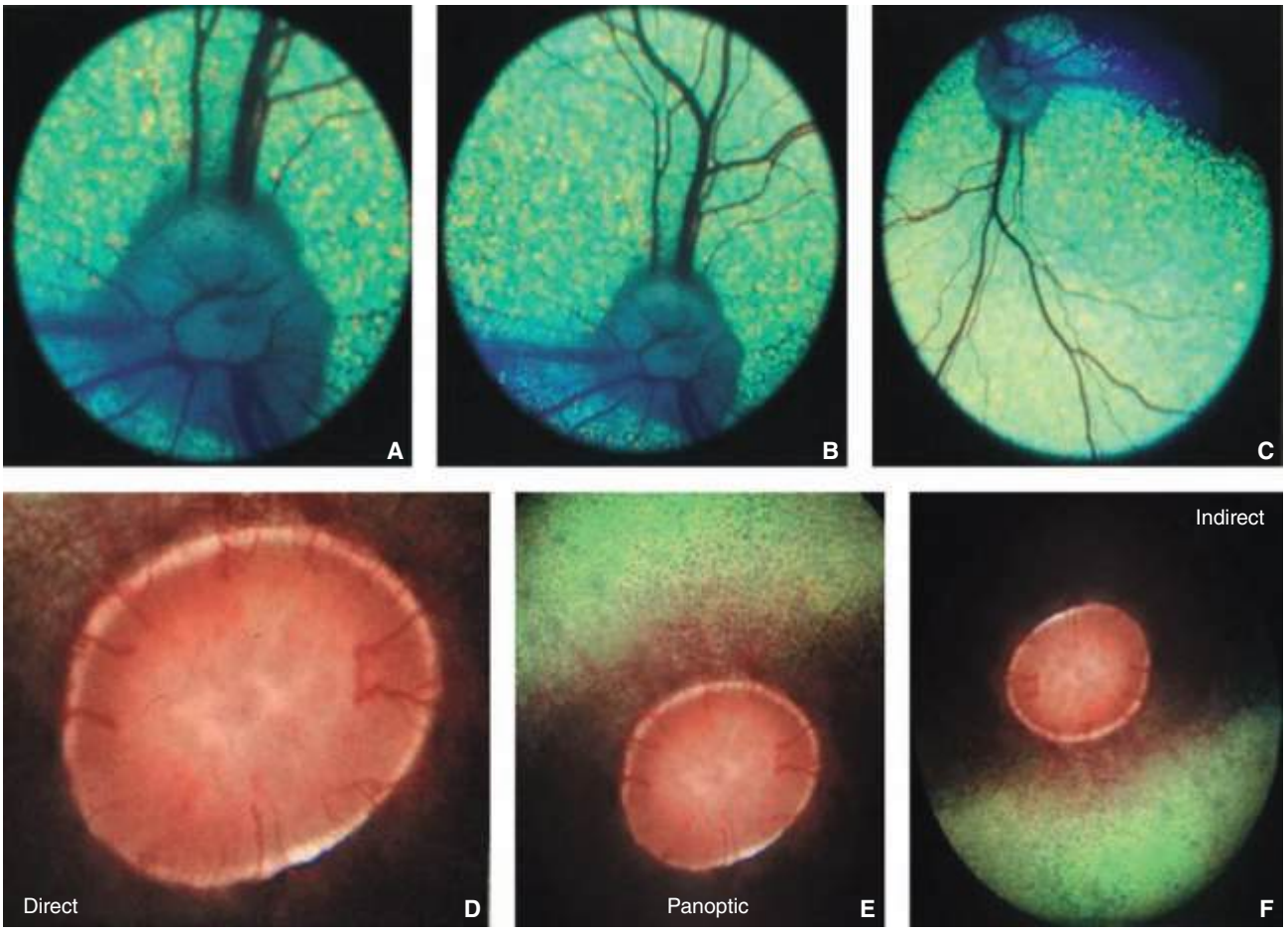


Figure 10.1.32 Comparison of direct, panoptic, and indirect ophthalmoscopy. These photographs illustrate the different appearances in terms of magnification and orientation of the canine and equine ocular fundus with each of the three methods of ophthalmoscopy: direct (**A**, **D**), panoptic (**B**, **E**), and indirect (**C**, **F**) ophthalmoscopy.

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Figure 10.1.33 Binocular indirect ophthalmoscopy. In this technique, the observer does not only have stereopsis, but also has one hand free to hold the patient's head.



Figure 10.1.34 Monocular indirect ophthalmoscopy. The technique can be carried out with minimal equipment, but stereopsis is lost and the observer relies on the help of an assistant to stabilize the patient's head.

fundus can be achieved (see Fig. 10.1.32 and Table 10.1.4; Murphy & Howland, 1987). The two methods often complement each other, particularly if a lesion detected with the indirect method is then examined more closely, at greater magnification, with the direct method (Murphy & Howland, 1987). The necessary components of indirect ophthalmoscopy are a strong, focal light source and a converging lens.

Indirect ophthalmoscopy has additional advantages over direct ophthalmoscopy when a binocular indirect ophthalmoscope is utilized, including stereopsis and the ability to use both hands for patient manipulation. Binocular indirect ophthalmoscopy uses a halogen, xenon, or LED light source, a mirror to direct light into the patient's eye, a handheld converging lens to magnify the reflected image, and two prisms to split the reflected light so that it can be directed into both of the examiner's eyes, thereby permitting stereopsis (Fig. 10.1.35). The ophthalmoscope and light source are fitted onto a headband or spectacle frame that can be adjusted to comfortably fit the examiner (Fig. 10.1.36). Eyepieces are adjusted to match the distance between the examiner's eyes and light intensity is altered with a rheostat. Most binocular indirect ophthalmoscopes have interchangeable apertures and filters, as well as permanent or detachable teaching mirrors. The headset provides the light necessary for the examination, frees the operator's hands to hold the lens and position the patient's head (frequently without the aid of an assistant; see Fig. 10.1.33), and optically narrows the examiner's interpupillary distance to permit a binocular view and stereopsis. Newer, head-mounted indirect ophthalmoscopes enable the observer's interpupillary distance to be optically reduced to a minimal setting to allow retinal examination through small pupils, in situations where mydriasis is undesired or cannot be induced while still preserving stereopsis.

If a binocular headset is unavailable or cost prohibitive, indirect ophthalmoscopy can be performed quite adequately without it. Monocular indirect ophthalmoscopy employs only a bright, handheld light source (e.g., transilluminator, direct ophthalmoscope or strong otoscope, fiberoptic bundle,

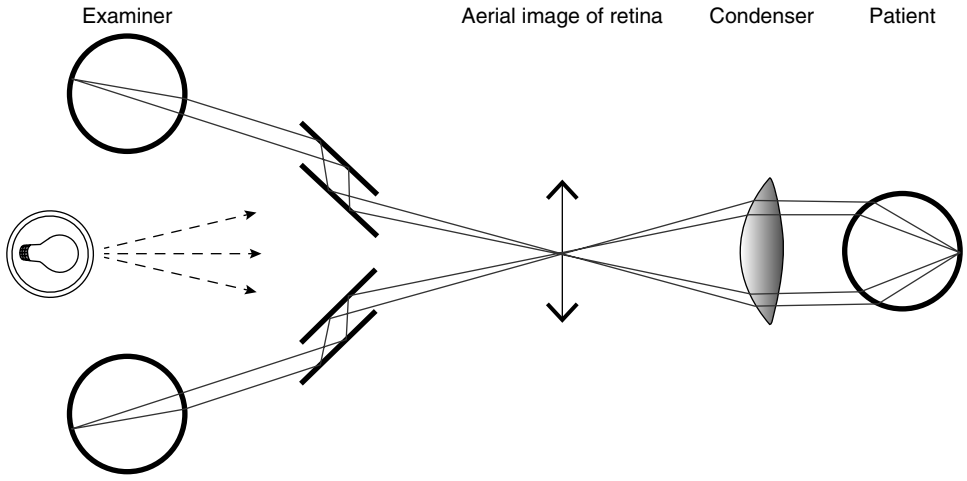


Figure 10.1.35 Optics in binocular indirect ophthalmoscopy. In this technique, the light returning from the patient's fundus is split via a prism into both of the observer's eyes, allowing stereopsis. The image created is virtual and inverted.

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Figure 10.1.36 **A**. Keeler (Broomall, PA, USA and Windsor, UK) Vantage indirect head-mounted ophthalmoscope and Volk (Mentor, OH, USA) 20 D, 30 D, 90 D, and 2.2 Pan-retinal condensing lenses. The halogen ophthalmoscope is powered by a battery included into the headband and is thus ideal for examination of all veterinary patients. **B**. The panoptic ophthalmoscope is a good compromise between the direct and indirect methods of ophthalmoscopy, proving a real image (neither inverted nor reversed) and intermediate in magnifications between the two.

penlight) and a handheld lens (see Fig. 10.1.34). This method does not provide stereopsis and requires an assistant to restrain the patient and position the head, but nonetheless gives an overall view of the fundus.

To perform the fundic examination following induction of mydriasis, the examiner grasps the patient's muzzle with one hand and stabilizes the head. The other hand is used both to hold the eyelids open and to position the lens 2–4 cm in front of the patient's cornea. When a binocular headset is unavailable, an assistant positions the head and holds the eyelids open, while the examiner uses one hand to hold the light source against his or her temple so that both the head and the light source move as a unit, and the other hand to hold and position the lens. The lens is held with the thumb and forefinger and positioned so that the strongest convex surface is facing the examiner (or flatter surface toward patient) for the best image. From a distance of approximately 0.50–0.75 m (at arm's length), the examiner then directs the light into the patient's eye and identifies the fundic reflex. The light should be adjusted so that its intensity permits adequate, but not excessive, illumination of the ocular fundus. Excessively bright light can obscure details and cause patient discomfort and thus lack of cooperation. Many indirect head-mounted ophthalmoscopes will offer the option of a light diffuser, which provides softer light to make the examination more comfortable for the patient. Another benefit of diffuse light is the elimination of shadows on the edge of the condensing light, which allows a significantly increased view of the peripheral retina. Anesthetized patients that cannot move may develop retinal burns when the light utilized for the examination is too strong. Light-induced retinal damage can also be caused by ophthalmoscopic examination in canine patients with T4R RHO retinal degeneration (Cideciyan et al., 2005; Gu et al., 2007). Following indirect ophthalmoscopy, an increased interval of at least 60 minutes of light adaptation has been recommended before performing ERG (Tuntivanich et al., 2005). In animals that have a tapetum, the light should be decreased for examination of that region and may need to be increased for examination of the atapetal fundus (Martin, 2005). Reflections from the surface of the handheld lens occasionally obscure part of the fundic image, but these can be easily eliminated by slightly tilting the lens.

Once the fundic reflex is identified, opacities of the cornea, lens, and vitreous can be seen as dark areas highlighted against the fundic reflection, as in distant direct ophthalmoscopy. Again, as with distant direct ophthalmoscopy, lesions can be approximately localized in an anteroposterior direction with the help of the phenomenon of parallax (see the previous section). Opacities in the anterior chamber or vitreous may oscillate or float with eye movement. Lesions anterior to the retina or optic nerve (e.g., persistent hyaloid artery) will change position with respect to their background when viewed from a different angle, an example of the parallax phenomenon. Slight manipulations of the handheld lens itself can reveal subtle hyperreflectivity or streaking in the tapetal fundus. Examination of the fundus with indirect ophthalmoscopy should proceed in an orderly fashion, as with direct ophthalmoscopy, taking care to examine the optic nerve, the retinal vasculature, and the tapetal and nontapetal fundus and the periphery. The extreme peripheral retina at the ora ciliaris can be visualized with practice and good mydriasis, especially ventrally and temporally.

There are many different lenses available for use with indirect ophthalmoscopy, ranging in diopter strength from +5.5 D to +90 D (see Fig. 10.1.36). The choice of lens will vary depending on the required magnification, field of view, stereopsis, and the size of the patient's pupil. Fundic magnification varies

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with lens and species (see Table 10.1.4; Murphy & Howland, 1987). The magnification of the image is equal to the diopter strength of the eye divided by the diopter strength of the lens (Goldbaum et al., 1980; Martin, 2005), so the smaller the diopter rating of the lens, the greater the magnification of the image (smaller number, larger image). It is important to take into account that additional magnification is built into the binocular headset, so that the image perceived with its use will be even more magnified than with the lens alone. The strength of the lens also affects the depth perception of the examiner. The higher the diopter strength of the lens, the less stereopsis there will be (larger number, less stereopsis; Martin, 2005). It is also important to consider the size of the animal's pupil when selecting a lens. The higher the diopter strength of the lens, the easier it will be for the examiner to see through a small pupil (smaller pupil, higher number; Goldbaum et al., 1980). In general, a high diopter strength lens results in a smaller image but a larger field of view, less stereopsis, and easier examination through a smaller pupil (Goldbaum et al., 1980; Martin, 2005). The 2.2 panretinal lens is the most versatile lens for the clinician who wishes to only acquire one lens, as it provides the best compromise between magnification and field of view (Snead et al., 1992).

Various models of binocular indirect ophthalmoscopes are available from Heine, Keeler, Propper, Topcon, Xonix, and Zeiss. Camera and video attachments are available for some models, thus allowing the examiner to display and record findings for teaching and research purposes. Commercial monocular indirect ophthalmoscopes are manufactured by Reichert and the American Optical Corporation. These instruments use an internal lens to magnify the reflected fundic image. The American Optical monocular scope is useful for looking through small pupils and produces an erect image.

The panoptic ophthalmoscope presents a good compromise between the direct and indirect ophthalmoscopes. The image is real and intermediate in magnification between the two types (Fig. 10.1.35B).

Indirect ophthalmoscopy can also be used to semiqualify the refractive error of an animal. By slowly withdrawing the handheld lens from the eye and observing any change in magnification of the image, the clinician can roughly estimate the refractive power of the patient. If the fundic image becomes larger, then the animal is somewhat myopic; if it becomes smaller, then the patient is hyperopic; and if the size of the image remains static, then the animal is emmetropic (Rubin, 1960). Indirect ophthalmoscopy is an essential technique, and its main disadvantage is the cost of the head-mounted binocular equipment.

Magnification in Ophthalmoscopy

In both direct and indirect ophthalmoscopy, lateral and axial magnification have to be considered when interpreting fundic lesions. Lateral magnification describes the magnification of an area across an axis perpendicular to the observer's view, for example in a lateral-to-medial and dorsal-to-ventral direction with regard to the fundus. Lateral magnification can be exemplified by the action of a slide projector throwing an image onto a screen. Axial magnification describes magnification along the axis of viewing; that is, in depth. In particular, axial magnification describes the ratio of the distance along the optical axis between two corresponding points in object space. Axial magnification is useful when considering an image in its three dimensions. Clinically, it is important when assessing the thickness of retinal or fundic lesions (Murphy & Howland, 1987).

In both direct and indirect ophthalmoscopy, lateral magnification varies inversely with the focal length of the eye and axial magnification varies with the inverse square of the focal length (Murphy & Howland, 1987). Given the large variation of eye size in veterinary patients, this has significant implications when performing fundoscopy in the different species. Small eyes (which have high dioptric power) usually have high lateral and axial magnification, in contrast to large eyes (which have low dioptric power) with low lateral and axial magnification. As a result, ophthalmoscopically visible elevations of retina or disc margin in an equine fundus should be given more significance as a clinical finding than in a canine or feline eye (see Table 10.1.4; Murphy & Howland, 1987).

Retinoscopy

Retinoscopy, also known as skiascopy, is the objective determination of the dioptric state or refractive error of the eye. Commonly used in human ophthalmology and optometry, this technique has also found use in veterinary ophthalmology, particularly to define the normal, pathologic, and surgically induced refractive state of eyes and in the evaluation and improvement of intraocular lens implants (Davidson, 1997; Davidson et al., 1993; Gaiddon et al., 1996; Gift et al., 2009; Grinninger et al., 2010; Kubai et al., 2008; McMullen et al., 2010; Millichamp & Dziezyc, 2000; Murphy et al., 1992, 1997; Mutti et al., 1999; Pollet, 1982; Roberts, 1992).

When light rays are projected onto an eye from infinity, they emerge from an emmetropic eye as parallel rays, from a myopic eye as converging rays, and from a hyperopic eye as diverging rays. The location at which these emergent light rays form a focal point or plane is called the far point. The far point is at infinity, in front of infinity, and beyond infinity for the emmetropic, myopic, and hyperopic eye, respectively (Davidson, 1997). The procedure of retinoscopy utilizes a lens placed in front of the eye to modify the image produced (Fig. 10.1.37). The power of the lens that corrects the image, or neutralizes the movement of the fundic reflex, permits an estimation of the dioptric power of the patient's eye and its difference from emmetropia. Retinoscopy allows veterinary ophthalmologists to quantitatively determine the refractive

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Figure 10.1.37 Retinoscopy carried out in a dog. Note the working distance of 67 cm between examiner and patient. The skiascopy bar or rack is positioned in front of the dog's eye; it contains a series of plus and minus spherical lenses in increments of 0.5–1.0 D to quantify the eye's refractive error.

error of the eye to within 0.25–0.50 D of its true refractive state (Davidson, 1997).

The retinoscope, either streak or spot, consists of a tungsten bulb filament, a condensing lens, a circular or linear aperture, and an angulated plane mirror (Fig. 10.1.38). Streak retinoscopes produce a linear band of light, whereas spot retinoscopes produce a circular beam; newer models combine both options. Streak retinoscopes are more commonly employed in veterinary ophthalmology. A sleeve in the handle of the streak retinoscope is moved up and down to change the orientation of the mirror and bulb, thus affecting the vergence of the emitted light. Rotating the sleeve clockwise or counterclockwise affects the orientation of the streak itself. Both streak and spot retinoscopes are available from Copeland, Heine, Keeler, Propper, Reichert, and Welch Allyn. Plus or minus spherical lenses, which are available in increments of 0.25 D, are placed between the retinoscope and the patient to quantitate the refractive error of the eye. A skiascopy bar or rack, which contains a series of plus and minus spherical lenses in increments of 0.5–1.0 D, is a simple, convenient, and inexpensive tool for quantifying the refractive error of an animal's eye. In the United States, positive lenses are usually marked black, while negative lenses are marked red, and it may be important for the examiner to know that this is the exact opposite in Europe.

As most domestic animals have limited accommodative ability, the cycloplegia afforded by the mydriatic agents is not necessary (Murphy et al., 1992), and it has been shown in dogs and horses that the induction of cycloplegia does not significantly alter the results of streak retinoscopy from the noncycloplegged eye (Groth et al., 2013; McMullen et al., 2014; Rull-Cotrina et al., 2013). The induction of mydriasis prior to streak retinoscopy may even make the procedure more difficult, due to blurry or reversing streak reflexes following the application of topical tropicamide (McMullen et al., 2014). With the retinoscope resting against the brow,



Figure 10.1.38 Keeler streak retinoscope®.

the examiner is positioned 0.67 m (about arm's length) from the patient's eye (a measured 0.67 m string attached to the retinoscope is useful for maintaining this working distance; see Fig. 10.1.37). The sleeve is moved either down (i.e., Heine and Welch Allyn retinoscopes, Welch Allyn, Scaneateles Falls, NY, USA) or up (i.e., Copeland retinoscope) such that the projected light rays are very slightly divergent (i.e., plane mirror effect) and the streak is positioned vertically. Purkinje images from the patient's cornea and lens are superimposed, and the streak is swept horizontally across the animal's pupil. The streak is then rotated horizontally and is swept vertically across the pupil. Finally, a trial lens or skiascopy bar is placed 1–2 cm from the patient's cornea, and the process is repeated. As the streak is slowly swept across the pupil, the fundic reflex will move in either the same or the opposite direction, depending on the refractive error of the patient. With no refractive lens, the fundic reflex will move in the same direction as the sweep with emmetropic and hyperopic eyes ("with motion"), and in the opposite direction to the sweep with less than 1.5 D myopic eyes ("against motion"). If a "with motion" is observed, plus lenses of increasing dioptric strength are placed in front of the patient's eye until an "against motion" is observed or neutralization is reached. Neutralization is characterized by a fundic reflex that completely fills the pupil without any notable direction of movement. If an "against motion" is observed, minus lenses of increasing dioptric strength are used to achieve neutrality. At a working distance of 0.67 m, a

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+1.5 D lens is needed to achieve neutralization with an emmetropic eye; therefore, the refractive error of an eye is determined by subtracting 1.5 D from the gross refraction needed to achieve neutrality (Davidson, 1997).

Retinoscopy in the canine reveals that most phakic dogs are within 1.0 D of emmetropia (Kubai et al., 2008; Murphy et al., 1992; Pollet, 1982). One study of 14,400 adult dogs revealed anisometropia in only 6% of all dogs (Kubai et al., 2008). Attempts to correlate refractive error with animal size and environment have yielded variable results. Results of one study suggest that indoor dogs and small to medium breeds show a tendency toward myopia, whereas outdoor and large-breed dogs show a tendency toward hyperopia (Gaiddon et al., 1996). However, a familial predisposition to slight myopia has also been reported in some populations of large working dogs, including the German Shepherd, the Rottweiler, and the Labrador Retriever (Kubai et al., 2008; Murphy et al., 1992; Mutti et al., 1999). The degree of myopia was found to increase with increasing age across all breeds (Kubai et al., 2008). Astigmatism is reported to be rare in dogs, with only 1% of 1440 adults dogs affected in one study, and only the German Shepherd Dog appeared to be predisposed, with 3% of the examined 90 dogs affected (Kubai et al., 2008).

Retinoscopic results of aphakic canine eyes suggest that the mean refractive error ranges from +14.0 D to +15.2 D, and that a +41.5 D lens will usually correct this error to within 1.2 D of emmetropia (Davidson et al., 1993; Gaiddon et al., 1991, 1996; Gift et al., 2009; Pollet, 1982). At the same dioptric strength, however, lens material and design may have an impact on the refractive state of canine patients after cataract surgery (Gift et al., 2009). In domestic cats of all ages, the mean refractive state ranged from –0.78 D to +1.37 D. The mean refractive error in cats changed significantly as a function of age, with kittens under the age of 4 months ranging from –2.45 D to +1.75 D, while in adult cats it measured from –0.39 D to +0.85 D (Konrade et al., 2012). Refractive error in normal horses has been reported to range from −3 to +3 D, but most appear to be within 1 D of emmetropia (Bracun et al., 2014; Grinninger et al., 2010; Roberts, 1992; Rull-Cotrina et al., 2013). A further study surveying 333 horses and ponies showed that 83.63% of eyes were emmetropic, with 68.5% of horses being emmetropic in both eyes (Bracun et al., 2014). In the same study, only 2.7% of eyes showed ametropia greater than 1.5 D, with 54% of affected eyes being hyperopic and 46% of eyes being myopic. Anisometropia was found in 30.3% of horses. Horses affected with multiple congenital ocular anomalies due to being homozygous for the *Silver* mutation were found with myopia of –2 D or more, while horses heterozygous for the mutation were only showing an increased tendency to myopia once over 16 years of age (Johansson et al., 2017). After cataract surgery, the aphakic equine eye has been reported to be hyperopic at +9.94 D (Millichamp & Dziezyc, 2000). A 30 D strength lens implant has been suggested to be able to correct hyperopia after equine cataract surgery, based on calculations using biometry and keratometry results obtained in the normal horse (McMullen & Gilger, 2006; McMullen & Utter, 2010). However, implantation of a 30 D lens in enucleated equine globes and a 25 D lens in the adult equine eye following phacoemulsification still resulted in overcorrection of refractive error by −2.47 D and −3.94 D, respectively (McMullen et al., 2010). Retinoscopy is also readily applicable in avian patients, and a 13.8 D lens implant corrected aphakia in a Great Horned Owl to within −0.75 D of emmetropia following phacoemulsification (Carter et al., 2007).

Retinoscopy in 10 healthy rabbits revealed the majority of rabbits to be within 0.5 D of emmetropia (Sanchez et al., 2017). In four pet rabbits, placement of a 58 D posterior chamber lens implant resulted in streak refraction values from –1.5 D to +1 D (Sanchez et al., 2017, 2018).

Retinoscopy has become a firmly established procedure in clinical veterinary ophthalmology. However, considerable practice is necessary to produce consistent results with retinoscopy in animals. For that reason, model eyes are available for teaching and practice purposes (Wessels et al., 1995). With increased use, retinoscopy will not only continue to improve our selection of intraocular lens implants for patients undergoing cataract surgery, but also assist with evaluating performance problems associated with ametropia in working animals (Murphy et al., 1997).

Corneal Esthesiometry

The corneal reflex is one of the most sensitive reflexes in the body and its purpose is to protect the eye. The corneal reflex is assessed by touching the peripheral cornea, to avoid a menace response, with a noninjurious object, such as a wisp of cotton wool, swab tip, or fiber from an esthesiometer. The expected result is retraction of the globe, protraction of the nictitating membrane, and closure of the eyelids (Fig. 10.1.39). The afferent arm of the corneal reflex is the ophthalmic branch of cranial nerve V, and the efferent arm is mediated by cranial nerves VI (globe retraction) and VII (eyelid closure).

Corneal esthesiometry uses the corneal reflex to quantitatively evaluate corneal sensitivity and thereby indirectly assess corneal innervation. Different types of corneal esthesiometers include Cochet–Bonnet, Larson–Millodot (Luneau USA, Westport, CT, USA), and noncontact air jet esthesiometers (Golebiowski et al., 2011; Millodot & Larson, 1969). The Cochet–Bonnet esthesiometer is used most commonly in veterinary ophthalmology (see Fig. 10.1.39A). It consists of a nylon filament that is 0.12 mm in diameter and has a variable length of 0.5–6 cm (the filament is platinum in the Larson–Millodot esthesiometer). A change in filament length relates to a change in pressure exerted on the cornea by the filament tip; shorter filament lengths apply more

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Figure 10.1.39 **A**. Cochet–Bonnet esthesiometer®. **B**. Corneal sensation can be assessed quantitatively by a Cochet–Bonnet esthesiometer. (Courtesy of N. Hamzianpour and R. Pinheiro de Lacerda, Willows Referral Service, UK.)

pressure to the cornea and vice versa. The pressure ranges from 5 to 180 mg/0.0113 mm (0.4–15.9 g/mm). Corneal esthesiometry should be performed in a quiet environment with minimal restraint to the head and eyelids. The instrument is held perpendicular to the cornea, with the filament extended to its maximum length and advanced until the filament contacts the cornea, creating a slight bend in the fiber (Fig. 10.1.39B). The corneal touch threshold (CTT) is the degree of corneal stimulation that is required to elicit a blink reflex. Corneal sensitivity and CTT are inversely proportional. The CTT is defined as the pressure at which the majority of touch stimuli elicit a blink; this is quantified in most studies. For example, when more than 50% of the attempts result in a blink reflex, the filament is shortened by 0.5 cm decrements. The CTT in centimeters is converted to pressure in milligrams per S (S = 0.0113 mm^2 sectional area of the filament) and grams per square millimeter using the conversion table provided by the esthesiometer manufacturer. Sensitivity can be assessed in different regions, for example central, dorsal, temporal, ventral, and nasal regions.

Numerous factors influence corneal sensitivity and include species, age, skull shape, region of cornea, systemic disease, and topical anesthetic agents. It is difficult and potentially inaccurate to compare results from different studies because multiple measuring units have been reported, some nonidentifiable, and the nylon filament of the Cochet–Bonnet esthesiometer and conversion table were changed by the manufacturer (Western Ophthalmics, Lynwood, WA, USA) between 1990 and 2010. Furthermore, there is no available corrective formula for deviations from the recommended ambient temperature and humidity (Wieser et al., 2012). Ambient humidity influences results, with a longer filament length eliciting a blink response at a lower humidity (Dorbandt et al., 2017). Results from different studies can only be compared if the filament strength used and units of applied pressure (mg/0.0113 mm^2 or g/mm^2) are uniform. When comparing studies that reported values in mg/0.0113 mm^2, the order of most sensitive to least sensitive is cria (Rankin et al., 2011a), human (Millodot, 1977), adult alpaca (Rankin et al., 2011a), cat (Chan-Ling, 1989), pigmented rabbit (Millodot, 1978), albino rabbit (Millodot, 1978), and nonbrachycephalic dog (Barrett et al., 1991). When comparing studies that reported values in g/mm^2, the order of most sensitive to least sensitive is cria (Rankin et al., 2011a), chinchilla (Lima et al., 2010; Müller et al., 2010), sheep (Wieser et al., 2012), horse (Wieser et al., 2012), calf (Wieser et al., 2012), goat (Wieser et al., 2012), normoglycemic dog (Good et al., 2003), cow (Wieser et al., 2012), Domestic Shorthaired Cat (Blocker & van der Woerdt, 2001), dog with diabetes (Good et al., 2003), adult alpaca (Rankin et al., 2011a), guinea pig (Trost et al., 2007), and brachycephalic cat (Blocker & van der Woerdt, 2001).

Brachycephalic cats and dogs have reduced corneal sensitivity compared with nonbrachycephalic breeds (Barrett et al., 1991; Blocker & van der Woerdt, 2001). Age influences corneal sensitivity in several species, including the horse (Brooks et al., 2000b; Miller et al., 2013), alpaca (Rankin et al., 2011a), cattle (Tofflemire et al., 2014), and birds (Lacerda et al., 2014). Corneal sensitivity is higher in neonatal foals, crias, calves, and fledglings (*Athene noctua* and *Strix aluco*) than in their adult counterparts (Brooks et al., 2000b; Lacerda et al., 2014; Miller et al., 2013; Rankin et al., 2011a; Tofflemire et al., 2014). Human corneal sensitivity has been shown to vary with age, gender, and iris pigmentation (Acosta et al., 2006; Millodot, 1977).

The central cornea is usually the most sensitive region in many species, including the dog (Barrett et al., 1991; Good et al., 2003), cat (Blocker & van der Woerdt, 2001), horse (Brooks et al., 2000b; Kaps et al., 2003), alpaca (Rankin et al., 2011a; Welihozkiy et al., 2011), and guinea pig (Trost et al., 2007), although the difference is not always significant. In dogs (Barrett et al., 1991), cats (Chan-Ling, 1989), and

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nonhuman primates (Zander & Weddell, 1951), the maximum sensitivity of the central cornea correlates to the highest density of nerve fibers. The dorsal region of the cornea is typically less sensitive than other regions, and this has been hypothesized, in humans, to be a result of desensitization from contact with the upper eyelid (Millodot & Larson, 1969). The effect of surgical procedures for canine glaucoma on corneal sensitivity has been studied (Blocker et al., 2007; Weigt et al., 2002). Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser therapy reduces both the corneal sensitivity and the number of major corneal nerve bundles in treated eyes (Weigt et al., 2002). Sensitivity of the central cornea is lower in buphthalmic glaucomatous eyes than in normal eyes, but is not reduced further by the dorsal scleral incision required for evisceration and placement of an intrascleral prosthesis (Blocker et al., 2007). In horses, corneal sensation is reduced in eyes with keratitis as compared to eyes with other ocular disease (Knickelbein et al., 2018). Corneal esthesiometry has been used to objectively measure the effect of different agents (Arnold et al., 2014; Binder & Herring, 2006; Chen & Powell, 2015; Dorbandt et al., 2016; Douet et al., 2013; Giudici et al., 2015; Gordon et al., 2018; Herring et al., 2005; Kalf et al., 2008; Kim et al., 2013; Pucket et al., 2013; Sharrow-Reabe & Townsend, 2012; Venturi et al., 2017; Wotman & Utter, 2010).

Tear Tests

The tear film can be assessed in quantitative and qualitative terms. Three quantitative tests are described in this section: the Schirmer tear test (STT), the phenol red thread (PRT) tear test, and the most recent, endodontic absorbent paper point test (EAPTT; see later Fig. 10.1.41). The tear film breakup time (TBUT), a qualitative test, is described under "External Ophthalmic Dyes."

Schirmer Tear Test

The STT quantifies production of the aqueous component of the tear film. First described by Schirmer in 1903, a standardized strip of filter paper is placed in the conjunctival sac to measure wetting in millimeters over 1 min (mm/min). Schirmer I (STT I), without topical anesthesia, measures basal and reflex tearing. Schirmer II (STT II), performed after topical anesthesia, measures only basal tearing. In 1961, Halberg and Berens (1961) introduced a standardized 5 × 35 mm strip of Whatman no. 41 filter paper with a rounded tip and a notch 5 mm from the end for bending. Commercial strips have a millimeter scale and may be impregnated with blue dye at the 5 mm point to highlight tear fluid migration (Hirsh & Kaswan, 1995; Wyman et al., 1995). The use of a modified strip has been described in the dog; the strip is 5 mm wide for the first 10 mm and then 7 mm beyond (van der Woerdt & Adamcak, 2000).

The STT was first described in the dog in 1962 (Roberts & Erickson, 1962), followed by several reports over the next decade (Gelatt et al., 1975; Hamor et al., 2000; Harker, 1970; Roberts & Erickson, 1962; Rubin et al., 1965), and in the cat in 1970 (Veith et al., 1970). Despite criticism of its poor repeatability and inconsistencies, the STT remains the standard method for quantifying aqueous tear production in veterinary ophthalmology (Hawkins & Murphy, 1986). It has been used extensively to establish normal values in domestic and nondomestic species (Table 10.1.5) to determine the relative contributions of aqueous from the lacrimal and nictitans glands, and to assess the influence of different factors such as signalment, environment, and drugs on tear production (Hartley et al., 2006; McLaughlin et al., 1988; Saito et al., 2001; Williams et al., 1979).

The STT should be performed early in the ophthalmic examination to minimize the effect of reflex tearing from eyelid manipulation and before any topical agents are applied to the eye. The strips are supplied in sterile packs of two. The strip should be bent slightly at the notch before removal from the pack; it is preferable to avoid touching the short end of the strip to maintain sterility, and because skin lipid may interfere with aqueous tear absorption. The short folded end is placed in the lateral half of the lower conjunctival sac so that the notch is at the level of the lid margin and the strip is in contact with the cornea (Fig. 10.1.40). The strip is left in place for 1 min and tears are measured immediately upon removal. It has long been accepted that the eyelids can be open or held closed, but a recent study in normal horses showed that STT values were significantly lower when the eyelids were open (Trbolova & Ghaffari, 2017). Premature



Figure 10.1.40 Aqueous tear production can be accessed by the Schirmer tear test. The short folded end of the paper strip is placed in the lateral half of the lower conjunctival sac so that it is in direct contact with the cornea, in order to measure both basal and reflex tear reproduction.

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Table 10.1.5A Values for tear production and intraocular pressure in domesticated mammals.

Species	IOP Mean ± SD (mmHg)	STT (mm/min)	PRT (mm/15 s)	EAPTT (mm/min)	Authors
Cat	18.4 ± 0.5 (TP-XL, TP-Vet) 20.74 ± 0.5 (TV)	18 (9–34)	29 (15–37)		Passaglia et al. (2004) Rusanen et al. (2010) McLellan & Miller (2011) Sebbag et al. (2015) **Refer to text – multiple studies**
Dog	11.7 ± 2.5 (7-20) (TP-XL) 14.3 ± 4.0 (8-25) (AcP) 15.6 ± 4.2 (6-25) (TP-XL) 15.0 ± 3.2 (7-22) (TV) 19.2 ±3.1 (11-25) (TV Plus) 12.8 ± 2.9 (6-19) (TP-Avia)	18.64 ± 4.47 to 23.90 ± 5.12			Tofflemire et al. (2017) **Refer to text – multiple studies** Kato (2014) Ben-Shlomo & Muirhead (2020) **Refer to text – multiple studies**
Horse	23.2 ± 6.89 (7-37) (TP)	20.6 ± 6.5 to 24.8 ± 4.8			Miller et al. (1990, 1991) Refer to text – multiple studies
Cow	23 (12-40) (TV) 16 (8-27) (TP-Avia)	24.18 ± 6.5 mm/30 s			Whitley & Moore (1984) Peche & Eule (2018)
Calf (dairy)	15.2 ± 5.2 (TV)	20.4 ± 5.0			Tofflemire et al. (2015)
Sheep	11 (7-20) (TV) 10 (5-18) (TV-Avia)				Peche & Eule (2018)
Pig		15.6 ± 3.7 (10–22)			Trbolova & Ghaffari (2012)
Llama	13.10 ± 0.35 (TP)				Willis et al. (2000)
	16.96 ± 3.51 (TP)				Nuhsbaum et al. (2000)
		20.30 ± 2.96			Pigatto et al. (2010b)
Alpaca	14.85 ± 0.45 (TP)				Willis et al. (2000)
	16.14 ± 3.74 (TP)				Nuhsbaum et al. (2000)
	14.21 ± 2.73 (TV) 12.51 ± 2.78 (TP-XL)				McDonald et al. (2017)
Rabbit		4.85	20.88		Biricik et al. (2005)
Angora		5.4 ± 1.6	25.0 ± 2.7	18.8 ± 2.1	Rajaei et al. (2016c)
Dutch		4.6 ± 1.2	23.6 ± 2.3	16.9 ± 1.7	Rajaei et al. (2016c)
New Zealand		7.58 ± 2.3			Whittaker & Williams (2015)
		5.2 ± 1.0		13.8 ± 1.5	Lima et al. (2015)
		5.30 ± 2.96			Abrams et al. (1990)
Guinea pig		0.36 ± 1.09	16 ± 4.7		Trost et al. (2007)
	6.81 ± 1.41 (TV)		14.33 ± 1.35	8.54 ± 1.08	Rajaei et al. (2016a)
Rat	17.30 ± 5.25 (TP)			6.18 ± 2.06	Mermoud et al. (1994) Lange et al. (2014)
Mouse				4.39 ± 1.45	Lange et al. (2014)
Ferret	14.50 ± 3.27 (TP)	5.31 ± 1.32			Montiani-Ferreira et al. (2006)
Chinchilla	17.71 ± 4.17 (TP-XL)	1.07 ± 0.54			Lima et al. (2010)
	2.9 ± 1.8 (TV)	Unreliable	14.6 ± 3.5		Müller et al. (2010)
ex vivo	9.7 ± 2.5 (TV; "d" setting)				Snyder et al. (2017)

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Table 10.1.5A (Continued)

Species	IOP Mean ± SD (mmHg)	STT (mm/min)	PRT (mm/15 s)	EAPTT (mm/min)	Authors
Hamster			6.8 ± 2.3		Rajaei et al. (2013)
	4.55 ± 1.33 (TV)				
			5.57 ± 1.51	4.52 ± 1.55	Rajaei et al. (2016b)
Hedgehog	20.4 ± 4.0 (TP)	1.7 ± 1.2 (range 0–4)			Ghaffari and Hajikhani (2011)
	12.6 ± 1.8 (TV)				Williams et al. (2017)
Goat	23 (9-37) (TV)				Peche & Eule (2018)
	13 (4-25) (TVP-Avia)				
Pygmy goat	10.8 (8–14) (TP-XL)	15.8 (range 10–30)			Broadwater et al. (2007)
	11.8 (9–14) (TV-D)				Broadwater et al. (2007)
	7.9				Broadwater et al. (2007)
Donkey	17.8 ± 3.7 (13.5–24.5) (TP)	22.1 ± 6.9 (range 13–35)			Ghaffari et al. (2017)

AcP, Accupen; EAPTT, endodontic absorbent paper point test; IOP, intraocular pressure; PRT, phenol red thread; SD, standard deviation; STT, Schirmer tear test; TP, Tono-Pen; TP-XL, Tono-Pen XL; TV, TonoVet; TV-D, TonoVet (dog); TV-Plus, TonoVet Plus.

loss of the strip is probably less likely if the eyelids are held closed. The STT is considered to be well tolerated, but a recent study in rabbits quantified an increase in corneal sensitivity for up to 16 min following the STT (Lima et al., 2015). This highlights the fundamental principle of the test, which is to measure reflex lacrimation as well as the tear film meniscus and basal lacrimation.

STT I values in the normal adult dog vary from 18.64 ± 4.47 mm/min to 23.90 ± 5.12 mm/min (Gelatt et al., 1975; Hamor et al., 2000; Harker, 1970; Hirsh & Kaswan, 1995; Saito & Kotani, 2001; Wyman et al., 1995). In the dog, values less than 5 mm/min are considered to be diagnostic for KCS, and values less than 10 mm/min are suspicious if combined with characteristic clinical signs. STT I values in the normal adult cat vary from 14.3 ± 4.7 mm/min to 16.92 ± 5.73 mm/min (Arnett et al., 1984; Cullen et al., 2005b; Margadant et al., 2003; McLaughlin et al., 1988; Veith et al., 1970). Low STT values in the cat must be carefully interpreted together with the clinical signs, because the range of values in normal cats is wide; in one study of 76 cats, STT I values ranged from 1 to 33 mm/min (Waters, 1994). In a recent study of selected tear film tests in 135 cats, the median STT I value was 18 mm/min (range 9–34 mm/min; Sebbag et al., 2015). Tear production in the horse is greater than in the dog and cat and may overwhelm commercial strips in less than the standard 1 min period (Beech et al., 2003; Brightman et al., 1983; Crispin, 2000; Harling, 1988; Marts et al., 1977). STT I values in the normal adult horse, using a standard 5 × 35 mm test strip, vary from 20.6 ± 6.5 mm/min to 24.8 ± 4.8 mm/min (Beech et al., 2003; Brightman et al., 1983; Harling, 1988; Regnier, 2002). Two additional studies present STT I values more broadly as 11 to more than 30 mm/min and 15–20 mm/30 s (Marts et al., 1977; Moore, 1992). In the horse, STT I values of less than 10 mm/min are diagnostic for KCS (Crispin, 2000). The STT I value in the normal adult cow is 24.18 ± 6.5 mm/30 s (Whitley & Moore, 1984), and in the pig is 15.6 ± 3.7 mm/min (range, 10–22 mm/min; Trbolova & Ghaffari, 2012).

Tear absorption has been shown to be nonlinear in dogs (Williams, 2005) and horses (Cutler, 2002). Because of the initial rapid absorption of tear fluid, it has been suggested that temporal examination of the STT may be more precise than the standard method (Williams, 2005).

STT II measures only basal tear production, because reflex tear production is eliminated by topical anesthesia. The STT II test is used more widely in humans, where high reflex tear production may mask low basal tear production. One drop of topical anesthetic is applied to the eye and the excess is blotted away with a swab or cotton-tipped applicator; a few minutes are allowed to elapse. The test is then performed as for STT I. Reported STT II values in the normal adult dog are 6.2 ± 3.1 mm/min (Gelatt et al., 1975), 9.52 ± 4.55 mm/min (Saito & Kotani, 2001), and 11.6 ± 6.1 mm/min (Hamor et al., 2000). The STT II value in the normal adult cat is 13.2 ± 3.4 mm/min, approximately 80% of the STT I result in the same study (McLaughlin et al., 1988). As in the dog and cat, the mean STT II values are lower than the STT I values in other species, including the pig (Trbolova & Ghaffari, 2012) and the camel (Marzok et al., 2017), but not in the horse

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Table 10.1.5B Values for tear production and intraocular pressure in nondomesticated (zoo) mammals.

Species	IOP Mean ± SD (mmHg)	STT (mm/min)	PRT (mm/15s)	EAPTT (mm/min)	Authors
Prairie dog	7.7 ± 2.2 (TV)	1.2 ± 0.9 (modified)	13.6 ± 7.8		Meekins et al. (2015b)
Camel					
Calf		14–18			Marzok et al. (2017)
Immature	> 32.5 (TP)	22–26			Marzok et al. (2015, 2017)
Mature	> 28.5 (TP)	30–34			Marzok et al. (2015, 2017)
African giant pouched rat	7.7 ± 2.9 (TV)				Heller et al. (2017)
Capybara	18.4 ± 3.8 (TP-XL)	14.9 ± 5.1			Montiani-Ferreira et al. (2008b)
Paca	6.34 ± 0.43 (TP-Vet)	4.10 ± 0.44			Balthazar da Silveira et al. (2017)
Beaver	17.95 (TP-XL)				Cullen (2003)
Grant's Zebra	25.30 ± 3.06 (Sch)				Ofri et al. (1998b)
	29.47 ± 3.43 (TP)				Ofri et al. (1998b)
Burchell's zebra		23.4 ± 3.4			Ofri et al. (1999a)
Nubian Ibex	17.95 ± 4.78 (Sch)				Ofri et al. (1998b)
		13.2 ± 5.1			Ofri et al. (1999a)
Arabian Oryx	22.68 ± 8.15 (Sch)				Ofri et al. (1998b)
	11.76 ± 3.43 (Sch)				Ofri et al. (1998b)
		12.7 ± 4.8			Ofri et al. (1999a)
Eland	14.6 ± 4.0 (app)	18.7 ± 5.9			Ofri et al. (2001)
Fallow Deer	11.9 ± 3.3 (app)	10.5 ± 6.5			Ofri et al. (2001)
	14.1 ± 2.48	17.8 ± 3.16			Kvapil et al. (2018)
Thomson's Gazelle	7.6 ± 1.6 (TP-XL)				Ofri et al. (2000)
Addax Antelope	11.2 ± 3.2 (TP-XL)	28.8 ± 8.3			Ofri et al. (2002a)
Impala	8.0 ± 1.2 (TP-XL)	18.8 ± 1.8			Ofri et al. (2002a)
Wildebeest	15.5 ± 3.7 (TP-XL)	19.3 ± 4.6			Ofri et al. (2002a)
Oryx	15.8 ± 1.5 (TP-XL)				Ofri et al. (2002a)
Sambar deer	11.4 ± 2.8 (TP-XL)	18.8 ± 4.7			Oriá et al. (2015a)
Mouflon	14.9 ± 2.20	17.9 ± 3.87			Kvapil et al. (2018)
Ibex	13.1 ± 2.43	11.7 ± 3.87			Kvapil et al. (2018)
Chamois	10.2 ± 2.5	14.5 ± 3.0			Kvapil et al. (2018)
Rhinoceros	32.1 ± 10.4 (TP-XL)	17.6 ± 3.1			Ofri et al. (2002a)
	31.2 ± 6.62 (app)	18.2 ± 3.49			Bapodra & Wolfe (2014)
Capuchin Monkey	18.4 ± 3.8 (TP)	14.9 ± 5.1			Montiani-Ferreira et al. (2008a)
Marmoset		–0.46 ± 3.41		13.27 ± 5.41	Lange et al. (2012)
Lemur (gray mouse)	20.3 ± 2.8 (TV/TP)				Dubicanac et al. (2016)
Koala					
Conscious	15.3 ± 5.1 (TP-Vet)	10.3 ± 3.6			Grundon et al. (2011)
Anesthetized	13.8 ± 3.4 (TP-Vet)	3.8 ± 4.0			Grundon et al. (2011)
Lion					
Male	24.9 ± 2.0 (Sch)				Ofri et al. (1998b)
Female	20.9 ± 2.4 (Sch)				Ofri et al. (1998b)
≤ 1 year	12.8 ± 4.1 (TP)				Ofri et al. (2008)
> 1 year	23.9 ± 4.1 (TP)				Ofri et al. (2008)

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Table 10.1.5B (Continued)

Species	IOP Mean ± SD (mmHg)	STT (mm/min)	PRT (mm/15s)	EAPTT (mm/min)	Authors
Luteal female	27.07 ± 2.15 (Sch)				Ofri et al. (1999b)
Nonluteal female	21.61 ± 2.70 (Sch)				Ofri et al. (1999b)
Fruit bat					
Hanging	19.38 ± 0.77 (TV)		23 ± 1.28		Blackwood et al. (2010)
Upright	13.95 ± 0.60 (TV)				Blackwood et al. (2010)

Source: app, applanation; EAPTT, endodontic absorbent paper point test; IOP, intraocular pressure; PRT, phenol red thread; Sch, Schiøtz; SD, standard deviation; STT, Schirmer tear test; TP, Tono-Pen; TP-Vet, Tono-Pen Vet; TP-XL, Tono-Pen XL; TV, TonoVet.

(Beech et al., 2003; Williams et al., 1979). Reflex tear production may not exist in the guinea pig, because there is no significant difference between the mean STT 1 and STT II values (Trost et al., 2007). The correlation between reflex tear production and corneal sensitivity was assessed in several species, with inconclusive results (Wieser et al., 2012).

The PRT tear test also quantifies production of the aqueous component of the tear film (Brown et al., 1996; Sakamoto et al., 1993). Kurihashi et al. first described the use of thread to measure tear production in 1975. The method was refined by Hamano et al. in 1982 by impregnating the thread with phenol red, a pH-sensitive indicator. The standardized cotton thread is 75 mm long with a fold 3 mm from one end (Menicon, Clovis, CA, USA). The folded end is placed in the lower conjunctival fornix for 15 s. As the slightly alkaline tears wick along the thread, the pale yellow thread turns orange (Fig. 10.1.41A). The length of color change in millimeters is read from the end of the thread (not the bend), immediately upon removal from the eye. PRT tear test values are 34.15 ± 4.45 mm and 23.04 ± 2.23 mm in the dog and cat, respectively (Brown et al., 1996, 1997). A recent study in the horse provided PRT tear test values of 30.22 ± 0.99 mm and 31.00 ± 1.4 mm in the Arabian and Thoroughbred Horse, respectively (Sindak et al., 2010). The main advantage of the PRT tear test in veterinary ophthalmology is that it can be used in small eyes and is therefore appropriate for many nondomestic species (see the next section).

The EAPPT was first reported in marmosets by Lange in 2012. Like the STT and the PRT test, the EAPPT quantifies the aqueous portion of tears. Like the PRT test, the EAPTT is particularly suitable for eyes with very low tear production and/or for very small eyes. The suitability for small eyes is highlighted by results from a seed finch weighing 20 g with a palpebral length of 4.46 ± 0.09 mm (the width of a standard STT strip is 5 mm; Lange et al., 2014). The strip is used in dentistry and is highly absorptive and sterile. The standard length is 28 mm and the diameter of the conical tip varies from 0.15 to 0.80 mm, making it highly applicable to species with small eyes. The Lange marmoset study used a 0.3 mm

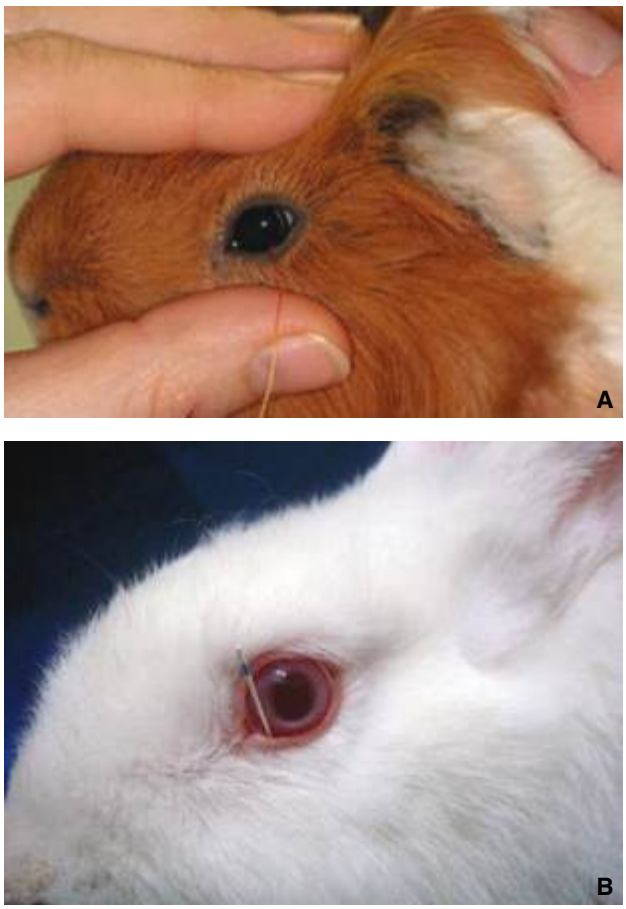


Figure 10.1.41 **A**. Aqueous tear production can be assessed quantitatively by the phenol red thread tear test in a guinea pig. The folded end of the thread is placed in the lower conjunctival fornix. The pale yellow thread turns orange as the slightly alkaline tears wick along it. (Reproduced with permission from Walde, I., Nell, B., Schäffer, E. et al. (2008) *Augenheilkunde*, 3rd ed. Stuttgart: Schattauer, p. 765.) **B**. Aqueous tear production can be assessed quantitatively by the endodontic absorbent paper tear test. The result in this rabbit is 13 mm/min. (Courtesy of Leandro Lima and Fabiano Montiani-Ferreira, Comparative Ophthalmology Lab – Laboratório de Oftalmologia Comparada da Universidade Federal do Paraná, Curitiba-PR, Brazil.)

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Table 10.1.5C Values for tear production and intraocular pressure in avian species.

Species	IOP Mean ± SD (mmHg)	STT (mm/min)	PRT (mm/15 s)	EAPTT (mm/min)	Authors
Chicken	17.51 ± 0.13 (TV)				Prashar et al. (2007)
Pigeon	11.7 ± 1.6 (TV)				Park et al. (2017)
Red-Tailed Hawk	20.6 ± 3.4 (app)				Stiles et al. (1994)
Swainson's Hawk	20.8 ± 2.3 (app)				Stiles et al. (1994)
Golden Eagle	21.5 ± 3.0 (app)				Stiles et al. (1994)
Bald Eagle	20.6 ± 2.0 (app)				Stiles et al. (1994)
Great Horned Owl	10.8 ± 3.6 (app)				Stiles et al. (1994)
Screech Owl	11 ± 1.9 (TP-XL)	≤ 2 (2–6)	15 ± 4.3		Harris et al. (2008)
	14 ± 2.4 (TV-D)				Harris et al. (2008)
Eurasian Eagle Owl	9.35 ± 1.81 (TP-XL)				Jeong et al. (2007)
Psittaciformes		3.2 ±.7 to 7.5 ± 2.6			Korbel & Leitenstorfer (1998)
Falconiformes		4.1 ± 2.7 to 14.4 ± 7.2			Korbel & Leitenstorfer (1998)
			30.6 ± 4.2		Smith et al. (2015)
Accipitriformes		10.7 ± 4.0 to 11.5 ±5.4			Korbel & Leitenstorfer (1998)
Strigiformes		<3			Korbel & Leitenstorfer (1998)
Parrot		7.9 ± 2.6	12.0 ± 5.0		Storey et al. (2009)
Saffron Finch				5.10 ± 0.26	Lange et al. (2014)
Seed Finch				4.10 ±0.34	Lange et al. (2014)
Duck	10.2 ± 2.2 (TV)	6.2 ± 2.2			Ansari Mood et al. (2017)
Goose	9.1 ± 2.0 (TV)				Ansari Mood et al. (2017)
Guinea Fowl	9.1 ± 0.9 (TV)		16.5 ± 1.3		Rajaei & Mood (2016)
Murre (Guillemot)	23 ± 2.6 (TV)		20 ± 3.6 mm		Freeman et al. (2017)
Flamingo	16.1 ± 4.2 (TP-XL) 9.5 ± 1.7 (TV)	12.3 ± 4.5 (modified)	24.2 ± 4.4		Meekins et al. (2015a)
Pelican	9.0 ± 1.41		14.9 ± 7.84		Kinney et al. (2017)
Penguin					
Rockhopper	20.0 ± 5.77 (TP-XL) 24.1 ± 5.09 (TV)	11.0 ± 3.96	25.1 ± 7.07		Bliss et al. (2015)
Macaroni	21.9 ± 7.05 (TP-XL) 29.1 ± 7.16 (TV)	12.1 ± 5.43	24.7 ± 6.37		Bliss et al. (2015)
Black-footed	31.77 ± 3.3 (TV)				Gonzalez-Alonso-Alegre et al. (2015)
Humboldt	28.0 ± 9 (TV)	9 ± 4			Sheldon et al. (2017)
	20.36 ± 4.1 (10-27) (TP-XL)	6.45 ± 2.9 (1-12)			Swinger et al. (2009)

Source: app, applanation; EAPTT, endodontic absorbent paper point test; IOP, intraocular pressure; PRT, phenol red thread; SD, standard deviation; STT, Schirmer tear test; TP-XL, Tono-Pen XL; TV, TonoVet; TV-D, TonoVet (dog).

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Table 10.1.5D Values for tear production and intraocular pressure in fish, reptiles, and amphibians.

Species	IOP Mean ± SD (mmHg)	STT (mm/min)	PRT (mm/15s)	EAPTT (mm/min)	Authors
Alligator					
≤ 50 cm long	23.7 ± 2.1 (app)				Whittaker et al. (1995)
> 50 cm long	11.6 ± 0.5 (app)				Whittaker et al. (1995)
Caiman	12.9 ± 6.2 (TP-XL)	3.4 ± 3.6		17.1 ± 2.5	Oriá et al. (2015c)
Broad-Snouted					
Yacare	9.56 ± 2.69 (TP-XL)				Ruiz et al. (2015)
Red-Footed Tortoise					
Male, DV	11.5 ± 2.8 (TP-XL)	12.0 ± 3.5			Oriá et al. (2015b)
Female, DV	14.0 ± 3.5 (TP-XL)				Oriá et al. (2015b)
Male, VD	18.0 ± 3.2 (TP-XL)				Oriá et al. (2015b)
Female, VD	24.1 ± 3.0 (TP-XL)				Oriá et al. (2015b)
				15.9 ± 0.7 @ 32°C 15.4 ± 0.4 @ 18°C	
					Oriá et al. (2015b)
Red-Eared Slider Turtle	5.42 ± 1.7 (TV)	2.55 ± 3.4 (modified)			Somma et al. (2014)
	11.32 ± 1.7 (TV)			8.79 ± 0.38	Delgado et al. (2014) Lange et al. (2014)
Yellow-Footed Tortoise	14.2 ± 1.2 (TP)				Selmi et al. (2003)
Hermann's Tortoise	15.74 ± 0.20 (TV)				Selleri et al. (2012)
Kemp's Ridley Turtle	6.5 ± 1.0 (TV; "h" setting)				Gornik et al. (2016)
Sea Turtle					
DV/VD	5/7				Chittick & Harms (2001)
Head-down	23 (TP-XL)				Chittick & Harms (2001)
Gulf Coast Turtle	6.7 ± 1.4 (TV)				Espinheira Gomes et al. (2016)
Three-Toed Turtle	8.3 ± 1.5 (TV)				Espinheira Gomes et al. (2016)
Koi Fish	4.9 (TV)				Lynch et al. (2007)
Bullfrog	4 (TV) 16 (TP-AVIA)				Cannizzo et al. (2017)
Bearded Dragon	6.16 (TV)				Schuster et al. (2015)

Source: app, applanation; DV, dorsoventral; EAPTT, endodontic absorbent paper point test; IOP, intraocular pressure; PRT, phenol red thread; SD, standard deviation; STT, Schirmer tear test; TP, Tono-Pen; TP-AVIA, Tono-Pen AVIA; TP-XL, Tono-Pen XL; TV, TonoVet; VD, ventrodorsal.

tip (Sterile Roeko Top Color, size 30, Roeko, Langenau, Germany). The strip is placed in the lower conjunctival fornix for 1 min. After removal, the length of wetting is measured in millimeters. The authors found the test easier to perform, even with a single examiner, than the modified STT I and PRT. Furthermore, there was less variation in the data obtained from the EAPPT compared to the modified STT and PRT data. A study in New Zealand rabbits showed objectively that the EAPPT was well tolerated; there was no difference in the CTT between control rabbits and EAPTT rabbits, whereas corneal sensitivity increased for 16 min following a standard STT (Lima et al., 2015). Values for EAPPT have since been published in several species, including the rabbit (Lima et al., 2015; Rajaei et al., 2016c), guinea pig (Rajaei et al., 2016a), caiman (Oriá et al., 2015c), Syrian hamster (Rajaei et al., 2016b), red-footed tortoise (Oriá et al., 2015b), and the finch, mouse, and rat (Lange et al., 2014).

Multiple factors influence tear production. The influence of signalment (age, gender, and breed) has been studied in several species. Age has been shown to affect tear production in

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the dog, cat, horse, pig, and camel. As a general rule, there is a positive correlation between tear production and age (as compared to a negative correlation between IOP and age). However, conflicting results have been found in different studies in dogs. An early study in the dog showed that age had no effect (Hamor et al., 2000), whereas a subsequent study showed that tear production decreased with increasing age at a rate of 0.44 mm/year (Hartley et al., 2006). Three more recent studies have shown that tear production in the dog increases with age, as in most other species (Broadwater et al., 2010; da Silva et al., 2013; Verboven et al., 2014). The Broadwater study looked specifically at juvenile dogs (less than 6 months old) and found that age and weight had a significant effect on tear production, as STT I values increased by 0.15 mm/min for each 1 day increase in age, and by 0.84 mm/min for each 1 kg increase in bodyweight; adult values were reached by 9–10 weeks of age (Broadwater et al., 2010). STT II values were significantly lower in cats less than 1 year old compared to those more than 1 year old (Waters, 1994). Neonatal foals, both sick and healthy, have lower tear production than adult horses (Brooks et al., 2000b). Sick neonatal foals, healthy neonatal foals, and healthy adult horses have STT I values of 14.2 ± 1 mm/min, 12.8 ± 2.4 mm/min, and 18.3 ± 2.1 mm/min, respectively (Brooks et al., 2000b). STT I and II values are lower in the juvenile pig than in the adult pig (Trbolova & Ghaffari, 2012). Tear production in camels increased with age, being 14–18 mm/min in the calf and 30–34 mm/min in the mature camel (Marzok et al., 2017).

The effect of gender on tear production has been described in dogs, horses, and Syrian hamsters. Gender affects tear production in the juvenile dog (Hartley et al., 2006), but not in the adult dog (Hamor et al., 2000). The influence of gender in the adult horse is inconsistent (Beech et al., 2003; Piccione et al., 2008; Regnier, 2002). Tear production is significantly higher in the female Syrian hamster compared to the male (Rajaei et al., 2016b).

Diurnal rhythm has been shown to have a significant effect on tear production in the dog (Berger & King, 1998; Giannetto et al., 2009; Hakanson & Arnesson, 1997), whereas the results in the horse were variable (Beech et al., 2003; Piccione et al., 2008; Regnier, 2002). Early studies in the horse found no daily fluctuations or seasonal effects (Beech et al., 2003; Regnier, 2002), in contrast to the circadian rhythm in tear production described more recently (Piccione et al., 2008). The variability in tear production between eyes in the same horse has also been found to be inconsistent (Beech et al., 2003; Piccione et al., 2008; Regnier, 2002). STT values were significantly lower in nocturnal species of raptors as compared to diurnal species (Beckwith-Cohen et al., 2015).

The effect of topical tropicamide 1% on tear production varies with species. It had no effect in the dog (Margadant et al., 2003), but significantly reduced tear production at 1 hour in both the treated and untreated eye in the cat (Margadant et al., 2003), and only at 4 hours in just the treated eye in the horse (Ghaffari et al., 2009). Topical atropine reduced tear production in the dog, exerting its maximum effect at 120 min and returning to baseline at 300 min, but also affected both eyes (Hollingsworth et al., 1992). Systemic atropine sulfate has been shown to reduce tear production in the cat and the dog (Arnett et al., 1984; Ludders & Heavner, 1979). In contrast, topical 1% cyclopentolate hydrochloride had no effect on tear production (nor IOP) in normal dogs (Costa et al., 2016).

The potential for systemic sulfonamides to cause KCS in the dog, as a result of toxicity to the glandular tissue, has been known since the early 1990s (Berger et al., 1995; Diehl & Roberts, 1991). Recent studies found that trimethoprim-sulfamethoxazole significantly reduced tear production in the New Zealand white rabbit (Shirani et al., 2010) and the Syrian hamster (Rajaei et al., 2015), whereas trimethoprim-sulfadiazine had no effect in the horse (Rothschild et al., 2004) or the guinea pig (Asadi et al., 2016). The effect of numerous drugs on tear parameters in the dog has been studied. Oral diphenhydramine (antihistamine) did not affect tear production in dogs (Montgomery et al., 2011), but did reduce tear film stability and increase corneal sensitivity (Evans et al., 2012). Topical 0.3% naltrexone (Arnold et al., 2014), and oral propranolol (Ghaffari et al., 2011) had no effect on tear production in dogs. Glycopyrrolate (anticholinergic) caused reduced STT values, but had no effect on IOP in dogs (Doering et al., 2016).

Several studies evaluated the effect of sedation and general anesthesia on tear production in different species, including the dog (Biricik et al., 2004; Costa et al., 2015; Dodam et al., 1998; Komnenou et al., 2013; Sanchez et al., 2006), cat (Arnett et al., 1984; Peche et al., 2015), horse (Brightman et al., 1983), lion (Ofri et al., 1998a), and koala (Grundon et al., 2011). Tear production is usually reduced by sedation and/or general anesthesia. General anesthesia has been shown to reduce tear production in the dog (Herring et al., 2000), horse (Brightman et al., 1983), cat (Peche et al., 2015), and koala (Grundon et al., 2011). General anesthesia lowered tear production in the dog for up to 24 hours and the return to normal was prolonged when the duration of anesthesia was more than 2 hours (Herring et al., 2000). Another study showed that tear production was reduced for up to 10 hours irrespective of the duration of the anesthesia (1–4 hours; Shepard et al., 2011). Dogs hospitalized in intensive care units had reduced tear production (Chandler et al., 2013). Several studies, mostly in dogs, have assessed the effect of both individual agents and multiagent protocols. The combination of pethidine and fentanyl caused a significant reduction in tear production in dogs; the STT I value fell to 5 mm/min in one dog and less than 10 mm/min in two dogs (Biricik et al., 2004). Intravenous medetomidine or medetomidine-butorphanol in dogs caused a significant

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decrease in tear production 15 min after sedation; readings returned close to the baseline within 15 min of reversal with atipamazole in most dogs (Sanchez et al., 2006). Alfaxalone reduced tear production at 10 and 20 mins, in contrast to propofol, which had no effect (Costa et al., 2015). Tear production was reduced in dogs receiving medetomidine, propofol, carprofen, and halothane (Komnenou et al., 2013), and morphine, alfaxalone, midazolam, and sevoflurane (Mayordomo-Febrer et al., 2017), but was unaffected by acepromazine maleate, morphine, and sevoflurane (Mouney et al., 2011). In a study comparing several sedative and opioid drugs, the combination of xylazine and butorphanol had the maximum effect on lowering tear production in normal dogs (Dodam et al., 1998). In contrast, sedation with xylazine did not affect tear production in the horse (Brightman et al., 1983). Sedation with acepromazine, xylazine, or ketamine reduced tear production in cats (Arnett et al., 1984; Ghaffari et al., 2010a). Anesthesia with medetomidine-ketamine in normal cats caused a significant decrease in tear production, but the STT I values returned nearly to preanesthetic values within 15 min after reversal with atipamezole, whereas the STT I values for the control group were still low at that point (Di Pietro et al., 2016).

As would be expected, tear levels can be affected by changes involving tear production and tear drainage. Removal of the TEL gland in the dog resulted in a 26% reduction in tear production within 3–7 months, but it almost recovered by 1 year (Saito et al., 2001). New Zealand rabbits developed clinical signs of dry eye without a reduction in STT values following removal of the nictitating membrane, the Harderian gland, and the main lacrimal gland (Bhattacharya et al., 2015). The placement of upper and/or lower punctal plugs has limited effect on STT values in normal dogs, but has been shown to increase STT readings significantly in patients with KCS (Gelatt et al., 2006; Williams, 2002).

Tear production is significantly lower in dogs with endocrine disease (diabetes mellitus, hypothyroidism, hyperadrenocorticism; Cullen et al., 2005a; Gemensky-Metzler et al., 2015; Williams et al., 2007). Surgical procedures that have been associated with reduced tear production in dogs include placement of an intrascleral prosthesis for glaucoma (Blocker et al., 2007) and phacoemulsification (Gemensky-Metzler et al., 2015). STT values increased in cats experimentally infected with feline herpesvirus-1 (FHV-1), but the increase remained within the reference range and did not differ from the control group (Lim et al., 2009). In cats with conjunctivitis, there was poor correlation between STT and TBUT (Lim & Cullen, 2005). Dogs with unilateral ulcerative keratitis had increased STT values and reduced IOP values (Williams & Burg, 2017).

Tear production has been assessed in many nondomestic species using either the standard or modified STT, the PRT tear test, or, more recently, the EAPPT (Lange et al., 2012; Table 10.1.5). The highest reported tear production is in the addax antelope (28.8 ± 8.3 mm/min; Ofri et al., 2002a). By comparison, the lowest reported STT I value is in the guinea pig (0.36 ± 1.09 mm/min; Trost et al., 2007), although a negative value was reported in the marmoset (Lange et al., 2012). The first publication of a range of normal values for tear production in birds (42 species, 7 orders) was produced from Germany in 1998 (Korbel & Leitenstorfer, 1998). A standardized 5 mm wide strip was used in most birds, but the small palpebral fissure in some species necessitated the strips to be trimmed to 2 or 4 mm wide (modified STT). Schirmer values were less than 3 mm/min in the owl (Strigiformes), a species known to have no lacrimal gland. The authors also described an additional assessment test, Schirmer III, under gaseous anesthesia. A later study found the PRT tear test to be a practical method for measuring tear production in large Psittaciformes, although adaptations to the established technique were necessary to overcome anatomic differences between species (Holt et al., 2006). There was poor repeatability between tests, but geographic location appeared to significantly influence results. Tear production, before and after topical anesthesia, has also been determined by Schirmer and PRT tear tests in Hispaniolan Amazon Parrots (Storey et al., 2009). Both methods were found to be practical, in accordance with the earlier studies (Korbel & Leitenstorfer, 1998). Topical anesthesia significantly reduced the STT values (i.e., mean STT II value was lower than mean STT I value), as found in the original German study, but had no significant effect on the PRT tear test values (Korbel & Leitenstorfer, 1998).

The modified STT has been described in several studies, but is not standardized. The PRT test and the EAPPT are more appropriate in species with very low tear production and/or small eyes, and this is reflected in the increasing number of studies (see Table 10.1.5).

Other Tear Tests

The Schirmer and PRT tear tests are relatively invasive and modify the very parameter they are designed to measure. Noninvasive or minimally invasive tests aim to overcome this problem and provide more reproducible and objective data. They have been developed extensively in humans and are beginning to be adopted in veterinary ophthalmology (Yokoi & Komuro, 2004; Yokoi et al., 2005). Techniques include meniscometry (indirect assessment of tear volume by measurement of the tear meniscus radius), interferometry (assessment of tear film thickness and analysis of the lipid layer), and meibometry (quantification of the amount of meibomian lipid on the lid margin; Dogru et al., 2006; Hosaka et al., 2011; Ibrahim et al., 2011; Yokoi et al., 2005).

The first study on meibometry performed in healthy dogs was reported in 2007 (Ofri et al., 2007). The study established

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that the technique could be readily performed in conscious dogs and provided baseline values for reference. The mean meibomian level in 84 eyes was 179 ± 60 MU (meibometer units). The results were not affected by age, gender, or laterality (Ofri et al., 2007). A subsequent study evaluated the precision of the Meibometer MB550 (Courage-Khazaka Electronic, Cologne, Germany) in 20 eyes of healthy dogs (Benz et al., 2008). The mean meibomian lipid level was 211 ± 48 MU and 205 ± 41 MU in the right and left eyes, respectively. In accordance with the first study, the results were not affected by gender or laterality. However, there was a broad distribution in values; there was a significant difference between the two examiners and between the set of measurements performed in the first 5 days compared with those in the following 5 days (Benz et al., 2008). The first meibometry study in healthy cats was reported in 2015 (Sebbag et al., 2015). The median meibomian level was 32 MU. Direct visual examination of meibomian gland structure by noncontact infrared meibography has been described in dogs and cats (Endo et al., 2012).

Tear film osmolarity has been assessed in cats (Davis & Townsend, 2011; Sebbag et al., 2015) and dogs (Sebbag et al., 2017) using the Tear Lab™ Osmolarity System (TearLab Corporation, San Diego, CA, USA). In general, the system was easy to use and well tolerated, but required multiple readings to be informative. The median tear osmolarity of normal cats was similar in both studies: 322 mOsm/L (Sebbag et al., 2015) and 328.5 mOsm/L (Davis & Townsend, 2011) and was not significantly different from cats with conjunctivitis (Davis & Townsend, 2011). The mean tear osmolarity in normal dogs was 337.4 mOsm/L and was lower at 306.2 mOsm/L in dogs with untreated KCS (Sebbag et al., 2017). Tear film *osmolality* was performed in horses and the mean value was 283.51 (9.33) mmol/kg (Best et al., 2015).

Strip meniscometry (SM) was performed in normal adult dogs, cats, and rabbits to establish normal values and to compare the results with STT I (Rajaei et al., 2017). Mean SM values for dogs, cats, and rabbits were 9.66 ± 2.15 mm/5 s, 10.50 ± 0.7 mm/5 s, and 4.72 ± 1.20 mm/5 s, respectively. There was correlation between SM and STT I values in the dog only. Interferometry in pinnipeds revealed the absence of a lipid layer in the outer tear film (Kelleher Davis et al., 2013), consistent with living in an aquatic environment.

The tear ferning test (TFT) has been described in dogs (Oriá et al., 2018) and horses (Silva et al., 2017). The TFT provides important information about the gross biochemical composition of the tear film. It is a simple and low-cost diagnostic test that complements evaluation of the ocular surface in conjunction with standard tests such as STT. In brief, a tear sample is obtained, for example from an STT paper strip, and dried onto a microscope slide. The ferning pattern is observed under a polarized light microscope and classified according to the Rolando and Masmali grading scales, which divide the pattern into normal and abnormal.

Examination after Topical Anesthetic Application

At this stage in the examination, it may be necessary to examine the posterior (bulbar) surface of the TEL. Indications include suspected foreign body and examination of the lymphoid follicles. Topical anesthetic (e.g., proparacaine) is instilled prior to protraction of the TEL with atraumatic forceps (e.g., von Graefe forceps, Sklar Surgical Instruments, West Chester, PA, USA; Bennett cilia forceps, John Weiss, Milton Keynes, UK; Miltex, Plainsboro, NJ, USA; Fig. 10.1.42). To minimize the risk of iatrogenic trauma to the TEL, the animal's head must be adequately restrained and the forceps should grasp the TEL away from its free edge and overlying the TEL T-shaped cartilage.

Laboratory Sampling

The eye and adnexa are unusual in that they allow a detailed and direct visual examination, more so than any other body structure other than the skin. Laboratory tests are therefore often unnecessary. If they are required, the clinician must be well informed with regard to the appropriate laboratory test for the suspected disease process, the correct method of sample collection and handling, and interpretation of the results. Close communication with the laboratory will facilitate and further define these aspects. For further detail, see Chapter 7, "Clinical Microbiology and Parasitology."

Corneoconjunctival Culture

Corneal and conjunctival culture can aid in the diagnosis and determination of appropriate antimicrobial therapy in many ocular diseases. Sampling is quick and straightforward and is tolerated without topical anesthesia in most compliant animals. However, if the eye is very painful, sedation and regional nerve blocks may be necessary, and this applies in particular to the horse.

To obtain a sample, the eyelids are gently retracted and the sampling tool is applied to the area of interest. A sample for culture can be collected by either a swab or a scraping. Swabs are available in different materials (e.g., cotton, Dacron, rayon), but of most importance is the selection of a swab that is designated for either microbiology or virology, as required; any swab type can be used for polymerase chain reaction (PCR). Standard and minitip swabs are available and the latter is helpful for small eyes or delicate areas, for example deep corneal ulcer (Fig. 10.1.43A). The swab can be premoistened with sterile saline to improve the yield of viable organisms, and to make the procedure more comfortable. A scraping can be made using either a sterile surgical blade or a Kimura spatula (Storz, St. Louis, MO, USA), a specific instrument for the procedure. The choice of sampling tool depends on the area of interest and examiner preference.

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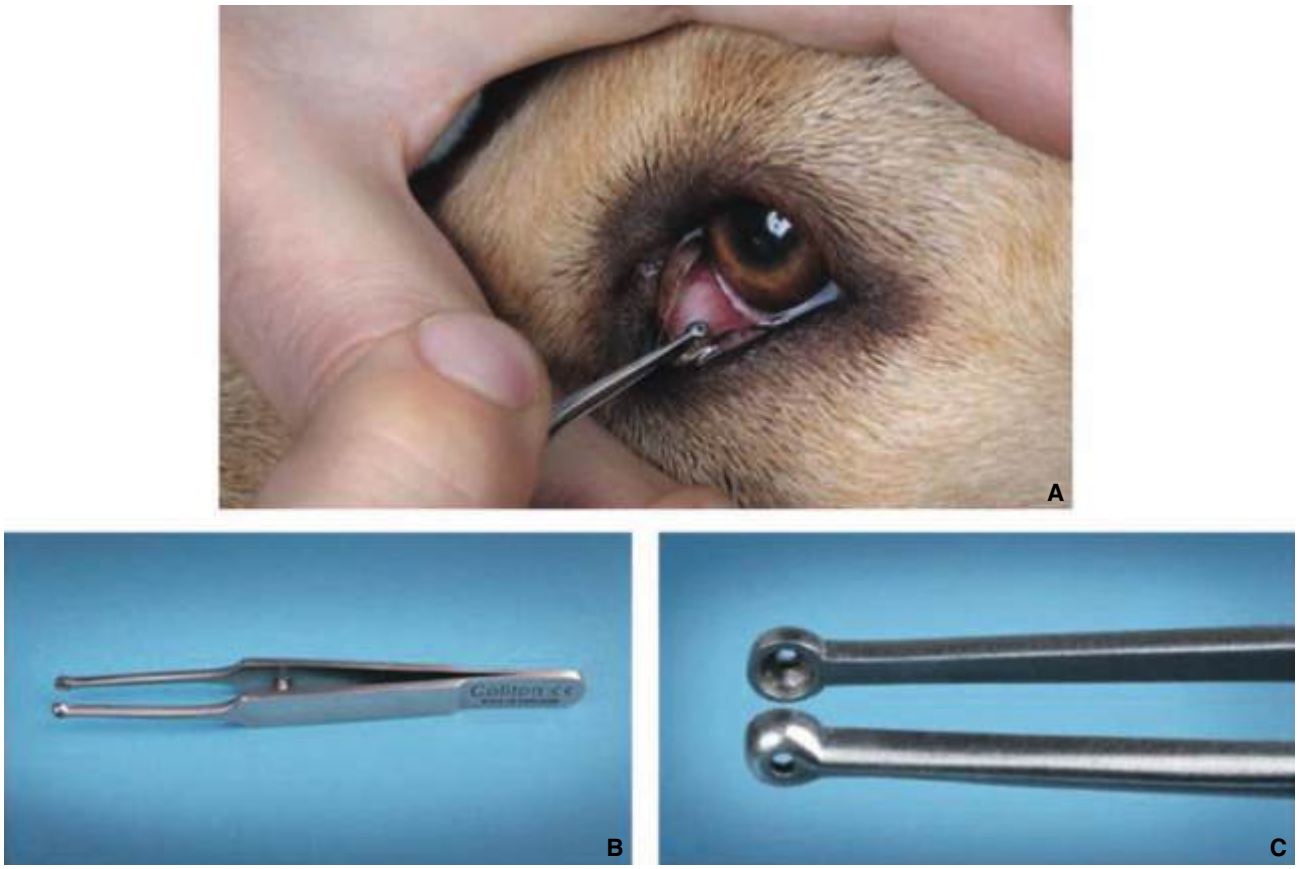


Figure 10.1.42 **A**. Examination of the posterior (bulbar) surface of the third eyelid is performed following topical anesthesia and with the aid of atraumatic forceps, for example Bennett's cilia forceps. **B**. Bennett's cilia forceps. **C**. Atraumatic, smooth, cupped tips of Bennett's cilia forceps.

To obtain a corneal sample using a swab, the swab is gently rubbed or rolled over the lesion; for a conjunctival sample, the swab is rolled in the lower conjunctival sac anterior to the TEL (facilitated by retropulsion to protrude the TEL; Fig. 10.1.43B). To obtain corneal material by scraping, the blunt end of a sterile surgical blade or a Kimura spatula is used in a scraping motion, ideally in one direction to create a "pile of cells." The material is then transferred onto a sterile swab tip. Conjunctival scrapings can be performed in the same way, but are less commonly done because conjunctiva is freely movable. Care should be taken not to contaminate the sample by inadvertently touching the eyelid margins, hair, skin, and other nearby structures.

Specimens for culture should be taken as early as possible in the examination, and ideally before the administration of topical agents. This is because many topical ophthalmic preparations contain preservatives that may impair culture results, and some topical agents (e.g., proparacaine, tetracaine, ophthalmic dyes) have themselves been shown to inhibit organism growth (Kleinfeld & Ellis, 1966, 1967; Storey et al., 2002). In contrast to fluorescein, which can support bacterial growth and virus viability, Rose Bengal and lissamine green are both bacteriocidal and virucidal (Cello & Lasmanis, 1958; Seitzman et al., 2006; Storey et al., 2002). In humans, Rose Bengal and lissamine green have been shown to inhibit the detection of herpes simplex virus by PCR (Stroop et al., 2000). The effect of commonly used topical agents in cats with ocular surface disease on PCR assays for *Chlamydophila felis* and FHV-1 was assessed *in vitro* (Segarra et al., 2011). Proxymetacaine (proparacaine) and fluorescein did not interfere with the PCR assay; fusidic acid (a commonly used topical antibiotic in small animals in Europe) caused a small inhibitory effect of doubtful clinical significance (Segarra et al., 2011). In the clinical setting, it is considered acceptable to apply a topical anesthetic agent prior to sampling painful eyes and in uncooperative animals. This view is supported further by one study, which specifically demonstrated that a single application of a topical anesthetic drug is unlikely to inhibit culture results (Champagne & Pickett, 1995). Sampling should, however, be performed prior to the application of ophthalmic dyes.

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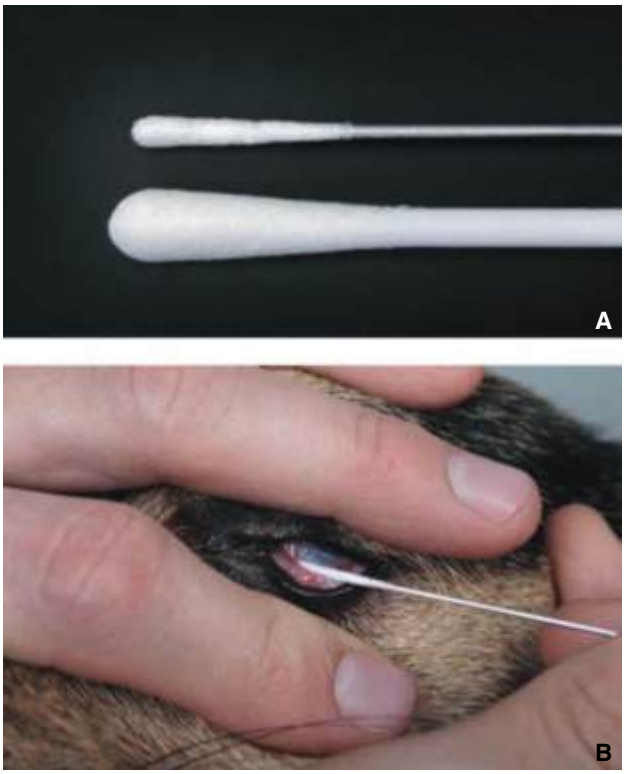


Figure 10.1.43 **A**. Standard and minitip swabs. Minitip swabs are useful for taking samples from small eyes and delicate areas, for example deep corneal ulcer. **B**. To obtain a conjunctival sample, for either microbiology or cytology, the swab is gently rolled in the lower conjunctival sac anterior to the third eyelid (TEL). This is facilitated by retropulsion to protrude the TEL. Care must be taken to ensure that the swab touches only the area of interest to avoid contamination from nearby structures, for example eyelids.

Bacteriology samples should ideally be collected before antibiotic therapy is started, but organisms that persist with concurrent antibiotic therapy are relevant. In general terms, samples taken from the ocular surface should be submitted for aerobic culture, whereas those from deeper tissues, such as the orbit, should be submitted for both aerobic and anaerobic culture. Anaerobic bacteria do however occur on the ocular surface; in a study of 330 domestic animals (dog, cat, horse, alpaca) with ulcerative keratitis, anaerobic bacteria were isolated from 13.0% of corneal samples and the majority of infections were mixed (aerobic and anaerobic), unless antimicrobial therapy had been administered prior to presentation (Ledbetter & Scarlett, 2008).

Bacteria, chlamydiae, mycoplasma, fungi, and viruses have different culture requirements in terms of transport medium, storage, and transport conditions (Table 10.1.6). Two general but important guidelines are that the designated laboratory should be contacted in advance for advice and to obtain the appropriate required materials; and the delay between sampling, shipping, and arrival at the laboratory should always be minimized. Swabs for microbiology (bacteriology or fungal culture) can be placed in a dry sterile tube or into gel or charcoal medium; refrigeration until shipping is beneficial but not essential (Allen, 2011). Virus isolation is especially dependent on optimal collection and transport conditions. A swab dedicated for virology (i.e., not a plain swab or a microbiology swab) should be used and placed into virus transport medium (a buffered medium containing antibiotic to prevent bacterial overgrowth). Shipping on ice or with a freezer pack is ideal, but is not essential; freezing should be avoided because the freeze–thaw process may damage the virus (Erles, 2011).

One disadvantage of corneoconjunctival culture is the inherent unavoidable delay in results. In clinical ophthalmology, immediate therapy is required in eyes with serious and/or rapidly progressive ocular surface disease, for example keratomalacia (melting ulcer) or suspected mycotic keratitis. Corneoconjunctival cytology should be considered, as it may provide immediate information about the causative organism(s). Culture is nevertheless more sensitive than cytology and is often essential to successful case management. For example, in 10 equine eyes with keratomycosis, fungal infection was diagnosed by cytology in 4 out of 9 eyes and by culture in 8 out of 10 eyes (Galan et al., 2009).

Corneoconjunctival Cytology

Corneoconjunctival cytology is a quick and simple method to characterize, and in some cases diagnose, the disease process involving the ocular surface. It can be used either alone or in combination with culture to provide rapid results that may influence the immediate course of therapy (Bourges-Abella et al., 2007; Gerding et al., 1988; Jegou & Liotet, 1993; Lavach et al., 1977; Murphy, 1988; Willis et al., 1997). Although less sensitive than culture, exfoliative cytology is a very rewarding tool in clinical ophthalmology. It can identify organisms (e.g., bacteria, fungal hyphae, yeast bodies) and provide information in terms of morphology (e.g., rods/cocci), staining characteristics (Gram-positive or -negative), number, and location (intracellular/extracellular). Excessive surface debris and mucus should be removed before cytology, and samples for culture should be taken first, because cytologic techniques could alter the population of microorganisms present.

The ideal sample provides a monolayer of an adequate number of cells with unaltered structure. Additionally, sample collection should produce minimal irritation to the animal. Instruments for collecting cytologic samples include those used for culture: swab (standard or minitip) and the blunt end of a sterile surgical blade, as well as specialized tools (e.g., cytobrush, Kimura spatula; Fig. 10.1.44). Topical anesthetic, microscope slides, stain(s), and a microscope are also required.

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Table 10.1.6 Recommendations for laboratory sampling.

Test	Sampling Tool	Transport Medium	Shipping Conditions
Bacteriology	Designated microbiology swab	Gel or charcoal medium	Refrigerate until shipping, normal post
Fungal culture	Designated microbiology swab	Gel or charcoal medium	Refrigerate until shipping, normal post
Virus isolation	Designated virology swab	Virus transport medium	Refrigerate until shipping, normal post
Polymerase chain reaction	Swab (any swab type)	Dry tube	Normal post
	Scraping	Freeze in sterile saline or transfer material to swab tip (as above)	Ship on ice or normal post
	Tissue biopsy	Dry tube or in sterile saline or in moist gauze swab	Normal post
Cytology	Swab (any swab type)	Roll gently onto microscope slide	Normal post
	Scraping (spatula/ scalpel blade)	Transfer to microscope slide	Normal post
	Cytobrush	Roll gently onto microscope slide	Normal post
	Impression smear	Transfer to microscope slide	Normal post
Histopathology	Forceps/scissors	10% formalin	Normal post

The swab is the least traumatic method to the eye for sample collection (Bauer et al., 1996). This technique is recommended when excessive manipulation is contraindicated, for example deep corneal ulcer and keratomalacia. Swabs preserve cellular integrity, but the number of cells collected is often too low to make a diagnosis. Samples should be gently rolled (not rubbed) onto glass slides to minimize cell damage (Villiers & Dunn, 1998). Swabs are more commonly used for the collection of samples for microbiology than for cytology.

The Kimura spatula provides a more precise method of collecting cells from specific areas, and greater numbers of deeper cells are usually obtained. This technique remains the standard in diagnostic veterinary ophthalmology. However, this method may lead to greater damage to both the sample (overlapping cells and crushing artifact) and the eye (Bauer et al., 1996; Willis et al., 1997). The blunt end of a scalpel blade functions similarly to a spatula, but with a slightly greater risk of trauma to the eye.

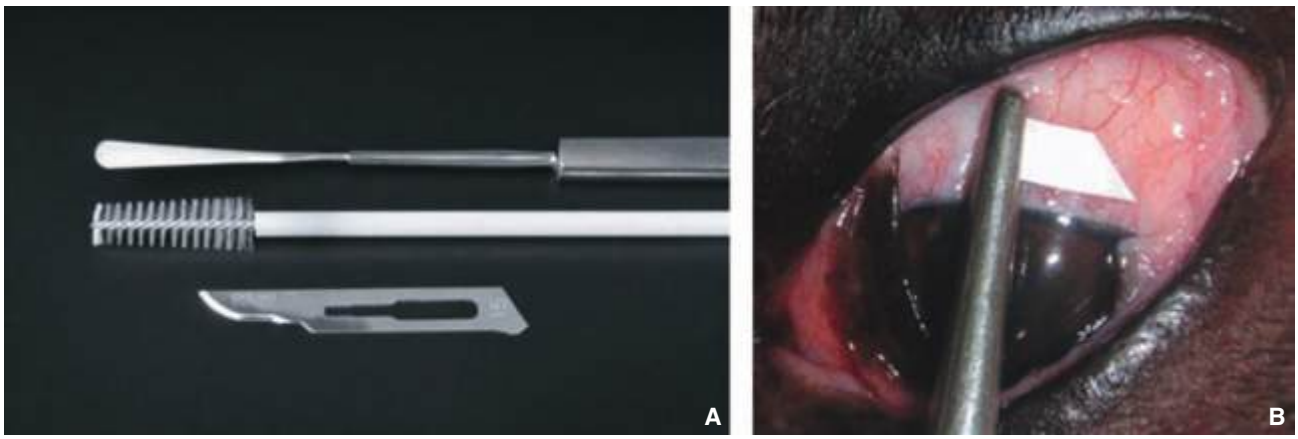


Figure 10.1.44 **A**. Instruments for corneoconjunctival cytology include Kimura spatula (top), cytobrush (middle), and scalpel blade (bottom). **B**. Impression cytology of the dorsal bulbar conjunctiva using a strip of Millipore paper. (Courtesy of J.L. Laus and A.A. Bolzan.)

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The cytobrush has proved to be superior for all cytologic parameters studied when compared to cotton-tipped swabs and two different spatulas in dogs, cats, sheep, goats, cattle, and horses (see Fig. 10.1.44B; Bauer et al., 1996; Bourges-Abella et al., 2007; Willis et al., 1997). The advantages of this technique include an increase in sample cellularity, acquisition of cells from deeper layers with less intervention, and improved morphologic appearance of each cell because of reduced cell overlap (i.e., a good monolayer; Willis et al., 1997). The nylon-bristled brush is an 8 cm long plastic instrument with a tapered tip containing a nest of nonabsorbent, soft nylon bristles (3–4 mm long) at one end. The large size of the cytobrush is a disadvantage in small animals, but not in the large equine eye, where it successfully diagnosed *Histoplasma* spp. in a case of equine keratitis (Richter et al., 2003).

Topical anesthetic is required in all techniques except perhaps for a swab. Care must be taken with all samples during collection and transfer to the slides to minimize cell damage and to create a monolayer. The examiner should roll rather than rub the swab, roll rather than spin the cytobrush, and use a needle to tease material off a blade/spatula, or use the blade like a paintbrush to form a smear (Bauer et al., 1996; Villiers & Dunn, 1998).

Impression cytology relies on cells that exfoliate easily and is therefore most readily applied to the investigation of superficial conjunctival disease. It can be performed with a clean glass slide, cellulose acetate strip, Biopore membrane device (EMD Millipore Corporation, Billerica, MA, USA), or asymmetric strips of Millipore paper (Millipore HAWP04700, Millipore, São Paulo, Brazil; see Fig. 10.1.44C; Bolzan et al., 2005; McKelvie, 2003). Impression cytology provides a good number of cells, but cell clumping is common. Eördögh et al. (2015) studied different methods for conjunctival impression cytology in the cat. Biopore membrane (0.4 µm) held within the intended device, applied to the dorsal bulbar conjunctiva following topical anesthetic drops and drying, yielded the best samples in terms of cellularity and quality, and also caused the least discomfort. Impression cytology was shown to cause significantly less irritation than cytobrush sampling in horses with and without ocular surface disease (Braus et al., 2017).

The material on the slide needs to be fixed immediately to prevent cellular degeneration. A simple practical method for rapid fixing is to apply heat from a hairdryer to the underside of the slide. A special cytologic fixative spray can also be applied immediately, while the sample is wet. Rapid staining kits (e.g., Diff-Quik, Polysciences, Warrington, PA, USA) have a fixative incorporated into the staining process (Villiers & Dunn, 1998). If possible, several slides with adequate sample material should be prepared to permit the use of different stains if needed. Commonly used stains include the Gram stain and various Romanowsky-type stains (e.g., Diff-Quik, modified Wright–Giemsa stain). The Romanowsky-type stains are excellent for nuclear and cytoplasmic detail and are generally adequate for the detection of bacteria, fungal hyphae, yeast bodies, inclusion bodies (viral, mycoplasmal, or chlamydial), and inflammatory and neoplastic cells (Fig. 10.1.45; Villiers & Dunn, 1998). The Gram stain provides further information about any identified bacteria. Fungal hyphae may be difficult to identify on routine staining, and more specialized stains for fungal elements include periodic acid-Schiff and Gomori's methenamine silver (see Fig. 10.1.45B; Forster et al., 1976).

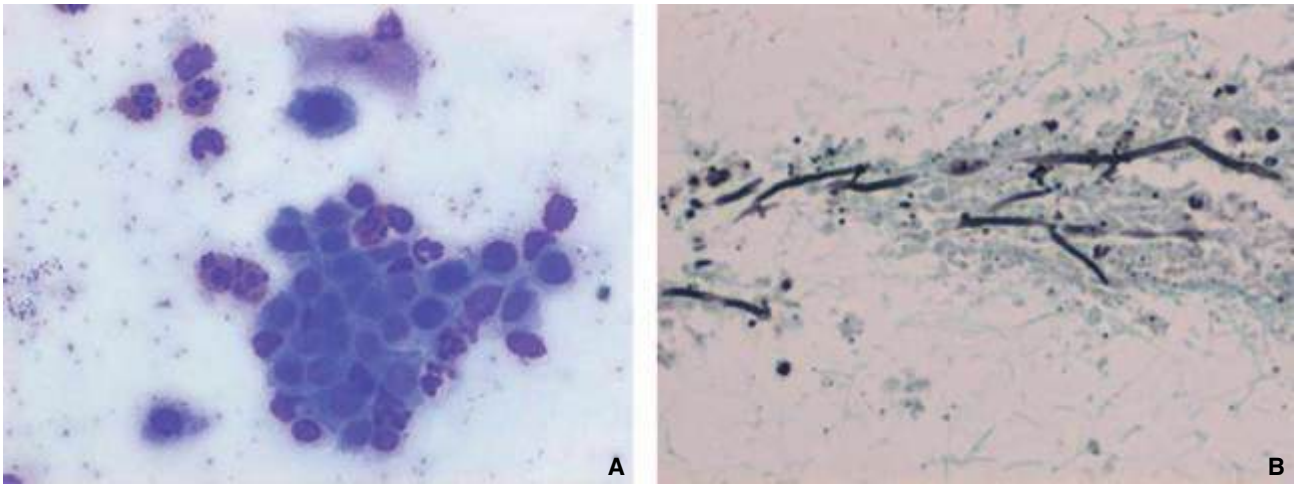


Figure 10.1.45 **A**. Corneal cytology from a cat reveals a moderate number of eosinophils interspersed with sheets of epithelial cells, indicative of eosinophilic keratitis (modified Wright–Giemsa stain, 400×). **B**. Fungal hyphae of *Aspergillus* sp. are highlighted black with Gomori's methenamine-silver stain (200×). (Courtesy of Emma Scurrell.)

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The types of cells commonly encountered from a healthy conjunctiva are sheets of squamous and columnar epithelial cells and goblet cells. Occasional bacteria may be present, and lymphocytes, polymorphonuclear cells, monocytes, and plasma cells are rarely seen; mast cells and eosinophils are absent (Gerding et al., 1988; Giuliano & Moore, 2002; Lavach et al., 1977; Murphy, 1988; Prasse & Winston, 1999; Raskin, 2001). The types of cells commonly encountered in a healthy cornea are nonkeratinized epithelial cells (squamous and intermediate), lymphocytes, and polymorphonuclear cells. Nuclei, keratin debris, mucus, and bacteria are also observed; mast cells and eosinophils are absent. In bacterial keratitis, polymorphonuclear cells are the predominant cells and bacteria are present (Gerding et al., 1988; Giuliano & Moore, 2002; Murphy, 1988; Prasse & Winston, 1999; Raskin, 2001).

Additional Tests

Additional tests that can be performed on corneal and conjunctival samples include PCR and immunofluorescent antibody (IFA) tests for *C. felis*, FHV-1, equine herpesvirus (EHV-1, EHV-2, EHV-4), and fungal DNA (Vengayil et al., 2009). In PCR testing (the detection of organism DNA or RNA), nucleic acid can be affected by heat, ultraviolet light, and enzymes from damaged tissue. Any type of swab can be used for sample collection, unlike for microbiology (designated microbiology swab). The swab tip should be placed in a dry, plain tube without any sort of medium. Alternatively, the swab can be frozen and shipped on dry ice, but this is not essential and is rarely performed for clinical work (Erles, 2011). Samples for IFA testing should be collected before staining with fluorescein to prevent false-positive results (da Silva Curiel et al., 1991).

For PCR, a highly cellular sample is most likely to yield positive results. In other words, a positive result is more likely to be obtained from, in decreasing order, a biopsy sample, a scraping, and lastly a swab. In support of this, corneal tissue was found to be more helpful than a corneal swab for the detection of FHV-1 DNA in cats with sequestra (Volopich et al., 2005). However, conjunctival swabs were significantly better at obtaining viral DNA samples than conjunctival biopsy in horses with keratoconjunctivitis (Hollingsworth et al., 2015). A swab for PCR is nonetheless often submitted from clinical cases (e.g., *C. felis*, FHV-1) because sample collection is very quick and simple.

The benefit of performing more than one sampling technique has been demonstrated in the cat and horse (Massa et al., 1999; Volopich et al., 2005; Zeiss et al., 2013). In 48 horses with ulcerative keratitis, infection was identified in 35 eyes using cytology, culture, or both, as opposed to 26 and 29 eyes by cytology or culture alone, respectively (Massa et al., 1999). In the horse, a comparison of conjunctival cytology (cytobrush technique) and conjunctival histopathology provided information that was considered similar to that in the dog (Bourges-Abella et al., 2007). In equine ulcerative keratitis, nested PCR identified a greater spectrum of agents than either culture or quantitative PCR (Zeiss et al., 2013).

Conjunctival Histology

Conjunctival biopsy can be readily performed on most animals without sedation. The area of conjunctiva to be sampled is anesthetized by the application of one or two drops of local anesthetic, for example proparacaine/proxymetacaine. Given the highly vascular nature of the conjunctiva, a more sustained application of topical anesthetic agent may be helpful. This is achieved by soaking a cotton-tipped applicator or swab in the local anesthetic agent and applying it to the area of interest for 20–30 s. While an assistant restrains the animal's head and everts the eyelid, a small piece of conjunctiva is delicately elevated using fine-toothed forceps, for example Bishop-Harmon forceps. A small snip biopsy is harvested by cutting across the base of the tented conjunctiva using small tenotomy scissors. Hemorrhage is minimal and can usually be controlled with gentle digital pressure; no sutures are required. Multiple samples, typically two to three, can be obtained from the same eye. Conjunctival tissue is usually submitted for histopathology, but can also be submitted for PCR testing. The sample should be placed in 10% formalin for routine histopathology. Given the small size of the samples attained, it is helpful to place them within a net inside a small cassette, which is then placed into the formalin container. For PCR, the sample can be submitted in a dry sterile tube, in sterile saline, or wrapped in gauze moistened with sterile saline.

Although it is relatively straightforward to obtain a conjunctival biopsy, conjunctival histopathology may be unrewarding in cases of chronic conjunctivitis; it is not uncommon for the histopathologist to report nonspecific lymphoplasmacytic inflammation of unknown etiology. Conjunctival histopathology can, however, be very helpful to detect neoplasia (e.g., lymphoma, mast cell; Fife et al., 2011), proliferative conjunctivitis (Allgoewer et al., 2001), infectious organisms (e.g., leishmaniasis; Peña et al., 2008), onchocerciasis (Schmidt et al., 1982), and to aid in the diagnosis of qualitative tear film disorders (Cullen et al., 1999; Grahn et al., 2005; Moore, 1990). For the latter, the quantification of conjunctival goblet and epithelial cells determines the goblet cell index (ratio of goblet cells to epithelial cells) and provides information on mucin deficiencies and ocular surface conditions (Cullen et al., 1999; Evans et al., 2012; Grahn et al., 2005; Lim et al., 2009; Moore, 1990; Sebbag et al., 2016; Thomasy et al., 2011). The goblet cell index was assessed in cats with and without sequestra and no

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significant difference was found (Grahn et al., 2005). A more recent study evaluated goblet cell density (GCD) and distribution in cats without clinical evidence of ocular surface disease and without histologic evidence of conjunctival disease. The mean GCD ranged widely by region: 48.8% from the anterior surface of the TEL, 47.0% from the fornices, 38.5% from the palpebral regions, 19.6% from the bulbar regions, and 12.6% from the posterior surface of the TEL. The anterior surface of the TEL is the recommended site for sampling because of the high GCD and its accessibility. In a study on tear ferning patterns in the horse, the mean goblet cell values were 50 ± 11.4 cells/field (Silva et al., 2017).

EXTERNAL OPHTHALMIC DYES

External ophthalmic dyes are routinely used in veterinary medicine to aid in the diagnosis of corneal, conjunctival, lacrimal, and nasolacrimal diseases. The most commonly used dye is fluorescein, but Rose Bengal and trypan blue are also used by veterinary ophthalmologists (Brooks et al., 2000a; Feenstra & Tseng, 1992; Gelatt, 1972; Herring, 2007; Laroche & Campbell, 1988; Slatter, 1973). Other ophthalmic stains include lissamine green, Alcian blue, and methylene blue (Kim, 2000; Slatter, 1973).

Fluorescein Dye

The most common use for topical sodium fluorescein is in the detection of corneal ulceration (Fig. 10.1.46, Fig. 10.1.47, and Fig. 10.1.48). It is also used to detect conjunctival epithelial defects, aqueous humor leakage (Seidel test), qualitative tear film abnormalities (TBUT), and to assess tear film dynamics and the physiologic flow of the nasolacrimal system (Jones test). The dilution of tear fluorescein was assessed in normal dogs to evaluate the effect of lacrimal punctal plugs (Gelatt et al., 2006). Tear film dynamics was assessed in normal horses (Chen & Ward, 2010). Less common but important uses include some methods of applanation tonometry, fluorophotometry (e.g., determination of aqueous humor flow rate), angiography, tear film studies, and pharmacology studies (e.g., topical ophthalmic drug delivery device in the horse; Alario et al., 2013a, 2013b; Allbaugh et al., 2011; Bellhorn et al., 2017; Chen & Ward, 2010; Crumley et al., 2012; Gelatt et al., 2006; Jones & Ward, 2012; LoPinto et al., 2017; Miller et al., 2012; Myrna & Herring, 2006; Pirie & Alario, 2015; Pirie et al., 2012; Ward et al., 2001).

Sodium fluorescein is a water-soluble weak dibasic acid of the xanthene group that is detectable in solution at concentrations as low as 1 ppm. Its absorption spectrum peaks at 490 nm (i.e., blue light). Sodium fluorescein converts almost 100% of absorbed light to emitted fluorescent light with a peak wavelength of 520 nm (i.e., green light). Fluorescence is most intense at alkaline pH (e.g., saline solution or the tear film); at acid pH, sodium fluorescein appears yellow or orange. Fluorescein is available as a 2.0% alkaline solution or as an impregnated paper strip (Kimura, 1951). Only disposable sources (e.g., impregnated paper strips, single-dose vials) should be used for topical application, because multidose solutions have been associated with bacterial contamination (Cello & Lasmanis, 1958). Common preservatives



Figure 10.1.46 Ophthalmic stains. **A**. Fluorescein dye is available as a sterile impregnated paper strip and can be made into a solution by mixing with sterile water, saline, or eyewash. **B**. Fluorescein dye stains the exposed hydrophilic corneal stroma in a large superficial ulcer in a cat.



Figure 10.1.47 Application of fluorescein dye. The fluorescein-impregnated strip is moistened with, for example, sterile saline or eyewash, and then gently touched once to the dorsal bulbar conjunctiva, with the upper lid retracted. The eyelids are then closed or the animal allowed to blink to distribute the fluorescein across the ocular surface.

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such as benzalkonium chloride and chlorobutanol are inactivated by fluorescein, and ocular infection caused by *Pseudomonas aeruginosa* has been reported in the dog (Cello & Lasmanis, 1958). Viruses can also survive in fluorescein solution: feline calicivirus (a nonenveloped virus) remained viable in a multidose bottle of fluorescein for up to 7 days (Storey et al., 2002). In the same study, two enveloped viruses, EHV-4 and FHV-1, were not detected at 1 hour. In small animals, the strip should be moistened with sterile normal saline or eyewash and gently touched once to the dorsal bulbar conjunctiva (see Fig. 10.1.47). Alternatively, one drop of fluorescein solution can be applied to each eye. In large animals, for example horses, the easiest method of application is to squirt fluorescein solution directly from a 3 mL syringe through the hub of a 25-gauge needle *that has been manually broken off*. Care must be taken to ensure that the needle hub is firmly attached to the syringe. To create the solution of fluorescein, a strip can be placed in the empty syringe prior to drawing up the irrigating solution (Gilger & Stoppini, 2011). After application, regardless of the method used, the eyelids should be closed or the animal allowed to blink to distribute the fluorescein across the ocular surface. The eye is then irrigated (if tolerated) with additional saline or eyewash to remove excess dye from the ocular surface. This important step reduces the potential to make a false-positive diagnosis of a corneal ulcer (see Fig. 10.1.48).

Fluorescein is highly lipophobic and hydrophilic. Thus, when applied to the surface of the eye, it does not remain in contact with the lipid-containing cell membranes of the epithelium (conjunctival and corneal), but adheres to, and is absorbed by, any exposed stroma. It also stains intercellular spaces because of exposed hydrophilic substance, and therefore assists in the detection of corneal erosions (which by definition do not penetrate the basement membrane of the epithelium). Fluorescein does not stain Descemet's membrane (see Fig. 10.1.48B). Interpretation is usually straightforward, but false-positive results can occur. Direct contact between the paper strip and the cornea may leave a mark that resembles a corneal defect, especially if viewed with slit-lamp biomicroscopy; topical anesthetic agents are epitheliotoxic and sometimes create subtle fluorescein-positive staining in a punctate pattern; fluorescein solution can "pool" in surface irregularities, for example epithelial facet (a stromal ulcer that has re-epithelialized). The use of magnification and/or an ultraviolet or blue light, usually available on a direct ophthalmoscope or a slit-lamp biomicroscope, improves visualization of the dye, but is not usually necessary.

Fluorescein may also be used to detect the leakage of aqueous humor through the cornea (Seidel test). To perform the Seidel test, fluorescein is applied to the cornea without subsequent flushing. The resulting high concentration of dye causes it to fluoresce at wavelengths closer to the yellow and orange spectra. If the corneal integrity is compromised, aqueous humor leakage locally dilutes the fluorescein as it exits the corneal defect, and makes the dye appear green. A positive Seidel test is most easily observed with some form of magnification, for example a slit-lamp biomicroscope. While the aforementioned description is theoretically correct, a more practical description is: a positive Seidel test typically appears as a dark area, representing an exiting wave of aqueous humor, which rapidly increases in size and flows downward over the cornea as the leak continues, pushing the fluorescein solution away as an advancing green band (Fig. 10.1.49).

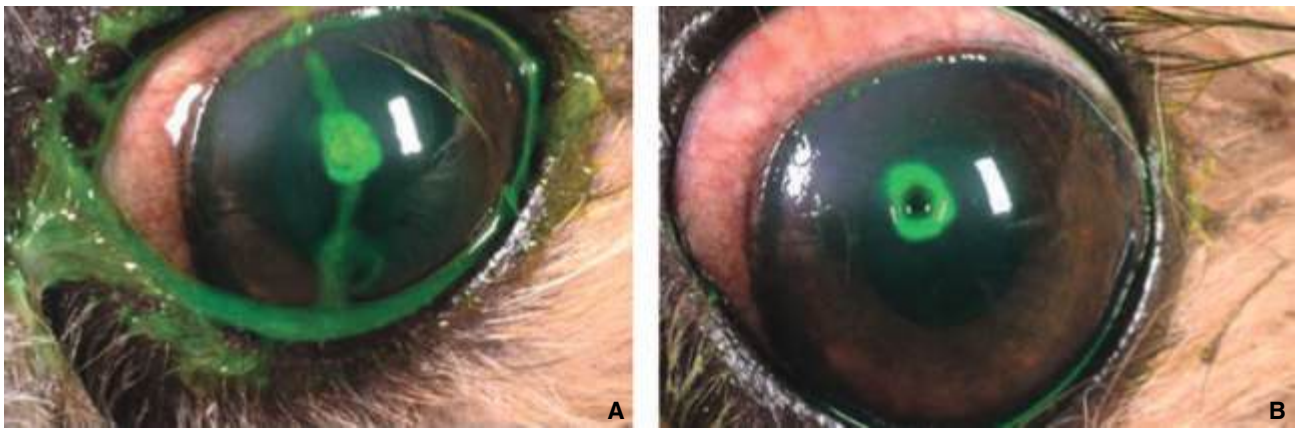


Figure 10.1.48 It is important to irrigate excess fluorescein dye from the ocular surface to reduce the risk of making a false-positive diagnosis. **A**. The entire surface of the focal, well-demarcated lesion in the paraxial cornea appears to stain with fluorescein dye; the lesion would be interpreted as a stromal ulcer. Fluorescein dye also adheres to a strand of mucus and a hair on the cornea and the dorsal limbus; it forms a prominent tear meniscus, which has spread onto periocular hair. **B**. The same eye is depicted immediately after irrigation of the ocular surface. The corneal lesion is accurately interpreted as a descemetocele because its base does not stain with fluorescein dye.

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Figure 10.1.49 Positive Seidel test depicts a leaking corneal wound at 12 o'clock.

Fluorescein is used to evaluate the stability of the tear film by measurement of the TBUT. The TBUT indirectly evaluates the mucin and/or lipid layers of the tear film by measuring the time it takes for fluorescein dye, and hence the tear film, to dissociate from the corneal surface (Cullen et al., 2005b; Moore, 1990). It is a provocative test insofar as fluorescein shortens the normal TBUT. To perform this test, fluorescein solution is applied to the eye, the animal is allowed to blink, and the eyelids are then held open until the tear film begins to dissociate from the corneal surface. Dissociation results in the formation of a dry spot, which appears as a dark round area within the fluorescent tear film. Observation is facilitated by slit-lamp biomicroscopy using a cobalt blue filter. In the dog, the mean TBUT ranges from 19.7 ± 5 to 21.53 ± 7.42 seconds (Beagle; Moore, 1990; Saito & Kotani, 2001). Oral diphenhydramine decreased TBUT in healthy adult dogs, but the effect was not clinically significant (Evans et al., 2012).

Values for the mean TBUT in the cat are 16.7 (± 4.5) seconds in the juvenile cat (Cullen et al., 2005b), and vary from 12.4 seconds (Sebbag et al., 2015) to 21 (± 12) seconds in the adult cat (Grahn et al., 2005). TBUT is reduced (accelerated) in cats with conjunctivitis, ulcerative keratitis, and experimental infection with FHV-1 (Cullen et al., 1999; Davis & Townsend, 2011; Lim & Cullen, 2005; Lim et al., 2009). TBUT is also reduced in eyes with sequestra (14 ± 13 seconds), but the difference is not significant from that in normal eyes (Grahn et al., 2005). In the cats experimentally infected with FHV-1, TBUT provided a reasonable estimate of the GCD, but did not correlate with aqueous tear production (STT values) in cats with conjunctivitis (Lim et al., 2009). Two reports for TBUT values in the horse provide mean values from 8.3 ± 1.3 seconds to more than 13 seconds (Harling, 1988; Monclin et al., 2011). In the more recent of the two studies, TBUT was reduced by topical tetracaine hydrochloride (Monclin et al., 2011). In a rabbit model of dry eye, topical liposome-bound tetracycline was found to improve tear quantity and quality, respectively determined by STT and TBUT tests (Shafaa et al., 2011).

The fluorescein drainage test (Jones test) assesses the entire mechanism of tear drainage by determining both the anatomic and physiologic patency of the nasolacrimal system. It does so without altering the natural state of the nasolacrimal system, in contrast to nasolacrimal flushing (see later section). Fluorescein is applied to the eye as described previously, but without subsequent rinsing. The Jones test is the timing of the passage of fluorescein through the system to the ipsilateral nares (Jones, 1961). The test is performed on both sides and the times compared (Fig. 10.1.50). The reported values for normal passage times in different species are highly variable. In dogs and cats, the following values have been reported: 30–60 seconds in the dog; from 30 seconds to 5 minutes in dogs and from 15 seconds to 1 minute in cats; within 5 minutes in dogs and cats; and up to 5–10 minutes in clinically normal dogs (Maggs, 2008; Martin, 2005; Ollivier et al., 2007). In the horse, the normal passage time is less than 5 minutes, but may be up to 20 minutes (Gilger & Stoppini, 2011; Harling, 1988). Binder and Herring (2010) performed an objective evaluation of fluorescein nasolacrimal transit time in normal dogs and nonbrachycephalic cats using two methods for the Jones test (impregnated strip and 0.2% fluorescein solution). In dogs, the median transit time following dye transfer by a moistened fluorescein strip was 248 seconds (approximately 4 minutes) and 48 seconds by fluorescein solution; in cats, the times were 46 seconds and 7 seconds, respectively. Thus, in both dogs and cats, transit times were faster with fluorescein solution than with the fluorescein strip, and were also highly variable. In dogs, several variables had a significant effect on transit time, including cephalic conformation (skull shape), snout length, age, and reproductive status. The test was not considered to be clinically useful in brachycephalic dogs. Similarly, another study in cats showed that breeds with severe brachycephalia have reduced tear drainage, because the nasolacrimal duct is forced to follow a steep V-shaped course around the canine tooth, as determined by computed tomography (CT) and CT-dacryocystography (Schlueter et al., 2009). A positive result is definitive for a patent duct, but does not confirm that the system is anatomically normal. A negative result is only suggestive of a problem, because there are several reasons that can give a false-negative result. Practical variables include the amount of fluorescein applied and head position; a negative result will occur if the volume of dye applied is less than the volume capacity of the drainage system, particularly in the horse (Dziezyc, 1992; Latimer et al., 1984). In small animals, it is important to observe the dye as it emerges from the external nares before licking spreads the dye over both sides or removes visible traces completely. An early study found that approximately 40% of dogs have an additional communication between the duct and the ventral nasal meatus at the level of the canine tooth

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Figure 10.1.50 Jones test (fluorescein dye passage test) in a 1-year-old Labrador Retriever with a swelling ventral to the medial canthus of the right eye. **A**. Fluorescein dye flows onto the skin at the medial canthus of the right eye. **B**. An absence of fluorescein dye at the medial canthus of the left eye suggests that the dye has entered the nasolacrimal drainage apparatus. **C**. A positive Jones test result at the left nostril confirms nasolacrimal patency on that side. A negative result on the right side suggests that the ipsilateral nasolacrimal duct is blocked or partially blocked. (Reproduced with permission from Featherstone, H., & Holt, E. (2011) *Small Animal Ophthalmology: What's Your Diagnosis?* Chichester: Wiley-Blackwell, Fig. 4.1c, p. 63.) **D**. A positive Jones result at the right nostril in a horse.

root (Michel, 1955). Many authors state that brachycephalic dogs have anomalous tear drainage into the caudal nasal cavity and then into the nasopharynx (Grahn & Sandmeyer, 2007; Kern, 1986; Ollivier et al., 2007). The same situation is believed to be true in brachycephalic cats (Breit et al., 2003; Kern, 1986). In theory, this may be observed as dye in the oropharynx or on the tongue, but is not always practical (Binder & Herring, 2010). Jones testing was performed by subspectacular injection of fluorescein in a study of the lacrimal system in snakes (Souza et al., 2015).

Despite its inherent problems, the Jones test is a quick and simple diagnostic procedure and is the most common test for nasolacrimal patency. If the Jones test is negative and the clinical signs suggest a problem with tear drainage, further investigations are indicated, usually in the form of a nasolacrimal flush and imaging techniques (CT and dacryocystorhinography; see the section "Nasolacrimal Flush" and Chapter 10.2; Nykamp et al., 2004; Rached et al., 2011; Schlueter et al., 2009).

Rose Bengal

Rose Bengal is used in veterinary medicine to aid in the diagnosis of tear film disorders and superficial corneal epithelial abnormalities (Fig. 10.1.51; Gelatt, 1972). Rose Bengal is not a vital dye. It is toxic to normal healthy corneal epithelial cells in a dose-dependent manner, which includes routine concentrations (Feenstra & Tseng, 1992; Kim, 2000; Kim & Foulks, 1999). Negative stain uptake is a result of normal tear film components, such as mucin and albumin, protecting the epithelial cells from the dye; positive stain uptake therefore represents a tear film abnormality (Feenstra & Tseng, 1992; Kim, 2000). This is different from the previous belief that Rose Bengal simply stains dead and degenerating cells and mucus.

Rose Bengal (tetrachloro-tetra-iodo-fluorescein) is a dark pink dye. Like fluorescein, it is available as a solution and as an impregnated paper strip (Gelatt, 1972; Slatter, 1973). Use of the 0.5% or lower concentrations can reduce the irritancy associated with the 1.0% solution (Slatter, 1973). The

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Figure 10.1.51 **A**. Rose Bengal dye is available as a sterile impregnated paper strip and can be made into a dark pink solution by mixing with sterile water, saline, or eyewash. **B**. Rose Bengal dye stains superficial irregular linear corneal erosions in the dorsal cornea of a cat with feline herpesvirus-1 infection. Note the fluorescein dye within the tear meniscus, showing that fluorescein had been applied immediately prior to the Rose Bengal and had not highlighted the lesions.

dye is applied to the ocular surface in the same way as that described for fluorescein. It can be applied before or after fluorescein application, or even at the same time because the stain properties are unaffected by mixing (Korb et al., 2008; Slatter, 1973). In addition to its use in tear film assessment, Rose Bengal can demonstrate superficial corneal erosions or early ulcers that may not stain with fluorescein, for example punctate keratitis, herpetic keratitis, and early keratomycosis (Brooks et al., 2000a; Brooks et al., 2013; Ledbetter et al., 2009).

Other Ophthalmic Dyes

Lissamine green is an organic acid dye. It is used widely in human ophthalmology, but its use in veterinary ophthalmology is mostly limited to those countries in which Rose Bengal is not available (Gerriets et al., 2012; Kim, 2000; Norn, 1973; Oriá et al., 2018; Silva et al., 2017). It has been characterized as a true vital dye because it does not stain healthy cells, even in the absence of the tear film (unlike Rose Bengal; Chodosh et al., 1994). Despite this difference, lissamine green has a similar staining pattern to Rose Bengal and has been used in cases of KCS (Machado et al., 2009; Manning et al., 1995; Yoon et al., 2011). At concentrations of 0.5% and 1%, lissamine green is less toxic than Rose Bengal and is less irritant (Kim, 2000; Machado et al., 2009; Manning et al., 1995). As previously mentioned, different dyes can be applied alone, sequentially, or at the same time as mixing, and this does not affect staining properties (Korb et al., 2008; Slatter, 1973). In humans, fluorescein has traditionally been considered the premier dye for corneal staining and, similarly, Rose Bengal for conjunctival staining. However, in a study that assessed the efficacy of fluorescein, Rose Bengal, and lissamine green, the mixture of 2% fluorescein and 1% lissamine green was found to offer excellent simultaneous corneal and bulbar conjunctival staining and was well tolerated (Korb et al., 2008).

Trypan blue, an azo dye, has been used extensively in human cataract surgery over the last decade, and its utilization has been extended to other anterior segment surgeries including trabeculectomy and corneal transplantation (Jhanji et al., 2011; Norn, 1973). Trypan blue stains the anterior lens capsule and thus aids in its visualization during capsulorrhexis; it is used by many veterinary ophthalmologists for this purpose (Jacob et al., 2002; Pigatto et al., 2010a). Trypan blue is also used in research in both human and veterinary fields. Two recent studies have involved work on the equine cornea: an *in vitro* model for corneal scarring and a novel method of gene delivery (Buss et al., 2010a, 2010b).

Topical ophthalmic dyes can interfere with the detection of infectious agents by culture and PCR, and, more specifically, fluorescein can cause false-positive results in IFA testing (da Silva Curiel et al., 1991). In contrast to fluorescein, which can support bacterial growth and virus viability, Rose Bengal and lissamine green are bacteriocidal and virucidal (Cello & Lasmanis, 1958; Seitzman et al., 2006; Storey et al., 2002). Although fluorescein did not interfere with the PCR assay for *C. felis* and FHV-1 (an *in vitro* study), Rose Bengal and lissamine green inhibited the detection of herpes simplex virus by PCR (Segarra et al., 2011; Seitzman et al., 2006; Stroop et al., 2000). In summary, sample collection for infectious agents should ideally be performed prior to the topical application of ophthalmic dyes if possible.

Tonometry

Tonometry is the measurement of IOP and is an essential diagnostic procedure for a thorough ophthalmic examination. Direct tonometry via a manometer is the most accurate method, but is invasive and therefore impractical for clinical use. Indirect tonometry, the measurement of corneal tension, is the technique used to determine IOP in clinical ophthalmology. It is a quick, simple, and noninvasive procedure that can be performed with minimal discomfort to the patient, and the results determine not only the diagnosis, but the prognosis and treatment options. Tonometry should not

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be restricted to the diagnosis of glaucoma; it should be used in the assessment of a red eye (e.g., conjunctivitis, keratitis, episcleritis, scleritis, anterior uveitis), focal or diffuse corneal edema, orbital disease, and a history of glaucoma or lens luxation in the opposite eye. Tonometry should also not be restricted to making the initial diagnosis and it is an essential part of good ongoing case management. Although tonometry in the outpatient clinic provides only a "snapshot" measurement of IOP, repeat tonometry is invaluable for effective monitoring of the disease itself and response to therapy.

The range of normal IOP in most animals is somewhere between 15 and 25 mmHg because of the conservation between species. The mean IOP and range for an individual species varies with different studies, but general values in common domestic species are 15–18 mmHg (dog), 17–19 mmHg (cat), 15–20 mmHg (rabbit), and 17–28 mmHg (horse; Gum et al., 2007). The highest mean IOP recorded in any species is 32.1 ± 10.4 mmHg in the rhinoceros (Ofri et al., 2002a), and the lowest is 3 mmHg in the chinchilla (Müller et al., 2010). Generally, the difference in IOP between fellow eyes should be less than 8 mmHg (Lovekin, 1964). If this is not the case, a thorough examination of both eyes should be performed to identify any relevant pathology.

Indirect tonometry is performed by digital palpation or instrumental tonometry, of which three techniques are used in veterinary medicine: indentation, applanation, and rebound tonometry.

Digital Tonometry

Digital tonometry is the estimation of IOP by digital palpation. It was reported as early as pre-Hippocratic times, and it is still practiced by some human and veterinary ophthalmologists. To perform this technique, the forefinger is placed on the closed upper eyelid, over the globe, and slight pressure is applied to estimate how hard the eye feels. This is ideally performed simultaneously on both eyes for comparison. Digital tonometry is a crude technique and basically differentiates between very soft and very hard eyes. It is of no value in monitoring IOP once therapy has been started, because it is too insensitive. Its use in humans is generally limited to patients who do not have access to specialized eye care, such as in rural areas or underdeveloped countries. Experience has been shown to be an important factor if any level of accuracy is to be achieved: a study using a cadaveric cornea eye model showed that an experienced examiner could estimate IOP within 5 mmHg 100% of the time, as compared with 62% for an inexperienced examiner (Birnbach & Leen, 1998). In a study comparing digital tonometry with Goldmann applanation tonometry, glaucoma specialists were able to digitally identify most eyes with an IOP of greater than 30 mmHg (Baum et al., 1995).

Instrumental Tonometry

The ideal tonometer should be easy to use, atraumatic, require minimal restraint, and provide accurate and repeatable estimates of IOP in both normal and diseased eyes. Tonometers designed for use in veterinary medicine should also be accurate across a wide range of species with different ocular anatomy. Instrumental tonometry includes certain assumptions about various physical factors such as corneal thickness and curvature, corneal and scleral rigidity, tear film viscosity, temperature, and the effects of any topical medications that might be present.

Indentation Tonometry

The first indentation tonometer was reported by von Graefe in 1862 (Kronfeld, 1996). This was followed by reports of a similar device from Donders in 1863. In 1905, Schiøtz developed and described an indentation tonometer, the Schiøtz tonometer, which became widely used. In this method, a standard force is applied with a weighted plunger to the anesthetized cornea. The instrument measures the amount of corneal indentation produced by a given weight. The degree of corneal indentation is inversely proportional to the IOP (Fig. 10.1.52). Various models are available, but the fundamental design comprises three parts: footplate, plunger, and handle (holding bracket and recording scale; Fig. 10.1.53). The convex corneal footplate is attached to a 3 mm diameter, low-friction, jewel-mounted plunger (metal rod) within a holding bracket attached to a recording scale. The footplate approximates the curvature of the human cornea, and the metal rod protrudes slightly from its concave surface. The plunger weighs 5.5 g; weights of 7.5, 10.0, or 15.0 g can be added to the system. The greater the weight applied to the eye at a given IOP, the greater the indentation of the rod. Depending on the corneal rigidity, the metal rod indents the cornea variably, such that each 0.05 mm of indentation moves the recording needle one scale unit. Scale readings are converted to mmHg via the instrument's calibration or conversion table. Although conversion tables have been calculated for the dog and the cat from invasive manometry, these tables are less accurate than the human calibration table supplied with the instrument, perhaps because of differences in ocular rigidity (Gelatt & Gum, 1995; Miller & Pickett, 1992a, 1992b; Peiffer et al., 1977, 1988). The data are recorded as scale reading/weight/IOP, for example 5.0 units/5.5 g/21 mmHg.

Before use, the tonometer should be calibrated using the stainless-steel dome provided with the instrument. It is also important to check that the plunger assembly is clean, because an accumulation of debris will prevent free movement of the metal rod and cause inaccurate results. Following the topical administration of an anesthetic eye drop, the instrument, which relies on gravity, is placed vertically on the central horizontal cornea (see Fig. 10.1.53B). This means

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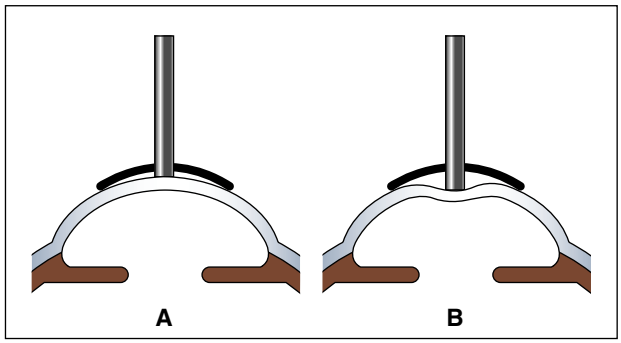


Figure 10.1.52 Indentation tonometry: the degree of indentation by the metal rod is inversely proportional to the intraocular pressure (IOP). **A**. The metal rod protrudes slightly from the curved corneal footplate when used on an eye with a normal or raised IOP. **B.** The metal rod protrudes more in an eye with hypotony (low IOP). (Illustration by H. Featherstone and Simon Scurrell.)

that the animal must be restrained in such a way as to elevate the nose so that the cornea lies in a horizontal plane. The eyelids are gently retracted, avoiding pressure on the globe itself, to allow the footplate to sit on the cornea. The footplate must be placed away from the TEL. Three separate readings are taken, and the closest two results are averaged. Because of the weight of the instrument pressing on the globe, consecutive readings may become progressively lower.

There are several disadvantages with a Schiøtz tonometer. Indentation tonometry is inherently subject to some degree of inaccuracy. The main practical problems include difficulty in restraint of the animal in order to achieve the correct head and eye position and prevent movement, and correct alignment of the instrument on the cornea while avoiding the TEL (the footplate can be slipped under the leading edge of the TEL, or forceps can be used for gentle retraction). It should not be used after recent corneal and intraocular surgery and corneal pathology may give inaccurate results. The footplate is designed to match the curvature of the human cornea and its accuracy may vary in veterinary patients: large eyes with "flat" corneas generally give falsely low readings, whereas small eyes with greater corneal curvature tend to give falsely high readings (Strubbe & Gelatt, 1999). The diameter of the footplate is approximately 9 mm, so use in very small eyes is impossible. Ocular rigidity is variable and may affect the accuracy of indentation tonometry. Ocular rigidity is the resistance offered by the fibrous tunics of the eye (sclera and cornea) to a change in intraocular volume. It is a constant characteristic of each eye, but varies with IOP.

The dog and cat have greater scleral elasticity than the adult human and therefore present less resistance to indentation tonometry. Readings taken at the limbus give higher values than those from the central cornea, which is considered more accurate (Khan et al., 1991). A simple assessment of the influence of ocular rigidity can be performed by measuring the IOP with two different weights, using the lighter weight first: if the IOP results are similar, the influence of ocular rigidity is small, and vice versa. Any procedure that alters the rigidity of the ocular fibrous coat may affect accu-

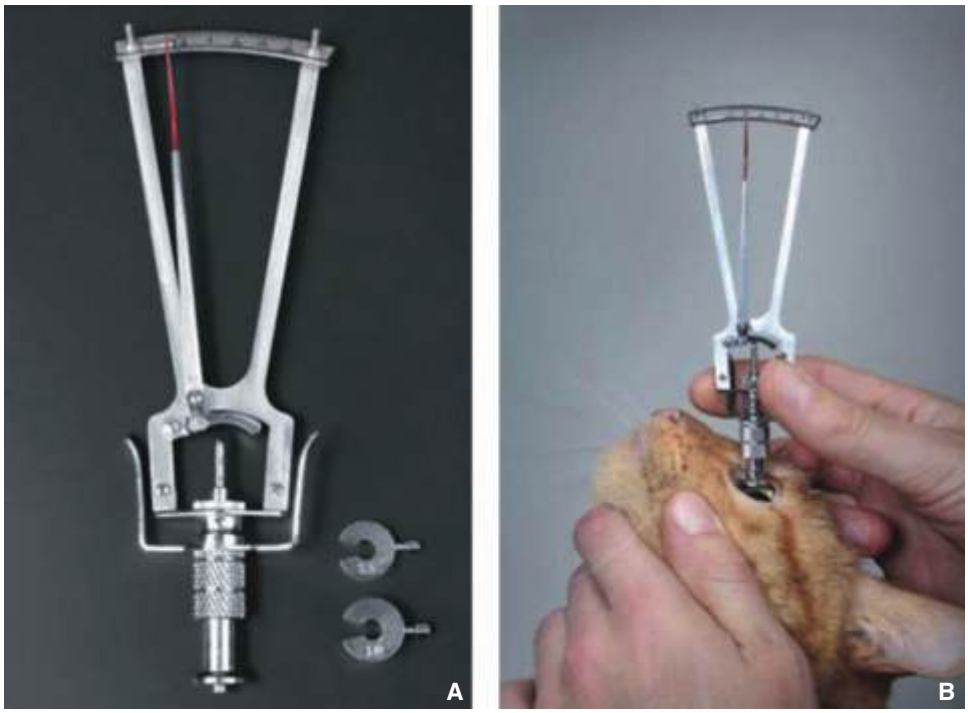


Figure 10.1.53 Indentation tonometry. **A**. Schiøtz tonometer with 7.5 and 10.0 g weights. **B**. Schiøtz tonometer in use on a cat.

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racy (e.g., scleral buckling, glaucoma filtration procedures). It is however interesting that the Schiøtz tonometer was more accurate in human eyes with a sutured keratoprosthesis than applanation tonometry and digital manometry (Estrovich et al., 2015). Schiøtz tonometry is impractical in the horse and other large species with laterally positioned globes without general anesthesia (lateral recumbency; Gilger & Stoppini, 2011). However, normal values for the Schiøtz tonometer in the horse have been reported as between 14 and 22 mmHg (Severin, 1976). Mean IOP values obtained by Schiøtz tonometry have been reported in three large wildlife herbivores (Nubian Ibex, Grant Zebra, and Arabian Oryx; Table 10.1.5; Ofri et al., 1998b).

Despite the potential for inaccuracy, results of studies comparing the Schiøtz instrument (5.5 and 7.5 g weights) and the Mackay–Marg or Tono-Pen applanation tonometers suggest that reasonable correlations are possible (Miller & Pickett, 1992a, 1992b). It can provide a reasonable estimation of IOP (probably ± 4 to 5 mmHg), but is less accurate than applanation and rebound tonometry and harder to use.

Applanation Tonometry

Maklakoff engineered the first applanation tonometer in 1885, and a modification of this device (Tonomat) was created by Posner and Inglima in 1964 (Albert & Edwards, 1996). Verhoeff developed the Souter applanation tonometer in 1916, reporting its use for optical estimations of IOP, and in 1954 Goldmann developed a slit-lamp biomicroscope-mounted applanation tonometer, which has become the standard for applanation tonometry in human ophthalmology.

Applanation tonometers measure the force required to flatten, or applanate, a constant area of cornea (pressure = force/area; Fig. 10.1.54). Applanation tonometry works on the principle of Goldmann's Imbert-Fick "law": "The pressure in a sphere filled with liquid and surrounded by an infinitely thin membrane is measured by the counter-pressure which just flattens the membrane." The force required to flatten a known area of the cornea provides an estimate of the IOP. There is a variety of applanation tonometers: Goldmann (Veach Ophthalmic Instruments, Tempe, AZ, USA), Draeger, Perkins (Haag-Streit USA, Mason, OH, USA), Halberg, Maklakoff, Mackay–Marg, Tono-Pen® (Reichert, Buffalo, NY, USA), AccuPen (Accutome, Malvern, PA, USA), and pneumatonograph tonometers. A feature common to all is a contact probe with a 3–4 mm diameter planosurface that flattens a corresponding area of the cornea. At this diameter, the resistance of the cornea to flattening is counterbalanced by the capillary attraction of the tear film meniscus for the tonometer head. The force used is evaluated either optically (with a split-field prism and fluorescein) or electronically (linear transducer, gas-suspended probe, or air-pulse noncontact sensor). The Goldmann, Draeger, Perkins, and Halberg applanation tonometers estimate IOP by aligning a corneal contact prism with a hand dial or small motor to calculate the force of applanation. A common requirement is that the eye must remain stationary for several seconds to obtain an accurate reading. The Goldmann tonometer is fixed to a table-mounted slit-lamp biomicroscope and is the most accurate applanation tonometer in human ophthalmology; the Draeger, Perkins, and Halberg applanation tonometers are handheld instruments. Although these instruments are not widely used in veterinary ophthalmology, the Perkins tonometer has recently been evaluated in the dog, cat, horse, and cow (Andrade et al., 2009, 2011). In all four species, there was excellent correlation between the Perkins tonometer and direct tonometry. Its use has also been described in sedated rabbits (Lim et al., 2005).

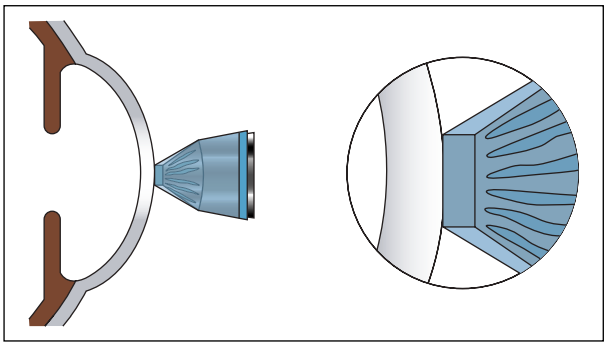


Figure 10.1.54 Applanation tonometry: the force required to flatten, or applanate, a constant area of cornea is measured (pressure = force/area). (Illustration by H. Featherstone and Simon Scurrell.)

Electronic applanation tonometers are available as countertop or handheld instruments. The Mackay–Marg is a countertop tonometer which uses a ceramic actuating rod suspended within the tip of a stainless-steel probe to activate a position transducer. The high-frequency, alternating current supplied to the transducer by an amplifier–recorder unit is subsequently modified and returned to the recorder. The lowest repeatable measurements represent the IOP. The Mackay–Marg tonometer produced reliable results in comparison with direct tonometry in the dog, rabbit, and horse (Cohen & Reinke, 1970; Gelatt et al., 1977b, 1981; Priehs et al., 1990). It underestimates higher IOPs in the cat (Miller et al., 1991).

The Tono-Pen is a digital handheld applanation tonometer based on the Mackay–Marg tonometer (Fig. 10.1.55). It is battery operated and portable. The footplate of the instrument contains a central, pressure-sensitive tip, which protrudes from and is surrounded by an insensitive ring (see Fig. 10.1.55B). When the tip makes contact with the cornea, the tip applanates or flattens the predetermined area of the cornea; the point of applanation is read electronically (amplified, digitized, and passed through a single-chip microprocessor). A degree of indentation occurs with con-

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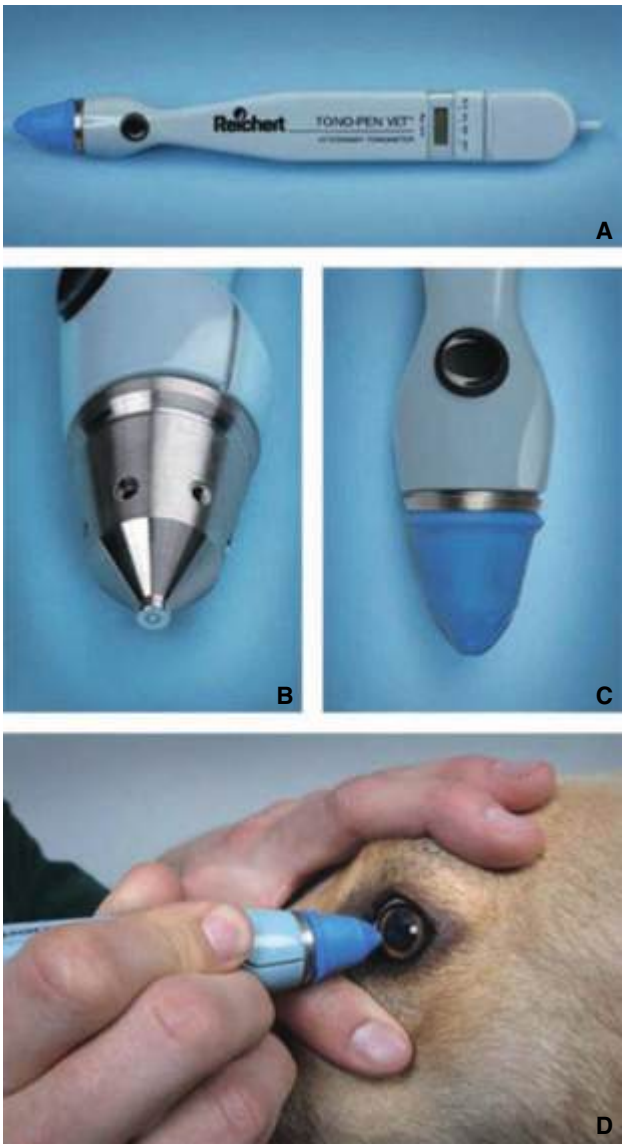


Figure 10.1.55 Applanation tonometry. **A**. Tono-Pen Vet. **B**. The footplate contains a central pressure-sensitive tip, which protrudes from and is surrounded by an insensitive ring. **C**. The tip is covered by a disposable latex membrane that protects the sensitive plunger and prevents disease transmission. **D**. Tono-Pen Vet in use on a dog.

tinued advancement of the tip, but the true IOP is determined only by the moment of applanation.

The tip is covered by a disposable latex membrane that protects the sensitive plunger and prevents disease transmission (see Fig. 10.1.55C). Following topical anesthesia, the eyelids are gently retracted with the nondominant hand, taking care to avoid pressure on the globe. Using the dominant hand, the instrument is held perpendicular to the cornea so that the flat tip is parallel to the cornea (see Fig. 10.1.55D). The tip is tapped very lightly on the central cornea multiple times without causing a visible indentation. Readings taken from the central two-thirds of the cornea are most accurate (Khan et al., 1991). IOP measurements are displayed on a liquid crystal screen. Brief clicks indicate when individual readings have been recorded, and a sustained tone indicates when a mean IOP has been calculated. The mean IOP is then displayed along with the coefficient of variance (i.e., 5%, 10%, 20%, or more than 20%). If the coefficient of variance is more than 5%, tonometry should be repeated. Because of its ease of use, portability, reliability, and cost, the Tono-Pen has become a popular tonometer among veterinary ophthalmologists. The design has been modified over the years (Tono-Pen, Tono-Pen 2, Tono-Pen XL, Tono-Pen Vet, Tono-Pen Avia), but the basic utility is unchanged.

The Tono-Pen has been used in a variety of domestic and nondomestic species (see Table 10.1.5; Abrams et al., 1996; Balthazar da Silveira et al., 2017; Barsotti et al, 2013; Bito et al., 1979; Dziezyc et al., 1992; Gelatt et al., 1977b; Kotani et al., 1993; McDonald et al., 2017; Mermoud et al., 1995; Miller et al., 1988, 1990, 1991; Ofri et al., 2000, 2001; Oriá et al., 2015a, 2015b, 2015c; Passaglia et al., 2004; Peterson et al., 1996; Priehs et al., 1990; Stoiber et al., 2006; Tofflemire et al., 2017). The calibration of the Tono-Pen is based mainly on IOPs within the normal range and up to about 30 mmHg, and therefore it will yield lower readings than actual IOP when IOP climbs into range of 40–50 mmHg or more! The majority of humans with early primary open-angle glaucoma present with IOP levels less than 30 mmHg.

Recent studies report a mean IOP of 11.7 ± 2.9 mmHg (Tofflemire et al., 2017) and 15.6 ± 4.2 mmHg (Kato, 2014) when normal canine eyes were evaluated by means of the Tono-Pen XL. The reported mean IOP for the Tono-Pen Avia (which is similar to the Tono-Pen Avia Vet), the newest model of the Tono-Pen, is 12.8 ± 2.9 mmHg (Ben-Shlomo & Muirhead, 2020). Using a Tono-Pen, the mean IOP in the cat was 19.7 ± 5.6 mmHg and the mean IOP in the horse was 23.3 ± 6.89 mmHg (Miller et al., 1990, 1991). The reported mean IOP in dogs estimated by the AccuPen, a relatively new applanation tonometer, is 14.3 ± 4.0 mmHg in one study (Tofflemire et al., 2017) and 13.4 ± 4.7 mmHg in another (Kato, 2014). Mean IOP values for some domestic and nondomestic species are provided in Table 10.1.5.

The pneumatonograph is an applanation tonometer–tonographer that measures IOP via a gas-suspended plunger. Compressed air is directed into a sensor housing that contains a hollow, metal plunger with a silicone sensor membrane at its tip. Part of the gas supports the plunger, thereby allowing it to move in a near-frictionless state; the rest of the gas passes through the plunger (i.e., measurement chamber), gently pressing the sensor against the cornea during applanation. Pressure from the eye restricts the flow of gas between the sensor membrane and the plunger tip, thus increasing the pressure within the measurement chamber.

To record IOP with the pneumatonograph, the cornea is anesthetized and the eyelids are gently retracted. With the

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plunger extended, the silicone footplate contacts the central cornea. Pressure is then applied until the plunger is depressed approximately halfway into the sensor housing, as indicated by red and green marks on the plunger, and contact is maintained for 3–5 seconds. In the cat, the pneumatonograph underestimates higher IOPs (more than 20 mmHg) and overestimates lower IOPs (less than 15 mmHg; Stoiber et al., 2006); it may underestimate IOP in the horse and the cow (Kotani et al., 1993). Only the pneumatonograph is commercially available and performs tonography in addition to tonometry.

The different types of applanation tonometers have been compared within and between species (Boothe et al., 1988; Dziezyc et al., 1992; Gorig et al., 2006; Gum et al., 1998; McLellan et al., 2013; Miller et al., 1988, 1990, 1991; Passaglia et al., 2004; Priehs et al., 1990; Stoiber et al., 2006; Tofflemire et al., 2017). The Tono-Pen is very accurate in the physiologic range, but tends to overestimate IOP in the low range and underestimate IOP in the high range in dogs (Priehs et al., 1990), cats (McLellan et al., 2009; Stoiber et al., 2006), and humans (Boothe et al., 1988). In the dog and cat, there was strong correlation between the IOP values obtained by direct manometry, Tono-Pen XL, and Perkins tonometers (Andrade et al., 2012). The Tono-Pen XL underestimates IOP in the cat, cow, and sheep (McLellan et al., 2009; Passaglia et al., 2004). The pneumatonograph and the MMAC-II (Professional Technologies, Redding, CA, USA) gave significantly different IOP values from MacKay–Marg and Tono-Pen XL tonometers in a study of four different applanation tonometers in the dog (Gelatt & MacKay, 1998). In both the cat and the horse, Tono-Pen and Mackay–Marg applanation tonometers underestimate IOP when compared to direct manometry, but do so in a predictable manner; the linear regression is easily corrected to enable IOP in the live animal to be measured accurately (Miller et al., 1990, 1991). The Tono-Pen and Mackay–Marg tonometers correlate well in the horse and in the dairy cow (Tono-Pen XL; Gum et al., 1998).

Rebound Tonometry

Rebound (impact or dynamic) tonometry uses a different mechanical principle to measure IOP. A small probe (such as a metal pin with a rounded end) is rapidly and electromagnetically propelled, from a fixed distance from the cornea, to contact the cornea before returning (rebounding) to the instrument (Fig. 10.1.56 and Fig. 10.1.57). The instrument assesses the rebound characteristics (probe deceleration): eyes with a higher IOP cause a slower deceleration of the probe and shorter return time to the instrument than those with a lower IOP. The technique is affected by ocular surface tension and should ideally be performed before the applica-

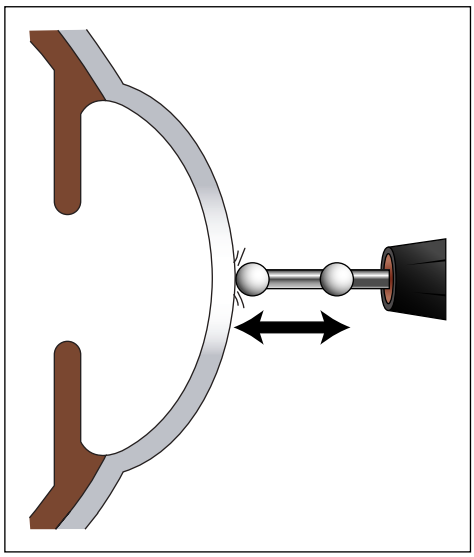


Figure 10.1.56 Rebound tonometry: a small probe is rapidly propelled from a fixed distance to contact the cornea before returning (rebounding) to the instrument. The rebound characteristics, including probe deceleration, are assessed to determine the intraocular pressure. (Illustration by H. Featherstone and Simon Scurrell.)

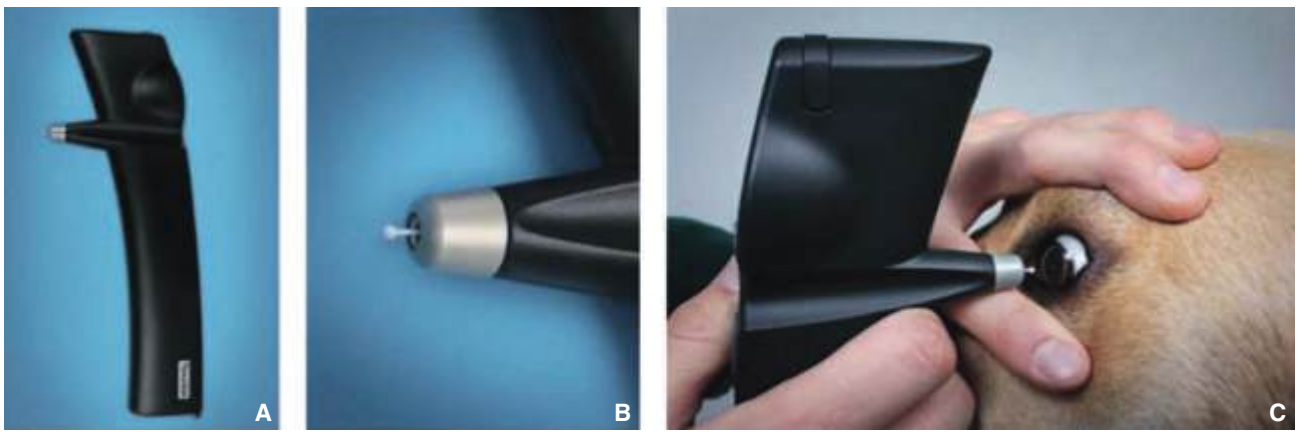


Figure 10.1.57 Rebound tonometry. **A**. TonoVet. **B**. Small metal pin with rounded plastic tip. **C**. TonoVet in use on a dog.

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tion of any topical medications, including topical anesthetic. Despite this recommendation, studies found that the IOP results were unaffected by topical anesthesia (Gorig et al., 2006; Kim et al., 2013; Rusanen et al., 2010; Schuster et al., 2015; Tofflemire et al., 2017).

Advantages of the rebound tonometer are that topical anesthesia is not necessary; a very small probe tip (1.3–1.8 mm) makes it suitable for very small eyes, as in many exotic species, and in the presence of significant corneal disease; and the tip is disposable (see Fig. 10.1.57B). One disadvantage is that the instrument must be held upright during measurement so that the probe is propelled horizontally; this may make its use difficult in recalcitrant or recumbent patients (see Fig. 10.1.57C). Common types of alignment errors that can occur with rebound tonometry were simulated and assessed in the chicken (*in vivo* and *in vitro*; Prashar et al., 2007). Accuracy was unaffected by a variation in the probe-to-cornea distance over the range 3–5 mm and by lateral displacement of the probe from the visual over the range 0–2 mm. Although there was slightly more effect if the probe was angled away from the visual axis over the range 0–20 degrees, none of the alignment errors was considered to be clinically relevant in conscious birds.

The TonoVet rebound tonometer is becoming increasingly popular in veterinary ophthalmology. A strong linear correlation between rebound tonometry and direct manometry has been demonstrated in the dog, cat, and horse (Knollinger et al., 2005; McLellan et al., 2013; Rusanen et al., 2010; Tofflemire et al., 2017). In contrast, rebound tonometry underestimated the IOP by 37%–60% in enucleated rabbit eyes and 17%–63% in enucleated porcine eyes, as compared to direct manometry (Lobler et al., 2011). When compared to the Tono-PenVet, rebound tonometry underestimated the IOP by an average of 2 mmHg in the dog (Knollinger et al., 2005) and overestimated the IOP by 1 mmHg in the horse (Knollinger et al., 2005). In the cat, the TonoVet is more accurate than the Tono-Pen XL in normal and glaucomatous eyes (McLellan et al., 2013). In the pig (*ex vivo* porcine eyes), the TonoVet was more accurate than the Tono-Pen Vet (Lewin & Miller, 2017). The TonoVet in "d" (dog) setting was found to be the most accurate of three tonometers in the *ex vivo* chinchilla eye (Snyder et al., 2017). Rebound tonometry has also been reported in the prairie dog (Meekins et al., 2015a), alpaca (McDonald et al., 2017), pygmy goat (Broadwater et al., 2007), rabbit (Pereira et al., 2011), dairy calf (Tofflemire et al., 2015), birds of prey (Harris et al., 2008; Jeong et al., 2007; Labelle et al., 2012; Reuter et al., 2010), chicken (Prashar et al., 2007), pigeon (Park et al., 2017), ducks and geese (Ansari Mood et al., 2017), murres (guillemot; Freeman et al., 2018), chinchilla (Müller et al., 2010), African giant pouched rat (Heller et al., 2018), turtle (Delgado et al., 2014; Espinheira Gomes et al., 2016; Somma et al., 2014), gray mouse lemur (Dubicanac et al., 2018), Yacare caiman (Ruiz et al., 2015), penguin (Bliss et al., 2015; Gonzalez-Alonso-Alegre et al., 2015; Sheldon et al., 2017), American bullfrog (Cannizzo et al., 2017), and koi fish (Lynch et al., 2007). The TonoVet Plus, a new model of the TonoVet, has been recently introduced. Together with improved user interphase and ergonomics, the device has been recalibrated for four species including the dog, cat, horse, and rabbit. The IOP values in normal canine eyes were reported to be 19.2 ± 3.1 mmHg, significantly higher than with the TonoVet and TonoPen Avia (Ben-Shlomo & Muirhead, 2020). A manometry study suggests that the TonoVet Plus trends towards increased accuracy and precision when compared to the TonoVet, Tono-Pen Avia, and Tono-Pen XL (Minella et al., 2019).

The IOP values obtained by the human-calibrated rebound tonometer ICare® (Tiolat, Helsinki, Finland) were significantly lower than those for the Tono-Pen XL in normal dog eyes (Leiva et al., 2006). Given this, and the results of other studies (Knollinger et al., 2005; Rusanen et al., 2010), the TonoVet has been calibrated for dogs, cats, and horses. The TonoLab rebound tonometer is specifically designed for performing tonometry in rodents (rat/mouse; Kim et al., 2013). The TonoLab was more accurate than the TonoVet when used in red-eared slider turtles (Delgado et al., 2014). In the Kemp's Ridley sea turtle, the mean IOP measured by the rebound tonometer on the "h" (horse) setting was approximately twice that for the "P" (nonspecified) setting (Gornik et al., 2016). It is thus important to select the correct software, when known, for each species before performing tonometry.

The aforementioned studies were performed in clinically normal animals, with the exception of the study in cats (McLellan et al., 2013). There are several studies that describe the use of tonometry in glaucomatous canine and feline eyes (Gorig et al., 2006; McLellan et al., 2013; Slack et al., 2011; von Spiessen et al., 2015). Both the TonoVet and Tono-Pen XL provide reproducible IOP measurements in cats, but the TonoVet is more accurate in normal cats and for the detection of ocular hypertension and/or glaucoma in cats in a clinical setting (McLellan et al., 2013). In the dog, there was a 1:1 relationship between the TonoVet and the MacKay–Marg tonometer (Gorig et al., 2006), in contrast to an overestimation of IOP by the TonoVet compared with the TonoVet-XL (Slack et al., 2011; Tofflemire et al., 2017).

Factors That Influence Tonometry

Multiple factors can influence tonometric readings. Some factors are inherent to the type of tonometer (e.g., size of probe on a cornea with extensive pathology) and to the technique (e.g., head position), whereas others are beyond the control of the examiner (e.g., age, gender, season). In the clinical setting, tonometry can usually be performed in most common domestic species in conscious animals with minimal restraint. In cooperative patients, the main factors that influence the IOP results include improper or inexperienced

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use of equipment or a disease process affecting one or both globes. In large species such as the horse, and when an eye is painful, adjunctive methods are required for reliable tonometry and can affect the IOP results. These include sedation, general anesthesia, and regional nerve blocks. The method of restraint (physical or chemical) and body and head position can also have a dramatic effect. The importance of striving to perform tonometry on an eye with minimal influencing factors has been demonstrated in a mouse model for glaucoma: tonometry results were more consistent and reliable in mice that had undergone successful behavioral training to accept tonometry conscious, than in mice that were placed in a restrainer device (Ding et al., 2011). It is important to try to perform tonometry before the application of topical mydriatic agents because of their potential effect on IOP. This includes short-acting agents such as tropicamide, which is widely and routinely used for diagnostic purposes. Topical tropicamide 1% has been shown to cause a substantial increase in IOP (up to 6–7 mmHg) in both normal and glaucomatous cats (Gomes et al., 2011; Stadtbaumer et al., 2002, 2006). In contrast to the cat, topical tropicamide 1% has less effect on IOP in the dog, although clinically relevant increases (13.6 mmHg) in individual animals (Hacker & Farver, 1988) and interbreed variations have been recognized (Taylor et al., 2007). Topical and intramuscular atropine (0.06 mg/kg) both caused a significant increase in the IOP in healthy dogs (Kovalcuka et al., 2015). In contrast, topical cyclopentolate did not affect IOP (or tear production) and could therefore be considered when a cycloplegic drug is needed without adverse effects on those parameters (Costa et al., 2016).

The effect of sedation and general anesthesia on IOP is an important consideration when performing tonometry on eyes with corneal trauma, glaucoma, or those undergoing intraocular surgery. In the horse, IOP is reduced by xylazine alone (by up to 23%; van der Woerdt et al., 1995) and by the combination of acepromazine and xylazine (McClure et al., 1976), but not by the combination of ketamine and xylazine (Smith et al., 1990; Trim et al., 1985). Romifidine caused a significant decrease in IOP in the horse in two studies (Marzok et al., 2014; Stine et al., 2014). In the dog, ketamine alone causes a significant and clinically important increase in IOP (Hofmeister et al., 2006a). Such an increase can be avoided, however, with concurrent use of diazepam or midazolam (Ghaffari et al., 2010b; Hofmeister et al., 2006a). Sedation with medetomidine and atipamezole in healthy Golden Retrievers undergoing routine health screening had no effect on IOP (Wallin-Hakanson & Wallin-Hakanson, 2001). Sedation with dexmedetomidine did not affect the IOP in dogs until 20 minutes, when it caused a reduction (Artigas et al., 2012). Propofol has shown conflicting effects on IOP in dogs in different studies. Dogs induced with intravenous propofol developed a significant increase in IOP before intubation and the increase was not prevented by administering higher doses (Hofmeister et al., 2009). This increase was also seen when propofol was compared to thiopental (Hofmeister et al., 2008). An increase in IOP was also seen with the combination of midazolam-propofol and midazolam-etomidate (Gunderson et al., 2013). However, in a more recent study, propofol and alfaxalone both decreased the IOP in dogs at 2 minutes following induction and were therefore considered appropriate induction agents for intraocular surgery (Costa et al., 2015). The use of nitrous oxide did not affect IOP in dogs induced by propofol and maintained with desflurane (Almeida et al., 2008). IOP was increased in dogs receiving morphine, alfaxalone, midazolam, and sevoflurane, and the authors advised against this protocol for intraocular surgery (Mayordomo-Febrer et al., 2017). The combination of tiletamine and zolazepam had no effect on IOP in healthy dogs (Jang et al., 2015).

It has long been recognized that pressure on the jugular veins from excessive restraint or a tight-fitting collar may falsely elevate the IOP, particularly in brachycephalic dogs. These and related factors have been objectively assessed by two studies. IOP in dogs is significantly increased by applying neck pressure via a collar but not via a harness (Pauli et al., 2006). The effect of eyelid manipulation and manual compression of the jugular vein(s) on applanation tonometry in normal dogs was assessed (H.E. Klein et al., 2011). The greatest increase in IOP occurred with simultaneous bilateral jugular vein compression and lateral eyelid extension (increase of 17.6 mmHg), and lateral eyelid extension alone (16.5 mmHg). It has been suggested that horses without an auriculopalpebral nerve block may have an elevated IOP (Trim et al., 1985), but this has not been supported by two other studies (Miller et al., 1990; van der Woerdt et al., 1995). For reliable tonometry in the clinical setting, the use of an auriculopalpebral nerve block is recommended in the horse (Gilger & Stoppini, 2011). Different methods of manual head restraint were compared in the red-eared turtle (Delgado et al., 2014). Rostral head restraint is preferred because it did not affect IOP, in contrast to neck restraint, which significantly increased IOP.

The effect of body position on IOP was assessed using applanation tonometry in healthy dogs without glaucoma (Broadwater et al., 2008). Three different body positions were compared (sternal recumbency, dorsal recumbency, and sitting position) and were found to affect IOP. During the 5-minute examination, IOP decreased significantly in dogs that were dorsally recumbent or sitting, but did not change significantly in dogs that were sternally recumbent. The effect of body position on IOP has also been assessed in the mouse, together with the effect on episcleral venous pressure (EVP; Aihara et al., 2003). Both IOP and EVP increased with a head-down body position (16.5 ± 0.6, 18.2 ± 0.6, and 19.5 ± 1.8 mmHg for the horizontal/awake position, 30 degree head-down position, and 60 degree head-down position, respectively). In contrast to these studies in the dog

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and mouse, the IOP was unaffected by body position in young healthy calves in lateral recumbency, as compared to a normal standing position (Kurt et al., 2018).

Head position was also found to have a significant effect on IOP in normal horses (Komáromy et al., 2006). Two different head positions, above and below heart level, were assessed following sedation (intravenous detomidine), auriculopalpebral nerve block, and topical corneal anesthesia. The IOP was increased in 87% of eyes when the head was below heart level, and there was a significant difference from the mean IOP when the head was above (17.5 ± 0.8 mmHg) or below (25.7 ± 1.2 mmHg) heart level. The effect on IOP of different head and body positions (sitting, recumbent, and hyperextension of the head) has been evaluated in humans using three different tonometers. The IOP of recumbent patients was only slightly higher than for sitting patients, but was significantly higher when the head was hyperextended using the Tono-Pen (A. Klein et al., 2011). Head and body position affects IOP in the fruit bat and in the loggerhead sea turtle (Blackwood et al., 2010; Chittick & Harms, 2001). The IOP in the upright fruit bat is lower than when hanging (Blackwood et al., 2010). The IOP in the sea turtle is significantly higher when suspended in a head-down position, as compared with dorsoventral and ventrodorsal positions (positions commonly used for restraint for medical and surgical procedures; Chittick & Harms, 2001). The IOP in the red-footed tortoise is also affected by different body positions, with higher values in the ventrodorsal position as compared to the dorsoventral position (Oriá et al., 2015b).

A major advantage of the handheld electronic applanation tonometer (Tono-Pen models, AccuPen) is that it can be used with the animal in any position. In contrast, the rebound tonometer probe must be horizontal (parallel to the floor), as mentioned previously (Takenaka et al., 2011). The need for the cornea to be horizontal is an obvious disadvantage for the Schiøtz tonometer.

The effects of corneal thickness and corneal pathology have varied with different studies. Corneal thickness has been shown to affect IOP results with both the TonoVet and the Tono-Pen XL (Park et al., 2011). For every 100 µm increase in corneal thickness, the IOP increases by 1 mmHg for the Tono-Pen XL and 2 mmHg for the TonoVet. However, a later study found that the IOP was not affected by central corneal thickness with two different applanation tonometers (Tono-Pen XL and AccuPen; Kato, 2014). Another study showed that IOP values obtained by the AccuPen applanation tonometer in dogs underestimated the true IOP (obtained by manometry), and when corrected for central corneal thickness (which is a feature of the AccuPen), the calculated IOP further decreased compared to manometry. Hence, it was concluded that when using the AccuPen in dogs, the AccuPen default CCT setting should be used without further adjustment for the true CCT (Tofflemire et al., 2017). Von Spiessen et al. (2015) found that corneal pathology affected IOP values with both the TonoVet and the Tono-Pen Vet. If corneal pathology is present, it is prudent to take readings from the most normal part of the cornea. This factor is affected by the size of the footplate of the tonometer: the small area of the rebound tonometer probe (1.3 mm) and Tono-Pen tip (approximately 3 mm) are more advantageous than the large footplate of the Schiøtz tonometer. Despite the influence of corneal pathology on IOP, the presence of a therapeutic soft contact lens has no clinically significant effect on IOP in humans (A. Klein et al., 2011) and by applanation tonometry (MacKay–Marg) in the dog (Miller & Murphy, 1995). A more recent study in the dog showed that measurements were more reliable in the presence of a soft contact lens with the Tono-Pen XL than with the TonoVet rebound tonometer (Ahn et al., 2012).

The effect of age on IOP has been reported in several species, including the dog (Gelatt & MacKay, 1998; Mughannam et al., 2004; Verboven et al., 2014), domestic cat (Kroll et al., 2001), lion (Ofri et al., 2008), camel (Marzok & El-khodery, 2015), and sambar deer (Oriá et al., 2015a). As a general rule, there is a negative association between age and IOP (in contrast to a positive association between age and tear production). This is true for the dog, cat, and camel, but not for the lion (Ofri et al., 2008) and sambar deer (Oriá et al., 2015a). Several studies have demonstrated changes in IOP during maturation, in addition to changes from a mature adult to a geriatric animal. The IOP increased significantly in Beagle puppies from 2 weeks old (Verboven et al., 2014), but was unaffected in Labrador Retrievers during maturation from 6 weeks to 1 year old (Mughannam et al., 2004). IOP in the dog declines by 2–4 mmHg as age increases from less than 2 years to greater than 6 years (Gelatt & MacKay, 1998). IOP is considerably lower in geriatric cats than in young cats; higher in adolescent than in adult cats; and lower in young kittens within the first few weeks of life than in adolescent cats (Kroll et al., 2001). In cats in which IOP was measured on multiple occasions over time, IOP decreased progressively, and it was not unusual for aged cats to have very low IOPs (≤ 7 mmHg) in the absence of any signs of anterior uveitis. This reduction in IOP may reflect reduction in active secretion of aqueous humor associated with declining systemic health. In the lion, IOP increases with age during the first 20 months of life, plateaus until approximately 40 months, and then gradually declines (Ofri et al., 2008). In sambar deer, IOP was significantly higher in older animals (Oriá et al., 2015a).

Although most studies have shown that gender has no effect on IOP, it has a significant effect on IOP in the lion: IOP in the male lion is significantly higher than in the female (Ofri et al., 1998a). Reproductive status was shown to have a significant effect in both the domestic cat and in the lion: the IOP was higher in cats in estrus and in lions in luteal phase (elevated progesterone) compared with those that were not (Ofri et al., 1999b, 2002b).

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Circadian rhythm affects the IOP in the dog, cat, and horse (Bertolucci et al., 2009; Del Sole et al., 2007; Giannetto et al., 2009), and probably other species. In the dog there is a diurnal acrophase (left eye: 09:33 ± 00:50 hours; right eye: 09:25 ± 00:22 hours; Giannetto et al., 2009). The IOP (and central corneal thickness) was lower in the afternoon/evening in normal dogs (Garzón-Ariza et al., 2018). In the cat, maximal IOP values were detected at night (by about 4–5 mmHg) and a gradual decline in IOP occurred during the day (with IOP in mid to late afternoon about 1–1.5 mmHg lower than morning values; Del Sole et al., 2007). In the horse, IOP was low during the dark phase and high during the light phase, with a peak at the end of the light phase (Bertolucci et al., 2009). The mouse has a biphasic 24-hour pattern in IOP (Aihara et al., 2003). The IOP is lower during the day than at night in the New Zealand white rabbit (Wang et al., 2013).

The relationship between IOP and body length has been studied in the American alligator and the red-footed tortoise (Selmi et al., 2002; Whittaker et al., 1995). IOP and body length are related in the alligator but not in the tortoise. The IOP was significantly higher in alligators shorter than or equal to 50 cm in length compared with those longer than 50 cm; the relationship was nonlinear. In contrast, there was no relationship between carapace length and IOP in the red-footed tortoise (Selmi et al., 2002).

Collating the results of the various studies, the examiner should be consistent when recording IOP values in terms of instrument used, time of day, head/body position, method of restraint (physical and chemical), sedation, and the use of an auriculopalpebral nerve block. This is especially important in monitoring for small changes by serial tonometry in the same animal.

TONOGRAPHY

Tonography is the use of continuous tonometry to noninvasively estimate the pressure-sensitive facility of conventional aqueous humor outflow. In this technique, a tonometer is allowed to rest on the cornea for a set time period, usually 2–4 minutes. In theory, the weight of the tonographic probe on the cornea increases the rate of aqueous humor outflow, without changing the rate of aqueous humor production, and hence decreases the IOP. The subsequent decline in IOP (decay curve) allows an estimation in µl/mmHg/minute of the conventional outflow (corneoscleral trabecular outflow). The unconventional (uveoscleral) outflow is pressure independent and therefore cannot be estimated by tonography.

Schiøtz first described reduction of IOP through repeated tonometry in 1905, noting that pressure reduction occurred to a greater degree in normal than in glaucomatous eyes (Albert & Edwards, 1996). In 1911, Polak-van Gelda reported similar results using intermittent Schiøtz tonometry over a period of 1–2 minutes. The following year, Schoenberg described the application of continuous tonometry on the human eye, recording the decay curve for both normal and glaucomatous eyes. By the 1960s, tonography had become a routine part of the diagnostic regimen for human glaucoma. Sole reliance on tonography to detect glaucoma should be avoided, however, because misinterpretation and misdiagnosis may occur as a result of some overlap between the facility of aqueous outflow in normal versus early glaucomatous eyes (Hetland-Eriksen & Odberg, 1975). Tonography remains an important, noninvasive, and repeatable clinical diagnostic procedure for the estimation of conventional aqueous humor outflow.

The results of tonography have been reported in the rabbit, cat, dog, horse, and nonhuman primates (Bill & Barany, 1966; Eakins, 1969; Helper, 1974; Kornbluth & Linner, 1955; Zhao et al., 2010). It has further been used to compare the facility of aqueous humor outflow in normal and glaucomatous Beagles (Gelatt et al., 1977a, 1996). Tonography has established that there is increased resistance to aqueous humor outflow in dogs with glaucoma (Gelatt et al., 1977a, 1996). The technique appears to be very accurate when compared with the traditional, invasive, constant-pressure, and two-step perfusion techniques of measuring aqueous humor outflow (Peiffer et al., 1976). The typical tonogram waveform is a gradually descending line with only slight fluctuations, which reflect pulse and respiration. The descending line represents decreasing IOP. The slope of the line is greater with normal than with glaucomatous eyes. Human tonography tables have been used to calculate the coefficient of aqueous humor outflow in the dog, cat, and horse. Using either the Schiøtz tonograph or the pneumatonograph, the facility of aqueous humor outflow (C-value) is from 0.24 ± 0.07 µL/mmHg/min to 0.297 ± 0.149 µL/mmHg/min for the normal dog eye, from 0.27 to 0.32 µL/mmHg/min for the normal cat eye, and 0.88 ± 0.65 µL/mmHg/min for the normal horse eye (Gelatt et al., 1996; Smith et al., 1990; Toris et al., 1995). Two types of tonographs are available: those that utilize indentation and those that utilize applanation to estimate changes in IOP. The Schiøtz tonograph is an indentation-type instrument, consisting of an electronic Schiøtz tonometer connected to a transducer. Readings are displayed on a console. The Schiøtz probe is large, covering most of the corneal surface, and has all the mechanical problems associated with this type of tonometer. It is not available as a new instrument. Applanation tonography is performed with a pneumatonograph or a modified Mackay–Marg tonometer. The pneumatonograph uses a compressed air–supported, silicone-tipped plunger to flatten or applanate a focal area of the cornea, thus displaying both digital and waveform results in a manner similar to the Schiøtz tonograph. The pneumatonograph probe® (Reichert, Buffalo, NY, USA) is smaller than the Schiøtz instrument and is more easily maintained on the center of the cornea.

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Sedation or general anesthesia is necessary when performing tonography because the eye must be immobile for 2–4 minutes during the procedure, and most veterinary patients are unwilling or unable to cooperate for that long without pharmacologic restraint. The two most important requirements are constant blood pressure and an immobile eye in a normal position so that the cornea is vertical. The agents for sedation or anesthesia must be chosen carefully, however, because many drugs can cause significant changes in venous blood pressure, IOP, and pupil size, and thereby potentially affect the facility of aqueous humor outflow. Gelatt et al. (1977a, 1996) described a protocol using acepromazine (0.5 mg/kg intravenously) followed 5 minutes later by ketamine (10 mg/kg intramuscularly).

The use of halothane anesthesia has also been reported for patient anesthesia prior to pneumatonography (Glover et al., 1995; Spiess, 1995), and seems not to affect outflow results. Gaseous anesthesia is now generally more accessible and familiar, but the general health status of each individual patient must be considered carefully before choosing any one particular protocol. Topical anesthetic is applied to the cornea, and if necessary to permit probe placement and prevent blinking; an auriculopalpebral nerve block may be performed. Regardless of the method of restraint, the patient is placed in dorsal recumbency, and the eyelids are held open manually or with an eyelid speculum. The speculum should not be so tight fitting as to put direct pressure on the globe, and the cornea should be kept moist to avoid damage to the epithelium. The contact surface of the tonograph probe is carefully placed against the central cornea, and measurements are continuously recorded for a period of 2–4 minutes. During this time, the contact probe should remain in a fixed position to minimize artifacts, which may result from probe movement, probe malfunction, nystagmus, blinking, sneezing, and hyperventilation.

Tonography is not commonly utilized in clinical veterinary ophthalmology. Lack of consistency and the difficulties associated with recording data in untrained animals and the need for either heavy sedation or anesthesia make this tool most useful in the research setting. In the latter, tonography is routinely used in the assessment of antiglaucoma medications and their mechanisms of action, and surgical techniques. Additional information on tonography can be found in Chapters 3 ("Physiology of the Eye") and 20 ("The Canine Glaucomas").

GONIOSCOPY

Gonioscopy describes the technique that allows examination of the anterior face of the iridocorneal angle (ICA) and ciliary cleft (CC). The clinical examination of this region is an integral part of the evaluation of the aqueous outflow pathways and may provide insight into the pathogenesis of a glaucomatous state (Bedford, 1975, 1980a, 1980b; Gelatt & Ladds, 1971; Grozdanic et al., 2010; Lovekin, 1964).

Dellaporta (1975) provides a detailed history of gonioscopy. Trantas first reported direct visualization of the human ICA in 1907 with the help of a direct ophthalmoscope, digital pressure on the sclera, and a +4 D to +15 D lens, and he published his first paper specifically describing the clinical examination of the ICA and Schlemm's canal in 1918. Salzmann later constructed the first goniolens from a modified Fick keratoconus contact lens (Dellaporta, 1975). Between 1919 and 1920, Koeppe described gonioscopy using a slit-lamp biomicroscope and a special steeper contact lens. Troncoso modified the Koeppe goniolens in 1920, using a monocular instrument called a gonioscope to magnify the angle by a power of 13–21. In 1938, Barkan described gonioscopy as a diagnostic aid for human primary glaucoma (Becker, 1972), and in that same year Goldmann introduced the indirect goniolens, which allowed visualization of all 360 degrees of the ICA simply by rotating the mirror of the goniolens. In 1942, Troncoso introduced the binocular gonioscope, which was a handheld instrument allowing stereoscopic visualization of the ICA (Troncoso, 1948). In 1936, Troncoso and Castroviejo published the comparative gonioscopic anatomy of the rabbit, pig, cat, dog, and nonhuman primate. In 1960, Calkins published a phylogenetic study of the ICA in a variety of species, and Magrane (1957) and Lovekin (1964) also briefly described gonioscopy. Lescure (1963) photographed the canine ICA and CC using the Goldmann lens. Gelatt and Bedford published photographs of the normal canine ICA and CC using the Koeppe (Ocular Instruments, Bellevue, WA, USA) and Barkan lenses (Medical Works Ocular Instruments, Bellevue, WA, USA) and KOWA fundus camera (KOWA Optimed, Torrance, CA, USA; Bedford, 1973).

The ICA of most animals and humans cannot be directly visualized because it is obscured by the scleral shelf (Troncoso, 1948). This is in contrast to other structures in the anterior chamber, which are visible without instrumental aid because light rays returning from them to the examiner's eye are largely refracted and only partially internally reflected along their passage from aqueous humor and cornea to air (Fig. 10.1.58). Light rays directed at the ICA do not return to the examiner's eye even if viewed obliquely, as they are totally internally reflected. The phenomenon of total internal reflection occurs when light rays exceed a "critical angle" as they attempt to pass from a medium of higher refractive index (1.376 for cornea) to one of lower refractive index (1.00 for air). The application of a contact lens to the eye can overcome this problem by removing the cornea-to-air interface and creating a new contact lens-to-air interface instead (see Fig. 10.1.58C; Martin, 1969a; Troncoso, 1948). Only a few animals with very large and deep anterior chambers, such as felids, have ICAs and C s that are somewhat visible to the unaided eye (McLellan & Miller, 2011). The examination of the feline ICA is thus possible without a gonioscopy lens, using a focal light source or an indirect ophthalmoscope and a condensing

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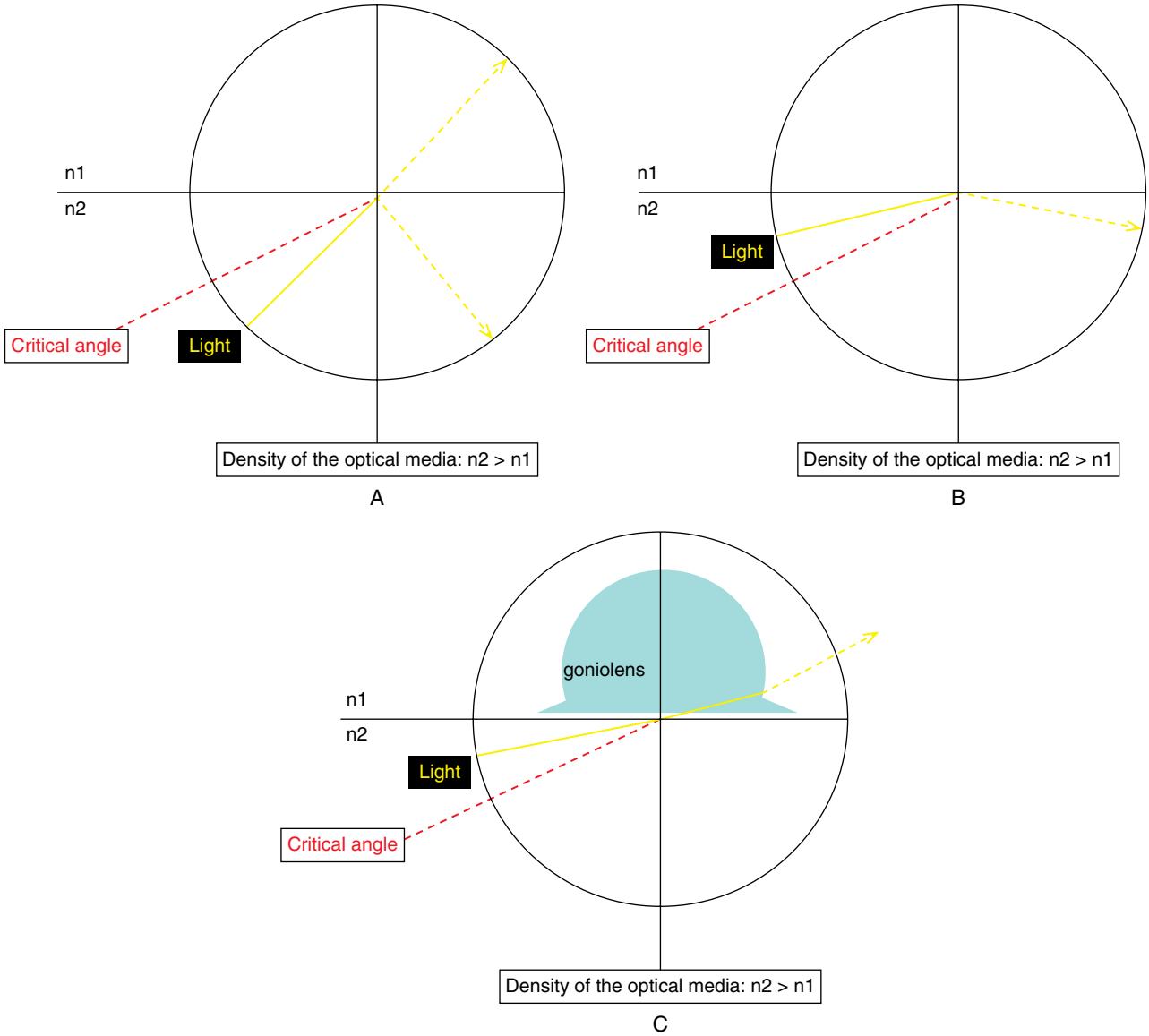


Figure 10.1.58 Phenomenon of total internal reflection. **A**. When a light beam passes from a medium of higher refractive index (n2) to one of lower refractive index (n1) – in the case of the anterior chamber aqueous to air – it is partially refracted and partially reflected. **B**. If the angle at which the light beam hits the interphase between the two media is greater than the so-called critical angle, the beam is completely reflected. **C**. With the application of a contact lens, this problem can be overcome by creating a new interphase between the different media (in this case, creating an aqueous-to-contact lens and contact lens-to-air interphase).

lens at an extreme angle (McLellan & Miller, 2011; Samuelson et al., 1989) or a standard glass slide to flatten the cornea. In the adult horse, it is possible to directly visualize the entrance to the ICA without any instrumental aid in the lateral and medial regions where the scleral shelf is absent (Samuelson et al., 1989).

Many different designs of goniolens are available commercially, but all fall into two categories: direct or indirect (Fig. 10.1.59). Direct goniolenses are very convex to avoid reaching the critical angle and allow the examiner to look obliquely across the anterior chamber to the opposite ICA segment (see Fig. 10.1.59A). The image in direct gonioscopy is real and magnified 1.5–3×, but the examiner must change positions to examine the entire 360 degrees (Martin, 1969a; Troncoso, 1948). The Koeppe and Lovac-Barkan lenses are both direct gonioscopy lenses that are commonly used in the dog (Fig. 10.1.60). The Koeppe lens is held in place by a combination of the vacuum created by pressing the lens onto the anesthetized corneal surface and the small "flange" placed into the conjunctival fornices, whereas the Lovac-Barkan lens is held in place by a vacuum created via a syringe and a silicone tube attachment

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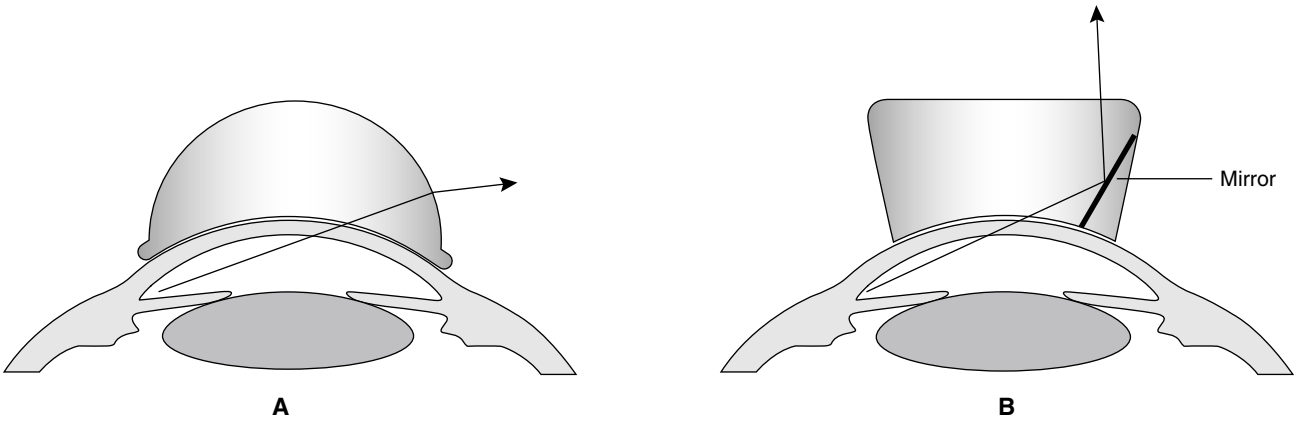


Figure 10.1.59 Gonioscopy lenses can be divided into direct and indirect. **A**. Direct gonioscopy lenses allow examination of the iridocorneal angle opposite to the viewing position of the examiner and create a real image. **B**. Indirect goniolenses for gonioprisms form a virtual image that the observer examines from a frontal position.



Figure 10.1.60 Direct gonioscopy lenses provide a magnified image, as demonstrated here by the Koeppe (left) and Lovac-Barkan (right) lenses.



Figure 10.1.61 Koeppe lens *in situ*. The lens is retained by suction on the corneal surface, freeing the examiner's hands.

(Fig. 10.1.61 and Fig. 10.1.62). Other less commonly used direct gonioscopy lenses include the Cardona and Swan-Jacob models (Ocular Instruments), which are useful in small eyes, as well as the Franklin and Troncoso models, which have silicone flanges and tube handles, respectively. Indirect gonioscopy lenses use single or multiple mirrors or prisms that reflect the light rays emanating from the ICA through a plano anterior contact lens, ensuring that the critical angle is not reached (Fig. 10.1.63). Indirect lenses allow the ICA and opening of the CC to be visualized from directly in front of the patient. The entire circumference of the angle can thus be observed simply by minimal rotation of the lens or by changing focus from mirror to mirror. However, indirect goniolenses or prisms are designed for human corneas, which are significantly smaller and have a more acute curvature than canine corneas, and can result in some image distortion. Indirect gonioscopy lenses do not provide magnification, unlike the direct ones.



Figure 10.1.62 Lovac-Barkan lens *in situ*. The lens is retained in place with a vacuum created by a fluid column in the attached tube, which is free hanging. It is not necessary for additional vacuum to be created by aspiration with a syringe at the end of the tubing during the procedure.

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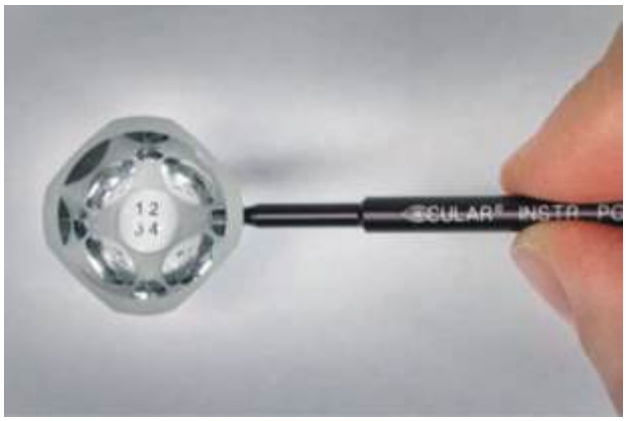


Figure 10.1.63 Posner indirect gonioprism. The observer can assess multiple quadrants of the iridocorneal angle at the same time from a frontal position, but no magnification is provided and the prism must be held in place by the observer.

Furthermore, indirect goniolenses are more difficult to use in the conscious patient, because they will not adhere to the eye via a vacuum mechanism, but require active application to the cornea with one of the examiner's hands via a handle or a tube extension. However, some examiners prefer the use of indirect goniolenses, and the ICA is easier to photograph through the flat surface (Miller & Bentley 2015). The Karickhoff diagnostic lens, Posner gonioprisms (Ocular Instruments), and Sussman gonioscope (Ocular Instruments) are examples of indirect gonioscopy lenses. There are various other single-, two-, and three-mirrored forms as well, some of which allow concurrent examination of the ICA and the ocular fundus via separate mirrors.

Practical Application of Gonioscopy

Gonioscopy can usually be performed in the conscious patient following topical anesthesia; sedation is only required in a few uncooperative patients (Bedford, 1973, 1977a, 1977b). Restraint of the patient's head should ideally be provided by a trained assistant, as the examiner will require both hands for the procedure. Both sitting and lateral recumbent positions have been described for canine gonioscopy (Martin, 1969a; Bedford, 1973, 1977b). Examination under sedation or anesthesia may be necessary if a lesion is within a less accessible area, for example the 12 o'clock position. Proparacaine (proxymetacaine) is a suitable local anesthetic in veterinary patients (Bedford, 1973). Gonioscopy lenses should be cleaned between patients by means of a 5-minute soak with 3% hydrogen peroxide to prevent the transmission of infectious diseases. The use of alcohol wipes may not be adequate and may cause material damage (Neubauer et al., 2009). It is important to flush the lens thoroughly prior to use to remove all traces of disinfectant.

After the topical anesthetic is instilled, 0.5%–2.5% methylcellulose solution is placed on the concave contact surface of the gonioscopy lens, which is then applied to the cornea by the examiner with one hand while the other hand keeps the eyelids open. The patient's head should be tilted slightly laterally or "nose down" by the assistant and the inferior edge of the lens is placed first, which will both prevent loss of the coupling agent and will help to displace the TEL. When applying a direct contact lens such as the Koeppe lens, initial gentle pressure onto the lens is required to create a vacuum, which will then allow retention of the lens on the cornea without further manual support for the remainder of the examination. The continued application of pressure to the globe via the contact lens should be avoided, as this might distort the relationship of the ICA structures, unless dynamic gonioscopy is actually required to screen for temporary peripheral adhesions (see the next section). Less viscous solutions, such as 0.9% saline, are not as effective at preventing air entering between the lens and the cornea. Air bubbles should be avoided, as they will prevent adequate visualization of the ICA. An exception with regard to the coupling medium is made, however, when a Lovac-Barkan lens is used. Here, the silicone tubing attached to the lens is flushed with sterile saline until the small well on the concave side of the lens is filled with fluid. The lens is then applied to the eye as previously described and the eyelids are closed firmly over the lens while further saline is flushed through the silicone tube via an attached syringe (Bedford, 1973). Once all air bubbles have been displaced between the lens and the cornea, the syringe is detached and the silicone tube is left to hang freely, creating gentle suction, which secures the lens on the corneal surface without additional manual support (see Fig. 10.1.62).

When using indirect gonioscopy lenses, no coupling medium may be required or 0.5% methylcellulose is used. After the lens is in place, a light source is required to illuminate the region of the ICA. A portable slit-lamp biomicroscope is ideal for providing magnification and stereopsis, but a handheld fundus camera can also provide good magnification and will allow photodocumentation of the ICA entrance (Bedford, 1973). Some examiners traditionally use an otoscope with the speculum removed, which obviously affords less magnification (Bjerkas et al., 2002). With direct gonioscopy lenses, the examiner must look into the lens from all four quadrants to obtain a complete image of the ICA, with the dorsal and lateral quadrants being the least accessible in the awake and upright patient. When performing indirect gonioscopy, the examiner must remember that the area of ICA visualized is opposite the position of the mirror (James, 2007). Gonioscopy is performed after routine intraocular examination because the coupling agent will obscure the view. Most manufacturers recommend extensive cleaning protocols for the use of gonioscopy lenses between patients, which in practice are rarely adhered to, but even with limited cleaning protocols there appears to be a very small risk

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of transfer of bacterial infection between canine eyes (Grundon et al., 2018).

The entire ICA and opening of the CC are systematically evaluated, with special attention given to angle width and pectinate ligament conformation. The normal canine pectinate ligament consists of fine strands of tissue that originate as solitary or "tent-like" structures from the iris base, traverse the CC, often interweaving, and insert onto the corneal endothelial surface (Fig. 10.1.64 and Fig. 10.1.65; Bedford, 1973, 1977b; Martin, 1969a; Troncoso, 1948; Wyman, 1973). The insertion line is somewhat variable in thickness and pigmentation, but can be seen in most pigmented dogs and is referred to as the deep pigmented line (Martin, 1969a; Wyman, 1973). A less densely pigmented line is visible in most dogs extending superficially and more axially along the cornea. This area, referred to as the superficial pigment line, represents the pigmentation at the corneoscleral limbus (see Fig. 10.1.64 and Fig. 10.1.65; Martin, 1969a; Wyman, 1973). The presence of both the superficial and deep pigment lines varies even between different quadrants of the same eye (Martin, 1969a). The canine pectinate ligament is less "comb like" than that of the ungulate, but not as thin and delicate as in the feline, and has been described as "trees in a forest" (McLellan & Miller, 2011; Troncoso, 1948). The appearance of the canine pectinate ligament varies both between breeds and within individual animals (Bedford, 1977b). Dogs with dark irides usually have darkly pigmented pectinate ligaments, although even in such individuals, the degree of pigmentation may vary, not only between eyes, but also in different quadrants within the same eye (Bedford, 1977b). In dogs with reduced iris pigment, the pectinate ligaments can be extremely fine and difficult to visualize (see Fig. 10.1.64).

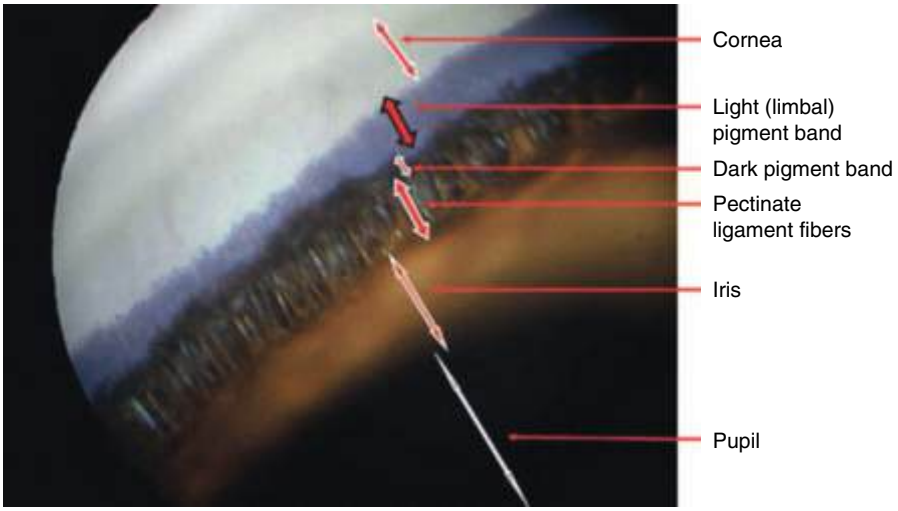


Figure 10.1.64 Normal iridocorneal angle in a Flat-Coated Retriever. (Courtesy of S. Ellis.)

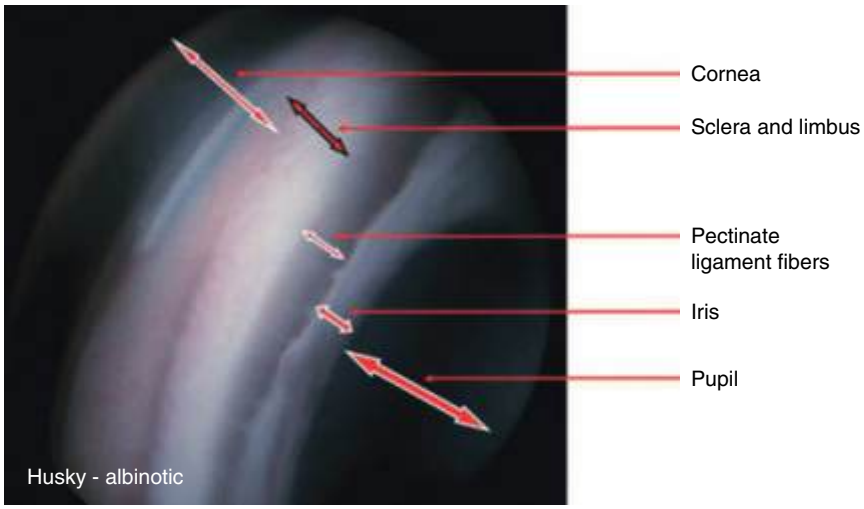


Figure 10.1.65 Normal iridocorneal angle in a blue-eyed Siberian Husky. (Courtesy of S. Ellis.)

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A small percentage of broader fibers (also termed *fibrae latae*) is considered a normal variation (Fig. 10.1.66), as opposed to the extensive abnormal and thickened fibers or sheets of tissue that characterize pectinate ligament dysplasia (PLD; Fig. 10.1.67). However, the percentage of "normal" focally dysplastic pectinate fibers proposed by investigators ranges from 6% to 12.5% to 25% of angle circumference (Bjerkas et al., 2002; Ekesten & Narfstrom, 1991; Read et al., 1998; Wood et al., 2001). The presence of synechia (especially peripheral anterior synechia), peripheral iris cysts, foreign bodies, neoplasia, granulomas, traumatic iridal dialyses or other injuries, and anterior segment colobomas should also be noted (Bedford, 1977b; Gelatt & Ladds, 1971; Lovekin, 1964; Martin, 1969a; Vainisi, 1970; Wyman, 1973). Gonioscopy has been used to identify intraocular extension of limbal masses such as melanomas (Featherstone et al., 2009; Gelatt & Ladds, 1971) and to define the extent of intraocular neoplasia, for example uveal neoplasia (Cook & Wilkie, 1999; Gelatt & Ladds, 1971; Gwin et al., 1982).

Indentation or dynamic gonioscopy may differentiate reversible ICA apposition from angle closure associated with peripheral anterior synechiae by the application of slight pressure at the peripheral cornea to try for separation (James, 2007). This method is not routinely applied in veterinary ophthalmology and may require sedation or anesthesia.

Gonioscopy is most commonly performed in the dog as an essential tool in the management of glaucoma (the ICA and CC may change as the disease progresses) and to distinguish between open- and closed-angle glaucoma (Bedford, 1975, 1977a; Bjerkas et al., 2002; Ekesten & Narfstrom, 1991; Gelatt & Ladds, 1971; Kato et al., 2006a, 2006b; van de Sandt et al., 2003; Wood et al., 2001). Canine patients presenting with unilateral glaucoma often have marked corneal pathology in the affected eye because of the elevated IOP, and it may not be possible to visualize the face of the ICA. Gonioscopic evaluation of the entrance to the ICA in the fellow eye is used in this situation to extrapolate information about the etiology of the glaucoma in the affected eye (Bedford, 1975). The appearance of the entrance to the ICA not only helps to elucidate the etiology of the glaucoma, but also is a possible predictor for the heritability of primary closed-angle glaucoma associated with goniodysgenesis (Bjerkas et al., 2002; Read et al., 1998; Wood et al., 1998, 2001). Key criteria to evaluate the entrance to the ICA include the morphology of the pectinate ligament 360° and angle–CC width (Bedford, 1975, 1977a, 1977b, 1980a, 1980b; Bjerkas et al., 2002; Cottrell & Barnett, 1988; Ekesten & Narfstrom, 1991; Gelatt & Ladds, 1971; Kato et al., 2006a; Wood et al., 1998, 2001).

PLD has been proposed as a marker for primary closed-angle glaucoma in a number of studies (Bjerkas et al., 2002; Ekesten & Narfstrom, 1991; Kato et al., 2006a; Read et al., 1998; Wood et al., 1998, 2001). Recently, it has been brought into question whether PLD is truly a congenital condition as progression of PLD has been described (Pearl et al., 2015), and instead of a one-off examination, it is recommended that gonioscopy is carried out at regular intervals to identify changes commensurate with PLD in predisposed dogs as they age. The width of the entrance to the ICA has also been investigated in correlation with IOP and primary closed-angle glaucoma in the dog (Bjerkas et al., 2002; Ekesten & Narfstrom, 1991). Subjectively, the ICA can be described as open, narrow, or closed. An attempt to make an objective assessment of the

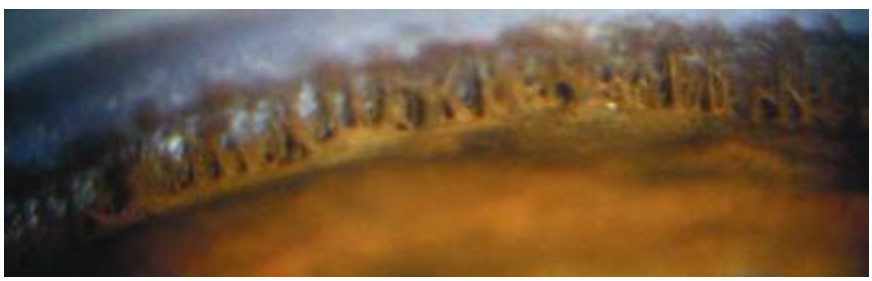


Figure 10.1.66 Focal fibrae latae in an otherwise normal iridocorneal angle of a Flat-Coated Retriever. (Courtesy of S. Ellis.)



Figure 10.1.67 Severely dysplastic pectinal ligament visible on gonioscopy in a Flat-Coated Retriever. (Courtesy of S. Ellis.)

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ICA entrance has been made by Ekesten and Narfstrom (1991) by estimation of the relative width of the ciliary cleft. In this method, the ratio between the anterior width of the CC (length of pectinate ligament from origin at iris base to its insertion at the deep limbal pigment band) and the total distance of the pectinate ligament from origin to the inner corneal surface is determined with the help of measurements obtained from goniophotographs. The ratio for the two variables is calculated and used to establish a grading system of angle width with five grades (closed, narrow, slightly narrow, open, and wide open; Ekesten & Narfstrom, 1991).

When performing gonioscopy, the examiner must remember the possible limitations of the technique and, in particular, that the examined area is limited to the entrance of the ICA (Gibson et al., 1998). In cases of extensive PLD, visual assessment of the deeper structures of the CC is not possible with gonioscopy. This means that an at least partially open CC may be present behind solid sheets of dysplastic pectinate ligament (van der Linde-Sipman, 1987). Additional diagnostic aids such as high-resolution ultrasound and ultrasound biomicroscopy may eclipse gonioscopy, as they will be able to provide a more complete picture of the ICA and CC (Bentley et al., 2005; Gibson et al., 1998).

Nasolacrimal Flush

Nasolacrimal flush is the manual irrigation of the nasolacrimal system to determine anatomic patency. Indications include delayed or absent fluorescein passage from the eye to the ipsilateral distal punctum (negative Jones test), epiphora without an identified cause, mucopurulent ocular or nasal punctal discharge (the latter in the horse), and dacryohemorrhea. The flush can be performed in either a normograde (orthograde; from the eyelid or lacrimal puncta) or retrograde (from the nasal punctum) direction; the choice depends on the species and the clinical signs. With the exception of the horse, normograde irrigation is routine in most species because identification and cannulation of the small nasal punctum are difficult; in the horse, the distal nasal punctum is large and easy to identify. The level of restraint required varies between species and individuals. The technique can be performed conscious in many dogs, rabbits, and cattle, whereas horses usually require sedation and cats usually require sedation or general anesthesia (because the puncta are very small and difficult to cannulate).

Topical anesthesia is achieved by topical anesthetic eye drops applied to the conjunctival sac (for a normograde flush) and by lidocaine gel to the nares (for a retrograde flush). With the aid of illumination and magnification (depending on the species), the upper and lower puncta are identified. The lacrimal puncta are slit-like openings in most species, but are round in the cat. In the dog, the slit-like puncta are 1 mm long by 0.3 mm wide and are located 2–5 mm lateral to the medial canthus, on the palpebral conjunctiva, where the line of meibomian glands end (Grahn & Sandmeyer, 2007). In the horse, the 2 mm slit-like puncta are located 8–9 mm lateral to the medial canthus (Latimer et al., 1984). The rabbit has a single lower punctum and the pig has a single upper punctum. In some animals, identification of the lacrimal puncta may be facilitated by a small amount of surrounding pigment. Cannulation of the upper lacrimal punctum first is recommended to avoid damage to the lower punctum (which is responsible for the majority of tear drainage) and because it is usually easier in terms of manual dexterity. A metal or Portex lacrimal cannula (e.g., Smiths Medical International, Brisbane, Australia) or intravenous catheter (without metal stylet) is appropriate for irrigation in the rabbit, cat (24- to 25-gauge), and dog (22- to 24-gauge; Fig. 10.1.68). Cannulation with a plastic cannula is made easier by cutting the end short and at an oblique angle (see Fig. 10.1.68B). A 2–5 mL syringe of sterile saline or eyewash is attached to the cannula prior to cannulation.

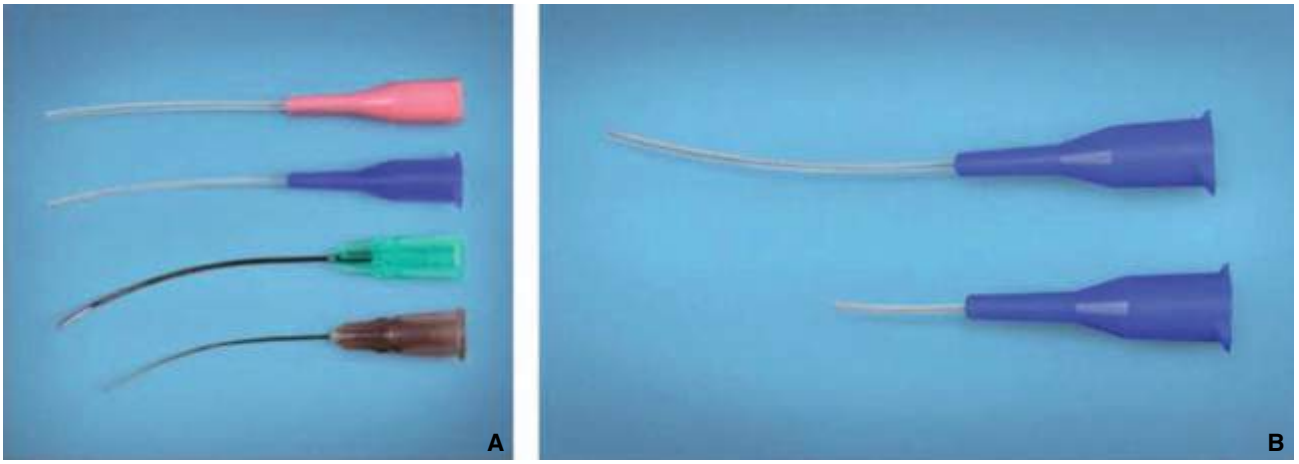


Figure 10.1.68 **A**. Selection of plastic and metal lacrimal cannulas suitable for performing a nasolacrimal flush in a small animal, for example a dog or cat. **B**. Cannulation with a plastic cannula is made easier by cutting the end short and at an oblique angle.

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With the upper lid everted to expose the upper punctum, the cannula is inserted in a ventromedial direction, following the line of the upper canaliculus (Fig. 10.1.69A, B). Fluid is slowly irrigated until it exits the lower punctum. This establishes patency of the upper and lower puncta, upper and lower canaliculi, and lacrimal sac. Digital pressure is then applied to occlude the lower punctum, diverting the irrigating fluid into the nasolacrimal duct. Fluid exiting from the ipsilateral nasal punctum establishes patency of the nasolacrimal duct. The muzzle should be directed ventrally to minimize fluid draining into the nasopharynx. Expelled debris may be collected for cytology, and culture and sensitivity if indicated. If necessary, the lower punctum can also be cannulated (Fig. 10.1.69C). If a normograde flush from either the upper or the lower punctum is unsuccessful, a retrograde flush can be performed under general anesthesia (conscious in the horse). Illumination and some form of speculum (e.g., vaginal speculum, otoscope head) are required to visualize the distal nasal punctum, which, in the dog, is ventrolateral near the alar fold. A Jackson's tomcat catheter is useful for cannulation of the nasal punctum in small animals; rigidity provided by the metal style facilitates initial cannulation.

In the horse, a retrograde flush is most commonly performed first (Crispin, 1988). The distal nasal punctum is large (3–4 mm in diameter) and therefore easily identified inside the external nares at the ventral mucocutaneous junction (Fig. 10.1.70A; Latimer et al., 1984). Suitable catheters are 4–6 Fr canine urinary catheter, 5 Fr feeding tube, or polyethylene tubing (Latimer et al., 1984). The tip of the catheter, coated with lidocaine gel, is inserted into the punctum for a distance of at least 5 cm (Fig. 10.1.70B). Gentle digital pressure should be applied to the surrounding area to minimize normograde fluid loss. A 10–20 mL syringe, filled with irrigating fluid (eyewash, sterile saline), is attached and gentle irrigation is continued until fluid exits the proximal puncta. Sneezing is common and may be violent. Each lacrimal punctum can be evaluated separately by occluding the opposite punctum with digital pressure. If retrograde irrigation is unsuccessful, normograde irrigation should be attempted, as previously described for small animals but with a larger cannula (e.g., open-ended tomcat catheter, teat tube syringe).

Gentle pulse pressure may be necessary to unblock an obstructed duct. However, excessive force, either during cannulation or irrigation, should be avoided to prevent iatrogenic trauma to the nasolacrimal system. Imaging in the form of plain and contrast skull radiography (dacryocystorhinography) and/or CT should be performed if irrigation is not possible (Noller et al., 2006; Nykamp et al., 2004; Rached et al., 2011; Schlueter et al., 2009).

PARACENTESIS

Paracentesis, the aspiration of fluid from a body cavity using a needle, can be performed on the eye for both diagnostic and therapeutic purposes. Aqueous and vitreous paracentesis requires some expertise and familiarity with ocular anatomy, and should only be used where its potential contribution to the management of the case is clearly understood.

Aqueous Paracentesis (Keratocentesis)

Aqueous paracentesis, the aspiration of a small amount of aqueous humor from the anterior chamber, has both diag-

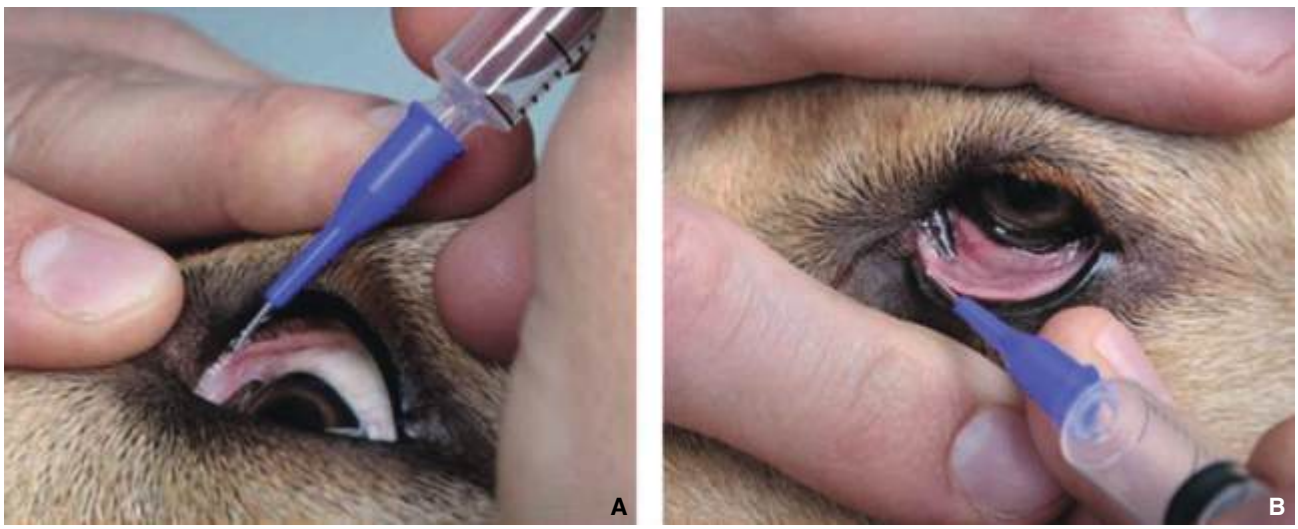


Figure 10.1.69 Nasolacrimal flush in a dog. **A**. With a 2–5 mL syringe of sterile saline or eye wash attached to the cannula, and the upper lid everted to expose the upper punctum, the cannula is inserted into the punctum in a ventromedial direction, following the line of the upper canaliculus. (Reproduced with permission from Featherstone, H., & Holt, E. (2011) *Small Animal Ophthalmology: What's Your Diagnosis?* Chichester: Wiley-Blackwell, Fig. 2.2d (B), p. 35.) **B**. Cannulation of the lower punctum.

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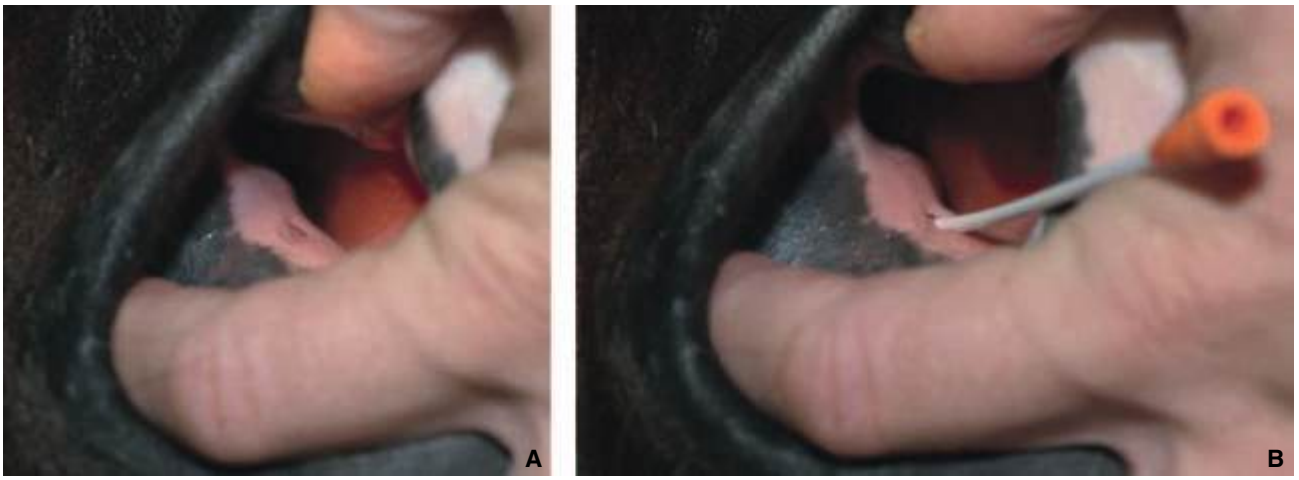


Figure 10.1.70 Nasolacrimal flush in a horse. **A**. The distal punctum is large (3–4 mm in diameter) and easily identified inside the external nares at the ventral mucocutaneous junction. **B**. The tip of a catheter, coated with, for example, lidocaine gel, is inserted into the punctum and directed proximally for several centimeters.

nostic and therapeutic purposes (Hazel et al., 1985; Olin, 1977). The procedure is relatively quick and simple if performed by someone with appropriate training and experience, but complications can occur. The procedure can be performed either with sedation and topical anesthesia or under short-acting general anesthesia. If performed in the standing horse under sedation, retrobulbar and auriculopalpebral nerve blocks should also be performed. Some clinicians perform aqueous paracentesis with only topical anesthesia, but the risk of complications is greater. The conjunctival sac, and most importantly the bulbar conjunctiva, should be cleaned with a dilute (5%) povidone–iodine solution followed by sterile saline solution or eyewash. Topical anesthetic eye drops are applied to the ocular surface; a cotton-tipped applicator soaked with the topical anesthetic agent can be pressed on the site of needle insertion to improve the level of anesthesia. Subconjunctival mepivacaine also facilitates the procedure in conscious or sedated animals. An eyelid speculum is placed.

In theory, the needle can be inserted at any point on the limbus circumference, but the dorsolateral quadrant tends to be practical to avoid the TEL and for comfortable hand placement. Furthermore, in large herbivores such as the horse, the dorsal to dorsolateral limbus is preferred to take advantage of the scleral extension beyond the iris base. The bulbar conjunctiva is grasped with small forceps near the site of entry, and a 27- to 30-gauge needle is inserted (bevel up) through the clear cornea immediately adjacent to the limbus or the subconjunctival limbus (Allbaugh et al., 2011). A gentle drilling and tunneling motion facilities passage through the sclera or cornea, and may facilitate rapid formation of a seal after the needle is withdrawn. The needle must enter the anterior chamber anterior to the iris and be directed parallel with the iris (Fig. 10.1.71A). The tip of the needle should be visualized all the time to avoid lacerating the iris or anterior lens capsule. Although not essential, some form of magnification (e.g., loupes) is helpful, particularly in small animals. The volume of the anterior chamber varies between species: 0.3 mL (rabbit), 0.4–0.77 mL (dog), 0.6 mL (cat), and 2.4–3 mL (horse; Gilger et al., 2005; Gum et al., 2007). A small volume (0.1–0.5 mL) of aqueous humor can be removed by one of several methods. A syringe may be attached to the needle, either before or after the needle has entered the anterior chamber, to slowly aspirate the aqueous humor. Alternatively, the aqueous humor that fills the needle hub may be collected into a capillary tube, without the need for a syringe. The latter is less awkward and offers better control over the needle (May & Noll, 1988). The use of a compact suction pipette has been described to reduce instrumentation and minimize needle dead space (O'Rourke et al., 1991, 2004). To prevent the profound hypotony post-paracentesis, an equal volume of saline or balanced salt solution can be injected, and IOP measured.

Possible complications of aqueous paracentesis include hyphema, anterior lens capsule rupture with subsequent phacoclastic uveitis, corneal edema associated with endothelial damage, anterior uveitis, endophthalmitis, choroidal edema, and hemorrhage. The technique is more challenging if the cornea is opaque and in the presence of iris thickening or displacement (e.g., iris bombé). Anterior uveitis will always develop following paracentesis, even if the technique is rapid and straightforward, and is detected as an increase in the prostaglandin and protein levels in the aqueous humor (Rankin et al., 2002, 2011b; Regnier et al., 1995; Ward, 1996; Ward et al., 1992). Inflammation can be minimized by using the appropriate needle gauge, very slow removal of aqueous humor, injecting an equal amount of sterile normal saline or balanced salt solution into the

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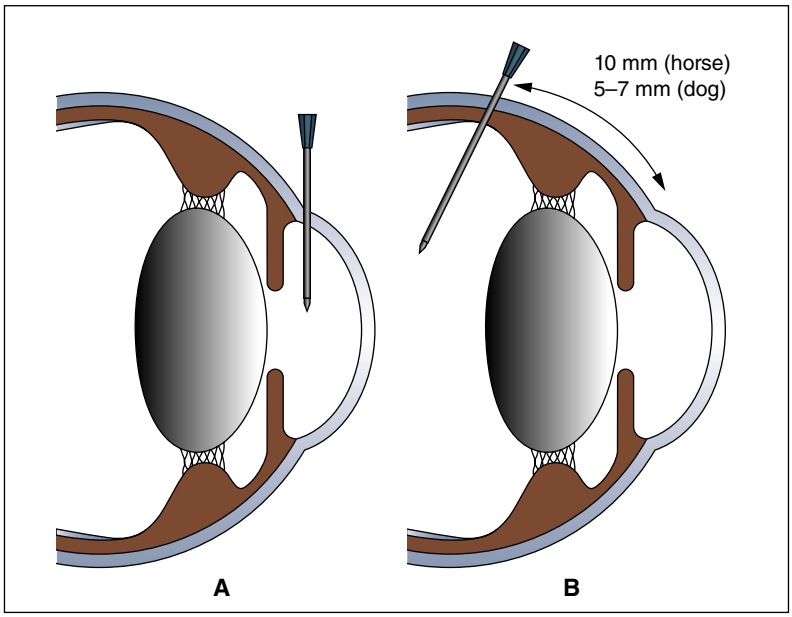


Figure 10.1.71 Paracentesis. **A**. Aqueous paracentesis. The needle is inserted (bevel up) through the clear cornea immediately adjacent to the limbus or the subconjunctival limbus. A tunneling motion facilitates passage through the sclera or cornea. The needle must enter the anterior chamber anterior to the iris and be directed parallel with the iris. **B**. Vitreous paracentesis. The needle is inserted posterior to the limbus (5–7 mm in the dog and 10–12 mm in the horse) and firmly tunneled through the sclera and pars plana of the ciliary body. The needle must be directed toward the posterior pole to avoid the lens. (Illustration by H. Featherstone and Simon Scurrell.)

anterior chamber (unless the aim of paracentesis was to reduce IOP), and not exceeding the appropriate volume for the species (Gilger & Stoppini, 2011; Strubbe & Gelatt, 1999). The effect of different needle sizes for aqueous paracentesis in normal dogs has been evaluated by tonometry and fluorophotometry (Allbaugh et al., 2011). Of the three sizes used, the largest (25-gauge) caused a significant increase in blood–aqueous barrier breakdown and transient ocular hypertension at 20 minutes, compared with the two smaller sizes (27- and 30-gauge). Furthermore, there was evidence of breakdown of the blood–aqueous barrier in the contralateral eye in all dogs and with all needle sizes.

Diagnostic tests for aqueous humor samples obtained by aqueous paracentesis include cytology, culture and sensitivity, protein measurement, PCR, and antibody titers (e.g., *Leptospira* spp., *Toxoplasma gondii*, *Bartonella* spp.; Chavkin et al., 1994; Faber et al., 2000; Gilger et al., 2008; Halliwell & Hines, 1985; Halliwell et al., 1985; Krohne et al., 1995; Lappin et al., 2000; Maggs et al., 1999; Matthews & Poulter, 1986; Olin, 1977; Powell et al., 2010; Wurster et al., 1982). Antibody titers can be used to calculate the Goldmann–Witmer coefficient (C-value), which compares the antibody titer in aqueous humor with that in the serum in order to establish the presence or absence of local antibody production (Chavkin et al., 1994). Aqueous paracentesis is also used extensively in research to determine drug levels in aqueous humor and other pharmacokinetic parameters (Clode et al., 2006, 2010, 2011; Gilger et al., 2000a, 2000b; Gilmour et al., 2005; Norcross et al., 2010; Regnier et al., 2003, 2008; Westermeyer et al., 2011; Yu-Speight et al., 2005).

There are several therapeutic indications for aqueous paracentesis. It can provide immediate relief of ocular hypertension (e.g., postoperative hypertension following phacoemulsification), which is useful when intravenous mannitol cannot be used or if topical therapy has been ineffective. It allows the intracameral injection of drugs, for example tissue plasminogen activator in eyes with postsurgical or traumatic hyphema and/or fibrin clots (Gerding et al., 1992). The procedure can also be used to aspirate uveal cysts.

Vitreous Paracentesis

Vitreous paracentesis (hyalocentesis) is the aspiration of small amounts of vitreous humor for both diagnostic and therapeutic purposes. Vitreous paracentesis is usually performed with the patient under short-acting general anesthesia or heavy sedation. Preparation is the same as for aqueous paracentesis in terms of aseptic preparation of the ocular surface and placement of an eyelid speculum. Visualization of the posterior segment is aided by inducing mydriasis with a short-acting mydriatic (e.g., tropicamide) if the anterior segment is clear. The site of needle entry is very important and varies with species. In the dog, the general recommendation is 5–7 mm posterior to the limbus, but the distance

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varies with the ocular quadrant and globe size. In the medium-sized mesaticephalic dog, the distances posterior to the limbus for safe needle entry are 7 mm (dorsolateral quadrant), 6 mm (ventrolateral quadrant), 5 mm (ventromedial quadrant), and 4–5 mm (dorsomedial quadrant; Fig. 10.1.71B; Smith et al., 1997). These sites are likely to be more posterior in larger dogs with larger eyes (Smith et al., 1997). In the horse, the recommended site is 10–12 mm posterior to the limbus in the dorsolateral quadrant (Miller et al., 2001; Stoppini & Gilger, 2017). The needle size varies from 26-gauge (dog, cat) to 23- to 25-gauge (horse). The globe is stabilized by grasping the bulbar conjunctiva with forceps adjacent to the site of needle entry. The needle is gently but firmly tunneled through the sclera and pars plana of the ciliary body, directed toward the posterior pole to avoid the lens. Using a syringe attached to the needle, 0.1–0.3 mL of fluid is slowly aspirated (sometimes more in the end-stage, glaucomatous eye). The volume of the vitreous varies between species: 1.5 mL (rabbit), 1.7–3.2 mL (dog), 2.8 mL (cat), and 26–28.8 mL (horse; Gilger et al., 2005; Gum et al., 2007). The needle may need to be repositioned to find areas of liquefied vitreous or gently flushed if the tip appears blocked. Normal vitreous and granulomatous or neoplastic material may require more aggressive aspiration and, in some cases, a larger-gauge needle. This procedure can also be performed with magnification, for example loupes or operating microscope, or with ultrasound guidance to improve the accuracy of needle placement.

Possible complications of vitreous paracentesis include intraocular hemorrhage, retinal tear or detachment, lens subluxation, cataract formation, uveitis, and endophthalmitis. The incidence of lens damage in humans is very low, 0.009% (2/21,653), when the technique is performed by experienced personnel (Meyer et al., 2010).

As for aqueous humor, diagnostic tests for vitreous humor samples obtained by paracentesis include cytology, culture and sensitivity, protein measurement, antibody titers (e.g., *Leptospira* spp.), and PCR (Wollanke et al., 2001). Vitreous paracentesis is also used extensively in research to determine drug levels in vitreous humor and drug pharmacokinetics (Gilger et al., 2000a, 2000b; Gilmour et al., 2005; Norcross et al., 2010; Regnier et al., 2008).

Aqueous and Vitreous Humor Samples

The general recommendation for cytology and culture of body fluids is to place the sample in an ethylenediaminetetraacetic acid (EDTA) tube and a sterile plain tube, respectively (culture cannot be performed from fluid from an EDTA tube; Table 10.1.7; Prasse & Winston, 1999; Raskin, 2001). A direct smear should also be submitted to enable the clinical pathologist to compare the cellularity of the sample and the appearance of the cells at the time of collection with that of the fluid received in the tube(s). A sediment smear is preferable to a direct smear for fluids of low cellularity (less than 2000 cells/μL), and is prepared by immediate cytocentrifugation (cytospin). If cytospin equipment is not available, a direct smear is still beneficial for fluids of low cellularity as well as for other body fluids. Both direct and sediment smears should be submitted unstained.

In clinical ophthalmology, microbiology and cytology are the most commonly required tests for aqueous and vitreous humor samples. The sample should be divided into the following submissions: fluid in a plain tube (for microbiology); fluid in a pediatric EDTA tube and an unstained sediment smear prepared by cytospin (for cytology; see Table 10.1.7). An unstained direct smear can also be submitted if cytospin is unavailable, but is most likely to be diagnostic if the humor is grossly turbid. Like cerebrospinal fluid, samples of aqueous and vitreous humors are low volume and usually of low cellularity. The following points further help the clinician to achieve a diagnostic sample: discuss the test(s) required with the chosen laboratory prior to sampling; use pediatric tubes if possible; and use a same-day courier to expedite arrival at the laboratory (to maximize cell preservation).

Given the risks of paracentesis, the examiner must consider the risk–benefit ratio before proceeding. In clinical practice, aqueous humor cytology is often not rewarding, with the exception of diagnosing intraocular lymphoma (Finger et al., 2006; Linn-Pearl et al., 2015). Linn-Pearl and colleagues (2015) assessed the validity of aqueocentesis as a component of the investigations in dogs and cats with anterior uveitis. The technique was primarily useful to diagnosis lymphoma in both species; aqueous humor cytology alone was not diagnostic in nonneoplastic cases, but supplemented other diagnostic tests. Other molecular techniques such as

Table 10.1.7 Recommendations for aqueous and vitreous samples.

Test	Transport Medium	Shipping Conditions
Cytology	Unstained sediment smear prepared by cytospin	Same-day courier
	Pediatric EDTA tube (plain tube if unavailable)	Same-day courier
	(Unstained direct smear if humor grossly turbid)	
Bacteriology	Plain tube (not EDTA) or designated microbiology swab	Refrigerate until shipping, normal post
Fungal culture	Plain tube (not EDTA) or designated microbiology swab	Refrigerate until shipping, normal post
Polymerase chain reaction	Plain tube	Normal post

EDTA, ethylenediaminetetraacetic acid.

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PCR for antigen receptor rearrangement can be used for further diagnostics (Pate et al., 2011). In contrast, aqueous humor testing was unhelpful in the diagnosis of feline infectious peritonitis (FIP). The utility of an immunocytochemical assay using aqueous humor was evaluated in 26 cats with confirmed FIP (Felten et al., 2017). False-positive results and an overall accuracy of 69.4% showed the limited benefit to this test. For endophthalmitis, diagnostic vitreous paracentesis is considered to have a higher sensitivity than aqueous paracentesis (Brightman et al., 1986; Martin, 2005).

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10.2

Ophthalmic Examination and Diagnostics

Part 2: Ocular Imaging

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Role of Conventional Radiography

In human medicine the role of the traditional skull or orbital radiograph has been supplanted in the modern era by cross-sectional imaging techniques, including computed tomography (CT) and magnetic resonance imaging (MRI; Lee et al., 2009; Moseley, 1991; Sanders et al., 1994). In veterinary ophthalmology the relative economy and availability of routine radiography when compared to cross-sectional imaging techniques ensures an ongoing role for this technique in the investigation of many cases of orbital and neuro-ophthalmic disease. Although the complex nature of the skull, the superimposition of tissues, and the poor ability to differentiate orbital soft tissues all impair radiographic assessment, important information can still be obtained with conventional radiographs. The main utility of conventional radiography in veterinary ophthalmology is to evaluate the bony orbit for evidence of osteolysis, bone remodeling, or fracture; to assess the nasal cavity, frontal sinuses, and maxillary dental arcades for pathology; and to assist in identification of radiodense foreign bodies. It should be noted that in some situations such as trauma with bony fracture and dental disease, conventional radiography may be superior to cross-sectional imaging techniques (Burk & Feeney, 2003). When an orbital or ocular malignancy is suspected, survey radiology of the thorax and abdomen, as well as abdominal ultrasound, is often performed at the time of orbital imaging, to help rule out metastatic disease.

Optimizing Conventional Radiographic Studies

Obtaining useful diagnostic information from conventional skull and orbital radiographs is challenging. To optimize the information obtained from conventional radiography, the following steps are necessary:

- Select appropriate radiographic views
- Obtain diagnostic radiographs
- Interpretation of the radiographs

Select Appropriate Radiographic Views

Selection of the most appropriate radiographic views for a specific disease presentation requires a good knowledge of basic and more topographically specific radiographic views available for the skull. A series of views is necessary to thoroughly assess the dorsal, medial, and lateral bony margins of the canine orbit. Both orbits are always imaged so that a comparison can be made of the two sides. A routine study should include lateral and dorsoventral (DV) and sometimes DV intraoral radiographs, which provides finer detail of the nasal cavity, maxillary recess, and medial orbital wall (Dennis, 2000).

Radiographic projections that are more topographically specific may be used to assess the orbit, nasal cavity and sinuses, maxillary molar teeth, and tympanic bullae. The recommended radiographic projections based on the region of the skull being investigated are reported for small animals (Burk & Feeney, 2003; Ferrell et al., 2007; Johnston & Feeney, 1980) and the horse (Ferrell et al., 2007; Park, 1993; Pease, 2007).

In the dog the lateral and lateral oblique projections are used to provide information regarding the cranial, dorsal, and lateral bony orbit, as well as the sinuses, nasal cavity, and maxillary dental arcades (Johnston & Feeney, 1980). The rostrocaudal (frontal) tangential projection is used to evaluate the frontal sinus, while the rostrocaudal open-mouthed projection delineates the tympanic bullae (Burk & Feeney, 2003; Ferrell et al., 2007). The rostrocaudal views also image the medial and lateral bony orbit (Johnston & Feeney, 1980) and are useful in identifying frontal bone osteolysis in cases of orbital neoplastic disease (Dennis, 2000). The ventrodorsal (VD) open-mouthed view is essential for evaluating the

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nasal cavity and frontal sinuses, and is also useful for evaluation of the maxillary teeth (Burk & Feeney, 2003) and the rostral extremity of the bony orbit (Johnston & Feeney, 1980). Improvised skyline views may be used to image any region of pathology identified on the skull's surface, and may provide information not discernible on routine orthogonal projections.

Obtain Diagnostic Radiographs

To obtain diagnostic radiographs, strict adherence to good basic radiographic technique is required. Full immobilization under general anesthesia is essential for high-quality diagnostic skull radiographs and to reduce operator exposure. Patient positioning is particularly critical for the skull, as rotation or tilting in any plane will severely compromise the interpretability of the radiographs. It is necessary to use various facial features (e.g., medial canthii or palpebral fissures) and palpable landmarks (e.g., frontal processes of zygomatic bones) to align certain planes precisely in relation to the film plane. Radiolucent foam pads and wedges are used to position the patient's head. Inaccurate positioning compromises symmetry, which is so important in the interpretation of skull radiographs (Ferrell et al., 2007).

Interpretation of the Radiographs

A good knowledge of the skull's complex gross and radiographic anatomy is essential for radiographic interpretation. Numerous publications are available describing and illustrating the radiographic anatomy of dogs and cats (Coulson & Lewis, 2002; Schebitz & Wilkens, 2004, 2005a; Smallwood & Spaulding, 2007), horses (Schebitz & Wilkens, 2005b; Smallwood & Spaulding, 2007), and a range of exotic species (Silverman & Tell, 2005), and access to such reference material while interpreting skull radiographs is recommended. A systematic approach to analysis of a radiographic skull study is needed and various topographic or regional systems have been described (Burke & Feeney, 2003; Ferrell et al., 2007).

The bilateral symmetry of the skull allows direct comparison of the right and left sides on VD/DV projections for differences in structure or opacity (Ferrell et al., 2007). The main aim of radiographic assessment of orbital disease is to identify bony pathology, including fractures, osteolysis, and osteoproliferative lesions. It is important to note that although bone lysis is highly suggestive of malignancy in dogs and cats (Boroffka et al., 2007; Calia et al., 1994; Dennis, 2000; Hendrix & Gelatt, 2000), a tissue diagnosis is still required to rule out infectious processes, in particular fungal disease (Calia et al., 1994; Halenda & Reed, 1997). Furthermore, orbital radiography may not be highly sensitive in detecting orbital bone pathology. In a study comparing MRI and radiography in small animals with orbital diseases, 11 of 16 cases with confirmed orbital disease had no radiologically apparent orbital bony changes, despite the fact that in 4 of the 11 cases MRI showed minor extension of the tumor beyond the orbit (Dennis, 2000). From this it was concluded that radiography was helpful only in cases in which neoplastic disease extended markedly beyond the confines of the orbit into the nasal chamber and paranasal sinuses (Dennis, 2000).

Diseases of structures adjacent to the orbit, including the sinuses, nasal cavity, and maxillary premolar and molar teeth, may be radiographically apparent. Other pathology, including orbital and periorbital emphysema and calcification of soft tissues, may also be identified. Orbital emphysema may follow infection or trauma (Johnston & Feeney, 1980) or be a complication of enucleation (Bedford, 1979; Martin, 1971). Calcification of the ocular and orbital tissues may be dystrophic or metastatic (Dutton, 2010a). Although soft tissue calcification may be apparent on conventional radiographs (Sundheim & Lapayowker, 1976), this pathology is best evaluated on computed tomography (Dutton, 2010a). In humans, ocular calcification has been described in optic nerve drusen, scleral plaques, phthisis bulbi, osteoma, and retinoblastoma, and has been associated with lacrimal gland epithelial tumors, meningiomas, gliomas, schwannomas, fibro-osseous tumors, epithelial cysts, dermoid cysts. and inflammatory diseases (Aviv & Miszkiel, 2005; Dutton, 2010a; Sundheim & Lapayowker, 1976; LeBedis & Sakai, 2008).

Conventional radiographs may be used to screen for radiodense foreign bodies. For accurate localization two orthogonal views are needed. Screening of patients to rule out intraorbital metallic foreign bodies prior to MRI may be indicated in some cases. Movement of such foreign bodies in the magnetic field may result in injury to the globe or other soft tissues within the skull (Lee et al., 2009).

Contrast Radiography

Contrast Radiography for Orbital Disease

Contrast radiographic techniques described for the investigation of orbital disease have included zygomatic sialography (Johnston & Feeney, 1980), positive and negative contrast orbitography (Burk & Feeney, 2003), venography (Burk & Feeney, 2003), angiography (Burk & Feeney, 2003; Gelatt et al., 1970), and optic thecography (Burk & Feeney, 2003). The aim of these techniques is to improve the ability to differentiate orbital soft tissue structures compared to standard radiographs, and potentially delineate tumors or inflammatory lesions. These techniques have not become established for the routine investigation of orbital disease and in the modern era they have been supplanted by cross-sectional imaging techniques.

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Zygomatic Sialography

Zygomatic sialography is the only contrast radiographic technique that is still utilized occasionally for the evaluation of orbital disease in dogs. Zygomatic sialography involves the retrograde instillation of a nonionic iodinated contrast medium into the zygomatic salivary gland duct. Lateral and DV radiographs are obtained to ensure correct exposures prior to contrast instillation. The zygomatic papilla is located lateral and caudal to the last upper molar tooth. The papilla is cannulated using a 22–25 gauge cannula and the contrast medium is instilled at 0.5–1 ml per 10 kg; instillation may be repeated prior to each exposure (Harvey, 1969; Wallack, 2003). Prior to instillation of contrast media, samples of saliva should be collected for cytology and culture and sensitivity testing. The sialoadenogram reveals the zygomatic salivary gland to be large, single lobed, and positioned ventral to the rostral end of the zygomatic arch (Harvey, 1969). Radiographic abnormalities may include filling defects, enlargement of the nasolacrimal duct, formation of fistulae, and displacement of the gland (Johnston & Feeney, 1980).

Dacryocystorhinography

Dacryocystorhinography (DCRG) is a contrast radiographic procedure that may be used to assess diseases affecting any level of the nasolacrimal system. The technique for performing clinical DCRG in the dog has been described (Johnston & Feeney, 1980; Gelatt et al., 1972; Yakely & Alexander, 1971). DCRG is performed with the patient under general anesthesia. Lateral and DV radiographs are obtained to ensure correct exposures prior to contrast instillation. The patient is positioned for a lateral radiograph with the affected side uppermost and the nose slightly lowered to prevent retrograde flow of contrast medium into the nasal cavity. The upper punctum is cannulated and the nasolacrimal system flushed with 0.9% saline. An iodinated contrast medium agent is injected via the upper punctum while digital pressure or forceps occlude the lower punctum. The volume of contrast medium needed for the DCRG varies from 0.5–1.0 mL in the dog, cat, and rabbit to 3.0–5.0 mL in the horse, cow, and llama (Källberg, 2007). The contrast medium is injected continuously until a few drops appear at the external nares, or reflux occurs from the upper punctum around the cannula, at which stage the radiograph is taken (Fig. 10.2.1A). Additional radiographic projections including DV and oblique views are obtained as required to characterize any pathology identified. Additional contrast medium should be instilled if incomplete filling of the nasolacrimal system is evident during the DCRG study.

Gross anatomic studies and DCRG have been used to study the normal anatomy of the nasolacrimal system in the dog (Gelatt et al., 1972; Johnston & Feeney, 1980; Yakely & Alexander, 1971), cat (Gelatt et al., 1972), horse (Latimer et al., 1984), llama (Sapienza et al., 1992), sheep (Gilanpour, 1979), goat (Shadkhast et al., 2008), one-humped camel (Shokry et al., 1987), and rabbit (Marini et al., 1996). Clinically DCRG has been used to study a variety of congenital nasolacrimal system anomalies, including nasolacrimal duct atresia in the alpaca (Mangan et al., 2008; Sandmeyer et al., 2011), llama (Sapienza et al., 1996), horse (Latimer et al., 1984; Lundvall & Carter, 1971), and cattle (Heider et al., 1975); anomalous nasolacrimal duct openings (McLaughlin et al., 1985; Wilkie & Rings, 1990) and dysplastic lacrimal puncta (van der Woerdt

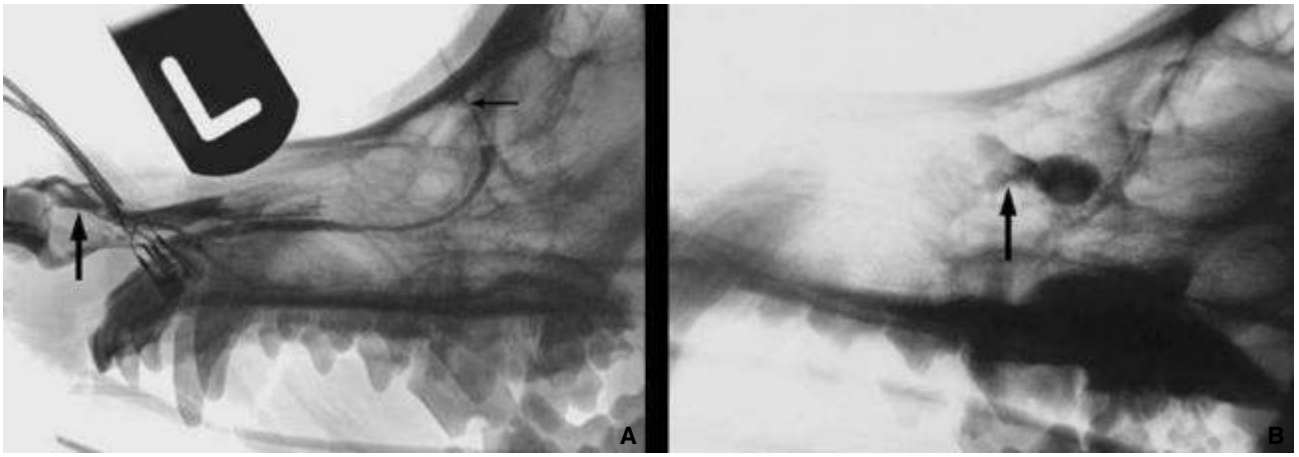


Figure 10.2.1 **A**. Dacryocystorhinogram of the normal nasolacrimal duct system of a 9-year-old West Highland White Terrier. The cannula placed via the upper puncta into the lacrimal sac is visible (small arrow). Contrast medium is present at the nares and refluxing into the nasal cavity (large arrow). Note that the metallic pulse oximetry device is superimposed over the rostral nares and maxillary region. **B**. Dacryocystorhinogram of a 3-year-old Labrador Retriever with chronic dacryocystitis affecting the right side. Obstruction of contrast is evident at the level of the third upper premolar tooth (arrow). Proximal to the obstruction there is an irregular cystic dilation of the duct. No contrast is visible distal (rostral) to the obstruction. Magnetic resonance imaging in this case revealed a cystic dilation of the nasolacrimal duct within the maxillary bone.

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et al., 1996) in cattle; and congenital lacrimal gland cyst (dacryops) in the dog (Cullen & Grahn, 2003; Grahn & Mason, 1995; Ota et al., 2009).

Acquired nasolacrimal diseases may arise from the nasolacrimal duct or contiguous structures, including the nasal cavity, frontal sinuses, and maxillary dentition. Primary or secondary nasolacrimal duct pathology due to trauma or neoplastic or inflammatory diseases may be recognized on DCRG as complete or partial obstruction, deviation, cystic dilatation, and/or irregularities of the nasolacrimal duct (Johnston & Feeney, 1980). DCRG is integral to the surgical treatment of nasolacrimal disorders, providing information regarding the nature and location of pathology. An abnormal dacryocystorhinogram with obstruction and an irregular cystic dilation of the nasolacrimal duct in a dog with chronic dacryocystitis is shown in Fig. 10.2.1B.

DCRG in cases of dacryocystitis in the dog have revealed cystic dilations of the nasolacrimal duct (Lussier & Carrier, 2004; Singh et al., 2004; van der Woerdt et al., 1996), periductal osteolysis (Yakely & Alexander, 1971), distention of the nasolacrimal sac associated with granuloma formation (Giuliano et al., 2006), and plant seed foreign bodies (Yakely & Alexander, 1971). In some cases of dacryocystitis, DCRG has facilitated surgical planning of drainage procedures in which communications are created between the cystic or dilated regions of the nasolacrimal duct and the nasal cavity (Giuliano et al., 2006; Lussier & Carrier, 2004; van der Woerdt et al., 1997). In cases of epiphora in the dog, DCRG has identified nasolacrimal duct obstruction due to dental disease (Gelatt et al., 1972; Yakely & Alexander, 1971) and nasal cavity neoplasia (Gelatt et al., 1972). In the horse, DCRG has been used to evaluate purulent dacryocystitis secondary to periapical tooth root infection (Ramzan & Payne, 2005), obstruction of the nasolacrimal duct with secondary epiphora due to lacrimomaxillary suture exostosis (Carslake, 2009), and posttraumatic injury (Cruz et al., 1997; Wilson & Levine, 1991).

Computed tomography dacryocystorhinography (CT-DCRG) provides superior imaging of the nasolacrimal system and may have a role in the evaluation of more complex nasolacrimal disorders in veterinary patients (see later section).

Cross-Sectional Imaging Techniques: Computed Tomography and Magnetic Resonance Imaging

The cross-sectional imaging techniques of CT and MRI have greatly improved the diagnosis and management of a diverse range of ocular, orbital, and neuro-ophthalmic conditions. In order to maximize the information gained from an imaging study, it is important for the clinician to understand the basic mechanics, indications, and contraindications of the specific imaging modality, and the specific sequences used in neuro-ophthalmic and orbital imaging (Lee et al., 2009). Furthermore, discussion with imaging colleagues regarding the reason for imaging the patient and the suspected nature and location of pathology will allow selection of the most appropriate imaging study.

The advantages of MRI over CT include the absence of ionizing radiation, direct multiplanar imaging that does not require changing the position of the patient in the gantry, enhanced anatomic detail, and soft tissue characterization. MRI is considered superior to CT for most neuro-ophthalmic indications, with better assessment of both the intra- and extraorbital optic nerve (Lee et al., 2009; Morgan et al., 1994; Penninck et al., 2001). The advantages of CT over MRI include shorter data acquisition time, decreased slice thickness and greater special resolution, more precise imaging of cortical bone and soft tissue mineralization, more precise imaging of acute hemorrhage, and the ability to image when magnetic foreign bodies are present (Lee et al., 2009; Morgan et al., 1994; Penninck et al., 2001). MRI and CT are therefore complementary and when combined often provide a more complete picture of the nature of disease.

Computed Tomography

Basic Principles and Physics

CT imaging utilizes the variable attenuation of X-ray photons by tissues of different densities to generate cross-sectional images of the body (Dutton, 2010b; Tidwell, 2007). The frame of the CT machine that houses the X-ray tube, collimators, and detectors is referred to as a gantry. The gantry has a large opening into which the patient is placed for CT imaging. Within the gantry of the CT machine an X-ray tube emits a thin, collimated, fan- shaped beam of X-rays that are attenuated as they pass through the patient. The transmitted X-rays are subsequently detected by an arc of detectors positioned on the opposite side of the gantry. The most recent generation of CT scanners utilize a helical (or spiral) technology in which the X-ray source rotates continuously in one direction as the patient moves forward at a constant rate, so the X-ray beam describes a spiral path around the body (Kalender et al., 1990). The continuous acquisition of data as the patient moves through the gantry reduces the imaging time, motion artifacts, and overall radiation exposure. Multislice or multidetector-slice CT scanners utilize the principles of helical scanners, but incorporate multiple rows of detectors that can therefore acquire multiple imaging slices per rotation of the X-ray tube, increasing the area scanned in a given time by the X-ray beam (Flohr et al., 2005).

The X-ray attenuation data collected by the detectors (from the multiple X-ray beam projection angles through the patient) are analyzed using a computer, and the density, or

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attenuation value, of each unit of tissue (voxel) within the slice is calculated. Using this attenuation value, a CT number for each voxel of tissue is calculated. The value of the CT number is expressed in Hounsfield units (HU) in honor of Sir Godfrey Hounsfield, who in 1967 developed the first modern CT scanner (Goldman, 2007). Hounsfield units represent an arbitrary scale in which the attenuation of water is assigned 0 HU, cortical bone +1000 HU (white on final image), and air −1000 HU (black on final image; Dutton, 2010b). To generate a CT image the CT number of each voxel within a slice is assigned to a specific shade of gray. This shade of gray is assigned to the corresponding picture element (pixel) within the reconstructed CT image matrix. The resultant CT image represents the voxel densities of tissues within the scanned slice of tissue, and therefore is displayed without the superimposition of overlying tissues, such as occurs with conventional radiography.

The range of CT numbers, from −1000 HU for air to +1000 HU for bone, which can potentially be represented as shades of gray, far exceeds that which is visually discernible (perhaps fewer than 100), and modern CT images are typically displayed using about 250 gray levels (Goldman, 2007). The simultaneous display of all gray-scale levels (i.e., the entire range of CT numbers) would mean that many soft tissue structures would be displayed with the same gray level as their surroundings, and thus would not be visible. This problem is solved by windowing, in which the radiologist interactively manipulates the gray scale to enhance the subtle differences between tissues of interest. This involves setting the window width (WW) and window level (WL). The WW is the range of CT numbers displayed as distinct gray levels; this varies with the tissues being examined, but is usually in the range of 350–400 HU. The WL is the level on which this range is centered (e.g., for orbital soft tissue a WL of +50 may be chosen; Dutton, 2010b), and should be set as close as possible to the mean density level of the tissue to be examined (Goldman, 2007). With respect to orbital imaging, the two most common gray-scale adjustments used are the bone and soft tissue windows (Penninck et al., 2001). As an example, consider a typical orbital soft tissue window with a WW of 400 HU and a WL of +50 HU. The image will display all CT numbers between −150 HU and +250 HU on a gray scale from black to white. All tissues with a CT number of −150 HU or less will be displayed as black, while all tissue with CT numbers of +250 HU or more will be displayed as white. The operator is able to switch between different windows while viewing different regions of interest on the CT image by using a mouse or tracker ball (Goldman, 2007).

Slice thickness is the thickness of tissue scanned, and this may vary from 1 to 10 mm (Naik et al., 2002). The use of thinner slices increases spatial resolution (Boroffka & Voorhout, 1999). With the latest CT scanners, slice thickness may be less than 1 mm, with slices as thin as 0.7 mm recommended for orbital scans in humans (Lee et al., 2009). Considering the longer scanning time and increased radiation doses required for thinner-slice CT scans, some authors recommend 2 mm slices as an optimal compromise for general imaging of the human eye and orbit, except in special situations such as evaluation of the orbital apex, in which thinner slices (1 mm) can be more informative (Naik et al., 2002). The concern regarding low-dose radiation exposure relates to the increase in future cancer risk, particularly in children needing multiple or sequential imaging studies (Brenner & Hall, 2007; Lee et al., 2009) and is not relevant to veterinary patients, where sequential imaging studies are uncommonly performed.

Unlike MRI, in which direct multiplanar imaging is possible without special positioning of the patient, direct image formation from a CT scan can only be formed in the plane parallel to the X-ray beam. Therefore, to obtain direct imaging for a particular scan plane (e.g., the dorsal plane of the orbit), the patient's head needs to be repositioned so the anatomic plane of interest is aligned parallel to the X-ray beam. As a result, the number of potential direct scan planes is limited by the ability to position the animal's head in relation to the X-ray beam. For example, direct CT imaging of the equine skull is limited to the transverse plane because of the size of the skull and limited diameter of the CT gantry (Ramirez & Tucker, 2004). In the modern setting patients are not repositioned for direct multiplanar imaging; typically the patient is positioned in sternal recumbency for direct transverse imaging. With the latest generation of CT scanners, the multiplanar constructions from these transverse images are of such high quality that direct multiplanar imaging is rarely considered necessary (Lee et al., 2004). Any degradation in image quality can be somewhat offset in modern CT scanners by using thin scans to acquire the data set (Lee et al., 2009). A routine series of the orbits should include transverse, dorsal oblique, and/or sagittal oblique image planes (Penninck et al., 2001). For localization purposes, it is important to view orbital anatomy and lesions in at least two orthogonal planes (Lee et al., 2009). Transverse views are often used as a survey examination and display the anatomic relationships between the extraocular muscles, optic nerve, and surrounding osseous structures very well. Evaluation of the optic nerve and extraocular muscles is optimized when the image plane is parallel to the optic nerve (Boroffka & Voorhout, 1999).

Contrast Studies

The contrast media utilized for CT scanning are usually iodine based and given intravenously. These contrast media increase the attenuation value of the vascular system and therefore of certain organs and tissues (Dutton, 2010b). Prior allergic reaction to iodinated contrast media or a history of renal failure may be contraindications to using contrast in CT (Lee et al., 2000; Morcos & Thomsen, 2001; Zagoria,

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1994). Although the intrinsic background contrast provided by orbital fat allows visualization of most orbital pathology (see below), the use of contrast media has been advocated for most ophthalmic conditions in humans, as it generally improves the sensitivity and specificity of CT scan interpretation (Lee et al., 2000, 2009). Although it has been reported that the use of contrast-enhanced CT scans does not typically provide additional diagnostic information for orbital lesions in dogs (LeCouteur et al., 1982), in practice contrast is routinely used in orbital studies in veterinary patients.

In some situations such as trauma and orbital or intracranial foreign bodies, contrast material adds little to the examination (Lee et al., 2009). The noncontrast study is superior for assessing the hyperdensity of acute blood and therefore a CT scan that is being performed for acute intracranial or intraorbital hemorrhage does not require the use of a contrast medium (Lee et al., 2009).

Three-Dimensional CT

Many new CT systems incorporate computers that can perform three-dimensional (3D) reconstructions, which can demonstrate superbly the anatomic relationships between osseous defects and sinus, orbital, or intracranial disease (Lee et al., 2009). A postcontrast 3D reformatted CT image of the skull of a dog showing the normal arterial vascular anatomy of the skull is illustrated in Fig. 10.2.2. To ensure optimal quality of the reconstructed images, all image slices should be thin and overlapping (Penninck et al., 2001).

The use of 3D reconstructions is especially useful to evaluate head trauma and skull deformity, and to delineate tumor borders when planning surgery (Penninck et al., 2001). However, caution has been advised against using 3D reconstructions exclusively, as the software involved in producing these images tends to smooth over abnormalities and may hide subtle pathology, such as a minimally displaced fracture (Lee et al., 2009). The two-dimensional (2D) source images should always be examined along with the 3D reconstructions.

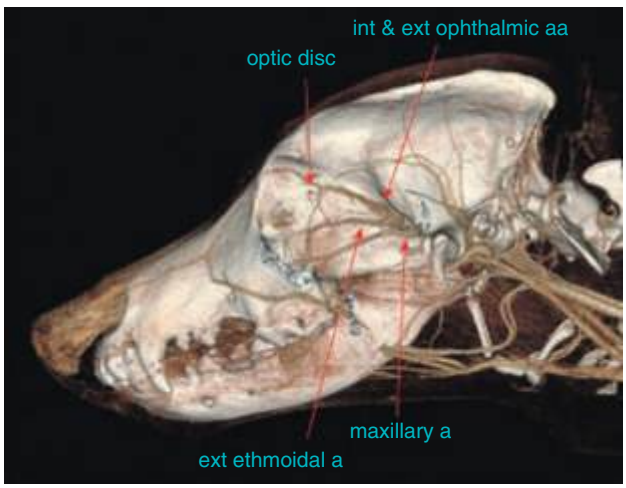


Figure 10.2.2 This postcontrast three-dimensional reformatted computed tomography image of the skull of a 5-year-old Golden Retriever shows the normal arterial vascular anatomy of the skull. The zygomatic arch has been removed to reveal the optic disc, the internal and external ophthalmic arteries, the maxillary artery, and the external ethmoidal artery. The dog and cat have no equivalent to the central retinal artery of humans. (Courtesy of Paul Mahoney, Willows Veterinary Centre & Referral Service, Solihull, UK.)

Orbital CT: Normal Anatomy

The normal CT appearance of the globe and orbit and the effect of using either bone or soft tissue windows are illustrated in Fig. 10.2.3. The excellent contrast provided by the retrobulbar fat during CT imaging of the orbit facilitates differentiation of anatomic structures including the globe, extraocular muscles, optic nerve, and cortical bone (Fike et al., 1984). The normal CT anatomy of the orbit of the dog (Boroffka & Voorhout, 1999; Fike et al., 1984), the cranial nerve emergence and associated skull foramina in cats (Gomes et al., 2009) and dogs (Couturier et al., 2005), and the skull of the dog (George & Smallwood, 1992), cat (Shojaei et al., 2003), and horse (Kinns & Pease, 2009; Smallwood et al., 2002; Solano & Brawer, 2004; Tucker & Farrell, 2001) have been described.

CT allows the confines of the orbit to be clearly defined with good delineation of dorsal (frontal bone, frontal sinus, and dorsal bony orbital rim), medial (frontal bone and palatine bone), ventral (medial pterygoid muscle, zygomatic salivary gland, and ventral fat cushion), and lateral (zygomatic arch and temporal muscle) borders (Boroffka & Voorhout, 1999). All extraocular muscles can be identified on CT imaging (Boroffka & Voorhout, 1999). The levator palpebrae superioris muscle cannot be distinguished from the dorsal rectus muscle (Boroffka & Voorhout, 1999). The optic nerve appears as an oval structure on transverse images, and on dorsal oblique and sagittal oblique images as a linear structure, surrounded by hypoattenuating fat (Boroffka & Voorhout, 1999).

The region of the orbital apex is poorly imaged with CT (Boroffka & Voorhout, 1999) and thinner CT slices may be useful to increase information obtained when this area is studied (Naik et al., 2002). Immediately rostral and lateral to the optic foramen the optic nerves are closely surrounded by extraocular muscles, and neither the optic nerve nor individual extraocular muscles can be imaged as separate structures (Boroffka & Voorhout, 1999).

Orbital CT: Pathologic Anatomy

Modern multislice CT imaging is associated with such rapid acquisition times that the whole head is typically imaged in small animals. The specific reconstructions needed for investigation of orbital and/or brain pathology are subsequently obtained from this data set. Other considerations include the

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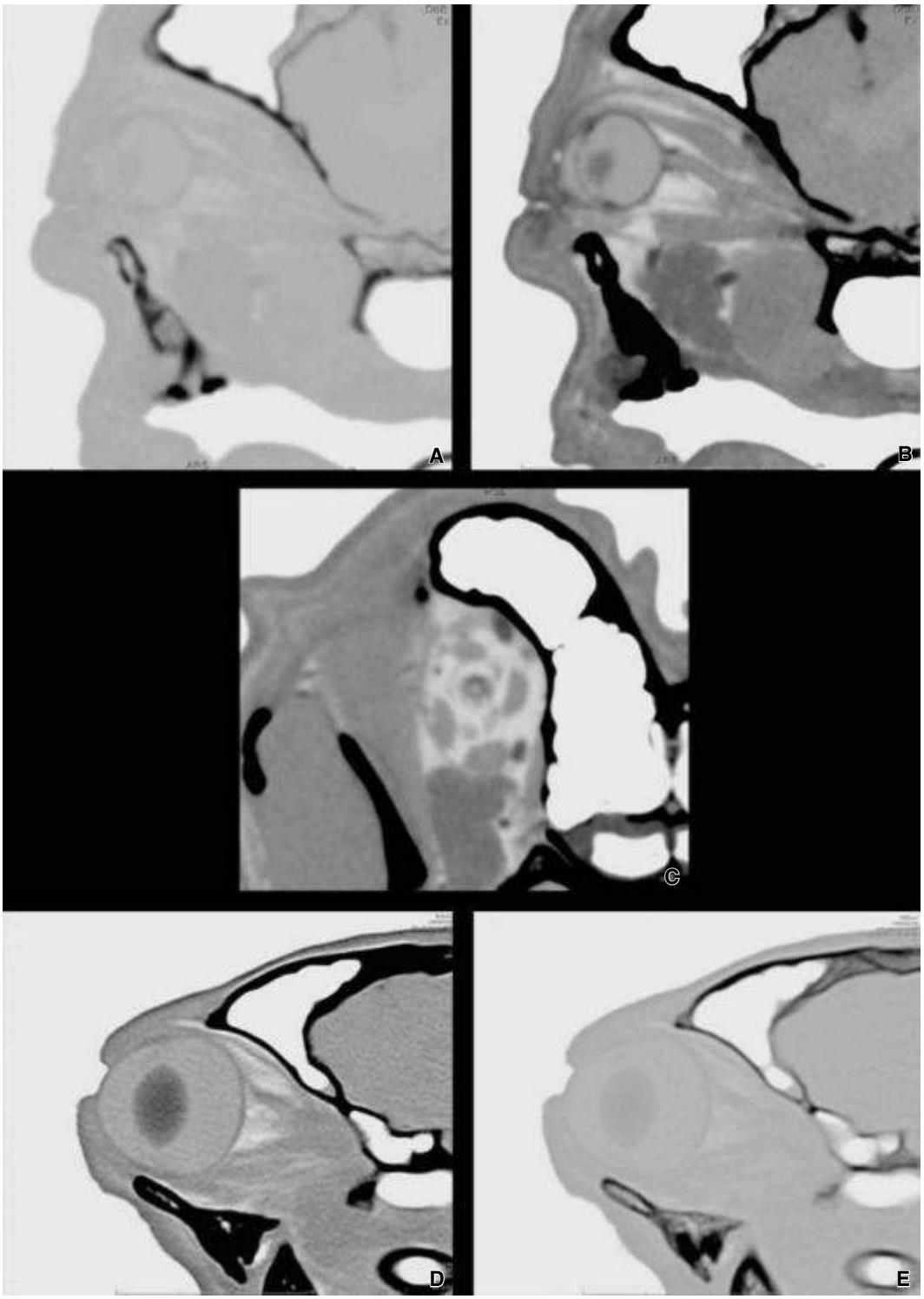


Figure 10.2.3 **A, B**. Postcontrast reformatted computed tomography (CT) sagittal oblique images through the globe and retrobulbar space of a 5-year-old Boxer dog, viewed with (**A**) a bone window (width [W] 2000, length [L] 400) and (**B**) a soft tissue window (W 426, L 55). **B**. The normal optic nerve can be followed along its path from the optic disc through the optic canal. **C**. This postcontrast reformatted transverse CT image through the retrobulbar area of the same dog shows the larger outer rectus muscles and the smaller inner fascicule of the retractor bulbi muscle surrounding the centrally located optic nerve. The zygomatic salivary gland can be seen ventral to the retrobulbar muscles on all three images. **D**, **E**. Reformatted sagittal CT images of the normal feline globe seen in (**D**) a soft tissue window (W 426, L 55) and (**E**) a bone window (W 2000, L 400) for comparison. (Courtesy of Paul Mahoney, Willows Veterinary Centre & Referral Service, Solihull, UK.)

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slice thickness, imaging planes, tissue windows, use of contrast enhancement, and potential 3D reconstructions.

Although MRI is considered the examination of choice for most orbital and neurophthalmic conditions due to its superior soft tissue discrimination, there are situations in which CT has particular utility in demonstrating osseous pathology and tissue mineralization, and ruling out radiodense foreign bodies. In reality, although the pros and cons of MRI versus CT for different diseases are often discussed, the two modalities are complementary, and in many situations combining the two can provide a more complete picture of the nature of a lesion than either study alone (Lee et al., 2009).

Human studies correlating the results of imaging studies (CT and MRI) to known orbital tissue diagnoses have led to the proposal of guidelines aimed at reducing the number of overall differential diagnoses under consideration and helping to establish appropriate management plans for patients with orbital disease (Aviv & Miszkiel, 2005; Ben Simon et al., 2005; Goh et al., 2008). The compartmental approach divides the orbital space into specific anatomic compartments, including sinus, bone, extraconal space, muscle cone, intraconal space, optic nerve, globe, and lacrimal fossa, and attempts to localize orbital pathology. Given that these compartments contain different tissues from which disease may arise or evolve, the number of differential diagnoses may be significantly reduced (Aviv & Miszkiel, 2005; Goh et al., 2008).

There are only a small number of studies and case reports in which CT has been used in the evaluation of veterinary ophthalmic patients, including orbital disease in dogs (Attali-Soussay et al., 2001; Boroffka et al., 2007; Calia et al., 1994; LeCouteur et al., 1982) and cats (Attali-Soussay et al., 2001; Calia et al., 1994; Zemljic et al., 2011). Individual case reports describe findings in a dog with cavernous sinus enlargement and unilateral exophthalmos (Tidwell et al., 1997), and a cat with fungal sinusitis (Halenda & Reed, 1997).

The correlation between orbital CT findings and specific diseases in animals is generally limited to the differentiation between neoplastic versus non-neoplastic disease. In one study, the CT imaging features detected significantly more frequently in neoplastic versus non-neoplastic diseases in dogs included focal mass effect, clearly delineated margins, bony involvement, and extraorbital extension (Boroffka et al., 2007). In this study the compartmental approach to interpreting orbital CT studies had limited value in differentiating neoplastic and non-neoplastic disease.

CT is very sensitive for identifying bone lysis, which is highly suggestive of orbital malignancy in the cat and dog (Boroffka et al., 2007; Calia et al., 1994; Dennis, 2000; Hendrix & Gelatt, 2000), although a tissue diagnosis is still required to rule out infectious processes, in particular fungal disease (Calia et al., 1994; Halenda & Reed, 1997). CT evidence of bony lysis has been reported in 82% of cats with orbital malignancy (Calia et al., 1994) and 48% of dogs with orbital neoplastic disease (Boroffka et al., 2007). Lysis of the medial bony orbital wall associated with an invasive nasal tumor is illustrated in Fig. 10.2.4). Orbital bone lysis in humans is occasionally seen as the result of chronic compression in benign conditions such as an orbital dermoid, epidermoid inclusion cysts, and fibrous dysplasia (Aviv & Miszkiel, 2005; Chung et al., 2007).

Mineralization may be a prominent feature in certain ophthalmic diseases in humans, including meningioma and retinoblastoma, and CT identification of this change may assist when considering differential diagnoses (Aviv & Miszkiel, 2005; Lee et al., 2009; Naik et al., 2002). Although CT imaging has identified mineralization of orbital tumors in dogs (Boroffka et al., 2007; Calia et al., 1994), no correlation between mineralization and specific tissue diagnoses of tumors has been reported.

In cases of orbital malignancy in dogs, exenteration is generally considered to be the treatment of choice (Boroffka et al., 2007). The ability of CT, particularly 3D CT, to accurately define the tumor boundaries and encroachment on other orbital structures and to assess the presence of extent and bone involvement makes it a valuable part of the presurgical assessment (Leib, 1994; Penninck et al., 2001).

In orbital inflammation an increased radiodensity of the orbital tissues is expected. Fluid and cellular infiltrate increase the normally low X-ray attenuation value of retrobulbar fat, which reduces the image contrast, obscuring visualization of the extraocular muscles, the optic nerve, and the globe. Although changes in the X-ray attenuation of the orbital tissues (both before and after contrast enhancement) are a prominent feature of orbital inflammation, this in isolation does not allow differentiating inflammatory from neoplastic orbital disease (Boroffka et al., 2007). In the same study (Boroffka et al., 2007), delineation of the margin of the lesion was shown to be the most important discriminator from cases of neoplastic orbital disease, with the margins of the inflammatory lesions being more ill-defined on postcontrast-enhanced CT.

CT is important in determining the location of orbital infection in humans (Hirsch & Lifshitz, 1988; LeBedis & Sakai, 2008; Naik et al., 2000). The location of an orbital infection is described with respect to the orbital septum, as either preseptal (periorbital) or postseptal (orbital; LeBedis & Sakai, 2008). The clinical staging of orbital cellulitis can be difficult and identification of postseptal disease is critical due to the potentially devastating complications, including cavernous sinus thrombosis and meningitis (LeBedis & Sakai, 2008). CT imaging of preseptal cellulitis reveals soft tissue thickening anterior to the orbital septum (LeBedis & Sakai, 2008). The earliest change associated with postseptal orbital involvement is a slight increase in the density of the orbital fat, which is followed by the development of discrete densities within the fat and extraocular muscle thickening as

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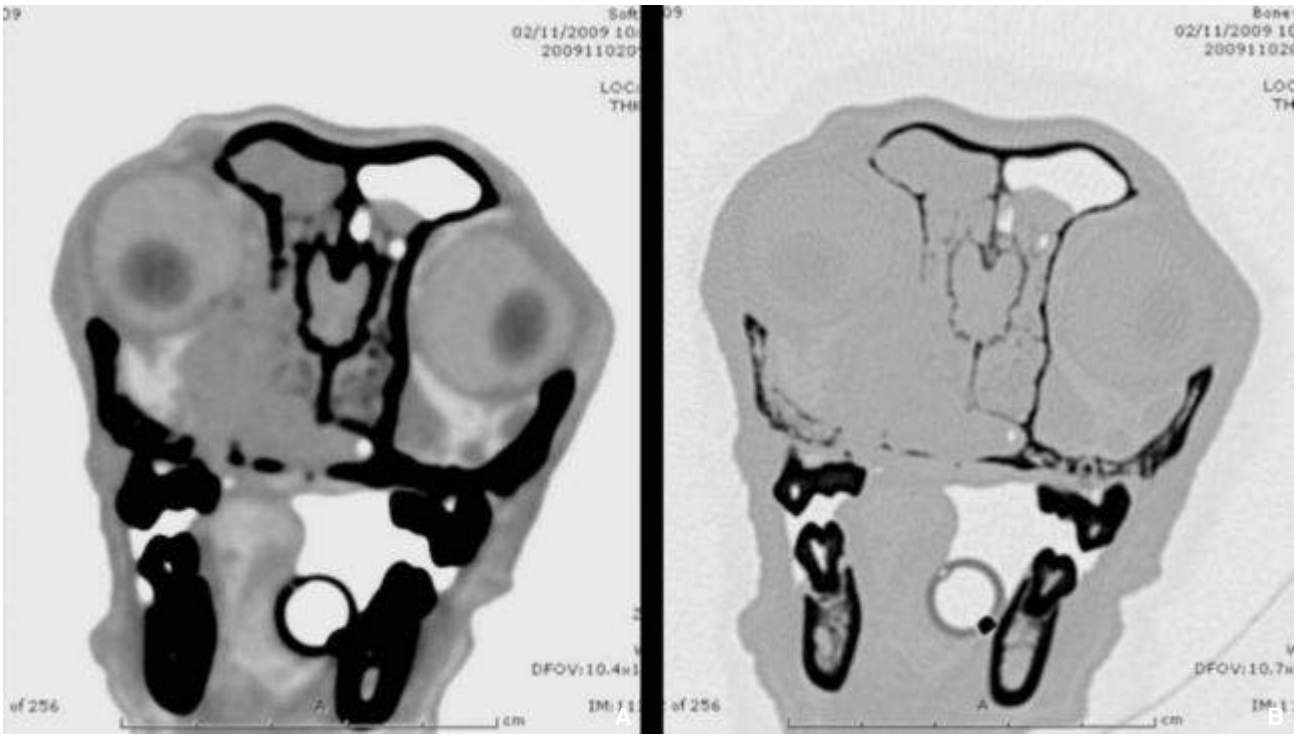


Figure 10.2.4 Aggressive osteolytic soft tissue nasal tumor invading the right orbit in a 9-year-old Dachshund. The computed tomography images show invasion through the medial bony orbital wall in (**A**) a soft tissue and (**B**) a bone window for comparison. (Courtesy of Paul Mahoney, Willows Veterinary Centre & Referral Service, Solihull, UK.)

the infection progresses (Naik et al., 2000). Although the use of CT to differentiate pre- and postseptal orbital cellulitis has not been described in veterinary species, it is likely to have similar utility for this condition. The CT appearance of an orbital abscess in a dog is illustrated in Fig. 10.2.5.

CT has particular utility in the evaluation of orbital trauma (Penninck et al., 2001), allowing detailed assessment of bony lesions with simultaneous evaluation of soft tissues, globe, orbit, and brain. The use of CT to establish the nature of orbital fractures in horses has been reported (Gilger & Stoppini, 2011). Orbital fractures are often complex and the use of 3D reconstruction is particularly useful in planning the surgical realignment of displaced fracture fragments in these cases (Fig. 10.2.6).

CT may also be useful in the identification of radiodense foreign material such as glass or metal, but in animals where pieces of plant material are usually the cause of orbital inflammation, such foreign bodies may be missed by CT imaging (Boroffka et al., 2007).

CT Dacryocystorhinography

CT-DCRG provides superior imaging of the nasolacrimal system, with better delineation of the adjacent soft tissues and bony structures when compared to conventional DCRG, CT, or MRI (Ashenhurst et al., 1991; Freitag et al., 2002; Udhay et al., 2008). The use of connectivity algorithms allows 3D CT-DCRG color-enhanced reconstructions, which facilitate understanding of complex pathology involving the nasolacrimal system, the relationships to the adjacent orbital and facial skeleton, and surgical planning (Freitag et al., 2002; Udhay et al., 2008).

CT-dacryocystography (CT-DCG) has been used to study the nasolacrimal system in the normal cat (Noeller et al., 2006; Schlueter et al., 2009) and dog (Rached et al., 2008, 2011). CT-DCRG may have a role in the evaluation of more complex nasolacrimal disorders in veterinary patients. CT-DCRG investigation of nasolacrimal disease has been described in the dog (Giuliano et al., 2006; Nykamp et al., 2004), horse (Nykamp et al., 2007), and donkey (Cleary et al., 2011). CT-DCG and 3D CT-DCRG in a case of chronic dacryocystitis in a dog are illustrated in Fig. 10.2.7.

CT-Guided Percutaneous Biopsy

The ability of CT to provide excellent imaging of orbital and skull topography, and detailed delineation of orbital tumor location and boundaries, makes it a valuable technique for aspiration biopsy guidance (Penninck et al., 2001). The technique for CT-guided percutaneous biopsy of orbital pathology in dogs has been described (Tidwell & Johnson, 1998). The technique has been recommended for lesions judged to be inaccessible (due to location or poor resolution) using other imaging techniques, including ultrasonography and

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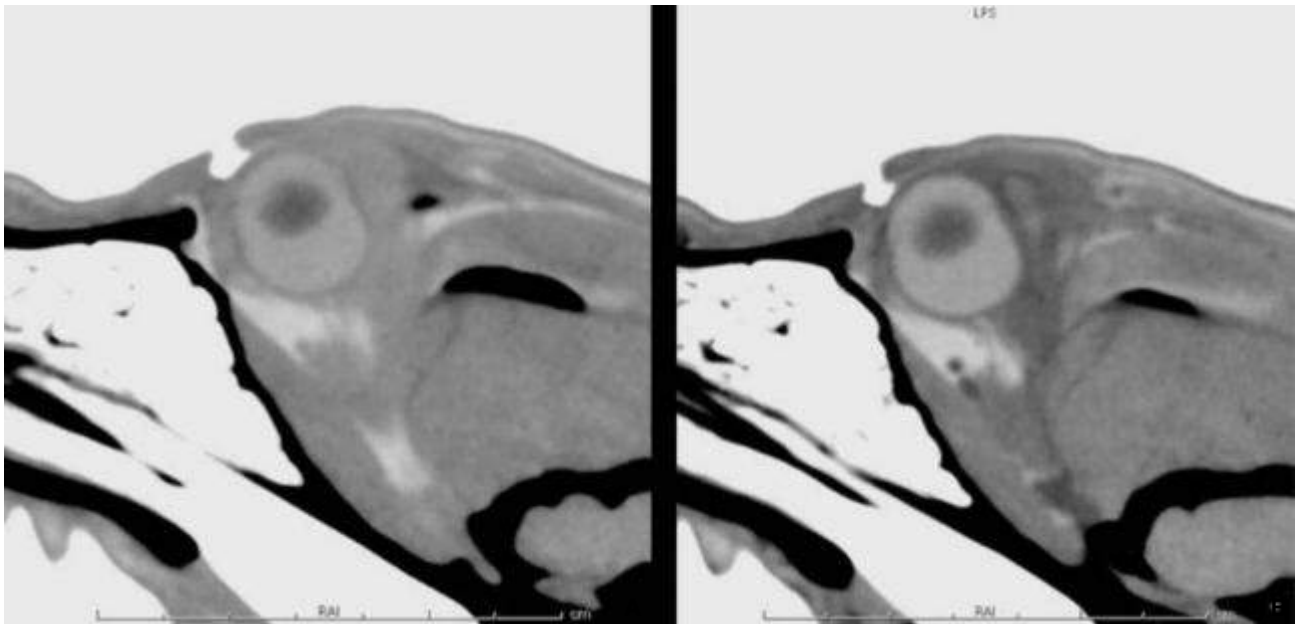


Figure 10.2.5 Orbital abscessation in a 4-year-old Dalmatian. Reformatted dorsolateral-ventromedial sagittal oblique computed tomography images through the globe and retrobulbar region (**A**) precontrast and (**B**) postcontrast administration. The postcontrast image (**B**) shows a teardrop-shaped region of nonenhancement, surrounded by an enhancing rim that extends caudally into the retrobulbar space. The lesion appears to be associated with indentation of the dorsolateral margin of the left globe, and most likely represents inflammation of the dorsolateral orbital soft tissue structures and abscess formation. The region was surgically explored and a grass seed was removed. (Courtesy of Paul Mahoney, Willows Veterinary Centre & Referral Service, Solihull, UK.)

fluoroscopy, or when CT is needed to provide additional information regarding diagnosis, staging, or therapy planning (Tidwell & Johnson, 1998).

Magnetic Resonance Imaging

Basic Principles and Physics

MRI is a technique for creating a cross-sectional image of the body based on the magnetic resonance (MR) of atomic nuclei. The physics of medical MRI has been comprehensibly reviewed (Dutton, 2010b; Pooley, 2005; Tidwell & Johnson, 1994; Weishaupt et al., 2008). The hydrogen nucleus is used for medical MRI because it is abundant in biologic tissue, being found in water and lipid molecules. The hydrogen nucleus is a proton and it is the resonance of these hydrogen protons in living tissues that is used to generate medical MR images. When a tissue is placed inside a powerful static magnetic field, some of its protons become aligned with the direction of the field (z-axis), producing a small amount of spin polarization, and as a result overall magnetization of the tissue. If a strong radiofrequency (RF) field of a certain frequency (known as resonance or Larmor frequency) is imposed at right angles to the static magnetic field, energy is absorbed that flips the spin of the aligned protons briefly into a higher energy state. In this state the axial alignment of the protons is parallel to the RF field (90 degrees to the static magnetic field). A second effect of the applied RF field is that the phase of the proton spins become synchronized.

When the RF signal is switched off, the protons, which have absorbed photons, relax back to the lower-energy spin state and realign with the static magnetic field. The most rapid form of relaxation involves dephasing of the proton spins (T2 relaxation) and subsequently realignment of the proton spins longitudinally within the static magnetic field (T1 relaxation). During this process, measurable amounts of RF signal are produced. This emission of electromagnetic radiation (RF signal) associated with spin relaxation of protons from high-energy states is referred to as nuclear magnetic resonance (NMR). Because tissues differ in their chemistry and physical states, their hydrogen protons are also held together differently. This causes fundamental differences between the T1 and T2 relaxation rates between different tissues, and as a result variation in the intensity of emitted RF signal duration relaxation. It is because of these differences in relaxation rates between tissues that contrast between tissues is detectable, thus making MRI possible. The RF coils are therefore needed to both transmit and receive the NMR signal. The emitted RF radiation from the relaxing tissues is received by the RF coil (antennae) and this information is analyzed by a computer to create the final MR image. At the most basic level, the tissues with high hydrogen proton content such as water and fat are imaged, while regions of bone or air appear as a signal void or black.

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Figure 10.2.6 Fracture of the left bony orbit in an 18-month-old Labrador Retriever. **A**. Axial computed tomography slice image shows multiple fractures involving the left bony orbit. **B**, **C**. Reformatted three-dimensional images allowed a greater appreciation of the nature of the comminuted fractures involving the bony orbit. (Courtesy of Paul Mahoney, Willows Veterinary Centre & Referral Service, Solihull, UK.)

Arteries and veins are not imaged by routine MR sequences, as the blood present at the time of the stimulating RF pulse has moved away by the time the resultant RF signal associated with tissue relaxation is being generated.

When performing medical MRI, the amount of rotation of the net tissue magnetization away from the longitudinal (z) axis (termed the flip angle) can be manipulated by changing the strength and duration of the RF pulse (Pooley, 2005). If the RF pulse rotates the net magnetization into the transverse plane, it is termed a 90° RF pulse, whereas if the RF pulse rotates the net magnetization in the –z direction, it is termed an 180° RF pulse. The strength and duration of the RF pulse can be manipulated to rotate the net magnetization to any flip angle, and these different flip angles are utilized when performing different MR sequences. For example, 90° and 180° RF pulses are used in the generation of the spin echo (SE) or fast spin echo (FSE) sequences, including T1- and T2-weighted images (T1WI and T2WI), while smaller flip angles are utilized when performing fast imaging techniques such as gradient recall echo (GRE; Pooley, 2005).

Two important MR image acquisition parameters, which affect the contrast of different tissues during MRI scanning, are the echo time (TE) and the repetition time (TR; Pooley, 2005). The TE is the time between the RF pulse and the detection of the radiofrequency waves by the coil. The TR is the time lapse between each RF pulse sequence. TE and TR are adjusted when acquiring different MR sequences. For example, an image is considered a T1WI when the TR and TE are short, while a long TR and a long TE produce a T2WI (Pooley, 2005).

The strength of a magnetic field is expressed by the SI unit Tesla (T). Modern medical MRI scanners may be "high field"

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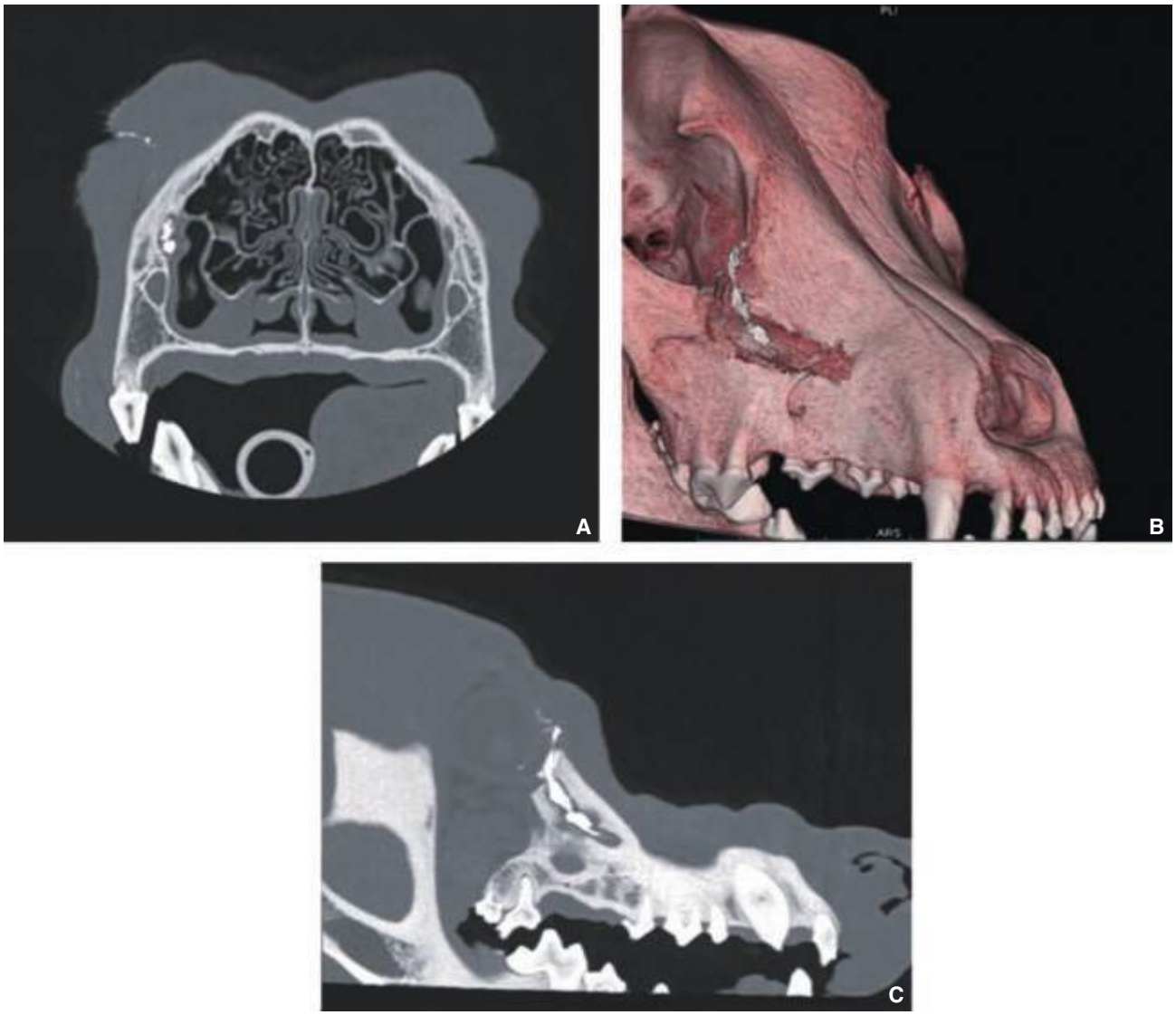


Figure 10.2.7 Dacryocystitis in a 3-year-old entire male Labrador Retriever. **A**. The transverse computed tomography image of a dacryocystorhinographic study through the midnasal region shows an area of dilation of the right nasolacrimal duct. **B**. The extent of this dilation can be appreciated on the reformatted sagittal image through the right nasolacrimal duct. **C**. The color-enhanced three-dimensional reconstruction has had the lateral surface of the right maxillary bone removed over the nasolacrimal duct. (Courtesy of Paul Mahoney, Willows Veterinary Centre & Referral Service, Solihull, UK.)

(1.5 and 3.0T) or "low field" (< 0.5T). Clinically stronger magnets provide improved image quality and therefore diagnostic accuracy for many applications (Lee et al., 2009). Despite these advantages, there are proponents of the expanding low-field MR scanners because of cost savings and open format (Hayashi et al., 2004).

Interpretation of Specific Magnetic Resonance Pulse Sequences

T1-weighted image MRI

The two most common MRI sequences are T1WI and T2WI, and these are typically acquired as part of the standard MR examination of the orbit and brain (Fig. 10.2.8A, B). Normal anatomy is best demonstrated on T1WI (Morgan et al., 1994). On T1WI fat has a hyperintense signal ("bright on T1"). As a result, a T1WI of the orbit is associated with bright signal intensity of the orbital fat. Structures of intermediate signal intensity include the extraocular muscles, optic nerve, and iris (Morgan et al., 1994; Penninck et al., 2001). The lens has a low signal intensity (black), while the vitreous has a signal intensity between the lens and the extraocular muscles (Morgan et al., 1994; Penninck et al., 2001). Very few pathologic lesions are hyperintense on precontrast T1WI. From an ophthalmic perspective, the most important lesions include subacute hemorrhage, highly proteinaceous fluid (e.g., sinus mucoceles), and melanin (e.g., melanoma; Caruso et al., 2001).

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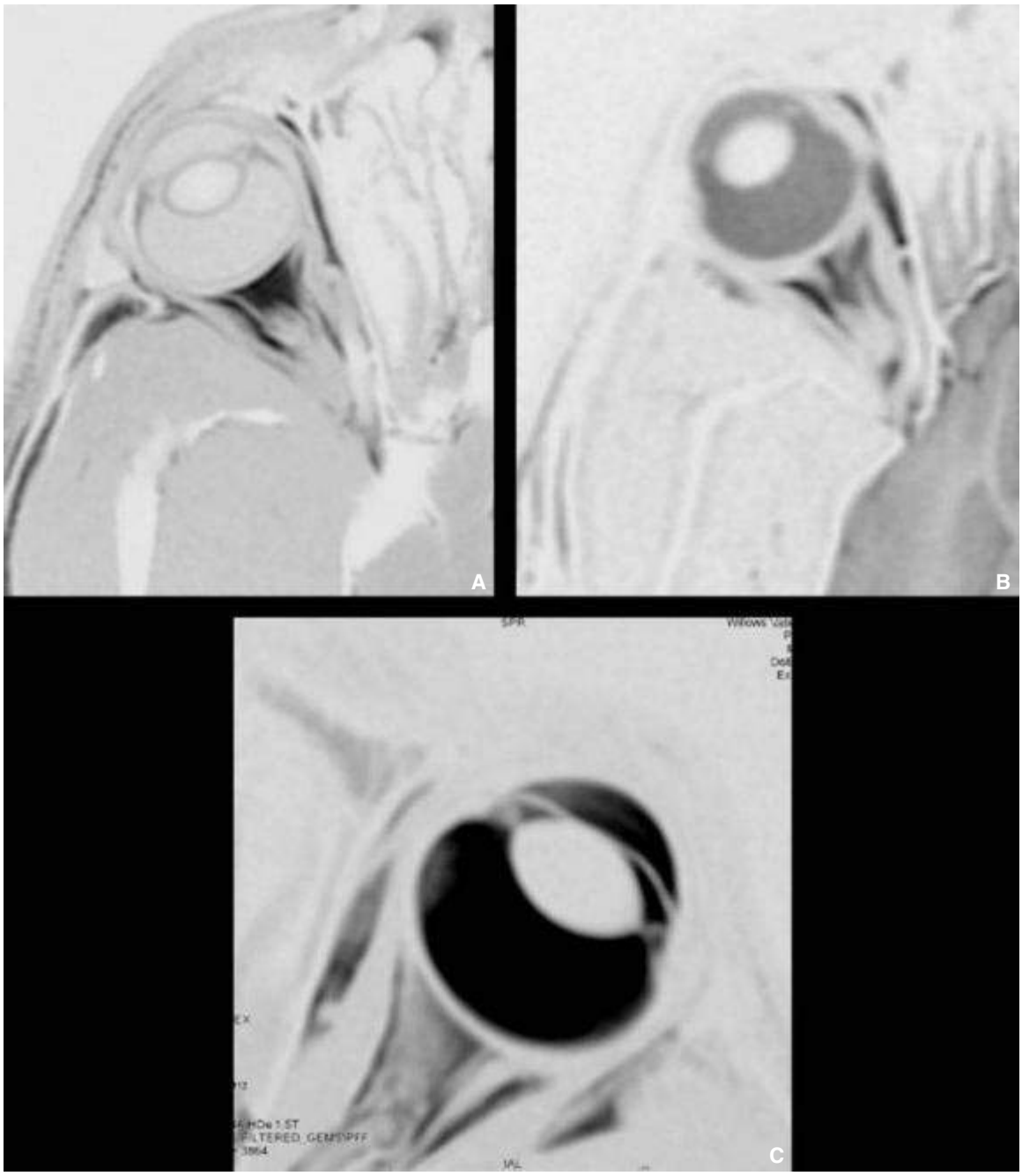


Figure 10.2.8 The appearance of the normal canine globe and orbit on dorsal (**A**) T1-weighted and (**B**) T2-weighted magnetic resonance imaging (MRI). **A**. The dorsal T1 image shows hyperintense retrobulbar fat, lens capsule, iris, and ciliary body. The aqueous humor and vitreous humor have a slightly lower signal when compared with muscle, and the normal lens has low signal characteristics. **B**. The dorsal T2 image shows the characteristic bright signal intensity of the vitreous and aqueous humor. The signal intensity of retrobulbar fat also appears hyperintense on fast spin echo T2, while the extraocular muscles, optic nerve, and brain have intermediate signal intensity. **C**. A dorsal reconstruction three-dimensional (3D) gradient recall echo (Fast Imaging Employing Steady State Acquisition [FIESTA], General Electric, Milwaukee, WI, USA) image of the normal MRI anatomy of the canine globe. The lens, iris, ciliary body, anterior chamber, posterior chamber, and vitreous are clearly seen. The 3D FIESTA sequence provides high signal-to-noise images, with good anatomic detail and short acquisition times. (A and C courtesy of Paul Mahoney, Willows Veterinary Centre & Referral Service, Solihull, UK.)

T2-Weighted Image MRI

T2WI MRI is typically better than T1WI for demonstrating intracranial or orbital pathology. On T2WI the cerebrospinal fluid (CSF) and the vitreous are hyperintense ("bright on T2"). Orbital fat will also appear hyperintense on FSE T2WI (Conneely et al., 2008). The extraocular muscles, optic nerve, and brain have an intermediate signal intensity (Morgan et al., 1994; Penninck et al., 2001). In contrast to T1WI, most

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pathology is hyperintense on T2WI. These include demyelinating lesions (e.g., optic neuropathies), ischemia (e.g., stroke), inflammatory disease, toxic or metabolic disorders, and neoplasms (Lee et al., 2009). T2WI are also useful in differentiating a fluid-filled versus a soft tissue lesion, as the latter will have lower signal intensity (Penninck et al., 2001).

Gradient Recall Echo Imaging

GRE (or T2*, "T2 star") sequences highlight the presence of blood products. GRE MR sequences can demonstrate hemorrhage, which is essential in human patients with underlying arteriovenous or cavernous malformations, intra- or extraaxial intracranial hemorrhage, or traumatic brain injury (Lee et al., 2004, 2009). Even trace amounts of hemorrhage may be detected because of the profound signal loss caused by the paramagnetic effects of deoxyhemoglobin and methemoglobin (Lee et al., 2009). By using GRE, along with T1WI and T2WI, the approximate age of a hematoma may be determined (Jutler et al., 2006). In veterinary patients brain hemorrhages can also be detected earlier on GRE MR sequences than on spin echo sequences (i.e., T1WI and T2WI), with the hematoma appearing as a black signal void within a few hours of the onset of bleeding (Tidwell, 2007). The gradient echo signal voids in a dog with multiple cerebral hemorrhagic infarcts are illustrated in Fig. 10.2.9.

Rapid 3D GRE sequences have been designed for faster acquisition of data that can give improved image quality comparable to 2D imaging (Dutton, 2010b). The appearance of the globe and orbit on a 3D GRE sequence is illustrated in Fig. 10.2.8C.

Fat Suppression

To improve visualization of pathologies, it is possible to suppress the high signal intensity of fat on T1WI (i.e., "fat suppression" or "fat saturation"; Lee et al., 2009). Fat suppression may be achieved by using imaging techniques including spectral fat suppression or short tau inversion recovery (STIR; D'Anjou et al., 2011; Dutton, 2010b). Spectral fat suppression techniques are useful in evaluating T1WI images of the orbit, where the normally hyperintense fat signal cannot be distinguished from the high signal of the contrast enhancement associated with an optic neuritis or an optic nerve sheath meningioma (Lee et al., 2009; Penninck et al., 2001). The suppression of the orbital fat signal on a T1-weighted postcontrast MRI in a dog with optic neuritis is illustrated in Fig. 10.2.10. Fat suppression techniques can also confirm the content of fat-containing lesions, such as orbital dermoid cysts and lipomas (Lee et al., 2009).

Alternatively, fat suppression may be achieved by STIR sequences. On these images, lesions are typically hyperintense and contrast well with the suppressed fat signal (Penninck et al., 2001; Tidwell, 2007). STIR images have relatively poor detail, but are good to screen tissues for pathol-



Figure 10.2.9 Multiple cerebral hemorrhagic infarcts in a 10-year-old cross-bred dog. The dog presented with an 8-month history of seizures. Neurologic examination was normal apart from a reduced menace response on the right side. Transverse gradient recall echo magnetic resonance imaging revealed multiple areas of gradient echo signal voids, including the left thalamus (arrow), consistent with hemorrhagic lesions.



Figure 10.2.10 Optic neuritis in an 11-year-old Golden Retriever. Sagittal oblique T1-weighted postcontrast magnetic resonance imaging with fat suppression. The sagittal oblique image allows visualization of the optic nerve throughout its length. There is marked thickening and contrast enhancement of the optic nerve (large arrows). Suppression of the orbital fat signal (small arrows) facilitates identification of the optic nerve contrast enhancement.

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ogy and therefore identify the regions requiring more detailed investigation (Fig. 10.2.11).

Fluid Attenuation Inversion Recovery

Fluid attenuation inversion recovery (FLAIR) is a sequence that suppresses the normally high signal intensity of CSF on T2WI, and therefore improves visualization of subtle adjacent pathologic hyperintensity of the brain or the optic chiasm (Arakia et al., 1999; Barkhof & Scheltens, 2002; Kawamoto et al., 1997; Penninck et al., 2001). FLAIR images are more sensitive in detecting many pathologic processes of intracranial tissues surrounded by CSF, including neoplasia and inflammation, when compared to T2WI (Fig. 10.2.12). The FLAIR technique may be useful to distinguish cystic lesions (low signal) from tissues with high fluid content (high signal; Tidwell, 2007).

Contrast MRI

Many pathologic processes in the brain are associated with increased tissue fluid content and/or increased tissue vascularity. MR scanning with intravenous paramagnetic agent contrast agents such as gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) may be used to enhance the appearance of these changes (Lee, 1991). Contrast-enhanced MRI improves visualization of blood vessels, breakdown of the blood–brain barrier, tumors, or inflammation (Dutton, 2010b). The accumulation of contrast medium appears as increased signal intensity on T1WI MR (Fig. 10.2.13; Tidwell & Jones, 1999). Generally the use of contrast enhancement is recommended for most cases of orbital or neuro-ophthalmic disease, but it may not be necessary for acute hemorrhage or in trauma cases (Lee et al., 2009). In the series of orbital diseases reported by Dennis (2000), contrast enhancement was helpful in delineating mass lesions, demonstrating intracranial extension, outlining abscesses, and showing muscle changes associated with inflammatory disease.

Serious side effects associated with gadolinium-based contrast agents are uncommon in humans and veterinary patients. Anaphylactic/anaphylactoid reactions following intravenous gadolinium-based contrast agents have been reported in humans (Abujudeh et al., 2010; Shellock et al., 2006) and dogs (Girard & Leece, 2010). Nephrogenic systemic fibrosis has been reported following gadolinium in human patients with kidney failure (Cowper, 2008; Marckmann et al., 2006), but not in the veterinary literature.

MRI in Ocular, Orbital and Neuro-Ophthalmic Disease: Normal Anatomy and Pathologic Findings

On MR images tissues vary in signal intensity from very dark, dark, intermediate, bright, to very bright, and therefore provide excellent soft tissue contrast. The signal intensity from diseased tissues is described as hyperintense, isointense, or hypointense, usually relative to the signal from tissue such as fat, muscle, or gray matter. When interpreting MRI studies used for investigation of ocular, orbital, and neuro-ophthalmic diseases, knowledge of the normal appearance of these tissues is necessary. MRI of the normal eye and orbit of the dog and cat (Morgan et al., 1994) and horse (Morgan et al., 1993), the canine optic nerve (Boroffka et al., 2008), the canine brain (Leigh et al., 2008), and the cranial nerves of the dog (Couturier et al., 2005) and cat (Gomes et al., 2009) have been described.

In humans, the MRI findings of many ocular, orbital, and neuro-ophthalmic conditions associated with congenital, traumatic, vascular, inflammatory, degenerative, and neoplastic diseases have been comprehensively described (Aviv & Miszkiel, 2005; Dutton, 2010b; Goh et al., 2008; Jäger, 2005; LeBedis & Sakai, 2008; Müller-Forell, 2004). The MRI findings reported in veterinary patients with ocular, orbital, and neuro-ophthalmic disease include uveal melanoma in the dog (Kato et al., 2005; Miwa et al., 2005), orbital neoplasia in the dog (Armour et al., 2011; Dennis, 2000) and cat (Armour et al., 2011; Dennis, 2000; Morgan et al., 1996), orbital inflammation in the dog and cat (Armour et al., 2011; Dennis, 2000; Kneissl et al., 2007), orbital varix in the dog

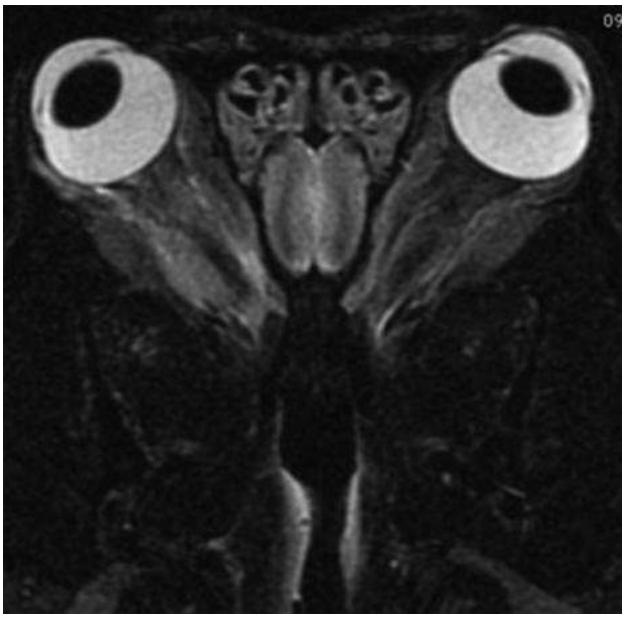


Figure 10.2.11 Extraocular muscle myositis in a 7-year-old Border Terrier. Dorsal short tau inversion recovery (STIR) magnetic resonance imaging (MRI). The extraocular muscles are thickened and have an increased signal on this sequence. There are no changes to the optic nerves; however, there are focal areas of increased signal within the left and right medial pterygoid muscles, which likely represented inflammatory change. Although the detail is not as good as other MRI sequences, the regions of fluid accumulation within tissues and therefore the location of pathology are clearly illustrated. (Courtesy of Paul Mahoney, Willows Veterinary Centre & Referral Service, Solihull, UK.)

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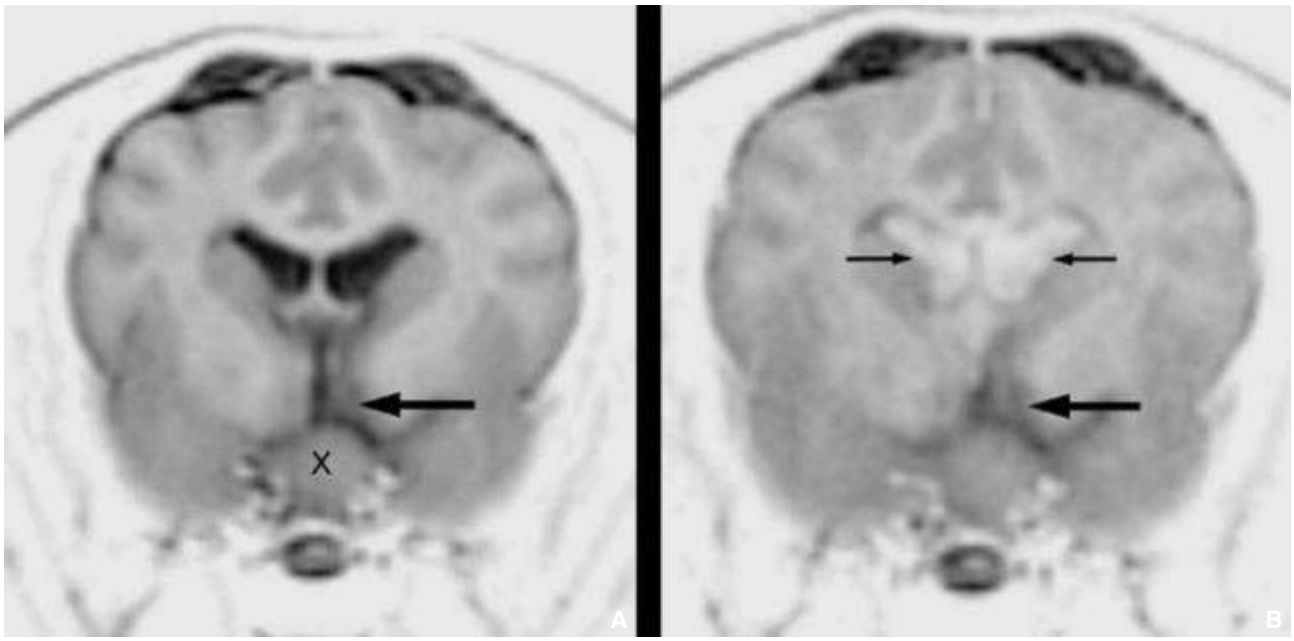


Figure 10.2.12 Optic neuritis in a 6-year-old Jack Russell Terrier. **A**. Transverse T2-weighted magnetic resonance imaging (MRI): enlargement of the optic chiasm (×) and an apparent hyperintensity of white matter (large arrow). It is difficult to determine the extent of the central nervous system white matter pathology due to the hyperintense signal of the cerebrospinal fluid (CSF). **B**. Transverse T2-weighted fluid attenuation inversion recovery (FLAIR) MRI in which the CSF signal is suppressed (small arrows show the effect of CSF signal suppression in the lateral ventricles). This allows the hyperintense white matter lesions (large arrow) to be appreciated.

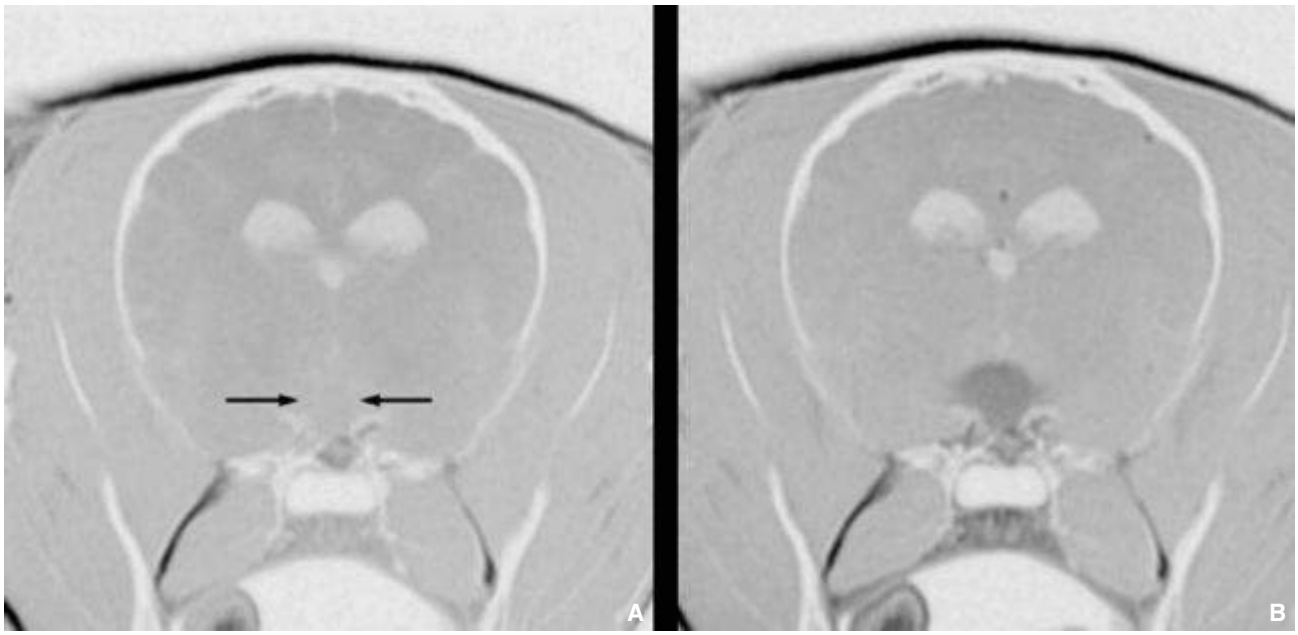


Figure 10.2.13 Optic neuritis and granulomatous meningoencephalitis in a 3-year-old Cavalier King Charles Spaniel. **A**. Transverse T1-weighted magnetic resonance imaging (MRI) at the level of the optic chiasm (arrows). **B**. Transverse T1-weighted postcontrast MRI demonstrating enlargement and enhancement of the optic chiasm. Although subtle changes are present in the precontrast image (**A**), these could easily be overlooked, while the postcontrast appearance unequivocally demonstrates pathology in this region.

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(Holloway, 2015), optic neuritis in the dog (Armour et al., 2011; Kitagawa et al., 2009; Seruca et al., 2010) and cat (Armour et al., 2011), optic atrophy associated with sphenopalatine disease in the horse (Barnett et al., 2008), optic nerve meningioma in the dog (Morgan et al., 1996; Regan et al., 2011; Seruca et al., 2011) and horse (Naylor et al., 2010), sphenoid bone osteomyelitis in the dog and cat (Busse et al., 2009), sphenoid bone neoplasia in a dog (Beltran et al., 2010), and cases of CNS pathology affecting the central visual pathways in the dog (Cherubini et al., 2006; Cullen et al., 2002; Kitagawa et al., 2009; Kraft et al., 1997; Rossmeisl et al., 2007; Sturges et al., 2008; Thomas et al., 1996) and cat (Troxel et al., 2004; Seruca et al., 2011).

In humans, MRI has been used to investigate many ocular conditions, including anophthalmos and microphthalmos, globe rupture, intraocular foreign body, retinal and choroidal detachment, uveitis and posterior scleritis, and primary and metastatic neoplasia (Chung et al., 2007; DePotter et al., 1998; Dutton, 2010b; LeBedis & Sakai, 2008). In veterinary ophthalmology, the imaging of most ocular abnormalities is performed using B-mode ultrasound. One scenario in which MRI may be used in veterinary patients is in the assessment of ocular melanoma. The MRI appearance of human choroidal melanoma is a relatively hyperintense T1WI and relatively hypointense T2WI (Gomori et al., 1986; Lee et al., 2009; Mafee et al., 1987) mass lesion due to the paramagnetic properties of the melanin (Damadian et al., 1973; Lambrecht et al., 1988). This characteristic is helpful in evaluating choroidal melanomas or intracranial melanoma metastases (Caruso et al., 2001). Only isolated case reports of MRI of uveal melanomas have been published in the dog, with Kato et al. (2005) describing hyperintense T1WI/hypointense T2WI in an anterior uveal melanoma in a dog, while a case of a choroidal melanoma in a dog lacked these characteristic MRI findings (Miwa et al., 2005). The paramagnetic effect of melanin in a cat with a ciliary body melanoma is illustrated in Fig. 10.2.14.

The MRI findings in cases of orbital neoplasia are largely provided by Dennis (2000), who reviewed the MRI findings of 25 small animal patients with signs of orbital disease, and Armour et al. (2011), who reviewed the distribution of orbital and intracranial disease in 79 canine and 13 feline patients referred for MRI studies by a veterinary ophthalmologist. In both series the most common type of orbital pathology was neoplasia: Armour et al. (2011) 53/92 (57.6%) and Dennis (2000) 16/25 (64%). In the study by Armour et al. (2011), carcinomas and sarcomas were the most prevalent tumor types, and both behaved in a locally invasive manner, frequently demonstrating heterogenous MR signal enhancement with extensive associated facial bone lysis, aggressive sinonasal infiltration, and intracranial extension (Fig. 10.2.15). In contrast, lymphoma tends to be less aggressive, with fewer cases extending beyond the bony orbit and with an MR signal intensity varying from heterogenous to homogenous (Armour et al., 2011). In the review by Dennis (2000), tumors appeared as discrete masses of medium signal intensity on T1WI MR and variable but mainly high signal intensity on T2WI MR. All

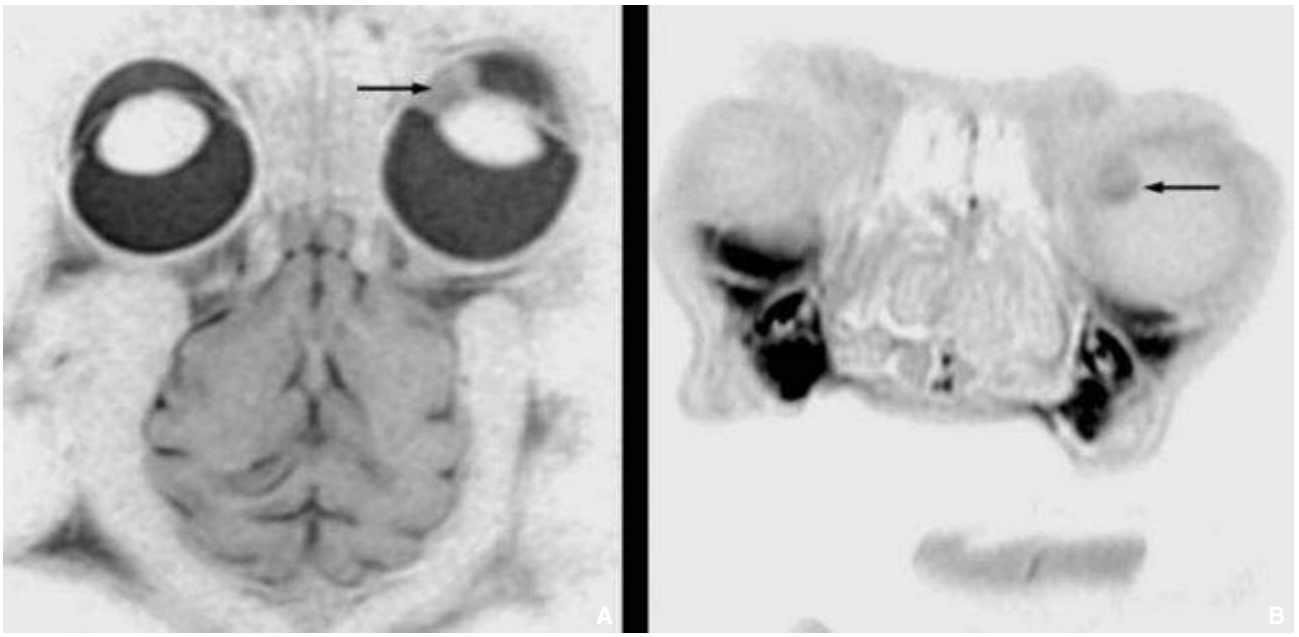


Figure 10.2.14 Ciliary body melanoma affecting the left eye of a 3-year-old Birman cat. **A.** Dorsal T2-weighted magnetic resonance imaging (MRI) showing a hypointense mass lesion in the ciliary body of the left globe (arrow). **B**. Transverse T1-weighted MRI showing a slightly hyperintense mass lesion corresponding to the mass lesion identified in (**A**). These changes are consistent with the paramagnetic effect of melanin.

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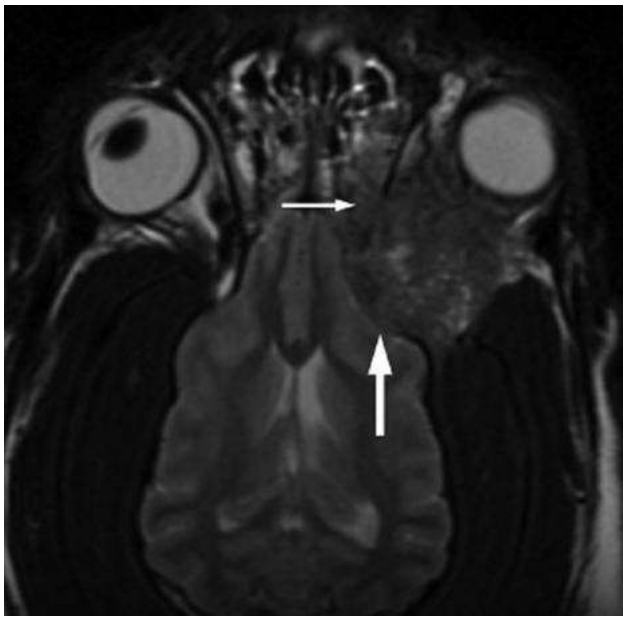


Figure 10.2.15 Orbital carcinoma in a 4-year-old Irish Water Spaniel. Dorsal T2-weighted magnetic resonance imaging. The large irregular mass of low signal intensity is filling the left orbit, has eroded through the left medial bony orbital wall (frontal bone), and extended into the nasal cavity (small arrow). Extension though the orbital apex into the cranial vault has led to compression and distortion of the left frontal lobe of the brain (large arrow).

showed mild diffuse contrast enhancement after intravenous gadolinium administration. The extent of tumors was more clearly defined on MRI than with radiology or ultrasound, and osteolysis involving the bony orbit and extension of the disease beyond the orbit were considered reliable indicators of malignancy (Dennis, 2000). In addition, and in contrast to radiographs, the MRI allowed distinction between fluid accumulation and solid tissue in the frontal sinus, as the fluid appeared hypointense on T1WI and hyperintense on T2WI (Dennis, 2000).

The MRI appearance of orbital cellulitis is characterized by diffuse connective tissue swelling without loss of the normal architecture (Dennis, 2000), allowing differentiation from orbital neoplasia (Armour et al., 2011). Orbital abscesses demonstrate markedly enhancing walls around fluid-filled cavities on T1-weighted postcontrast images (Dennis, 2000). Although hydrated wooden foreign bodies may not be directly detectable on MRI (Woolfson & Wesley, 1990), the associated inflammatory reactions may be identified (Dennis, 2000). Larger wooden foreign bodies may be hypointense on MRI (Hartley et al., 2007). The MRI appearance of orbital inflammation with intracranial extension has been described in dogs (Kneissl et al., 2007); the condition was best identified by abnormal MR signal increase within the orbital fissure on transverse T2WI and dorsal STIR images, or on transverse or dorsal postcontrast T1WI.

MRI is the modality of choice when assessing the optic nerves and chiasm, providing the best morphologic assessment of these structures (Penninck et al., 2001). Oblique dorsal and oblique sagittal planes allow visualization of both the globe and the retrobulbar tissues in the same section, and with serial sections the entire optic nerve is consistently imaged (Morgan et al., 1994). As already discussed, the use of imaging sequences that suppress the normally hyperintense fat signal from the orbit may improve the visualization of the contrast enhancement associated with optic nerve pathologies (Lee et al., 2009; Penninck et al., 2001). In humans, MRI is very useful in evaluating optic nerve meningioma (Aviv & Miszkiel, 2005; Dutton, 2010b; Goh et al., 2008; Jäger, 2005; LeBedis & Sakai, 2008; Müller-Forell, 2004). Although MRI is not as reliable as CT in detecting intratumoral calcification, it provides better definition of the posterior (caudal) extent of the tumor (Morgan et al., 1996). Most human orbital meningiomas are isointense to the optic nerve on T1WI and T2WI, although they may be hypointense on T1WI and hyperintense on T2WI (Aviv & Miszkiel, 2005). Fat-saturated, contrast-enhanced T1WI demonstrate the lesion best in humans (Aviv & Miszkiel, 2005). In the dog, optic nerve meningiomas have been described as isointense on T1WI and hyperintense or isointense on T2WI, and with marked homogenous contrast enhancement (Grahn et al., 1993; Seruca et al., 2011). Armour et al. (2011) described a dural tail sign in five of nine cases of presumed orbital and intracranial meningioma; the dural tail sign is a linear contrast-enhancing region of the dura mater strongly supportive of meningioma, although false positives are reported (Graham et al., 1998). The MRI findings in a horse with optic nerve meningioma, including strong contrast enhancement, association with the optic nerve, and its tapering caudal margin, are illustrated in Fig. 10.2.16.

Optic neuritis in humans is characterized by an enlarged optic nerve that is contrast enhancing and hyperintense on T2WI in acute disease, whereas chronic optic neuritis classically is associated with an atrophic nonenhancing optic nerve that is hyperintense on T2WI (LeBedis & Sakai, 2008). Although the hyperintense optic nerve on T2WI is not specific and may occur with several pathologies including edema, demyelination with axonal loss, as well as chronic gliosis, the contrast enhancement reflects disruption of the blood–brain barrier and is characteristic of acute inflammation (Gass & Moseley, 2000; Jäger, 2005). The MRI findings of presumed optic neuritis in the dog included unilateral optic nerve hyperintensity (3/13, 23.0%), bilateral optic nerve hyperintensity (1/13, 7.7%), and optic chiasmal hyperintensity (3/13, 23.0%); all of the hyperintensities were noted on T2WI or FLAIR sequences (Armour et al., 2011; Armour personal communication, 2012). The majority demonstrated optic nerve enhancement and/or multifocal patchy intracranial contrast enhancement (7/13, 53.8%), reflecting a more

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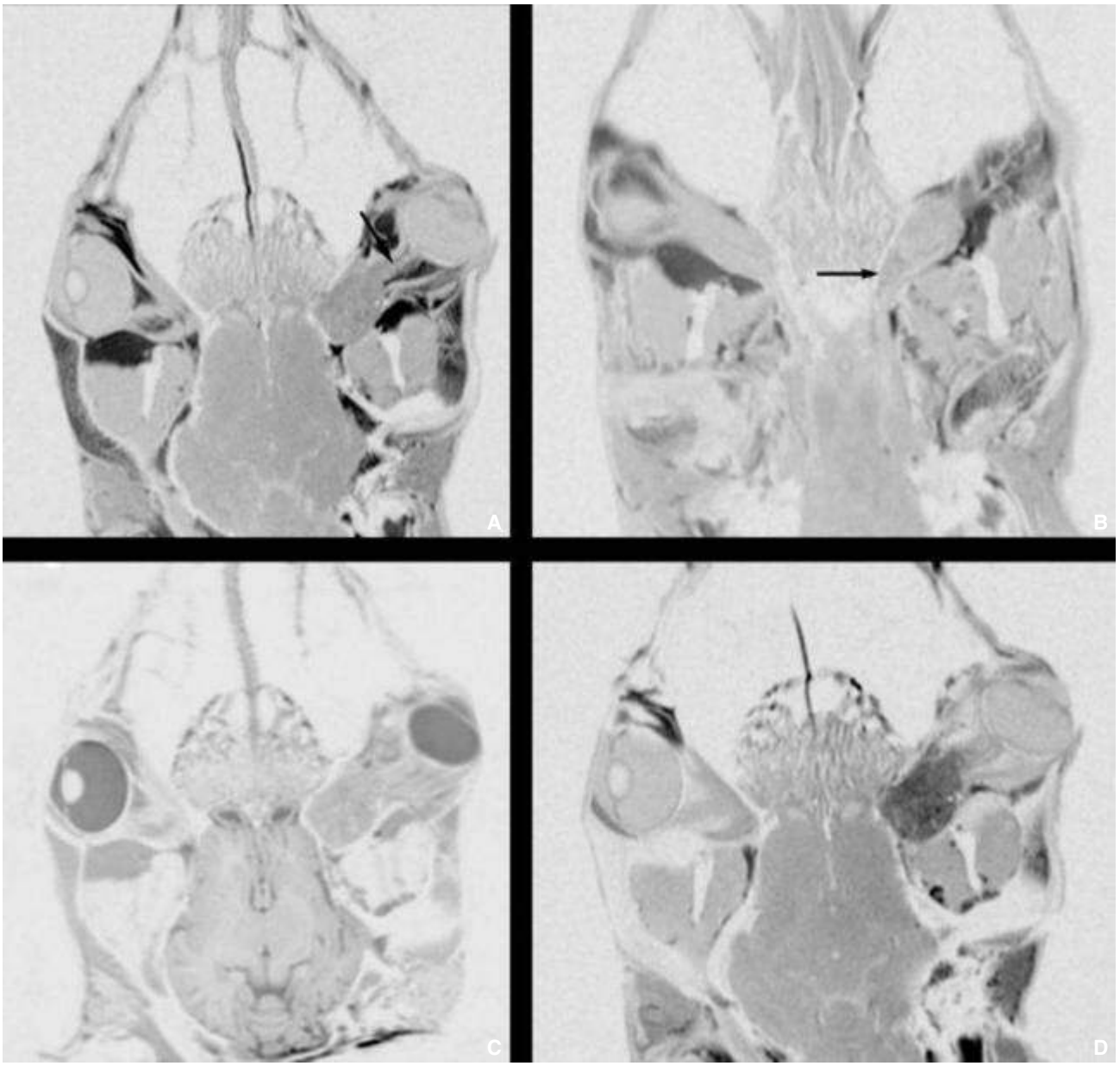


Figure 10.2.16 Optic nerve meningioma in a 16-year-old Thoroughbred gelding. **A**. Dorsal T1-weighted magnetic resonance imaging (MRI). There is a well-defined orbital mass, which is intimately associated with the optic nerve (arrow). The mass has a signal intensity similar to that of the brain parenchyma. Rostral displacement of the globe is apparent. **B**. Dorsal T1-weighted MRI. This image slice is slightly ventral to image (**A**) and shows the tumor tapering caudally along the margin of the optic nerve (arrow). **C**. Dorsal T2-weighted MRI. The mass has a signal intensity similar to that of the brain parenchyma. D. Dorsal T1-weighted MRI postcontrast with fat suppression. The mass shows strong, uniform, and homogenous contrast enhancement. The discrete nature of the mass, strong contrast enhancement, association with the optic nerve, and its caudal tapering margin were suggestive of a meningioma arising from the optic nerve sheath. This was subsequently confirmed on histopathology. MRI accurately defined the posterior extent of the tumor, identifying that complete surgical excision would not be feasible, and that adjunctive radiotherapy would need to be used as part of the treatment plan.

generalized concurrent CNS inflammatory disease (Armour et al., 2011). In the two cases of clinically apparent optic neuritis described by Seruca et al. (2011), one demonstrated hyperintensity of the optic nerve on T2WI and STIR sequences and moderate contrast enhancement on T1WI of both optic nerves. Granulomatous meningoencephalomyelitis (GME) is the most commonly reported cause of optic neuritis in the dog (Cherubini et al., 2006; Nell, 2008) and as such MRI studies of the brain may be indicated in cases of clinically apparent optic neuritis to assess for CNS pathology

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consistent with GME or neoplasia (Armour et al., 2011; Seruca et al., 2011). The MRI findings typical in cases of acute optic neuritis include optic nerve enlargement, contrast enhancement, and loss of CSF signal, which are illustrated in Fig. 10.2.10 and Fig. 10.2.17.

MRI findings in traumatic chiasmal lesions have been reported in humans (Arkin et al., 1996; Dilly & Imes, 2001; Gurses et al., 2006; Mark et al., 1992; Segal & Gans, 2009), but to the authors' knowledge not in the veterinary literature. In humans, high-resolution (1.5 T magnet or greater) MRI with gadolinium contrast enhancement is considered the best imaging modality for lesions involving the optic chiasm (Foroozan, 2003), but in clinical practice CT remains the imaging modality of choice following acute head trauma with posttraumatic blindness, due to its increased sensitivity at detecting treatable optic canal fractures (Mark et al., 1992).

Tear Film Imaging

Evaluation of the tear film, and its implications for ocular surface health, has long been an area of research in ophthalmology. In the medical field a number of tear film parameters are measured or assessed, but these have yet to become mainstream in veterinary ophthalmology (Foulks & Pfugfelder, 2014).

Tear Ferning

Collection of a nonstimulated tear sample by micropipette, microcapillary tube, or via a Schirmer tear test strip can be undertaken and a small sample of tear fluid applied to a slide. This typically will dry on the slide in less than 10 min (although this is temperature and humidity dependent). The characteristic crystallization pattern (referred to as the "tear fern") of the dried tear sample viewed by light microscopy has correlation to the tear film composition (in particular osmolarity and mucin content). The tear fern is graded (Rolando type I–IV or Masmali grade 0–4 scales) and is typically dense and full in a normal healthy sample, but fragmented or absent with large spaces in a keratoconjunctivitis sicca (KCS) sample.

Clinical Applications

Tear ferning has been described in horses, and was found to be easy to perform, inexpensive, and without patient risk (Silva et al., 2016). Silva et al. also used a "STEPanizer" software program to more objectively assess the crystallization pattern of microphotographs, in addition to standard Rolando grading. Silva et al. (2016) recommended further work correlating tear ferning results with other tear film parameters (e.g., tear osmolarity) for standardization of this modality.

Tear ferning has been described in healthy dogs and sampling methods (micropipette, microcapillary tubes, and

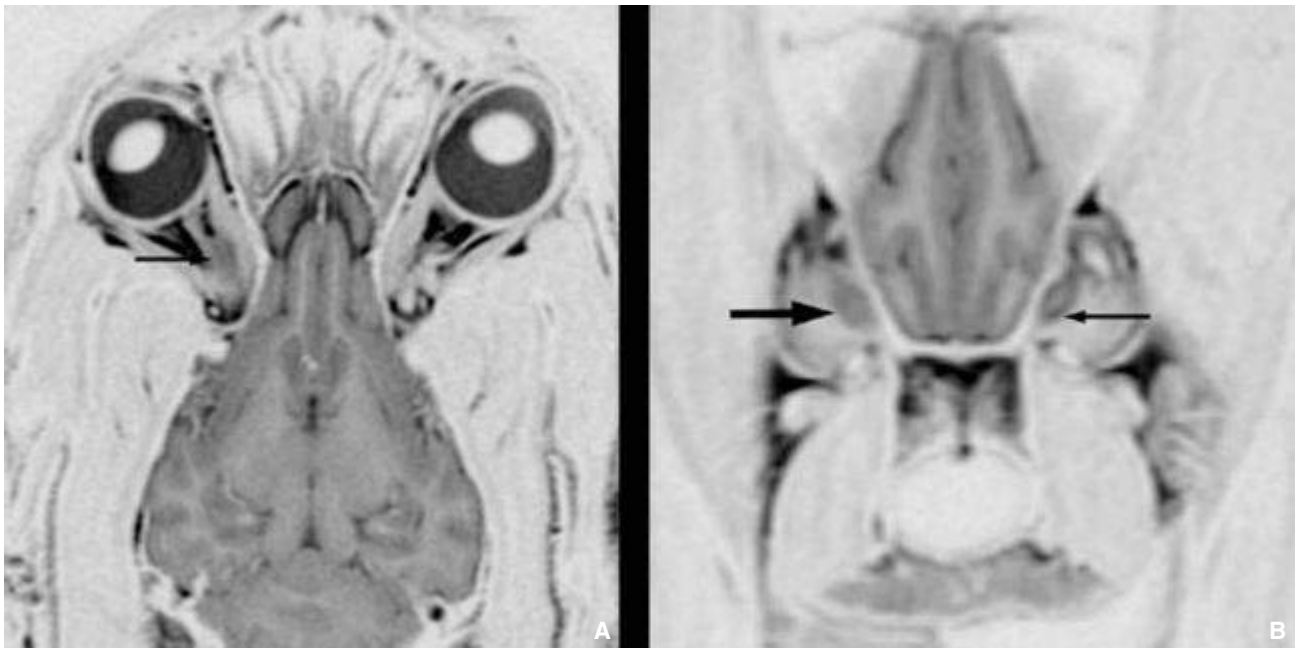


Figure 10.2.17 Optic neuritis affecting the right side in an 8-year-old Labrador Retriever dog. **A**. Dorsal T2-weighted magnetic resonance imaging (MRI). The right optic nerve is enlarged and moderately hyperintense (arrow). **B**. Transverse T2-weighted MRI. The enlargement of the right optic nerve is evident (large arrow) and also the attenuation of the cerebrospinal fluid signal, which is clearly visible on the contralateral side (small arrow).

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Schirmer tear test strips) compared (Oria et al., 2017). Oria et al. (2017) also used both the Rolando and Masmali grading schemes and found the test to be simple and low cost, recommending its adoption in routine clinical practice (Fig. 10.2.18 and Fig. 10.2.19). Williams and Hewitt (2017) described tear ferning patterns in healthy normal dogs and in dogs with KCS, using a microcapillary tube collection and grading according to the Rolando scale. The KCS patients had "abnormal" tear ferning patterns (Rolando types III and IV); however, some normal, healthy dogs also had abnormal grades. The authors commented on variability and familiarity with sampling technique having an effect on the tear ferning result (e.g., stimulated vs. nonstimulated tears, presence of mucoid discharge and avoidance of sampling this).

Noninvasive Tear Film Break-Up Time

Keeler Tearscope-Plus

The Keeler Tearscope-Plus™ (Keeler, Windsor, UK) is a handheld noninvasive instrument used to assess tear film break-up time (TFBUT) without the need for instillation of fluorescein. As fluorescein potentially destabilizes the tear film, and there is variation in the fluorescein volume applied (especially with fluorescein-impregnated strips), this was felt to limit the practical usefulness of the TFBUT in the clinical setting. The Tearscope provides a colored interference pattern of the tear film from reflected white light. The instrument still has some subjectivity, as the observer is responsible for timing and judging the period until the first appearance of tear film disruption occurs (Markoulli et al., 2018). This is further compounded in veterinary ophthalmology as a forced blink is used at the start of the measurement, unlike in humans with a self-controlled blink, which may have unintended implications for tear film stability and the TFBUT measurement (Wei et al., 2013).

Clinical Applications

The Tearscope has been used to demonstrate the longer TFBUT in rabbits compared with humans (Wei et al., 2013) and to draw conclusions about the relative stability of the tear film in rabbits versus humans.

Oculus Keratograph 5M

The Oculus® Keratograph 5M (Oculus, Wetzlar, Germany) uses an infrared light source (wavelength 880 nm) to project a ring pattern onto the tear film, and changes in the regularity of the reflected image (captured by video camera) indicate the onset of tear film break-up. This disruption of the reflected image is detected by the instrument software and reported as the time to first point of TFBUT, as well as the average time of all break-up points measured (Markoulli et al., 2018). As yet publications on the noninvasive TFBUT using the Oculus Keratograph 5M in veterinary patients are lacking.

Tear Film Optical Coherence Tomography

Tear film optical coherence tomography (OCT) imaging has been applied to contact lens assessments, tear meniscus assessment in KCS, and nasolacrimal obstruction (functionally or physically), as well as on the effect of artificial tear film agents and blinking on tear film dynamics in humans (Chen et al., 2010; Ibrahim et al., 2010; Koh et al., 2010; Palakuru et al., 2007, 2008). See "Optical Coherence Tomography" later in this chapter.

Corneal Imaging

Pachymetry

Ex vivo measurements of corneal thickness are subject to inaccuracy due to postmortem/postsurgical swelling of the

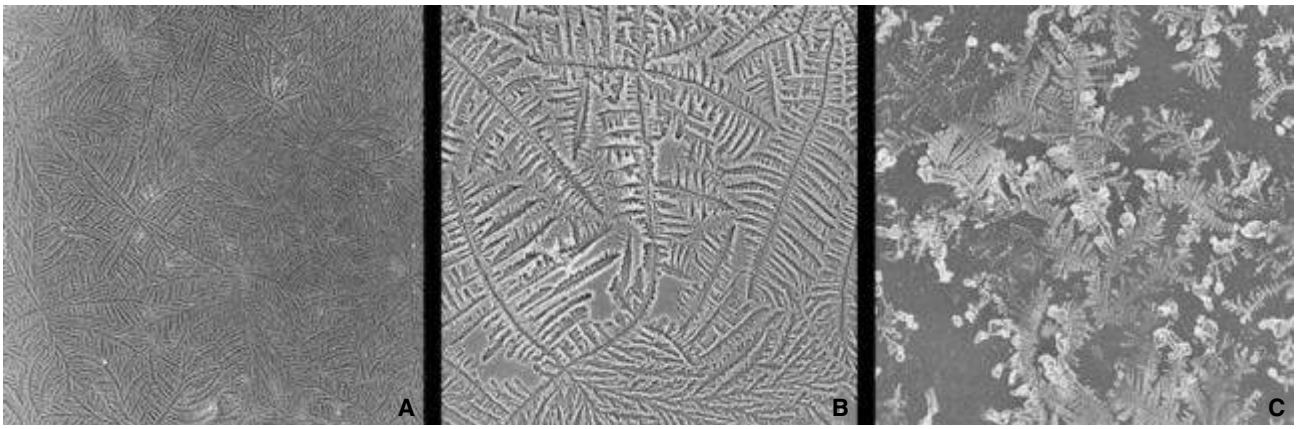


Figure 10.2.18 Tear ferning patterns in healthy dogs according to the Rolando grading scale. **A**. Type I representation, dendritic fern growth is uniform, and there are no spaces between branches. **B**. Small spaces begin to appear between the stems. **C**. Incomplete crystallization process, single and small formations, and branches are rare or nonexistent. (Reproduced with permission from Oria A.P., Raposo A.C.S, Araujo N.L.L.C., et al (2017) Tear ferning test in healthy dogs. *Veterinary Ophthalmology*, **1**, 1–8.)

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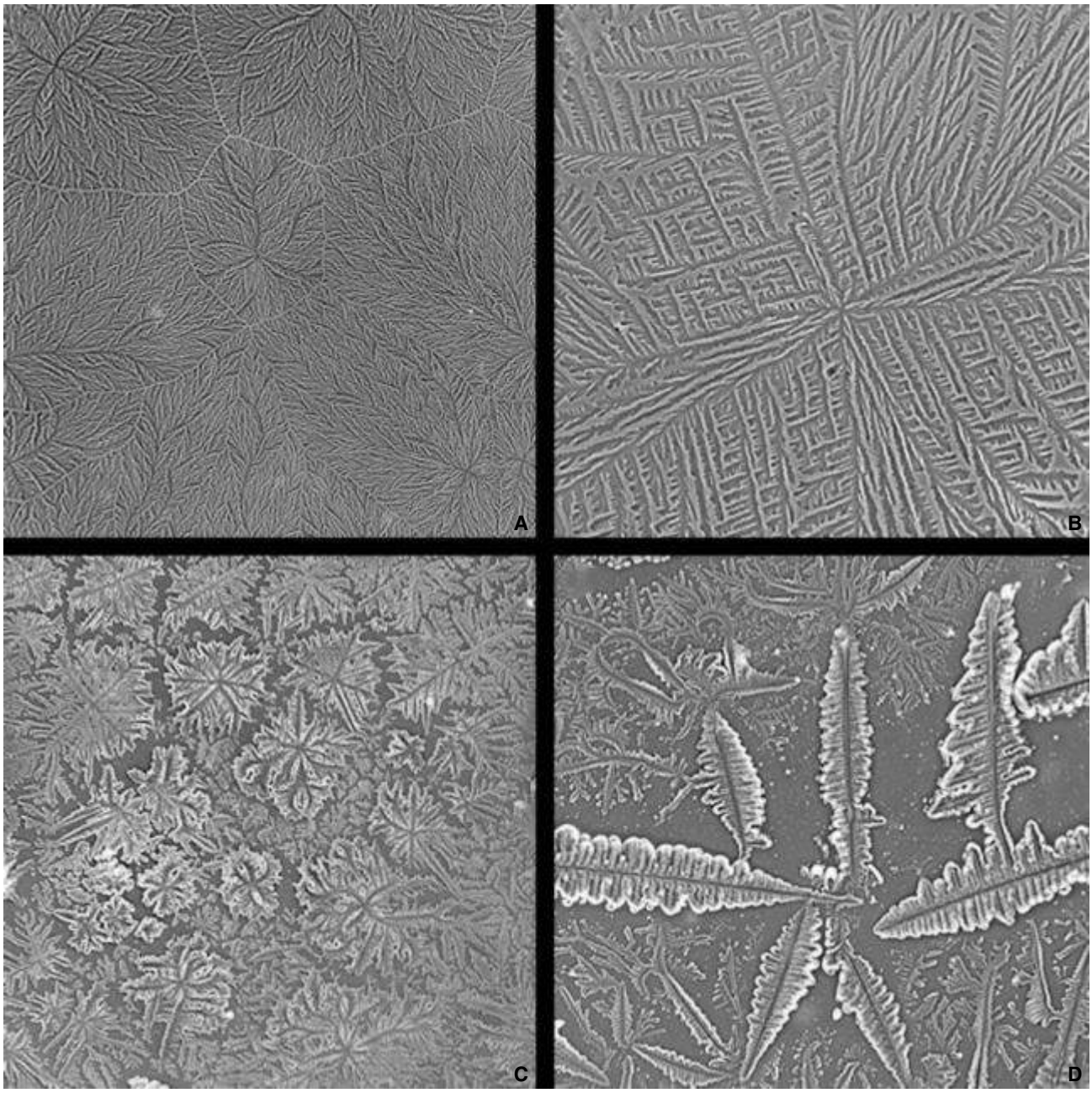


Figure 10.2.19 Tear ferning patterns of healthy dogs according to Masmali's grading criteria. **A**. Representation of grade 0, with full crystallization without gaps between the ferns and branches. **B**. Representation of grade 1, decreased density of the branches, and appearance of small spaces between them. **C**. There are small branches, sometimes thick and large, with clear gaps between the ferns, representing grade 2. **D**. Characteristics of grade 3, in which spaces and gaps are increased, and coarse crystals are formed. (Reproduced with permission from Oria A.P., Raposo A.C.S, Araujo N.L.L.C., et al. (2017) Tear ferning test in healthy dogs. *Veterinary Ophthalmology*, **1**, 1–8.)

tissue, especially if immersed in storage medium or fixative, and are therefore of limited value in the clinical setting. Various technologies are available to provide accurate measurement of *in vivo* corneal thickness, including ultrasound pachymetry (e.g., AccuPach® or Pach-Pen®, Accutome, Malvern, PA, USA), *in vivo* confocal microscopy (IVCM; e.g., Confoscan4™, Nidek, Albignasego, Italy; Heidelberg Retina Tomograph – Rostock Corneal Module [HRT II RCM®], Heidelberg Engineering, Heidelberg, Germany), optical biometry with a Scheimpflug camera (e.g., Pentacam®, Oculus; Sirius®, Schwind, Kleinostheim, Germany; or Galilei®, Ziemer Ophthalmic Systems, Port, Switzerland),

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OCT (e.g., Visante®, Carl Zeiss Meditec, Jena, Germany), and optical coherence pachymetry (e.g., Orbscan®, Bausch + Lomb, Rochester, NY, USA).

Optical pachymetry measures corneal thickness using an oblique light source across the cornea (often attached to a slit-lamp biomicroscope and Scheimpflug camera) and calculating the distance between the observed epithelial and endothelial reflections based on the angle of incidence and magnification (Scheimpflug principle). Use of optical pachymetry requires clear corneal reflections and is therefore limited in cases of corneal edema, fibrosis, or infiltrates. There is interobserver variability with manual systems, and both the radius of curvature of the cornea and the refractive index of the cornea are added variables to the measurement. Development of automated optical coherence pachymetry systems (e.g., Orbscan) reduced interobserver variability, thereby increasing reproducibility and reliability. Orbscan uses a large number of slit-beam images across the cornea, providing a topographic image of corneal thickness. OCT and *in vivo* confocal microscopy can also be used to gain corneal thickness measurements (see "Optical Coherence Tomography" and "*In Vivo* Confocal Microscopy of the Cornea"), although their technology was not originally developed for this facility.

Ultrasound pachymetry uses ultrasound energy reflected from interfaces of differing refractive indices to measure corneal thickness, and is therefore equivalent to an ultrasound A-scan. Probes can vary from 20 to 65 MHz and measure from the anterior tear film to the posterior surface of the endothelium. The distance between reflections is then calculated based on the speed of ultrasound through the cornea (1550–1639 m/s depending on species). Conversion factors are useful when calculating measurements in nonhuman species. For example, the feline cornea has an ultrasound velocity of 1590 m/s, and therefore human pachymeters will overestimate feline corneal thickness based on the human corneal ultrasound velocity of 1640 m/s.

This technology can be used in the face of concurrent corneal opacity (edema, scarring, etc.). Ultrasound pachymetry has high intraobserver reproducibility, with lower interobserver variability than optical pachymetry (Salz et al., 1983). Careful placement of the probe both centrally and perpendicular to the corneal surface is important, and user errors are sources of variability. Modern machines offer alignment detection and have smaller probe tips, which allow their use in a wider range of species (see Fig. 10.2.20 and Fig. 10.2.21). Ultrasound pachymetry is the preferred method (gold standard) of pachymetry in human patients, with readings independent of patient fixation, improved reproducibility, accuracy, and portability.

Reported sources of error with both optical and ultrasound pachymetry include dehydration of the cornea (causing decreased corneal thickness readings), hydration of the cornea (e.g., after periods of eyelid closure and reduced tear evaporation), patient positioning (e.g., recumbency increases corneal thickness measurements in humans), marking of the cornea, and taking repeated measurements.

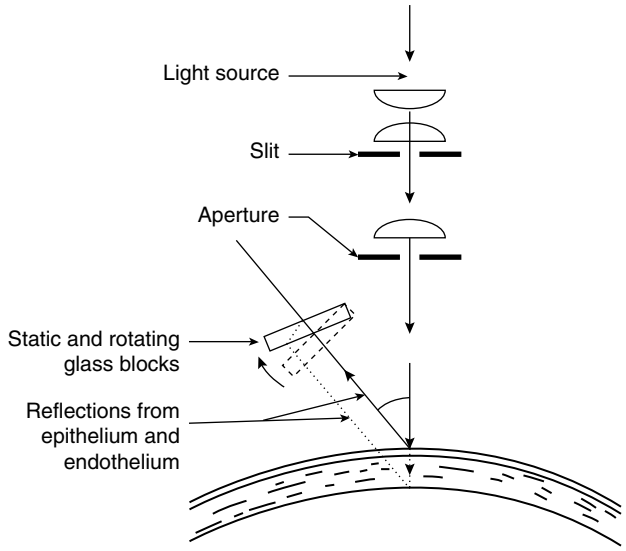


Figure 10.2.20 Schematic illustration of optical pachymeter. (Illustration by Roser Tetas Pont.)

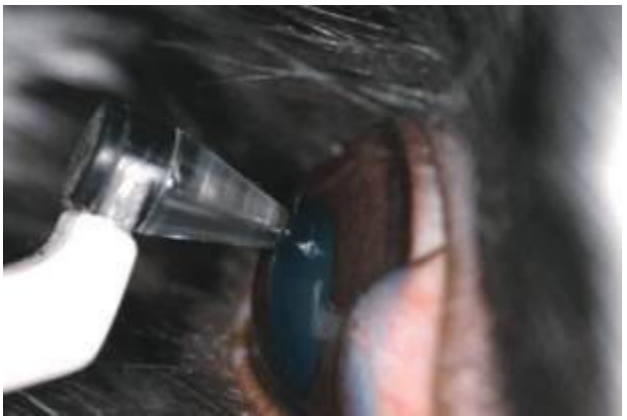


Figure 10.2.21 Pachymetry being performed on a normal rabbit cornea. (Courtesy of Dr. Ellison Bentley.)

Clinical Applications

Pachymetry is used in human patients prior to laser-assisted *in situ* keratomileusis (LASIK) procedures to ensure sufficient preoperative corneal thickness to avoid corneal ectasia complications postoperatively. Pachymetry has also been used to investigate the effects of corneal cross-linking with riboflavin and ultraviolet-A irradiation as a treatment for keratoconus, both *ex vivo* and *in vivo*, in animal models (Dong & Zhou, 2011; Kampik et al., 2010). Corneal transplant rejection has been objectively assessed using ultrasound pachymetry, with an increased thickness of the donor graft associated with rejection (more

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traditionally assessed subjectively by increasing corneal opacity; Flynn et al., 2010).

Corneal thickness is important in the early detection of glaucoma, for interpretation of tonometry results, and for prediction of development of glaucomatous visual deficits (Brandt et al., 2001; Gordon et al., 2002; Herndon et al., 2004; Kourkoutas et al., 2009). Central corneal thickness (CCT) has a bearing on the accuracy of indentation and applanation tonometers, as changes in the elasticity (in turn related to thickness, rigidity, and astigmatism) of the cornea affects these results. Increased corneal thickness will result in elevated indentation or applanation tonometry readings, while thinner corneas will produce reduced intraocular pressure readings. Linear scale correction factors of 1–3.6 mmHg per 50 µm of increased CCT, as well as a mathematic formula (Orssengo and Pye algorithm) incorporating factors of anterior corneal curvature, corneal thickness, and elasticity (Poisson's ratio), have been proposed to adjust intraocular pressure (IOP) readings for CCT (Shih et al., 2004).

Aside from the accuracy of IOP readings, CCT is a predictor of glaucoma damage, and hence pachymetry has been used extensively in the investigation and management of human glaucoma patients. A large study in humans (Ocular Hypertension Treatment Study, OHTS) demonstrated that CCT is also a risk factor for initial glaucoma damage (visual field loss) among people with ocular hypertension (Gordon et al., 2002). It has been postulated that this may not be entirely due to the link with tonometry reading accuracy (and therefore initiation of early treatment), but CCT may be linked to corneoscleral shell (and lamina cribrosa) composition, and associated with optic disc response to IOP-induced stress. This hypothesis has been questioned by a study on enucleated eyes comparing central corneal thickness with optic nerve head parameters, which found no association between measurements (Jonas & Holbach, 2005). A similar study on enucleated globes from Chinese patients with and without glaucoma also revealed no association between lamina cribrosa thickness and CCT, casting further doubt on the hypothesis (Ren et al., 2010).

In vivo CCT measurements in guinea pigs (*Cavia porcellus*) using ultrasound pachymetry has been reported as part of a study describing the normal guinea pig cornea (Cafaro et al., 2009). CCT values (227.9 ± 14.1 µm) were not significantly different from peripheral corneal measurements, or between albino and pigmented animals, or males and females. Similarly, ultrasound pachymetry results have been reported for five western lowland gorillas (*Gorilla gorilla gorilla*; mean CCT 489 ± 52 µm) as part of a study reporting normal ocular findings in the species anesthetized for nonocular reasons (Liang et al., 2005). Ultrasound pachymetry has also been used to measure CCT in normal koi fish (*Cyprinus carpio*; mean 325.9 µm), with increased CCT in females compared to males. Increasing CCT was also demonstrated with increasing age, body length, vertical corneal diameter, and horizontal corneal diameter in Koi fish (Lynch et al., 2007).

The postnatal changes in CCT of domestic chickens (*Gallus gallus domesticus*) from hatching to day 450 have also been documented using ultrasound pachymetry (Montiani-Ferriera et al., 2004). This study demonstrated an initial decrease in CCT from hatching until day 12 post hatch (postulated to be due to endothelial cell maturation and reduction of corneal hydration), followed by a gradual increase to maximal CCT at day 70. There was no effect of gender on CCT in the chicks. Central corneal thickness has also been measured by ultrasound pachymetry in captive black-footed penguins (*Spheniscus dermersus*), and no correlation found with CCT and IOP (unlike in humans, dogs, and chickens), or with CCT and age or bodyweight (Gonzalez-Alonso-Alegre et al., 2015).

Postnatal development of CCT in dogs has also been studied from eyelid opening to 42 weeks of age (Montiani-Ferriera et al., 2003). This showed a similar initial decrease in CCT up to 6 weeks of age, followed by an increase in CCT, which became a more gradual increase at 30 weeks of age. Breed-specific differences in CCT were identified in this study, with Labrador Retrievers having significantly thicker corneas than Briard × Beagle dogs. An earlier study using ultrasound pachymetry reported canine CCT measurements of 520–597 µm, thicker peripheral versus central corneal readings and male versus female readings, as well as increasing thickness with increasing bodyweight (Gilger et al., 1991).

Feline corneas have been assessed by both optical pachymetry (755 ± 33 µm; Carrington & Woodward, 1986) and ultrasound pachymetry (CCT 578 ± 64 µm; Gilger et al., 1993), and 546 ± 48 µm (Schoster et al., 1995). Feline CCT measured by ultrasound pachymetry was reported to increase with age (up to 100 months or 8 years), but no gender influence was apparent. Variations in corneal thickness topographically were not apparent in one study (Gilger et al., 1991), while another study reported the thickest corneal readings laterally and subperiaxially, and the thinnest measurements dorsomedially in cats (Schoster et al., 1995).

Corneal thickness has been investigated in horses, and within different breeds of horse. Mean CCT in horses is 770–893 µm and is unaffected by gender (Andrew et al., 2001; Plummer et al., 2003; Ramsey et al., 1999; van der Woerdt et al., 1995). The peripheral cornea is significantly thicker than the central cornea in the horse (831–924 µm), and there was no apparent effect of age, xylazine sedation, or auriculopalpebral nerve block on readings (van der Woerdt et al., 1995). Measurements of CCT in Miniature Horses revealed similar values to those recorded in full-sized horses (Plummer et al., 2003). No correlation between endothelial cell density and CCT was found in enucleated eyes from normal horses (after euthanasia), but an

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association at critical endothelial cell densities was not ruled out (Andrew et al., 2001).

Ultrasound pachymetry has been used to demonstrate that American Quarter Horses affected with hereditary equine regional dermal asthenia (HERDA) have statistically thinner corneas than unaffected Quarter Horses (Badial et al., 2015; Mochal et al., 2010). HERDA is an autosomal recessive generalized connective tissue disorder of horses, resulting in abnormal elasticity and excessive fragility of the skin, analogous to Ehlers–Danlos syndrome in humans. Alterations of collagen microarchitecture have been demonstrated within the cornea as well as in dermal tissues in HERDA-affected horses. Affected horses also have an increased risk of corneal ulceration. Ehlers–Danlos-affected patients demonstrate corneal thinning, increasing the risk of keratoconus, keratoglobus, corneal plana, corneal rupture, and ocular fragility (Hyams et al., 1969; Segev et al., 2006).

Ultrasound pachymetry has also determined the mean CCT for alpacas as 595 µm and for llamas 608 µm, with no gender or age effect on CCT in either species (Andrew et al., 2002; Fig. 10.2.22). Spectral domain OCT pachymetry has been used to measure mean CCT in normal sheep (741 µm), goats (617 µm), and alpacas (635 µm), and was able to determine the thickness of specific corneal layers *in vivo* (epithelium, stroma, Descemet's membrane; Lo Pinto et al., 2017b).

Ultrasound pachymetry has also demonstrated a transiently increased CCT in canine phacoemulsification patients postoperatively (from a mean of 611 µm preoperatively to a peak of 741 µm on day one postoperatively), returning to baseline values by one month postsurgery. The same study also showed that the mean diabetic canine CCT was greater over all time points than nondiabetic canine CCT (Lynch & Brinkis, 2006). Specular microscopy was not undertaken to assess corneal endothelial morphology or density in this study, but speculation remains that an increase in postoperative corneal thickness is due to loss of endothelial function (as demonstrated in human diabetic patients; Ziadi et al., 2002).



Figure 10.2.22 Pachymetry being performed on a normal llama cornea. (Courtesy of Dr. Stacy Andrew.)

Similarly, increases in corneal thickness in human patients following cataract surgery are reported, with reduction to presurgical values three months postoperatively, despite a permanent reduction in endothelial cell density (Ventura et al., 2001). In humans, endothelial density correlates poorly with CCT until a critical minimum endothelial density is reached (Ventura et al., 2001).

Ultrasound pachymetry has been used (in conjunction with spectral domain OCT and IVCM) to assess the effect of superficial keratectomy and conjunctival advancement hood flap in the treatment of canine spontaneous bullous keratopathy (Horikawa et al., 2016). This study demonstrated significant reductions in mean central corneal thickness associated with this surgical treatment, and owners reported increased corneal clarity and vision in their dogs postoperatively.

The effect of intracameral preservative-free lidocaine on corneal thickness, as well as on endothelial cell density and morphology, has been investigated in dogs, and no significant difference from pretreatment values was detected, suggesting a lack of adverse ocular effects (Gerding et al., 2004).

Ultrasound pachymetry has also been used to assess the best preservation fluid for enucleated porcine eyes for use in wet labs, which was demonstrated to be tap water (compared to 14 other preservation methods) for up to 48 hours (Nibourg et al., 2014).

Specular Microscopy

Specular microscopy is an imaging modality that allows morphologic analysis of the corneal endothelium, although the technology can be applied to image the corneal epithelium and stroma, as well as the lens. The first specular microscope for *ex vivo* endothelial cell photography (500× magnification) was developed by Maurice in 1968 (Maurice, 1968), although descriptions of the use of the specular reflex to examine the corneal endothelium were first published in 1920 (Volt, 1920). Just as light microscopy reveals an image from light transmitted through a tissue, specular microscopy provides an image from light reflected from a tissue. The specular reflex occurs at the interface of two refractive indices, and light is reflected back to an observer. The refractive index of the endothelium is greater than for aqueous humor, and therefore 0.022% of the projected light will be reflected (i.e., the majority of the incident light is transmitted or absorbed; McCarey et al., 2008). Light scattered within the corneal stroma (by collagen lamellae and keratocytes) will reduce the contrast of the endothelial image. Increased light scatter associated with a corneal opacity or edema further reduces the specular reflex, and therefore the image quality.

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The area of endothelium that can be inspected with this system is dependent on two factors: the curvature of the cornea and the corneal thickness. The surface area of the specular reflex is confined by the radius of the curvature of the reflecting surface (cornea). Light reflected from a cylinder (as opposed to a flat surface) is condensed 90° to the axis of the curved surface. In addition, the epithelial surface is highly reflective due to the large refractive index difference between air and the tear film–cornea interface. The proximity of this anterior reflection to the endothelial specular reflex restricts the viewable area of the endothelium to a relatively small area.

Original specular microscopes were contact microscopes, where the objective lens was placed directly against the corneal epithelium, therefore requiring topical anesthetic (and a compliant patient). Contact with the cornea applanates the surface, flattening the curvature and enlarging the specular reflex. Noncontact specular microscopes were later developed, utilizing automatic focusing technology, which generally have a smaller field of view but allow for greater patient comfort (Fig. 10.2.23). Specular microscopes may utilize a stationary slit beam, a moving slit beam, or spot illumination to obtain images, with modern machines using multiple slit beams that scan a wider area of cornea to increase the field of view. The width of the slit/spot beam will affect the size of the field of endothelial cells seen; however, increasing the beam width can be at the cost of increased light scatter across anterior corneal tissue (and therefore reduced image quality). This may be overcome by using multiple or scanning beams of finer width to create a composite image of the endothelium (Laing et al., 1979).

There are four zones of specular reflection, the first at the corneal surface between the interface lens, coupling fluid, and corneal epithelium. The second is light reflected from the corneal stroma, and the third is from the endothelium. The last zone is at the level of the aqueous where there is very little reflection and it therefore appears dark. Images obtained thus have a dark boundary representing the intraocular surface of the cornea and the light boundary at the limit of the endothelium (Fig. 10.2.24 and Fig. 10.2.25).

Techniques for determining endothelial cell density include the comparison method, the frame method, the corner method, and the center method. The comparison method uses a subjective visual comparison of the patient's endothelial cell pattern to a known set of hexagonal patterns for set cell densities. The frame method uses a count of the number of cells within a frame; cells that extend over two frames along a border are counted as full cells over two adjacent borders, but are not counted on the corresponding adjacent two borders. The corner method identifies cell borders and defines the cell areas on a digital tablet. This is reliant on the subjective decision of defining a cell borders as well as the quality of the specular microscope image. The estimated error for this method is 5% (McCarey et al., 2008). The center method is the most commonly adopted technique, whereby the approximate center of each cell is marked with a dot and computer analysis calculates the cell area based on the radius to the center of adjacent cells. The technique is reliant on the diligence and expertise of the technician performing the analysis; the error range for the center method is reported as 0.5%–5% (McCarey et al., 2008).

Image quality has a bearing on error rates, with excellent-quality images, unsurprisingly, having fewer interobserver differences reported (Lass et al., 2005). It is recommended that prospective studies utilizing specular microscopy should use the same microscope manufacturer, settings, and technician for capturing images (or similarly trained staff if multicenter, with periodic review of standards) and the same technician analyzing the images. Multicenter clinical trials

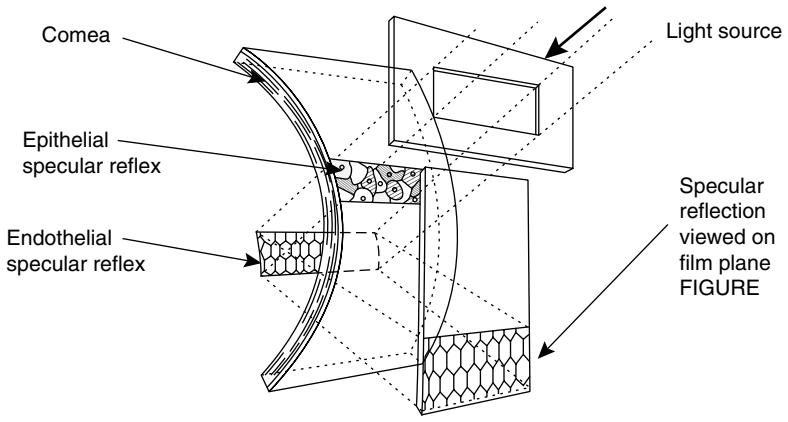


Figure 10.2.23 Simplified illustration of a specular microscope. Light illuminates a section of the cornea and is reflected from the epithelium and endothelium of the cornea (only one layer will be in focus at a time) and viewed in a different plane (angle) from the incident light. As the surface that the light is reflected on is not flat (corneal curvature), the illuminated area of cornea (field of view) is flattened dorsoventrally (perpendicular to the axis of the curvature). (Illustration by Roser Tetas Pont.)

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Figure 10.2.24 **A**. Noncontact specular microscopy being undertaken on an anesthetized Beagle cross-bred dog. **B**. Specular microscopy image of the central corneal endothelium of a normal 9-month-old cross-bred dog. (Courtesy of Dr. Matt Chandler.)



Figure 10.2.25 Specular microscopy (Topcon SP. 2000P, Topcon Medical Systems, Oakland, NJ) from a normal male 4-year-old rhesus monkey (**A**) and a normal 17-year-old Thoroughbred gelding (**B**). Note the brighter and darker borders of the image corresponding to the stromal and aqueous sides of the endothelium respectively. Avg, average cell size; CD, endothelial cell density; CV, coefficient of variation; Max, maximum cell size; Min, minimum cell size; N, number of cells; SD, standard deviation; T, thickness. (Courtesy of Dr. Stacy Andrew.)

have an estimated cell density variability of ± 10% (McCarey et al., 2008).

As a general rule, three images from the central cornea and three images from the paracentral cornea, each with a minimum of 150 cells per image, are recommended in endothelial assessment of human patients. The contact specular microscopes are reported as being capable of capturing 700–3000 cells per image (although 3000 cells per image is considered exceptional) and noncontact specular microscopes capable of 120–170 cells per image (McCarey et al., 2008).

Specular microscopy is used clinically to assess corneal endothelial cell density, rate of polymegathism (or coefficient of variation in cell size, i.e., an objective measure of cellular morphology variation), and pleomorphism (variation in cell shape, i.e., an subjective assessment of cell morphology differences). These assessments are often used sequentially in longitudinal studies on the effect of disease processes (e.g., Fuch's endothelial dystrophy), surgical interventions (e.g., cataract surgeries, including intracapsular, extracapsular, and phacoemulsification techniques), surgical devices (e.g., phakic or anterior chamber intraocular lenses utilized in human ophthalmology), topical and intraocular drugs, and contact lens wear over repeated examinations (Acar et al., 2011; Alanko & Airaksinen, 1983;

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Cremona et al., 2009; Esgin & Erda, 2000; Esquenazi et al., 2011; Inaba et al., 1985; Zhao et al., 2008).

In a normal human endothelium, more than 60% of the cells are hexagonal, and this is the most efficient cell shape to maintain intercellular tight junctions and a continuous monolayer (Dougherty, 1998). Endothelial cell density and pattern vary with phylogeny, with birds and mammals having a mainly hexagonal pattern (goose 79%, dog 78%, rat 58–76%, rabbit 71% hexagonal) and higher densities, and amphibians, reptiles, and fish having lower densities with jigsaw-like to polygonal patterns (Yee et al., 1987). The coefficient of variation (CV) in a normal human corneal endothelium is 0.22–0.31 (McCarey et al., 2008). Increased polymegathism is usually the first evidence of endothelial disease, with readings of 0.32–0.40 considered elevated and above 0.40 viewed as abnormal (McCarey et al., 2008). Although the endothelium may be adequately functional in these corneas, susceptibility to trauma (e.g., intraocular surgery, glaucoma, contact lens wear) may be increased. Polymegathism is reported with extended contact lens wear, particularly with lenses that have poorer oxygen permeability. This endothelial change is slow to recover, even when contact lens wear is discontinued (Liesagang, 2002; McCarey et al., 2008).

Clinical Applications

Aging is associated with a gradual reduction in endothelial cell counts (young adults have densities of 3000–4000 cells/mm^2, reducing to 2400–2700 cells/mm^2 for octogenarians). This has also been demonstrated in cats in a recent study, in association with increased polymorphism and polymegathism with greater age (Franzen et al., 2010). An older study suggested that the endothelial cell density reduction with age in cats was not statistically significant, but reported increasing polymegathism with age (Tailoi & Curmi, 1988). A similar reduction in endothelial cell density with age is reported in the dog (Bahn et al., 1986; Gwin et al., 1982) and horse (Andrew et al., 2001). An endothelial cell density decrease, with endothelial cell polymegathism and polymorphism increases, has also been demonstrated in chinchillas (*Chinchilla lanigera*) associated with age (Bercht et al., 2015).

Diabetes in humans, and in canine models, is associated with endothelial polymorphism and polymegathism (Lee et al., 2006; Matsuda et al., 1990; Neuenschwander et al., 1995; Yee et al., 1985). In galactose-fed dogs receiving the oral aldose reductase inhibitor sorbinil concomitantly, endothelial morphologic changes were prevented (Datiles et al., 1990). Reduced endothelial changes were also reported in experimentally induced diabetic rats receiving a topical aldose reductase inhibitor compared to nontreated diabetic rats (Matsuda et al., 1987).

Surgical trauma is associated with reduced cell densities, and this reduction continues postoperatively at an accelerated rate compared to age-matched controls for the following 10 years (Bourne et al., 1994b). Routine phacoemulsification in humans is associated with a 5%–11% loss of endothelial cells (Bourne et al., 2004; Oxford Cataract Treatment and Evaluation Team [OCTET], 1986). Interestingly, using the phacoemulsification needle in a "bevel down" position resulted in twice the endothelial cell loss (13.6% vs. 5.9%) compared to the conventional "bevel up" position (Faramarzi et al., 2011). Risk factors for a clinically significant endotheliopathy (postoperative corneal edema) in humans include previous ocular surgery or inflammation, diabetes, glaucoma, preexisting polymegethism or pleomorphism, presence of corneal guttata, and Fuch's endothelial dystrophy (Fig. 10.2.26; American Academy of Ophthalmology, 1997; Giasson et al., 2007).

Specular microscopy has been utilized to evaluate the effect on endothelial cell density and polymorphism of increasing cataract maturity in dogs (Renzo et al., 2014). This study showed no correlation in endothelial cell density or polymorphism (decreased "hexagonality") between eyes with mature cataract (nondiabetic), hypermature cataract (nondiabetic), or an age-matched control group with no cataract.

Endothelial cell loss and damage during cataract surgery (by both phacoemulsification and extracapsular lens extraction surgery) have also been demonstrated in dogs with specular microscopy, and phacoemulsification time was not correlated with degree of cell loss (unlike in humans; Gwin et al., 1983). Bottle height (i.e., irrigation rate) during phacoemulsification surgery was negatively correlated with postoperative endothelial cell density in a rabbit model (Suzuki et al., 2009). Specular microscopy has demonstrated that phacoemulsification causes endothelial cell damage and loss by the generation of free radicals (Murano, 2008), and the addition of an antioxidant to phacoemulsification solutions has been shown to be beneficial in some animal and *in vitro* models (Nemet et al., 2007; Rubowitz et al., 2003). An experimental study in dogs using differing intraocular irrigating solutions (saline, balanced salt solution, and balanced salt solution with added glutathione), however, failed to demonstrate any endothelial morphologic changes between groups using specular microscopy or transmission electron microscopy (Nasisse et al., 1986). Specular microscopy has also been used to assess the corneal endothelial effect of different artificial intraocular lenses (IOLs) following phacoemulsification, in particular the increased endothelial cell loss associated with anterior chamber IOLs (20% loss vs. 12% loss with posterior chamber IOLs; Werblin, 1993).

The use of topical Rho-Kinase (ROCK) inhibitor eye drops in primates with experimentally induced endothelial cell dysfunction has been demonstrated to aid endothelial healing and cell density, although results were less encouraging in a human clinical trial of eight patients, with clinical improvement only apparent in those with central corneal

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Figure 10.2.26 **A**. Llama endothelial cells imaged by specular microscopy. **B**. Close-up view of the same endothelial cells. Polymegathism and pleomorphism are present with guttata. (Courtesy of Dr. Stacy Andrew.)

edema (Okumura et al., 2013). In contrast to the potential endothelial benefits shown in this study, the same group demonstrated transient (< 24 hr) morphologic changes in the corneal endothelium of human patients and rabbits using specular microscopy and slit-lamp biomicroscopy, associated with the topical use of another ROCK inhibitor (Ripasudil, licensed for the treatment of glaucoma; Okumura et al., 2015).

Corneal endothelial cell recovery following experimental endothelial chemical injury in rabbits, and in three human patients with unilateral ocular chemical injuries, has been studied using specular microscopy, ultrasound pachymetry, and slit-lamp biomicroscopy, and it was suggested that endothelial cell migration occurred from the peripheral cornea, which may act as a resource for corneal endothelial recovery (Choi et al., 2015).

The effect of intraocular drugs on the corneal endothelium can also be assessed using specular microcopy. Studies in the rabbit model have used specular microscopy to assess the endothelial effect of intracameral moxifloxacin, levofloxacin, cefazolin, vancomycin, lidocaine, carbachol, epinephrine, bevacizumab, ethylenediaminetetraacetic acid (EDTA), and viscoelastic agents, among others (Hazra et al., 2012; Kim et al., 2008; Lindquist & Robinson, 1996; Liou et al., 2002, 2004; Park et al., 2008; Roberts & Pfeiffer, 1989). Specular microscopy has been used in cats to assess the effect of intracameral air versus fluorocarbons (SF6; Landry et al., 2011) and viscoelastic materials (Ohguro et al., 1991), as well as endothelial cell healing from experimental injuries (Bourne et al., 1994a; Brogdon et al., 1989; Huang et al., 1989). Both specular microscopy and ultrasound pachymetry have been used to assess the effects of intracameral lidocaine on the canine corneal endothelium, demonstrating no toxic effects of 0.1 ml of 1% or 2% preservative-free lidocaine (Gerding et al., 2004).

The endothelial effects of numerous topical drugs, preservatives, and antiseptics have been assessed by specular microscopy and pachymetry in animal models to assess their safety for clinical use (Burstein, 1980; Chang, 2004; Jiang et al., 2009; Matsuda et al., 1989; McGee et al., 2005).

In Vivo Confocal Microscopy of the Cornea

The technique of confocal microscopy was first developed by Minsky in 1957 (Winston, 2016), where both the illumination (condenser) and the observation (objective) systems have common focal points ("confocal"). Reflected light is separated from incident light by a beam splitter (mirror) and the detector aperture obscures light that is not coming from the focal point (i.e., scatter), resulting in sharper images with increased resolution compared to conventional microscopy techniques. The high resolution was at the cost of field of view, and this was overcome by synchronized scanning of the tissue, and reconstruction of an image at both high magnification and resolution, with a reasonable field of view (200 × 300 µm). The microscope provides images of optical sections of structures with lateral resolutions of 1–2 µm and axial (depth of field) resolutions of 5–10 µm without the need to physically section or process the tissue (Jalbert et al., 2003). Cross-sectional images of the tissue can be obtained using oblique views.

Resolution at the cellular level has been demonstrated and compared encouragingly with histologic assessment of the same tissue (Masters, 1992, 2009; Petroll et al., 1994). Perhaps

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the most important aspect of confocal microscopy is the application to *in vivo* situations. This allows disease progression of structures to be imaged sequentially, and cellular observations when biopsy and histology are not feasible or desirable.

Three microscope types have been described: tandem scanning confocal microscopes (TSCM), slit scanning confocal microscopes (SSCM), and laser scanning confocal microscopes (LSCM, also known as confocal scanning laser ophthalmoscopes or CLSO). TSCMs use rotating Nipkow discs, which consist of a metal plate with microscopic holes arranged in an arithmetic spiral, providing multiple single spots of illumination (Fig. 10.2.27). Rapid disc rotation allows scanning of the whole specimen. TSCMs are no longer in production and were replaced by SSCMs. SSCMs use rapid scanning thin optical slits, and are therefore only truly confocal in one axis only, but they do offer increased light output and reduced scanning time (as all points in the axis of the slit are scanned simultaneously) compared to TSCMs. Adjustments of the slit width will vary the thickness of the optical section, and variation of the slit width controls the amount of illumination reaching the specimen. SSCMs are commercially available (e.g., Confoscan 4™, Nidek Technologies, Aichi, Japan; Confoscan P4™, Tomey, Phoenix, AZ, USA; Leica TCS™, Leica Microsystems, Wetzlar, Germany).

LSCMs use a high-intensity laser light source focused through a pinhole diaphragm, and oscillating mirrors to scan the tissue point by point. Sequential scans allow the development of 2D images. By altering the focal plane, deeper optical sections can be achieved, and with successive series and computer assistance, 3D constructs of the tissue imaged can be produced.

The Heidelberg retina tomograph (HRT) is a commercially available LSCM with a 670 µm diode laser, originally developed to evaluate the topography of the retina and optic nerve head. Development of the modification of a detachable objective "Rostock cornea module" by Stave et al. (2002; HRT II RCM) allowed visualization of the cornea at the cellular level (Fig. 10.2.28). A sterile single-use contact element

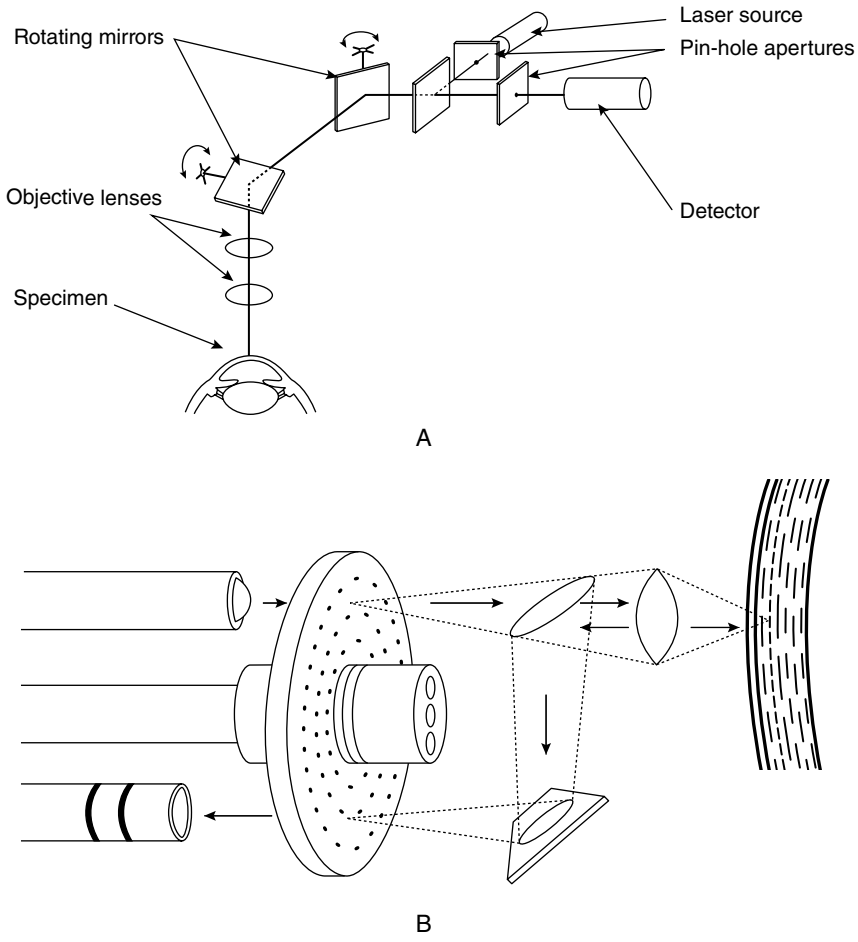


Figure 10.2.27 **A**. Schematic illustration of the confocal microscopy principle where a small pinhole aperture eliminates any scattered reflected light, resulting in sharper images. **B**. Schematic illustration of a tandem-scanning confocal microscope using a Nipkow disc to provide multiple spots of illumination. (Illustrations by Roser Tetas Pont.)

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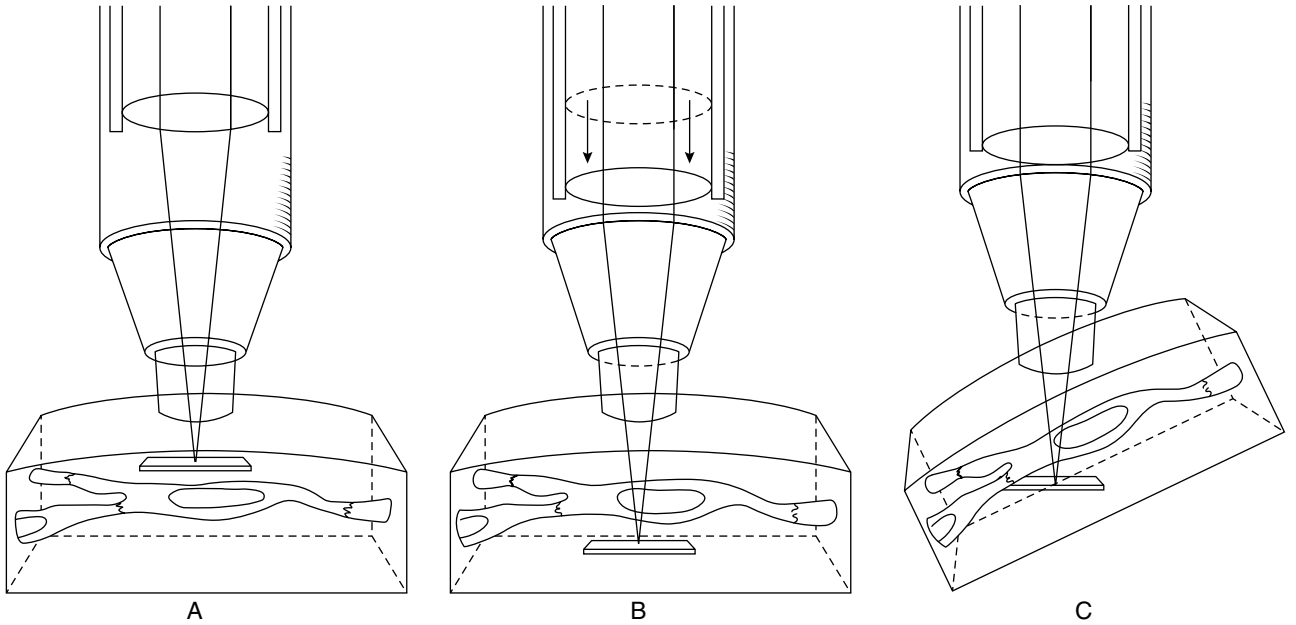


Figure 10.2.28 **A**, **B**. Illustration of a confocal microscope at differing focal depths within a tissue. **C**. Use of the confocal corneal module probe at an oblique angle allows a cross-sectional focal plane. (Illustrations by Roser Tetas Pont.)

(TomoCap™, Heidelberg) made from polymethylmethacrylate (PMMA) is coupled optically to the lens with the aid of a gel, and the cap is then coupled to the cornea via the tear film or a protective gel to the eye (Fig. 10.2.29). This modification can also achieve imaging of anterior chamber structures and the lens *in vivo*, provided the cornea is clear. This was further modified by Kafarnik et al. (2007) for use in veterinary patients and has subsequently yielded normal *in vivo* structural data for a number of veterinary species (Ledbetter & Scarlett, 2009).

Clinical Applications

Corneal confocal microscopy has been utilized in human patients to diagnose and monitor the progression of a number of human keratitides, including *Acanthomoeba spp*. keratitis, fungal keratitis, and keratoconus, postrefractive surgery patients, and conditions associated with contact lens wear (Efron & Hollingsworth, 2008; Guthoff et al., 2009; Kobayashi et al., 2008; Niederer et al., 2010; Patel & McGhee, 2009). A recent study of IVCM in cases of suspected *Acanthamoeba* keratitis has suggested that care should be taken interpreting images with "bright spots" as *Acanthamoeba* structures, as these were also present in keratitis cases associated with bacterial and fungal keratitides (less specificity than previously assumed; Fust et al., 2017). Much attention has been focused on corneal innervation and its implications for KCS, diabetes mellitus–associated peripheral neuropathy, LASIK, and laser-assisted subepithelial keratomileusis (LASEK; Cai et al., 2014; Choi et al., 2015; Patel & McGhee, 2009), and more recently the corneal effects of collagen-cross-linking treatments and autologous cultured limbal stem cell grafts (Hovakimyan et al., 2016; Pedrotti et al., 2015).

IVCM has also been used to perform endothelial cell counts, although specular microscopy remains the gold standard technique in donor bank systems (van Schaick et al., 2005). IVCM has been used to diagnose a microsporidial keratoconjunctivitis in a human patient following Descemet's stripping automated endothelial keratoplasty that mimicked graft rejection, and prevented further inappropriate mismanagement with topical steroids over topical fluconazole (Devi et al., 2017). IVCM has been used to study the effect on corneal permeability of novel vehicles (micelles, nanoparticles, and niosomes) for commonly used topical drugs. For example, IVCM was used in a study investigating the beneficial penetration effects of hyaluronic acid–coated niosomes on tacrolimus in a rabbit model. with implications for prevention of rejection of corneal allografts in human patients (Zeng et al., 2016). This study may also have potentially promising benefits for veterinary patients suffering with immune-mediated keratitis. Similarly, IVCM has been used to assess coulomb-controlled idontophoresis delivery of riboflavin compounds for corneal cross-linking treatment, in both epithelium-debrided and epithelium-intact corneas (Arboleda et al., 2014).

IVCM has been used to assess the feasibility of using tissue-engineered living corneal stroma, along with slit-lamp biomicroscopy, immunofluorescence, and transmission electron microscopy, in a feline model (Boulze Pankert et al., 2014). It has also been utilized to study the effects of stem

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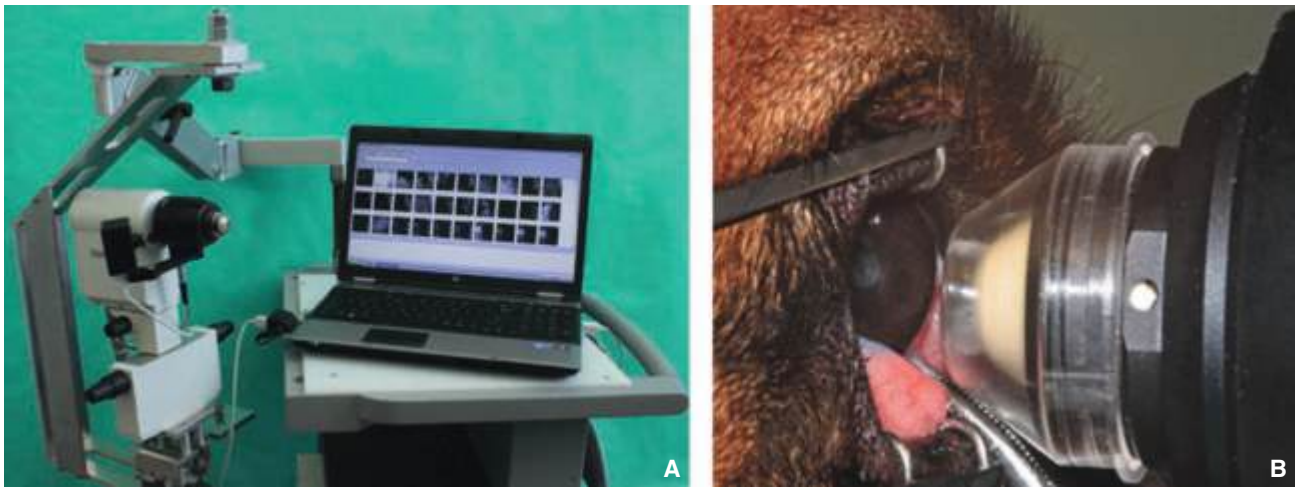


Figure 10.2.29 **A**. Image of Heidelberg *in vivo* confocal microscope with attached Rostock Corneal Module (HRT II RCM). **B**. RCM with TomoCap about to be applied to the cornea of a Boxer dog under general anesthesia.

cell treatment and gene therapy on inherited ocular diseases (Rocca et al., 2015; Serratrice et al., 2014). Although expensive, the microscope is already becoming available to human patients in clinical settings, and this is likely to be mirrored in veterinary ophthalmology in the future.

Following on from studies of normal cat, dog, bird, and equine corneal IVCM (Kafarnik et al., 2007; Ledbetter & Scarlett, 2009), studies of the normal corneal innervation of differing dog and cat breeds (brachycephalic vs. mesocephalic) have also been undertaken (Kafarnik et al., 2008). Figure 10.2.30 shows IVCM from adult canine and feline corneas, illustrating the variable focal depths achievable with the HRT II-RCM. IVCM has been utilized to examine corneal innervation in diabetic and nondiabetic canine patients with reference to tear parameters, corneal sensation, and keratitis in a clinical study (Kafarnik, unpublished data). IVCM of type 2 diabetic human patients has demonstrated a progressive loss of corneal nerve density (Lagali et al., 2017), and some authors have hypothesized that testing of corneal sensitivity may be an alternative method for the early identification of diabetic polyneuropathy (Yorek et al., 2016). Endothelial dystrophy in Boston Terriers (as a model for Fuch's endothelial dystrophy in human patients) has been studied with IVCM, and demonstrated reduced endothelial cell counts and increased polymegathism and polymorphism in affected patients (Thomasy at al., 2016).

IVCM has been used to create a baseline of data in the normal healthy laboratory Beagle as a reference for IVCM use in the development of ophthalmic drugs and devices tested on this species and breed (Strom et al., 2016a, 2016b).

The use of IVCM in clinical cases of equine keratomycosis has been described and demonstrated to be more sensitive than fungal culture at identifying the presence of fungi (Ledbetter et al., 2011). Figure 10.2.31 is the confocal microscopy image of an *ex vivo* keratectomy sample from a horse with *Aspergillus spp*. keratomycosis. Similarly, IVCM has been used in clinical cases of alpaca keratomycosis to demonstrate fungal elements (Ledbetter et al., 2013), and to image microscopic corneal foreign bodies in five horses (Ledbetter et al., 2014). A recent study also described canine mycotic keratitis, both *in vivo* in clinical patients and *ex vivo* in experimentally infected corneal samples, and was able to monitor therapeutic response (Ledbetter et al., 2016).

Comparison of IVCM with histologic findings has been attempted but can be problematic, as the field of view with IVCM is small, identification of the identical area imaged on histology can be extremely difficult, and, as yet, no large-scale 2D mapping procedures of the cornea exist. While IVCM has also been described for conjunctival tissue, sclera, limbus, eyelid, lacrimal gland, and tear film, the greatest application has been to corneal imaging.

IVCM has been used for corneal pachymetry, and measurement of defined layer thicknesses of the cornea (e.g. epithelium, stroma) as well as keratocyte counts *in vivo* in rabbits (Petroll et al., 2013), and following superficial keratectomy and conjunctival advancement hood grafts in dogs with spontaneous bullous keratopathy (Horikawa et al., 2016).

Ex vivo confocal microscopy has been successfully used to reconstruct the 3D retinal circulation of the porcine retina as a model for the human retina (Fouquet et al., 2017). The authors postulated a serial arrangement of retinal blood flow from superficial vascular plexus to intermediate vascular plexus and finally the deep vascular plexus, as opposed to a parallel arrangement with each layer relying on its own arteriolar supply and venous drainage.

As IVCM reveals optical sections of a tissue, the opacity of the structure in question, or structures between the microscope and the area of interest, will obscure the image. This limits its application to those disorders where the opacity is

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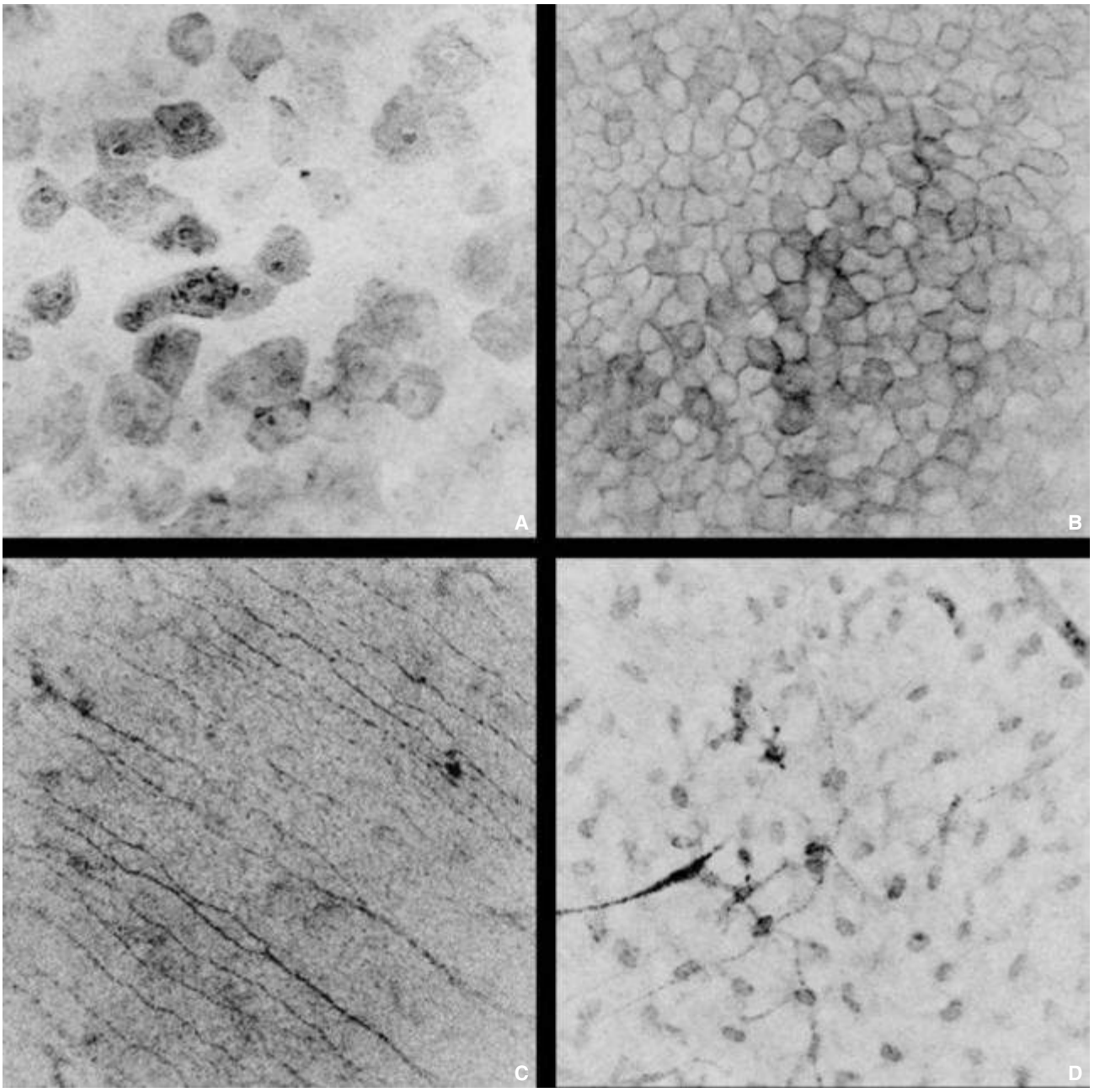


Figure 10.2.30 Confocal microscopy images from normal canine and feline corneas using HRT II RCM. The bar represents 50 μm. **A**. Canine superficial corneal epithelial cells (1 μm depth of focus). **B**. Canine polyhedral intermediate epithelial cells (15 μm depth of focus). **C**. Canine subbasal nerve plexus (47 μm depth of focus). **D**. Feline keratocytes and corneal nerves in the anterior stroma (89 μm depth of focus). **E**. Canine keratocytes in the midstromal cornea (257 μm depth of focus). **F**. Canine corneal endothelial cells (541 μm depth of focus). **G**. Feline corneal nerve trunk in the midstromal cornea, with the fine black lines demonstrating compression lines (174 μm depth of focus). **H**. Cross-image through the anterior stroma and epithelium showing a stromal nerve and small nerve fibers entering the epithelium.

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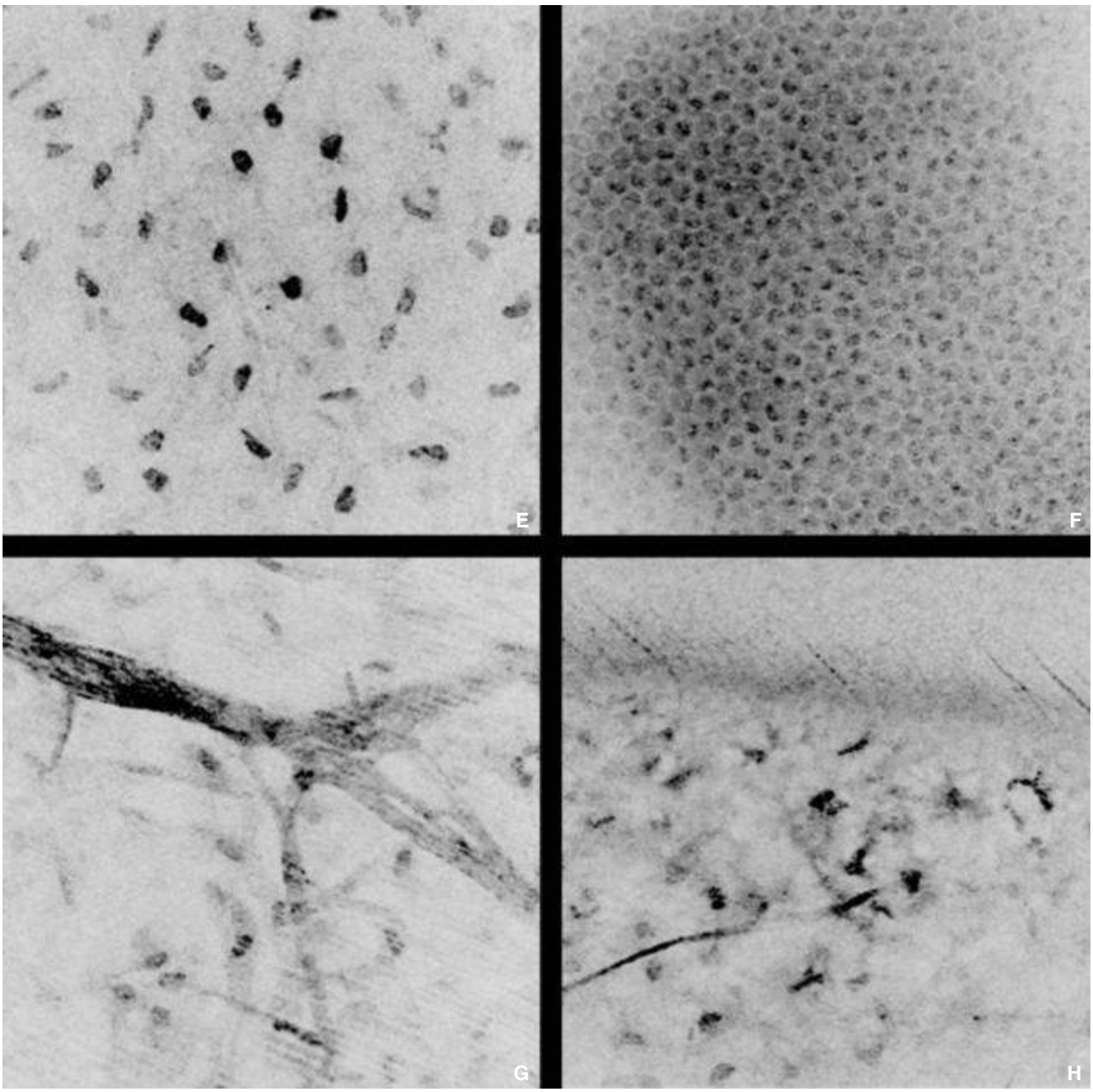


Figure 10.2.30 (Continued)

not dense enough to obliterate light reflected through it if assessment beyond the surface reflection of the opacity is desired.

Corneal Optical Coherence Tomography

Corneal imaging OCT applications include pre- and postrefractive surgery (including pachymetry), keratoconus, pre- and postpenetrating keratoplasties and lamellar keratectomies, assessment of pterygium, assessment of keratocyte numbers and morphology, endothelial dystrophies, pre- and postautomated Descemet's membrane stripping procedures, among other corneal diseases (Yadav et al., 2011). The corneal topography can also be illustrated in 3D using corneal OCT and has applications to the diagnosis and treatment of astigmatism (Maeda, 2010). See "Optical Coherence Tomography" later in this chapter.

Ultra-high-resolution OCT has been used to image rabbit corneal epithelial cells *in vitro* with an impressive spatial resolution of 1.3 μm (Reiser et al., 2005). OCT of 8–10-week-

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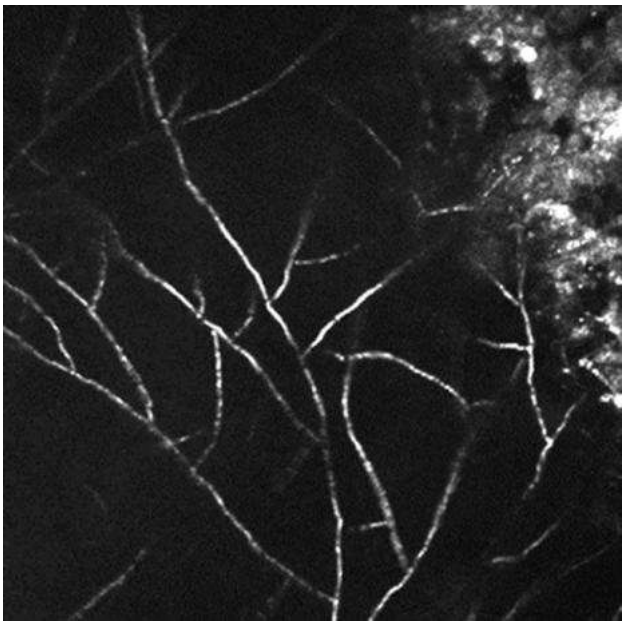


Figure 10.2.31 Fungal hyphae (*Cylindrocarpon spp.*) in the excised corneal button after deep lamellar keratoplasty in a Thoroughbred horse (30 µm depth of focus, using HRT II RCM. The bar represents 50 µm.

old rabbit globes was undertaken within 6 hours of harvesting. This study demonstrated that rabbit epithelial depth was significantly thicker at the center of the cornea than at the limbus. The authors postulated that this could be a protective function against the increased exposure of the central cornea to ambient radiation.

Both time-domain and spectral-domain OCT have been used for pachymetry in Beagle dogs and compared against traditional ultrasound pachymetry (Strom et al., 2016a). This study demonstrated that time-domain OCT and ultrasound pachymetry gave significantly thicker values for CCT compared with spectral-domain OCT. This mirrored a similar previous study comparing spectral-domain OCT with ultrasound pachymetry in normal anesthetized dogs (3 client-owned dogs and 12 adult Beagle dogs), which reported an increased CCT measurement with spectral-domain OCT pachymetry compared to ultrasound pachymetry (Alario & Pirie, 2014). This may be due to inherent errors associated with ultrasound velocity preset as 1636 m/s, while the canine cornea has been reported to have an ultrasound velocity of 1590 m/s. Strom et al. (2016b) also reported increasing canine CCT with increasing age and bodyweight, and thicker corneas in intact male dogs compared to female dogs. This contrasts with the Alario and Pirie (2014) study, which found no difference in CCT with gender or age.

Spectral-domain OCT (Optovue®, Optovue, Freemont, CA, USA) has been compared with ultrasound pachymetry (Pentacam) for measurement of feline CCT. While there was a statistically significant difference in measurement with the two instruments (OCT giving lower CCT results), the authors felt this was not clinically significant (approx. 4%) given the magnitude of normal diurnal variation in CCT (approx. 8%) in this species (Cleymaet et al., 2016). In this study they found that CCT did not vary with gender, which contrasts with the earlier study by Alario and Pirie (2013b) that demonstrated higher CCT values in spayed female cats compared to castrated males. Spectral-domain OCT has an advantage over ultrasound pachymetry in allowing measurement of specific layers of the cornea (not just CCT), and this has been utilized in a number of studies across different species (Alario & Pirie, 2013a, 2013b; Gornik et al., 2016; Lo Pinto et al., 2017a, 2017b; Pinto et al., 2014; Strom et al., 2016a, 2017b; Wang & Wu, 2013).

The Optovue iVue® spectral-domain OCT has been used in a clinical study of canine and feline cases with selected corneal diseases, and found to be reliable and accurate in most of the studied cases (Famose, 2013). Assessment of feline corneal sequestra was possible, but in some dense cases was limited by acoustic shadow posterior to the lesion, so that an accurate depth of the lesion could not be ascertained. The noncontact methodology of OCT (compared with ultrasound biomicroscopy) was felt to be an advantage; however, all patients required sedation to obtain usable images due to the fine focus required at high resolutions.

Anterior Segment and Retinal Imaging

Retinal *In Vivo* Confocal Microscopy and Confocal Scanning Laser Ophthalmoscopy

Confocal scanning laser ophthalmoscopy (cSLO) is synonymous with LSCM, but has been improved with the addition of adaptive optics (AO). This reduces optical aberrations, as well as lessening the impact of eye saccades on image quality. Irregularities in the corneal and lens surfaces, and astigmatism, are capable of generating aberrations that are difficult to correct. AO was developed by Dreher and colleagues in 1989, allowing corrections for astigmatism and defocus. It was further improved with the development of a Shack Hartmann wavefront sensor for the eye by Laing et al. in 1979. This wavefront sensor could accurately and rapidly measure the eye's optical aberrations. In 1996, Williams and colleagues built the first AO microscope capable of correcting higher-order aberrations (Roorda, 2010).

Further modification of an LSCM system to incorporate fluorescein angiography aspects (fluorescein adaptive optics or FAO-SLO) has allowed detailed imaging of the retinal vasculature within the nerve fiber layer, and results have precisely correlated with histologic comparisons (Scoles et al., 2009).

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As IVCM utilizes optical sections of a tissue, it stands to reason that the opacity of the structure in question, or structures between the microscope and the area of interest (e.g., optic nerve head), limits the reflected light and thus the image formed.

Clinical Applications

cSLO is utilized clinically in assessment of optic nerve head parameters (such as disc volume and rim and cup ratios) and glaucomatous cupping in people (Cankaya & Simsek, 2011). Assessment of optic and retinal vascular abnormalities associated with glaucoma is also currently the focus of extensive research using this technology. cSLO in combination with OCT has been used for investigation of many macular diseases in humans (Lima et al., 2011). AO-cSLO is capable of imaging individual rod and cone photoreceptors, retinal pigment epithelial (RPE) cells, and white blood cells (Godara et al., 2010; Hofer et al., 2011).

cSLO has been reported in normal Beagle dogs, cynomolgus monkeys, and Göttingen minipigs (Fig. 10.2.32). It was combined with fluorescein angiography in the same study (Rosolen et al., 2001). cSLO has been used to demonstrate spontaneous occurring fundus findings in Sprague Dawley rats, including a diffuse hyperfluorescent region at the posterior pole in all the studied rats (ultimately considered a normal finding; Joshi et al., 2016). The study authors suggested that a baseline using *in vivo* screening should be taken prior to investigations for toxicologic/interventional studies.

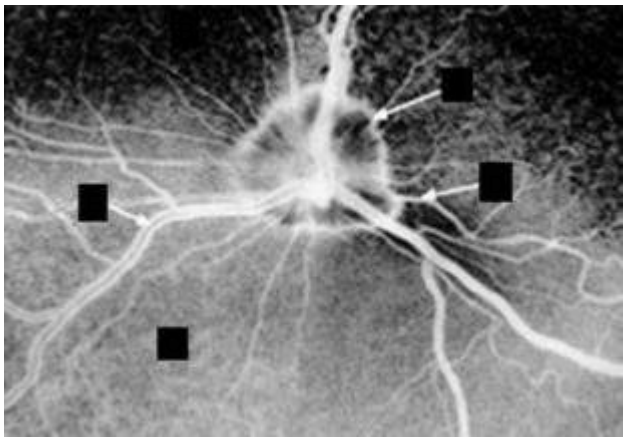


Figure 10.2.32 cSLO in a dog: (**A**) optic disc, (**B**) tapetal fundus, (**C**) nontapetal fundus, (**D**) retinal artery, and (**E**) retinal vein. (Reproduced with permission from Rosolen, S.G., Saint-Macary, G., Gautier, V., & LeGargasson, J.-F. (2001) Ocular fundus images with confocal scanning laser ophthalmoscopy in the dog, monkey and minipig. *Veterinary Ophthalmology*, **4**, 41–45.)

Scanning Laser Polarimetry

The retinal nerve fiber layer (RNFL) has birefringent properties due to retinal ganglion cell axon microtubules and neurofilaments being highly ordered and paralleled. Polarized light is composed of two orthogonal components; these components travel at different velocities when they pass through a birefringent tissue, which creates a relative phase shift. The phase shift is termed "retardation," and the amount of phase shift or retardation is proportional to the thickness of the RNFL (Fig. 10.2.33). This modality has been shown to correlate well with histopathologic measurements of RNFL (Weinreb et al., 1990).

The cornea and lens, with their ordered parallel arrangements of structures (collagen fibrils or lens fibers, respectively), also have birefringent properties. Measurement and compensation for anterior segment birefringence increases the accuracy of RNFL thickness measurements (Zhou & Weinreb, 2002).

The first commercially released scanning laser polarimeter was the GDx Nerve Fiber Analyzer™ (Laser Diagnostic Technologies, San Diego, CA, USA). This was subsequently upgraded to include an anterior segment birefringent compensation with the GDx VCC (variable cornea and lens compensator). The GDx technology was bought by Carl Zeiss

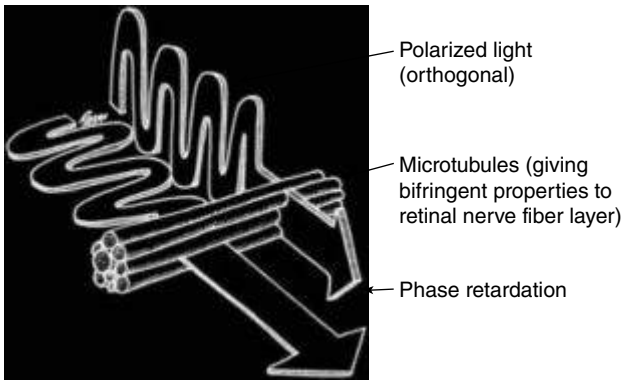


Figure 10.2.33 Schematic illustration of phase retardation of polarized light through birefringent tissue. (Illustration by Roser Tetas Pont.)

Meditec International (Jena, Germany), and is currently marketed as the GDx PRO™.

Changes in RNFL thickness precede visual field loss and optic nerve head changes, and therefore monitoring of RNFL thickness can assist in the early detection of glaucoma patients (Quigley et al., 1992; Sommer et al., 1991). Scanning laser polarimetry and assessment of RNFL thickness are also used for long-term monitoring of glaucoma patients and response to therapy (Da Pozzo et al., 2009; Greenfield & Weinreb, 2008). Measurement of RNFL is also utilized in the assessment of optic neuritis associated with multiple sclerosis (Kolappan et al., 2009).

Optical Coherence Tomography

OCT was originally developed to image the retina and optic nerve head with micron-scale resolution (Huang et al.,

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1991). This first description demonstrated the remarkable comparison of histology with *ex vivo* OCT of the human retina and optic nerve. *In vivo* use was described in 1994 with imaging of the anterior segment of the human eye (Izatt et al., 1994). The ability to measure retinal layer and optic nerve head thickness allows *in vivo* assessment of the progression of a number of ophthalmic and neurologic diseases. OCT is capable of providing highly sensitive monitoring of the progression of many ophthalmic conditions, including macular diseases, glaucoma, optic neuropathies, and other neurologic diseases such as multiple sclerosis. Quantification of the retinal nerve fiber layer thickness also provides an indirect measure of axonal and neuronal loss in the inner retina.

OCT uses interferometric technology. Light in an OCT system can be considered as broken into two arms: a sample arm (light reflected from the tissue of interest) and a reference arm (light reflected from a mirror of known optical distance from the light source). When these two arms combine an interference pattern occurs, which is dependent on the light wavelength and optical distance from the reflected tissue (or mirror for the reference beam), such that only light in each arm that has traveled less than a coherence length will interfere and contribute to the image. As only coherent (nonscattered) light is detected, high resolution of the imaged tissue is achieved.

The use of a longer wavelength of light (near infrared, ~800 nm) allows deeper penetration of translucent or opaque tissues (millimeters) compared to confocal microscopy (5–10 μm; Fulimoto & Huang, 2010; Sainter et al., 2004). Later OCT systems utilize light of longer wavelengths (~1300 nm), allowing reduced optical scattering and improved image penetration depth (21 mm). The images are illustrated using a false color scale, where different magnitudes of backscattered light are displayed as different colors on a rainbow scale. The RNFL is seen as a highly backscattering layer (red) that decreases in thickness further from the optic disc. The RPE and choroid are seen as a single thin highly backscattering layer posterior to the retina. Nuclear layers are weakly backscattering and appear blue-black in color-scale OCT images.

The position and intensity of the reflection from the tissue can be mapped along a line of set depth through the retina (A-scan). The image contains information about the spatial arrangement of structures within the tissue, and serial axial scans (i.e., at different depths) can be combined to give a cross-sectional image (B-scan). Further combination of images can allow a 3D image to be obtained by the latest generation of OCT machines (spectral-domain OCT; Fig. 10.2.34, Fig. 10.2.35, and Fig. 10.2.36). En face images (C-scan) can also be obtained by some machines, providing information on the topography of the tissue, and are particularly useful when imaging the optic nerve head and cup. These scans achieve images of retinal layers parallel to the surface of the retina at differing depths. Irrespective of scan type, the patient is asked to fixate on a point during each scan, and digital processing of the captured signal is required to correct for small eye movements, as well as improving the signal-to-noise ratio. In veterinary patients, OCT is typically performed under general anesthesia to reduce eye movement.

Measurement of the time of light delay reflected from the retina, compared to the time of light delay from the reference mirror of known optical distances, provides quantitative data on the position of retinal structures, and is known as time-domain OCT. Current time-domain OCT technologies can achieve axial resolution of approximately 10–15 μm (Townsend et al., 2009). Swanson et al. (1993) published the first retinal images obtained by time-domain OCT in 1993, although the same group first described the technology in 1991 (Huang et al., 1991). Time-domain OCT is limited in speed of image capture, as data is collected pixel by pixel along an A-scan, and acquisition is approximately 400 A-scans/s. Eye movement artifacts limit the number of scans that can be undertaken at a time. More recently, spectral-domain (also known as Fourier-domain) OCT has been developed that has higher spatial resolution (3–6 μm) and is considerably faster at acquiring scans than time-domain OCT (Fercher et al., 1995). Spectral-domain OCT uses a broad bandwidth of light frequency with a stationary reference mirror, with the reflected images collected simultaneously by a spectrometer. Each frequency of light represents a different tissue depth and can be therefore mapped to differing retinal locations (Townsend et al., 2009). As each A-scan is captured almost instantaneously, spectral-domain acquisition can reach 24,000 and 55,000 A-scans/s. Spectral-domain images and measurements cannot be directly compared to time-domain OCT results, and it is likely that spectral-domain OCT will be widely adopted in the future due to the impressive and rapid images obtained.

A new generation of OCT known as "swept-source" is available within the research community, but is not yet available clinically. Swept-source OCT (SS-OCT) has similarities to spectral-domain OCT (the location of the reflection is encoded by frequency of the light), but instead of detecting a single broadband reflection, SS-OCT covers the range of frequencies one at a time. This allows the scan acquisition rate to be greater than 200,000 A-scans/s, thereby almost eliminating motion artifacts (Townsend et al., 2009).

Ultra-high-resolution OCT retinal imaging was first demonstrated in 2001, and could achieve axial resolutions of approximately 3 μm, in comparison to commercially available OCT instruments with axial resolution of approximately 10 μm (Drexler et al., 2001). These images compare favorably with histologic studies and allow the identification of individual retinal layers, including the photoreceptor layer (Gloesmann et al., 2003; Srinivasan et al., 2008). Even the junction between the inner and outer segments of

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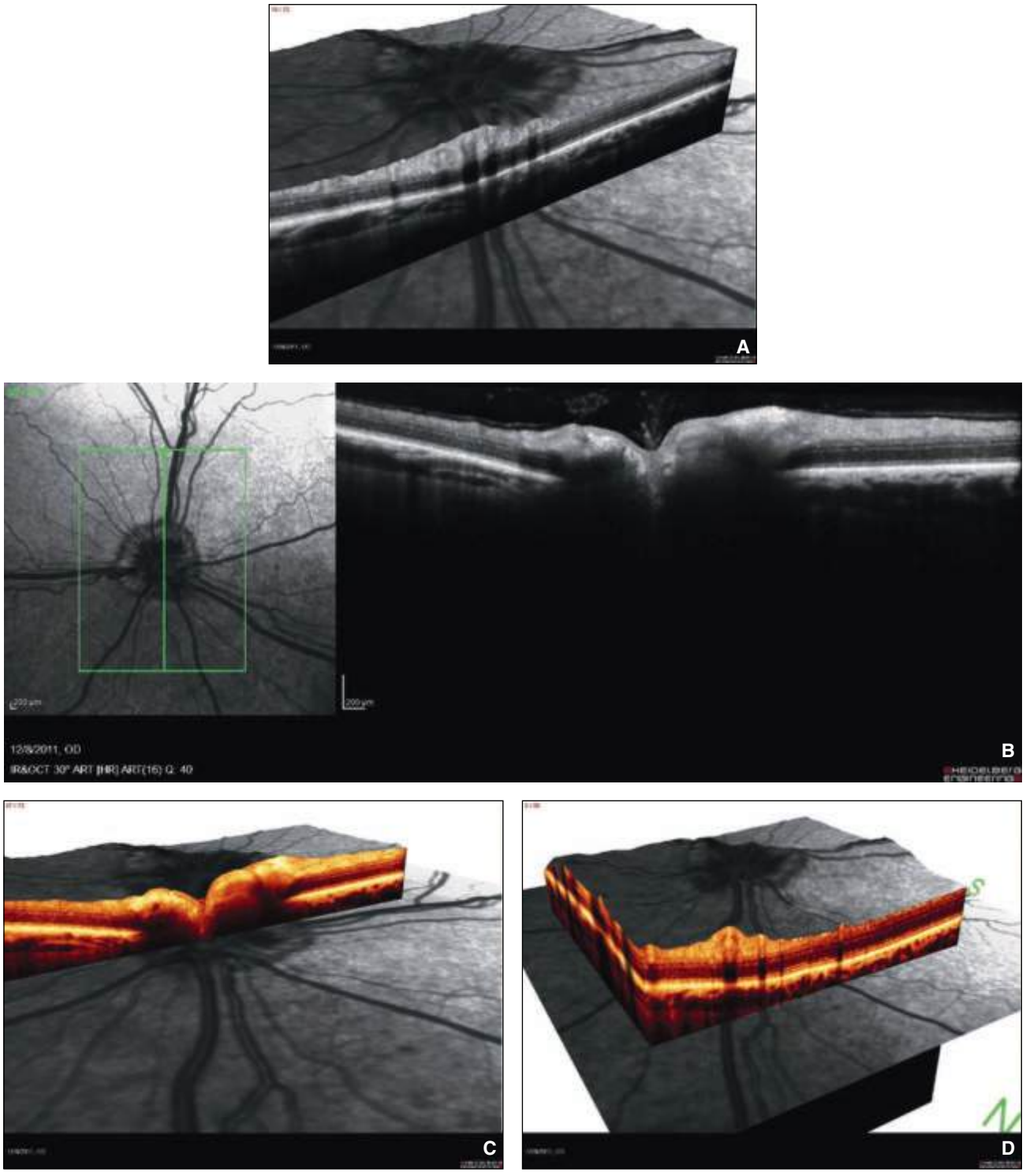


Figure 10.2.34 Optical coherence tomography two-dimensional (2D) and three-dimensional (3D) reconstruction images of a normal adult Beagle fundus. **A**. Cross-section and 3D reconstruction at peripapillary region. **B**. Fundus image and 2D cross-sectional image at the level of the optic nerve head, location illustrated by the central green line on the fundus photograph. **C**. Cross-section and 3D reconstruction image at the optic nerve head. **D**. Cross-section and 3D reconstruction image medial to the optic disc. **E**. Cross-section and 3D reconstruction image at the limit of the optic cup of the optic disc. (Courtesy of Matthew Annear and Simon Petersen-Jones, Michigan State University.)

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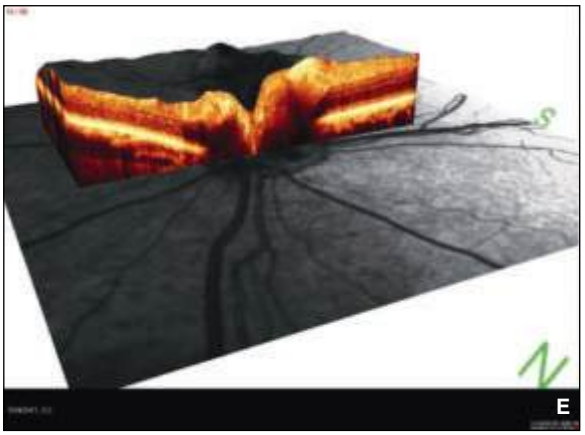


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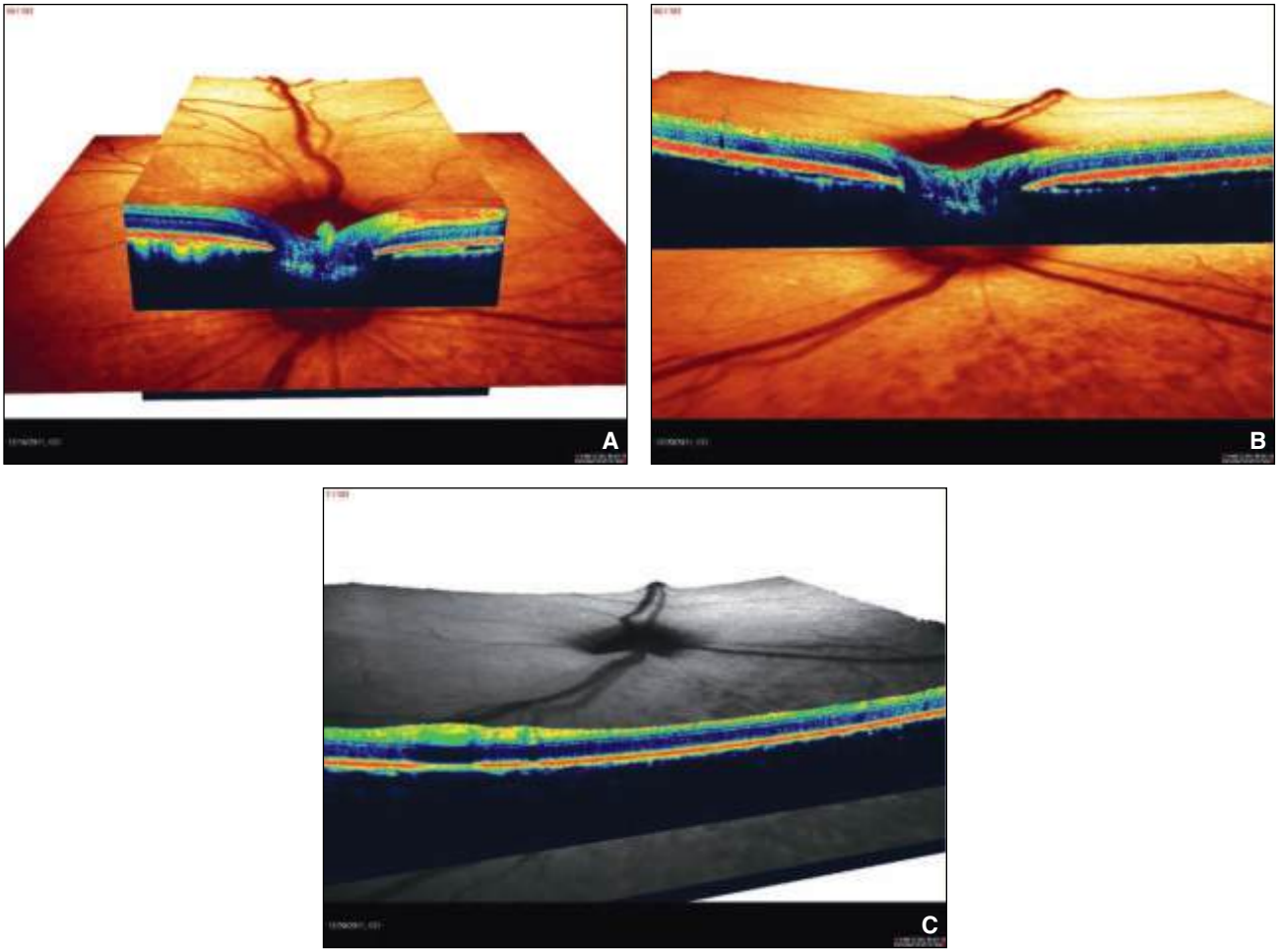
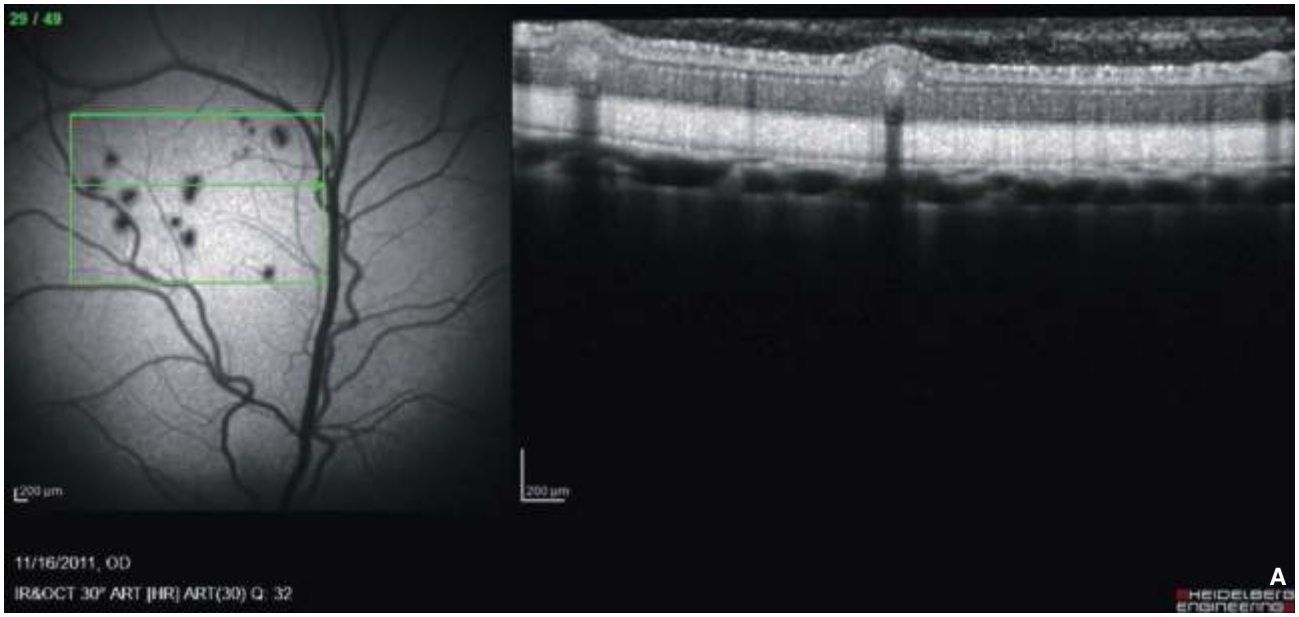


Figure 10.2.35 Optical coherence tomography with three-dimensional (3D) reconstruction images of a normal feline (Domestic Shorthair kitten) fundus. **A**. Cross-section and 3D reconstruction image at the optic disc of a 12-week-old kitten. **B**. Cross-section and 3D reconstruction image at the optic disc of a 15-week-old kitten. **C**. Cross-section and 3D reconstruction image of the peripheral retina in a 15-week-old kitten. (Courtesy of Laurence Ocelli and Simon Petersen-Jones, Michigan State University.)

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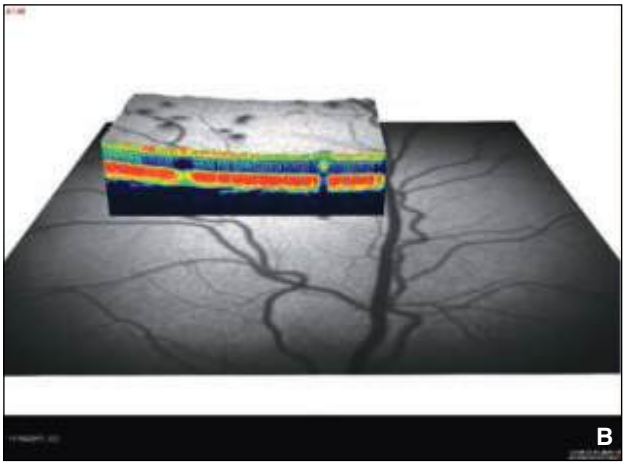


Figure 10.2.36 Optical coherence tomography (OCT) two-dimensional (2D) and three-dimensional (3D) reconstruction images of a feline fundus with multifocal retinal dysplasia (12-week-old Domestic Shorthair kitten). **A**. Fundus photograph and 2D cross-section OCT at level of retinal dysplastic lesions. **B**. Cross-section and 3D reconstruction at site of retinal dysplastic lesions. (Courtesy of Laurence Ocelli and Simon Petersen-Jones, Michigan State University.)

photoreceptors can be identified with ultra-high-resolution OCT, due to the increased backscatter from the refractive change between the inner segments and the tightly stacked membranous discs of the outer segments.

Corneal modules have been developed that allow imaging of the anterior segment (e.g., Visante OCT 3.0™, Carl Zeiss Meditec; Cornea-Anterior Module RTVue™, Optovue) from the tear film to the iris and anterior lens (see "Clinical Applications" following).

The combination of cSLO with OCT has allowed high-resolution en face images of individual retinal layers to be achieved (Podoleanu, 2006). Polarization-sensitive OCT combines the benefits of scanning laser polarimetry with OCT for imaging of the RNFL (Townsend et al., 2009).

Clinical Applications

OCT is used extensively for the monitoring of retinal and optic nerve head diseases within clinical settings. Descriptions of the macula, optic nerve head, and RNFL are the most common in the literature, and longitudinal assessment of qualitative and quantitative information for each area can be obtained. Early studies established OCT as means of monitoring macular diseases such as macular edema, macular holes, age-related macular degeneration (AMD), and choroidal neovascularization. OCT imaging can also be used to provide quantitative measurements using image-processing algorithms to automatically extract values for retinal and retinal nerve fiber thicknesses. OCT is also used extensively in differentiating (and subsequent

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monitoring of) glaucomatous from nonglaucomatous optic nerve head cupping in humans (Gupta et al., 2011; Schuman et al., 1995).

The RNFL has high reflectance due to the arrangement of nerve fibers perpendicular to the angle of the OCT light beam, and due to its anterior location in the retina. Thinning of the RNFL is encountered in many diseases, including glaucoma and following acute optic neuritis, multiple sclerosis, and other neuropathies, and can be used as a highly sensitive method of assessing structural loss. OCT is able to distinguish subtle changes in tissue thicknesses prior to lesions being funduscopically obvious. Correlation with functional deficits has also been demonstrated at thresholds of retinal nerve fiber thickness (75 µm; Wollstein et al., 2012).

Polarization-sensitive OCT is a technology used in glaucoma imaging research. The high axial resolution of OCT combined with measurement of tissue birefringence of scanning laser polarimetry could allow greater contrast between the RNFL and other retinal layers, and therefore more precise measurements of this layer. The retinal surface is used as a reference so that corneal compensation of birefringence is adjusted for, increasing the accuracy of measurements. Polarization-sensitive OCT has also been used to study the RPE) with reference to age-related macular degeneration) as well as the cornea (Gabriele et al., 2011).

Descriptions of whole-eye OCT imaging have been published in rodent eyes using stepped focal planes (i.e., increasing depths through the eye at which OCT is focused) in research settings (Zhou et al., 2008). Anterior segment OCT has been used extensively in humans both clinically and experimentally. OCT also has the advantage of being a noncontact imaging modality and therefore provides increased patient comfort.

Anterior segment biometry with OCT can assist in the selection of appropriate IOLs, as well as providing information on anterior chamber depth, width, and crystalline lens vault. Assessment of the iridocorneal angle (ICA) with OCT has also been achieved, resulting in detailed assessment of the angle opening distance, angle recess area, trabeculo-iris area and meshwork, the ICA in degrees, Schlemm's canal, and Schwalbe's line. The ICA has been quantitatively measured using time-domain OCT (Visante Anterior Segment OCT) undertaken in several healthy mammalian species and normal baseline data reported (Almazan et al., 2013). It is also able to provide images of anterior segment tumors (anterior to iris; posterior to iris ultrasound biomicroscopy is superior), iris cysts, nevi or melanoma, and iridoschisis (Konstantopoulos et al., 2007; Ramos & Huang, 2009).

OCT of the canine retina was described by Panzan et al. in 2004, and comparisons of retinal thickness with dogs affected with progressive retinal atrophy (PRA) caused by the rcd1 mutation were made. Normal dogs have a thicker retina in the tapetal fundus compared to nontapetal fundus, and rcd1-affected dogs had reduced retinal thickness at the area centralis and dorsal retina. The nerve fiber layer thickness was similar in both rcd1-affected and normal dogs (Panzan et al., 2004). Figure 10.2.37 illustrates the fundus photographs and OCT images of a normal Papillon dog and a PRA-affected Papillon dog.

Progression of RPGRIP-1 early-onset PRA in the Miniature long-haired Dachshund has been investigated with serial OCT examinations of the retina 3 mm dorsal to the optic disc. Progressive thinning of the outer nuclear layer was documented over a 2-year period in affected dogs. Comparisons with histopathology and TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling) immunohistochemistry of retinas from affected dogs revealed that this thinning was due to photoreceptor apoptosis (Lhériteau et al., 2009).

The multifocal retinopathy of Cotton de Tulear dogs was reported by Grahn and Wolfer (1997). Investigations included clinical ophthalmologic examination, electroretinographic studies, fluorescein angiography, indocyanine green angiography, ultrasonography, and OCT (Grahn et al., 2008). OCT revealed large retinal detachments in early life, with elevation of the inner limiting membrane of the retina several millimeters into the vitreous. The serous content of the bullae diminished after several years, leaving focal areas of hyper-reflectivity visible on ophthalmoscopy.

The effect of experimentally induced acute IOP elevation has been studied in dogs using OCT and demonstrated significant thinning (by approx 30 µm) of the ventral retina at days 15 and 30 compared to pre-IOP elevation thicknesses. The dorsal retinal thickness was not significantly different from baseline values (Grozdanic et al., 2007).

OCT has also been used to assess the effect of subretinal injections of recombinant adeno-associated virus 2/2 (rAAV2/2), carrying the RPE65 gene (as a gene therapy of RPE65-deficient retinal dystrophy in Briard dogs), on retinal thickness and morphology. The localized retinal detachment caused by the injection was reported to resolve by 24–48 hrs in all dogs, with most retaining normal retinal morphology on OCT images. Retinal thinning was seen in some areas by OCT and these areas corresponded to fluorescent antibody-evident hyperfluorescent areas (Le Meur et al., 2007).

Time-domain OCT has been used to image the posterior segment of cats and was found to be useful for longitudinal studies and quantifying retinal thickness (Gekeler et al., 2007). The resolution of this system was documented as 10–20 µm, which has been superseded by higher resolutions achievable by later generations of OCT (e.g., spectral-domain and swept-source OCT). A subsequent review article by McLellan and Rasmussen (2012) highlighted some of the constraints, limitations, and practical considerations for the use of OCT (both time-domain and spectral-domain) in posterior segment imaging of animal species.

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Figure 10.2.37 **A**. Fundus photograph and optical coherence tomography (OCT) image of normal adult Papillon dog. **B**. Fundus photograph and OCT image of a young adult Papillon dog with progressive retinal atrophy. Note the marked outer nuclear layer thinning. (Courtesy of Simon Petersen-Jones, Michigan State University.)

OCT has been used extensively in chickens as animal models for human disease, but OCT in other avian species to investigate visual acuity and foveal characteristics, retinal structure, and pathologies has also been described (Potier et al., 2016; Rauscher et al., 2013; Ruggeri et al., 2010). Reptile species have also been examined using OCT, but these studies have been limited to the spectacle, cornea, and/or anterior segment (Cazalot et al., 2015; Da Silva et al., 2014; Gornik et al., 2016; Rival et al., 2015; Tusler et al., 2015).

Laser Doppler Flowmetry

Another technology capable of measuring retinal blood flow utilizing Doppler principles is laser Doppler flowmetry (LDF), and this has been used experimentally to determine blood flow through superficial microcirculations in many tissues, including neural, muscle, skin, bone, respiratory, and intestine. LDF has also been used to investigate the pathophysiology of equine laminitis, as well as endoscopically to investigate inhalational injuries in a sheep

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model for smoke inhalation in humans (Adair et al., 2000; Loick et al., 1991).

LDF uses a lower-power laser, often helium-neon (633 nm), although laser sources used in LDF can range from 540 to 780 nm. The light source must be monochromatic (single wavelength) so that the Doppler frequency shift in backscatter causes a broadening of the frequency of the original monochromatic light source, which is subsequently quantified.

Ocular applications have been in experimental studies of animal models for human diseases and treatments. These research areas include glaucoma, AMD, diabetic retinopathy, retinopathy of prematurity, and other ocular diseases. Improved blood flow of the optic nerve head has been demonstrated with prostaglandin analogs in animal models (e.g., rabbits, cats, and nonhuman primates) using LDF technology (Ishii et al., 2001; Izumi et al., 2008a; Kurashima et al., 2010). Topical dorzolamide has been reported to have no effect on choroidal blood flow in rabbits measured by LDF, but it reduced aqueous production (demonstrated by laser fluorophotometry; Reitsamer et al., 2009).

A study in cats using LDF demonstrated that acute hyperoxia induced vasoconstriction, and reduced blood velocity and flow, which subsequently returned to baseline within 10 minutes after hyperoxia ended. The same study also revealed that this effect could be ablated by intravitreal injection of BQ-123 (specific vascular endothelin type A receptor antagonist) 60 min prior to hyperoxia. The authors suggested the results indicated that nitrous oxide contributes to retinal blood flow recovery after hyperoxia, probably through the action of endothelial nitric oxide synthase via the endothelin type B receptor in the vascular endothelium of the retinal arterioles. However, in the same study, intravitreal injections of BQ-123 did not have a substantial effect on retinal circulatory parameters before the induction of hyperoxia, suggesting that endothelin-1 did not play an important role in regulating retinal circulation under basal condition (normoxia; Izumi et al., 2008b).

LDF has been used to demonstrate increased retinal blood flow in response to acute hyperglycemia in cats. Sogawa et al. (2010) concluded that acute hyperglycemia increased the retinal circulation, probably via increased serum osmolality, and might cause endothelial dysfunction in the retinal microcirculation in healthy cats. This effect had also been reported using fluorescein angiography in an earlier study, in which the effect of an increased circulatory volume was mimicked using equisomolar mannitol and revealed that retinal autoregulation was maintained by vasoconstriction. Vessel diameter, however, remained unchanged in the presence of hyperglycemia, resulting in a significantly increased retinal blood flow (Atherton et al., 1980).

Color Doppler Optical Coherence Tomography

Doppler OCT is based on the principle that moving particles (such as red blood cells) inside a blood vessel cause a Doppler frequency shift to the scattered light. The frequency shift is dependent on the refractive index of the medium, the incident light wavelength, the angle between the incident light and the flow direction, and the velocity of the flow. The phase difference between sequential axial scans at each pixel is determined to calculate the Doppler shift. The time difference between sequential scans limits the maximum detectable flow velocity (e.g., for RTVue OCT with a line rate of 27,230 Hz the maximum detectable flow velocity is 4.21 mm/s; Wang & Huang, 2010).

If the flow velocity and vessel dimensions can be measured, the volume of flow over time can be calculated. Background movement of the retina due to eye movements can be measured from the OCT image and subtracted from the blood flow velocity measurement.

Optical Coherence Tomography Angiography

Fluorescein angiography (FA) currently remains the gold standard for retinal and choroidal angiographic studies (De Oliveria et al., 2017; Naigel et al., 2015; Novais et al., 2016) and is described in greater detail later in the chapter. However, it is time consuming and invasive, with the risk of adverse events ranging from nausea to anaphylaxis. Optical coherence tomography angiography (OCTA) works by repeatedly scanning the same chorioretinal area and measuring the differences in signals from sequential scans (amplitude or phase variance). Static tissue generally demonstrates little change, whereas moving structures (blood cell flow) will generate variations from one image to another. Using algorithms, 2D and 3D images of angiography can be produced. OCTA is able to investigate deeper posterior segment vasculature within the eye (e.g., choroidal) that FA may struggle to delineate (due to obscured vessels by overlying hyperfluorescence). The limitations of OCTA include a small field of view (excluding some peripheral areas), sensitivity to eye motion artifacts, and the lack of information on vessel leakage or pooling that FA provides.

Optical microangiography (OMAG) combines both amplitude and phase variations in OCT signals to provide blood flow information within the scanned tissue volume. OMAG has an axial resolution of 8 μm (An et al., 2010; Dithmar & Holz, 2008) and, with the addition of a motion tracking system through an auxiliary line scan ophthalmoscope, has provided high-resolution wide-field OMAG (Zhang et al., 2016).

Laser Fluorophotometry and Laser Flare Cell Meters

Laser fluorophotometry provides a means of assessing aqueous production and outflow, and is used extensively in research to indirectly assess the blood–aqueous barrier

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(BAB). An increase in aqueous concentration of a plasma protein, indicating BAB breakdown, can be identified by paracentesis, but this procedure itself will induce BAB breakdown. Laser fluorophotometry is a means of quantifying BAB breakdown by the passage of a tracer substance (injected intravenously) across the barrier. The ratio of the aqueous to plasma level of the tracer indicates the permeability of the BAB to this tracer. Sodium fluorescein is a small molecule and therefore readily passes through an intact BAB. This can limit its use for the identification of BAB breakdown, but allows the dilution of fluorescein in the anterior chamber to be measured, and thereby an indirect measurement of aqueous production and outflow (Shah et al., 1993). Fluorescein-labeled albumin, which as a large molecule does not readily cross an intact BAB, is a useful tool for identifying BAB breakdown (Mitchell et al., 1986).

Laser flare-cell photometry can objectively, and noninvasively, monitor intraocular inflammation by quantifying aqueous flare and cells (Guex-Crosier et al., 1995; Ladas et al., 2005). To quantitatively measure protein (flare), the machine records the amount of scattered light (usually a helium-neon (He-Ne) beam) detected by a photomultiplier in a set volume of aqueous. For cell counts two optical scanners are used in synchrony across a fixed area of aqueous. When a large particle (cell) is scanned, a sharp peak (of reflected light) is detected and the number of peaks is reflected in a cell count.

Fluorescein Angiography

FA provides a means of examining the vascular components of the fundus. Some chemicals can be excited by light radiation, absorbing the radiant energy and causing free electrons within the chemical to reach higher levels of energy. The electrons are unstable in this state and ultimately release (emit) the absorbed energy. As the emitted radiation is of a lower energy than the absorbed radiation, the emitted radiation is always of a longer wavelength than the absorbed radiation wavelength.

The first report of FA use to image retinal circulation was described by Novotny and Alvis in 1961, although Chao and Flocks (1958) had used experimental intravascular trypan blue to outline the retinal circulation before this report. FA has also been described in the anterior segment, and is capable of illustrating iris vasculature, iritis in nonpigmented animal models of disease, as well as iridal tumors and vascular anomalies in human patients (Cavallerano, 1996; Dithmar & Holz, 2008).

Sodium fluorescein is water soluble and a weak acid with an absorption spectrum of 465–490 nm and an emission spectrum of 520–530 nm. Absorption and emission spectra are altered by pH and reach a maximum at pH 7.5–8.5 (Doughty, 2010). After intravenous injection, 70–80% of the sodium fluorescein is protein bound, largely by albumin. Unbound fluorescein is able to pass through blood vessel walls, except in the regions of blood–ocular and blood–brain barriers. Therefore, skin and mucosal surfaces (most noticeably the conjunctiva) take on a yellow appearance, which dissipates over a few minutes. Fluorescein is largely excreted by the kidneys, usually within 24 hrs in the absence of renal impairment, and resulting in discoloration of the patient's urine (Dithmar & Holz, 2008).

Sodium fluorescein is injected intravenously and the retina is illuminated with blue light (490 nm) using a barrier filter, which excites the fluorescein as it travels through the choroidal and retinal vasculature. Black and white fundus photography is undertaken using a red-free filter (525 nm) to increase the contrast of images and record the fluorescence of tissues. Contrast enhancement by the retina itself occurs due to the presence of the yellow pigment xanthophyll in the outer nuclear and plexiform layers, which absorbs the blue excitation light wavelengths (Davies & Morland, 2004). Baseline photographs are taken prior to fluorescein injection to identify (and thereby exclude in interpretations) autofluorescence of retinal structures. Photography is usually undertaken using black-and-white film to enhance the contrast of images; however, high-speed color film has also been used, and more recently digital images and movie clips have been recorded. Photographs are taken before and repeatedly after fluorescein injections to chart the stages of retinal circulation from the choroid to retinal vessels, and recirculation when present.

Autofluorescence is recorded when natural products within the eye (fluorophores) are excited by light of a particular wavelength. These products may occur naturally in the eye or may accumulate as a byproduct of a disease process (e.g., drusen, lipofuscin). Ceroid lipofuscinosis autofluorescence in dogs and sheep (animal models for human neuronal ceroid-lipofuscinosis disease) has been objectively quantified using a digital radiometer and FA, and compared to age-matched controls (Armstrong et al., 1988). Lipofuscin accumulates in RPE as part of the normal recycling mechanism of photoreceptor outer segments. With aging, or other disease processes, this may be increased, causing increased autofluorescence. For example, a study investigating the effects of a diet deficient in xanthine, lutein, and omega-3 fatty acids in rhesus macaques (from birth) demonstrated a greater retinal autofluorescence in deficient animals, equivalent to a 12–20 year accumulation of lipofuscin in animals fed a standard diet (McGill et al., 2016). Similarly, loss of RPE cells leads to a reduction in normal autofluorescence. As lipofuscin accumulation may precede RPE cell death, increased autofluorescence may be predictive of future atrophy in AMD (Holz et al., 2007).

The high level of protein binding of sodium fluorescein intravascularly is postulated to be partly responsible for the

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low toxicity observed to intravenous fluorescein injections. Emesis is reported in approximately 5% of small animals, and is the most commonly reported side effect. Side effects of FA in humans are reported as nausea in approximately 3% of patients, vomiting in approximately 1%, and skin reactions (flushing, itching, and urticaria) in 0.5% (Shahid & Salmon, 2010). Previous FA adverse events were associated with almost a 49% risk of a second adverse event on repeated FA in human patients (Kwiterovich et al., 1991). Rarely fatal anaphylaxis has been reported in humans, as well as cutaneous photosensitization (Danis & Stephens, 1997; Hitosugi et al., 2004). Prophylaxis with antihistamines has been reported to reduce side effects (nausea and dizziness) in human patients, although this was not correlated with a reduction in plasma histamine (Ellis et al., 1980). In a prospective study (Kalogeromitros et al., 2011), allergic skin testing or history of previous FA was not correlated with adverse reactions, leading the authors to conclude that adverse reactions were mediated by nonimmunologic means. Despite this, the authors recommended sodium fluorescein intradermal skin testing for predicting anaphylaxis in patients with risk factors in their medical history. This protocol is supported by another study of fluorescein anaphylactic reactions and the predictive value of intradermal skin tests (Matsuura et al., 1996). Investigation of a human patient suffering an adverse fluorescein reaction demonstrated positive skin tests and a dramatic increase in serum tryptase (a neutral protease from human mast cells) compared to nonreactive controls. The authors of this report postulated an immunoglobulin E-mediated mechanism for this adverse reaction (Lopez-Saez et al., 1998). Another prospective study described increased risk of adverse reactions following FA associated with allergic history, diabetes, or systemic hypertension (Lira et al., 2007). In contrast, systemic hypertension was reported to be associated with a decreased risk of adverse reaction in another study (Musa et al., 2006). Anecdotal reports of reduced FA adverse events after prewarming of sodium fluorescein prior to injection were not supported by a prospective study (Lee et al., 2001).

The sodium fluorescein solution is administered as a bolus injection via the jugular, cephalic, saphenous, ear, tail, or wing veins, depending on the species being investigated. A high-concentration small bolus is recommended to achieve a sharp and bright dye-front in the choroidal vasculature. Administration via an arterial vessel close to the eye (e.g., internal carotid artery) has also been recommended by some authors to avoid dilution of the bolus (Hayreh, 1974). Dosages of sodium fluorescein have been established for most species, which provide maximal fluorescence with minimal risk of adverse event.

FA is usually performed under deep sedation or anesthesia in veterinary species, to avoid eye movements disrupting photographic sequences. General anesthesia is sometimes avoided due to the downward deviation of the globe, making fundus photography more problematic. As both anesthesia and sedation have effects on the circulatory system, they might be expected to affect FA phase times. A comparative study examining different anesthetic protocols and FA in the dog has been reported, but failed to demonstrate any significant effect on FA phase times (Martin et al., 2001).

Other dyes have also been described for fundus angiography and include indocyanine green (ICG) angiography (peak absorption 790–805 nm, peak emission 825–835 nm), pyranine (peak absorption 455 nm, peak emission 520 nm), and rhodamine (peak absorption 555 nm, peak emission 585 nm). ICG is a tricarboxycyanine dye with absorption and emission spectra within the infrared spectrum. Infrared radiation can better penetrate tissues containing pigment (such as RPE), areas of exudation, or hemorrhages. Not surprisingly, therefore, ICG angiography has been found to be more sensitive than FA in delineating abnormalities deep in the neurosensory retina (Okada et al., 1998; see later Fig. 10.2.41 and Fig. 10.2.42). Intravascular ICG is 98% plasma-protein bound and is therefore almost completely confined to the intravascular space. ICG has a lower intensity of fluorescence and therefore larger doses are usually required to provide comparable angiography. It is metabolized in the liver. ICG is available as a solution with 5% iodine as a stabilizer, and is therefore contraindicated in cases of hyperthyroidism. A noniodine-containing agent incorporating infracyanine green is available to use in such circumstances. Both agents are also utilized intravitreally for staining of the inner-limiting membrane during vitreoretinal surgeries (e.g., epiretinal membrane peeling; Stansecu-Segall & Jackson, 2009).

Leukocyte staining with tracking of movement (and calculation of velocity) through the fundus has been undertaken experimentally in rodents and nonhuman primates using acridine orange (Nishiwaki et al., 1995; Ogura, 1999). Acridine orange is both carcinogenic and phototoxic to cellular lysosomes and is therefore not utilized in human or veterinary patients. Other leukocyte stains include fluorescein isothiocyanate, sodium fluorescein, ICG, and carboxyfluorescein diacetate (Fallacier et al., 1995; Khoobehi et al., 2003).

Fluorescence is witnessed in the fundus 5–50 seconds after intravenous injection, depending on species and cardiovascular factors. Following intravenous injection, fluorescein enters into the choriocapillaris and leaks into the choroidal interstitium via numerous large vascular fenestrae. Thereafter the fluorescein is observed in the retinal arterioles, followed by retinal capillaries, then retinal venules, and finally a recirculation may be seen. Fluorescein is normally retained within retinal vessels by the lack of endothelial fenestrations, and entry into the retina from the choroid is prevented by the tight junctions between RPE cells (retinal blood barrier). The presence of pigment within the RPE obscures the choroidal phase if present, and. similarly, the presence of a tapetum reduces the quality of FA images,

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thereby limiting the ability of FA to investigate abnormalities within the tapetal fundus.

Descriptions of the FA phases are largely derived from the human literature. These were first described as (1) choroidal flush; (2) early arteriolar phase; (3) late arteriolar phase; (4) capillary phase; (5) early venous phase; and (6) late venous phase. This has subsequently been simplified to (1) preretinal or choroidal phase; (2) retinal arterial phase; (3) retinal arteriovenous phase (lasting up to the first appearance of fluorescein in the retinal veins, and subdivided into early, intermediate, and late arteriovenous phases by some authors); (4) retinal venous phase; and (5) late phase (during which the fluorescein fades away and may include a recirculation phase; Dithmar & Holz, 2008; Hayreh, 1974).

Abnormalities in FA are broadly categorized into hypofluorescence and hyperfluorescence, and also by location and size of the abnormality. When interpreting pathologic fluorescence, the origin of the fluorescence (or lack of) and the temporal angiographic phase should be considered, as during the course of an angiogram hypofluorescence and hyperfluorescence can alternate in the same location(s). For example, chorioretinitis is typically associated with an initial hypofluorescence associated with retinal edema, followed by hyperfluorescence due to increased local vascular permeability.

Hypofluorescence can be associated with blocking of fluorescence, for example by the presence of vitreal or intraretinal hemorrhages, or a subretinal (choroidal or RPE) process, where retinal vessel fluorescence would be normal overlying choroidal hypofluorescence. Alternatively, hypofluorescence may occur due to vascular filling defects, such as retinal occlusions or decreased tissue perfusion. Hyperfluorescence can occur due to a window defect or increased accumulation of fluorescein dye. A window defect occurs where normal fluorescence is no longer blocked by normal tissue that is absent or reduced, for example RPE coloboma or a retinal hole. Fluorescein may accumulate due to leakage from vessels with increased permeability, pooling in anatomic space (e.g., under a serous RPE detachment where fluorescein from the choriocapillaris may collect) or by staining of a tissue with fluorescein. Staining can occur in normal tissues (e.g., the sclera, which might be visible through a coloboma) or in pathologic conditions (e.g., fibrotic scarring of the choroidal vascular tissues). Hyperfluorescence may also been seen in abnormal vasculature, in that those vessels, if patent, will also fill with fluorescein, such as is encountered with choroidal neovascularization.

Clinical Applications

FA is used to assess changes in posterior segment circulation, including choroidal or retinal neovascularization, aneurysms, increased vascular permeability, ischemia, or vessel occlusions. FA is useful in the investigation of neovascularization associated with retinal disorders such as age-related macular degeneration, diabetic retinopathy, and retinopathy of prematurity. FA allows both new vessel and increased vascular permeability imaging through various stages of diseases, as well as responses to treatments over time. FA has also been used to assess the effect of treatments of nonvascular diseases on posterior segment circulation (e.g., diode laser retinopexy for partial retinal detachment), as well as an objective means of assessing animal models of retinal/choroidal vascular diseases.

Hill and Young first described FA in the normal cat in 1973, and this work was followed by research on experimental laser-induced choroidal ischemia in cats illustrated by FA by the same authors (Hill & Young, 1973a, 1973b; Hill et al., 1973). Further FA work (combined with India ink histology) described the regional retinal circulation of the cat for the first time (Hill, 1977; Hill & Houseman, 1980; Hill & Young, 1976).

FA has been used to investigate the role of vascular disease in inherited retinal degenerative diseases in cats, and demonstrated no change in FA phase times or appearances in the studies (Bellhorn et al., 1974; Narfstrom, 1985; Rah et al., 2005). The treatment of inherited retinal degeneration with retinal allograft transplantation has also been studied in the cat, with the aid of FA (Seller et al., 2009).

Feline models for human retinal degeneration, retinal arteriolar branch occlusions, and serous retinal detachments have also been examined by FA (Hayashi et al., 1997; Lai et al., 1997; Levinger et al., 1987; Marmor & Yao, 1994). Experimental exudative retinal detachments in cats have been investigated using rose Bengal-induced (phototoxic) vascular occlusion, as a model for choroidal ischemia in humans (Wilson et al., 1991). FA in these cats demonstrated focal retinal and choroidal occlusions, followed by a progressive serous retinal detachment, which slowly resolved over 14–21 days. The safety of a subretinal microphotodiode array as a possible treatment for retinal degenerative disease has been investigated with both FA and OCT in a feline model (Volker et al., 2004).

Metastasis of angioinvasive pulmonary carcinoma to the ocular posterior segment in cats has been investigated by FA and histopathology, and revealed invasion and growth of neoplastic cells within the chorioretinal vasculature, resulting in secondary ischemic necrosis of the retina and choroid (Cassotis et al., 1999).

Alario et al. (2013a) described anterior segment fluorescein angiography (ASFA) in normal cats using sodium fluorescein and a modified digital single-lens reflex (dSLR) camera (Canon 7D™). Their protocol included premedication with maropitant and diphenhydramine, and no adverse events were reported. The authors postulated that the feline iris contains greater proportions of pheomelanin relative to eumelanin (unlike the canine iris), with a corresponding lower absorption coefficient (435–530 nm wavelength

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required to excite fluorescein) and therefore enhanced image quality (Fig. 10.2.38 and Fig. 10.2.39). Pirie and Alario (2015) reported the use of fluorescein and ICG for the anterior segment angiography of normal cats. The authors felt that ICG angiography was superior to FA; however, both were of diagnostic quality.

Gelatt and others first described FA in the normal Beagle, as well as in Beagles with chorioretinitis, in 1976 (Gelatt et al., 1976). The optimum fluorescein dose was devised, and FA was recorded using high-speed color film in a portable fundus camera. Filling defects have been reported in a normal dog associated with occlusion of the carotid artery by a technician holding the head for fundus photography (Martin et al., 2001). Alario et al. (2013b) also described ASFA in normal dogs using sodium fluorescein and a modified dSLR camera. The authors premedicated with maropitant and diphenhydramine and noted no adverse events (Gelatt et al., 1976 reported emesis in 15% of dogs), matching their findings in cats. They also recommended general anesthesia for optimal image quality, and that heavily pigmented irides precluded assessment of iridal vessels (see Fig. 10.2.40). Alario and Pirie (2015) reported fluorescein gonioangiography in normal dogs using sodium fluorescein (20 mg/kg of 10% sodium fluorescein) and a Lovac–Barkan goniolens, under general anesthesia and employing stay sutures in the perilimbal conjunctiva to aid globe positioning. They used the same maropitant and diphenhydramine premedication and reported no adverse events. Diffuse hyperfluorescence of the underlying sclera was evident within the drainage angle, but no angiographic phases (arterial, venous, capillary) were identified within the pectinate ligament (Alario & Pirie, 2015).

The FA abnormalities associated with PRA in poodles have been described with two main FA appearances: a diffuse choriocapillary atrophy (hypofluorescence), or a patchy choroidal atrophy associated with major retinal vessels. Interestingly, carrier dogs also showed FA abnormalities, with patchy hyperfluorescence associated with depigmentation, arteriolar narrowing, and irregularities, and indistinct capillary beds compared to normal Poodles (Koskinen et al., 1985). FA has also been undertaken in Tibetan Terriers with PRA, but failed to identify vascular abnormalities earlier than were visible on ophthalmoscopy (Millichamp et al., 1988).

Gene therapy of RPE-65–deficient Briard dogs with rAAV2/2, -2/1, or -2/5–mediated delivery of the RPE65 gene has also been investigated using FA. Focal zones of hyperfluorescence, corresponding to the areas of subretinal injection (and focal retinal detachment), were considered secondary to the trauma of injection. Interestingly, however, this abnormality was not seen in normal Briard dogs receiving the vehicle alone by subretinal injection, or in normal Beagle dogs receiving either the AAV2/4.hrpe65 or the AAV2/2.hrpe65 vector alone, perhaps suggesting a trauma vulnerability in affected Briard dogs (Le Meur et al., 2005, 2007).

The inherited (autosomal recessive) nonprogressive multifocal retinopathy (canine multifocal retinopathy, CMR) of Great Pyrenees has been documented using FA, revealing areas of choroidal hypoperfusion, followed by fluorescein pooling into sub-RPE defects, with no leakage of fluorescein into the overlying serous retinal detachments (suggesting that tight junctions between RPE cells remain intact). Light microscopy and electron microscopy confirmed the presence of multifocal serous retinal detachments at a young age, with focal retinal degeneration as noted on ophthalmoscopy. The retinal detachments were accompanied by hypertrophy, hyperplasia, increased pigmentation, and vacuolation of the retinal pigment epithelium (Grahn & Cullen, 2001; Grahn et al., 1999). These findings led the authors to postulate that the multifocal serous retinal detachments were secondary to focal secretion and absorption defects in the RPE cells, with similarities to central serous retinopathy in humans.

A similar clinical presentation is seen in young Coton de Tulear dogs with nonprogressive multifocal serous retinal detachments as an inherited (autosomal recessive) condition. FA of affected dogs also showed no fluorescein leakage into the retinal detachments, confirming the lack of BRB breakdown (Grahn et al., 2008; Fig. 10.2.41 and Fig. 10.2.42). In contrast to Great Pyrenees with multifocal retinopathy, however, there was no pooling of fluorescein into sub-RPE defects.

Multifocal retinopathy encountered in Dachshunds with CLN2 neuronal ceroid lipofuscinosis has been investigated using both OCT and FA (Whiting et al., 2015). The retinopathy was demonstrated to be multifocal serous retinal detachments with no fluorescein pooling on FA, resembling the findings in CMR described by Grahn and colleagues. Genetic investigations ruled out a causative mutation in BEST1 (like CMR), but a mutation in TPP1.

FA investigation of inherited multifocal chorioretinal lesions in Borzoi dogs revealed intact blood–ocular barriers (no fluorescein leakage), focal RPE hypertrophy, and focal absence of the choroiocapillaris (hypofluorescence) corresponding to chronic, focal lesions (Storey et al., 2005). Initial hyperfluorescence in acute lesions within the tapetal fundus were interpreted as window defects, and later hypofluorescence of the same region as RPE hypertrophy.

FA examination of Bernese Mountain dogs with a suspected inherited retinopathy revealed hypofluorescence in a horizontal region lateral and dorsal to the optic disc (interpreted as an ischemic lesion) and fluorescein epithelial leakage from peripheral capillaries (Chadieu & Molon-Noblot, 2004).

Retinal degeneration associated with vitamin E deficiency has been described in hunting dogs fed on a scrap meat diet (Davidson et al., 1998). FA descriptions were also reported in

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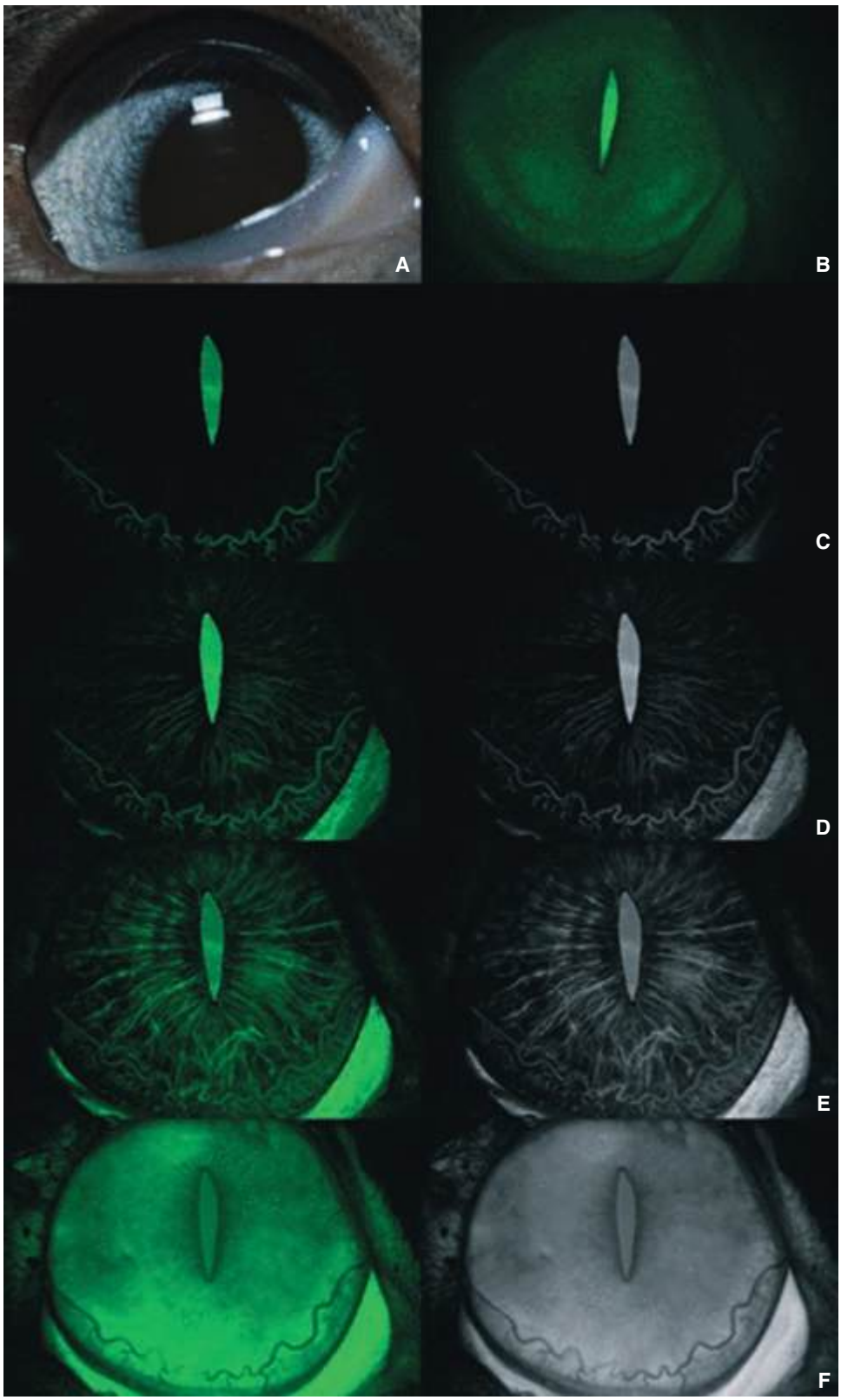


Figure 10.2.38 Standard (**A**), red-free (**B**), and anterior segment fluorescein angiography (ASFA; **C**–**F**) images obtained from a blue-eyed 2-year-old male neutered Siamese cat. For ASFA images, phases include (**C**) arterial phase (7 s), (**D**) capillary phase (10 s), (**E**) venous phase (16 s), and (**F**) late time period (10 min). Color and black-and-white* ASFA images are represented. A complete major arterial circle (MAC) is readily apparent in **C** and **D**. Additionally, slightly tortuous radial iris arterioles, some of which originate from radial ciliary arteries, are noted. Presence of a rudimentary minor arterial circle is noted in **E**. In **F**, leakage of fluorescein within the iris stroma is apparent, producing a negative contrast image (MAC is now black). *Black-and-white images were generated from color images obtained using Adobe Photoshop CS4 black-and-white tool function.

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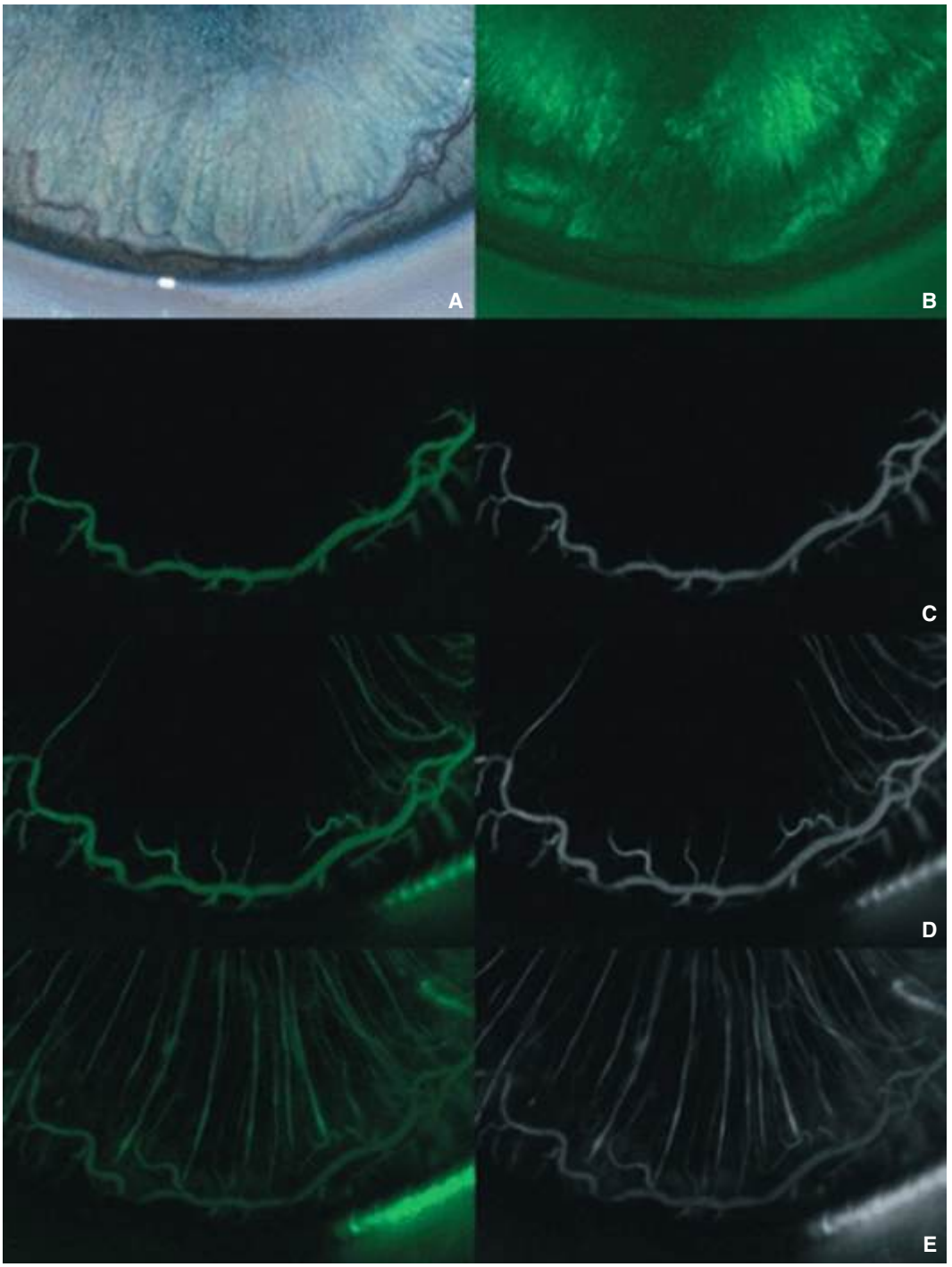


Figure 10.2.39 Standard (**A**), red-free (**B**), and anterior segment fluorescein angiography (ASFA; **C**–**E**) images obtained from a blue-eyed 3-year-old MN Domestic Shorthair cat. Images are magnified by a factor of 4 (400%) to demonstrate the finer vascular detail around the major arterial circle (MAC). Phases include (**C**) early arterial phase (6 s), (**D**) arterial phase (9 s), and (**E**) late venous phase (29 s). Color and black-and-white* ASFA images are represented. A complete MAC is apparent in **C**, demonstrating filling of both radial ciliary arteries, and iris arterioles in **C** and **D**. Several radial iris arterioles are noted to originate from radial ciliary arteries. Venous dilation is demonstrated in **E**. *Black-and-white images were generated from color images obtained using Adobe Photoshop CS4 black-and-white tool function.

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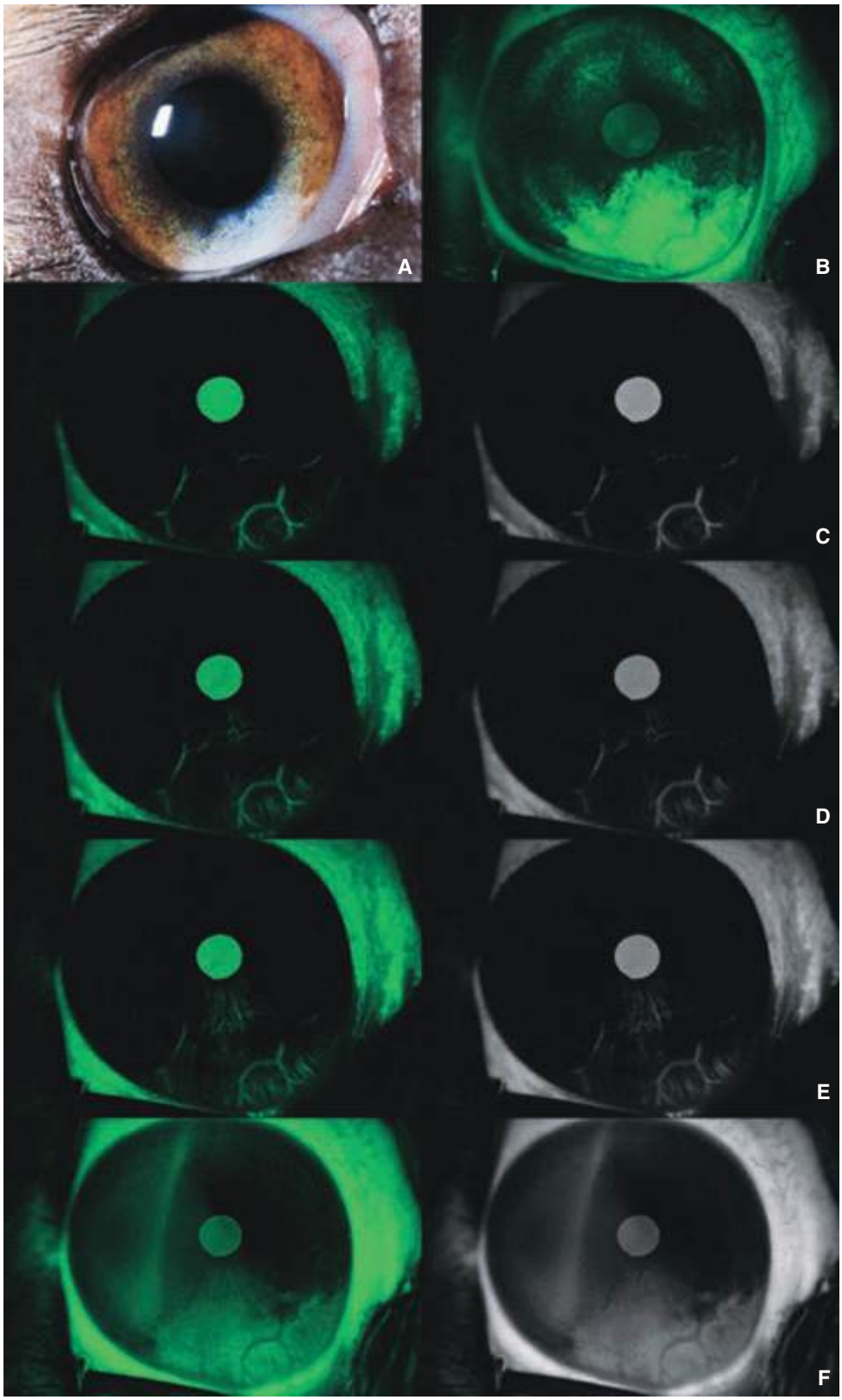


Figure 10.2.40 Standard (**A**), red-free (**B**), and anterior segment fluorescein angiography (ASFA; **C**–**F**) images obtained using propofol from a heterochromic 1-year-old spayed female Australian Shepherd dog. For ASFA images, phases include (**C**) arterial phase (11 s), (**D**) capillary phase (15 s), (**E**) venous phase (20 s), and (**F**) late stage (10 min). Color and black-and-white* ASFA images are represented. Sectoral hypopigmentation located within the ventromedial iris is apparent in **A** and **B**. Fluorescence and the presence of iris vasculature are apparent only within this hypopigmented region (**C**–**F**). Fluorescein leakage within the iris stroma is apparent in **F**, creating a negative contrast image. Additionally, aqueous humor leakage creating a vertical line is noted. *Black-and-white images were generated from color images obtained using Adobe Photoshop CS4 black-and-white tool function.

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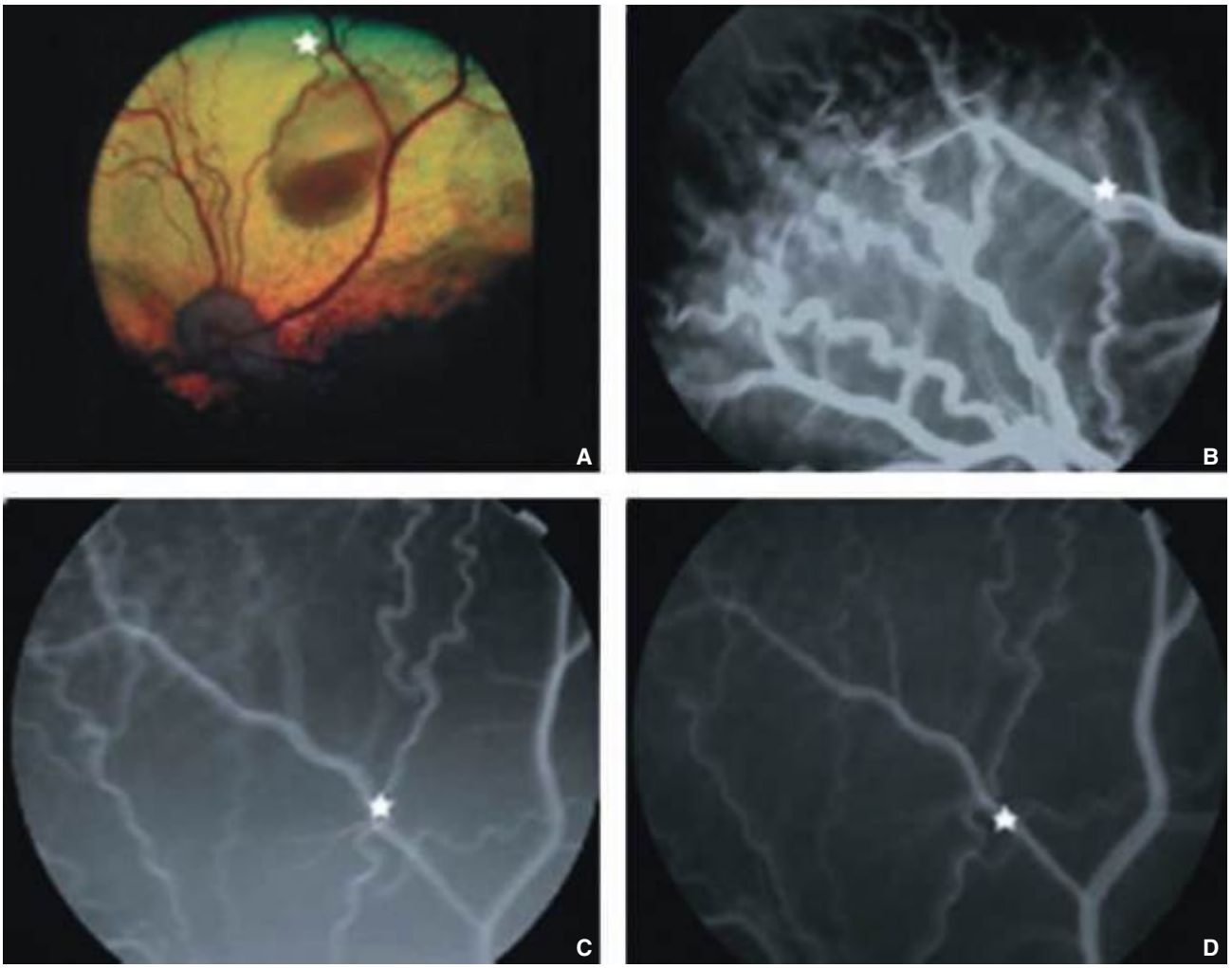


Figure 10.2.41 **A**. Fundus photograph from 6-month-old Coton de Tulear dog affected with multifocal retinopathy. **B**. Arterial phase of fluorescein angiogram. **C**. Venous phase. **D**. Recirculation phase. White star denotes the same fundus location in each image. Note the lack of fluorescein leakage or pooling (suggesting no blood–retinal barrier breakdown). (Reproduced with permission from Grahn, B.H., Sandmeyer, L.L., & Breaux, C. (2008) Retinopathy of Coton de Tulear dogs: Clinical manifestations, electroretinographic, ultrasonographic, fluorescein and indocyanine green angiographic, and optical coherence tomographic findings. *Veterinary Ophthalmology*, **11**(4), 242–249.)

this study and documented early-phase multifocal coalescing areas of hypofluorescence, predominantly in the tapetal fundus, corresponding to areas of ophthalmoscopically visible pigment clumps. These areas were hyperfluorescent later in the course of the angiograms, suggesting disruption of the BRB. Retinal vascular attenuation, narrowing, and constriction could also be visualized in areas of ophthalmoscopically visible retinal degeneration.

FA has documented increased retinal vascular permeability in cases of experimental infection with *Ricketsii ricketsii* in dogs. While 50% of the experimentally infected cases showed increased vascular permeability on day 6 postinfection, this reduced to 6% of cases by day 17 (Drost et al., 1997).

FA studies of transpupillary diode laser retinopexy in normal Beagle dogs showed disruption of the BRB at the level of the RPE. Fluorescein leakage into the subsensory retinal space was also seen in most lesions at 24 hrs, was minimal at 3 days, and had resolved by 1 week (Pizzirani et al., 2003; Fig. 10.2.43).

Investigation of a canine model for diabetic retinopathy using galactose-fed dogs (over 66 months) has been undertaken using fundus photography, FA, and histopathology (Takahashi et al., 1992). This study demonstrated broad areas of nonperfusion, cystoid bodies (soft exudates), retinal microvascular changes, occluded retinal arterioles, preretinal and intravitreal hemorrhages, and optic nerve head neovascularization associated with the galactose diet. A further study to assess the potential of an antiangiogenic drug, combretastatin a-4, in long-term galactose-fed dogs has also been investigated with FA. Sub Tenon's, intravitreal, and

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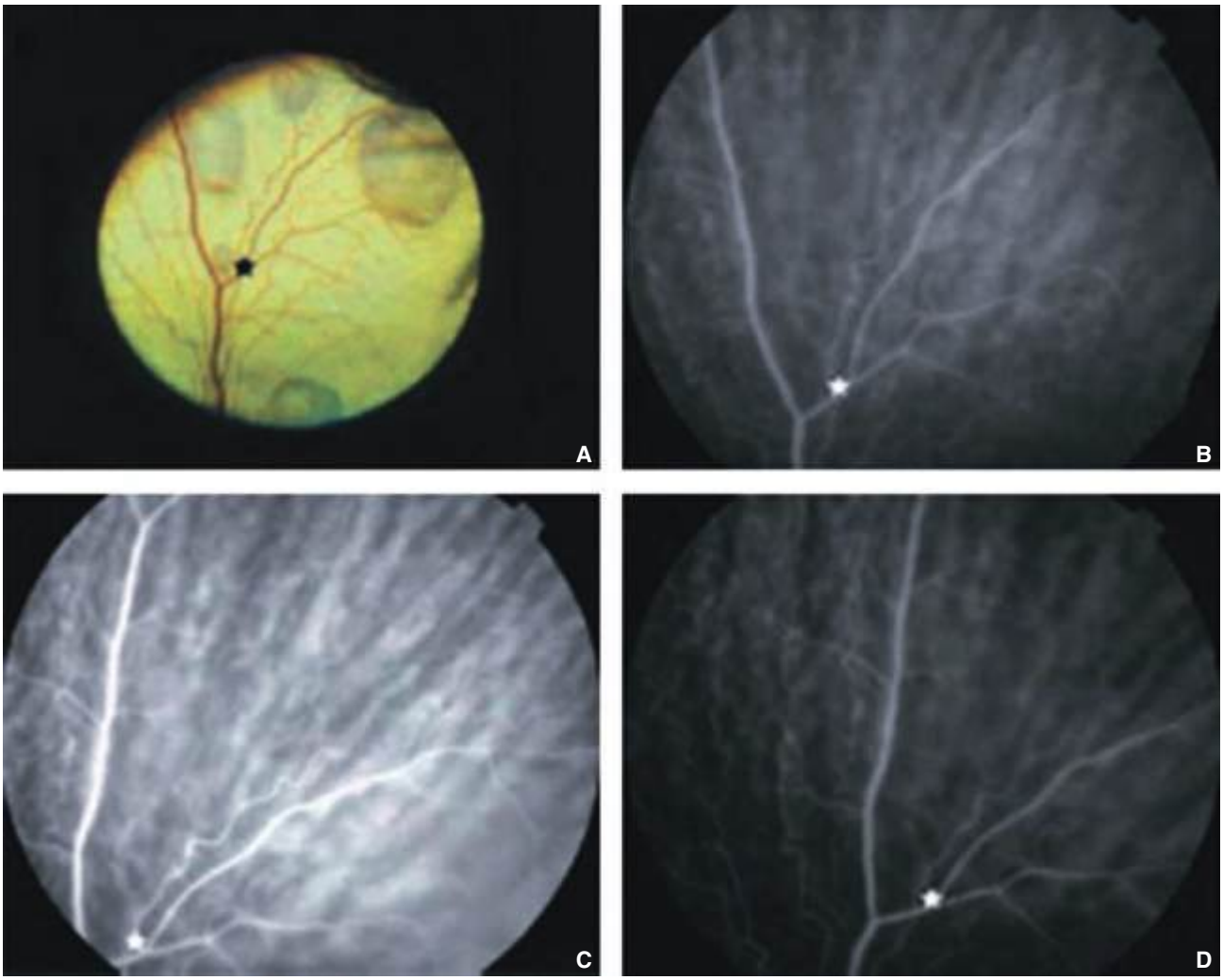


Figure 10.2.42 **A**. Fundus image from a 2-year-old Coton de Tulear dog affected with multifocal retinopathy. **B**. Early phase of indocyanine green (ICG) angiography. **C**. Midphase. **D**. Late phase. White star denotes the same fundus location in each image. Note no ICG leakage or pooling (suggesting no blood–retinal barrier breakdown) and increased visibility of choroidal vasculature compared with fluorescein images. (Reproduced with permission from Grahn, B.H., Sandmeyer, L.L., & Breaux, C. (2008) Retinopathy of Coton de Tulear dogs: Clinical manifestations, electroretinographic, ultrasonographic, fluorescein and indocyanine green angiographic, and optical coherence tomographic findings. *Veterinary Ophthalmology*, **11**(4), 242–249.)

intravenous administration of the drug failed to cause regression of retinal neovascularization established in the canine model for diabetic retinopathy (Kador et al., 2007).

A canine model for retinopathy of prematurity has been reported by exposing neonatal puppies to 95%–100% oxygen for 4 days followed by 22–45 days of room air before FA, euthanasia, and histopathology. FA abnormalities included dilated and tortuous retinal vessels, pigmentary changes, incomplete vascularization of the peripheral retina, vitreal hemorrhages, and persistence of massive intravitreal neovascularization (McLeod et al., 1998).

Retinal vein occlusion (RVO) is a relatively common cause of vision loss in humans with atherosclerotic or hypertensive vascular disease, and a canine model for this disease has been studied by FA. The potential treatment of RVO by laser-induced venous anastomosis of choroidal and retinal vessels has also been studied by FA and histopathology, in the same canine model (McAllister et al., 1992). Smaller-caliber anastomoses could also be created in the absence of RVO, but over a longer period (6–8 weeks instead of 3–6 weeks) compared to those created in dogs with previously induced partial RVOs. The same iatrogenic anastomosis procedure was repeated in rats to determine whether chorioretinal venous anastomoses could be induced in an animal with a Bruch's membrane that is well developed, as it is in humans (unlike in the dog) and was successful (Vijayasekaran et al., 1994).

Assessment of the biocompatibility of an epiretinal prosthesis prototype in mixed-breed normal dogs has been

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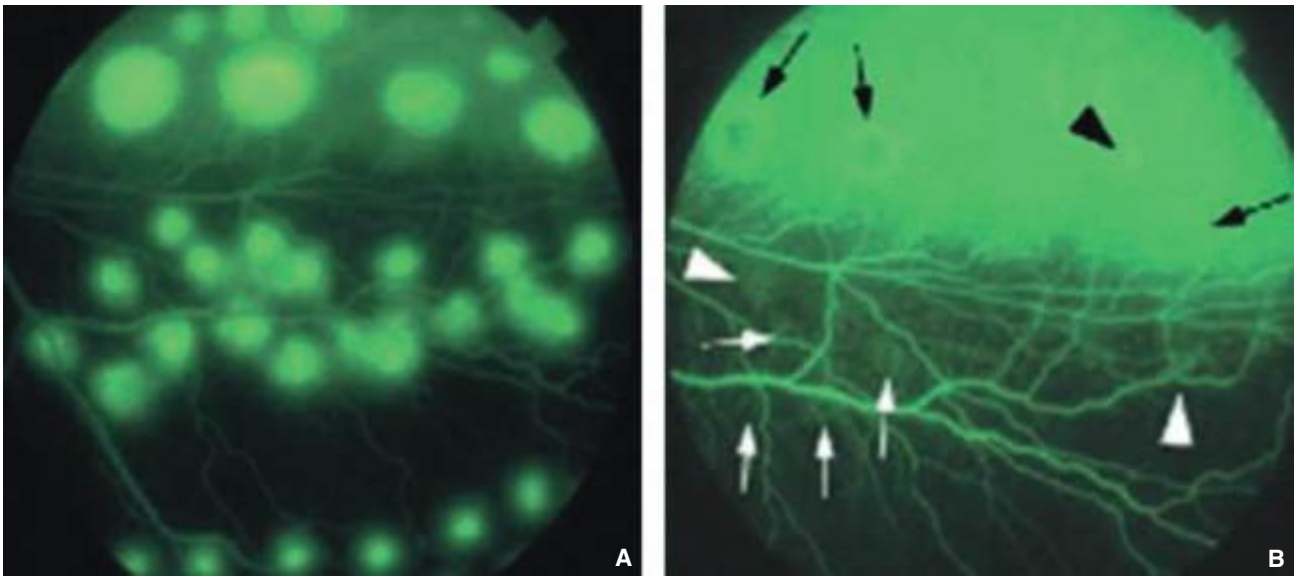


Figure 10.2.43 **A**. Fluorescein angiogram of the right eye of a Beagle 24 hours after transpupillary diode laser retinopexy. Late venous phase. Multiple lesions demonstrate fluorescein leakage (hyperfluorescence) in both the tapetal and nontapetal regions of the fundus. **B**. The same dog and eye after 7 days. Late venous phase. No fluorescein pooling is seen. A blocking effect (hypofluorescent center; retinal pigment epithelial [RPE] hypertrophy, and pigmentation) is seen surrounded by a window defect (hyperfluorescent ring) in some of the most severe postdiode retinopexy lesions (black arrows). White arrows correspond to areas of blocking defect (RPE hypertrophy and repigmentation) surrounded by window defect (nonpigmented RPE). White arrowheads correspond to milder areas of milder retinopexy lesions with no blocking or window defects. (Reproduced with permission from Pizzirani, S., Davidson, M.G., & Gilger B.C. (2003) Transpupillary diode laser retinopexy in dogs: Ophthalmoscopic, fluorescein angiographic and histopathologic study. *Veterinary Ophthalmology*, **6**(3), 227–235.)

undertaken with a view to developing a multielectrode array prosthesis capable of providing ambulatory vision in humans with photoreceptor loss. FA, as well as electroretinography and histopathology, demonstrated good tolerance of the implant in dogs (Majji et al., 1999). A similar procedure was used to assess the safety and feasibility of an epiretinal electrode array made from polydimethylsiloxane, including FA, OCT, electrophysiologic studies, and histopathology. FA demonstrated good retinal perfusion under the array (Guven et al., 2006).

Confocal scanning ophthalmoscopy has been combined with FA to give sharper and more numerous angiographic images in the normal dog, cynomolgus monkey, and minipig (Rosolen et al., 2001). The authors felt that the increased rate of image capture (25 frames per second compared to the 8 frames per second of traditional FA capturing techniques) gave enhanced information on the retinal microcirculation and dynamics. Images were obtainable using a single piece of equipment and even in the face of moderate lens nucleus opacities.

FA of the normal horse was first described by Walde in 1977. FA in normal horses under standing sedation and palpebral nerve blockade was later reported with two main phases, a choriopapillary phase and a retinal vascular phase (Molleda et al., 2008; Fig. 10.2.44). The retinal vascular phase was further subdivided into three phases: a filling phase, a maximal fluorescent phase, and a fading phase. The choriopapillary phase started at 46.95 ± 9.48 s and was followed at 47.79 ± 10.38 s by the retinal vascular phase. Retinal arterioles and venules could not be distinguished on FA, as both vessel types filled with fluorescein simultaneously. The maximal fluorescent point was 59.79 ± 10.39 s and the retinal vascular fade was complete at 74.76 ± 9.81 s. This study also demonstrated sparse and shorter retinal vessels ventral to the optic disc, rather than an absolute deficiency of vascularization.

FA has been described in the investigation of bilateral chorioretinal colobomas in a donkey (Martin-Suarez et al., 2009). The donkey presented with typical colobomas of both irides and optic discs (extending into adjacent peripapillary retina and choroid). FA abnormalities of hypofluorescence in the region of the colobomas and leakage of fluorescein from choroidal vessels at the border of the colobomas were described. The authors postulated that the hypofluorescent areas were due to absence of normal choroidal vessels, and the leakage of fluorescein may have occurred from abnormal choroidal neovascularization.

An FA study of the normal sheep and goat has been published (Galan et al., 2006) and images were obtained without sedation or anesthesia of the animals. Sodium fluorescein

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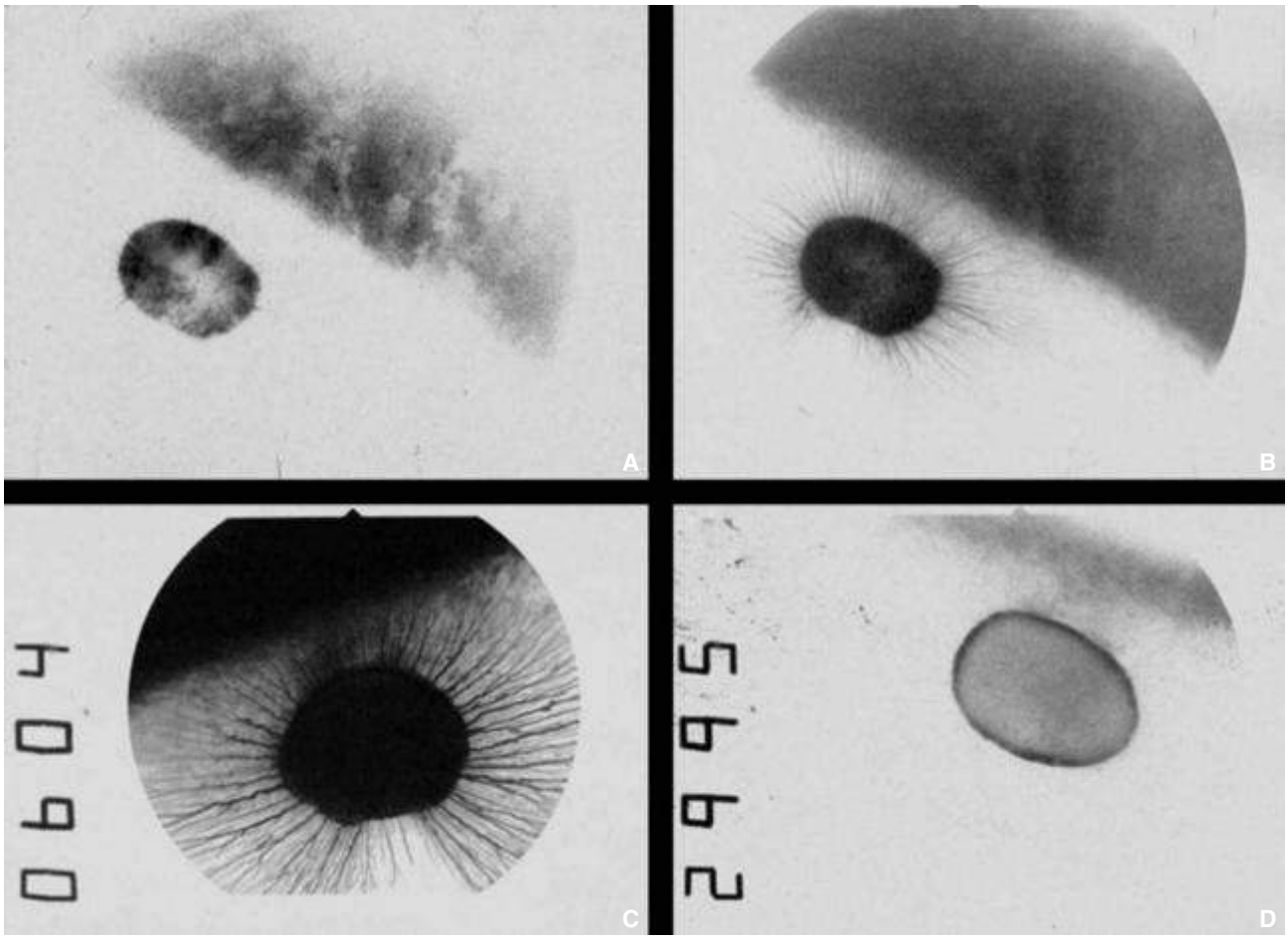


Figure 10.2.44 Normal equine fluorescein angiography images. **A**. Choroidal phase (patchy fluorescein filling). **B**. Retinal vascular phase. **C**. Maximal fluorescence (retinal arterial and venous phase). **D**. Fading phase (fluorescence of optic disc rim from diffusion of fluorescein into optic nerve sheath). (Reproduced with permission from Molleda, J.M., Cervantes, I., Galan, A., et al. (2008) Fluorangiographic study of the ocular fundus in normal horses. *Veterinary Ophthalmology*, **11**(1), 2–7.)

was administered via the jugular vein and serial fundus photographs obtained. The phases of FA could be identified and mean angiographic times obtained for both species (Fig. 10.2.45). FA of the anterior segment of normal goats, sheep, and alpacas has subsequently been undertaken using both sodium fluorescein and ICG and a dSLR camera adaptor under general anesthesia, with no reported adverse events (Lo Pinto et al., 2017a). Sodium FA of iris vasculature was not possible in all tested alpacas due to the heavy iridal pigmentation, or in the more heavily pigmented irides of sheep and goats. Sodium fluorescein extravasation that has also been reported in cats and dogs (Alario et al., 2013a, 2013b) was encountered in sheep and alpacas, but not in goats. ICGA was able to provide diagnostic angiography images regardless of degree of iridal pigmentation in all three farm animal species (Lo Pinto, 2017a).

FA has been used extensively in laboratory small mammals for the research of animal models of ocular posterior segment disease in humans, but that is beyond the scope of this chapter.

Elegant FA studies have illustrated the role of the pecten in the ocular perfusion of birds. Lack of retinal blood vessels would normally limit the thickness of the retina to the theoretical oxygen diffusion maximum of approximately 140 µm; however, this is not the case in birds, whose retinal thickness may reach 300 µm (Pettigrew et al., 1990). FA studies have demonstrated that the pleated or cone-like vascular structure of the pecten in birds acts as a primary source of nutrients to the inner retina. Saccadic oscillations, peculiar to birds, are responsible for the pecten "agitating" nutrients toward the central retina (Pettigrew et al., 1990).

FA was also undertaken to characterize the nutrition of the avascular retina of *Megachiroptera* (fruit bats), specifically *Pteropus poliocephalus* (Brudenall et al., 2007; Fig. 10.2.46). In the same study, vascular resin casts illustrated vascular loops emanating from the margins of the

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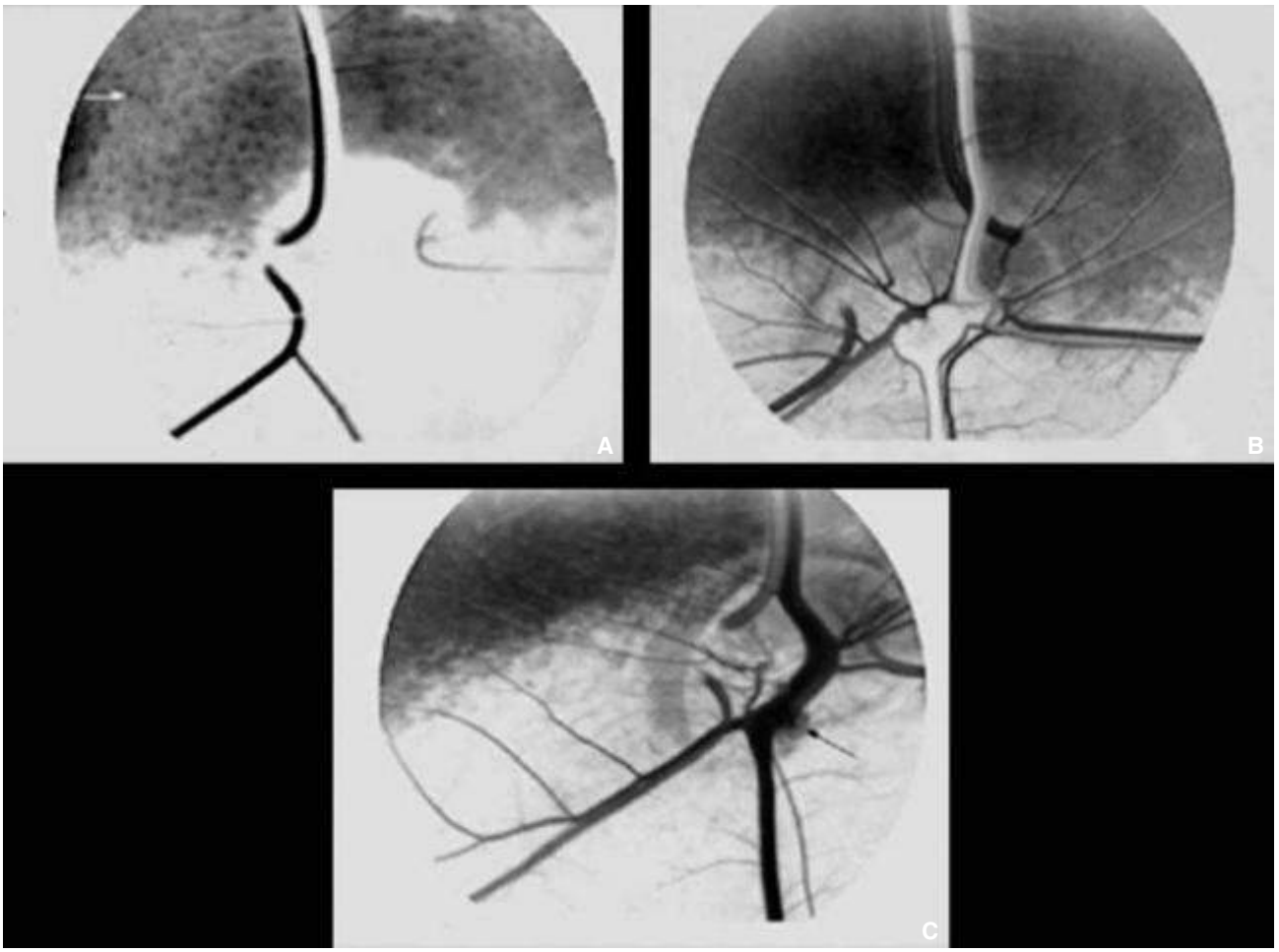


Figure 10.2.45 Fluorescein angiography images of a sheep. **A**. Arterial phase. Stars of Winslow are visible with choroidal fluorescence (black arrow); optic disc shows no fluorescence at this stage. **B**. Arteriovenous phase. Tapetal fundus has more homogenous fluorescence, with light fluorescence seen in nontapetal fundus. Optic disc is now fluorescent. Laminar flow is seen in dorsal vein. **C**. Venous phase with all veins fluorescent. Nontapetal fundus fluorescence is decreasing. Bergmeister's papilla is fluorescent (arrow). (Reproduced with permission from Galan, A., Martion Suarez, E.M., Granados, M.M., et al. (2006) Comparative fluorescein angiography of the normal sheep and goat ocular fundi. *Veterinary Ophthalmology*, **9**(1), 7–15.)

optic disc, forming a truncated cone. Each vascular loop was shown to extend approximately 450 µm into the vitreous cavity. Following intravenous sodium fluorescein injection via a wing vein, the vascular loops showed the presence of fluorescein, and reached a maximum intensity by 20 s. Fluorescein was then seen to diffuse into the peripapillary vitreous from the vascular loops. Between 25 s and 30 s postinjection, the intensity of diffusing fluorescence at the optic disc obscured the vascular loops.

Future Directions

An imaging system that combined the benefits of cSLO (including fluorescence data) and OCT has been described and was able to longitudinally image individual retinal ganglion cells, microglia, and Muller glia in a mouse model (Zhang et al., 2015). This combination system was able to harness the advantages of both imaging modalities, while minimizing the impact of the limitations for each individual modality.

Two-photon nonlinear microscopy (or multiphoton microscopy) is a fluorescence technique that allows *in vivo* and *ex vivo* imaging of the eye. A nonlinear microscope excites fluorescence at a focal point of an infrared laser at an intensity high enough to allow a dye molecule to absorb two infrared photons simultaneously. Scanning this focal point (using an adaptive optics scanning light microscope) in three dimensions allows construction of a 3D image, while reducing background interference and reducing photo-induced damage to the tissue. *In vivo* two-photon fluorescence imaging of the retina has the potential to provide images of

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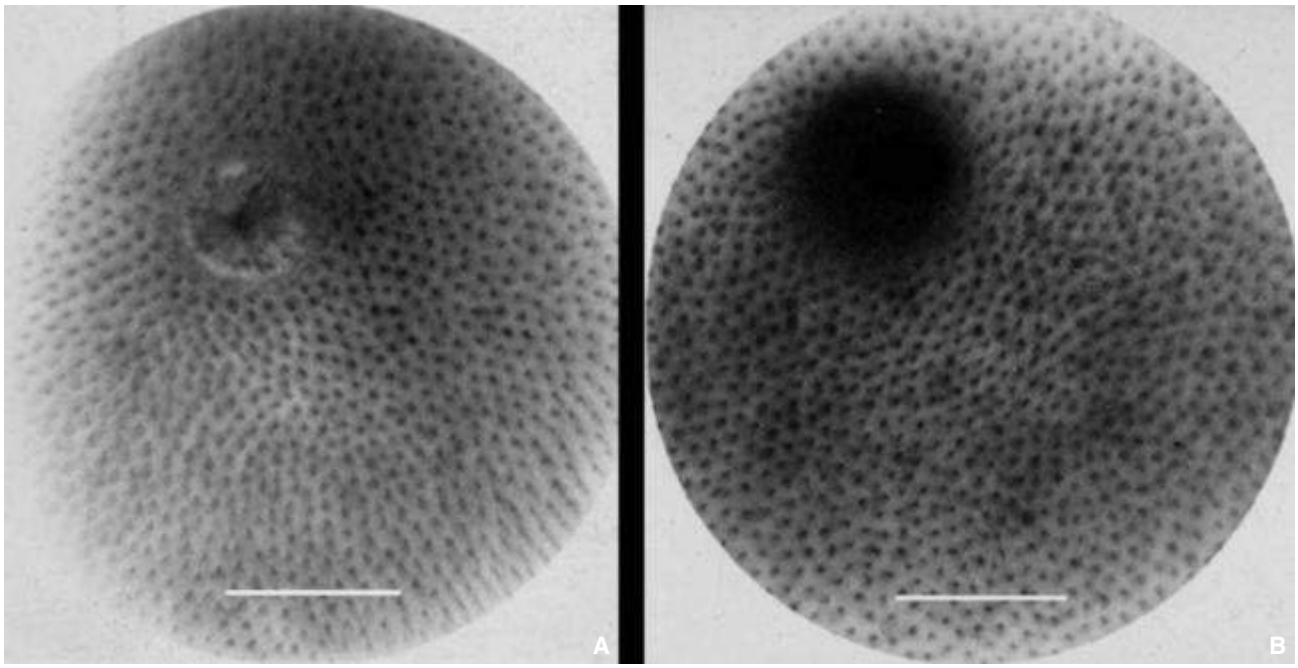


Figure 10.2.46 Fundoscopic view of *Pteropus poliocephalus* (**A**) 11 s and (**B**) 32 s after intravenous fluorescein injection, showing filling of vessels at the optic disc (central circular region) and subtending choroidal papillae. The intensity of fluorescein increases within the optic disc vessels by 32 s, and diffusion of fluorescein into the vitreous obscures the detail of individual vessel loops. Scale bar equals 800 µm. (Reproduced with permission from Brudenall, D.K., Schwab, I.R., Lloyd, W., III., et al. (2007) Optimized architecture for nutrition in the vascular retina of *Megachiroptera*. *Anatomy, Histology and Embryology*, **36**(5), 382–388.)

cellular structures, information on retinal function in health and disease, and also on the response to therapeutic interventions (Jayabalan et al., 2017; Sharma et al., 2017).

Intraoperative OCT systems are being developed, and were first described in use in anterior segment surgery (Geerling et al., 2005) and subsequently in macular surgery (Dayani et al., 2009). It has been speculated that this may be further advanced to provide a virtual OCT image over the surgical site for the benefit of the surgeon (Gabriele et al., 2011).

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10.3

Ophthalmic Examination and Diagnostics

Part 3: Diagnostic Ophthalmic Ultrasound

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The inability to directly observe intraocular and periocular structures due to diseases causing media opacities or changes in anterior architecture, as well as the inability to directly examine orbital tissues, has triggered the search for easily performed, noninvasive, real-time, high-detail diagnostic modalities to detect morphologic changes when standard routine ophthalmoscopy methods are unsuccessful. Due to the eye's accessibility and fluid compartmental structure, it is ideal for multiple imaging technologies (Silverman, 2009). In 1956, Mundt and Hughes (Mundt & Hughes, 1956) used an amplitude scan (A-scan) on an intraocular tumor, demonstrating the possible use of ultrasound in ophthalmology. Soon thereafter, a body of research developed on the sound velocities of various tissues and compartments of the eye, and in the 1960s ultrasound began to be used to measure distances in the eye. Later, Ossoinig (1979) developed the standardized A-scan, which is used to differentiate tissues, particularly tumors. Brightness scan (B-scan) instruments, developed in the 1970s, were originally used through closed eyelids, but later evolved to transcorneal and transscleral use. In the 1990s high-frequency ultrasound developed, which greatly improved the resolution and ability to examine anterior segment structures (Pavlin et al., 1991). Recent developments include the digitization of ultrasound allowing for three-dimensional imaging, higher-frequency imaging, artifact-reducing technology, improvement of Doppler imaging, and the use of contrast-enhanced ultrasound (CEUS).

Clinical ophthalmologists can easily use several different types of ultrasound during daily practice, without the need for sedation or general anesthesia, to examine ocular structures. Investigation of orbital tissues may be more challenging due to the bones surrounding the orbital space. Ocular and orbital ultrasonography, however, offer advantageous information in real time and with limited invasiveness, and may complement cross-sectional modalities such as computed tomography (CT) or magnetic resonance imaging (MRI). A full understanding of its indications, including basic physics and principles, proper examination techniques, and limitations, will allow the clinician to gather a vast and useful amount of information.

Principles of Ultrasound

Ultrasound uses acoustic waves whose frequency is above the human hearing range (> 20 KHz or > 20,000 oscillations/second). In ophthalmic ultrasound, frequencies are measured in megahertz (MHz = 1,000,000 hertz) and transducers are typically between 8 MHz and 65 MHz (with higher frequencies in development). Higher frequencies are associated with shorter wavelengths, a property that makes ultrasound waves easily reflected off small surfaces. Therefore, higher frequencies can recognize smaller differences, increasing the resolution, which is an essential parameter when examining the delicate structures of the eye. Higher resolution comes with the price of lower tissue penetration, as shorter, more frequent wavelengths cannot penetrate tissue as deeply as longer wavelengths. Most standard B-mode transducers for globe imaging are 10–15 MHz and can penetrate about 60–40 mm. High-resolution transducers are generally around 20–40 MHz and penetrate about 30 mm or less. Ultrasound biomicroscopy (UBM) is usually considered to be 50 MHz or higher, limiting tissue penetration to about 10 mm (Byrne & Green, 2002; Szabo & Lewin, 2013). Penetration is not a synonym for focal depth or resolution, nor a discrete fixed, given number, since it depends on tissue density, relative attenuation and backscatter, and transducer acoustic output. Penetration within the eye is favored by the presence of fluids and hydrated tissues with low attenuation values.

Average sound velocity in the eye has been suggested to be between 1547.5 and 1555 m/sec (Hoffer, 1994; Oksala &

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Lehtinen, 1958). However, some debate exists about the acoustic wave velocity in various ocular tissues and different species. One study (Schiffer et al., 1982) found a mean velocity of 1710 m/s using two canine lenses. Later, Gorig et al. (2006) used 40 canine lenses and established a mean sound wave velocity of 1707 m/s. This study also established a mean sound wave velocity in the vitreous of 1535 m/s. The equine lens is reported to be 1529 m/s, and the equine vitreous 1527 m/s (Meister et al., 2014). In humans, the velocity through the crystalline lens is reported as 1641 m/s, and 1532 m/s in the vitreous. Although it may seem that a difference of a few m/s when measuring millimeters is inconsequential using the human values for intraocular lens (IOL) calculation, using biometry measurements from a dog would result in a mean calculated IOL power of 43 diopters (D) rather than 41.8 (Gorig et al., 2006).

An A-scan is a one-dimensional display where echoes are depicted as spikes arising from the baseline. A thin, parallel sound beam passing through a small point in the eye forms an A-scan. The greater the difference between interfaces, the higher the spike will be, hence the name amplitude scan, or time amplitude display. A B-scan is essentially an oscillating A-scan that passes through a cross-section of tissue, with the echoes in a B-scan represented as dots rather than spikes. The configuration of the dots and the brightness of the dots create the image. The greater the difference between interfaces (acoustic impedance) or the stronger the echo, the brighter the dot will be, hence the name brightness scan, or brightness intensity-modulated display.

Sound waves behave essentially like light rays and so many of the same principles of refraction and reflection apply. Just like light rays, the longitudinal sound wave can be reflected back toward its source when it strikes a tissue interface. This reflected wave is called an echo. Similar to the refractive index, acoustic impedance between two media influences the production of an echo. Sharp hyperechoic lines can be observed at the transition between ocular structures with very different densities or impedances, like corneal layers, or aqueous–lens and lens–vitreous interfaces. The greater the difference in acoustic impedance between two media, the stronger the reflected sound wave will be. For example, the difference between the anterior lens surface and the aqueous is much greater than the difference between hypopyon and the lens, so the corresponding echo would be shorter (less distinguishable) in an eye with hypopyon. Other factors that affect the formation of the echo are absorption and refraction, the angle of sound incidence, and the size, shape, and texture of the acoustic interfaces (Byrne & Green, 2002).

The angle at which the sound beam strikes an interface influences the strength, formation, and quality of the echo. The angle of incidence is equal to the angle of reflection, so when a beam strikes an interface perpendicularly, the echo is reflected directly back toward the direction of origination (i.e., the transducer). Sound waves striking in an oblique fashion result in reflected sound waves diverted away from the direction of origin, leading to a weaker echo. When doing a clinical exam, brighter structures are often perpendicular to the sound beam. This property can be used to assess perpendicularity to the structures being examined.

The size, shape, and texture of an interface also determine the character of the echo. A smooth surface is a specular reflector of sound, so if the sound wave strikes perpendicularly, it will reflect nearly all the wave back to its source. An ocular example of this is the lens capsule, whose sharp brightness is enhanced by the acoustic impedance between the fluids surrounding it. An irregular surface (for example the iris) will result in scattering reflector of sound, which means that the returning echo will be weaker, even if the original sound wave was perpendicular.

Ultrasound energy is absorbed by the tissues it passes through. Absorption is related to frequency, sound velocity, and the thickness and density of the tissue through which it passes. Higher frequencies are absorbed to a greater degree, hence the decreased penetration. Greater tissue thickness and/or density also result in greater absorption of the sound waves, and can sometimes result in artifacts. Examples of absorption artifact are the "posterior shadowing" that occurs behind coarse calcified tissue or the "comet tail" reverberation distal to a metallic foreign body.

Reflection, refraction, absorption, and scattering of the sound influence the attenuation of the beam through the tissue. Different tissue densities will also impact attenuation and limit image quality in the distal structures. The reader is referred to other textbooks for more details of ultrasound physics (Zagzebski, 1996).

Instrumentation and Processing

Essential components of an ultrasonographic system are the transducer, the console, and the display screen. An ultrasound transducer functions as both a transmitter and a receiver. Ultrasound exploits the piezoelectric effect of some crystals (usually thin ceramic layers) that produce waves when resonating from electrical impulses, or may alternatively transform received echoes into an electrical signal. The piezoelectric crystal is electrically stimulated, causing a mechanical vibration. The vibration leads to the release of a longitudinal sound wave that passes through the tissue. After each vibration (pulse), a pause of several microseconds occurs so that the transducer can receive returning echoes. The returning echo causes the piezoelectric crystal to vibrate, which then produces an electrical signal that is transmitted to the machine and an image is made on the display screen. This pulse–echo process is repeated a thousand or more times per second to produce a "real-time" display.

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Frequency and pulse length both relate directly to spatial resolution (axial and lateral). Axial and lateral resolution partially (other factors contribute to the final image) indicate the quality of the image that can be obtained and define the sensitivity of the transducer. Axial resolution indicates how close two reflectors can be in the direction of the sound wave and still be distinguishable. A higher axial resolution means the ability to distinguish more accurately two different tissues or layers that are closer together. Lateral resolution refers to the ability to distinguish two different reflectors positioned next to each other in a line perpendicular to the direction of the sound wave. Lateral resolution is inferior to axial resolution. The relationship between axial and lateral resolution is influenced by several parameters; however, lateral resolution of transducers of different frequencies can be 2.4–4 times less than the axial resolution (Foster et al., 2000).

The resolution depends on several factors including the type of transducer, the frequency, the focal length, and the beam aperture. The latter two factors can be indicated by the ratio of the focal length to the transducer diameter (*f*-number); a lower number indicates a higher resolution. Usually, transducers that have an *f*-number of 1.2–2.2 are used for ocular UBM (Pavlin & Foster, 1995). While axial resolution usually does not change greatly with distance, lateral resolution is generally affected more, decreasing with increasing distance to become much less reliable in the far field, especially when transducers with diverging beams are used. See Table 10.3.1.

Gain is another important factor in ultrasound display. It is essentially turning up the volume or amplifying the brightness of the displayed signal. Gain is measured in decibels (dB), which are relative units of ultrasound intensity. Adjusting the gain does not alter the amount of energy produced by the transducer; rather, it only changes the displayed intensity or brightness of the returning echo displayed on the screen. Increasing gain increases sensitivity to weaker echoes and allows for the display of weaker signals. Overadjustment of gain can cause saturation in more echogenic structures, which can decrease resolution and lesion conspicuity. As the gain is lowered, the sensitivity to weak echoes decreases, and both lateral and axial resolution increase. For example, increasing the gain allows the display of weaker signals like vitreous opacities, then as gain is decreased, weak vitreal opacities will go away, but stronger echoes (retina, sclera, masses) will remain (Fig. 10.3.1). Lowering gain effectively narrows the sound beam, because the strongest echoes are in the central axis of the returning sound wave. Since weaker echoes from deeper tissue are not amplified enough to be displayed, lowering gain also effectively decreases the depth of penetration. Many instruments have manual or automatic time gain compensation (TGC), which allows for selective gain adjustment by depth. This enables greater latitude in adjusting the amplification of distant, weaker tissues compared to closer, stronger echoes, which helps equalize echoes from similar tissues located at varying distances from the transducer.

Ultrasound Modalities

A-Scan

A-scans are one-dimensional displays in which returning echoes are reflected as vertical spikes from a baseline. Spacing between the spikes depends on the time it takes for the sound beam to reach the interface and for the echo to return to the transducer. The time between spikes can be converted to distance by knowing the sound velocity of the medium through which the echoes are traveling, which is expressed through the formula:

$$\text{Distance} = \text{velocity} \times \text{time}$$

The height of the spikes indicates the strength, or amplitude, of the echoes.

There are different types of A-scans in ophthalmology. One type is biometry, in which an A-scan is for axial eye length measurements. Biometric A-scans typically use linear amplification, a focused transducer, and a frequency between 10 and 15 MHz (Fig. 10.3.2). A vector A-scan is used simultaneously with B-scan echograms and has similar characteristics to the B-scan, usually logarithmic amplification, a

Table 10.3.1 Calculated wavelengths and axial resolutions based on averaged sound velocity in the eye for most commonly used frequencies in ocular ultrasonography, with two and three cycle pulse lengths.

Frequency	Wavelength	Axial Resolution
10 MHz	155 µm	155–232 µm
15 MHz	104 µm	104–155 µm
20 MHz	78 µm	78–117 µm
35 MHz	44 µm	44–67 µm
50 MHz	31 µm	31–47 µm

Source: Derived from Ng & Swanevelder (2011).

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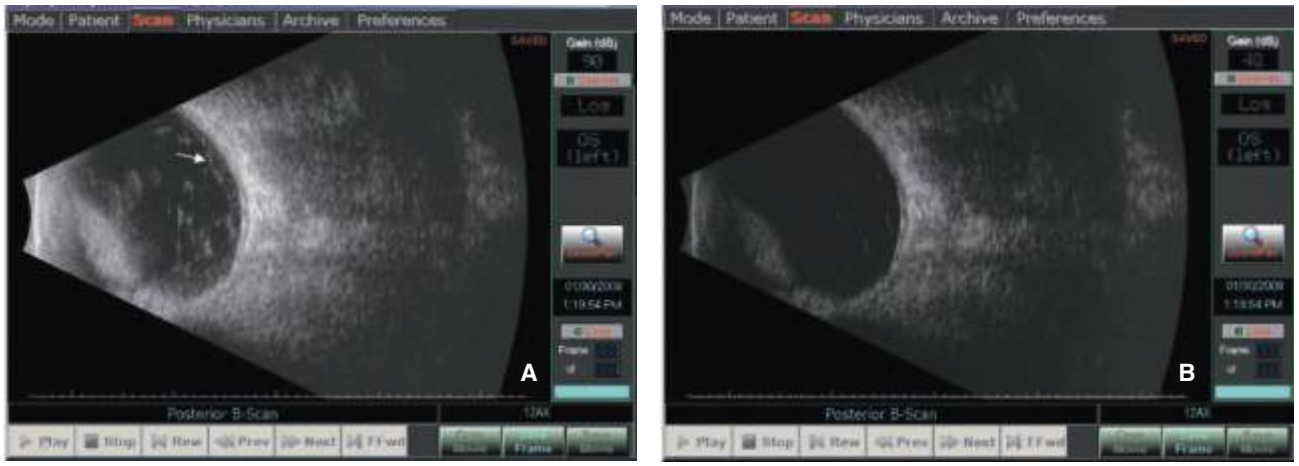


Figure 10.3.1 **A**. B-mode ultrasound image using a 10 MHz transducer with gain of 90 dB in a dog. Note multiple unorganized echogenic foci randomly distributed through the vitreous cavity, and a small linear object adjacent to the retina, choroid, sclera complex (arrow). **B**. Same image as in **A**, with gain set at 48 dB instead of 90 dB. Note that the linear opacity has almost disappeared, more consistent with a posterior vitreous detachment rather than retinal detachment.

focused transducer, and a frequency of 10 MHz (Fig. 10.3.2). Vector A-scans can be used for more precise measurement of lesions and may be as accurate as a linear A-scan (Berges et al., 1998).

The standardized A-scan was developed by Ossoinig (1979) to enhance tissue differentiation. Standardized A-scans use S-shaped amplification, a nonfocused 8 MHz transducer, and a parallel sound beam. Each transducer/instrument combination is externally standardized using a tissue model, which determines the decibel setting. This decibel setting is referred to as tissue sensitivity and is unique to each transducer. Images are then compared to known patterns to make a diagnosis. Standardized A-scans have been used extensively in physician-based ophthalmology, and experienced users can make very definitive diagnoses of tumor and exudate type based on recognition of these patterns. Since its axial positioning is critical and the aiming beam necessary for positioning requires patient cooperation, its use is more challenging in veterinary medicine, hence there are limited reports. Therefore, use of A-scan sonography in veterinary clinical patients is mostly relegated to biometric studies.

Biometry is sometimes used for determining changes in ocular distances during disease, such as increased axial length in buphthalmic globes in glaucoma. Biometry can also be used to attempt to elucidate underlying pathophysiologies of diseases, such as documenting shallow anterior chambers due to anterior shifting of the lens–iris diaphragm in cats with aqueous humor misdirection syndrome (Czederpiltz et al., 2005). Ekesten and Torrang (1995) found that lens thickness increased with age in Samoyeds, leading to a shallower anterior chamber.

The main use of biometric A-scans is to determine the optical characteristics of the globe to calculate IOL strengths and the source of refractive errors. Schiffer et al. (1982) first described anterior chamber, lens thickness, vitreal chamber, and overall axial length measurements in 32 dogs in 1982. Cottrill et al. (1989) described A-scan characteristics of mesocephalic and dolichocephalic dogs and found that dolichocephalic dogs had longer axial globe lengths. Murphy et al. (1992) investigated a population of myopic German Shepherd dogs used as guide dogs for the blind and found no difference in axial length in myopic versus nonmyopic eyes, although later a vitreous based myopia was demonstrated in Labrador Retrievers (Mutti et al., 1999). Gilger et al. (1998b) used biometry, combined with keratometry, to predict an IOL strength of 53–55 D in cats. Follow-up studies of IOL implantation in research cats demonstrated that a 52–53 D IOL is required to achieve emmetropia in cats (Gilger et al., 1998a). Several studies (McMullen & Gilger, 2006; McMullen et al., 2010) used biometry and keratometry to predict an IOL strength in horses (although the large equine eye may result in positioning differences that make it difficult to achieve emmetropia postoperatively in the equine eye).

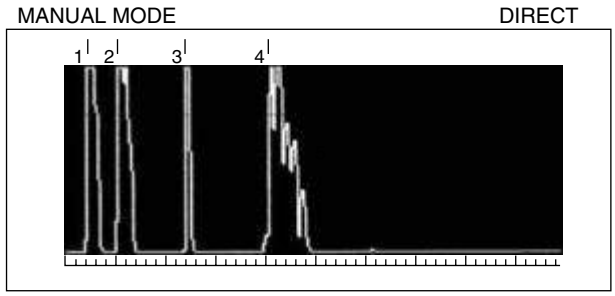
A-scan exams can be easily performed in awake, sedated, or anesthetized animals. The transducer can be placed directly on the cornea or used with a scleral shell and water bath (immersion technique). The transducer should always be placed axially and a reliable scan is one in which the heights of the spikes from baseline are equal. Each spike should start at a perpendicular and at a nonsloping angle from baseline (Fig. 10.3.2A, B).

B-Scan

The B-scan emits an oscillating sound beam that "slices" through a tissue, producing a two-dimensional acoustic section. B-scans are essentially a combination of multiple

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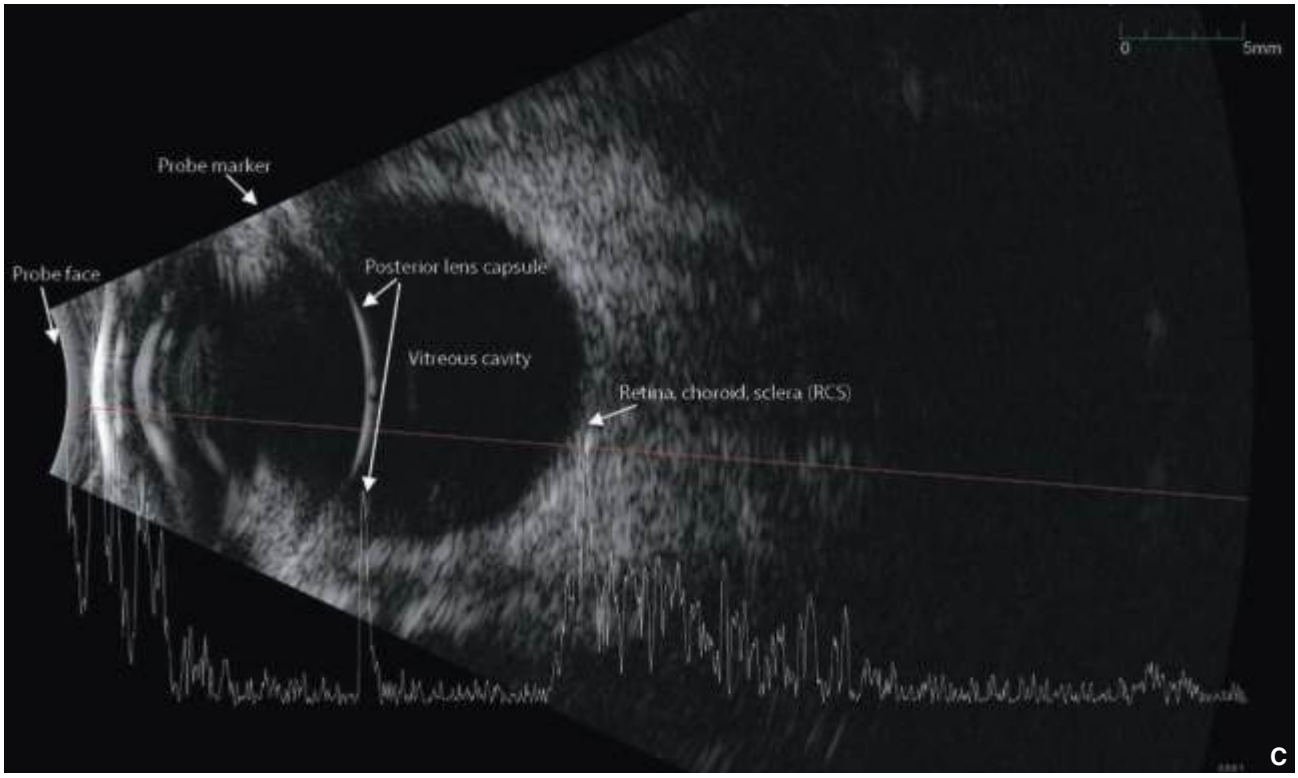


Figure 10.3.2 **A**. A-scan transducer on a dog's eye. **B**. A-scan ultrasound image of a normal dog. The first peak on the left (1) is the transducer/cornea complex, the second peak (2) is the anterior lens capsule, the third peak (3) is the posterior lens capsule, and the last peak is the retina, choroid, and sclera (4), while 5 is the orbital tissues. **C**. B-mode ultrasound image using a 10 MHz transducer with a vector A-scan. The red line corresponds to the vector A-scan at the bottom of the image.

A- scans. Each echo is represented by a dot and the brightness of the dot represents the strength or amplitude of the returning echo (Fig. 10.3.2C). Transducers have a marker to indicate the direction of the slice, which corresponds to an icon in the upper portion of the displayed image on ophthalmic machines. The slice display width of most B-scans approximates 180 degrees. B-scan transducers used on ophthalmic-specific machines typically have a frequency of 10 MHz. Lower-MHz transducers are necessary for orbital imaging, as the penetration of a 10 MHz transducer and the presence of orbital bone do not allow for the consistent ability to characterize orbital lesions well.

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Artifacts in Ultrasonography

Artifacts are images that appear on the display, but do not represent real anatomic or pathologic structures. Acoustic shadows or enhanced signals must be recognized and distinguished from true echoes to avoid false interpretations (d'Anjou & Penninck, 2015; Penninck & d'Anjou, 2015).

External multiple signals result from reverberations between the transducer tip and a highly reflective acoustic interface (Feldman et al., 2009). Examples of objects that produce external multiple signals are the surface of the crystalline lens, an artificial intraocular lens, an air bubble, the sclera, or bone (such as the orbital bone). The multiple reverberations are the result of the reflection of a sound wave of significant magnitude back to the transducer. When this true echo is strong enough, a portion of it will be reflected off the transducer surface and will go back to the original interface. The second wave will then produce a reverberation echo that appears distal to the true echo in the ultrasound image because it takes longer to return to the transducer (Fig. 10.3.3). Additional reverberation echoes may be produced by additional round trips of the sound wave. The true echo and the reverberation echoes are equidistant, and the reverberation echoes usually decrease in strength with increasing distance from the true echo. The most common occurrence of this reverberation artifact in ocular ultrasonography is from the lens capsule (Leo & Carmody, 2011), typically the posterior lens capsule in dogs.

Internal multiple signals occur by reverberations within certain types of foreign bodies or small calcifications. They are associated with the sound beam striking a spherical foreign body, such as a BB pellet, shotgun pellet, or a small bubble of air or gas. Flat foreign bodies with closely spaced, parallel surfaces, such as slivers of glass, can also cause internal multiple signals. Internal multiple signals appear as a chain of closely spaced signals emanating from the foreign body echo, or a "comet tail," a hyperechoic artifact. This is generated by some of the energy from the sound wave being trapped between two reflective interfaces (Feldman et al., 2009). The trapped energy bounces back and forth, with portions escaping and returning to the transducer. This results in a chain of echoes of decreasing amplitude extending from the foreign body. A comet tail artifact can be useful in identifying the type of foreign body.

Strong sound attenuation in a focal area (like coarse calcifications or microcalcification aggregates) causes "posterior shadowing." A geometric, well-defined absence of echoes posterior to an extremely dense (hyperechoic) interface such as bone, calcium, or a large foreign body is due to complete acoustic shadowing. Partial acoustic shadowing leads to reduction of the echoes posterior to a lesion, which occurs in the case of large dense tumors, for example. Shadowing may make evaluation of structures behind the source of shadowing difficult, but can aid in diagnosis. Acoustic shadowing can also occur due to refraction at the edges of a smooth curved interface rather than solely by sound attenuation (Fig. 10.3.4). This occurs at the edge of the globe or from a cystic lesion (Sofferman, 2012).



Figure 10.3.3 B-mode high-resolution ultrasound using a 40 MHz transducer of an intraocular lens luxated into the anterior chamber of a dog (red arrow). Note external multiple signals (white arrows).

Baum's Bumps

Baum's bumps appear as elevation of the peripheral fundus and are B-scan artifacts. These artifacts are thought to be created by refraction of the sound beam as it sweeps through the peripheral aspect of the lens in an axial transducer position. Repositioning the transducer peripheral to the limbus to avoid the lens should eliminate these artifacts.

Routine Globe Evaluation with B-Scans

Most commonly in veterinary ophthalmology, a 10–20 MHz transducer on an ophthalmic-specific system is used to evaluate the intraocular structures, with most practitioners concentrating on the posterior segment. The transducer is usually positioned directly on the globe after application of topical anesthetic. A coupling medium, such as methylcellulose or a thick artificial tear (not ointment), is applied to the transducer face prior to application. Examination through closed lids can be more difficult due to Bell's phenomenon (rotation of the globe with the eyes closed) and attenuation caused by the lids. On the screen, the initial line that appears on the echogram represents the transducer face (often displayed on the left on ophthalmic-specific machines). The transducer marker will correspond to one

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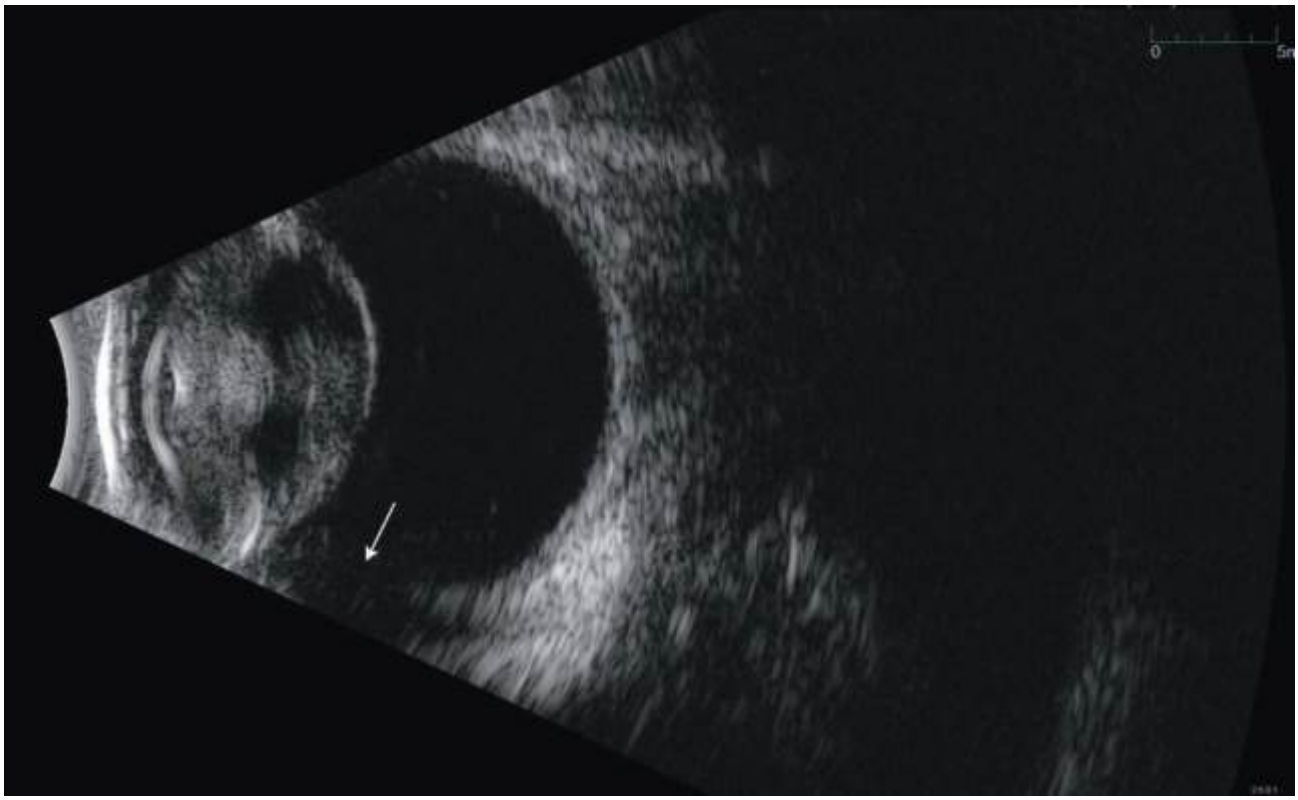


Figure 10.3.4 B-mode ultrasound image using a 10 MHz transducer of a dog with a cataract (note the heterogenous lens). This image demonstrates shadowing or edge artifact due to refraction of sound waves from the curved surface of the globe. This weakens the returning echoes and causes the globe wall to drop out (arrow) and a shadow.

side of the image (usually the top on ophthalmic-specific machines). The operator should know where the marker corresponds to on different systems in order to orient the transducer correctly, and the same approach should be used in order for standardization of the exam. Since the best resolution is in the central portion of the transducer face, lesions should be centered within the ultrasound image whenever possible. A 10 MHz transducer is useful for evaluation of the globe and of the orbit; deep orbital spaces may benefit from lower frequencies, while high-resolution ultrasound (HRUS) is needed to provide adequate imaging of the cornea and anterior chamber, and is discussed later in the chapter. Ultrasonographic evaluation is a dynamic test, and multiple, repeated wide scans, changing the position and orientation of the beam, provide better real-time assessment that cannot be fully rendered by a still image.

To examine the entire globe, and particularly the orbit, with a more complete ultrasound unit, linear transducers offer more appropriate resolution; however, they are more difficult to use on the curved shape of the globe. Sectorial, convex or semi-convex transducers have smaller contact surfaces; however, lateral resolution fades in the far field. Enlisting the aid of an experienced radiologist can greatly increase the quality of the exam. Operators should also be able to select different transducers according to the anatomic sector to be evaluated. Each transducer and frequency has advantages and limitations. Full knowledge of the technical properties of the machine(s) being used will result in a better assessment.

Ultrasound imaging provides the location, density characteristics, and morphology of normal and abnormal tissues, without directly providing the exact composition of the tissue. Although several different ocular conditions manifest with specific ultrasonographic characteristics, specificity and sensitivity may vary, and not all the alterations can be etiologically or pathologically diagnosed with ultrasonography (Gallhoefer et al., 2013).

Transducer Positioning

For standardization purposes, a well-codified sectioning approach should be used, and then personalized, customized sections can be tailored to adapt to the specific case. Standardized examinations and labeling increase the likelihood of accurate evaluation of serial ultrasounds (Sandinha et al., 2017). The transducer landmark, regardless of the frequency or the kind of exam, should be routinely kept dorsal (12 o'clock) or medial (3 o'clock on the right eye or OD, and

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9 o'clock on the left eye or OS) for standardization and orientation of the obtained digital image. Note that labeled clock sections correspond to opposite positions in the two eyes, while the orientation of the image on the screen will be similar.

Because the globe is a sphere, terminology used in section orientation is slightly different from that used in other body sections. Axial sections include the central cornea and the central lens or optic nerve, and are obtained with the transducer on the cornea. The section can be vertical, horizontal, or oblique, and images can be labeled using clock hours according to the position of the transducer marker. Any section that includes the central area of the lens and is paraxial on the cornea is labeled meridional, and can be vertical, horizontal, or oblique (Fig. 10.3.5). Paraxial, parallel sections can also be used and should be labeled latitudinal with the associated orientation (vertical, horizontal, or oblique). Transverse sections are those using the transducer



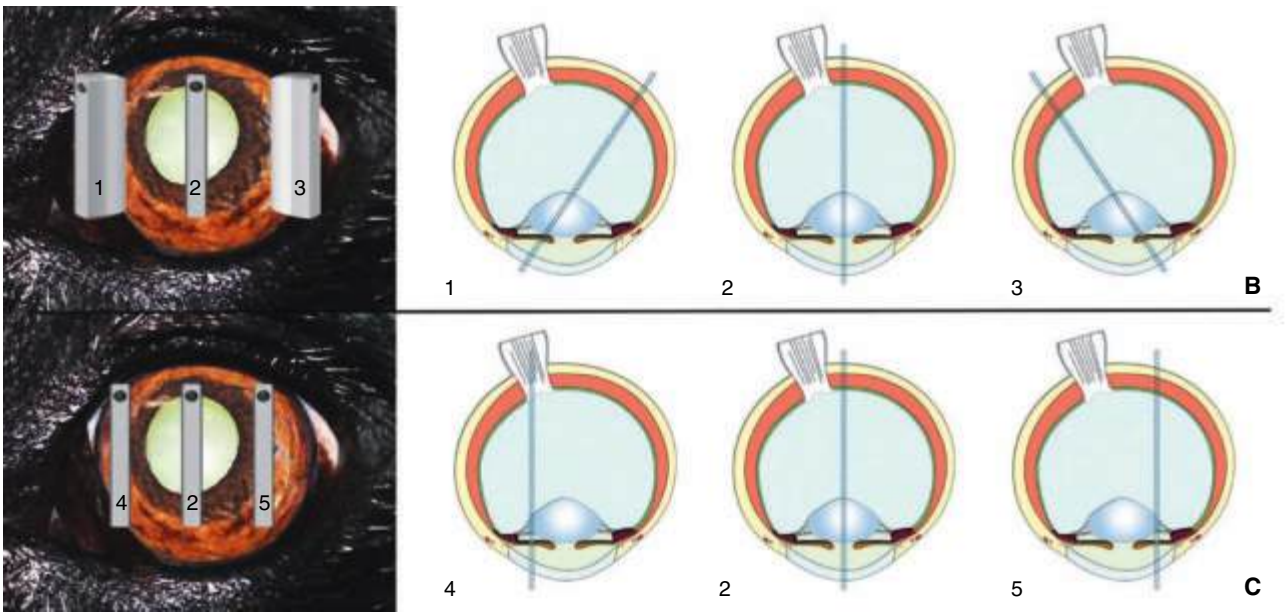


Figure 10.3.5 **A**. 10 MHz sectoral transducer used directly on the cornea of a dog. **B**. Position 1 can be labeled 10 meridional (for the transducer marker at 10 o'clock on the globe face), position 2 is 12 axial, and position 3 is 2 meridional. **C**. Position 4 can be labeled 10 latitudinal, position 2 is again 12 axial, and position 5 is 2 latitudinal. For both orientations, a complete scan can be performed by orienting the transducer perpendicular to the original scan plane, and again labeling by the clock hour of the transducer marker and the orientation. Oblique scans can also be obtained as needed. (Images from Pizzirani, S., Penninck, D., & Spaulding, K. (2015) Eye and orbit. In: *Atlas of Small Animal Ultrasonography* (eds. D. Penninck & M.-A. d'Anjou), pp. 19–54. Ames, IA: Wiley Blackwell).

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perpendicular to the visual axis. Transverse sections can be dorsal, ventral, medial, and lateral as standard exams are performed, and then oblique and differently oriented sections can be used customized to the specific case. Moving the transducer posteriorly can produce equatorial or paraequatorial transverse sections (Fig. 10.3.6).

Lower-frequency transducers should be used for complete orbital evaluation, as their penetration depth is more appropriate for the distances involved. Transcorneal transducer positions can be used, and orbital sections are labeled longitudinal (vertical, horizontal, or clock hours) when the plane of section is along the orbital axis, and transverse (dorsal or lateral, with medial and ventral difficult to perform) when the section is perpendicular to the orbital axis. Longitudinal latitudinal sections are variants and complementary sections. Alternative approaches include a window through the temporal fossa, which is performed by placing the transducer dorsocaudal to the orbital ligament. This is also a useful window when intraocular imaging is needed in a case with severe corneal damage, when information about intraocular anatomy may be crucial. Mesocephalic and dolichocephalic dogs are best suited to this approach (Stuhr & Scagliotti, 1996). An additional approach involves transducer placement inferior to the zygomatic arch caudoventral to the globe, which will allow imaging of the zygomatic gland and ventral orbital space (Pizzirani et al., 2015).

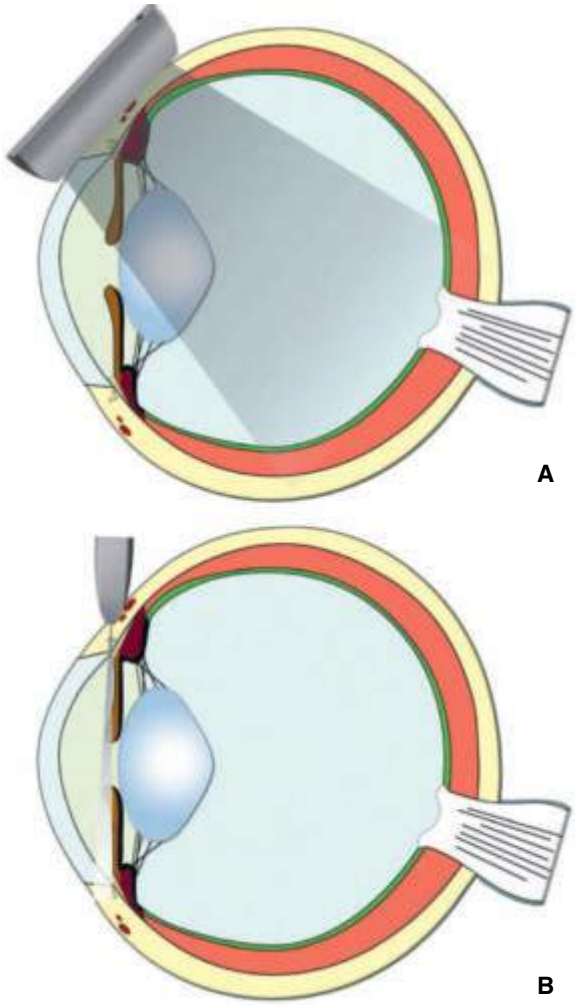


Figure 10.3.6 Perilimbal and limbal approach. Radial (**A**) or transverse (**B**) sections are obtained by placing the transducer on the limbus in dogs with anatomy that allows sufficient limbal exposure. These are labeled by the clock hour of the transducer marker and position (perilimbal radial versus transverse), and can be rotated around the globe as needed. (Images from Pizzirani, S., Penninck, D., & Spaulding, K. (2015) Eye and orbit. In: *Atlas of Small Animal Ultrasonography* (eds. D. Penninck & M.-A. d'Anjou), pp. 19–54. Ames, IA: Wiley Blackwell).

Normal Ultrasonographic Anatomy

When using higher frequencies, the cornea is seen as two parallel echogenic lines divided by a nearly homogenous anechoic space, while the sclera is highly reflective. The well-organized lamellae of the corneal stroma reflect less than the irregular scleral collagen bundles. The gradual transition between the two tissues at the limbus can be easily recognized and provides a useful landmark. The anterior chamber is anechoic, while the iris is echogenic and less well defined than the anterior lens capsule reflector, which is seen as a well-defined hyperechoic line. The normal lens is anechoic; however, the lens capsules are seen as very sharp hyperechoic lines (Thijssen et al., 1985). With age, there is a decrease in water content in the nucleus, and the interfaces between the nucleus and peripheral cortex can be seen as a poorly delineated linear hypoechoic reflection within the lens.

The anterior segment is best imaged with HRUS, as discussed later in this chapter, and/or using a standoff with a lower-frequency transducer. Without a standoff, because of the focal length of the transducer, the most prominent echoes are the posterior lens capsule, which is seen as a curvilinear hyperechoic interface (see Fig. 10.3.2C). The normal vitreous is anechoic, and the posterior eye wall hyperechoic, thicker, and less well defined than the lens capsule. The sonographic posterior wall of the globe is represented ultrasonographically by the retina, choroid, and sclera. In the normal eye, these three layers are sonographically indistinguishable and are referred to as the RCS complex (De La Hoz Polo et al., 2016). The RCS complex is observed as a concave echogenic structure that is interrupted by the optic disc or papilla (a small hyperechoic line). The retrobulbar space contains the orbital cone, including the extraocular muscles, arteries and veins, and optic nerve. The optic nerve and the extraocular muscles may be identified as hypoechoic tubular structures surrounded by hyperechoic fat.

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Ocular and Orbital Abnormalities

The standard 10–15 MHz transducers are not useful for examining the anterior segment. See the section on high-resolution ultrasound for a description of anterior segment abnormalities.

Lens

Cataracts are echogenic. An incipient cataract will have only a small echogenic area corresponding to the area of opacity. Cortical and nuclear opacities may be differentiated. Compared with age-matched eyes, lens thickness will increase with some types of cataracts, such as the osmotic cataracts seen in diabetes (Fig. 10.3.7). Lens thickness will decrease as the lens becomes hypermature and begins to resorb. In these cases, the convexity of the anterior capsule decreases and flattening and wrinkling can be seen, depending on the stage of the cataract. Ultrasound evaluation of equatorial lens is useful to assess possible capsular tears and cortical herniation. Luxated lenses are easily identifiable in an abnormal position. Phacodonesis can be seen with subluxations and the iris may appear more posteriorly positioned. Congenital defects such as persistent hyaloid arteries/persistent hyperplastic primary vitreous (PHPV) and associated lenticonus can be identified with ultrasound. These lesions are important in planning cataract surgery and often cannot be seen through a cataractous lens in the course of normal ocular examination. In these cases, evaluation using a color Doppler (power) mode can be used before surgery to ascertain if vascular patency is present (Fig. 10.3.8).

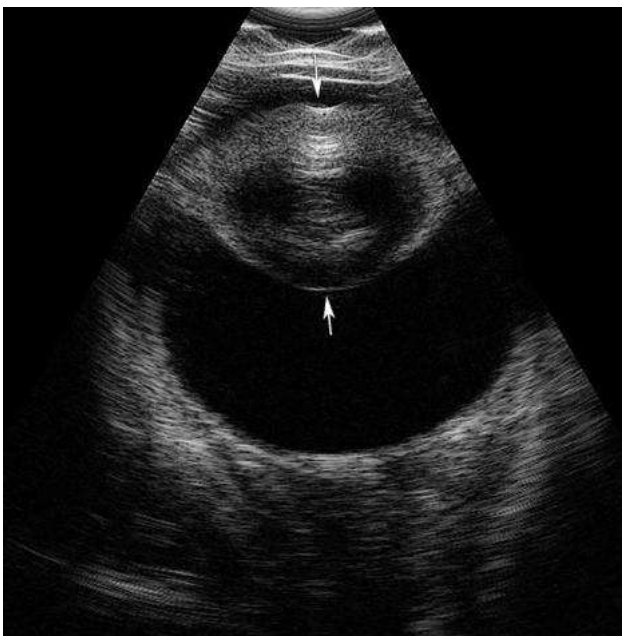


Figure 10.3.7 B-mode ultrasound image using a 20 MHz sectoral transducer of a dog with a diabetic cataract. Note the increased thickness of the lens (arrows), and multifocal heterogenous echogenicity within the lens consistent with cortical and nuclear cataractous changes.

Vitreous

Posterior vitreal detachments are often identified on cataract screening evaluations; however, their significance in veterinary medicine has not been yet determined. They can appear very similar to retinal detachments, but tend to be thinner and less reflective; they usually disappear as gain is decreased. The more echogenic detached retina will continue to be visible, while posterior vitreal detachments (and most vitreal opacities) will rapidly disappear. Evidence of vascular flow can also be helpful to differentiate vitreal membranes from retinal tissue. More difficult is the differentiation of retinal versus nonretinal tissue when thick fibrovascular membranes are present (Fig. 10.3.9). Floaters can often be seen in the vitreous from a variety of causes (Fig. 10.3.10). Typically, vitreal degeneration appears as hyperechoic dots or/and linear strands that are freely floating in the vitreous (Labruyere et al., 2008). Asteroid hyalosis appears as multiple small hyperreflective echoes in the vitreous, and some reverberation artifact is possible in the most advanced cases. In synchysis scintillans, the crystals are freely floating because of associated vitreal syneresis, assume different positions depending on ocular movements, and sink due to gravity when the globe is steady.

Differentiation of vitreal hemorrhage, exudates, and tumors can be difficult (Gallhoefer et al., 2013) since they are all similarly hyperechoic. Vitreal hemorrhage varies in appearance depending on the location, amount, and duration. With severe vitreal hemorrhage, the entire posterior segment may appear hyperechoic, while with focal, confined hemorrhages, opacities of varying size can occur. Hemorrhage tends to settle ventrally, and fresh hemorrhage will move with eye movement. If pseudomembranes or fibrovascular membranes occur (making hemorrhage appear to be a retinal detachment), they must be followed carefully to determine their endpoint. Pseudomembranes from hemorrhage or inflammatory exudate will end in the vitreous, while retinal detachments will still be attached at the optic nerve at least, if not the ora ciliaris retinae. In some cases, differentiation between retinal detachments and fibrovascular membranes is still difficult (see Fig. 10.3.9). Hemorrhages and exudates are more likely to disappear as gain is decreased than tumors, but differentiation with this method becomes more difficult in chronic cases. While fresh hemorrhage is usually less echogenic, older, organized hemorrhage can be more echogenic and therefore may not disappear with decreased gain (Fig. 10.3.11). Careful monitoring over time with consistent transducer positioning and gain settings can help to distinguish hemorrhage or exudate from

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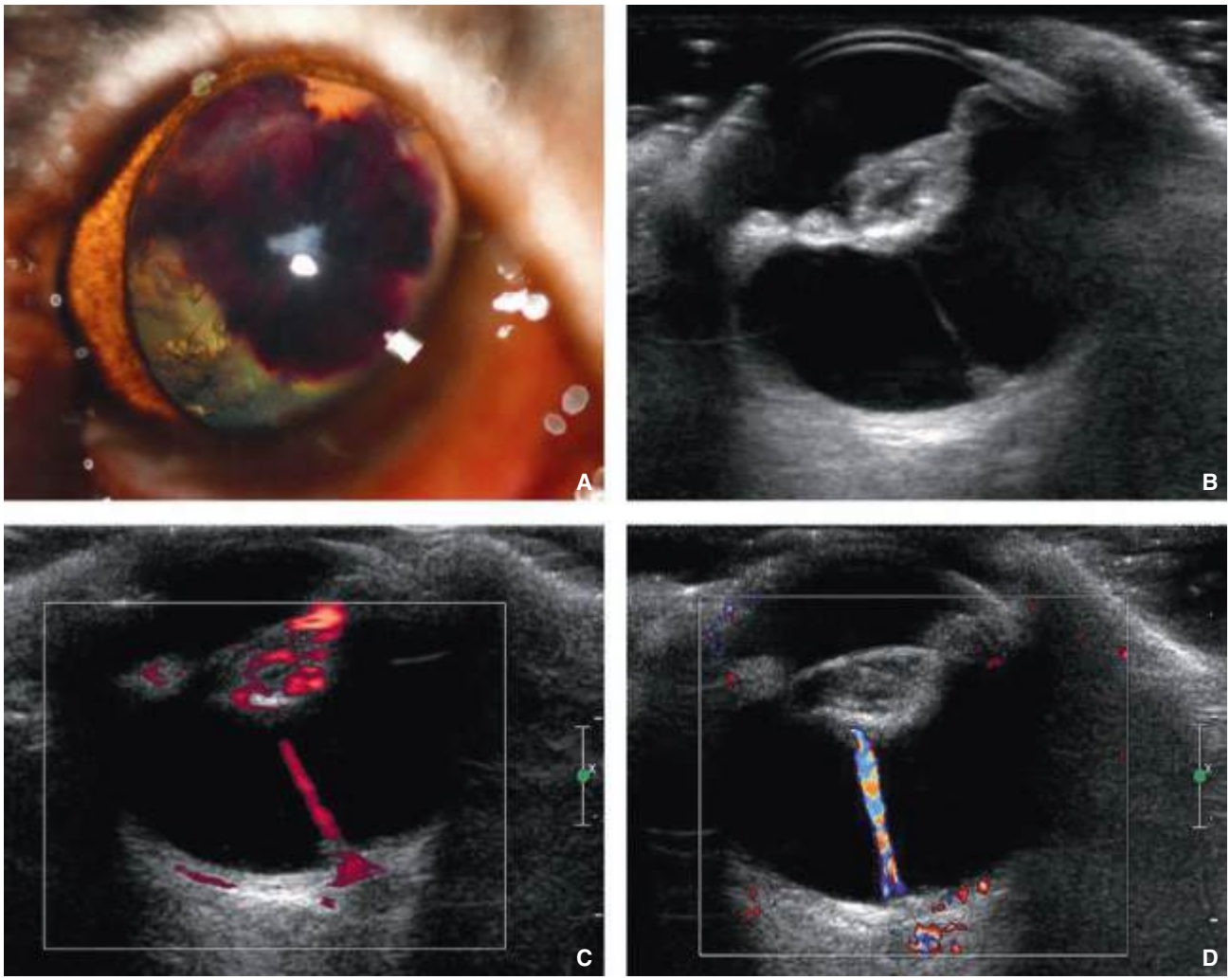


Figure 10.3.8 Persistent hyaloid vasculature in a dog. **A**. Clinical photo demonstrating cataract and intralenticular hemorrhage. **B**. Two-dimensional B-mode ultrasound vertical axial image, demonstrating a heterogenous and irregular lens, with a thin linear echogenic strand extending from posterior lens capsule to optic nerve, consistent with persistent primary vitreous/hyaloid vessel. **C**. Power Doppler confirms vascularization of the lens. **D**. Continuous wave Doppler demonstrates blood flow within the vessel.

tumors. Special techniques such as Doppler and contrast-enhanced ultrasound may be useful as well, and are discussed later in this chapter (Bertolotto et al., 2014; Lacelli et al., 2009; Sconfienza et al., 2010).

Other lesions that can be identified in the vitreous are foreign bodies. These are typically highly reflective and may or may not cause shadowing or multiple echoes, depending on their composition.

Retina

Retinal detachments are probably the most common indication for ophthalmic ultrasound. The classic appearance of a retinal detachment is the "gull"-wing appearance, which occurs when the retina remains attached at the ora ciliaris retinae and the optic nerve. However, a detached retina can have many different ultrasonographic appearances, depending on whether it is acute or chronic, partial or complete, exudative or disinsertional (rhegmatogenous or tractional). Following a membrane located on an ultrasound examination to the optic nerve will generally confirm a retinal detachment. Again, when the gain is decreased, the reflective retina will remain on the image while the less echogenic vitreal opacities will often disappear. Contrast-enhanced ultrasound or Doppler (power) mode can also be used to recognize retinal vasculature. Subretinal exudate is generally associated with hemorrhage or infection, and will appear echogenic and often homogenous posterior to the retina (Fig. 10.3.12). In many cases veterinary ophthalmologists examine patients with chronic retinal detachments, when retinal gliosis may cause a highly reflective membrane that will appear thickened and hyperechoic.

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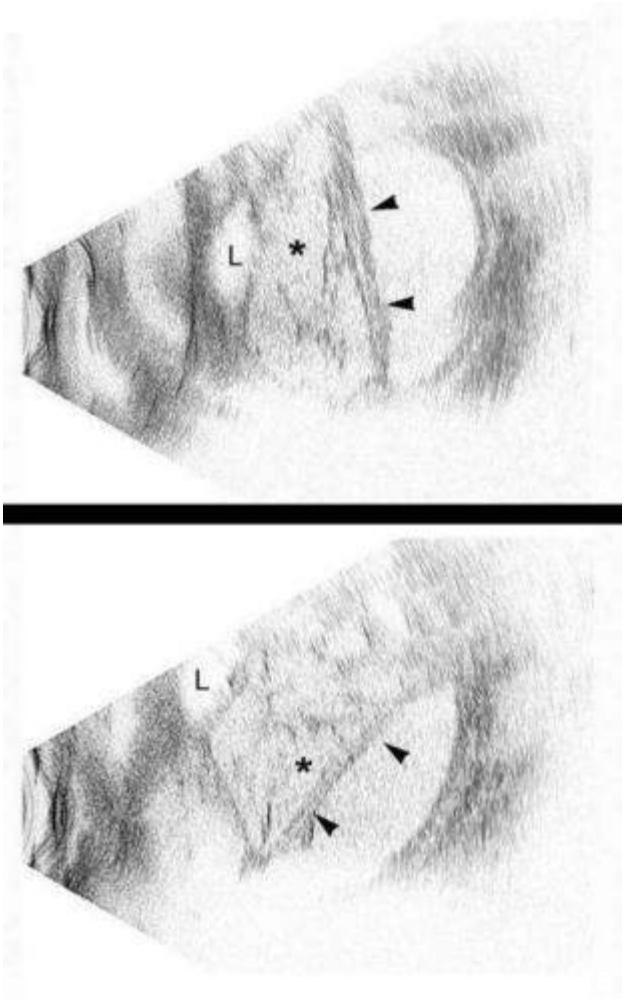


Figure 10.3.9 B-mode ultrasound using a 10 MHz transducer. Two different meridional sections of the right eye of a Golden Retriever, presented for severe corneal edema, intraocular hemorrhage, and chronic glaucoma. Eye was enucleated and found to be affected with canine ocular gliovascular syndrome. Note hyperechoic fibrogliovascular membranes subtending the vitreal cavity in different directions (arrow heads). The hypoechoic homogenous material within the membrane frame represents hemorrhagic material (asterisks). L, lens.

Choroid

Chorioretinitis typically appears as a thickening of the RCS complex (Fig. 10.3.12B). Although the resolution may be not ideal for this diagnosis, usually an increased-thickness hypoechoic zone is seen between the more echogenic retinal and scleral layers.

Sclera

Scleral ruptures can be identified in trauma with careful examination to identify a loss of continuity. Often a hemorrhagic track will lead to the area of scleral rupture. Posterior

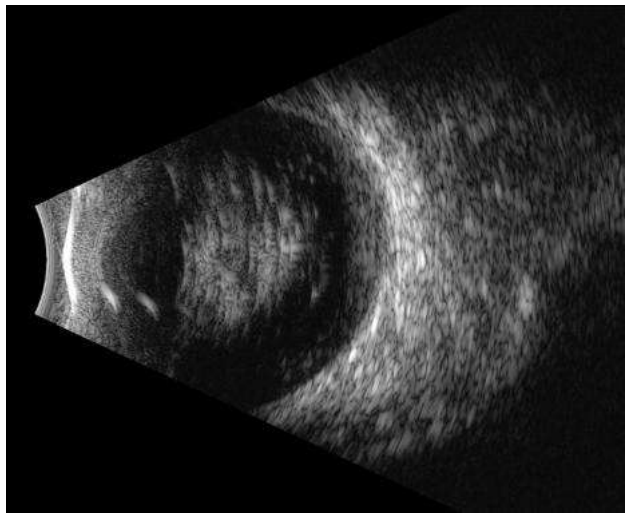


Figure 10.3.10 B-mode ultrasound image using a 10 MHz transducer in the 12 axial position of asteroid hyalosis in a dog. Note the multifocal echogenic punctate to coalescing foci in the vitreous cavity.

scleritis has a typical ultrasonographic appearance (McCluskey et al., 1999) of diffuse thickening of the posterior sclera, often associated with diffuse retinal and choroidal thickening (Fig. 10.3.13). Elongation of the globe can also be possible, and the vitreal cavity can be deformed to almost a triangular shape with a posterior vertex. Episcleral inflammation causes distention of sub-Tenon's space, producing a hypoechoic space outside the globe. When this occurs around the optic nerve, it is referred to as the "T-sign" (Byrne & Green, 2002).

Orbit

Orbital disease can cause ultrasonographic deformities of the posterior aspect of the globe; blunting of the posterior aspect of the globe; diffuse increased or decreased echogenicity of the retrobulbar space, prohibiting delineation of the optic nerve; and discrete hypo/hyperechoic, sometimes cavitated masses in the retrobulbar space (Mason et al., 2001). Tumors have variable echogenicity, can cause deformities of the posterior aspect of the globe, and appear as discrete or infiltrative masses depending on their nature (Fig. 10.3.14). Inflammatory retrobulbar processes can be diffusely heterogenous to distinct hypoechoic or heterogenous masses. Diffuse, hypoechoic, ill-defined, nondeforming lesions are most consistent with cellulitis. Although some retrobulbar masses can mimic an abscess, the latter is more likely when fluid contained in an ill-defined thick hyperechoic wall is identified. Clinical signs and history are helpful, while aspirates and biopsies have higher diagnostic yield.

Orbital cysts have thinner walls and usually less echoic content. These lesions can be differentiated by ultrasound-guided aspirates. Orbital foreign bodies are challenging to

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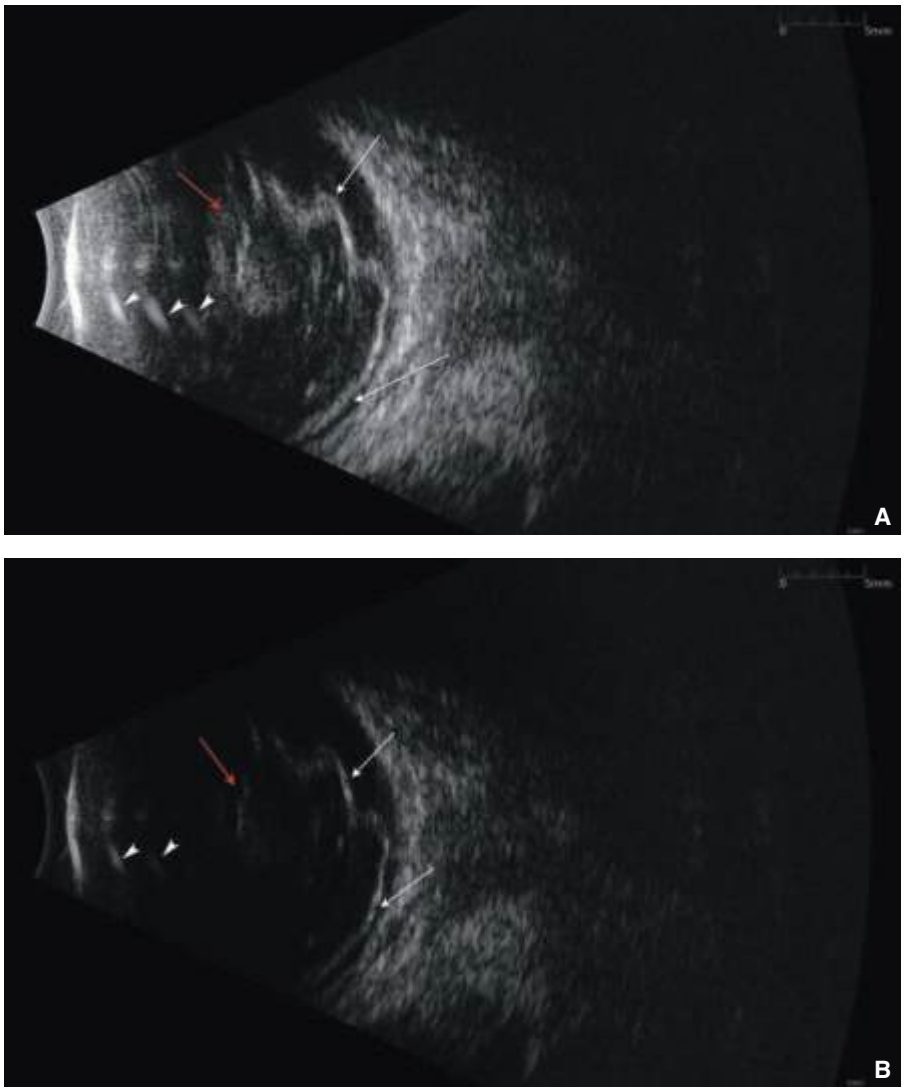


Figure 10.3.11 B-mode ultrasound images of a dog. **A**. Note vitreal hemorrhage (red arrow) and retinal detachment (white arrows) with gain at 90 dB. Arrowheads denote reverberation artifact due to interaction of the sound wave with a highly reflective surface, in this case the corneal/gel interface. **B**. Same image as **A**, with gain of 57 dB. Note that the hemorrhage has faded from the image, while the retina remains.

image; however, orbital ultrasonography can be very helpful, depending on the composition, size, and location of the material. Shadowing and reverberations are possible. Tubular materials like porcupine quills can be identified, although with smaller plant materials both sensitivity and specificity are not reliable (Welihozkiy et al., 2011). The optic nerve may become diffusely enlarged due to inflammation; diffuse or focal enlargements can also be caused by neoplasia. Extraocular muscles will increase in volume and become hypoechoic due to myositis. Other cross-sectional imaging techniques such as CT and MRI can provide a better evaluation of the complex structures of the orbit, particularly given that the bone surrounding the orbital cone limits sonographic assessment (Boroffka et al., 2007; Penninck et al., 2001), and are often used in conjunction with ultrasound.

High-Resolution Ultrasound/ Ultrasound Biomicroscopy

Visualization of the relationship between living tissues *in vivo* at a microscopic level is a goal of many imaging modalities. Higher-frequency ultrasound transducers have been developed with frequencies ranging from 20 MHz (HRUS) to 60 MHz (UBM), which allow imaging at axial resolutions comparable to low-power microscopic views (20–80 µm; Coleman et al., 2006). Conventional 10 MHz transducers

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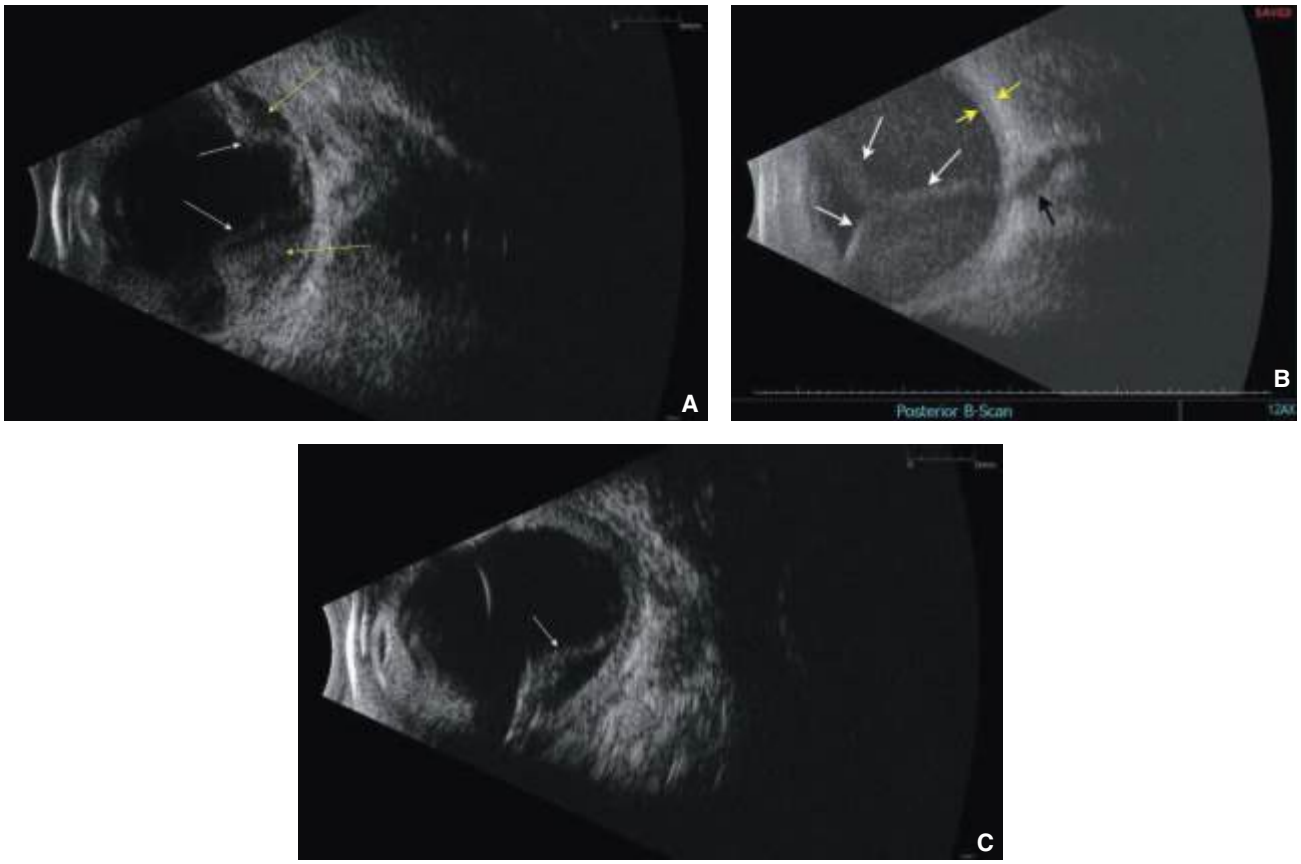


Figure 10.3.12 B-mode ultrasound images using a 10 MHz transducer. **A**. Image of a dog with blastomycosis. Note retinal detachment (white arrows) and subretinal exudate (yellow arrows). **B**. Sonogram of a dog with blastomycosis. Again, note extensive retinal detachment (white arrows) and less defined subretinal exudate. Also note thickened choroid (yellow arrows) and optic nerve (black arrow). **C**. Partial retinal detachment in a dog without subretinal exudate (arrow).

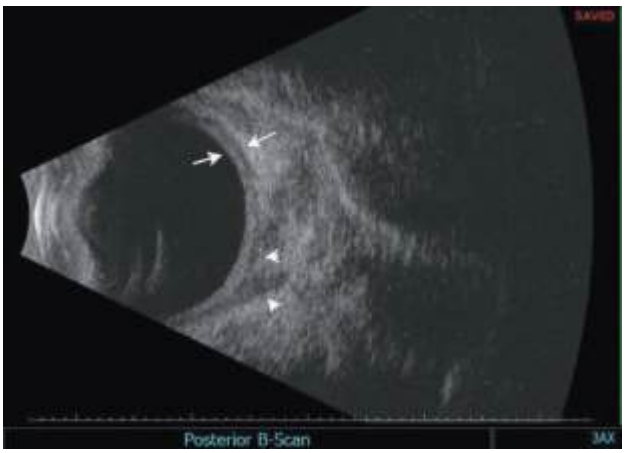


Figure 10.3.13 B-mode ultrasound image using a 10 MHz transducer of a dog with scleritis. Note the thickened retina, choroid, sclera complex (arrows) and the hyperechoic space external to the globe (arrowheads), suggestive of scleritis.

have axial and lateral resolutions of about 200 and 500 µm, respectively (Pavlin & Foster, 1998). With improved image detail afforded by the higher-frequency transducers, tissue penetration is limited to 5–15 mm. For ophthalmic applications, however, the critically important but optically occult structures of the anterior segment of the eye are within this range (Bentley et al., 2003).

Clinical ophthalmic applications of HRUS in physician-based ophthalmology include evaluation of anterior segment tumors and cysts, scleral disease, intraocular lens assessment, trauma, and differentiation of the various forms of glaucoma. Several *in vivo* studies using UBM in dogs have been published (Aubin et al., 2003; Crumley et al., 2009; Gibson et al., 1998; Rose et al., 2008). Although these studies showed the promise of UBM, originally UBM required heavy sedation or general anesthesia in small animal patients, because obtaining an image involved using a water-filled cup for the exposed oscillating transducer, which made patient positioning critical. These limitations have gradually been decreasing as higher and higher-resolution handheld transducers with covers have been developed (Bentley et al., 2003, 2005). Imaging with currently available handheld high-resolution transducers (20–50 MHz) does not typically require anesthesia or sedation, and can be performed with the animal sitting in almost any position. The investigation

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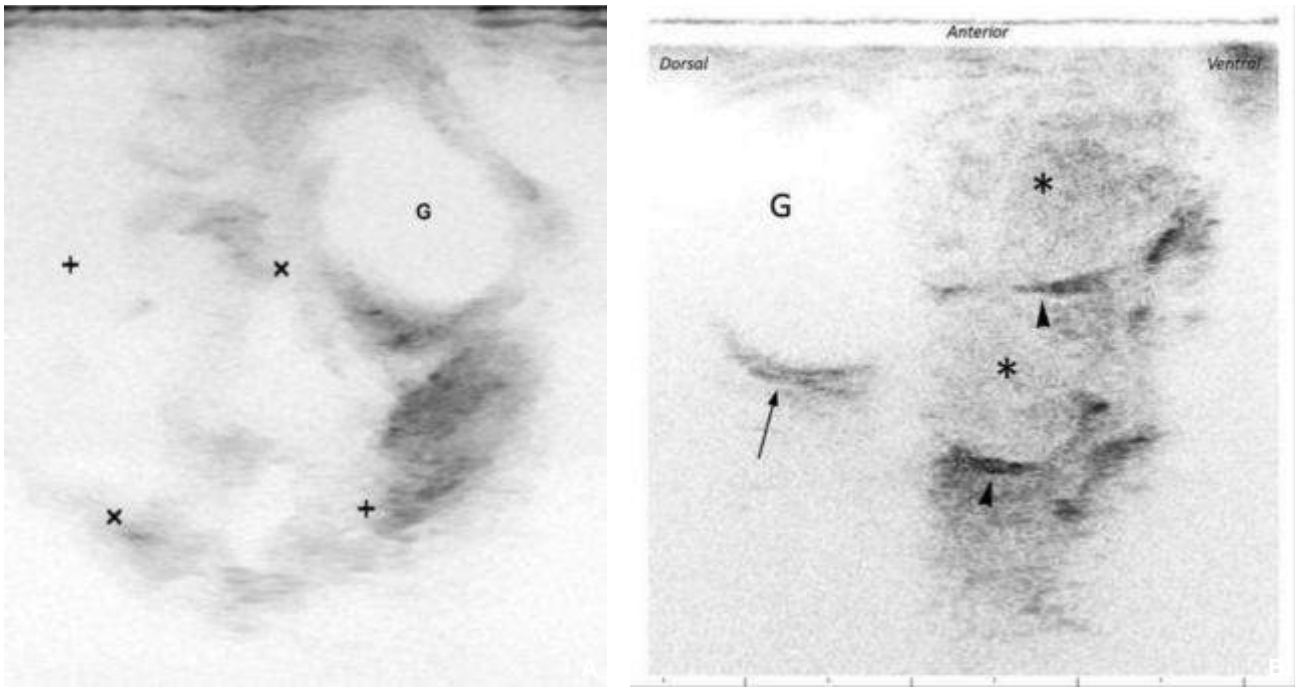


Figure 10.3.14 **A**. B-mode ultrasound image of a retrobulbar abscess in a dog using a high-frequency linear transducer. Note the heterogenously hypoechoic cavitary mass posterior to the globe (G; mass margins delineated by crosses). Retrobulbar fat is abnormally hyperechoic. **B**. Canine patient affected with adenocarcinoma of the third eyelid. Longitudinal vertical section of the orbit, B-scan, linear 15 MHz transducer. The globe is anechoic (G) while the posterior wall is hyperechoic (arrow). Ventrally to the globe there is a large (25 mm × 20 mm) hyperechoic, slightly heterogenous lobulated mass associated with the rostral and medial aspect of the orbit (asterisks). The mass is encapsulated (arrowheads) and does not appear to invade the adjacent bone, globe, or retrobulbar tissues. (Courtesy of Federica Maggio.)

of medioventral sectors is, however, difficult due to the size of the transducer, the presence of a third eyelid, and the proximity of the nasal bones. Brachycephalic breeds are obviously easier to examine.

Technique

Most animals can be examined with manual restraint while sitting or in sternal recumbency following administration of topical anesthetic agents. Some animals may require light sedation and/or need to be examined in lateral recumbency. The transducer can be easily positioned to examine the superior and temporal quadrants of the eye, but light to deep sedation may be required in some cases to accurately examine the ventral and nasal quadrants.

The eyelids are manually held open and the transducer is placed directly over the cornea or sclera. To examine the peripheral cornea and sclera, iridocorneal drainage angle, iris, ciliary body, and lens, scans are obtained with the transducer held perpendicular to the globe and the scan plane perpendicular to the direction of the limbus (radial paraxial limbal transducer position). To examine multiple ciliary processes circumferentially and the iris tangentially, the transducer is held perpendicular to the globe with the scan plane parallel to the limbus (transverse transducer position) and perpendicular to the visual axis (Fig. 10.3.15). Images are generally labeled with the clock hour and transducer position. Structures and distances can be measured using the internal calipers on the ultrasound machine.

Cornea/Sclera

The cornea is seen as two parallel reflective lines with a hypoechoic to anechoic space between them, in contrast to the highly reflective sclera. The limbal anatomy should be identifiable in normal eyes. Corneal thickness may be assessed with a high-resolution transducer, although an ultrasound pachymeter is likely more accurate and easier to use (Al-Farhan & Al-Otaibi, 2012; Fante et al., 2013; Jeong et al., 2017). Both tumors and sequestra are hyperechoic. HRUS can be used to assess lesion depth, although our experience suggests that it is more accurate for tumor depth than sequestrum depth due to shadowing in thick sequestra. In less dense sequestra, the most superficial portion of the sequestrum corresponds with the hyperechoic signal on the ultrasound image, while the less stained deep tissue may appear normal on ultrasound (Bentley et al., 2003). The faint pigment seen clinically probably does not cause enough alteration of the corneal stroma to reflect more than normal tissue, which correlates with the minimal changes seen histopathologically on

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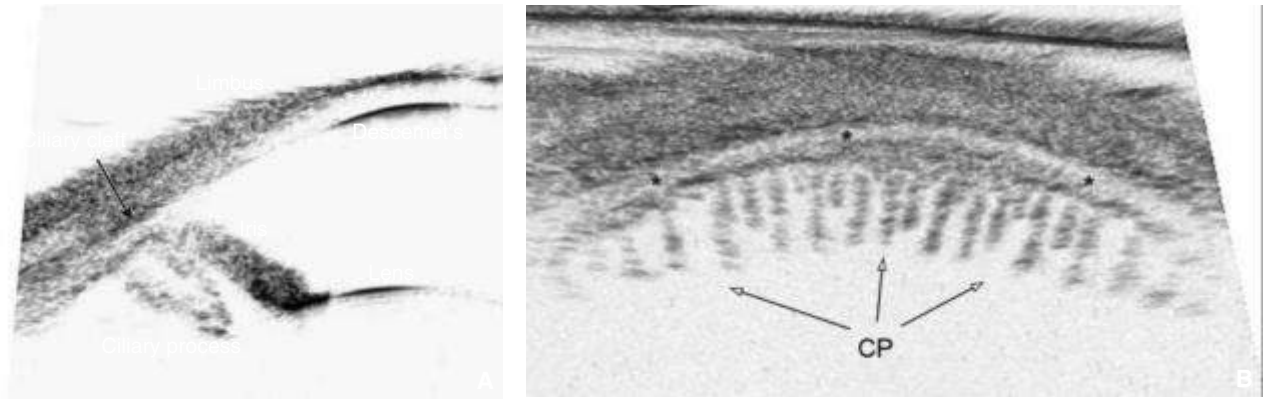


Figure 10.3.15 **A**. B-mode ultrasound of a normal dog with a 40 MHz transducer in the radial position with section perpendicular to the limbus. Note the labeled normal structures. **B**. B-mode ultrasound of a normal dog with the transducer in the transverse position. Note the slender hyperechoic structures corresponding to the ciliary processes (CP) and the thin, linear hyperechoic space adjacent to the ciliary body (asterisks), which corresponds with the ciliary cleft.

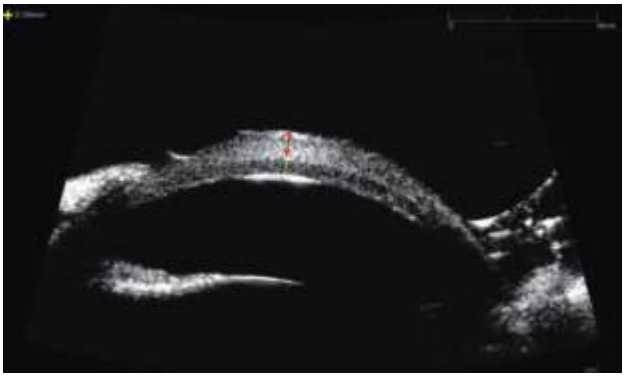


Figure 10.3.16 A B-mode ultrasound using a 40 MHz transducer to evaluate corneal sequestrum in a cat. Note the internal calipers on the machine used to measure normal less echoic cornea (yellow double arrows, 0.39 mm), underlying the more hyperechoic sequestrum (red arrows).

such lesions. Nevertheless, useful information regarding depth can be obtained preoperatively with a high-resolution transducer (Fig. 10.3.16). HRUS can also be useful for determining the extent of intraocular extension of superficial tumors, like epibulbar limbal melanocytomas, evaluation of episcleral nodules, granulomatous episcleritis, and possible staphylomas. HRUS of the cornea can be used to confirm the cystic cavity in epidermal inclusion cysts.

Anterior Chamber

The anterior chamber can be evaluated for the presence of exudate, hyphema, fibrin, and other abnormal pathologic variations. Most anterior chamber exudates are echogenic and often move with eye movement. Congenital abnormalities, such as Peters' anomaly, can be identified as posterior keratoconus, endothelial plaques, and strands of iridal tissue spanning from iris to cornea (Fig. 10.3.17). Changes in anterior chamber depth can also be evaluated via HRUS, which can be useful in cases of lens luxation or some types of glaucoma (Czederpiltz et al., 2005). Using the contralateral normal eye as a control can be useful to determine changes in anterior chamber depth. When used for this purpose, positioning of the transducer is critical. The operator should look for symmetry of the iridal leaflets and be careful not to exert pressure on the axial cornea. Using abundant surface gel is usually helpful.

Uvea

The iris should appear as a moderately hyperechoic leaflet with somewhat ill-defined margins. Its shape and thickness vary depending on pupil size. The ciliary body appears as a triangular leaflet when the transducer is positioned correctly. However, a full ciliary process is not imaged in every position. Full assessment of multiple ciliary processes is best achieved through the transverse paralimbal position (Fig. 10.3.15B).

Differentiation between iris cysts and iris masses, as well as evaluation of tumor extent, is facilitated by a high-resolution transducer (Bentley et al., 2003; Taylor et al., 2015). Cysts can appear as thin-walled, fluid-filled structures, or anterior displacement of the iris due to the cysts can be noted. Difficult cases are those in which the cysts are peripheral and posterior to the iris, causing an apparent mass lesion. Careful assessment of the posterior aspect of the iris for anterior bowing on ultrasound is usually diagnostic, even if cysts cannot be easily imaged due to their thin walls (Fig. 10.3.18). One study found that 14 of 15 feline eyes submitted for tumors that were not found on histopathology had cysts (Fragola et al., 2017). Only one of these eyes had prior ultrasound, performed with a 10 MHz transducer, suggesting that HRUS is underutilized for assessment of these conditions. Cysts located peripherally in the medial and ventral sectors can also be challenging to visualize. Identification of cystic cavities in corpora nigra in horses is helpful in cases where they may not be obvious clinically, and ultrasound can provide useful information for treatment or longitudinal monitoring (Fig. 10.3.19). Tumors are easily recognized as

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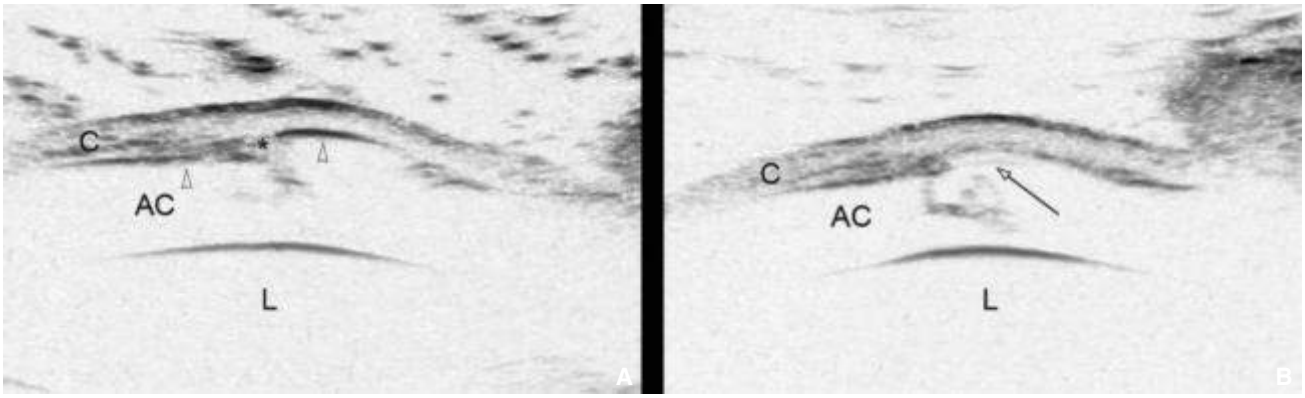


Figure 10.3.17 Axial and paraxial views with a 35 MHz sectorial transducer of the anterior chamber (AC) in a 6-month-old Dachshund with corneal opacities and Peters' anomaly. **A**. The different thickness of the cornea (C) is highlighted with the two arrowheads that point to a Descemet's membrane (hyperechoic discrete lines) on different levels due to embryologic neurocrest tissue attached to the endothelial aspect of the cornea. The asterisk corresponds to an area of absent Descemet's with a strand of tissue extending into the anterior chamber (AC). **B**. Descemet's membrane cannot be clearly visualized, likely due to a minor posterior keratoconus. A strand of neurocrest tissue is spanning from the iris to the cornea (arrow). L, lens.

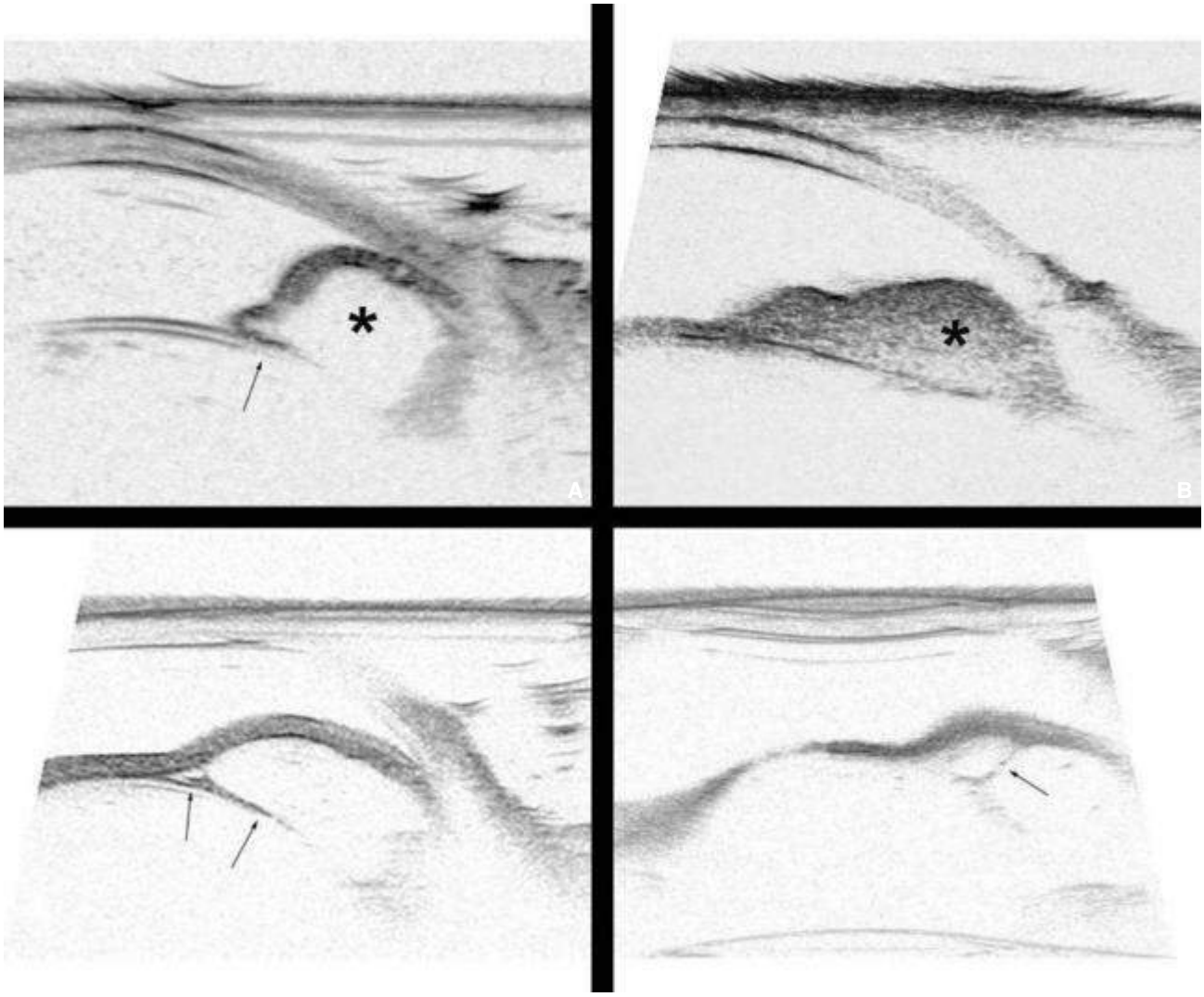


Figure 10.3.18 High-resolution ultrasound with 35 MHz transducer of the anterior chamber in three canine patients presenting with similar findings of focal anterior iris bulging. Ultrasonography allows characterization of the different lesions. **A**. Dog with iris bombe caused by posterior synechia (arrow). The asterisk marks the posterior chamber behind the iris. **B**. Dog with iris neoplasia. The mass is composed by solid homogeneously and moderately hyperechoic tissue (*; histopathology revealed iris melanocytoma). **C** and **D**. Golden Retriever with multiple iridociliary cysts causing dilation of the posterior chamber and bowing forward of the iris. The arrows indicate the thin hyperechoic capsule of the cysts.

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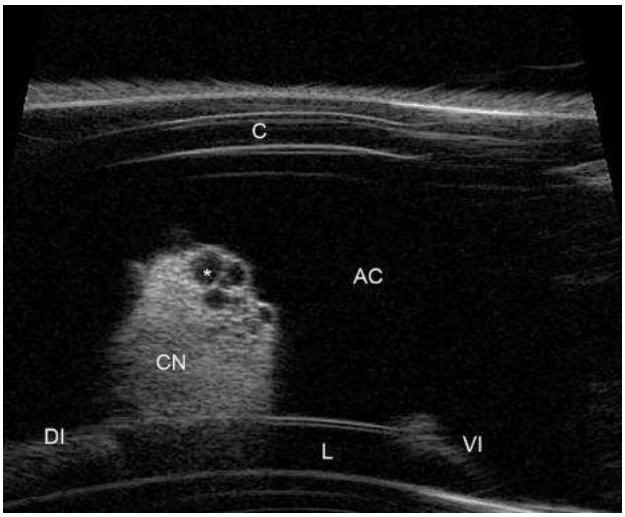


Figure 10.3.19 Ultrasound biomicroscopy scan of the anterior chamber in a horse using a 35 MHz sectorial transducer. Vertical axial section through the pupil. The corpora nigra (CN) is usually hyperechoic. In this case four small cysts (asterisk, anechoic voids) are present. Standard B-scan transducers will not detect the cystic cavities. AC, anterior chamber; C, cornea; DI, dorsal iris; L, lens; VI, ventral iris.

hyperechoic masses, and judging the extent of the tumor is helpful to determine appropriate treatment options. HRUS is better for identifying peripheral iridal and ciliary body extension of the neoplastic process when compared to conventional B-scans (Conway et al., 2005). HRUS can also be used to locate the ciliary processes for more accurate transscleral cyclophotocoagulation.

Lens

The high-resolution transducer can be useful to evaluate the lens for peripheral lens capsule ruptures, which cannot be easily seen with slit-lamp biomicroscopy. UBM transducers with frequencies of 35 and 50 MHz do not penetrate beyond the anterior cortex and can be used to evaluate changes in the anterior and equatorial lens only. Because of the much higher resolution and the impedances between the aqueous and the anterior lens capsule and the anterior lens capsule and the anterior cortex, two defined hyperechoic lines in the anterior lens are normally detected with UBM transducers.

Iridocorneal Angle and Uveal Drainage System

The iridocorneal angle and the ciliary cleft can be easily identified with both paraxial radial and transverse positions of the transducer. The ciliary cleft appears as a hypoechoic space between the ciliary body and the sclera, and often has a teardrop or rectangular shape. Measurement of the aperture is difficult due to the indistinct boundaries and lack of objective landmarks. The ciliary body base becomes more echoic with age due to deposition of collagen at the base of the ciliary processes. The assessment of the ciliary cleft is complementary to gonioscopy. Evaluation of the ciliary cleft can be useful in evaluating glaucoma patients or potential glaucoma patients, as the ciliary cleft can be assessed as being open or closed (Fig. 10.3.20). A narrow or closed ciliary cleft in animals predisposed to glaucoma has been shown to increase the risk of glaucoma development (Dubin et al., 2017). Evaluation of the iridocorneal drainage angle and ciliary cleft is also a tool to investigate the mechanism by which various antiglaucoma drugs lower intraocular pressure in domestic animals (Gomes et al., 2011; Kawata & Hasegawa, 2013; Kawata et al., 2010; Kwak et al., 2017; Tsai et al., 2012).

Contrast-Enhanced Ultrasonography/ Doppler

One study in veterinary medicine has correlated histopathologic diagnoses with ultrasonographic diagnoses, and found overall acceptable correlation for most categories (neoplasia, hemorrhage, retinal detachment, subretinal exudate; Gallhoefer et al., 2013). Some findings, such as retinal tears, were not often detected via ultrasonography, and the ability to diagnosis other categories, such as subretinal exudate, varied by location. This study found that it can be difficult to differentiate hemorrhage from neoplasia, and that clinicians should be cautious when trying to determine ultrasonographic diagnoses in eyes with extensive solid, nonfloating hemorrhages. Additionally, several cases were identified with vitreous membranes that looked remarkably similar to retinal detachments on ultrasonography. Therefore, other methods to differentiate blood from intraocular masses and definitively determine retinal detachments could be a useful addition to clinical ultrasound.

In 1968, investigators reported visualizing cardiac shunts with ultrasound using air bubbles via injection, and CEUS began (Gramiak & Shah, 1968). Free air bubbles were too large to pass in the pulmonary circulation, which limited their use. Over time, specific contrast ultrasound agents were developed for intravenous use, typically in a bolus. These agents are essentially high molecular weight/low solubility gas microbubbles (perfluorocarbons or sulfur hexafluoride) stabilized by a lipid polymer or albumin shell (Haers & Saunders, 2009: Seiler et al., 2013). These bubbles can pass through the pulmonary circulation given their small size (1–10 μm) and have a longer half-life than normal air bubbles. Ultrasound contrast agents are strictly intravascular, making them ideal for differentiating vascular versus avascular structures, such as intraocular tumors versus hemorrhage or retinal detachment in the face of hemorrhage or vitreal membranes.

Unfortunately, B-mode, grayscale imaging results in poor detectability of ultrasound contrast agents in tissue. The

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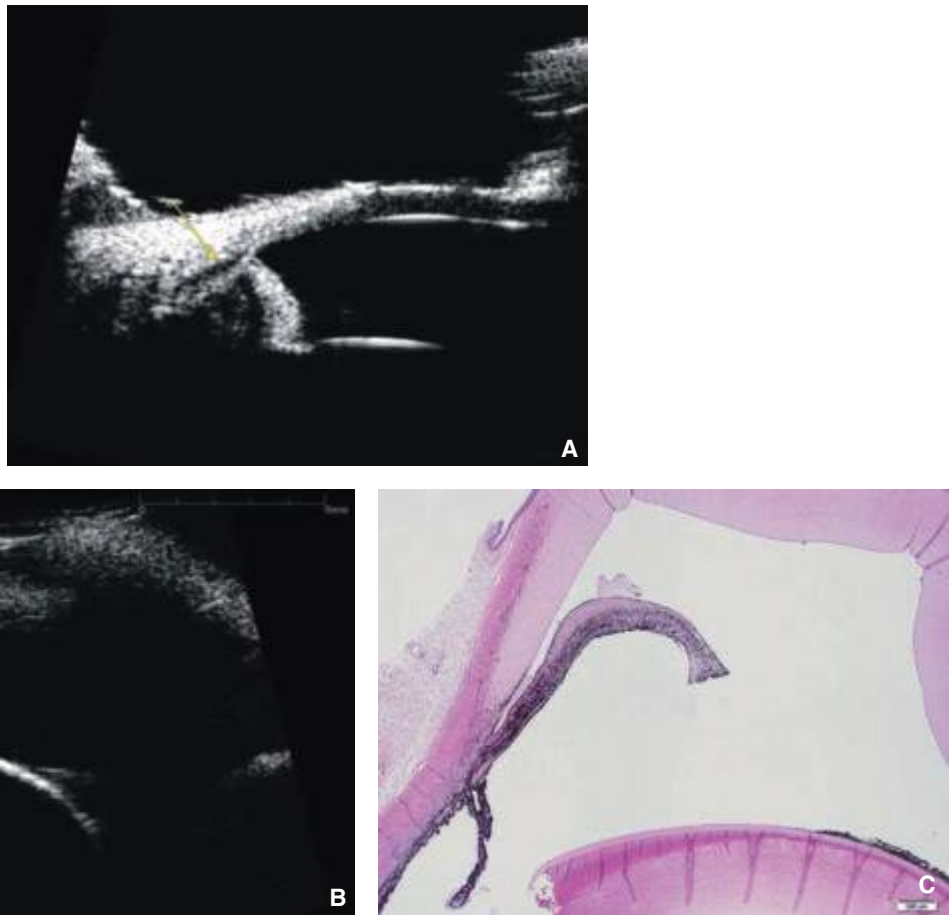


Figure 10.3.20 **A**. B-mode ultrasound image using a 40 MHz transducer of the normal eye of a dog affected with glaucoma in the contralateral eye. Note the open ciliary cleft in the radial 12 o'clock position. **B**. B-mode ultrasound image using a 40 MHz transducer in the eye of a dog affected with secondary glaucoma. Note the ciliary cleft cannot be imaged. **C**. Subgross view of the same eye imaged in **B**. Note the correlating absence of identifiable ciliary cleft. (Courtesy of the Comparative Ocular Pathology Laboratory of Wisconsin.)

microbubbles of ultrasound contrast agents are very small and behave as scattering reflectors, and the microbubbles expand and contract when insonified, which means they produce echoes that are at multiples of the fundamental (transducer) frequency (i.e., harmonics; Haers & Saunders, 2009; Silverman et al., 2005). At the fundamental frequency, contrast agents are echogenic only at high doses and are severely attenuating, which means that signal strength is lost deep to enhanced structures. Fundamental imaging generally utilizes a high acoustic output, which is destructive to the circulating microbubbles, limiting their longevity. In order to better image the contrast agents, contrast harmonic imaging is used. Contrast harmonic imaging utilizes the nonlinear oscillation of the contrast agents, which occurs due to the expansion and contraction of the contrast agent microbubbles as sound passes through them, which then generates harmonic frequencies. Harmonic imaging is a technique in which the beam is sent at one frequency (fundamental or transducer frequency) while the machine receives a different returned frequency.

An initial small study in veterinary patients noted an anaphylactic reaction to Optison™ (perflutren protein type A; GE Healthcare, Princeton, NJ, USA) in two dogs (Yamaya et al., 2004). A later study (Seiler et al., 2013) evaluated the safety of ultrasound contrast agents in 488 dogs and cats that received an ultrasound contrast agent compared to 262 patients that had ultrasonography alone. Only dogs were noted to have adverse effects, and those were vomiting and syncope, occurring in 0.2% of dogs (Seiler et al., 2013).

In an experimental setting, visualization of the normal rabbit choroid was possible, and iatrogenic avascular lesions could also be demonstrated (Hirokawa et al., 2002). High-frequency ultrasound was used to assess experimentally induced choroidal melanomas in mice and rabbits, and findings correlated well with histology (Kang et al., 2013).

Early studies in physician-based ophthalmology demonstrated the utility of CEUS in evaluation of tumors, mostly choroidal melanomas. Prior to treatment, choroidal melanomas were well perfused on contrast harmonic imaging, while Doppler failed to highlight some of the same tumors

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(Schlottmann et al., 2005). Contrast ultrasound also highlighted changes in vascularization of choroidal melanomas after treatment, demonstrating its possible use as a monitoring tool (Forte et al., 2005). While multiple publications investigate the use of CEUS in various abdominal organs in veterinary patients, only Labruyere et al. (2011) have published on the use of this technique in veterinary ophthalmology. This study also compared color Doppler ultrasonography with CEUS and found that in most eyes the color assessment was unsuccessful due to eye movement artifacts. CEUS, however, enabled visualization of blood flow in detached retinas in all cases and did not falsely show blood flow in vitreous membranes. The chapter authors have used CEUS to differentiate hemorrhage from vascularized tumors (Fig. 10.3.21).

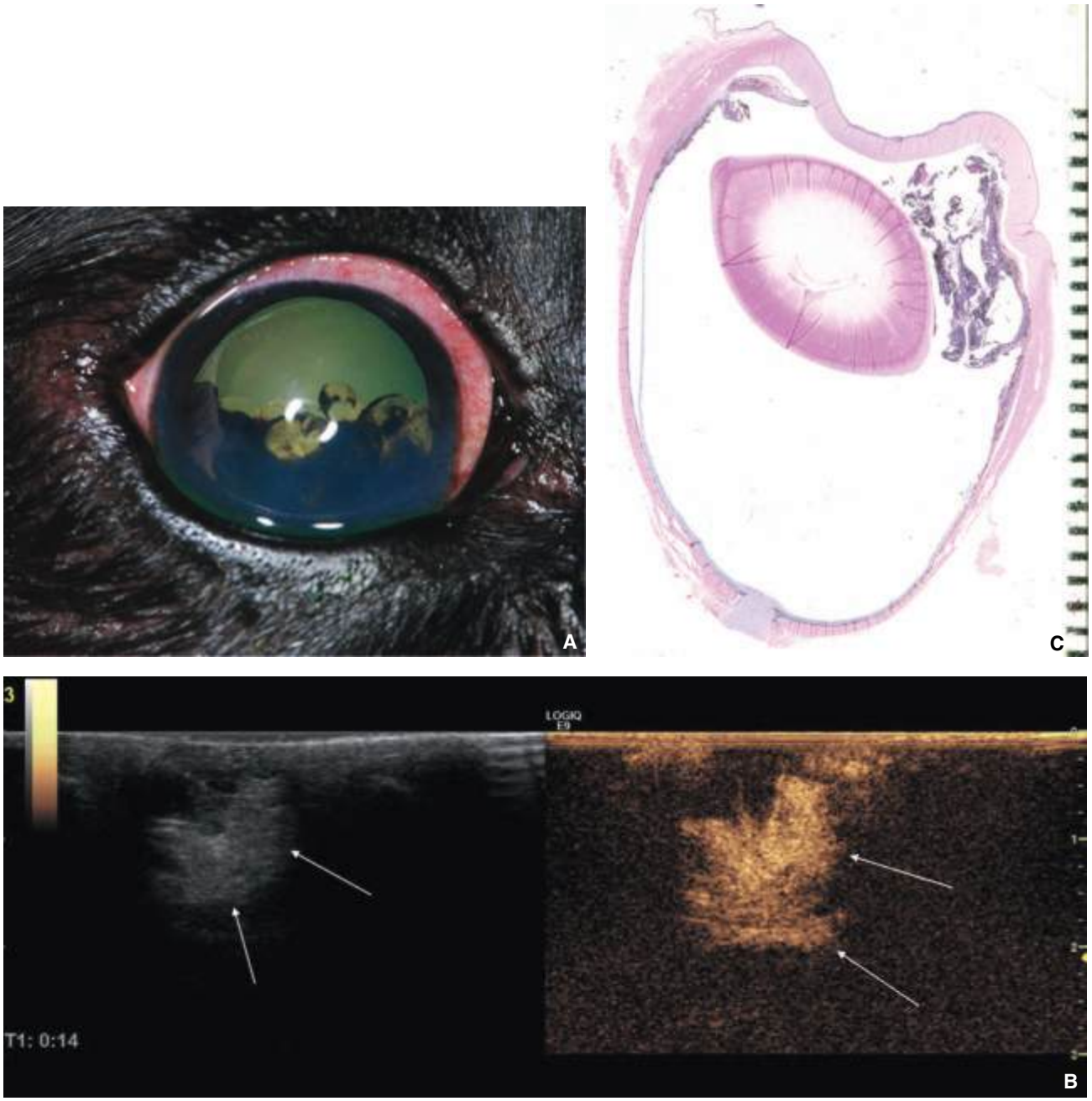


Figure 10.3.21 **A**. Photograph of a dog with iridociliary cysts, hyphema, and mass effect. **B**. Contrast-enhanced ultrasound of the same eye with a high-frequency linear transducer. The left panel is the fundamental frequency and the image on the right is the contrast harmonic mode. Note the irregular echogenic mass enhances (arrows), consistent with vascularized tissue rather than hyphema. **C**. Subgross photograph of the same eye, cut in the superior–inferior plane. The mass was diagnosed as a pigmented iridociliary adenoma. (Courtesy of the Comparative Ocular Pathology Laboratory of Wisconsin.)

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Blood vessels' presence and flow can be detected using the Doppler effect, which is based on an apparent shift in sound frequency when reflected off a moving target (e.g., red blood cells in vessels). Motion away from the transducer results in a lower frequency than the original, and motion toward the transducer results in a higher frequency, which is then displayed as a color map or graph. When applied to the eye, movements of the globe can create artifacts; however, with patience and repetition, consistent findings can be detected, and the modality offers advantages in some cases (Labruyere et al., 2011). Doppler modality in ultrasonography can be used with two different techniques, color Doppler (CD) or power Doppler (PD). While CD does not detect flows that are perpendicular to the beam, PD is not influenced by the angle of the beam relative to the flow. PD is more sensitive than CD and it provides useful information in the eye due to its ability to detect the smaller blood vessels of the eye independently of the direction of the flow or the position of the beam. The chapter authors found it useful in recognizing dubious retinal detachments or to detect blood flow in persistent hyaloid vessels (see Fig. 10.3.8). The CD technique has less sensitivity, and considering the caliper of ocular blood vessel, this may represent a disadvantage, along with the artifacts created by eye movement if performed in an awake or lightly sedated dog.

Three-Dimensional Ultrasound

Three-dimensional (3D) ultrasonography is best known through its use for prenatal imaging in humans. In this technique, sequential two-dimensional (2D) scans are combined with computerized reconstruction software. However, 2D images in three planes can also be obtained (Fig. 10.3.22). This allows the surfaces of structures and lesions to be rendered and the volume of lesions to be calculated. The use of

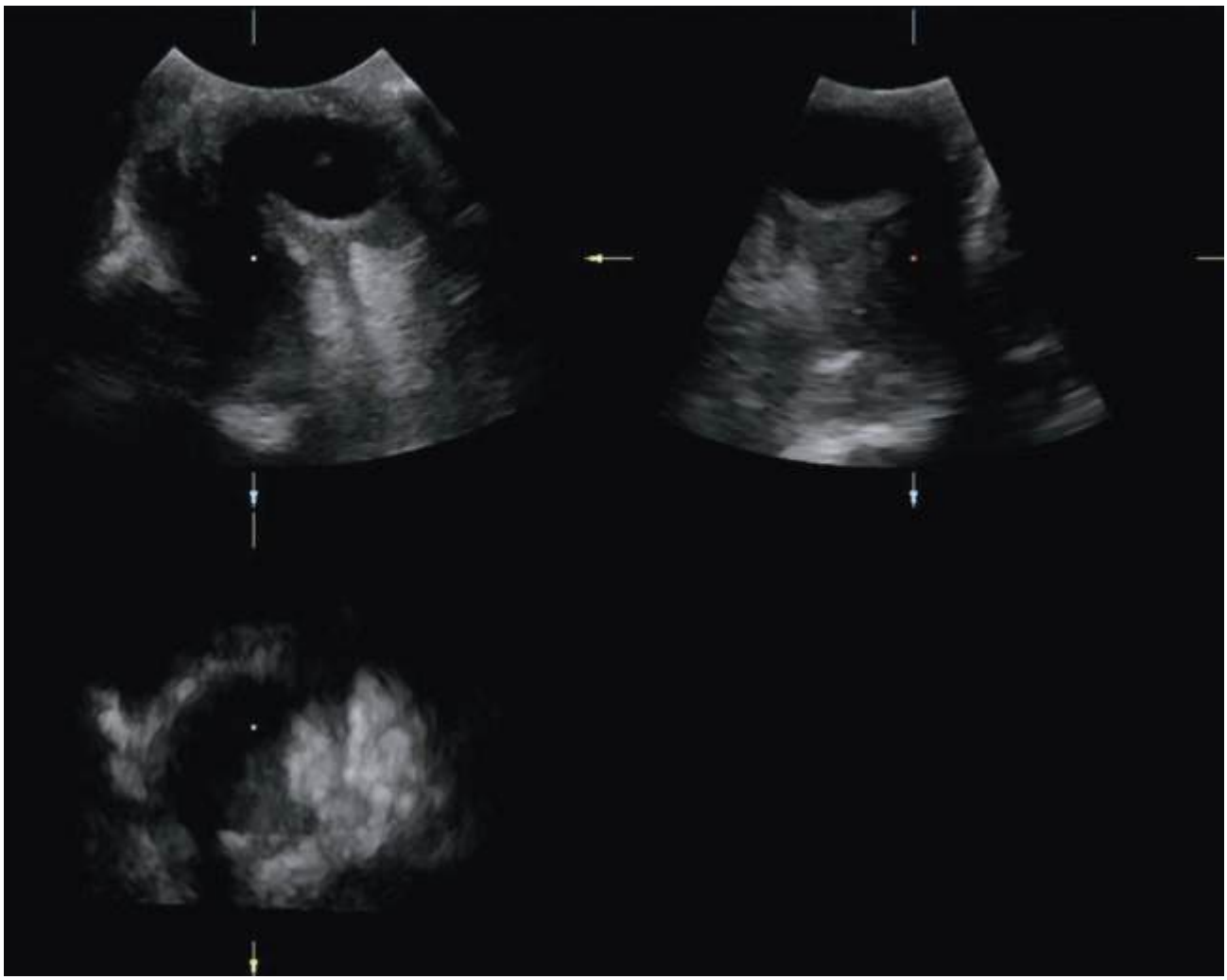


Figure 10.3.22 B-mode ultrasound multiplanar image using a three-dimensional transducer to allow simultaneous evaluation of X, Y, and Z planes of a retrobulbar abscess in a dog, with the planes centered around the small dot in the middle of the abscess.

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3D ultrasonography in ophthalmology has remained relatively limited and is mostly reported for the use of posterior segment and optic nerve tumors, including extraocular extension (Garcia et al., 2005; Sconfienza et al., 2010). At the moment, the need for specialized equipment limits its use in veterinary medicine, although the utility of 3D imaging and printing diagnosis and surgical planning is obvious (Dorbandt et al., 2017).

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10.4

Ophthalmic Examination and Diagnostics

Part 4: Clinical Electrodiagnostic Evaluation of the Visual System

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When light enters the eye and stimulates the retinal photoreceptors, it triggers alteration of electrical potentials, which propagate through all layers of the neuroretina and the visual pathways to the visual cortex. Different electrodiagnostic techniques can be utilized for the recording of this electrical activity. These techniques provide objective, noninvasive means to evaluate the visual system's function. They are particularly useful in veterinary ophthalmology due to the lack of verbal communication between the examiner and the examinee, which makes the evaluation of the visual system challenging. However, it is important to note that electrodiagnostic testing is not a measure of vision. For example, an animal with normal retinal function may still be blind due to cataract or postretinal lesion. Conversely, an animal with altered electrical activity of the visual system may retain some degree of visual function (e.g., early stage of progressive retinal atrophy). Hence, the results of electrodiagnostic tests should be interpreted in light of medical history, complete physical examination findings, and behavioral tests of vision such as maze testing and the ability to maneuver through an obstacle course.

Different electrodiagnostic techniques can be used to assess different parts of the visual system, and these will be discussed in this chapter. However, since full field electroretinography (ERG) is the only routine visual electrodiagnostic test performed in clinical veterinary ophthalmology, it will be the focus of this chapter. Changes associated with specific pathologies of the visual system are beyond the scope of this chapter and are discussed in the respective chapters. Understanding the retinal physiology is crucial to the understanding of the ERG and is reviewed in detail in Chapter 4.

The Full Field Electroretinogram (fERG)

The full field electroretinogram (also known as flash ERG or fERG) was the first electrodiagnostic test of the visual system, originally reported in 1865 (Holmgren, 1865). In performing the fERG, a light stimulus (i.e., a flash of light) is projected on the tested eye, illuminating the retina. The change in illumination generates electrical responses by the retina that can be recorded and analyzed. Retinal photoreceptors and bipolar cells are the main generators of the fERG, and the recorded trace is the sum of all retinal electrical activity. Since the introduction of the first commercial ERG machine in the second half of the 20th century, its popularity and use have increased dramatically in veterinary ophthalmology, and today it is considered essential equipment for veterinary ophthalmologists. The fERG is most commonly used for screening patients prior to cataract surgery, and as a diagnostic test in patients with visual impairment or blindness, to differentiate retinal from postretinal blindness.

Equipment and Technical Considerations

Initially, recording systems that were designed and built by individual researchers were used to record ERG for research purposes only. With the advancement of electronic amplification and recording equipment in the mid-20th century, clinical application was possible in humans, and later in veterinary patients (Karpe, 1946; Parry et al., 1953). Since then, further technologic advances and cooperation between system designers and clinicians/researchers have led to a rapid improvement in the quality of commercial electrodiagnostic systems. Today, high-quality commercial ERG machines are readily available and negate the need for profound technical skills, and knowledge in physics and electronics, in order to perform the test. Moreover, handheld ERG devices have become available in recent years. These handheld devices are highly mobile and easy to use, which is an advantage for the veterinary ophthalmologist, facilitating ERG evaluation in various locations (e.g., in the clinic, barn, zoo, etc.) and easy adjustment to the patient's head position, especially when the ERG is performed on conscious patients (Fig. 10.4.1).

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Figure 10.4.1 A handheld ERG machine with a mini-Ganzfeld stimulator is held in front of the patient's eye, and can be adjusted easily and quickly to the head position as needed. (Reproduced with permission from Ben-Shlomo, G., Plummer, C., Barrie, K., & Brooks, D. (2012) Characterization of the normal dark adaptation curve of the horse. *Veterinary Ophthalmology*, **15**, 42–45.)

Stimulator

Modern commercial ERG machines include a full-field (Ganzfeld or mini-Ganzfeld) stimulator. The Ganzfeld-type stimulator (vs. a strobe flash) is a dome, or a half-sphere bowl, with an integrated photo-stimulator, allowing homogenous luminance over the entire retina, and is the preferred type of stimulator for ERG testing (Fig. 10.4.2; Mcculloch et al., 2015). Furthermore, the Ganzfeld/mini-Ganzfeld stimulator can also provide background illumination when light adaptation is needed. Rather than placing the whole head of the examined animal inside a dome, handheld mini-Ganzfeld stimulators are placed over the tested eye, which is more practical in clinical veterinary ophthalmology, especially when the tested animal is conscious or is large (e.g., a horse; Fig. 10.4.1 and Fig. 10.4.2). Some stimulators include an integrated infrared camera that allows monitoring of the eye and corneal electrode positions while the eye is covered by the stimulator (Fig. 10.4.2C). Contact lens electrodes with an integrated light stimulator have also been used successfully for fERG in dogs (Kim et al., 2008; Maehara et al., 2005; Yu et al., 2007). These devices need to meet all requirements for a Ganzfeld-type stimulator, including appropriate calibration and verification of uniform retinal illumination, in order to achieve reliable and reproducible readings.

Stimulation

While different light sources can be used for ERG stimulation (e.g., xenon flash lamp), light-emitting diodes (LED) are superior to others since they are inexpensive, small, and can be controlled by simple electronic means to give either continuous light output or brief flashes, over a wide range of intensities. Additionally, their light output changes very little over extended use (Hogg, 2006). Over the last decade, major advances have been made in LED technology, leading to the widespread use of LED as the light source in many modern machines. Calibration of the stimulator on a regular basis, according to the manufacturer's instructions, is recommended to ensure reliable and consistent results (Mcculloch et al., 2015). Due to the LED properties, these stimulators require calibration less frequently than other light sources.

The recommended flash duration should not exceed 5 msec, which is shorter than the integration time of any photoreceptor. Stimulus intensity is measured by its time-integrated luminance, and the most common units used for ERG are candela-seconds per meter squared ($cd \cdot s/m^2$). Specific light intensities for fERG will be discussed later in this chapter. Chromatic stimuli (i.e., blue and red lights) may be used to facilitate enhanced separation of rod and cone ERGs. Blue stimuli over a red background will favor the rod system, while red stimuli over a blue background will favor the cone system. The red or blue backgrounds will suppress the response from the cone or rod photoreceptors, respectively. While chromatic ERG may be used for advanced protocols, only white flashes (and background) are used for routine clinical ERG (Ekesten et al., 2013; Mcculloch et al., 2015). An in-depth review of the principles of chromatic ERG is available (Estevez and Spekreijse, 1982).

Amplification and Signal Filtering

The electrical potentials generated by the retina and visual system are too small to be recorded and accurately analyzed. Therefore, a system of pre-amplifiers and amplifiers is needed to increase the voltage of the signal (usually 1000× for the fERG). The ERG system has a set of three inputs (i.e., positive, negative, and ground), which are connected to a differential amplifier. The differential amplifier amplifies only the difference in signals between the recording and reference electrodes, as discussed in the following section on electrodes. The recording electrode is connected to the positive input, the reference electrode to the negative one, and the common (or ground electrode) to the ground input; hence, the positive potential occurs at the recording electrode. Inadvertent connection of the recording electrode to the negative input and the reference electrode to the positive one will result in inverted trace (see the later section on interpretation of the results and Fig. 10.4.11). A set of positive and negative inputs (i.e., recording and reference electrodes) are referred to as a channel. One channel allows ERG recording from one eye. Some recording systems are equipped with two

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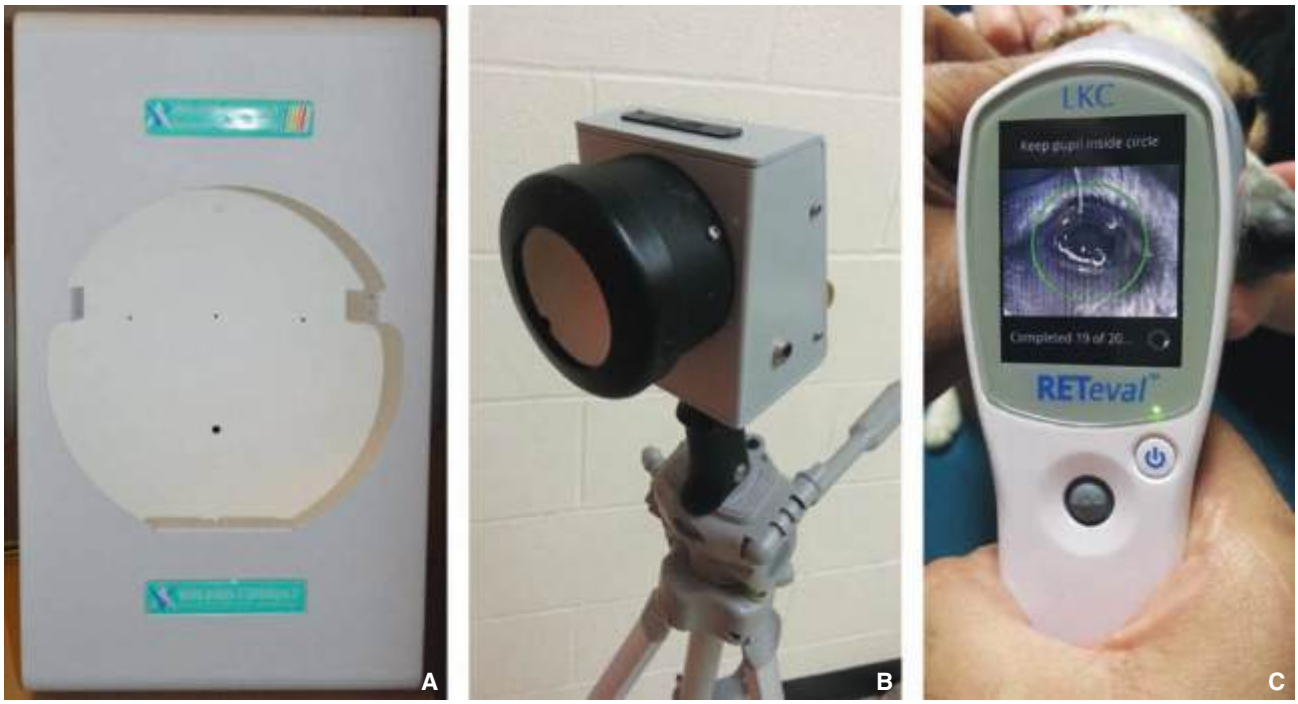


Figure 10.4.2 Ganzfeld (**A**) and mini-Ganzfeld (**B**) stimulators. These stimulators provide a flash of light that illuminates the retina homogenously. The mini-Ganzfeld in (**B**) is part of a handheld ERG system. An infrared camera integrated into the mini-Ganzfeld stimulator of a handheld ERG device allows monitoring of the eye and electrode position during the testing (**C**). The green circle on the screen aids the examiner in positioning the stimulator centrally and ensures even stimulation of the retina.

channels for simultaneous recording of both eyes. However, when mini-Ganzfeld stimulators are used, positioning two stimulators over both eyes (one stimulator over each eye) may be challenging in a conscious animal.

The amplifier also filters the signal, and should be set to record frequencies between 0.3 Hz and 300 Hz, which is the range of signals generated from the various structures of the visual system. Frequencies below or above these frequencies will be rejected (band-pass filter). Modern machines are preset for these settings. Changing the frequencies of the high- or low-pass filters will affect the amplitude and implicit time of the ERGs (Mcculloch et al., 2015) and, as such, should be avoided. Comparisons between ERG recordings should be done, ideally, after recording with the same band-pass filter. Nonetheless, the ERG machine should allow the change of the low (high-pass) and high (low-pass) filters in order to record oscillatory potentials (OPs), which are high-frequency wavelets originating from the inner retina. In addition, the OPs can be extracted from a recorded trace *post hoc* using the ERG machine's software or mathematic software. In order to separate the OPs from the ERG, the low filter must be set to 75–100 Hz; this will eliminate the slow components of the ERG (i.e., the a- and b-waves) that mask the OPs (for more information, see "Analysis of the fERG" below). "Notch filters" can be applied to reject 50 Hz or 60 Hz "noise" and thus improve the appearance of the recorded trace. However, such filtering affects the waveform, and should be avoided. Alternatively, periodic interfering signals (such as the electrical system's 50 Hz or 60 Hz) can be removed by software after the recording, if warranted. This may be referred to as "smoothing" of the trace.

Electrodes

The principle of electroretinography testing is the amplification of the difference between two inputs coming from electrodes around the eye and rejection of noise or common signals. For example, a heartbeat that is generated from a location relatively distant from the eye, creating equal signals on the two electrodes at the eye (i.e., common signal), will not be recorded. Therefore, two electrodes are needed in order to record ERG from a single eye: a signal-receiving (or recording) electrode and a reference electrode. Historically, the recording electrode may be referred to as the "active" electrode. However, this is a misnomer, as this electrode passively records the electrical changes generated by the retina. A third, grounding electrode is needed to ground the patient and reduce power line frequency (mains) interference (60 Hz in the Americas and parts of Asia, and 50 Hz in large parts of the rest of the world). Electrodes that contact the cornea, the bulbar conjunctiva, or skin of the eyelid (upper or lower) may be used as recording electrodes (Mcculloch et al., 2015; Steiss et al., 1992; Fig. 10.4.3). The reference electrode is

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placed adjacent to the eye, usually posterior to the lateral canthus, and the grounding electrode is placed elsewhere on the body (see below).

Corneal contact lens electrodes (e.g., the ERG-Jet™, Fabrinal, La Chaux-de-Fonds, Switzerland) are most commonly used as the recording electrode in veterinary (and human) patients. They provide the most stable recording and higher amplitudes compared to other types of electrodes such as conjunctival or eyelid electrodes, and are recommended for clinical fERG recordings (Mcculloch et al., 2015; Steiss et al., 1992). However, other electrodes that contact the cornea, such as silver-impregnated microfiber (introduced by Dawson, Trick, and Litzkow and now referred to as the DTL electrode) and gold-coated foil strips, are also effective (Komaromy et al., 2003; Pereira et al., 2013; Strom and Ekesten, 2016). In small animals such as dogs and cats, the contact lens electrode covers most or all of the cornea, and has the added value of protecting the cornea from desiccation, especially when the test is being performed on sedated or anesthetized patients, or when an eyelid speculum is being used. Conversely, as its diameter is much smaller than the equine cornea, it does not protect the cornea from drying. Hence, the corneal surface of the horse (or other species with large corneas) should be moistened regularly, especially when a longer ERG protocol is being used, and particularly when the patient is sedated or anesthetized, and/or when blinking is blocked pharmacologically or by means of an eyelid speculum. It is worth noting that a contact lens electrode does not have to cover the whole cornea in order to be effective, and the commonly used ERG-jet electrode designed for human patients is effective and routinely used by this author and others for ERG recording in small and large animal patients alike (Ben-Shlomo and Grudzien, 2015; Ben-Shlomo et al., 2012; Church and Norman, 2012; Hepworth et al., 2014). In exotic animals with very small eyes, such as some types of birds, bats, or rodents, modified DTL or gold-loop electrodes can be used as the recording electrode (Fig. 10.4.3).

Needle electrodes (either platinum or stainless steel) are most commonly used in veterinary patients as the reference and grounding electrodes. However, a recent study showed that non-needle electrodes are effective as reference and grounding electrodes for ERG recording in dogs, and produce ERG traces similar in quality, amplitude, and implicit time to those obtained by needle electrodes (Ben-Shlomo and Grudzien, 2015), while decreasing patient discomfort and biohazard risk (Fig. 10.4.3).

After each use, reusable electrodes must be cleaned and sterilized appropriately to prevent transmission of infectious pathogens. Reusable electrodes should be carefully inspected for any damage prior to each recording, since damaged electrodes can negatively affect the quality of the recording and increase the level of noise.

Electrodes placement

The majority of artifacts affecting ERG recordings are almost always the result of defective electrodes or improper placement technique (Gehlbach and Purple, 1993; Hogg, 2006;

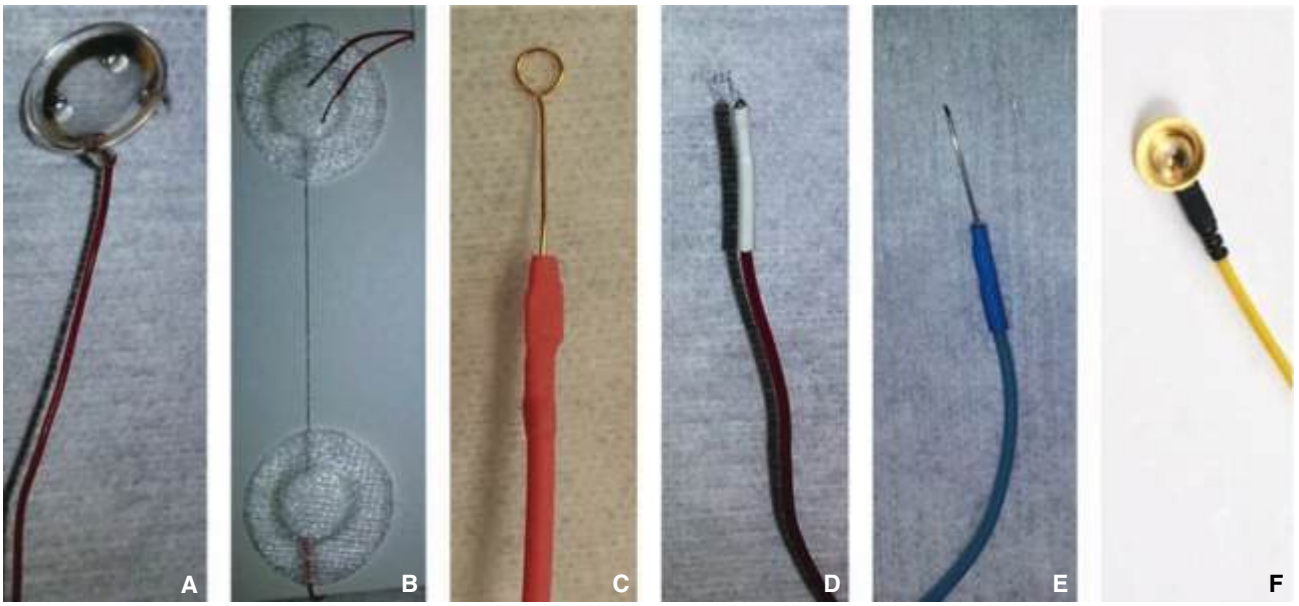


Figure 10.4.3 **A**. The ERG-Jet contact lens electrode is the most common recording electrode used by veterinary ophthalmologists. **B**. The DTL electrode has been used successfully in small and large animals. **C**. A gold-loop electrode of varying sizes (e.g., 2–3 mm in diameter) may be used for ERG recording in exotic animals with small eyes. **D**. A modified DTL electrode can also be used for smaller eyes. **E**. Platinum or stainless-steel needle electrodes are most commonly used as the reference and ground electrodes. **F**. A noninvasive, gold-cup electrode can also be used as reference and ground electrodes.

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Wong and Graham, 1995). Ensuring the integrity of the electrodes, especially when reusable ones are used, and mastering the technique (i.e., consistent electrode placement and acceptable electrode impedance) are of paramount importance for a good-quality and diagnostic recording. Most modern ERG systems include an integral impedance meter, allowing for the measurement of electrode impedance, which should be under 5 kΩ when connected to the patient. Higher impedance may suggest that the electrodes are defective, or that they are poorly connected to the patient. This will result in a poor-quality recording. Hence, checking the electrodes' impedance after connecting them to the patient and prior to the beginning of the ERG recording is recommended. Appropriate electrode impedance and placement will result in waveforms that are comparable to those of the International Society for Clinical Electrophysiology of Vision (ISCEV; Mcculloch et al., 2015), discussed later in this chapter.

The Recording Electrode

Corneal contact lens electrodes are recommended due to their reproducible and reliable recordings (Mcculloch et al., 2015), and are most commonly used in veterinary patients. Specifically, the ERG-Jet contact lens electrode is popular among veterinary ophthalmologists as it is lightweight, well tolerated, easy to place, and relatively inexpensive. In general, contact lens electrodes provide higher amplitudes compared to conjunctival or eyelid electrodes (Steiss et al., 1992). Topical anesthesia is required when a contact lens (or other corneal) electrode is used, and ionic conductive solution (e.g., artificial tears containing sodium chloride) should be applied to the cornea to protect it from drying during ERG recordings. When using a contact lens electrode, viscous eye drops such as 2.5% hypromellose (e.g., Gonak™, Akorn, Lake Forest, IL, USA; Goniovisc™, Hub Pharmaceuticals, Plymouth, MI, USA) will ensure good adhesion of the contact lens to the cornea, in addition to improving the conductivity of the signal. The recording electrode should be connected to the positive input of the recording system.

The Reference Electrode

Either subdermal needle (platinum or stainless steel) or non-needle electrodes can be used as the reference electrode. Appropriate skin preparation with skin preparation gel (e.g., NuPren®, Weaver and Company, Aurora, CO, USA) and application of conductive paste (e.g., Ten20®, Weaver and Company) are of great importance in order to achieve appropriate conductivity and to maintain impedance of 5 kΩ or less when non-needle electrodes are being used. A gold cup electrode is effective as a non-needle electrode. The cup should be filled with a conductive paste mounted over the edge of the cup. Then, the patient's hair should be parted as much as possible (there is no need to shave the hair), and the electrode applied firmly to the skin in order to achieve good contact and adhesion of the electrode (Fig. 10.4.3F and Fig. 10.4.4; Ben-Shlomo and Grudzien, 2015). Needle electrodes should be introduced fully into the subdermal space (and not intradermal or left half out). Reusing needle electrodes over a long period of time or on a high number of patients will result in blunt needles and increased discomfort with placement. Placing reference electrodes over muscle masses should be avoided in order to minimize electromyogram interference. A common location for the reference electrode is posterior to the lateral canthus, over the zygomatic arch, which lacks muscle mass. Based on the clinical experience of this author, the closer the reference electrode is to the lateral canthus and eyelids, the greater is the chance for the ERG to be affected by the eyelids' muscle activity when the patient is conscious and blinking. Moreover, a study by Mentzer et al. (2005) evaluated the effect of reference electrode position on the ERG and showed that positioning the reference electrode 3–5 cm posterior to the lateral canthus resulted in significantly higher amplitudes in response to most light intensities, versus placing it only 1 cm posterior to the canthus. In horses and other large animals, the reference electrode should also be placed approximately 3 cm posterior to the lateral canthus (Ben-Shlomo et al., 2012; Komaromy et al., 2003).

The Burian-Allen electrode (Hansen Ophthalmic Development Laboratory, Coralville, IA, USA) incorporates both the reference and recording electrodes into one contact lens device ("bipolar electrode"). It consists of a corneal contact lens electrode that is held against the cornea with a spring, and an integral plastic eyelid speculum that prevents blinking. A reference electrode is assembled within the surface of the eyelid speculum and touches the conjunctiva. While the Burian-Allen electrode is commonly used in human patients, it is considered uncomfortable and poorly tolerated by pediatric patients, who often require sedation when this electrode is being used (Coupland, 2006). As such, it may not be tolerated well by conscious veterinary patients. In addition, it has been shown to produce significantly lower ERG amplitudes in dogs when compared to the recordings obtained by the ERG-Jet electrode and a reference electrode that was placed posterior to the lateral canthus (Mentzer et al., 2005). The reference electrode should be connected to the negative input of the ERG machine.

The Grounding (Common) Electrode

Either subdermal needle or non-needle electrodes can be used as grounding electrodes (Ben-Shlomo and Grudzien, 2015). They should be placed on to an indifferent point on the body; common placement sites include the neck, forehead, base of the ear, or at the midline on the top of the skull. In horses and other large animals, the grounding electrode may be placed on the middle of the neck (Ben-Shlomo et al., 2012). The grounding electrode should be connected to the common/ground input of the ERG machine.

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Figure 10.4.4 **A**. The ERG-Jet contact lens electrode is placed on the cornea of a conscious dog, and non-needle, gold-cup electrodes are used as the reference and ground (not seen in the picture) electrodes. The gold-cup electrodes are connected to the patient by means of a special, thick, conductive gel that also keeps the electrode from falling. The hair of the patient is parted as much as possible, and the electrode is applied to the skin. The electrodes are secured to the collar of the patient with medical tape to minimize their movement when the head moves. **B**. The small plastic rods on the surface of the contact lens electrode prevent the eyelids from blinking over the contact lens and blocking the light stimulus. The traces in Fig. 10.4.5A and Fig. 10.4.7B were recorded from this conscious patient with these electrodes, in one session.

Signal Averaging and Electrical Noise Reduction

Signal averaging can be used in order to decrease the effect of random background noise on the ERG. The ERG recording is triggered by the light stimulus and it is synchronized with it. Conversely, background noise and electromyogram are random with respect to the ERG stimulus. Consequently, as the repeated traces are being recorded and averaged, the noise is canceled out, resulting in a significant increase in the signal-to-noise ratio. Signal averaging is particularly useful to reduce noise generated by the patient's muscle activity, as it is truly random in relation to the light stimulus. However, most electrical noise is the result of a bad technique, such as poor maintenance or poor placement of the electrodes; prolonged averaging should not be used to compensate for bad technique. In addition, an electrical signal from the surrounding electrical system (i.e., 50 Hz or 60 Hz) may contaminate the ERG trace. It may be phase-locked (i.e., synchronized) with the light stimulus and, as a result, the averaging may not be effective (Odom, 2006).

The smaller the ERG amplitude, the more significant the effect of background electrical noise is (i.e., decreased signal–noise ratio). Consequently, when low-intensity flashes are used, more averaging may be needed, as low-intensity stimulus generates weaker responses with lower amplitudes. Conversely, less averaging may be needed when high-intensity flashes are used. In addition, the brighter the flashes are, the longer the interval between stimuli should be in order to allow recovery of the retinal photoreceptors between flashes (e.g., a frequency of ≥ 0.1 Hz). Low-intensity stimuli may be given in shorter intervals (e.g., ≥ 0.5 Hz). As a general rule, averaging should be minimized as much as possible.

The modern environment is saturated with electrical devices that produce electromagnetic contamination of the recorded signal. While modern ERG machines are designed to circumvent this problem, at least partially, recording systems should be kept away from high-powered electrical devices and electric motors in particular (e.g., refrigerators, air conditioners, elevators). Unplugging electrical equipment that is not needed for ERG recording may help reduce the electrical noise. Nevertheless, noise from electrical equipment can be transmitted through the power line for a significant distance. While there are solutions for this problem, such as the use of a Faraday cage (see the later section on light and dark adaptation and Fig. 10.4.6), an electrically shielded room, or a dedicated power supply to the ERG room (to ensure a clean power supply), these solutions are expensive. Alternatively, the use of battery-operated ERG devices that are not connected to the main power line during the recording may help decrease (or eliminate) main line interference (Fig. 10.4.1 and Fig. 10.4.2B–C).

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Protocols for fERG Recording

Many fERG protocols have been published by different researchers and laboratories. These protocols evolved over the years based on the progress of our understanding of retinal physiology as well as advances in technology and computing. In 1989, the ISCEV published the first standard for clinical fERG in human patients (ISCEV, 1989), which allowed recording of reproducible and comparable fERG throughout the world. The ISCEV standard triggered the publication of guidelines for fERG recording in dogs, which were first published in 2002 (Narfstrom et al., 2002). These protocols are updated periodically. The technique and protocols for ERG recording discussed later in this chapter are based on the latest updates of the ISCEV protocol and the guidelines for clinical ERG in dogs (see Recording the fERG section below) (Ekesten et al., 2013; Mcculloch et al., 2015; Robson et al., 2018). These recommendations should serve as the basis for clinical ERG in other species when specific recommendations are lacking. Following these recommendations allows for a more reliable comparison of results between different hospitals and laboratories, as well as results of scientific and clinical publications.

Patient Preparation

Mydriasis

Complete mydriasis is needed to achieve uniform stimulation of the whole retina, which is crucial for reliable and reproducible results. Pupil size should be evaluated before and at the end of the fERG recording.

Patient Restraint

When human patients undergo ERG testing, they are instructed to look at a fixation point incorporated into the stimulus source. Fixated gaze reduces movement-related artifacts, keeps the pupil fully exposed to the light stimulus, and prevents movement of the contact lens electrode. Clearly, this is not achievable with veterinary patients. However, the use of signal averaging, as discussed above, is very helpful in decreasing movement-related artifacts. Short fERG protocols can be performed successfully on conscious dogs with minimal manual restraint for quick evaluation of retinal function, such as when the cornea or lens is opaque (e.g., mature cataract) or in order to differentiate retinal from postretinal blindness (e.g., sudden acquired retinal degeneration syndrome vs. optic neuritis or a central lesion; Norman et al., 2008). The short protocols are well tolerated by most canine patients. Furthermore, a recent study has shown that while sedation and anesthesia resulted in significant attenuation and delay of the ERG responses in dogs, there was no significant effect on the quality of the recorded signal compared to fully conscious dogs (Freeman et al., 2013). In the last two decades, technologic advancements have led to the development of handheld ERG devices, such as the Multispecies ERG (RetVetCorp, Columbia, MO, USA) and the RETevet™ (LKC Technologies, Gaithersburg, MD, USA). These devices have significantly improved our ability to perform ERG on nonanesthetized animals, large and small, as it is easy to adjust their position to the animal's head position and minor movements. The RETevet machine is also equipped with an infrared camera that is built in to the mini-Ganzfeld and allows monitoring of the globe, eyelids, and contact lens electrode positions during the recording (Figure 10.4.2C).

Longer protocols or testing of anxious or aggressive animals may require chemical restraint. The published guidelines for clinical electrophysiology in the dog recommend the use of anesthesia for the recommended protocol, which is intended to test for inherited photoreceptor disorders, and include photopic and scotopic fERG (Ekesten et al., 2013). While under anesthesia, the eyelids (including the third eyelid) should be maintained open by means of an eyelid speculum, and subconjunctival stay sutures at the limbus may be used to stabilize the globe and ensure full exposure of the pupil to the light stimulus. However, long protocols (even longer than the recommended one) were performed successfully on sedated (Maehara et al., 2005) or conscious dogs (Kim et al., 2008; Yu et al., 2007), utilizing a contact lens electrode with a built-in light source. This author routinely and successfully performs extended protocols in conscious canine patients, utilizing handheld, mini-Ganzfeld–equipped ERG systems, as demonstrated by the traces shown in Fig. 10.4.5A and Fig. 10.4.7B which were all recorded in a conscious dog in one session.

Various sedation and anesthetic protocols have been utilized for fERG recordings in dogs and cats, and their effect on the fERG evaluated (Baro et al., 1990; Freeman et al., 2013; Jeong et al., 2009; Kommonen, 1988; Kommonen et al., 1988; Lin et al., 2009; Maehara et al., 2005; Narfstrom et al., 1985; Norman et al., 2008; Rosolen et al., 2002; Tanskanen et al., 1996). In general, both sedation and anesthesia decrease the fERG amplitudes and prolong the implicit time. In the clinical setting, it is crucial to compare fERG results of patients to normal values obtained using the same sedation or anesthesia protocols. Otherwise, drug-related attenuation of the fERG may be falsely attributed to retinal disease. If sedated or anesthetized, patients should be maintained well oxygenated, as hypoxemia results in attenuation of the fERG (Howard and Sawyer, 1975; Kang Derwent and Linsenmeier, 2000; Niemeyer et al., 1982). Hypercapnia, or decreased levels of carbon dioxide in the blood (secondary to hyperventilation), can also alter the fERG recording (Murray and Borda, 1984; Varela Lopez et al., 2010).

Equine fERG can be performed safely and effectively under standing sedation. An intravenous (IV) dose of 0.015 mg/kg detomidine is effective for short or long fERG protocols (Ben-Shlomo et al., 2012; Church and Norman, 2012; Hepworth et al., 2014; Komaromy et al., 2003; Sandmeyer et al., 2007). Therefore, general anesthesia is not required for a routine clinical ERG in the horse. In addition, sedation is safer and cheaper than general anesthesia,

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increasing the likelihood of approval of this testing modality by equine owners. In order to maximize the effect of sedation, this author starts the dark adaptation process when the horse is in the stocks and unsedated; approximately halfway through the dark adaptation time (i.e., 10 minutes), the sedation is administered intravenously under dim red light, followed by placement of the electrodes. Under these conditions, only an experienced clinician should administer the sedation, and extreme caution should be taken to avoid injection of the sedative drugs into the carotid artery, which can be lethal. Alternatively, an indwelling intravenous catheter may be placed prior to dark adaptation. The equine's orbicularis oculi muscle, which is responsible for blinking, is very strong. Therefore, eyelid akinesia by auriculopalpebral nerve block is strongly recommended. This will allow the examiner to keep the eyelids open, reduce blinking artifacts, and avoid displacement of the contact lens electrode. The cornea should be kept moist by periodic application of ionic eyewash solution to prevent desiccation of the cornea, especially since to date there is no contact lens electrode that covers the whole corneal surface of the horse eye.

In both small and large (nonanesthetized) animals, this author avoids the use of an eyelid speculum, as it seems to cause more patient discomfort and resistance when it is used. Manual opening of the eyelids just prior to administration of the light stimuli works very effectively in the clinic.

Light and Dark Adaptation

Both rods and cones contribute to the fERG and each responds in a characteristic way to different types of light stimulation. Therefore, manipulation of the intensity, duration, and frequency of the light stimulus, as well as the ambient light conditions, facilitates separation of rod and cone recordings. Under bright light conditions (photopic), rod photoreceptors are saturated and rhodopsin is bleached (Gouras, 1965). Hence, light adaptation will allow recording of the cone response, with minimal to no contribution from rods. At least 10 minutes of light adaptation using white background light of 30 cd/m^2 is recommended in human and canine patients in order to minimize rod input and achieve stable and reproducible light-adapted ERGs (Ekesten et al., 2013; Mcculloch et al., 2015).

Conversely, dark adaption allows rod photoreceptors to regenerate their photopigment and restore activity. The fERG amplitude gradually increases during the dark adaptation period until it reaches a plateau (Fig. 10.4.5). Appropriate dark adaptation time and recording under dark conditions (scotopic ERG) are crucial for reliable and reproducible recording of rod activity. Dark adaptation time may vary between species. The recommended dark adaptation time in the dog is 20 minutes (Ekesten et al., 2013; Yu et al., 2007), whereas in the horse a gradual increase of the fERG b-wave amplitude was documented up to 25 minutes of dark adaptation and plateaued thereafter (Ben-Shlomo et al., 2012). However, in that study, the mean b-wave amplitude after 20 minutes of dark adaptation was not statistically different from the mean b-wave amplitude at 25 minutes of dark adaptation (Fig. 10.4.5B). Thus, in the horse, the dark adaptation period prior to scotopic ERG recording should be at least 20 minutes (Ben-Shlomo et al., 2012). As a general rule, following dark adaptation, low-intensity stimuli should be presented prior to stronger stimuli. Specific characteristics of the light stimulus for the recording of rod and cone activity is discussed below.

Ideally, scotopic ERG should be recorded in a completely dark room. However, this is challenging when working with veterinary patients due to safety considerations for both examiner and examinee. Practically, red light with a

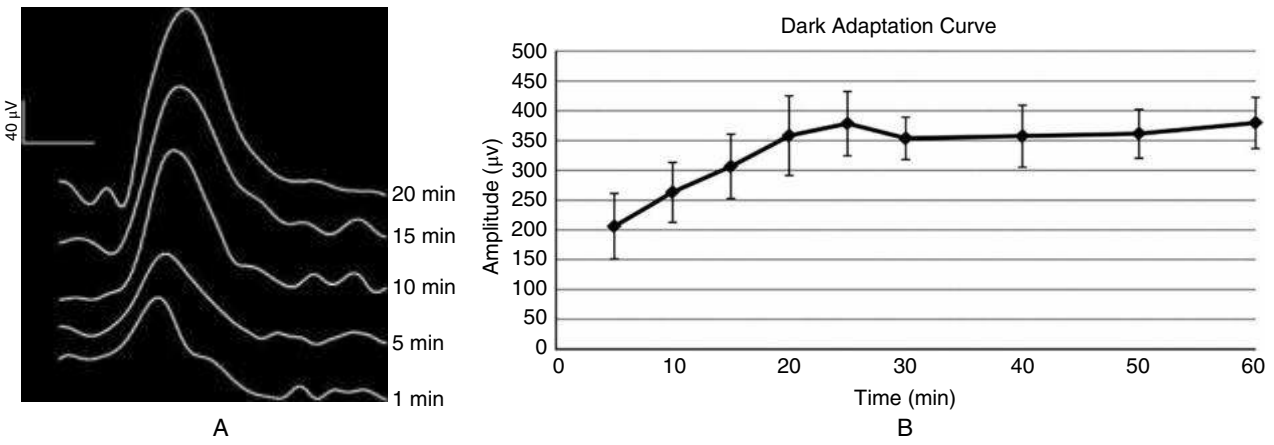


Figure 10.4.5 **A**. The b-wave amplitude of the fERG increases during dark adaptation. Representative traces recorded from a healthy dog under scotopic conditions, and in response to a light stimuli of 0.01 cd·s/m^2, during a 20-minute dark adaptation period. **B**. The dark adaptation curve of the horse, showing the mean b-wave amplitudes (± SEM, the standard error of the mean) for the different time points of dark adaptation. (Panel B reproduced with permission from Ben-Shlomo, G., Plummer, C., Barrie, K., & Brooks, D. (2012) Characterization of the normal dark adaptation curve of the horse. *Veterinary Ophthalmology*, **15**, 42–45.)

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wavelength of 625 nm or higher should be used, as this wavelength is above the spectrum of rod photoreceptors. The ambient red light should be kept dim, at the lowest intensity possible. When possible, the ambient dim red light should be turned off when not needed. Direct illumination of the eye with bright red light (e.g., while using a red flashlight in order to set or fix electrodes) should be avoided. Computer screens and monitoring devices (e.g., anesthesia monitor) should be covered with a red filter of 625 nm or higher (Fig. 10.4.6).

It is worth noting that photoreceptors require a significant amount of time to fully recover after exposure to bright light (Pugh, 1975). Tuntivanich et al. (2005) have shown that following indirect ophthalmoscopy and fundus photography in dogs, the fERG amplitudes and implicit times were significantly affected, and at least 60 minutes of dark adaptation was needed for the recovery of the fERG following these procedures. This should be taken into account when fERG is recorded in the clinic, usually following a complete eye examination that includes the use of bright lights. It should also be taken into consideration for research study designs when ERG testing is planned.

Recording the fERG

Rod Response

The rod response is recorded under scotopic conditions and should be the first to be recorded following an appropriate period of dark adaptation, as it is the most sensitive to light adaptation. The light stimulus is a weak flash of 0.01 cd·s/m^2, which is below the cone photoreceptors' threshold, and it will not trigger cone response. If needed, responses may be averaged (ideally not more than four averagings), applying the stimuli with a minimum interval of 2 s (0.5 Hz). If a single response is recorded (i.e., without averaging), repeating the recording once to ensure reproducibility is recommended. Rod function may be evaluated during the dark adaptation period. In this case, similar flash intensity (0.01 cd·s/m^2) can be used, starting immediately at the beginning of the dark adaptation period, and repeated every 4 minutes thereafter, up to 20 minutes. This protocol will demonstrate the changes in rod-driven responses over the dark adaptation period (see Fig. 10.4.5A).

Combined Rod–Cone Response

The combined rod–cone response is recorded under scotopic conditions, usually immediately after the recording of the rod response. The flash intensity used is 3 cd·s/m^2 ("standard flash"), and an interval of at least 10 s (0.1 Hz) between stimuli should be applied when averaging is used (Mcculloch et al., 2015). As few flashes as possible should be used to avoid light adaptation of the retina. The combined rod–cone response may be used as part of a longer protocol. However, it is probably most commonly used in the clinical setting as a standalone test for patient screening prior to cataract surgery, and to differentiate retinal from postretinal blindness when the fundus looks normal on fundoscopy (e.g., sudden acquired retinal degeneration syndrome vs. central blindness or retrobulbar optic neuritis). An additional high-intensity flash of 10 cd·s/m^2 may be used for the combined rod–cone response. The response to this high-intensity stimulus will result in a greater amplitude compared to the standard flash,



Figure 10.4.6 An ERG recording system, including a Ganzfeld stimulator, is located inside a Faraday cage, which is connected to a true ground cable (on the left). The doors of the Faraday cage allow access to it from the outside. The operator's station is located outside of the Faraday cage to decrease electrical noise. The monitor is covered with a 630 nm red filter. Other monitors (e.g., electrocardiogram monitors, pulse oximeter, etc.) should be covered similarly.

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and may provide more reliable responses in patients with opaque media (i.e., mature cataracts) or younger animals with immature retinas. The high-intensity flash should be used after the lower-intensity flash (3 cd·s/m^2) has been used. Averaging is not recommended with this high-intensity stimulus, as repeated stimuli may light-adapt the retina. If averaging is used, the number of stimuli should be kept to a minimum and given in intervals of at least 20 s (0.05 Hz; Mcculloch et al., 2015).

Cone Response

Single Flash

Cone response should be evaluated under photopic conditions, as previously discussed, to ensure reproducible light-adapted ERG and to minimize rod contribution to the recording. Following at least 10 minutes of light adaptation, a 3 cd·s/m^2 flash is delivered on the background of the adapting light. The intervals between stimuli should be at least 0.5 s (2 Hz).

Flicker ERG The flicker ERG evaluates the cone response and is performed under photopic conditions, after at least 10 minutes of light adaptation. The intensity of the flicker stimulus is 3 cd·s/m^2 given at a rate of 30 Hz. Choosing a frequency that is not an exact multiple of the power line frequency may help reduce related electric noise (a range of 28–33 Hz is acceptable). For example, in the USA, where the electrical system is 60 Hz, the flicker frequency can be set to 31 Hz. These flicker ERG settings are selective for the cone system, since rods have low temporal frequency and are unable to follow frequencies greater than approximately 15 Hz (Hecht & Shlaer, 1936).

Analysis of the fERG Recording

Light stimulus, through phototransduction, triggers hyperpolarization of the photoreceptors, through in turn leads to propagation of radial currents from the outer to the inner retina (i.e., from the photoreceptors, to the bi-polar cells, to the retinal ganglion cells [RGCs]), with the mediation of the horizontal and amacrine cells. These changes in the cells' electrical activity can be recorded and analyzed (Fig. 10.4.7). While the recording is a gross summation of all retinal cells, different cell types generate different components of the fERG trace. An in-depth review of retinal physiology, which is the basis for understanding the ERG, is beyond the scope of this chapter and is covered in Chapter 4.

The Components of the fERG

The a- and b-waves are the main components of the fERG, and are recorded and analyzed routinely in veterinary patients. The flicker ERG is also routinely performed. Clinical ERG is usually recorded over 250 msec post flash, plus at least a 20 msec baseline recording prior to the flash stimulus (Mcculloch et al., 2015). Analyzing these components is useful for the clinical diagnosis of retinal diseases.

The a-Wave

The a-wave is the first, slow, negative component of the fERG, and it is mainly associated with the hyperpolarization of the rod and cone photoreceptors. Under scotopic conditions, the low-intensity stimulus (0.01 cd·s/m^2) is not strong enough to trigger a recordable a-wave. A strong stimulus (e.g., 3 cd·s/m^2) will trigger a rod-driven a-wave from a dark-adapted retina, with a lesser contribution from the cone system (Brown, 1968; Frishman, 2006). Under photopic conditions, when the rods are saturated, the a-wave is cone driven. The a-wave amplitude is measured from the pre-stimulus baseline to the first negative trough (see Fig. 10.4.7). The a-wave implicit time (also known as "peak time") is measured from the time of the flash to the peak of the wave. The a-wave is truncated by the large, positive component of the fERG, the b-wave.

The b-Wave

The b-wave is the largest component of the fERG, generated primarily from depolarizing (ON) bi-polar cells, with a lesser contribution from Müller cells (the retinal glia cells; Karwoski & Xu, 1999; Robson & Frishman, 1995; Robson et al., 2004; Xu and Karwoski, 1994). Under scotopic conditions and a weak flash stimulus, the b-wave is predominantly rod driven. When a strong stimulus is given to a dark-adapted retina, cones also contribute to the b-wave, and a combined rod–cone response is recorded. Under photopic conditions and saturation of the rods, the b-wave will be cone driven. The b-wave amplitude is measured from the a-wave trough to the b-wave peak; the b-wave implicit time is measured from the time of the flash to the peak of the wave (see Fig. 10.4.7).

The Flicker ERG

The flickering stimuli result in a "steady-state" ERG. The amplitude of the flicker ERG is measured from a trough to the succeeding peak, and several (at least three) measurements may be averaged, avoiding the smallest and largest amplitudes. The implicit time is measured from the stimulus flash to the following peak. The response to the first stimulus of the flicker, which may resemble a flash ERG, should be avoided for both the amplitude and implicit time measurement (see Fig. 10.4.7). The flicker ERG can be also analyzed by Furrier analysis in the frequency domain.

Oscillatory Potentials

OPs consist of a series of high-frequency, low-amplitude wavelets superimposed on the b-waves, recorded in response to a strong stimulus. OPs can be recorded under photopic or scotopic conditions, with contribution from both rods and

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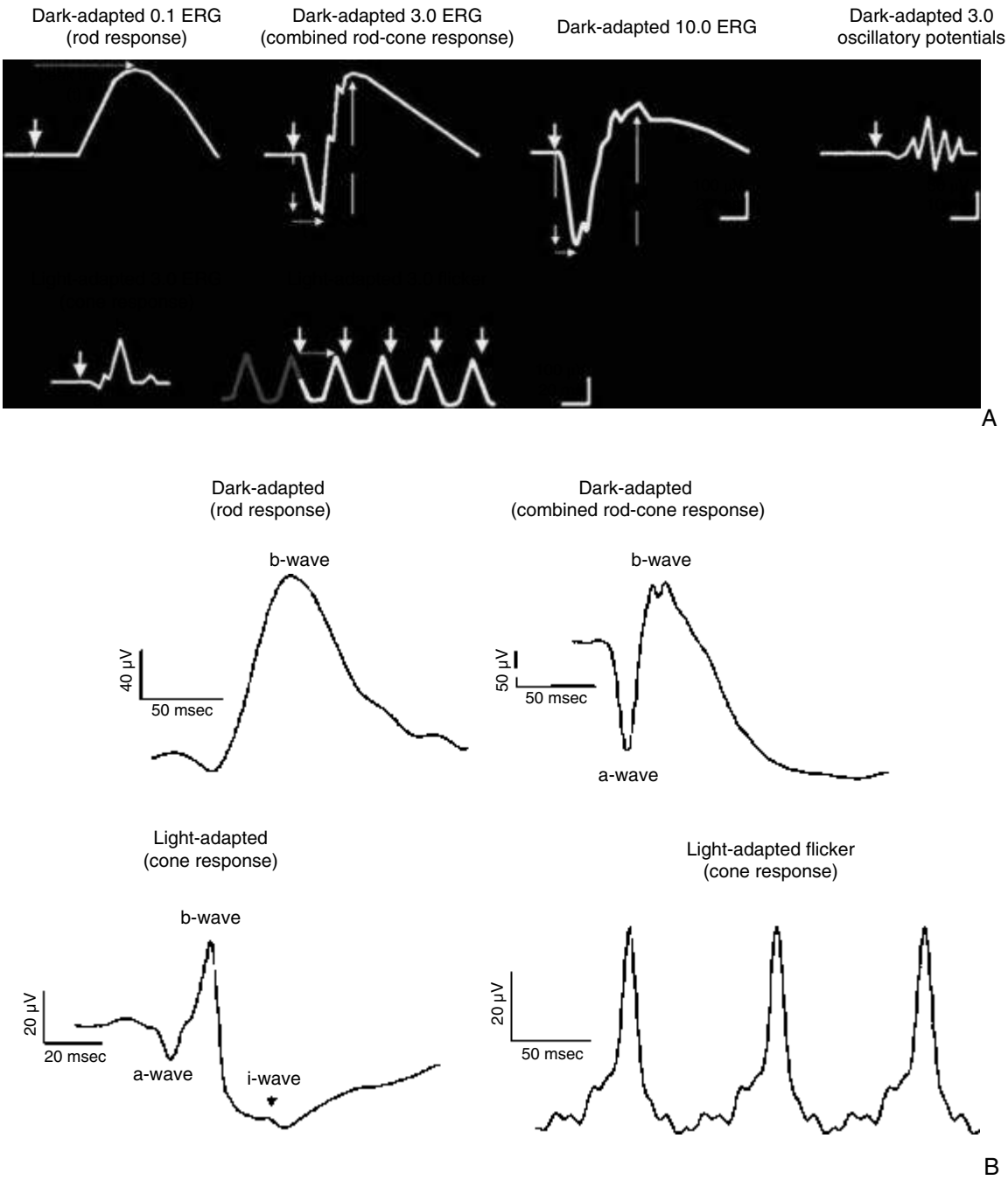


Figure 10.4.7 **A**. Diagram of the six basic ERGs defined by the ISCEV Standard. These waveforms are exemplary only and are not intended to indicate minimum, maximum, or typical values. Bold arrowheads indicate the stimulus flash; solid arrows illustrate a-wave and b-wave amplitudes; dotted arrows exemplify how to measure time to peak (t, implicit time or peak time). (Reproduced with permission from Mcculloch, D.L., Marmor, M.F., Brigell, M.G., et al. (2015) ISCEV Standard for full-field clinical electroretinography (2015 update). *Documenta Ophthalmologica*, **130**, 1–12.) **B**. Representative traces of basic ERG responses recorded from a healthy dog. See Fig. 10.4.8 for representative oscillatory potentials recorded from a healthy dog.

cones (Peachey et al., 1987). By convention, the OPs' peak is marked with the letter "O" followed by a number indicating its order of occurrence; that is, the first OP is O_1, the second is O_2, and so on (Wachtmeister & Dowling, 1978). The number of OPs varies depending on species, adaptation state, and stimulus characteristics (e.g., intensity, frequency). As such, there is no consensus on how to measure OPs. Observing the presence and waveform of OPs' peaks and comparing them qualitatively to normal controls may be adequate for most clinical needs (Mcculloch et al., 2015).

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OPs originate from the inner retina, most likely the inner plexiform layer, but they do not all have the same origin (Heynen et al., 1985; Wachtmeister, 1998). They have not received a lot of attention in the veterinary literature, but have been described in dogs (Sims, 1990; Sims & Brooks, 1990), cats (Doty & Kimura, 1963), and horses (Sandmeyer et al., 2007), among other species (Figs 10.4.7, 10.4.8).

Clinical Protocols

Along the years, different protocols have been used by different laboratories and hospitals for clinical evaluation of the fERG. In veterinary medicine, as mentioned above, guidelines for clinical ERG in dogs were published in order to facilitate reproducible and comparable results between different locations. This protocol is recommended for full evaluation of both rod and cone systems, and is useful for evaluation of photoreceptor disorders (Table 10.4.1; Ekesten et al., 2013).

Other, including more extensive, protocols are usually performed for research purposes, but can be applied to clinical cases if warranted, and be tailored to investigate the particular retinal cell of interest (Acland, 1988). In the clinic, shorter protocols may be, and often are, used in order to evaluate gross retinal function and differentiate retinal from postretinal blindness (e.g., optic neuritis, cortical blindness), or for preoperative screening of cataract patients. These may include the application of a bright flash (3 cd·s/m^2; four averaged flashes at 0.1 Hz) following 20 minutes of dark adaptation, which evaluates the combined rod–cone response. The QuickRetCheck protocol, designed by Narfström, evaluates retinal photoreceptor function under scotopic conditions over a very short period of time (Norman et al., 2008). In this protocol, following 20 minutes of dark adaptation, the rod system is evaluated by a weak light stimulus (0.01 cd·s/m^2; four averaged flashes at 0.5 Hz), followed by two single flashes of high light intensity (3 and 10 cd·s/m^2), evaluating the combined rod–cone response. These protocols last 40 s and 18 s, respectively. Such short protocols provide a crude interpretation of the overall retinal function and are not sufficient for a thorough investigation of retinal photoreceptor diseases.

Interpretation of the Results

Like any other diagnostic test, it is extremely important to interpret the ERG results based on a complete history and a thorough eye examination. This is crucial for accurate interpretation of the results. For example, a normal ERG response may be recorded from a blind dog with postretinal blindness (e.g., optic neuritis) or with mature cataracts.

The a- and b-wave amplitudes and implicit times should be compared to normal references. Decrease in amplitude, increase of implicit time, or absence of any component of the waveform compared to normal controls indicates pathology of the generator cells of the respective component. Each laboratory or hospital should establish their own normal references, as these may vary based on chemical restraint protocol, electrode type and location, stimulator type, stimulus characteristics (i.e., intensity and duration), and so on. Age and breed also add to the variability of the results. In dogs, postnatal retinal development affects the ERG's waveform and values. The b-wave first appears approximately 2 weeks after birth, and there is a marked increase in its amplitude over the first 4 weeks of life. Further increase of the fERG amplitudes and decrease of the implicit times are observed until 8 weeks of life, when they are approximating values of the adult dog (Gum et al., 1984; Kirk & Boyer, 1973). The flicker ERG also reaches adult values around 8 weeks of age (Acland & Aguirre, 1987). Additional changes to the fERG

Table 10.4.1 Stimulus and recording parameters for the recommended fERG protocol.

Dark Adaptation Time (Min)	Condition	Flash Intensity	Stimulator Background Light	Interstimulus Time (Rate)*	Test
0	Scotopic	0.01 cd·s/m^2	Off	≥ 2 s (≤ 0.5 Hz)	Rod response
4	Scotopic	0.01 cd·s/m^2	Off	≥ 2 s (≤ 0.5 Hz)	Rod response
8	Scotopic	0.01 cd·s/m^2	Off	≥ 2 s (≤ 0.5 Hz)	Rod response
12	Scotopic	0.01 cd·s/m^2	Off	≥ 2 s (≤ 0.5 Hz)	Rod response
16	Scotopic	0.01 cd·s/m^2	Off	≥ 2 s (≤ 0.5 Hz)	Rod response
20	Scotopic	0.01 cd·s/m^2	Off	≥ 2 s (≤ 0.5 Hz)	Rod response
20	Scotopic	3 cd·s/m^2	Off	≥ 10 s (≤ 0.1 Hz)	Combined rod–cone response
Light adaptation time (min)					
≥ 10	Photopic	3 cd·s/m^2	30 cd/m^2	≥ 0.5 s (≤ 2 Hz)	Cone response
≥ 10	Photopic	3 cd·s/m^2	30 cd/m^2	30 Hz	Cone response

Source: Ekesten et al. (2013).
* The recommended interstimulus time (and rate) is taken from the ISCEV protocol (Mcculloch et al., 2015).

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may occur over time, especially in older animals. Different breeds may also show different fERG values, as was well demonstrated by Sussadee et al. (2015). Hence, ideally, the fERG results of a patient should be compared to normal values that are age and breed matched, and are specific to each hospital or laboratory. However, comparing clinical fERG results to a breed and age matched controls may not be practical in all cases. The fERG of the cat also changes after birth, reflecting postnatal development of the retina. The b-wave appears during the first 10 days after birth, and adult values of the fERG are reached approximately 3 months after birth (Jacobson et al., 1987).

In the dog (as well as in other species), OPs cause notching in the peak of the b-wave. This may challenge the clinician as to where to place the marker in order to measure the b-wave amplitude and implicit time, and hence may affect the results. In the dog, peaks O_3 and O_4 are usually located at the peak of the b-wave (Fig. 10.4.8) and either of them may be the highest point on the b-wave. For consistent measurements of the ERG parameters, each hospital or laboratory should establish a protocol for dealing with this issue; that is, always placing the b-wave marker on O_3 or O_4, or averaging the values obtained by using O_3 and O_4 (Sims, 1990).

The electroretinographist should also be familiar with common sources of noise and artifacts, which in turn may help address them, and interpret the traces accordingly. On an awake or sedated animal, it is not uncommon to see a large positive component on the recorded trace, which is

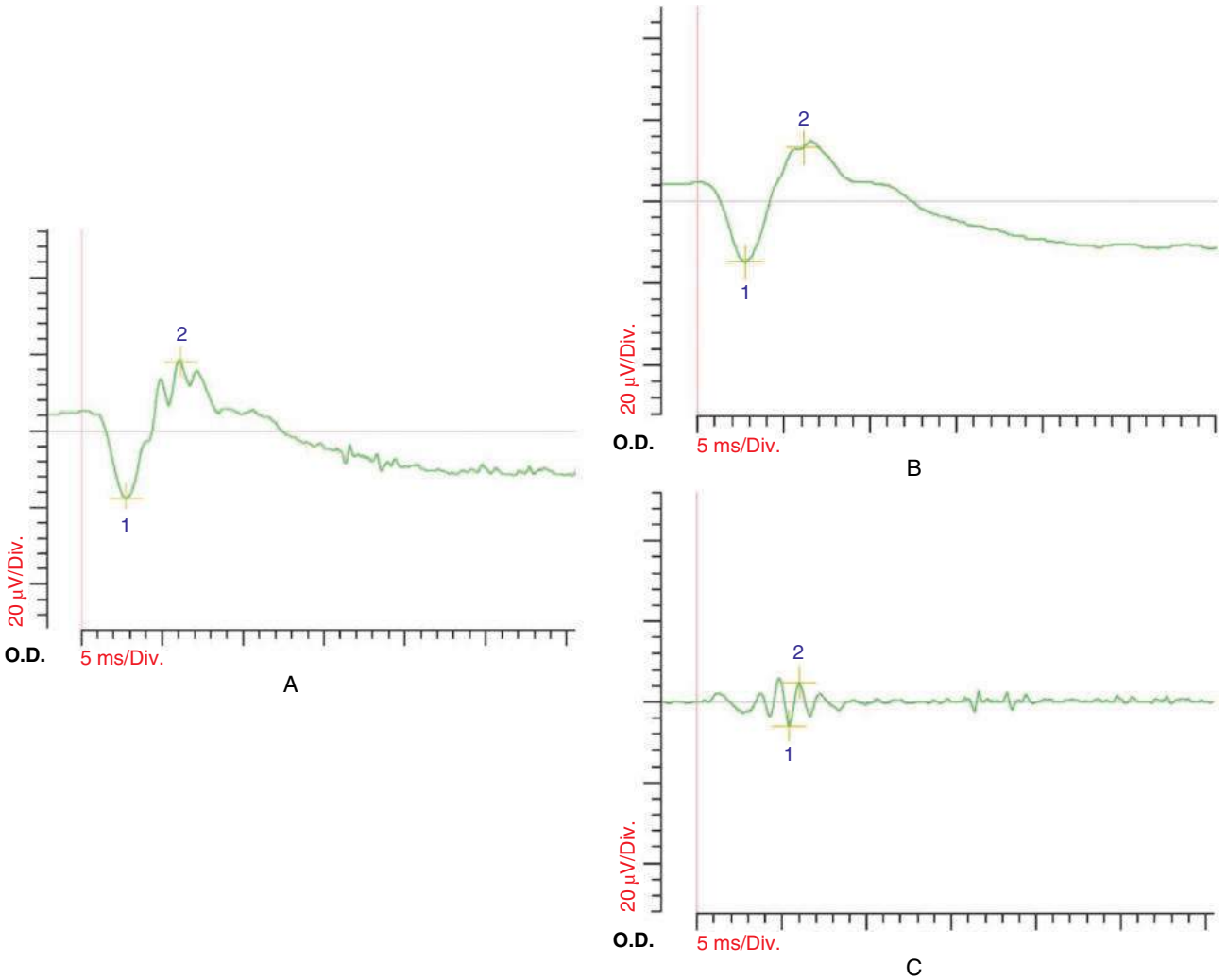


Figure 10.4.8 **A**. A combined rod–cone response. The a- and b-waves are clearly present (1 and 2, respectively). O_1 is noted on the ascending phase of the b-wave, and the oscillatory potentials (OPs) are notching the top of the b-wave, which is marked on top of O_3 (2). In this case, O_3 is also the highest point on the b-wave. The b-wave amplitude is measured from the a-wave trough (1) to the peak of the b-wave (2). **B**. In the same trace, the fast OPs were removed by *post hoc* filtering of frequencies faster than 70 Hz. Note that this also removed the high-frequency (low amplitude) noise observed on the trace after the peak of the b-wave. **C**. In the same trace, the slow components of the fERG (i.e., the a- and b-waves) were removed by *post hoc* filtering of frequencies slower than 70 Hz. This unmasked the OPs. The amplitude difference between markers 1 and 2 reflects the amplitude of O_3.

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the result of a postflash blink artifact (Fig. 10.4.9). This artifact should not be confused with the c-wave of the fERG (see below), which is recorded over a much longer period of time. Taking into consideration the implicit time of the c-wave will help with differentiating it from an artifact.

When noise is present, calculating its frequency based on the trace or Furrier analysis may help in identifying its source. Figure 10.4.10 clearly demonstrates a 60 Hz noise that originates from the main power line. Checking the ground electrode for appropriate placement, or replacing it if defective, may eliminate this noise.

Occasionally, the recording and reference electrodes may be switched accidently when they are connected to the inputs on the recording system. The lack of uniform color coding for these ports between different machines may add to the confusion. Switching these two electrodes will change the polarity of the trace, as seen in Fig. 10.4.11. Since the b-wave is defined as the first positive component of the fERG, the inverted a-wave may be confused with the b-wave, which will result in misinterpretation of the fERG trace. Apart of the waveform itself, paying attention to the implicit time should help identify the mistake, since the b-wave is expected approximately 30 msec after the flash (vs. approximately 11 msec for the a-wave).

Other Components of the fERG

In veterinary practice, clinical electroretinography is focused on recording and analyzing the a- and b-waves, and to a

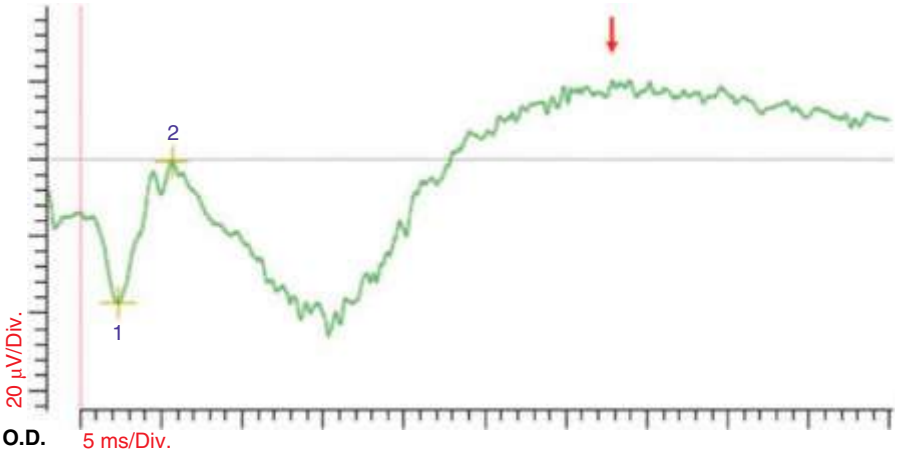


Figure 10.4.9 An fERG trace with a large, positive blink artifact (red arrow) that follows the a- and b-waves (peaks marked as 1 and 2, respectively). This artifact should not be confused with the c-wave.

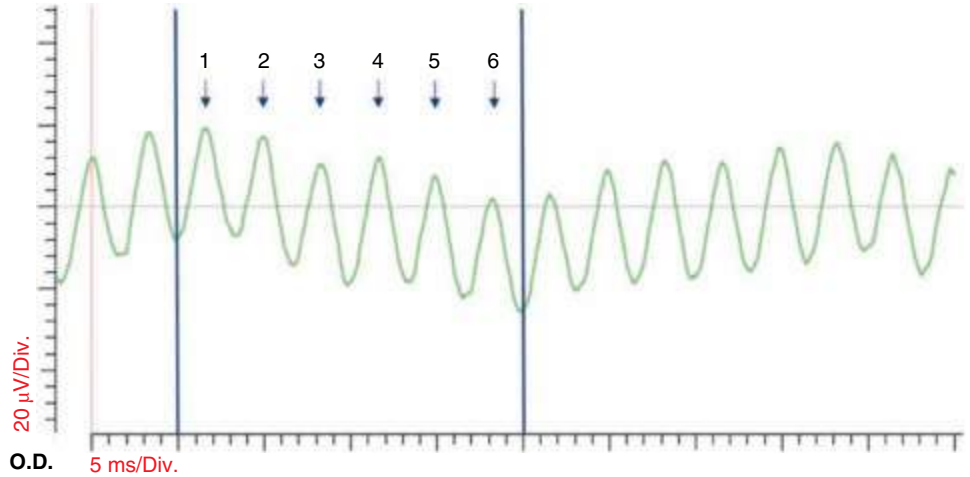


Figure 10.4.10 A large (~160 µV), regular sinusoidal wave, consistent with an electrical current, is masking the ERG wave form. There are 6 peaks (arrows) over a 100 msec period (marked by two blue vertical lines). Thus, this is a 60 Hz noise, which is the frequency of the electrical system in the USA. Checking the integrity of the electrode is a logical first step. Searching for major electrical equipment that may be the source of the noise is the second. Using a handheld, battery-operated ERG machine may help in eliminating a 60 Hz noise originating from the power line.

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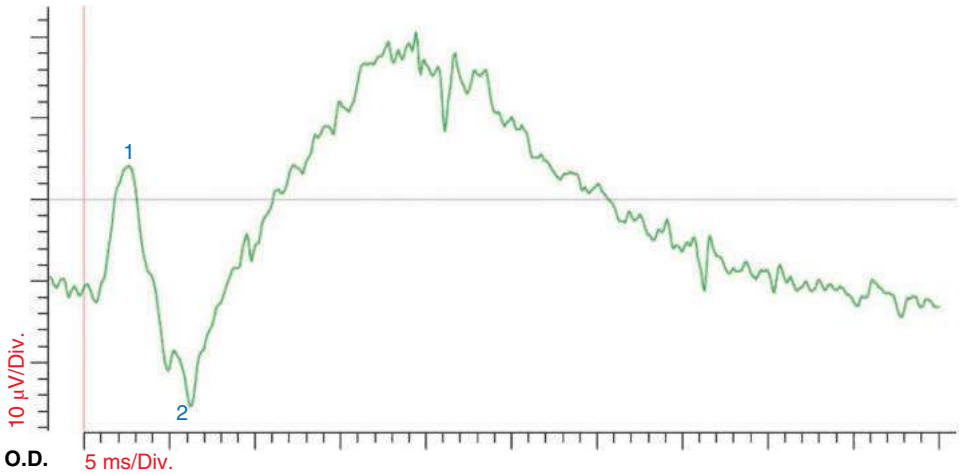


Figure 10.4.11 Connecting the recording electrode to the reference electrode's input on the pre-amplifier (and vice versa) results in an inverted trace. The a-wave (1) shows as the first positive wave, followed by the negative-looking b-wave (2). The implicit times of the two waves, approximately 12 msec for the first wave (1) and 30 msec for the second wave (2), should help identify the mistake. This emphasizes the need for the electroretinographist to be familiar with the recording system, as well as with the normal values of the different fERG components.

lesser degree the flicker ERG (and rarely the OPs). However, other components can be recorded by the fERG. To date, these components are mostly used for research, but they may also be used for the assessment of clinical cases. A brief description of additional selected components of the fERG is provided in this section.

The c-Wave

The c-wave is a late, positive potential, described in humans, dogs, cats, and other species (Dawson & Kommonen, 1995; Granit, 1933; Linsenmeier et al., 1983), and is considered to be a measure of interaction between the photoreceptors and retinal pigment epithelium (RPE; Linsenmeier et al., 1983). In humans as well as in the dog, the c-wave is not always present and there is great variability between individuals. When present, the c-wave peaks long seconds (species dependent) after the flash stimulus. The c-wave is not recorded during routine clinical fERG testing, as the latter is recorded over a much shorter period of 200–300 msec.

The i-Wave

The i-wave is a low-voltage, positive component of the fERG. It is recorded under photopic conditions, and follows the b-wave (Lachapelle, 1987; Peachey et al., 1989). The origin of the i-wave is believed to be the RGCs and/or the optic nerve (Rosolen et al., 2003; Rousseau et al., 1996); hence it may provide useful clinical information. However, the exact origin of the i-wave is yet to be determined. Rosolen et al. (2004) recorded the i-wave from the dog, cat, rabbit, mini-pig, cynomolgus monkey, and guinea pig. The i-wave in these species showed approximately 20 msec after the b-wave, and was absent in rats and mice (Rosolen et al., 2004; Fig. 10.4.12).

The Photopic Negative Response

The photopic negative response (PhNR) is a negative wave that occurs after the b-wave, and is measured from the baseline to the bottom of the negative trough following the b-wave (Kondo et al., 2008). Takada et al. (2017) have shown that the canine PhNR can be recorded in response to a series of light intensities under photopic conditions. However, up to 100 waveforms are needed to be averaged to reduce variability and background noise. They also showed that the origin of this component in the dog is the inner retina and RGCs. As such, the PhNR allows the evaluation of inner retinal damage in the glaucomatous canine patient (Whiteman et al., 2002).

The Scotopic Threshold Response

The scotopic threshold response (STR) is a small potential, recorded in response to very weak flashes (below the b-wave threshold) under scotopic conditions (Sieving & Nino, 1988). It has been recorded in several mammals, including dogs and cats (Sieving et al., 1986; Yanase et al., 1996). Although it is a negative response, it is different than the a-wave, and should not be confused with it. The STR is believed to reflect rod-driven activity of amacrine and RGCs, and has been shown to be affected by canine retinal degenerative disease (Kommonen et al., 1997).

Other Electrodiagnostic Tests

In human ophthalmology, electrodiagnostic testing of the visual system is performed by physicians or scientists who specialize in this field, as they require advanced training

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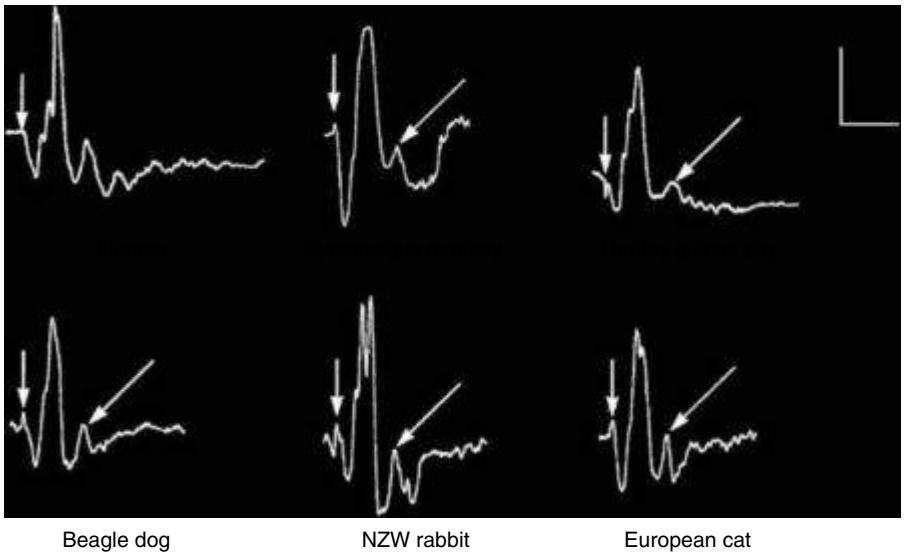


Figure 10.4.12 Representative examples of photopic ERGs from selected species. A vertical arrow (at the beginning of each tracing) identifies flash onset, while the oblique arrow after the b-wave points to the i-wave. a, a-wave; b, b-wave; i, i-wave. The calibration symbol is depicted at the side of the tracings: horizontal: 50 msec; vertical: 50 μV for human, cynomolgus monkey, and guinea pig and 100 μV for other species. (Reproduced with permission from Rosolen, S.G., Rigaudiere, F., Legargasson, J.F., et al. (2004) Comparing the photopic ERG i-wave in different species. *Veterinary Ophthalmology*, **7**, 189–192.)

and/or very expensive equipment. For these reasons, these tests are usually not available for, and are rarely performed in, veterinary patients. This section provides a brief overview of these tests.

Visual Evoked Potential

Like the fERG is the summed electrical activity of the retinal cells, the flash visual evoked potential (VEP) is the summed electrical potentials in the visual cortex triggered by visual stimulation and recorded at the scalp. The VEP reflects the function of the entire visual pathway from the retina to the visual cortex. As such, it may provide diagnostic information regarding the function of the visual system, and is used routinely in human medicine, complementary to the fERG. A basic VEP can be recorded using a single channel and this is probably the most practical one for veterinary patients. Multiple channel recording (to assess chiasmal and retrochiasmal activity) requires advanced equipment that is not available to most veterinary ophthalmologists. VEP was recorded from many species, including dogs (Boyer & Kirk, 1973; Kimotsuki et al., 2005; Sato et al., 1982; Sims et al., 1989; Strain et al., 1990), cats (Creel et al., 1973; Sims & Laratta, 1988), and horses (Strom & Ekesten, 2016), as well as other species.

In dogs, different techniques, including variation in the state of dark adaptation, mydriasis, and electrode locations, have led to variable results of VEP recordings. However, Strain and his colleagues established a reproducible VEP protocol, which was employed successfully in both anesthetized and conscious dogs (Kimotsuki et al., 2005, Kimotsuki et al., 2006; Strain et al., 1990). As the VEP amplitudes are much smaller than the fERG ones (up to approximately 15 μV), the VEP trace is more susceptible to noise (due to decreased signal-to-noise ratio). As a result, a higher number of averagings may be required. A narrower band-pass filter (1–100 Hz) may further help to reduce the noise level. The electrodes were placed on the midline of the scalp; the recording, reference, and ground electrodes were placed over the midline of the nuchal crest (Oz), forehead (Fpz), and vertex, respectively (Kimotsuki et al., 2005; Strain et al., 1990). The flash VEP protocol by Strain et al. (1990) resulted in three positive (P1, P2, and P3) and two negative (N1 and N2) components by 150 msec after the flash. The peaks' implicit times were approximately 15, 30, 55, 80, and 140 msec for P1, N1, P2, N2, and P3, respectively. Kimotsuki et al. (2005) have shown, utilizing a similar protocol, that P1 and N1 are referred to the retinal potentials, P2 is referred to the potentials from the retina to the brainstem, and N2 to those from the brainstem to the visual cortex.

Like the fERG, the VEP is changing rapidly in the postnatal period. The VEP was first recorded 10 days after birth in the dog, and the implicit times of the VEP components progressively decreased from day 16 to day 28 (Boyer & Kirk, 1973). Age-related differences were also noted in adult dogs (1–10 years of age), with the implicit times of P2, N2, and P3 being significantly delayed with aging. The amplitudes of

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P2–N2 and N2–P3 also showed a significant correlation with aging (Kimotsuki et al., 2006; Fig. 10.4.13). As such, like with the fERG, the results of the VEP should be compared to age- and breed-matched controls, using a similar technique.

More recently, a method was established for flash VEP recording in the horse (Strom & Ekesten, 2016). The ground electrode was placed at the forehead and the reference electrode approximately 3 cm caudal to the lateral canthus. The most consistent and reproducible recordings were achieved when the recording electrode was placed in the midline, rostral to the nuchal crest, and ≥ 100 responses were averaged. Like in dogs, intraindividual variability was noted. Reproducible components were recorded in all horses and include N1, P2, N2, and P4, with a mean implicit time of 26, 55, 141, and 216 msec, respectively. Additional studies are needed to assess the clinical application of this diagnostic tool in the horse.

A pattern reversal, or pattern onset-offset stimuli, can also be used for VEP recording. However, these tests require visual fixation, which can only be achieved under anesthesia in veterinary patients. The pattern-reversal VEP is most useful for evaluation of the optic nerve function (Robson et al., 2018). The need for both general anesthesia and additional, expensive equipment as well as advanced training is making the pattern VEP less practical in clinical veterinary ophthalmology.

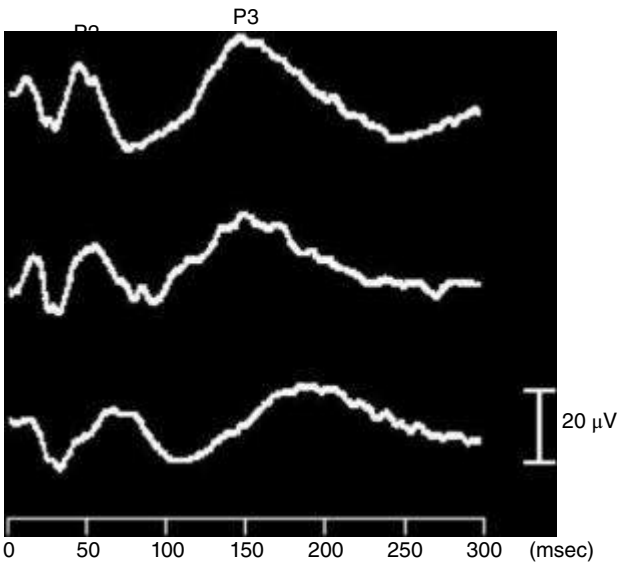


Figure 10.4.13 Typical waveforms of the flash visual evoked potential in young (1-year-old), middle-aged (9-year-old), and older (15-year-old) dogs. The latencies of P2 and N2 were delayed in older dogs, especially in the 15-year-old Beagle. (Reproduced with permission from Kimotsuki, T., Yasuda, M., Tamahara, S., et al. (2006) Age-associated changes of flash visual evoked potentials in dogs. *Journal of Veterinary Medical Science*, **68**, 79–82.)

Pattern Electroretinogram

The pattern electroretinogram (PERG) is an effective way to assess the inner retina, and mainly the ganglion cells, and as such it is an excellent tool to diagnose early glaucomatous damage (Ben-Shlomo et al., 2005; Forte et al., 2010; North et al., 2010). The exact generator of the PERG may vary by species. The location of the electrodes for the PERG is similar to that for the fERG. However, unlike the fERG, there is no change in illumination of the retina during PERG testing. Instead, the PERG is recorded to an alternating high-contrast checkerboard (preferably) (Robson et al., 2018) or gratings; that is, the black and white components of the checkerboard alternate in a predetermined rate, while the overall luminance stays constant. The size of the checkerboard as well as the reversal rate can be changed, and the stimulus can be tailored to a specific subset of ganglion cells (Ben-Shlomo et al., 2005; Forte et al., 2010). Like VEP, the amplitude of the PERG is much smaller than the fERG, making it more susceptible to noise contamination, and it requires a high number of averagings. The main components of the PERG are the first positive component and the second negative component, with approximate implicit times in human subjects of 50 msec and 95 msec, respectively, and as such they are named P50 and N95 (also known as P1 and N2; Fig. 10.4.14). The PERG has been used for research purposes to evaluate glaucoma damage in dogs (Grozdanic et al., 2010; Hamor et al., 2000; Ofri et al., 1993) and cats (Schallek et al., 2012). However, similar to the pattern VEP, in addition to the equipment and expertise needed, fixation of gaze is crucial for appropriate recording of the PERG, and as such it cannot be performed reliably on conscious animals. Therefore, the fERG i-wave is a more practical way to assess RGCs' function in canine and feline patients (Rosolen et al., 2004).

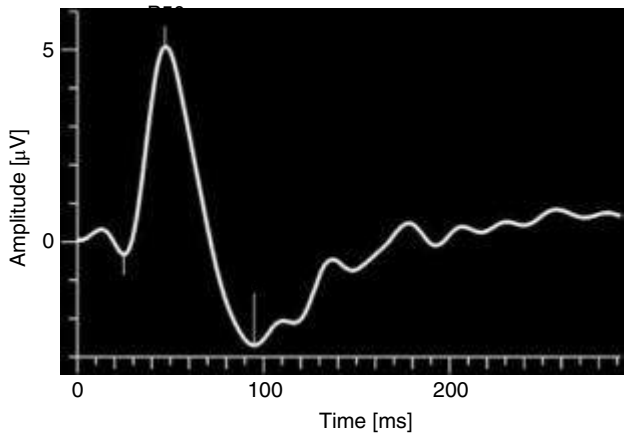


Figure 10.4.14 A pattern electroretinographic (PERG) trace. Note the low amplitude compared to the fERG. (Reproduced with permission from Bach M., Brigell M.G., Hawlina M., et al. (2012) ISCEV standard for clinical pattern electroretinography (PERG): 2012 update. *Documenta Ophthalmologica*, **126**, 1–7.)

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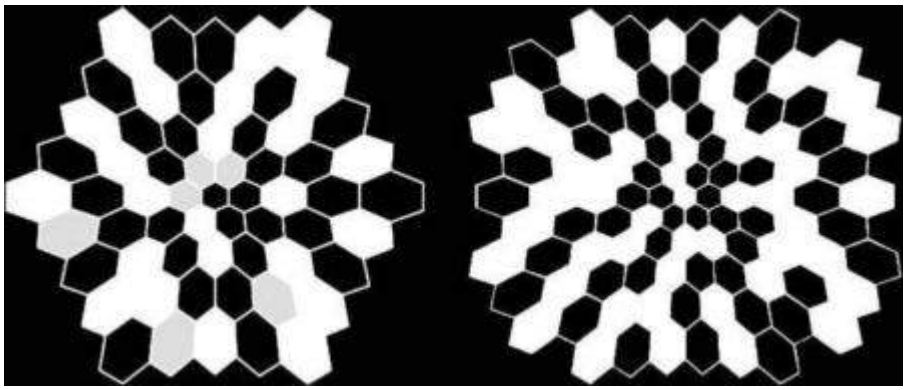


Figure 10.4.15 Multifocal electroretinography (mfERG). Stimulus pattern consisting of 61 (**A**) and 103 (**B**) scaled hexagons and typical mfERG trace arrays with 61 elements (**C**) and 103 elements (**D**). (Reproduced with permission from Hood, D.C., Bach, M., Brigell, M., et al. (2012) ISCEV standard for clinical multifocal electroretinography (mfERG) (2011 edition). *Documenta Ophthalmologica*, **124**, 1–13.)

Multifocal electroretinogram

The multifocal ERG (mfERG) is a relatively new electroretinographic test, providing geographic mapping of retinal activity. The electrode placement is similar to that for the fERG, and the stimulus displays an array of hexagons (usually 61 or 103) in different sizes (Fig. 10.4.15), covering 20° to 30° (radius) of the retina, and scaled to produce a local response of approximately equal amplitude for each hexagon, in the normal human retina (Sutter & Tran, 1992). During the recording, each hexagon flickers in a pseudo-random sequence of black and white presentation. This is in contrast to the PERG, where the black and white squares of the checkerboard are of equal size and number, and they always switch from black to white (and vice versa) at the same rate. Then, in the mfERG, through complex mathematic extraction and cross-correlation between the stimulation sequence and the recorded ERG, the signal attributed to each hexagon is presented (Hood, 2000). The standard mfERG is cone driven, and recording the mfERG rod response, though doable, is challenging (Hood et al., 1998).

The standard mfERG reflects electrical activity in the outer retina, mainly bipolar cells and to a lesser extent the cones. The inner retina (i.e., RGCs and amacrine cells) has a minor contribution to the mfERG (Hare & Ton, 2002; Hood et al., 2000). The standard mfERG shows an initial negative component (N1), a positive component (P1), and a second negative component (N2). In human subjects, N1 is composed of the same components as the a-wave of the fERG, and P1 is composed of the same components as the b-wave and OPs (Hood et al., 1997). As with other tests in this section, given the requirement for advanced training and costly equipment, as well as fixation of gaze (and hence the need for general anesthesia in veterinary patients), and the lack of substantial medical benefit from this test to the veterinary patient, it is unlikely to become a common diagnostic tool in veterinary ophthalmology.

Electro-oculogram

The electro-oculogram (EOG) evaluates the RPE and it is recorded by two electrodes placed at the medial and lateral canthi of each eye, and assesses the standing potential of the pigment epithelium. The maximum value measured under light adaptation divided by the smallest dark-adapted value represents the Arden light peak/dark trough ratio, which assesses the generalized function of the RPE/photoreceptor complex. With any severe rod dysfunction, the EOG will not provide diagnostic value (Heckenlively et al., 2006; Robson et al., 2018). In order to perform the test, the patient has to move the eyes horizontally, from side to side. Consequently, each time the eyes move from side to side, the different electrodes are being exposed to a different polarity of the eye, and the difference between the electrodes can be recorded. Since this test requires the patient's cooperation, it is impractical in veterinary patients.

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Ophthalmic Genetics and DNA Testing

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The Canine Genome

The first working draft of the canine genome was made available in 2004 (CanFam1.0), revised in 2005 (CanFam2.0) (Lindblad-Toh et al., 2005), and revised again in 2011 (CanFam3) (Fig. 11.1) (Hoeppner et al., 2014). The availability of a good quality sequence of the canine genome coupled with modern molecular techniques has greatly facilitated the study of genetic traits in this species.

The canine genome has approximately 2.4 billion basepairs of DNA spread across 38 pairs of autosomal chromosomes and two sex chromosomes (the human genome is just over 3 billion basepairs). Across the genome ~20,700 protein coding genes were predicted, most being homologues of human genes. Because an organism has two copies of autosomal chromosomes which are present in all cell nuclei, except for gametes, each individual has two copies of each gene that is on the autosome (one maternally derived, the other paternally derived). The two genes or chromosomal DNA features (the maternally and paternally derived) are known as alleles. Thus, an individual will have two alleles of each stretch of DNA on an autosomal chromosome.

The dog initially used to supply DNA for the canine genome project (National Human Genome Research Institute) was "Tasha," a female Boxer. A Boxer was chosen because the breed was reported to have low genetic variability. The genome sequence of dogs from multiple breeds are now available revealing the normal genetic variability between breeds.

Mapping of genetic traits can be performed using heritable variations in DNA sequence (polymorphisms) from across the genome. Prior to the sequencing of the genome, variations in genome sequence that were inherited in a Mendelian fashion had been identified and were used for mapping genetic traits. Microsatellites, which are stretches of repeated nucleotides, were identified and sets of microsatellites that are positioned reasonably evenly across the canine genome were established for use in mapping (Sargan et al., 2007). Studies using these sets of microsatellites in canine families allowed their relative positions across the genome to be established. Microsatellites are repeats of two (dinucleotide), three (trinucleotide), four (tetranucleotide), or more runs of nucleotides. The variability of these markers is in the number of repeats between different alleles. Variability in microsatellites arose because of mistakes that the cellular DNA replication machinery made in copying the repeated DNA units during meiosis, and these differences became fixed in the population. Sets of markers such as microsatellites that are located within or close to candidate genes for inherited retinal degenerations (IRDs) in dogs have been developed to be used to investigate any new IRD by testing for association between the marker locus and the IRD. An association would be suggested if the version of the marker was shared by all the dogs with the IRD under investigation (Winkler et al., 2017). Microsatellites are useful for this approach because each one can have several different versions within a population. Another type of variable marker that has become very important for mapping is the single-nucleotide polymorphism (SNP). SNPs are a variation of a single nucleotide at one particular locus. They therefore only have two variations (alleles) making them less powerful for mapping than microsatellites which may have multiple different alleles. However, the high density of SNPs across the genome makes them very valuable for mapping. SNPs, as well as additional microsatellites, were identified during the sequencing of the canine genome. Lists of SNPs are available online and have been used in construction of microarray mapping tools (see later section). The annotation of the genome also highlights repeat elements which include microsatellites, thus allowing the identification of additional microsatellites that if polymorphic (i.e., present as more than one version in the population) can be used for mapping purposes.

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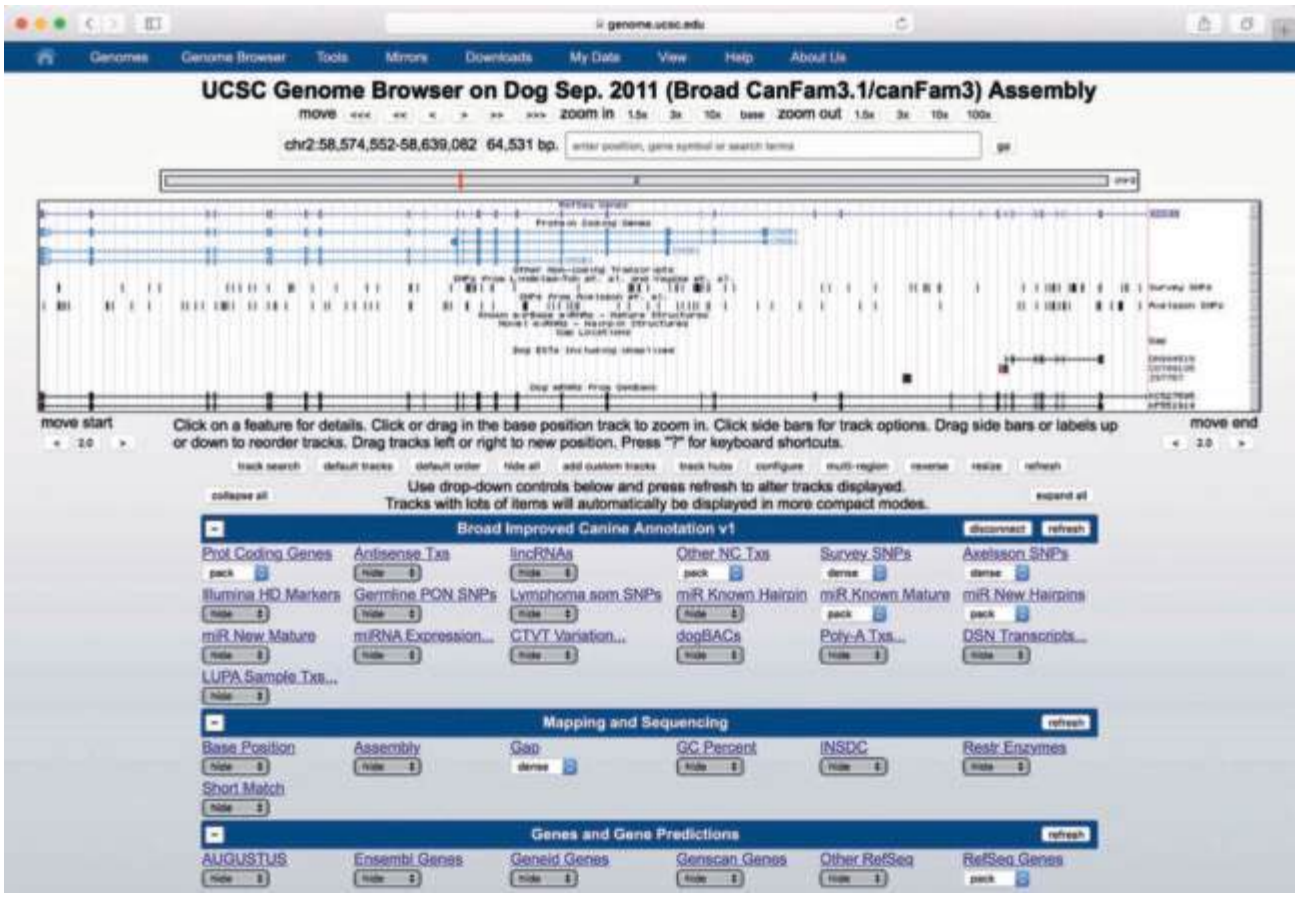


Figure 11.1 This is a screenshot of the UCSC Genome Browser showing the region of the canine *Cngb1* gene.

Other Genomes

The genomes of many other species (including cat, horse, and farm animals) have been sequenced above and are available through online sites such as: University of California Santa Cruz Genome browser (genome.ucsc.edu); Ensembl (ensembl.org); NCBI (ncbi.nlm.nih.gov/genome).

The Structure of Genes

DNA is formed from four nucleotides; two purines, adenine (A) and guanine (G) and two pyrimidines, cytosine (C) and thymine (T). In double-stranded DNA, adenine of one strand pairs with thymine on the other (complementary) strand and cytosine pairs with guanine. Genes are sections of DNA that code for protein production. The genes are made up of exons which have the genetic information that is transcribed into messenger RNA for subsequent translation into proteins. The coding DNA after translation into messenger RNA is read in triplets of nucleotides (codons). The first codon of the translated sequence, known as the start codon, consists of adenine, uracil (thymine in the DNA), and guanine (AUG), which codes for methionine and is the starting amino acid of the protein. Subsequently from the start codon, each three-nucleotide codon instructs the insertion of a particular amino acid or tells the cell to terminate the protein (a stop codon). Most amino acids are coded for by more than one triplet of nucleotides, for example, alanine is coded for by either GCA, GCC, GCG, or GCT. The exons (DNA of the gene that is converted into messenger RNA) are separated by noncoding stretches of DNA that are called introns. During formation of messenger RNA, the introns are removed or "spliced" out leaving a continuous stretch of coding RNA. The number of exons and intervening introns varies between genes. The roles of noncoding regions of DNA are becoming better understood and have been shown not to be the "junk" DNA they were once considered. Some noncoding portions of the DNA on the chromosomes are promoters for genes. Promoters control gene expression and respond to elements to increase or decrease levels of expression. They also control factors such as tissue specificity of expression. Noncoding functional RNAs originate from the noncoding DNA. These include ribosomal RNA, transfer RNA, and microRNAs. MicroRNAs are short RNA molecules that play an important role of regulation of mRNA

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translation and thus influence the production of proteins. Study of the role of genomic DNA that does not code for proteins is improving our understanding of the importance of these regions. Other noncoding elements include transposons and retrotransposons that are mobile genetic elements. These include both short interspersed nuclear elements (SINEs) and long interspersed nuclear elements (LINEs). SINEs are sometimes described as "jumping genes"; they are mobile elements that can propagate within the genome via a "copy and paste" mechanism. If the insertion of a SINE element occurs in a gene-coding region, it may result in altered gene function. For example, the merle coat pattern is caused by a SINE insertion in the *SILV* gene which is important in normal melanocyte function (Clark et al., 2006). Progressive retinal atrophy (PRA) in the Tibetan Terrier and Tibetan Spaniel is caused by a SINE insertion in the *FAM161A* gene (Downs & Mellersh, 2014).

Alternative Splicing of Genes

Alternative splicing allows for different gene products to be produced from the same gene. The exons used vary between the different gene products; for example, one exon may be included in some of the mRNAs and not in others. This may be dependent on factors such as which tissue the gene is being expressed in. Alternative splicing thus allows for multiple different proteins to be produced from a single gene and explains how complex organisms can be produced from what could be considered to be a low number of genes.

Genetic Traits

There is a complex interaction between the genetics of an individual and the environment, both of which combine to result in the individual's phenotype. The phenotype includes physical traits as well as pathological conditions. Some pathological conditions are straightforward inherited conditions, such that if the gene mutation causal for the condition is present, the individual will develop the condition. However, other factors such as interactions of other genes can alter the disease phenotype. For example, these factors might influence age of onset, rate of progression, or even whether the trait is expressed at all (thus contributing toward variable penetrance of some genetic traits). This is often described as "background genetic effects." Some hereditary conditions are under the influence of several genes and are described as having polygenic inheritance. Other genetic variation confers susceptibility or resistance to disease, for example, resistance to infection or predisposition to cancer formation. Thus, a genetic predisposition for a condition may be present, but unless there is an environmental influence, the condition may not develop, or may be less severe.

What DNA Changes Result in Hereditary Disease?

Disease Caused by Changes in Coding Regions of DNA

Gene mutations are changes in the genomic DNA sequence that affect coding regions of DNA. They can arise from external influences such as radiation or mutagenic chemicals or internal factors such as errors during meiosis or DNA replication. They can also result from insertions of retrotransposon mobile elements into genes as previously described. DNA mutations can be insertions or deletions of DNA (varying in size from one nucleotide to a large region of DNA) or be a change in a single nucleotide. DNA change within a coding region of a gene can alter the gene coding by changing the amino acid that is coded for (a missense mutation). They can change the coding from that for a particular amino acid to a stop codon (codes to terminate the protein production), known as a nonsense mutation or premature stop codon. Some DNA variations do not alter the amino acid that is being coded for (silent mutation) and are therefore not expected to alter the protein production in any significant way. Insertions or deletions can alter the reading frame thus changing the amino acids coded for and often leading to a premature stop codon. Frame deletions or insertions (removal or addition of codons without altering the "read" of the downstream codons) can occur and alter the coded protein that might alter its function or its folding to cause disease, or it might be tolerated.

Disease Caused by Changes in Noncoding Regions of DNA

Changes in DNA in noncoding regions can also result in disease. There are several possible mechanisms. These include DNA changes that involve regulatory regions such as gene promoters. The regulatory regions influence expression levels, and alterations in these regions might reduce gene expression. Some DNA changes in introns can alter the splicing of exons that occurs during messenger RNA production. An example of the latter is an alteration in an intron in *CEP290* that results in autosomal recessive PRA in the Abyssinian and other cat breeds (Menotti-Raymond et al., 2007, 2009). The change in the intron creates a new site for the exon/intron donor site adding additional nucleotides to the exon in question. These additional nucleotides change the "read" of the coding introducing a premature stop codon that is predicted to shorten the protein (Fig. 11.2).

Nonsense- Mediated mRNA Decay

Nonsense-mediated mRNA decay is a mechanism by which the cell prevents the translation of abnormally shortened

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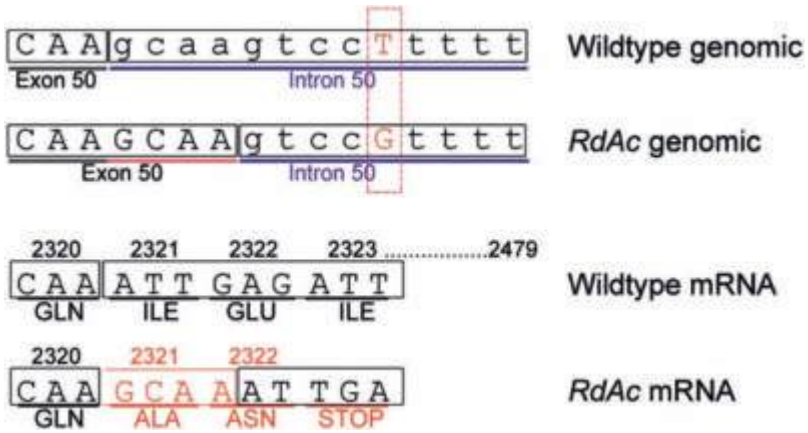


Figure 11.2 Details of the gene mutation in *CEP290* that causes the RdAc form of PRA in the Abyssinian and other breeds of cat (Menotti-Raymond et al., 2007). The region at the end of exon 50 and beginning of intron 50 is shown. There is a change of a T to a G nucleotide nine positions into the intron. This creates a strong splice donor site that in the mutant version is used instead of the wild-type splice site. In the lower part of the figure, the resulting wild type and RdAc mRNA and protein translation can be seen. The altered splice site adds four nucleotides to exon 50 (marked in red) leading to a frameshift and coding for two altered amino acids (shown in red) followed by a stop codon.

transcripts. It allows the cell to regulate whether alternatively spliced transcripts are translated or not. It is thought that many of the possible alternatively spliced transcripts do not produce a protein product because they are degraded in the cell by this surveillance mechanism. If a DNA mutation results in the introduction of a premature stop codon, the resulting transcript might undergo nonsense-mediated decay. This is more likely if the premature stop codon is positioned in the mRNA more than about 50 nucleotides upstream of the final exon. This mechanism means that the altered mRNA is not translated, preventing production of a shortened peptide that could have a deleterious effect on the cell. Abnormalities resulting from degradation of mRNA with a premature stop codon result from a lack of the gene product. A mutation that results in a loss of gene product often results in recessive conditions. The fact that the body can function normally with only one functional copy of the gene shows the flexibility that is present in many of the biochemical pathways in the body. The situation where a phenotype results from the lack of one functional copy of the gene in the presence of a normal copy of the gene is described as haploinsufficiency. A single functional copy of genes such as those controlling development may not be sufficient to create a normal phenotype. Haploinsufficiency is one mechanism for dominantly inherited disease.

Modes of Inheritance

Autosomal Recessive Inheritance

Autosomal recessive conditions are ones where the mutation is on an autosome and the animal heterozygous for the mutation does not have an obvious phenotype. Animals homozygous for the mutation will develop the disease. Mutations in genes coding for proteins in biochemical pathways where the presence of a reduced protein level (as in the heterozygous animal) does not result in a deleterious effect – known as being haplosufficient – cause recessively inherited conditions. The presence of carrier animals (heterozygotes) in the population makes eradication of such conditions difficult without having a DNA-based genetic test. The condition can skip generations.

Autosomal Dominant Inheritance

Conditions resulting from the presence of a mutation on an autosome that in the heterozygous state causes the condition are described as autosomal dominant. Dominant disease (if fully penetrant) does not skip generations. Another feature is that a cross between two affected animals can produce unaffected offspring (unlike autosomal recessive conditions where an affected to affected mating results in all offspring being affected). Dominant disease can result from mutations in structural genes, in developmental genes, and in circumstances where the mutated gene product is produced and has a deleterious effect. Examples of the latter would be when the mutated product is not trafficked appropriately within the cell and accumulates in an abnormal location, where it irreversibly binds a partner protein blocking a pathway, or when it is in some other way toxic to the cell. Such gene mutations are described as having a dominant negative effect. The mutation in the transcription factor *CRX* that was identified in Abyssinian cats with dominant early-onset PRA is one example of a condition which results when the mutant protein binds to gene transcription sites but fails to activate them (Menotti-Raymond et al., 2010; Occelli et al., 2016). Diseases that result when one copy of the gene is not produced and a single copy is not sufficient to create a

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normal phenotype are described as resulting from haploinsufficiency as described earlier.

X- Linked Dominant and Recessive Inheritance

Mutations that involve genes on the X chromosome lead to X-linked conditions. X-linked recessive disease is manifest where all copies of the X chromosome have the mutation thus affecting males (XY, which are described as being hemizygous) and females (XX) that are homozygous for the condition. Such conditions would be much more common in males than in females. X-linked dominant conditions would affect males (XY) and females (XX) heterozygous for the condition. Note that for avians, the males are homogametic (ZZ) whereas the females are heterogametic (ZW).

Random X Chromosome Inactivation (Lyonization)

Random X chromosome inactivation (Lyonization) is a normal phenomenon whereby only one X chromosome is active in the cells of females. This is required so that the female does not have both copies of X chromosome genes active (i.e., twice as many as the male). The inactivated X chromosome is visible in the nucleus on microscopy as the Barr body. In mammals, the inactivation of one of the chromosomes is random (i.e. either X chromosome could be inactivated) and occurs during development at the blastocyst stage. Once one X chromosome is inactivated, all daughter cells from that cell will have the same X chromosome inactivated. This has the effect that there are groups of cells with the same X chromosome active. The coat color pattern of tortoiseshell cats is a commonly quoted example of random X chromosome inactivation. The gene that confers black or orange color (dependent on the version of the gene) lies on the X chromosome. The patches of one coat color indicate that the cells in that region of the skin all have the same X chromosome inactivated. An ophthalmologic example is female dogs that are carriers of X-linked PRA. The retinas of these dogs have patches of cells with one X chromosome inactivated. In the regions where the normal copy of the gene is inactivated and the mutant copy is expressed, retinal degeneration develops (Beltran et al., 2004).

Mitochondrial Inheritance

Mitochondrially inherited conditions are those that are caused by mutations of the mitochondrial DNA. Mitochondrial DNA is inherited in a maternal fashion; that is, it is passed from the dam to her offspring. An ophthalmic example of a maternally inherited condition is Leber hereditary optic neuropathy in humans.

Complex Traits

Complex traits result from interaction of several genetic factors, often with additional environmental influences. Predisposition to certain disorders may be complex, multifactorial, or polygenic. The form of PRA (cone rod dystrophy type 1) in Miniature Longhaired Dachshunds and other breeds associated with a mutation in *RPGRIP1* has on further study been shown to be a complex condition with a second locus influencing expression of the phenotype and influences of additional loci being suspected (see below and Chapter 25 for more details). Conditions that result from conformational differences in dogs (entropion, ectropion, etc.) may be under the influence of several genes that control head conformation, eyelid length, etc.

Quantitative Trait Loci

Quantitative trait loci (QTL) describe the several genetic loci that contribute to a particular characteristic. Studies to identify the QTL that influence body conformation, fecundity, etc. in production animals are important. The QTL that influence the development of complex disease traits are also important. Some studies have been undertaken to try to identify the QTLs that influence the rate of progression of the progressive rod cone degeneration (*PRCD*) form of PRA (Zangerl et al., 2009). In mice, a QTL was mapped that influences susceptibility to light-induced retinopathy (Danciger et al., 2000). It was eventually identified as a polymorphism in the *RPE65* gene. The investigation of QTLs is going to become an important step in our understanding and development of therapies for diseases in the future.

Pharmacogenetics

Pharmacogenetics refers to the genetic variation that influences response to drugs. For example, genetic traits can influence drug metabolism in individuals. This can lead to certain individuals being at higher risk of drug side effects or drug reactions compared with other individuals. In the future, the study of pharmacogenetics might allow the tailoring of drug therapies to individuals to minimize side effects and allow for optimal outcomes. A gene mutation conferring sensitivity to neurotoxic side-effects of drugs such as ivermectin has been identified in dogs (Mealey et al., 2002).

The Process of Identification of Disease-Causing Mutations

Tools that allow identification of the DNA change underlying genetic disease and genetic traits have been developed, enabling these features to be investigated in many species. The investigation of genetic disease within a dog or cat breed should start with careful and precise phenotyping of the condition coupled with pedigree analysis to try to ascertain

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whether a simple Mendelian trait is present, whether the condition is heterogeneous, or is a complex genetic trait. The phenotyping and pedigree analysis might suggest potential candidate genes for the condition. Such candidate genes are based on those shown to cause analogous diseases in other breeds, or other species, or are based on the known function of particular genes. Some conditions have numerous potential candidate genes; for example, hereditary retinal dystrophies show great genetic heterogeneity, and there are several examples of breeds of dog in which several forms of PRA are segregating (Downs et al., 2014a).

In other conditions, there are just a few candidate genes that might be responsible for the condition. Screening of candidate genes within families in which the disease is segregating can be by use of genetic markers (such as microsatellites and SNPs) that are very closely linked to the candidate gene under investigation. These can be used to show if the disease status is linked to any of the potential candidate genes. Sequencing of any linked candidate gene to identify any potential disease-causing mutations is the next step.

Genome-Wide Association Study (GWAS)

The canine genome project led to the identification of large numbers of genetic variants across the canine genome. Variations at single nucleotides are known as SNPs. These are naturally occurring genetic variations that can be used for gene mapping. Microarrays that allow genotyping of individuals for large numbers of SNPs across the genome are available. Affymetrix and Illumina both manufacture microarrays for different species that can be used to genotype large numbers of SNPs. The Illumina canineHD whole genome genotyping BeadChip will genotype a dog at over 170,000 SNPs across the genome. At the time of writing, new high-density SNP arrays for dogs are being released detecting larger numbers of SNPs and insertion/deletions equally distributed across chromosomes. These are called Axiom arrays A and B and between them include approximately 1.1 million canine markers; Axiom array A having over 460,000 markers and B having over 670,000 markers. To investigate an hereditary trait, both diseased and control animals are genotyped using the SNP microarray. The animals used need to be carefully phenotyped to be as confident as possible that the diseased animals have the same hereditary condition. With conditions that show genetic heterogeneity, such as PRA, it can be difficult to be certain that the pool of diseased animals have the exact same condition (i.e., the same causal mutation). Computer programs are used to analyze the SNP genotyping data. For recessive disease, screening is performed to identify regions of homozygocity shared across the affected animals. If an association study is performed, the results at each SNP are analyzed to see if one version of a SNP is significantly correlated with the disease status.

DNA Sequencing

Several techniques have been developed for sequencing DNA. Some methods are suitable to ascertain the DNA sequence of a short stretch of DNA accurately – such as copies of a DNA sequence generated by a polymerase chain reaction (PCR). These most commonly use "Sanger sequencing" being based on the dideoxy termination method developed by Sanger and Coulson.

Next-generation sequencing techniques are used for large sequencing projects up to whole genome sequencing. These techniques most commonly ascertain the DNA sequence of vast numbers of short strands of DNA prepared from the DNA to be sequenced. There is "massive parallel" sequencing of these short strands such that the average number of repeat sequencing reads of each section of DNA of the target sequence gives good coverage of the genome, for example a "depth of coverage" of 30× might be chosen meaning that there are an average of 30 reads for each region of the genome. These short strands of DNA are typically aligned by computer software to the reference sequence of the organism being sequenced. Some other next-generation techniques are designed to sequence longer strands of DNA using different technologies. These long-read techniques are better at identifying structural DNA rearrangements than the short fragment typical next-generation sequencing. Further analysis of the result of sequencing includes the identification of where the sequences obtained differ from the reference genome or between samples. So, if a series of disease cases (for example animals with one specific genetic disease) were sequenced and compared with control samples (unaffected control animals) the software could identify where there were differences between the cases and controls and whether these DNA variations were in coding regions of genes, introns, or intergenic regions. If they were in coding regions it could also predict the effect on the protein that was being coded for. There are different methods of next generation sequencing that have specific advantages and disadvantages with regular advances being made in these technologies driving down the cost of sequencing.

Using the next generation sequencing technologies, the whole, or part, of the genome of an animal can be sequenced. Examples of sequencing just part of the genome include exome sequencing and targeted sequencing. In exome sequencing the exons and flanking introns are sequenced. Since the coding portions of the genome (exons of the genes) only make up a small proportion of the entire genome (~1%), exome sequencing can have much lower costs because only a small fraction of the DNA is sequenced using this approach. This can be effective in identifying coding region changes and intron/exon splice site mutations but will not identify other noncoding disease-causing variants. Targeted sequencing is used to sequence a specific portion of the genome.

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For example, if a genetic disease was mapped to a specific chromosomal region a targeted sequencing approach could be developed to sequence the DNA from just the mapped region. This approach is relatively expensive to set up, but once it is set up, it can be used cheaply on DNA from many individuals. Next generation sequencing can also be used to identify what genes are being expressed in a particular tissue. To do this, the RNA is isolated from the tissue in question and then sequenced (RNA-Seq). The resulting information on the genes active in that tissue is known as the transcriptome.

The constant improvements in these technologies and continued reduction in costs means the identification of disease-causing mutations becomes easier, and the use of genomic information and transcriptomes can improve our understanding of disease processes and help introduce approaches such as personalized medicine.

Tests for Genetic Disease

There are a rapidly increasing number of DNA-based genetic tests available as more gene mutations underlying hereditary diseases are identified (for a list of ophthalmic conditions for which DNA tests are available please refer to the ECVO Hereditary Eye Diseases Manual [Chapter 10] on the ECVO web site: ECVO.org). It is important to appreciate and explain to clients the information that the tests actually provide. When designed to identify a specific gene mutation, the test will do only that. This means that a test for PRA will only identify if an animal is affected or is not affected by (or in the case of recessive PRA, is a carrier for) that specific type of PRA. Some breeds of dogs have multiple forms of PRA, each caused by a different genetic mutation. Each test will only identify one of those forms. To use the Golden Retriever as an example, it is known that at least three forms of PRA are segregating within the breed. Dogs could have the *PRCD* form of PRA (which is common across several breeds of dog) (Zangerl et al., 2006), or they could have PRA caused by a mutation in the *SLC4A3* gene (Downs et al., 2011), or the *TTC8* gene (Downs et al., 2014b). In the Papillon, about 70% of PRA was shown to be caused by a mutation in *CNGB1* (Winkler et al., 2013), meaning that PRA in the breed can also result from one or more additional gene mutations. Thus, a Papillon could be clear of the *CNGB1* form of PRA and yet still develop PRA (caused by a non-*CNGB1* form of PRA).

DNA-based tests are completely specific for the one form of hereditary disease they were designed to identify, and they should also be very accurate, if they are well designed. Obviously, there is still opportunity for human errors to be made, for example, if samples are mislabeled, which is probably more of a risk if multiple dogs are being sampled at the same time.

The interpretation of tests can be complicated in some situations such as with more complex conditions where there may be more than one locus involved. For example, the cone rod dystrophy type 1 (CORD1) form of PRA originally associated with an *RPGRIP1* insertion mutation appears to require the presence of a variation in the *MAP9* gene and probably an additional unknown locus for the phenotype to develop (Das et al., 2017; Miyadera et al., 2011). The *RPGRIP1* insertion has been detected in several breeds of dog but does not appear to always be associated with retinal degeneration (Kuznetsova et al., 2012; Miyadera et al., 2009). In some breeds there is a high incidence of the *RPGRIP* insertion and yet a low incidence of PRA. For this reason the results of DNA tests for the *RPGRIP1* insertion should be interpreted with care until further research is completed to resolve the remaining questions about *RPGRIP1* insertion involvement in retinal disease. Further details are included in Chapter 25.

Sample Collection

To carry out a genetic (DNA-based) test, a DNA sample is required. This is commonly isolated from a blood sample or cheek swab. The instructions from the laboratory conducting the test should be followed. Care must be taken to ensure that the sample is not contaminated (e.g., with DNA from another animal or person) and is clearly labeled. When samples from multiple animals are being collected, particular care should be taken with identification of the animal, and the sample should be clearly and accurately labeled immediately after it is collected.

Mutation Detection Tests

A mutation detection test is one that is designed to specifically identify the DNA alteration that has been shown to cause the genetic trait being tested for. Such a test is very accurate and extremely specific. Dog owners and breeders need to appreciate that for conditions with genetic heterogeneity, for example, PRA, a test for one specific form of PRA will identify the presence/absence of only that form of PRA as discussed earlier.

Linked-Marker Test

When a genetic trait has been mapped and the mutation causing the defect has not yet been identified, it can still be possible to design a genetic test. When the disease-causing mutation arose, it would have happened on a chromosome with specific versions of the variable DNA (polymorphisms) across that chromosome. The mutation would be passed down the generations such that all affected animals are descendants of the founder animal. The region of the chromosome surrounding the mutation would be shared by all

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the affected animals (identity by descent). The shared region is thus "linked" to the disease mutation. If there is a closely linked DNA marker, the affected animals will share the same version of that marker. The version of that polymorphic marker present in the unaffected animals can be used to suggest that they do not have the disease allele. If an individual has the version of the marker that is not associated with the disease mutation, then it is likely that they are clear of the mutation. If an animal has the marker version associated with the disease, they may also have the disease allele; however, there is also a possibility that animals with the version of the marker associated with the mutation do not have the mutation. This is because when the mutation arose, some of the population had the same version of the marker as the founder animal, and descendants of those animals may exist in the current-day population. Thus, the interpretation of linked-marker tests can be problematic. If the marker is not very closely linked to the disease mutation, then a crossover between marker and mutation site can occur at meiosis, leading to further complications in interpretation. Before the causal mutation for the PRCD form of PRA was identified, a linked-marker test was made available and enabled breeders to make informed breeding plans. Direct-mutation detection tests are preferable whenever possible.

Multiplex Testing

Genetic testing in dogs is moving towards panel screening which utilizes a custom genotyping array. Such arrays can include multiple different known disease-causing mutations as well as test DNA variants underlying physical traits and be used to show degree of genetic diversity. Companies offering this service will test all submitted dog DNA samples on the genetic panel regardless of what diseases are known to segregate within the breed. Such an approach considerably reduces the costs of genetic testing and can reveal the presence of disease-associated mutations in dog breeds not previously recognized as being affected (Donner et al., 2016). There is a definite need for genetic counseling to enable dog owners and breeders to understand and interpret the mass of results provided from such panels.

Breeding from Carriers for Recessive Disease

Breeding from carriers of recessive disease where the underlying gene mutation is known can be performed without risk of producing affected offspring, so long as carriers are mated with genetically clear animals. In some circumstances, use of carrier animals in breeding programs can be important. If a recessive disease is present in a breed at a high incidence, avoiding breeding from all affected and carrier animals can considerably limit the available gene pool for breeding. Use of only a small proportion of available animals for breeding could run the risk of bringing out other "background" hereditary diseases that are in the population at low levels. It may also run the risk of losing some desirable characteristics from the breed. If there is a particularly good specimen that happens to be a carrier for a recessive disease that can be tested for, it may be sensible to use the animal in breeding programs (avoiding mating with another carrier animal). Then by selective breeding over a few generations, the desirable characteristics can be separated from the disease genotype (i.e., separating the "good genes" from the "bad genes").

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Fundamentals of Ophthalmic Microsurgery

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Introduction

Although microsurgery has principles and rules to be used as guides, surgery is also a very individual and personal activity with strong beliefs and personal opinions possessed by most veterinary ophthalmic surgeons. The rules of microsurgery are meant as a foundation to guide the novice veterinary ophthalmic surgeon and once understood, can occasionally be molded and adapted to suit the surgeon and the individual patient. However, the surgeon must always re-visit the basic microsurgical rules and principles when a new technique or procedure is to be performed. This chapter is intended as a guide and starting point for microsurgery. Specific procedures will be discussed in subsequent chapters and on occasion, opinions and techniques may differ slightly. Remember, surgery is both a technique and an art, and as such, artists will have differences of opinion.

Surgeons must have a goal and a plan to achieve the goal, but must also be adaptable and familiar with more than one technique so that obstacles encountered during the surgical procedure may be overcome. Not all surgeries proceed according to the plan. All eyes are different, and the surgeon who says "I always do it this way" is destined to encounter situations where their technique does not meet the patient's needs. Regardless of our individual variations, we must all follow the basic rules: to use appropriate magnification and instrumentation, to be efficient and precise, to ensure minimal tissue trauma, to minimize surgical time, to maintain the anterior chamber using small incisions and viscoelastic materials, to obtain excellent tissue wound apposition with the smallest and most appropriate suture materials, and finally, to achieve a successful, comfortable, cosmetic, and whenever possible, visual outcome.

Microsurgery can be defined as the dissection or repair of delicate and minute structures using magnification and handheld microsurgical instruments (Chang et al., 1986; Dorland, 2009). In veterinary ophthalmology, this would include surgery of the cornea, conjunctiva, intraocular tissues, and selected adnexal structures. The unique feature of ophthalmic microsurgery when compared with general surgery is the use of the operating microscope. In addition, the instrumentation, position of the surgeon, and the methods of holding and manipulating the surgical instruments differ from traditional general surgery techniques. The use of magnification enhances the surgeon's appreciation of subtle tissue differences and facilitates proper instrument and suture placement, minimizing tissue trauma and improving outcomes. The use of magnification has facilitated surgical procedures that would be impossible to undertake without assisted vision (Jarrett, 2004).

Surgical principles and techniques used in ophthalmic microsurgery differ considerably from those used in general surgery. Successful ophthalmic microsurgery requires that the surgeon understand not only the design and complexities of the operating microscope, but how tissues are affected by minute manipulations with microsurgical instruments. Furthermore, ophthalmic microsurgery requires a detailed understanding of how microsurgical techniques need to be adjusted to accommodate the unique features of ocular tissues such as conjunctiva, cornea, lens, and retina. A diligent effort to master the principles of ophthalmic microsurgery is probably the single most important prerequisite to becoming an accomplished ophthalmic surgeon.

The surgeon must at all times keep several ophthalmic microsurgical principles and rules in mind. The first principle is that time is trauma. With respect to ophthalmic tissues, the surgeon should be efficient and not waste time once the procedure has begun. Second, tissues should be handled as little and as efficiently as possible. The surgeon should not touch or grasp tissue unless they are ready to move the procedure forward, avoiding the mistakes of an inexperienced surgeon who often grasps, pushes, and pulls tissue as they contemplate the next maneuver. As with all surgeries, ophthalmic microsurgery procedures are composed of a series of

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steps in sequence, each one designed to move the surgery forward toward the goal. The surgeon must be familiar with these steps, perform them economically, efficiently, and atraumatically, making no wasted movements and moving steadily forward toward the surgical goal.

History of Ophthalmic Microsurgery

The use of magnification, provided by simple head loupes of limited optical power, to facilitate surgery first occurred in 1876 (Harms & Mackensen, 1967; Nasisse, 1997). Subsequently, a monocular operating microscope was described for aural surgery in 1921 (Chacha, 1979), and the first operating microscopy for human ophthalmic surgery was described in 1950 (Perrit, 1950). This operating microscope was subsequently used to facilitate a superficial keratectomy (Perrit, 1952). The operating microscope was improved with the addition of coaxial illumination by the Carl Zeiss Company (Littmann, 1971), the invention of the X–Y mechanism by Jose Barraquer, and a motorized zoom by Richard Troutman (1974).

In veterinary ophthalmology in the 1960s, microsurgery was performed using head loupes. Operating microscopes were first used in the mid-1970s (Gelatt, 2011a). Because of the high costs of operating microscopes, many veterinary ophthalmologists purchased and often still continue to purchase used, refurbished operating microscopes. As more models and improvements became available, veterinary ophthalmologists in both specialty practices and academic institutions embraced microsurgery. The higher magnifications of the operating microscope permitted observations of the surgical fields never appreciated before, enhanced surgical success, and improved patient care. As microscopes became commonplace, instrumentation and sutures were refined allowing more precise, accurate, and atraumatic surgery to be performed.

Magnification

The goals of magnification are to provide an improved view of the tissues of concern, allow a comfortable working distance for the surgeon, facilitate adjustment of the interpupillary distance to suit the surgeon, and permit a wide field of view. The correct working distance should allow the surgeon to sit upright with their back straight and their arms at a 90-degree angle at the elbow (Fig. 12.1). This will allow the surgeon to take advantage of armrests for stability, minimize neck and back fatigue, and thereby decrease hand tremors. The use of magnification is essential to ophthalmic surgery, and all ophthalmic procedures should be considered as requiring magnification. The amount of magnification is adjusted to suit the procedure with the use of surgical loupes appropriate for many eyelid and adnexal procedures whereas a microscope would be preferred for all corneal and intraocular procedures. It is essential to train young surgeons to use magnification for all ophthalmic surgery at the start of their training program. It will greatly improve their tissue handling and appreciation for tissue trauma and wound apposition. In addition, it is easier to begin with magnification at the start of their ophthalmic surgical career than to try and relearn its use later when presbyopia arrives and it becomes impossible to perform even the simplest adnexal surgeries without magnification. Finally, surgeons should be trained to use appropriate types of magnification, avoiding the inexpensive and frankly inappropriate simple loupes like the Optivisor® (Donegan Optical Co., Lenexa, KA, USA). Although the operating microscope is the recommended standard for current veterinary ophthalmic microsurgery worldwide, their use is largely confined to the operating room.



Figure 12.1 Surgeon seated at the operating microscope. The surgeon's back is straight, he is leaning forward slightly and his arms are bent at a 90-degree angle with his arms resting on armrests attached to the surgical chair and his hands on the vacuum pillow surrounding the patients head (insert).

Head Loupes

Head loupes are a less expensive, portable alternative to the operating microscope (Jarrett, 2004; Spaeth, 1990a). Choosing the correct surgical loupes for the application involves several factors, including resolution, working distance, field of view, depth of field, magnification, weight of the loupes, and the surgeon's interpupillary distance (Baker & Meals, 1997; Pieptu & Luchian, 2003). As a

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egeneral rule, as magnification of the loupes increases, the depth of field and field of view decreases (Stanbury & Elfar, 2011). Also, the longer the working distance, the greater the field of view. The larger the field of view, the less the surgeon will need to turn their head or manipulate the tissues. It is also important to consider the weight and fit of loupes. Lightweight loupes are more comfortable for longer periods of use, and they are less likely to slide down the surgeon's nose as they work. If loupes are to be used, they should be of high optical quality (Nasisse, 1997).

Resolution determines the amount of fine details that can be distinguished. The type of glass used in the lenses and coatings applied to it can affect the resolution of the loupes. To test a set of loupes, look through them at a piece of graph paper. Notice color distortions or curvature of the lines. A high-resolution loupe will have crisp, straight lines. The lines, seen through lower quality lenses, will be slightly blurred and curved.

The working distance is the distance at which the loupes will focus (Baker & Meals, 1997). The working distance must be equal to the distance from the loupe lens to the top of your subject. Each loupe has a defined working distance, but the working distance each surgeon requires will depend upon their height, posture, and table height. The working distance is also affected by whether the surgeon will be seated or standing (Baker & Meals, 1997) (Fig. 12.2 and Fig. 12.3). It is best to determine your personal desired working distance, and then choose a set of loupes that meets the surgeon's criteria. In general, the taller the surgeon, the longer the working distance required. This will also be affected by the surgeon's own vision corrective requirements and whether they are wearing their corrective eyewear when using the loupes. Most loupe manufacturers are able to include the surgeon's visual prescription in the loupe should this be desired.



Figure 12.2 The primary surgeon is seated and is using a pair of Zeiss Galilean 2.3× loupes. His arms are resting on the chair's armrests and his hands on the vacuum pillow.



Figure 12.3 Equine corneal surgery with all surgeons standing. The primary surgeon is wearing a pair of Zeiss prismatic 4× loupes whereas the assistant surgeons are wearing Heine 2.5× Galilean loupes (Heine Optotechnik, Herrsching, Germany). The surgeon is stabilizing his hands on the patient's head.

The area that is in focus when viewed through the loupes is the field of view (Baker & Meals, 1997). The longer the working distance of a loupe, the greater its field of view will be. Likewise, the lower the magnification factor, the larger the field of view. This trade-off must be considered carefully when choosing loupes. As a general rule, for every 30% increase in magnification, the width of field is decreased by approximately 2.5 cm (Baker & Meals, 1997). When using a Galilean loupe, the center of the image is clear, but the outer rim of the image is blurred, thereby decreasing the available field of view. With prism loupes, the image is sharp to the very edge of the field of view.

Like the field of view, the depth of field is directly related to the working distance and magnification factor. The depth of field is the amount of depth that is in focus when viewing the subject through the loupe (Baker & Meals, 1997). Greater depth of field is preferred, because you can see deeper into the subject without repositioning. For greater depth of field, choose a loupe with a longer working distance or a lower magnification factor. In ophthalmic surgery, this is less important because the tissues of concern (eyelids, conjunctiva, cornea) do not require much depth of field.

Head loupes are available in magnifications from 2.0 to 8.0× and can be mounted on glasses or a headband system (Baker & Meals, 1997) (Fig. 12.4). The least expensive and poorest quality loupes are the simple loupes, an example of which is the Optivisor®. Simple loupes consist of one pair of

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Figure 12.4 Zeiss prismatic loupes mounted on a headband and Zeiss and Heine Galilean loupes mounted on an eyeglass frame.



Figure 12.5 Galilean surgical loupes. The loupes on the left are Heine 2.5× mounted on a plastic glasses frame (Heine Optotechnik, Herrsching, Germany) whereas those on the right are Zeiss 2.3× on a wire frame.



Figure 12.6 Prismatic surgical loupes. The loupes on the left are Heine 3.5× mounted on a plastic glasses frame (Heine Optotechnik, Herrsching, Germany) whereas those on the right are Zeiss 4.0× on a headband.

positive meniscus lenses and are limited by spherical aberration and color fringing (Baker & Meals, 1997). These are of plastic construction, have a fixed interpupillary distance, and a very short working distance. The short working distance results in poor surgeon body and arm positions and strain on the surgeon's neck and back. The optical quality of the Optivisor® is poor, and except for limited fieldwork or very short procedures, use of these should be avoided if possible. Although simple loupes might be of historical interest and are acceptable for a general veterinarian who uses magnification rarely, they are not appropriate for the specialist with advanced training and surgical skills who wishes to be taken seriously as an ophthalmic microsurgeon.

There are several manufacturers of compound or Galilean-type loupes which are capable of providing up to 2.5× magnification (Stanbury & Elfar, 2011) (Fig. 12.5). Galilean loupes use multiple lenses to offer magnification and are generally lightweight and less expensive. These are usually mounted on glasses, have an adjustable interpupillary distance, and the working distance varies so that the surgeon may select a loupe with a comfortable working distance for themselves.

For greater magnification, up to 8.0×, prismatic loupes (Keplerian) are available and provide the highest optical quality available (Baker & Meals, 1997) (Fig. 12.6). Designed by Johannes Kepler, Kepler-type prismatic loupes use a series of lenses and prisms to magnify the subject. These are similar in principle to low-power telescopes (Stanbury & Elfar, 2011). They offer greater magnification, sharp resolution, and a greater depth of field. They are also heavier, more expensive, and have a longer tube or barrel to the loupe itself (Stanbury & Elfar, 2011). If magnification of 6.0× or higher is required, a microscope would be preferred because the shallow depth of field and surgeon's head movements makes working more difficult at this higher magnification.

Head loupes are most often used for microsurgery when operating microscopes are not available such as in the field or a large animal barn setting and for orbital and eyelid surgeries (see Fig. 12.2 and Fig. 12.3). Head loupes generally require a separate lighting source, although some models are now available with small lamps mounted on top of the telescope (Fig. 12.7). In general, most veterinary ophthalmologists should have a personal set of loupes adjusted to their interpupillary distance and that suit their working distance. If possible, a surgeon should have two sets of loupes: one, a lower magnification Galilean-type, and the other, a higher magnification prismatic loupe. This will allow the surgeon to choose the loupe and magnification that suit the procedure and tissue of concern.

Microscope

The surgical microscope is capable of providing magnification from 5× to 40× (Stanbury & Elfar, 2011). For ophthalmic microsurgery, magnification of 5–20× is generally sufficient. Although microscopes are vastly superior to the

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Figure 12.7 Zeiss 5.0× prismatic loupes with a light source and fiberoptic cable attached.

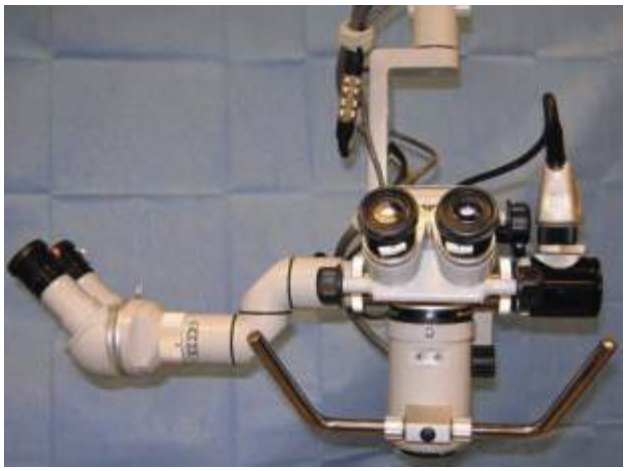


Figure 12.8 Headpiece of a Zeiss OPMI microscope® with a primary surgeon, assistant surgeon, and an HD video camera attached. The surgeon attaches sterile microscope handle covers to the silver microscope handles on the right and left side of the microscope column.

magnification provided by loupes, there is an increase in initial cost and maintenance, longer surgical setup time, less intraoperative positioning flexibility, and less portability (Stanbury & Elfar, 2011). There are several manufacturers of operating microscopes, but the most common and best quality are made by Zeiss, Leica, Wild, and Topcon. Modern operating microscopes have coaxial illumination, variable magnification, motorized zoom, focus, and X–Y axis adjustments. Light is provided by a halogen-tungsten lamp and fiberoptic coaxial illumination (Fig. 12.8). Foot controls are most often used to adjust the light, magnification, zoom, focus, and X–Y axis (Fig. 12.9). The microscope itself can be mounted on the table, a floor stand, or the ceiling. Modern operating microscopes can accommodate multiple surgeons and have the ability to add a still or video capture system for documentation and teaching. In addition, other delivery devices such as surgical lasers may be attached to the operating microscope providing flexibility to perform additional surgical procedures (Fig. 12.10). Keep in mind that as additional components are added to the operating microscope, the surgeon must be certain the microscope arm can support this added weight and the arms balance must be adjusted accordingly. There are also head-mounted operating microscopes that provide portability but have the issues of weight and associated neck strain, the need for the surgeon to hold their head completely still, and no assistant surgeon visibility (Fig. 12.11). The magnification of head-mounted microscopes is less (2.0–9.0×) than that provided by traditional operating microscopes. They are available with both foot control and video capability.

The standard operating microscope used by most veterinary ophthalmic surgeons is mounted on a floor stand with wheels to allow some degree of movement within the operating room. Although these units are mobile, moving them out of the operating room and to another part of the hospital is discouraged and may result in damage and misalignment of the optics. Attached to the floor base are several articulating arms that support the optical heads and allow movement and positioning over the eye (Fig. 12.12). Each moving arm has a



Figure 12.9 Foot control for a Zeiss operating microscope®. The surgeon controls zoom at the heel of the foot, focus at the ball of the foot and X–Y axis at the toe of the foot. The surgeon also controls an on/off switch for the microscope light.

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Figure 12.10 Headpiece of a Zeiss OPMI microscope® with an Iris Medical diode laser delivery device® attached to its base (large arrow). Note that a protective filter has also been installed in the microscope column to protect the surgeon and assistant surgeon (small arrow).



Figure 12.11 The Varioscope® (Leica Microsystems Inc., Buffalo Grove, IL, USA) M5 head mounted microscope from AcriVet is shown. This microscope has a capability of 2.0–9.0× zoom and has a video camera attached.

tension adjustment (pressure screw) that allows the surgeon to move the microscope into position and then lock it in position or leave the tension less tight, allowing further position adjustments once the patient is positioned. The tension or pressure adjustment should be such that the microscope may be moved and repositioned manually during surgery, but tight enough to avoid drift and keep the microscope in the



Figure 12.12 Zeiss OPMI microscope® with articulating arms mounted on a floor stand.

position the surgeon places it. Gross focus should be done manually, moving the microscope head into position and reserving the motorized fine focus for use during surgery.

The optical heads consist of several components. There will be a primary surgeon's eyepieces and then if equipped, a beam splitter, permitting observation by one or more assistant surgeons, and/or an image capture device. Generally, the assistant surgeon will be seated 90 degrees from the primary surgeon (see Fig. 12.8). Although the beam splitter does allow the assistant to see the same image as the surgeon, they are not permitted stereopsis in this position. Additionally, the beam splitter will allow a video and/or still camera to be attached, allowing viewing on a television screen and documentation of the procedure. If the operating microscope is to be used for laser procedures, a filter must be installed in the optical path to protect the surgeon and assistant surgeon (see Fig. 12.10). Most current operating microscopes have a continuous motorized zoom that is controlled by a foot pedal (see Fig. 12.9). Some older or less expensive models may have a fixed step magnification that requires manual changes.

The objective lens and surgeon's eyepieces may be changed to adjust the focal length and magnification. The focal lengths available range from 150 to 400 mm. Base objectives with shorter focal lengths increase the magnification, but reduce the microscope's working distance (between the

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patient's eye and base of the microscope and objective lens). Most ophthalmic surgeons will choose a focal length of 175 mm which provides a comfortable working distance for most animals (Gelatt, 2011a; Nasisse, 1997). The surgeon's oculars would most commonly have a magnification power of 10× or 12.5× (Gelatt, 2011a; Nasisse, 1997). The magnification for the surgeon and other viewing systems provided by the operating microscope is determined by the focal length of the binocular tubes, the focal length of the objective, the optical power of the oculars, and magnification changer according to the following formula (Chacha, 1979; Hoerenz, 1980; Murray, 1986; Nasisse, 1997):

$$\text{Magnification} = \frac{\text{Focal length of binocular tubes}}{\text{Focal length of the objective}} \times \text{magnifying power of the } \textit{eye} \text{ pieces} \times \text{magnification power of magnification changer.}$$

Prior to beginning any surgery, both the patient and the microscope must be properly positioned and adjusted (Fig. 12.13). The microscope must be set so that the X–Y axis is centered, the magnification set to the lowest setting, and the focus zeroed or set to neutral to permit maximum up and down fine focus. For most microscopes, the X–Y may be zeroed by pushing a small button on the top of the X–Y motorized box. The fine focus is zeroed using the foot pedal to align the focus dots usually located on the right side of the microscope column to ensure full range of up and down fine focus control during surgery. The interpupillary distance is set for each surgeon, and the microscope, surgical table and surgical chair, and armrest heights are adjusted to accommodate the primary surgeon. Once the eyepiece objectives are zeroed, the primary surgeon should ensure the assistant surgeon and video camera are all in focus when the primary surgeon is in focus. This should be checked and verified at the highest magnification that will be used during the procedure. The foot pedal is positioned where the surgeon can easily reach it and it can be on either the right or left side according to the surgeon's preference. If multiple foot pedals are required, as in the cases of phacoemulsification, vitrectomy, endocyclophotocoagulation (ECP), or other laser procedures, it is common for the microscope foot pedal to be controlled using the nondominant foot. Many surgeons choose to remove their shoes to allow them to feel the foot pedal more accurately. The foot pedal will have a middle rocker bar or foot rest, allowing the foot to be rested on the pedal and tipped forward or backward and left and right to control the fine focus and zoom (see Fig. 12.9). The X–Y axis joystick sits at the front of the foot switch. The primary surgeon must be familiar with the microscope foot switch and where the controls are so that its adjustment becomes intuitive during the surgical procedure. The surgeon must also use the features of the microscope, increasing and decreasing magnification, and adjusting focus for various steps of the procedure to improve visualization and outcome. Failure to adjust the microscope during various steps of a surgery would be like purchasing an expensive manual sports car and driving only in first gear. Your money was not well spent and you are failing to get the maximum output from the equipment. Remember, as magnification is increased, the field of view and depth of field will be decreased. The depth of field at 3.5× is 2.6 mm whereas at 20×, the depth of field is markedly reduced to 0.4 mm (Spaeth, 1990a; Troutman, 1974). The diameter of the operating field



Figure 12.13 Prior to surgery, the microscope, surgical chairs, and all other required equipment are positioned and adjusted. In this photo, an Alcon phacoemulsification machine® (Alcon, Fort Worth, TX, USA) and Stryker video image system® (Stryker, Kalamazoo, MI, USA) are also positioned where the surgeon requires them.

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of view also changes with increasing magnification with a diameter of 50 mm at 3.5× reduced to only 10 mm at 20× (Spaeth, 1990a).

When the patient is placed on the surgical table, the patient, head, and eye are positioned according to surgeon's preference. In general, the animal will be in lateral recumbency with the head flexed and the cornea parallel with the floor and looking up into the microscope. Some surgeons will prefer to place the patient in dorsal recumbency with the head tilted to the side. Sandbags and vacuum pillows are used to ensure the patient and the head do not move during the procedure (Fig. 12.14). Once the patient is draped, sterile handles (Fig. 12.15) or a sterile microscope drape (Fig 12.16) are attached to the operating microscope and the microscope is manually adjusted up or down for gross focus. Do not use the foot switch or fine focus at this time. Once seated, if required, the surgeon makes final adjustments to the table and chair height, and gross focus on the microscope (Fig. 12.17).



Figure 12.14 A vacuum pillow designed to allow the surgeon to position the patient's head and, by evacuating the air, custom fit the pillow to each patient and maintain stability and position during the surgery. The surgeon may also use the pillow to rest and stabilize their hands.



Figure 12.15 Sterile handles for the Zeiss OPMI microscope® to allow the surgeon to maneuver and manipulate the microscope during surgery.



Figure 12.16 A sterile microscope drape is used to provide the surgeon access to the microscope handles during surgery. (Photograph courtesy of John Sapienza.)

The microscope light is turned on, and most surgeons will then choose to turn off the operating room lights that illuminate the patient, leaving on only the light that illuminates the instrument table. This will provide the best view of the surgical field and minimize reflection and glare associated with nonessential illumination. To minimize the possibility of retinal phototoxicity, the light intensity on the microscope should be set to the lowest level acceptable and turned on only when required.

Anesthesia

At the time of, or immediately prior to anesthesia, depending on the procedure, many surgeons will choose to administer a systemic anti-inflammatory and/or an intravenous antibiotic. Inflammation results from surgical trauma and is best prevented or minimized by preoperative anti-inflammatories and atraumatic surgery. Despite our best efforts, the ocular surgical field is a contaminated one, and so intravenous antibiotics at the time of surgery are indicated when the surgery invades the intraocular tissues. If additional topical medications are required immediately prior to surgery, solutions rather than ointments should be used.

Although some ophthalmic surgical procedures can be performed with sedation and local nerve blocks, especially in large animals, microsurgery requires general anesthesia. Inhalation anesthesia with or without the use of nondepolarizing neuromuscular blocking agents is the standard of care for most ophthalmic microsurgical procedures. The use

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Figure 12.17 Intraoperative photograph during phacoemulsification. The primary and assistant surgeons are seated, the surgeon's arms and hands are stabilized, sterile microscope handles are attached to the microscope, the video is turned on, and the majority of the operating room lights have been turned off.

of neuromuscular blocking agents provides excellent globe exposure and will minimize globe compression as a result of extraocular muscle tension. Use of these agents is routine and standard of care for both small animal and equine corneal and intraocular surgery. The most commonly used neuromuscular blocking agent, atracurium besylate (0.2 mg/kg dog and cat; 0.02–0.06 mg/kg horse), administered intravenously, will provide approximately 20–25 minutes of paralysis. If needed, a second injection (at a dose of 0.1 mg/kg dog and cat; 0.025 mg/kg horse) may be administered for a bilateral procedure. Once atracurium is administered, the patient must be manually ventilated or preferably placed on a mechanical ventilator. Although some surgeons may choose to administer a lower dose of a neuromuscular blocking agent, achieving adequate globe position without respiratory paralysis, these animals must still be ventilated to avoid respiratory acidosis (Sullivan et al., 1996). The effects of atracurium may also be reversed at the end of a short procedure by administration of edrophonium 0.5 mg/kg or neostigmine 0.02 mg/kg intravenously. An anticholinergic (glycopyrrolate 0.02 mg/kg IV or atropine 0.04 mg/kg IV in small animals; glycopyrrolate 0.005 mg/kg IV in horses) should be administered concurrently with neostigmine.

Surgeon Positioning

When performing ophthalmic microsurgery, the surgeon should be seated when possible. Prior to initiating surgery, the patient and the surgeon should be positioned to ensure access to the surgical field while providing the surgeon with a stable and comfortable environment. A surgical chair with adjustable armrests, preferably ones that can be



Figure 12.18 Two hydraulic surgical chairs. The chair on the left with two armrests is used by the primary surgeon. The chair on the right is used by the assistant surgeon and the single arm rest is positioned in front of the surgeon. The armrests must be covered by sterile covers such as a mayo stand cover.

covered with a sterile drape or mayo stand cover, is essential (Fig. 12.18). The chair height should be able to be adjusted using a hydraulic foot pedal so that the surgeon can change this during surgery. A second chair, with adjustable height for the assistant surgeon, should also be used, but does not require armrests (see Fig. 12.18). When the surgeon is seated and the chair, armrests, surgical table, and microscope are adjusted properly, muscle strain on the surgeon's back, neck, and arms is minimized, allowing stable and controlled hand and finger movements (Nasisse, 1997). The surgeon's back is straight, they should lean

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Table 12.1 Microsurgical presurgical surgeon checklist.

Adjust chair height
Adjust chair armrest position
Adjust table height
Adjust microscope height
Set microscope fine focus to neutral
Center X–Y axis
Adjust microscope tilt
Adjust interpupillary distance
Set microscope to highest magnification to be used
Adjust focus of oculars
Ensure video and assistant images are also in focus
Return microscope to low magnification Place foot pedals to be comfortably accessible

Source: Modified from Nasisse, M.P. (1997) Principles of microsurgery. *The Veterinary Clinics of North America. Small Animal practice*, **27**, 987–1010.

slightly forward with their arms resting at a 90-degree angle and their hands stabilized with the wrists straight, allowing precise finger movements to control the surgical instruments (Macsai, 2007) (see Fig. 12.1). The optics on the microscope can also be tilted to suit the surgeon. The chair height should also allow for comfortable placement of the surgeon's legs and feet so that the foot pedals for the microscope and phacoemulsification, vitrectomy, or ECP units are accessible and able to be manipulated comfortably. When not using the foot pedal, the surgeon's feet are either flat on the floor or resting on the foot pedal. Once the surgery begins, the surgeon will typically lean forward slightly with the forearms resting to the level of the wrist on the armrest and the hands further supported on the vacuum cushion or patient (Fig. 12.17). The hands may be supported in this manner by resting the ball of the hand or extending the outside fifth finger for support. This will minimize hand tremor and allow for precisely controlled finger movements. For surgeons just beginning microsurgery, it helps to have a checklist of preparation steps to be performed prior to surgery (Table 12.1).

Patient Preparation and Globe Positioning

Pre- and perioperative medications will vary depending on the procedure to be performed. Typically, topical antibiotics, anti-inflammatories and mydriatics are administered starting a few hours to days prior to most corneal and intraocular surgery. Systemic antibiotics and nonsteroidal anti-inflammatory drugs are often administered in the immediate perioperative period for adnexal, corneal, and intraocular surgery. Specific medication protocols are found in the subsequent chapters by area of surgical interest.

Prior to surgery, depending on the procedure, the patient should be gently clipped to remove the adnexal hair. Avoid abrasions or excessive trauma to the periocular tissue that will result in patient irritation and rubbing after surgery. Avoid all surgical disinfectants containing alcohol or chlorhexidine diacetate because they are extremely toxic to the cornea and conjunctiva (Fowler & Schuh, 1992). The periocular tissues and globe can be rinsed and aseptically prepped using a repeated application of dilute 0.5% povidone iodine solution (1:20 dilution) followed by a gentle saline rinse (Gelatt, 2011a; Roberts et al., 1986). This procedure is repeated for at least 2 minutes ensuring the cornea and conjunctival cul-de-sac are gently irrigated. Once the patient has been positioned on the surgical table, a 10% povidone iodine swab may be used to paint the eyelids but must not come in contact with the cornea or conjunctiva. Use of ointments on the surgical eye is avoided because they interfere with the surgeon's view and are potentially irritating to the intraocular tissue. Protective ointments are advised, however, for the contralateral eye in cases of unilateral surgery. If a retrobulbar block is to be used, this is generally administered at the time of initial clipping and sterile preparation (Gelatt, 2011a).

Again, depending on the procedure and surgeon preference, the patient is most typically placed in lateral recumbency with the head at one end of the table where the surgeon will be seated. Some surgeons will prefer to place the patient in dorsal recumbency with the head tilted to the side. The head and neck are rotated so that the eye is looking up into the operating microscope and the cornea and eyelid are parallel to the floor. Sandbags and U-shaped vacuum pillows may be used to help stabilize the head position and ensure it remains stable throughout the procedure (see Fig. 12.14). If needed, ropes and tape can also be used to ensure patient position remains stable throughout the procedure (Fig. 12.19). The anesthesiologist will typically need to be at the opposite end of the table from the surgeon. To avoid kinking of the airway, a right-angle insert is placed at the end of the endotracheal tube and connected to the anesthetic tube or a guarded endotracheal tube is used. All monitoring equipment and access ports for the patient should be placed so that the anesthesiologist may access them without disturbing the surgeon and surgical field. The anesthesiologist should avoid using the end of the surgical table during the surgery because contact with the table will result in significant movement and disturbance of the surgical field under the operating microscope. For corneal and intraocular procedures, many surgeons will choose to use a nondepolarizing neuromuscular blocker to facilitate globe position and minimize risks of movement. The anesthesiologist should therefore be prepared to manually or mechanically ventilate the patient and to monitor the PO_2 and end tidal PCO_2 to

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Figure 12.19 A patient has been positioned in lateral recumbency. The cornea and eyelids of the superior eye are positioned parallel to the floor, looking up into the microscope, and the vacuum pillow is secured.

ensure adequate ventilation. Most nondepolarizing agents will have an effect in 30–60 seconds after administration with a duration effect of 20–25 minutes so they should be administered accordingly.

Horses are managed and positioned much the same as dogs (Gelatt & Wilkie, 2011). If the operation is for one eye only, the horse may be positioned in lateral recumbency and the head and eye rotated to permit the cornea to be as parallel as possible to the floor and looking up into the operating microscope's objective lens (Fig. 12.20). To stabilize and cushion the head and keep the ventral eye from laying on the operating table, the author uses a partially inflated inner tube (Fig. 12.21). For bilateral eye surgeries, the horse is positioned in dorsal recumbency and the head rotated to permit the operative eye to be as parallel to the operating microscope's objective as possible. Globe position can be more difficult to maintain in equine ophthalmic surgery as the eye position varies during the surgery with changes in the plane of anesthesia. Horses are generally maintained at a lighter plane of anesthesia compared with small animals and so changes in globe position throughout the surgery are common. As the horse's extraocular muscles are so massive, globe movement and deformation may occur during intraocular procedures under general anesthesia if the horse is light. During cataract surgery, the anterior chamber may collapse, the posterior lens capsule may move anteriorly and even rupture, permitting vitreous presentation. Hence, administration of neuromuscular blocking agents followed by mechanical ventilation in horses undergoing corneal and intraocular surgeries is highly recommended. Alternately, if mechanical ventilation is not possible, a retrobulbar nerve block may be performed prior to the procedure to paralyze the extraocular muscles and stabilize the globe.



Figure 12.20 A horse being prepared for unilateral phacoemulsification. The horse is in lateral recumbency with the microscope, Oertli phacoemulsification machine® (Oertli, Berneck, Switzerland), and Stryker video setup® (Stryker, Kalamazoo, MI, USA) in position.

Once positioned and prepped, the patient is sterilely draped using water repellant disposable paper drapes or disposable adhesive drapes according to surgeon preference. For ocular surgeries using significant fluid, such as

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Figure 12.21 A partially inflated inner tube is used to cushion the horse's head and prevent the down eye from laying on the operating table during surgery.

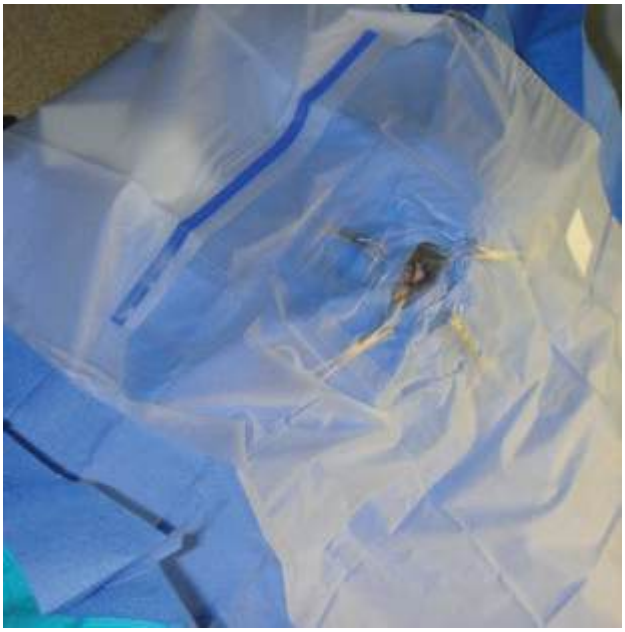


Figure 12.22 A disposable, sterile sticky drape with a fluid collection bag designed to collect excessive fluid during surgery. (Photograph courtesy of John Sapienza.)

phacoemulsification, sterile sticky drapes designed to collect excessive fluid are available (Fig 12.22). Care is taken to avoid external pressure on the globe or adnexal structures by the drapes. Such pressure may result in collapse of the anterior chamber, extrusion of viscoelastic material, iris prolapse, or vitreous expansion during surgery. Care is also taken during surgery to make certain the drape position has not shifted, resulting in pressure on the globe. External forces to the globe may also be created by an eyelid speculum that is improperly placed or is of the incorrect size.

To assist with hemostasis and decrease swelling, topical epinephrine (1 : 1000 to 1 : 10,000) may be applied to the cornea and conjunctiva prior to initiating the surgery. This will vasoconstrict the conjunctival vessels, minimize bleeding, and decrease fibrin and swelling postoperatively. It can be used in virtually all ophthalmic procedures and will help to maintain a blood-free surgical field.

If needed, one or more stay sutures may be placed to facilitate globe position and manipulation. Stay sutures are placed adjacent to the limbus and should be placed to hold deep to the conjunctiva, involving the episcleral tissue. If a single stay suture is used, it should be placed just posterior to the ventronasal limbus to both rotate the globe upward and displace the nictitans downward and out of the surgical field. Additional stay sutures are placed according to the procedure to be performed and field of view required. Once placed, a serrefine or other small clamp is attached to the ends of the stay suture for manipulation. If additional exposure is required, a lateral canthotomy may be performed to increase exposure and reduce eyelid tension on the globe. It is more common for novice surgeons to perform a lateral canthotomy with its use decreasing with increased experience. A lateral canthotomy is perhaps most commonly indicated for terriers with small palpebral fissures requiring a large corneal incision to manage a lens luxation. During the entire surgical procedure, the cornea and ocular tissues must be kept moist. This is generally a task for the assistant surgeon. Balanced salt solution or sterile saline is typically used for this purpose and applied using a small irrigation bottle and an irrigating cannula every 20–30 seconds.

Following surgery, the patient should have a calm recovery. The patient may recover in lateral recumbency with the operated eye up or in sternal recumbency for bilateral procedures. A cold compress may help decrease hemorrhage and swelling after eyelid and adnexal procedures. Some surgeons will choose to place a temporary, partial tarsorrhaphy suture for corneal and intraocular procedures as a means to decrease exposure and protect the surgical site. Elizabethan collars, exercise restriction, and systemic nonsteroidal anti-inflammatory drugs are common after most ophthalmic surgeries. In horses, a subpalpebral lavage delivery system may be placed at the end of the surgery to facilitate postoperative medication.

Instrumentation

With the evolution of microsurgery, it became apparent that standard ophthalmic instruments were too large as viewed under the operating microscope, and needed to be reduced in size to function at higher magnifications, but still large enough to be easily held by surgeons. Using standard instruments viewed through the operating microscope, incisions, tissue manipulations, and wound appositions were crude

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and inexact, and tissue trauma was severe. The bright illumination of the microsurgical operative field also requires the finish to be modified so the micro instruments do not reflect light back into the surgeon's eyes. In general, microsurgery instruments were developed by reducing the traditional or standard ophthalmic instruments by about one-third. The traditional or standard ophthalmic instruments were reduced from about 150 mm to about 100 mm to accommodate a working distance of 150–175 mm between the patient's eye and the base objective lens of the operating microscope (Gelatt, 2011a, 2011b). The size of the jaws, blades, or forceps tips were reduced further to permit atraumatic handling of the tissues, needles, and suture materials.

The instrumentation used in ophthalmic microsurgery begins with a basic ophthalmic microsurgical pack for eyelids, orbit, and other adnexal procedures (Table 12.2), but will then expand to include specialized microsurgical packs for cornea, cataract, or posterior segment work (Table 12.3). Phacoemulsification, irrigation/aspiration and vitrectomy, cryosurgery, laser, wet field cautery, and vitreoretinal instruments will often have their own surgical packs. The particular style of a specific instrument is often a matter of surgeon preference. Most surgeons will have several basic or minor ophthalmic surgical packs that will be used for adnexal and orbital procedures and several major ophthalmic microsurgical packs designed for cornea, cataract, and other anterior segment procedures. A basic ophthalmic pack will typically contain an eyelid speculum (Barraquer wire in several sizes) (Fig. 12.23), forceps (Brown-Adson, Colibri, Bishop-Harmon, scleral fixation, tying), scissors (Stevens and Westcott tenotomy), needle holders (large and small curved, nonlocking Barraquer type, and Derf or Alabama-Green type), Desmarres chalazion clamp (Fig. 12.24), Jaeger eyelid plate (Fig. 12.25), calipers (Jameson, Castroveijo) (Fig. 12.26), Carter sphere introducer (Fig. 12.27), muscle hooks, irrigating cannulas, and Beaver and Bard Parker blade handles (Fig. 12.28). Additional instruments may include mosquito hemostats, Martinez corneal dissector (Fig. 12.29), serrefine clamps (Fig. 12.30), cyclodialysis spatula, and other specific instruments according to the surgeon's preference. For a microsurgical corneal/intraocular pack, many of the same instruments will be included, but will have more delicate teeth and jaws. Additional instruments in a microsurgical pack may include intraocular scissors and forceps such as the Vannas scissor and Utrata forceps, lens loop, intraocular lens (IOL) forceps, IOL manipulators, phaco choppers, or other specific instruments according to surgeon preference.

Table 12.2 Basic ophthalmic microsurgical pack.

Eyelid speculum – Barraquer wire in several sizes
Forceps – Brown-Adson
Colibri utility 0.3 mm and 0.5 mm
Bishop-Harmon fine teeth
Castroviejo scleral fixation
Tying forceps
Scissors – Stevens tenotomy – blunt, curved
Westcott tenotomy – blunt, curved
Needle holders – Barraquer type medium and heavy curved
nonlocking, rounded, and knurled handle
Derf or Alabama-Green
Desmarres chalazion clamp
Jaeger eyelid plate
Calipers – Jameson, Castroviejo
Carter sphere introducer
Muscle hooks
Irrigating cannulas – 21, 23, 27, 30 gauge
Beaver and Bard Parker blade handles
Mosquito hemostats
Martinez corneal dissector
Serrefine clamps
Cyclodialysis spatula

Table 12.3 Basic corneal/intraocular ophthalmic microsurgical pack.

Eyelid speculum – Barraquer wire in several sizes
Forceps – Colibri utility 0.12 mm and 0.3 mm
Bishop-Harmon delicate teeth
Castroviejo scleral fixation
Utrata capsulorhexis
Intraocular lens folding
McPherson tying – straight and angled
Scissors – Stevens tenotomy – blunt, curved
Westcott tenotomy – blunt, curved
Vannas – curved with a sharp tip
Right and left corneal section scissors
Intraocular
Needle holders – Barraquer type delicate and fine curved,
nonlocking, rounded, and knurled handle
Lens dialer/manipulator
Phaco chopper
Calipers – Jameson, Castroviejo
Lens loop
Irrigating cannulas – 21, 23, 25, 30 gauge
Beaver blade handles
Martinez corneal dissector
Serrefine clamps
Cyclodialysis or iris spatula

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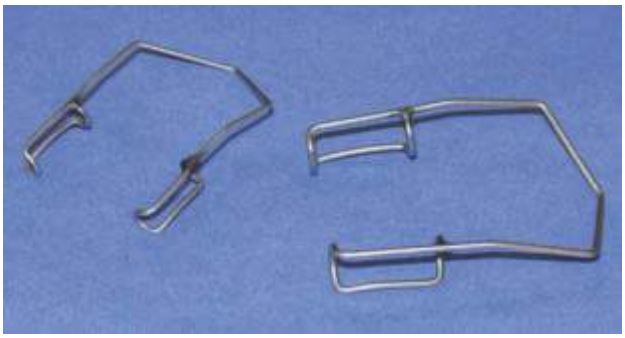


Figure 12.23 Barraquer wire eyelid speculums in adult and pediatric sizes.

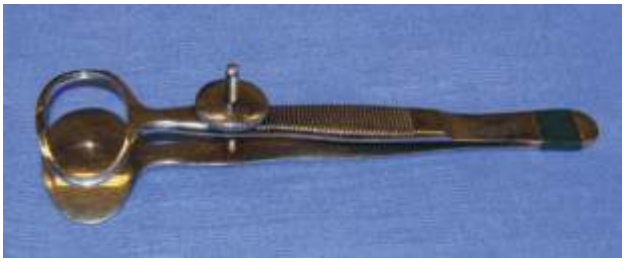


Figure 12.24 Demarres chalazion clamp.



Figure 12.25 Jaeger eyelid plate.



Figure 12.26 Jameson (top) and Castroviejo (bottom) calipers.



Figure 12.27 Carter sphere introducer.



Figure 12.28 Beaver handle with #64 blade (top) and Bard-Parker handle (bottom) with #15 blade.

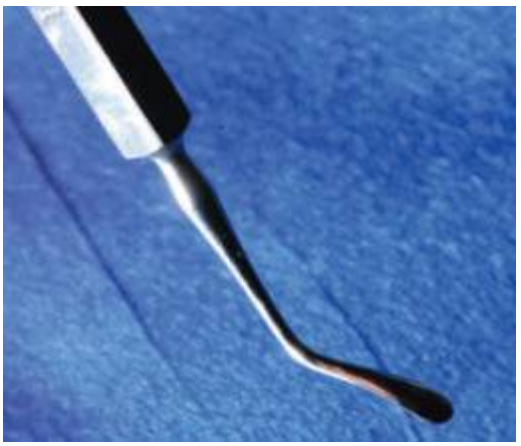


Figure 12.29 Martinez corneal dissector.

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Figure 12.30 Serrifine clamp.

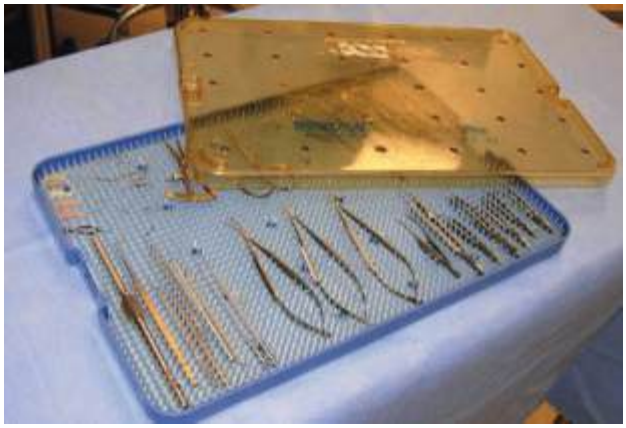


Figure 12.31 Autoclavable plastic microsurgical tray to store and protect microsurgical instruments.

In addition, a drape pack containing towel clamps, drapes, scissors, and a sterile bowl are used so that these instruments are not wrapped with the more delicate ophthalmic instruments. If vitreoretinal procedures are performed, this may require an additional set of microsurgical instruments. In addition, specialized packs for phacoemulsification or other procedures requiring specialized instrumentation may be indicated. Finally, if microsurgical procedures are to be performed on large animals, specifically horses, then additional equine microsurgical packs may be kept. All microsurgical instruments should be stored in a specialized tray with a lid to protect them from damage and prevent them from contacting each other (Fig. 12.31). Instruments that are not used on a routine basis should be wrapped and sterilized individually to minimize wear and tear on the instrument associated with cleaning and autoclaving. Immediately prior to initiating surgery, all instruments that will be required for the procedure should be selected, removed from the microsurgical tray, and arranged on the surgical table in the order they will be used (Fig. 12.32). Once used, they should be returned to the surgical table in the same order so both the surgeon and assistant surgeon can find them quickly.

When selecting microsurgical instruments, the surgeon has a variety of choices in styles and qualities of materials and manufacturing. The length of the instrument, size of the teeth and jaws, angle of the jaws, length of the jaws, sharp versus blunt tips, straight versus curved, flat versus rounded handles, serrated, six-sided, or knurled handle grips, locking versus nonlocking, with or without a tying platform, with or without a pin stop, dull versus polished finish, stainless steel versus titanium are just a few of the decisions to be made (Gelatt, 2011b; Troutman, 1974). Instruments that are to be rotated in the surgeon's fingers should be rounded or six-sided whereas those that are used without rotating should have flat handles (Fig. 12.33). To prevent slippage during manipulation, instrument handles are serrated, knurled, or six-sided (Troutman, 1974) (Fig. 12.33). Many ophthalmic microsurgical instruments are hinged using an X or box hinge design and spring handles as seen with Wescott tenotomy scissors or Barraquer needle holders. With spring handles, as the instrument is closed, the springs straighten, a pin stop prevents overclosing, and then the springs return to the curved position opening the jaws as finger pressure is released (Fig. 12.33). To work correctly, finger pressure must be placed over the pin stop (Eisner, 1990). A bar hinge design is used for most microsurgical forceps.

It is important to understand that not all stainless steel is of the same quality nor are all manufacturers equal in the quality of their product (Grevan, 1997). It is advisable to purchase higher quality stainless steel or titanium instruments for selected instruments such as the most delicate tissue and tying forceps, needle holders, and scissors. Titanium is stronger and more corrosion resistant than stainless steel and will retain its sharpness longer. Some of these decisions are dependent on surgeon preference and cost whereas others are made based on the use of the instrument and the target tissue. As is true for most things, you generally get what you pay for, and inexpensive microsurgical instruments of inferior quality will often corrode, break, or fail to grasp tissue, needles, or suture correctly and so in the long-term, do not save monies.

The delicate nature of microsurgical instruments requires a change in the methods for cleaning and storage. Immediately after surgery, instruments should be gently cleaned by hand using a soft toothbrush or microwipe and distilled water. Cleaning must remove all blood, tissue, saline, and viscoelastic materials from the instruments. Residual materials such as viscoelastics, if not removed, could be a factor in toxic anterior segment syndrome or fibrin in subsequent cases. If an ultrasonic cleaner is to be used, great care must be taken to separate the instruments and prevent contact with each other during the cleaning procedure to avoid damage to the delicate tips. Once clean, instruments are sprayed/coated with surgical instrument milk to lubricate and protect from rust and corrosion and then placed in a specialized microsurgical protective tray with a lid (Fig. 12.34). Do not rinse the instrument milk; rather, leave it on for the sterilization process. Only after this process is complete and the instruments are safely sealed in the tray should the instruments be handed over

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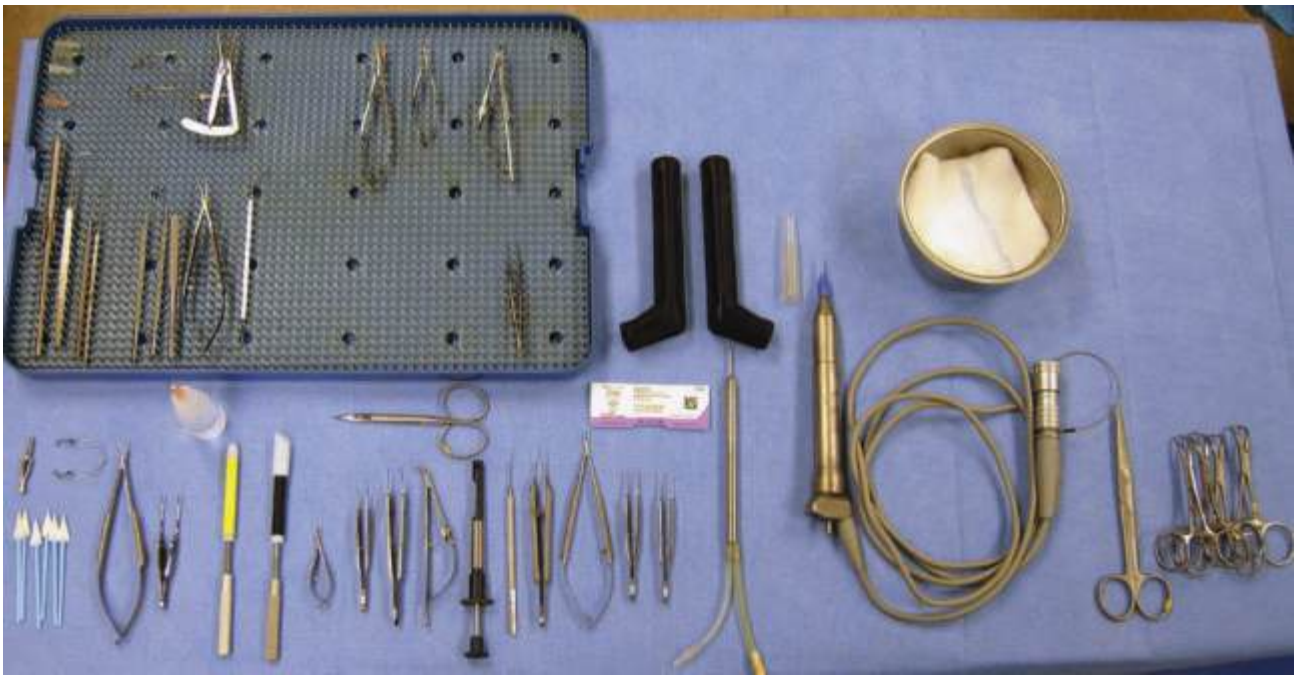


Figure 12.32 Instruments arranged on a surgical table in preparation for routine phacoemulsification and IOL insertion.

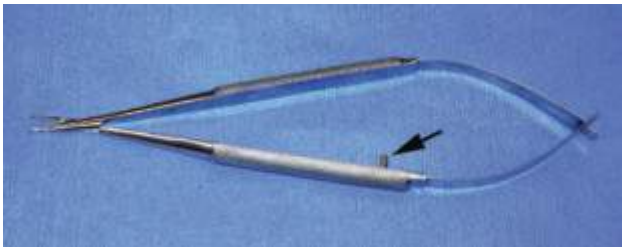


Figure 12.33 Barraquer fine needle holders with rounded and knurled handles to facilitate rotation in the surgeon's fingers and a pin stop (arrow) to prevent overclosure.



Figure 12.34 Microsurgical pack with instrument milk to lubricate and prevent corrosion.

for steam sterilization. Although young surgeons may feel this is a task best given to others, it is very appropriate to instill an appreciation for the care and maintenance of the instruments by having the surgeon perform this task as they are learning. If cannulas are to be reused, they must be copiously irrigated with distilled water followed by air. For other more specialized instruments such as the phacoemulsification and vitrectomy handpieces or ECP probe, the manufacturers' directions for care, cleaning, and maintenance should be followed. In general, any instrument with a lumen for irrigation/aspiration will need to be rinsed and again distilled water followed by air to dry is appropriate. Tips may be cleaned with a soft toothbrush or a delicate instrument sponge or surgical spear. There are also specialized systems such as the QuickRinse® (Advanced Optisurgical Inc., Lake Forest, CA, USA) that are specifically designed to flush debris from phaco and irrigation and aspiration handpieces, cannulas, vitrectomy cutters, reusable tubing, and any other microsurgical instruments with a lumen, using automated pressure rinsing and air drying cycles. It is essential to note that instruments with a lumen that are rinsed must be steam autoclaved because gas sterilization will not penetrate any residual liquid in the lumen and thus will not adequately sterilize these instruments.

Additional ophthalmic microsurgical instrumentation may include a cryosurgical unit for eyelid and lens luxation procedures, phacoemulsification machine with irrigation, aspiration, phacoemulsification, and vitrectomy abilities, wet-field cautery, diode laser with indirect, transscleral,

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microscope, intraocular, and endocyclocoagulation attachments, CO_2 laser, fluid–gas exchange pumps for vitreoretinal surgery, viscous oil injection and aspiration, corneal donor and recipient trephine devices for corneal transplantation, and other additional instrumentation depending on the surgeon's interest and capabilities.

Instrument Handling

As ophthalmic microsurgery requires extremely delicate and precise tissue and instrument manipulations, only finger movements are required. As a result, the instruments are held in a pencil-like grip and the hands and arms are supported by armrests, the surgical table, vacuum cushion, or the patient (see Fig. 12.17). The wrist and elbows are stable and locked when using the pencil-like grip, and only finger movements are used. To be more specific, microsurgical instruments held in a pencil-like grip are supported by resting against the first metacarpophalangeal joint of the first finger with the fingertips of the thumb and first finger used to control and rotate the instrument (Macsai, 2007) (Fig. 12.35). Hand stability is provided by resting the outside of the fifth finger on the vacuum pillow or patient's periorbital tissues. The surgeon must resist the tendency to grasp the instruments tightly because this will decrease flexibility, fatigue the hand and forearm, traumatize tissues, and damage instruments and needles. The palm grip, which is used to hold instruments in most other surgical procedures, does not allow for precise and delicate manipulations (Fig. 12.36). The palm grip is designed to allow movement of wrists and elbows providing power, but not control. The palm grip, although appropriate for Stevens tenotomy scissors, is to be avoided in most delicate ophthalmic procedures.



Figure 12.35 Westcott tenotomy scissors held in a pencil grip.



Figure 12.36 The palm grip may be used for Stevens tenotomy scissors but is not indicated for most other microsurgery instruments.

Incision

Blades

Incisions for ophthalmic surgery should be precise, accurate, and atraumatic. Although historically, some surgeons chose to crush or clamp adnexal tissues in a hemostat prior to cutting, this is unacceptable and results in excessive tissue trauma and scar formation. Although some may argue it provides hemostasis, it violates the rules of atraumatic surgery and should be strictly avoided.

Precise incisions may be performed using a blade or scissors. In general, blades are used to initiate corneal and skin incisions and scissors may be used to complete the incision. For conjunctival incisions, scissors alone are most often used. To ensure a precise incision, the tissue must be stabilized prior to initiating the incision. For eyelid incisions, stability may be provided by a Jaeger eyelid plate or a chalazion clamp (see Fig. 12.24 and Fig. 12.25). Bishop-Harmon forceps with fine teeth may be used to grasp eyelid skin. Eyelid incisions are most commonly performed using a No. 3 Bard-Parker handle and a No. 15 blade (see Fig. 12.28).

For corneal incisions, the tissue is immobilized by grasping the perilimbal tissues using a Colibri forceps, and the incision is initiated using a #64 Beaver or similar type blade (see Fig. 12.28). The forceps should be positioned as close to the incision as possible and the blade moved away from or toward the forceps depending on surgeon preference. If possible, the forceps should be positioned to ensure the entire incision may be completed without repositioning of the forceps because tissue trauma results from each grasp and release. When possible, incisions should be completed in one motion with respect to length and depth because repositioning of the blade will result in a jagged incision. The depth of the incision depends on the procedure being performed. If the surgery requires entry into

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the anterior chamber, the initial corneal incision should be >75% depth without penetrating the anterior chamber. This will make the entry wound easier and minimize the amount of tissue the corneal section scissors must incise. For phacoemulsification, a uniplanar or biplanar incision may be chosen according to the surgeon's preference, most commonly a 2.8–3.2 mm biplanar incision created following a deep 3.0–4.0 mm groove that will accommodate IOL insertion. Should it be required, enlargement of the wound using corneal section scissors can be performed. With deep corneal incisions, the surgeon may experience tissue chatter, which usually indicates a deep wound or a dull blade. If chatter is encountered, digital pressure should be slightly decreased. If this does not stop the chatter, the blade should be changed.

Microsurgical blades for corneal procedures differ from traditional Bard-Parker blades. Although the Bard-Parker system may be used for orbit and adnexal surgery, it is not indicated for corneal and intraocular surgery. The Beaver microsurgical blade system is indicated for disposable corneal knives. The most commonly used blades are the No. 64, No. 63, and No. 65 Beaver blades (Fig. 12.37). The No. 64 blade has a rounded tip, cuts on the tip and one edge, and is most commonly used to begin the corneal incision or for dissection of a keratectomy or corneoconjunctival transposition. The No. 65 or 63 blades have a sharp angled tip and may be used for the corneal entry. Alternatively, reuseable sapphire or diamond knives may be used for both corneal incisions and corneal entry incisions (Fig. 12.38). Sapphire and diamond knives are most commonly used for phacoemulsification incisions to create a deep limbal groove followed by an entry incision with a precise width that corresponds to the phaco needle used. Although initially sapphire and diamond knives are more expensive, if cared for properly, these blades will last through many incisions and are much sharper and more precise than disposable blades.



Figure 12.37 A Beaver handle with a #64 blade is held. The #65 and #63 Beaver blades are also shown.

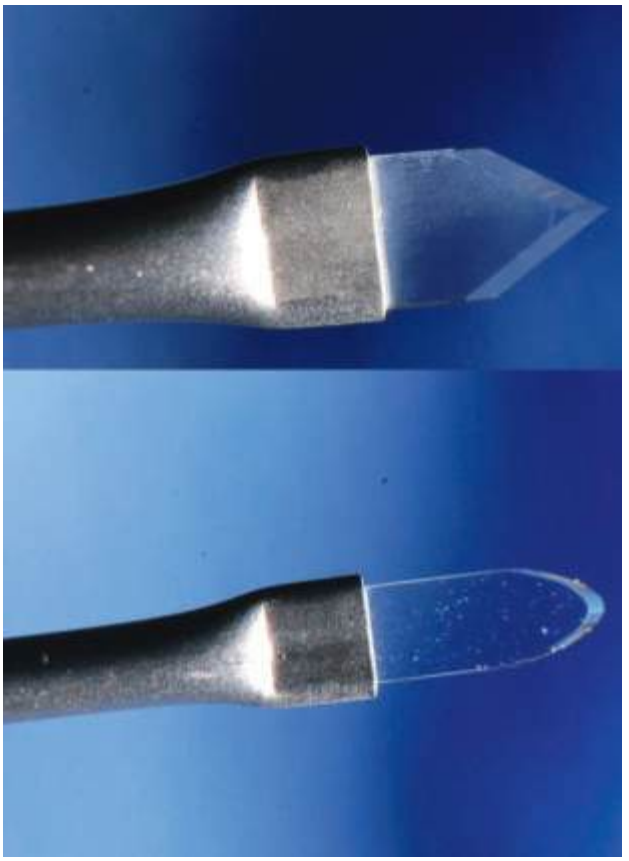


Figure 12.38 A 3.2 mm (top) and a round-tipped (bottom) sapphire knives are shown.

Scissors

Scissors may be used to complete an incision after an initial incision by a blade (cornea, skin) or may be used for the entire incision (conjunctiva, iris, lens capsule). Ophthalmic scissors vary in size, tip design, and handles. The tips of scissors may be sharp, rounded or semirounded, and straight or curved (Grevan, 1997). Scissor handles may be ringed, hinged, or spring-handled (Grevan, 1997) (Fig. 12.39). Ring-handled scissors are more traditional but should be used in a mini-tripod grip with the index finger placed at the fulcrum for maximum control (see Fig. 12.36). Scissors are designed for specific purposes and a variety of scissors will be required. Common ophthalmic scissors include Stevens and Westcott tenotomy, right and left corneal section, and Vannas and intraocular scissors such as the Duet MicroSurgical Technology® (Microsurgical Technology, Redmond, WA, USA) system scissors (Fig. 12.39, Fig. 12.40, Fig. 12.41, and Fig. 12.42). Scissors are used both to cut and to dissect tissue. For dissection of conjunctival tissue to create a conjunctival graft, blunt-tipped Stevens or Wescott tenotomy scissors are most common (see Fig. 12.39). More delicate scissors such as the Vannas are used to incise the anterior lens capsule or cut uveal tissue as seen with a uveal prolapse, iridectomy, or

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Figure 12.39 Curved, blunt-tipped, Stevens tenotomy scissors with ringed grips (top) and curved Westcott tenotomy spring-handled scissors (bottom).

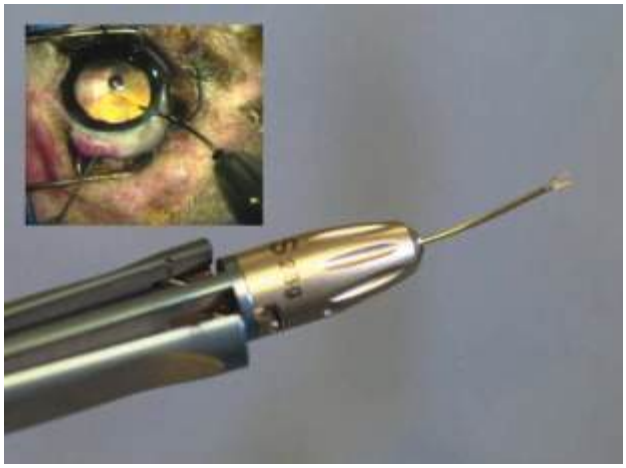


Figure 12.40 Curved intraocular MicroSurgical Technology® (Redmond, WA, USA) scissors are shown. The insert shows use of the Microsurgical Technology forceps while performing a modified ab externo sulcus IOL fixation.

sphincterotomy (Fig. 12.41). Corneal section scissors are curved and designed to cut in either the right or left direction (Fig. 12.42 and Fig. 12.43). They should be used to complete a corneal incision after an initial deep groove has been made with a blade. Following an initial deep groove and entry into the anterior chamber, the lower blade of the corneal section scissors is inserted into the anterior chamber. Care is taken to avoid iris trauma. The scissor blades are aligned with the groove and the lower blade is elevated slightly to open the incision and allow the superior blade smooth entry into the groove. Corneal section scissors should not be closed completely during the cutting stroke, allowing them to remain in the incision and to be advanced without having to be repositioned in the eye. To facilitate this, many corneal section scissors come with a *stop* that is lifted to prevent complete closure as the scissors are advanced (Fig. 12.44). Once the end of the incision is reached, the *stop* is depressed, the scissors are closed completely, and may then be removed



Figure 12.41 Curved Westcott tenotomy scissors (top) and curved Vannas lens capsule scissors (bottom) both with pin stops to prevent overclosure.

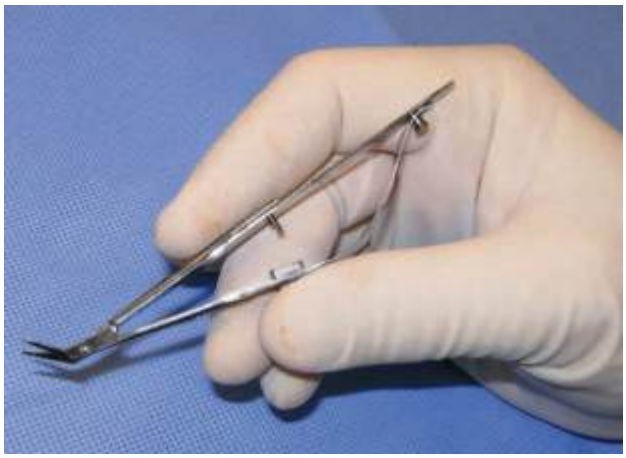


Figure 12.42 Troutman-Castroviejo corneal section scissors with a stop are shown in a pencil grip.

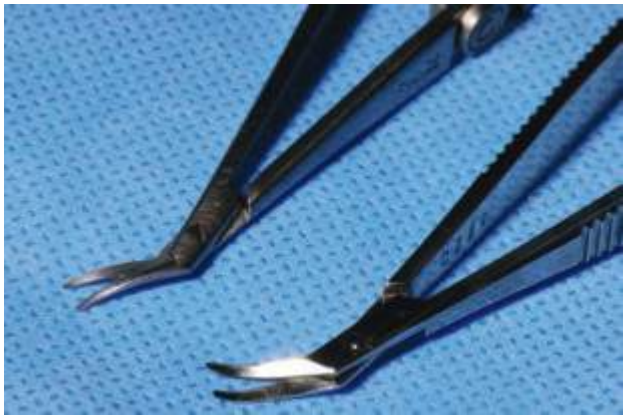


Figure 12.43 Right and left Troutman-Castroviejo corneal section scissors.

atraumatically. If no *stop* is present, then the blades should be closed halfway, opened, and advanced to avoid the need to reintroduce the blade with each cut. Intraocular scissors are designed to be worked from outside the eye whereas the

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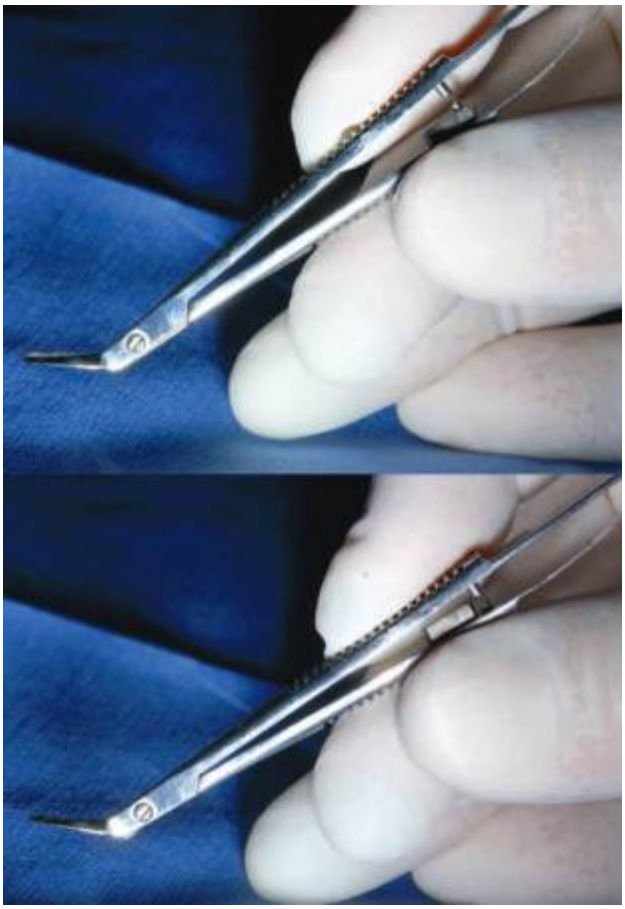


Figure 12.44 Troutman-Castroviejo corneal section scissors. In the upper image the thumb has elevated the stop, preventing complete closure of the blades. In the lower image, the thumb has lowered the stop, allowing complete closure of the blades.

scissor action occurs inside the eye (see Fig. 11.40 and Fig. 11.45). These are most commonly indicated for two-handed capsulorhexis, a posterior capsulorhexis, sutured IOL, or vitreoretinal surgery.

Suture

The function of the suture is to maintain apposition of the wound edges until the wound has attained sufficient strength to resist external forces (Macsai, 2007). The choices in suture material include absorbable versus nonabsorbable, braided versus monofilament, size of the suture, and size and type of needle. The surgeon must make the suture and needle selection based on tissue of interest, tensile strength of the tissue, the duration the suture will be required, suture pattern to be used, and whether the suture will be removed or remain (Nasisse, 1997). In general, monofilament sutures and nonabsorbable sutures will be less reactive than braided and absorbable materials. Nonabsorbable sutures, however, must



Figure 12.45 Storz® (Bausch and Lomb Storz, Manchester, MO, USA) intraocular scissors. The working movement of the scissors is outside the eye and is controlled using the thumb and index finger to control the action of the scissors inside the eye.

generally be removed at a later time. Although considered nonabsorbable, nylon loses its tensile strength beginning at 12–18 months, so for a more permanent suture as required for sulcus fixation of an IOL, polypropylene (Prolene®, Ethicon Inc., Somerville, NJ, USA) or sutures made from expanded polytetrafluoroethylene (Gore-Tex®) would be the suture of choice. The suture selected should be of the smallest size to achieve success, relying on delicate tissue handling, minimal tissue trauma, and excellent wound apposition to ensure primary intention healing with minimal reaction and scar. In general, most eyelid surgeries can be repaired in dogs, cats, and horses using 6-0–7-0 size suture whereas corneal surgery will work best with 8-0–10-0. Although historically, veterinary ophthalmic surgeons have relied on heavier gauge, absorbable suture material, this is not, in most instances, in the best interest of the outcome, and we must work instead to employ smaller, less reactive materials following the principles of microsurgery. Care must be taken to avoid suture trauma during suturing. The surgeon should avoid closure of instruments, such as forceps or needle holders, on suture material that will remain in the tissue. Closure of instruments on the suture results in crimping and weakening of the suture that may result in breakage and wound dehiscence (Abidin et al., 1989).

The most commonly used absorbable suture in veterinary ophthalmology is polyglactic acid (Vicryl®, Ethicon Inc., Somerville, NJ, USA) followed by polyglycolic acid (Polysorb®, Covidien, Mansfield, MA, USA) or polyester polydioxanone (PDS®, Ethicon Inc.). The first two are most commonly found as braided suture material and will elicit a tissue reaction, whereas PDS is a stiffer, longer lasting monofilament material. These are often used as buried sutures for orbital and adnexal procedures. If Vicryl or another absorbable suture is used in the cornea, to minimize irritation and tissue reaction, the smallest appropriate suture should be selected. In addition to this, there are two additional techniques to minimize reaction and subsequent scar formation. The first is to remove the suture from the cornea once it is no longer required, for example, when blood vessels have crossed the incision or graft site. The second is to select Vicryl as a monofilament rather than a braided suture. This can be done at a suture size of 9-0 or smaller. As a monofilament, this suture will handle in a similar manner to nylon and will elicit virtually no tissue reaction as it dissolves. This

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is the suture of choice for closure of most intraocular surgical procedures in small animals.

The most commonly used nonabsorbable sutures are monofilament nylon (Monosof®, Covidien) and monofilament polypropylene (SurgiPro®, Covidien; Prolene, Ethicon). Due to the lack of tissue reaction, these are excellent choices for eyelid skin suture material. They are, however, stiff, and so care must be taken to ensure all sutures are directed away from the cornea, and the smallest suture size that is acceptable, generally 6-0, should be used. There is significant elasticity and memory in these materials so to avoid unraveling, the first throw is usually a surgeon's knot with three single throws on top of this. Avoid the tendency to tie these too tightly; tissue apposition only is all that is typically required. Although some surgeons advocate the use of braided materials for the eyelid to ensure a soft end to the suture, braided materials will wick and are associated with more tissue inflammation and reaction at the suture sites, greater scar formation, and a less controlled cosmetic outcome. Regardless of the suture chosen, it is imperative that owners practice basic suture hygiene for all eyelid sutures. This involves a gentle, warm, wet compress once or twice daily to remove any debris that is adherent to the sutures and keep the wound clean. Nonabsorbable materials may also be used in the cornea at a size of 9-0 or smaller. Some surgeons will leave these sutures whereas others may choose to remove them in the future. Nonabsorbable materials are also used intraocularly, for example, to stabilize a sutured IOL. Although considered nonabsorbable, nylon starts to lose its tensile strength after 12–18 months, so for a more permanent suture as required for sulcus fixation of an IOL, polypropylene (Prolene) would be the suture of choice.

The size of ophthalmic suture used in veterinary ophthalmic microsurgery typically ranges from 6-0 to 10-0. Suture size is denoted by the United States Pharmacopoeia (USP) code. The suture number followed by a hyphen and a 0 is inversely proportional to the suture diameter with the larger number denoting the smaller suture (Table 12.4). The surgeon should keep in mind that the volume of suture material left in the tissue increases logarithmically with increasing diameter (Spaeth, 1990b). The volume of material in 7-0 and 8-0 sutures is 5× and 3× greater than in 9-0, respectively (Spaeth, 1990b). The surgeon must realize this increase in suture volume will result in an increase in suture reaction and also an increase in knot size and associated irritation.

Suture Pattern

The suture pattern will depend on the surgeon's preference, tissue being apposed, suture material used, and health of the adjacent tissues. The objective of the suture is to appose and align the tissues to ensure wound healing. In the case of the cornea, a water-tight seal is required and astigmatism is to be minimized. In general, for ophthalmic sutures, apposition is all that is required because tension is not usually a concern and minimal compression is needed. For more specific tissue-related suture patterns, the reader is referred to specific chapters listed by tissue of interest.

Corneal sutures may be placed using a simple interrupted or continuous pattern. Continuous patterns will include the various simple continuous, Ford-interlocking, and double continuous patterns. Corneal sutures are placed to secure a conjunctival or corneo-conjunctival graft, to close a corneal incision or laceration, or stabilize a corneal transplant. In general, simple interrupted sutures take longer to place, leave more knots behind, provide unidirectional tension vectors, and are more likely to leak or tear out. The compressive or appositional effect of a simple interrupted suture is maximal only in the plane of the suture tract (Eisner, 1990; Nasisse, 1997). Lateral to the suture tract the compressive effect diminishes, and the adjacent suture must be placed so that the compressive effects overlap to attain a water-tight closure. The lateral extent of the compression effect may be increased by increasing the size of the suture loop within the cornea (Eisner, 1990; Macsai, 2007). The result is that the larger the suture loop, the fewer sutures that will be required (Fig. 12.46). When overtightened, simple interrupted sutures cause the posterior aspect of the wound to gape, resulting in leakage and the surgeon then

Table 12.4 Suture material size based as defined by the United States Pharmacopoeia (USP) code.

USP designation	Collagen diameter (mm)<see snapshot b	Absorbable diameter (mm)	Nonabsorbable diameter (mm)
10-0	0.03	0.02	0.02
9-0	0.03	0.03	0.03
8-0	0.05	0.04	0.04
7-0	0.07	0.07	0.05
6-0	0.1	0.1	0.07
5-0	0.15	0.1	0.1
4-0	0.2	0.15	0.15

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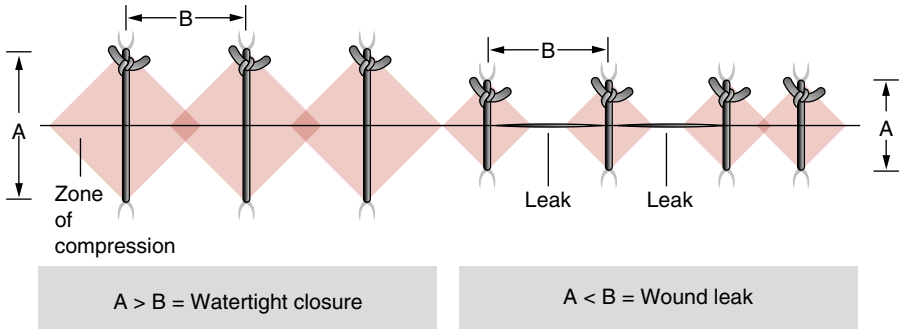


Figure 12.46 Zones of compression seen with simple interrupted sutures. Note how the different length of the suture bites alters the zones of compression. Failure to achieve overlap of the compression zones will result in wound leakage. (*Source:* Modified from Macsai, M.S. (2007) *Ophthalmic Microsurgical Suturing Techniques*. Berlin: Springer.)

attempting to compensate by placing additional and unnecessary sutures (Macsai, 2007).

Simple continuous sutures take less time to place as compared with interrupted, but may also result in lateral shifting, and a break in the suture will allow significant wound dehiscence. Unlike interrupted sutures, the force vectors created by a continuous suture are not limited to the plane of the suture loop (Eisner, 1990). Simple continuous patterns may be varied to alter the vector effects. In general, a symmetric sawtoothed pattern will provide nearly even vector forces in all directions (Eisner, 1990; Nasisse, 1997). A double continuous or counter suture pattern takes slightly longer to place and leaves more suture material, but has the advantages of even vector forces in all directions, a better water-tight seal, less astigmatism, and better wound integrity should a suture break occur. For accurate and stable closure of a corneal wound, a continuous double sawtooth pattern is best, followed by a symmetric sawtooth pattern (Fig. 12.47). The author prefers a double continuous pattern for corneo-conjunctival transpositions and some conjunctival grafts as well. If a simple continuous pattern is preferred, a Ford-interlocking pattern will work well for closure of conjunctival graft donor sites and may also be used for some conjunctival grafts themselves.

Sutures are tied using instruments, preferably two tying forceps. For efficiency with larger suture materials, many surgeons will use the tying platform on the Colibri forceps and the needle holder to tie, but this should not be done on smaller sutures because it will damage the suture material. For suture 8-0 and smaller, two tying forceps should be used. The McPherson tying forceps are most common and a straight and angle pair are best (Fig. 12.48). The surgeon must avoid over compression of these delicate forceps which will result in gaping of the tip and a failure to grasp the suture. A right-handed surgeon holds the straight forceps in their left hand and the angled forceps in the right (Troutman, 1974). The left forceps wraps the suture around the right. The first knot is usually a double or triple throw with three single throws on top of this knot. Care is taken that the

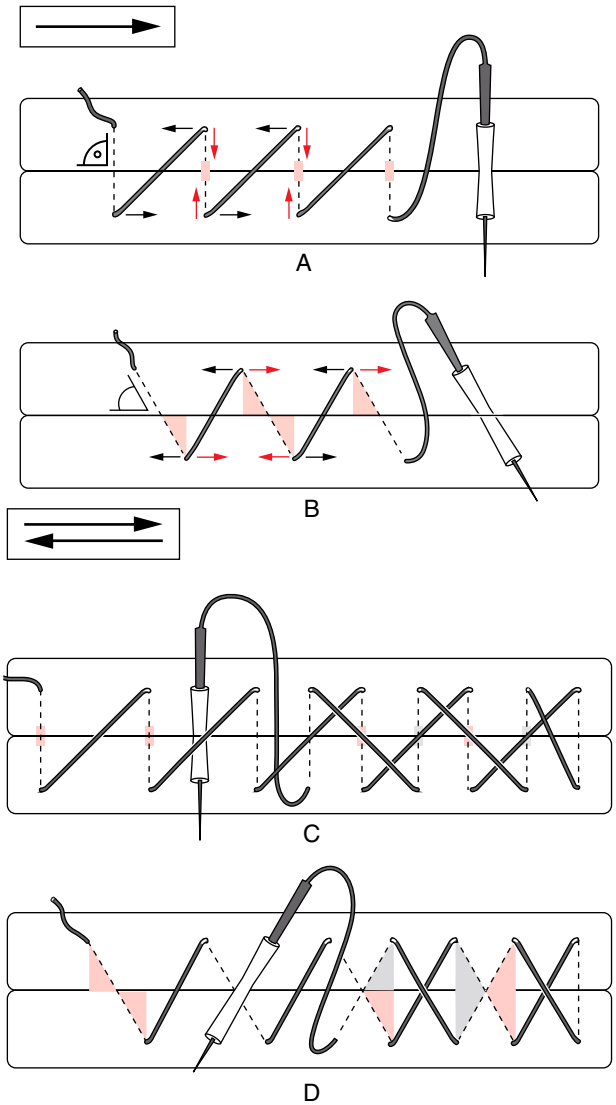


Figure 12.47 **A.** A simple sawtooth suture pattern. **B.** A symmetrical sawtooth suture pattern. **C.** A double sawtooth suture pattern. **D.** A symmetrical double sawtooth suture pattern. (*Source:* Modified from Eisner, G. (1990) *Eye Surgery: An Introduction to Operative Technique*. New York: Springer Verlag.)

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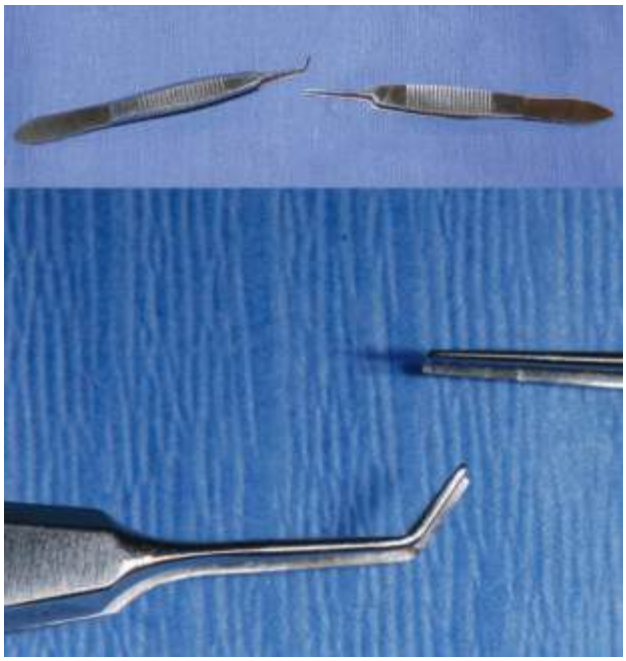


Figure 12.48 McPherson straight and angled tying forceps.

suture is pulled horizontally, 180 degrees across and at a right angle to the incision plane to ensure a square knot. The first knot is appositional and not too tight because it will tighten further when the second knot is tied. Knots are tied for apposition only and the suture ends are cut as close to the knot as possible for corneal sutures. If 9-0 or smaller interrupted sutures are used in the cornea, the knots may be buried in the suture tract. For adnexal skin sutures, the end of the suture must be left long enough to allow for removal of the suture but must not contact the cornea. In general, for adnexal sutures, the end of the suture directed toward the cornea is cut close to the knot whereas the end directed away from the cornea is left long to facilitate removal. With multiple adnexal sutures, the subsequent sutures may be used to incorporate the preceding sutures to direct them away from the cornea (Fig. 12.49).

Surgical Needles and Needle Holders

Needles for ophthalmic surgery are always swaged on because of the small size of the suture materials used and the need to be atraumatic. The most precise and least likely to deform is the laser-drilled swaged needle (Macsai, 2007). Needles may be described by the curve of the needle, the wire diameter, length of the needle, chord length, radius, and by the shape of the needle in cross section or point geometry (Fig. 12.50). The curve of microsurgical ophthalmic needles can be straight, 1/8, 1/4, 3/8, and 1/2 circles. For corneal surgery, needles with a 3/8 to 1/2 curve and a short 5–6 mm length are most common. The 3/8 needle will result



Figure 12.49 Large superior and inferior eyelid masses have been excised. Closure has been performed using 6-0 polypropylene skin sutures. A figure-eight suture pattern was used to align the eyelid margin followed by simple interrupted sutures. The ends of all sutures are left long and tucked under the subsequent suture to ensure they are directed away from the cornea.

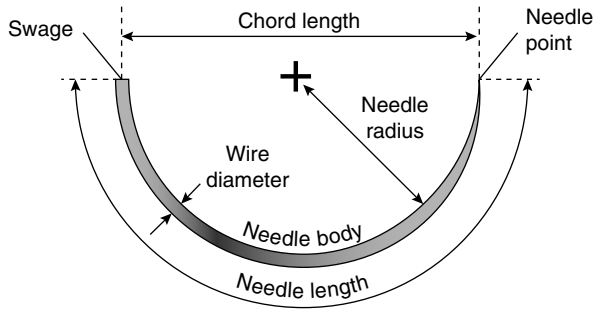


Figure 12.50 Terms used to describe the anatomy of a surgical needle.

in a larger shallower bite whereas the 1/2 needle results in a short, deep bite (Macsai, 2007). The length of a needle must be sufficient to allow both passage and retrieval without damage to the needle point as it is being withdrawn. The point geometry is described as taper (round needle with a taper point), cutting (cuts on the inside curve), reverse-cutting (cuts on the outside curve), tapercut (round needle ending in a triangular cutting tip), and side cutting or spatula (flat top and bottom, cuts on the side) (Fig. 12.51). In general, cutting/reverse-cutting needles are used for the eyelids and adnexa whereas spatula needles are used for corneal surgery. The advantage of the spatula tip is that the needle will split the tissue plane, remaining at the same depth and minimizing the risk of perforation and suture migration in thin and delicate tissues such as the cornea. For corneal closure in small animals, the author uses 9-0 monofilament Vicryl (polyglactin 910) on a CS160-8 spatula needle which has a 1/2 curve and a length of 5.5 mm.

Microneedle holders vary by the size of the jaw (delicate, fine, medium, heavy), straight or curved jaw, smooth or serrated jaw, locking or nonlocking, and the style of the handle

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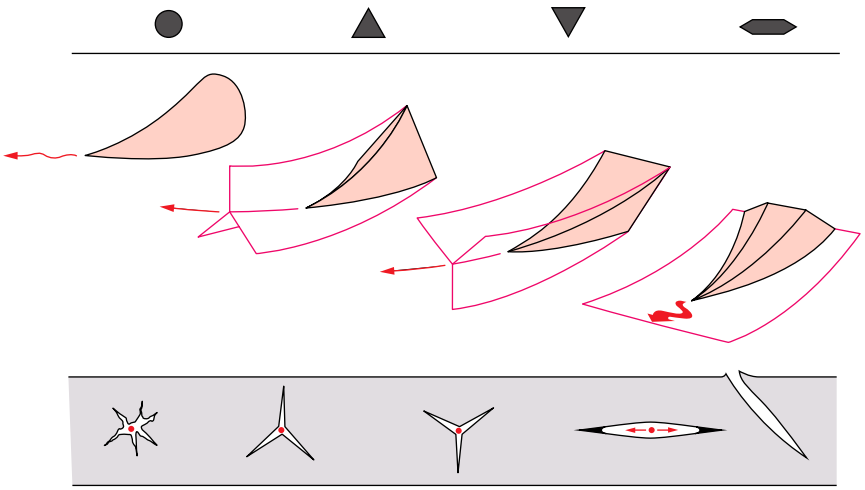


Figure 12.51 Various types and shapes of surgical needles and their effects on tissue penetration and suture placement. The top row shows the needle in cross section, the middle row shows the needle head in three dimensions, and the bottom row shows the needle track in cross section within the tissue. (*Source:* Modified from Eisner, G. (1990) *Eye Surgery: An Introduction to Operative Technique*. New York, Springer Verlag.)

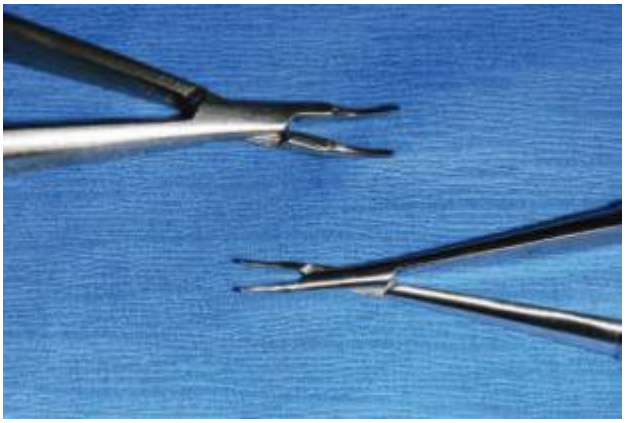


Figure 12.52 The jaws of two Barraquer microneedle holders. The jaws at the top are medium and those on the bottom are delicate in size.

(see Fig. 12.33). It is essential that the size of the instruments, specifically the jaw of the needle holder, used to grasp the needle correspond in size to match the needle selected (Fig. 12.52). If the jaws of the needle holder are too large, they will deform and flatten the needle when compressed, straightening the needle and weakening it, resulting in breaking of the needle and/or inaccurate depth of suture placement and dehiscence. In contrast, if a microneedle holder is used to grasp a large needle, the converse is true with the delicate needle holder jaws and hinge being damaged and sprung such that they will no longer hold the microneedles they were designed for. Microsurgical needles should be grasped slightly anterior of the midpoint. Grasping behind the midpoint (toward the swaged on suture) will result in bending of the needle as it is advanced. Grasping too far forward of the midpoint may damage and dull the tip. When using a curved needle holder, the needle is grasped with the jaws curving upward. Although novice surgeons may prefer a locking needle holder, nonlocking needle holders are best for most ophthalmic procedures to avoid the jerking movement of the needle associated with release of the locking mechanism. Curved, nonlocking, round-handled Barraquer or Castroviejo type needle holders are typically preferred for ophthalmic needles.

When passing a microsurgical needle, the tissue must be stabilized using appropriate forceps positioned adjacent to the point of needle insertion. If possible, when using toothed forceps to stabilize tissue, the forceps should be held so that the needle enters the tissue on the side of the forceps with the fewest teeth and with the force directed toward the side of the forceps with the greatest number of teeth (Macsai, 2007; Troutman, 1974). In order to permit a needle to be inserted and withdrawn, the needle length must be greater than the suture tract itself. This increased length may result in incongruity with the needle having a longer or shallower than intended bite if its radius of curvature is followed without manipulation of the tissues (Eisner, 1990). To adjust for this, the needle encounters the cornea perpendicular (90 degrees) to the surface and is inserted into the tissue stroma (Macsai, 2007). As the needle enters the stroma, the needle holder is rotated in the surgeon's fingers, allowing the needle to follow its natural curve while the forceps elevate and open or evert the wound slightly. The forceps are used to stabilize, provide counter pressure, and rotate the tissue as required to allow the needle to follow its path. With a two-step or beveled incision, the needle should exit the stroma at the junction of the deep initial corneal groove and the step cut initiated by the scissors. It should exit perpendicular to the cut surface. When closing a corneal incision/laceration, the needle is again placed perpendicular to the corneal stroma (parallel to the corneal surface) on the second side of the wound at the level of the step incision. When suturing a cornea without a two-step incision, the needle is placed to a depth of 75%–90% of the corneal stroma. The needle holder is rotated as the needle enters the stroma. The forceps should maintain control, stabilizing and slightly rotating the tissue

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until the needle has completed its path and exited perpendicular to the surface. Only then are the forceps released. When suturing a vertical incision, the needle should exit the tissue at a distance equidistant to the point of entry with respect to the incision (Macsai, 2007). For an oblique incision, the suture should emerge equidistant to the deep layer of the incision (Macsai, 2007). To complete a pass, as the needle is advanced, it is grasped and regrasped closer to the swaged end and the rotation movement continued. The needle should be advanced and exit out of the tissue far enough that it can be grasped and removed without grasping and damaging the needle tip. Although it has been suggested that when withdrawing the needle the curve of the needle holder should be reversed, this is not required or essential. When placing a continuous suture pattern, it is both efficient and acceptable to advance the needle far enough to allow the needle holder to regrasp it anterior to the midpoint and in a position that is correctly oriented for the next needle pass. The surgeon must then follow a path of rotation with their fingers to remove the needle without bending it while the forceps stabilize and provide counter pressure. This will decrease surgical time, is more efficient, and will minimize both suture and needle trauma. The result should be needle and suture passes of equal tissue depth and equal length with respect to the wound margin (Macsai, 2007). To avoid suture trauma and be efficient, the needle should remain in the surgical field during suture tying. This will reduce manipulation of the suture and associated suture trauma and will also save time.

For more details on suture selection and suture patterns, the reader is referred to the surgical sections in specific chapters for the tissue of interest.

Forceps

Forceps are designed for specific purposes, and it is essential to use the correct forceps for each step of the procedure. The basic functions of forceps are to manipulate and stabilize ocular tissues, tying of sutures, removal of foreign bodies or distichia, performing a capsulorhexis, and IOL manipulation (Grevan, 1997). Forceps may have teeth (variable in number and size) to grasp tissue, and in addition may have a tying platform behind the teeth to grasp and manipulate suture. The teeth may interdigitate in a 1×2 design (Gelatt, 2011a) as seen with the Colibri and Bishop-Harmon forceps or may simply appose as seen with the Utrata capsulorhexis forceps (Fig. 12.53 and Fig. 12.54). Teeth may arise at a 90-degree angle (dog-toothed) as seen with the Colibri and Bishop-Harmon forceps or emerge at a steeper angle as seen with scleral fixation forceps (mouse-toothed) (Fig. 12.55). The size of the teeth is variable in the same design of forceps with smaller teeth designed for more delicate tissues. Use of forceps with large or inappropriate teeth will result in excessive tissue trauma. Use of small and delicate forceps on thicker adnexal tissue may result in bending and damage to the teeth. Bishop-Harmon straight tissue forceps are most commonly used for eyelid (fine teeth) and conjunctiva (delicate teeth) manipulation. Although Brown-Adson forceps may be used for manipulation for skin during enucleation or orbital surgery, they are too traumatic for eyelid reconstruction procedures. Colibri forceps are most commonly used for corneal and conjunctival surgery and have 0.12 mm (cornea) or 0.3 mm and 0.5 mm teeth (conjunctiva). Colibri forceps are angled and should be held so that the tips are directed downward so that only the teeth contact the tissue. Typically, they will also have a tying platform to manipulate sutures. The use of angled forceps such as the Colibri will provide better visualization of the surgical field under the operating microscope compared with straight forceps like the Bishop-Harmon or Castroviejo.

There are tying forceps without teeth that are designed with smooth, rounded blade edges for suture manipulation (see Fig. 12.48). Although tying forceps, such as the McPherson, are designed for small and delicate suture materials, it must be understood that complete closure of even these forceps will damage and weaken sutures. If possible, only the suture ends that will be removed should be handled, and the surgeon should attempt to avoid closure of instruments on sutures that will remain in the eye. Grasping of needles with delicate tying forceps will damage and spring



Figure 12.53 Colibri 0.12 mm utility forceps (top) and Bishop-Harmon (delicate) forceps (bottom).

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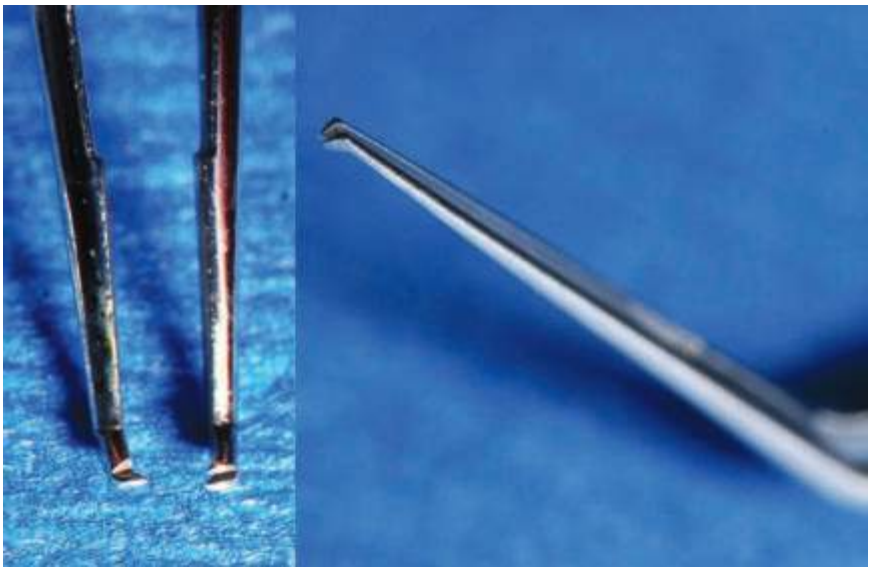


Figure 12.54 Colibri 0.12 mm utility forceps (left) with 1 × 2 teeth that interdigitate and Utrata capsulorhexis forceps (right) with 1 × 1 angled teeth that appose.

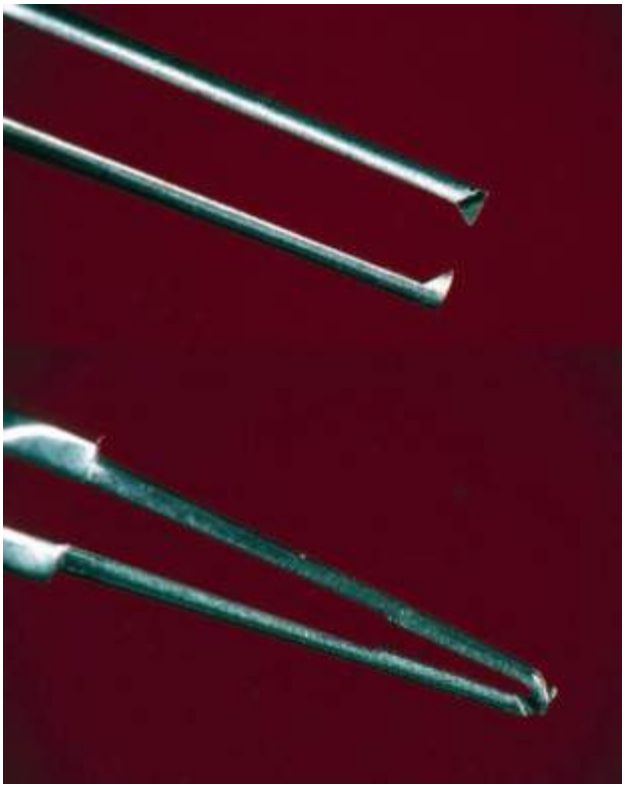


Figure 12.55 Bishop-Harmon fine, 1 × 2 straight teeth without a tying platform (top) and scleral fixation forceps with angled 1 × 2 teeth and a tying platform (bottom).

the jaws, resulting in a failure to subsequently grasp small suture materials. Instead, needles may be grasped ready to use in the needle holder as they emerge from the tissue. Alternately, the suture may be grasped in the tying forceps just behind the swaged on end of the needle and the needle suspended in the tear film to be grasped by the needle holder (Troutman, 1974).

Additional forceps may include those for IOL manipulation and those that are designed for deeper intraocular work where the action mechanism is outside the eye as seen with the MicroSurgical Technology® or Storz® forceps (Bausch and Lomb Storz, Manchester, MO, USA) (see Fig. 12.40 and Fig. 12.45).

It is essential to use the correct forceps for each step of the procedure. Use of forceps with large or inappropriate teeth will result in excessive tissue trauma. Use of small and delicate forceps on adnexal tissue or to grasp suture needles may result in bending and damage to the teeth. The novice surgeon must also work to resist the temptation to overpower the forceps, squeezing the forceps too hard, damaging both the tissue and the instrument.

Hemostasis

Hemostasis may be achieved by use of instruments such as a chalazion clamp for eyelid surgery (see Fig. 12.24), vasoconstrictive agents such as epinephrine, and wet-field cautery. Epinephrine used at a 1:10,000 dilution will provide vasoconstriction of conjunctival and eyelid vasculature when performing conjunctival or corneo-conjunctival grafts and adnexal procedures. It may also be used intracamerally to vasoconstrict the anterior uveal vasculature, dilate the pupil, and minimize fibrin formation. Intracameral epinephrine is applied at the start of the intraocular procedure and may be reapplied if intraoperative bleeding is encountered. Wet-field cautery is preferred over the battery-operated handheld

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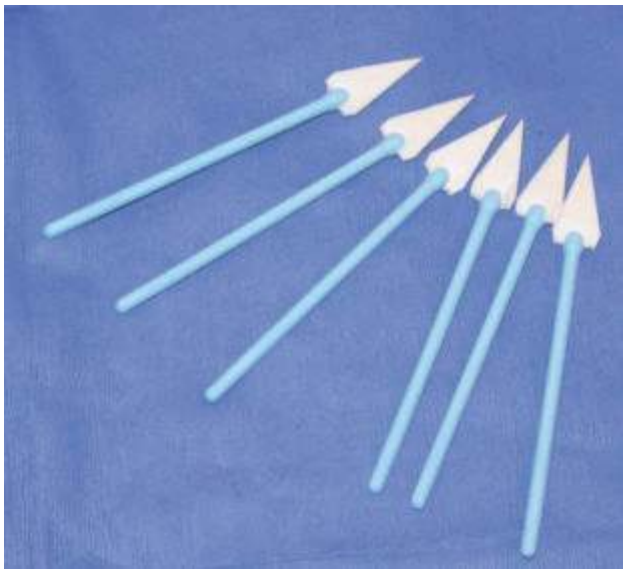


Figure 12.56 Cellulose surgical spears are absorbent without shedding fibers.

cautery units, but both have value. In general, the handheld battery units maybe used for minor adnexal bleeding whereas wet-field cautery is indicated for the management of bleeding associated with the globe, both external and internal. If bleeding occurs, cellulose sponges must be used for intraocular procedures to avoid the shedding of fibers associated with cotton swabs because these fibers may enter the eye (Fig. 12.56).

Viscoelastics

Viscoelastic substances are used in ophthalmic surgery to protect tissue and cells from mechanical trauma, create and preserve space for surgical manipulation, lubricate, separate tissues, prevent adhesions, tamponade hemorrhage, and to move or relocate tissue. They are, therefore, "tools for spacial tactics" (Eisner, 1990). The use of viscoelastic substances has been shown to minimize damage to and loss of corneal endothelial cells from all of these causes (Artola et al., 1993b, 1993a; Liesegang, 1990; Wilkie & Willis, 1999). Selection of a viscoelastic is dependent on the task required with no one viscoelastic fulfilling all needs, requiring the ophthalmic surgeon to be familiar with a variety of viscoelastic substances and their properties, and to select one most appropriate for the task performed. Viscoelastic substances must be sterile, nontoxic, nonpyrogenic, noninflammatory, and nonimmunogenic. In addition, they are balanced with respect to their electrolytes, osmolality, pH, and colloid osmotic pressure so that they are suitable for use in the anterior and posterior chambers and vitreous cavity. Injection of viscoelastic materials is critical, placing the viscoelastic precisely at the desired site and taking into consideration the volume shift that occurs with injection and the need to maintain pathways for these shifts to occur. Removal of viscoelastic material can be done using automated irrigation-aspiration, manual irrigation, or the viscoelastic material can be left in the anterior chamber if its effects are still required postoperatively, allowing removal by aqueous dilution and outflow. The decision to remove a viscoelastic material at the conclusion of surgery is based on preoperative gonioscopy, the need for visco-occupation in the postoperative period, manipulation and trauma associated with removal, and ultimately, surgeon preference. Viscoelastics have properties of both fluids and solids and are described based on their rheologic properties of viscosity, pseudoplasticity, viscoelasticity, and surface tension (Liesegang, 1990; Wilkie & Willis, 1999). A variety of viscoelastic materials are available, containing hyaluronic acid, hydroxypropylmethylcellulose (HPMC), chondroitin sulfate, polyacrylamide, or some combination thereof. Viscoelastics have been discussed as being either cohesive (high viscosity/molecular weight) such as 1–2% sodium hyaluronate or dispersive (low viscosity/molecular weight) such as Viscoat® (3% sodium hyaluronate plus 4% chondroitin sulfate) (Wilkie & Willis, 1999). For a detailed, more complete discussion of viscoelastics and their indications and properties, the reader is referred to the Surgery of the Lens (Chapter 23) and additional references (Liesegang, 1990; Wilkie & Willis, 1999).

Conclusion

Over the past decades, veterinary ophthalmic microsurgery has made significant advances with respect to small incision techniques, availability of high-quality magnification, refinement in surgical instrumentation, widespread use of viscoelastic materials and better suture materials, and precision-engineered needles. Phacoemulsification and foldable IOL implantation are now the accepted standard of care for cataracts and with this, the long-term success rate for cataract surgery and vision restoration has improved greatly for all species. Sutured IOLs and ECP techniques have been described and refined, improving outcomes for those patients for whom surgical success was previously less than acceptable. Finally, veterinary ophthalmic surgery continues to expand into the realm of posterior segment vitreoretinal surgery.

As ophthalmic surgeons, we must ensure we remain current in our understanding of these new techniques and procedures in order to provide the best possible care for our patients and to ensure the next generation of veterinary ophthalmic surgeons are trained effectively. We must always strive to improve on our outcomes, refuse to accept poor surgical results, and instead challenge ourselves to find better approaches to traditional techniques when outcomes are less than acceptable.

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As we seek to improve, we must all follow the basic rules: to use appropriate magnification and instrumentation, to be efficient and precise, to ensure minimal tissue trauma, to minimize surgical time, to maintain the anterior chamber using small incisions and viscoelastic materials, to obtain excellent tissue wound apposition with the smallest and most appropriate suture materials, and finally, to achieve a successful, comfortable, cosmetic, and whenever possible, visual outcome.

Finally, we must remember that microsurgery is both a technique and an art and as such we must constantly work to refine and improve ourselves as microsurgeons. We must also remain open to new ideas and respect the opinions of others who may have a different method to achieve success.

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13

Digital Ophthalmic Photography

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Photography is an essential part of veterinary ophthalmology, and the digitization of photography has been important in increasing both the quality and the availability of ophthalmic lesion images. Because digital cameras provide their user with instant feedback in terms of image composition, exposure, and definition, it takes relatively little time and effort to be able to capture clear, well-focused, and effectively composed images.

Although many readers are familiar with and may even possess vast archives of slides or printed photographs taken with film cameras, digital photography has superseded the era of film. The relatively low cost of quality digital photographic equipment allows for widespread use of this technique in every situation.

We have made a conscious decision to concentrate solely on digital photography in this chapter. The focus will be on providing guidelines and insights from the contributing authors to minimize the trial-and-error tactics of digital photography often employed by novice photographers. Although there is a plethora of digital photography equipment available, the information provided in this chapter pertaining to camera operation and image capturing techniques uses the digital single lens reflex (dSLR) camera as its basis. For this edition we have also chosen to include a section on smartphone ophthalmic photography. The technologic advances that have been made over the past few years have resulted in smartphone cameras that are both powerful and versatile. Since our phones are never out of arm's reach, they are often the first-choice camera in both our private and professional lives.

The chapter will cover general principles of digital photography, with the emphasis on utilizing different modes of operation (aperture priority, shutter priority, and manual). Photographic equipment, including cameras, lenses, and flash systems necessary to obtain high-quality images, will be evaluated, followed by a brief description of appropriate photographic technique. Discussion of specific techniques commonly used to accurately photograph ocular structures and commonly encountered artifacts will follow. Specific tips and appropriate settings for optimizing image capture will be given, which will allow accurate digital imaging of common lesions within specific ocular tissue. Finally, a summary of currently available hardware and software will be presented.

Photography Basics

Photography is a discipline requiring both technical skill and an artistic perspective. However, to obtain high-quality images consistently, the photographer must have a sound understanding of the equipment being used and the mechanics behind its operation. This section will focus on several key basic concepts of photography.

Exposure

Exposure is a fundamental concept in photography. Understanding exposure and knowing the parameters that control it is vital to becoming a better and more consistent photographer. There are several ways of defining exposure (e.g., overexposed vs. underexposed); however, a *correct* exposure is simply a matter of obtaining an image that is the way you want it to be (Peterson, 2010). To obtain this correct exposure, the photographer must always be in complete control of his/her equipment such that the necessary adjustments can be easily made. Simply relying on automatic settings and/or the meter reading of the camera itself may render a good exposure; however, the photographer may not consider it to be correct.

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Several parameters can affect the exposure within the final image, all of which are intricately related to one another. These include the scene light, shutter speed (e.g., exposure time), aperture (e.g., light intensity), and International Organization for Standardization (ISO) values (e.g., light sensitivity). All of these parameters will be discussed in more detail individually in the following sections. In the case of ophthalmic photography, however, scene light is generally not a significant consideration *per se*. Room lighting is usually not recommended as it creates several unwanted and often distracting specular reflections (Christopherson, 1982). Controlling light in the scene is often done by either a modeling light and/or a flash and will be discussed separately.

Prior to discussing shutter speed, aperture, and ISO values individually, it is important to understand their relationship to one another. Furthermore, it is useful to think of them in terms of stops. A full stop is defined as either doubling or halving any value (e.g., shutter speed). Each of these three parameters can be considered in terms of stops, and an adjustment in one can be compensated for by a reciprocal adjustment in one of the two other parameters. This is the principle behind reciprocity, whereby doubling a full stop in one parameter is equivalent to halving a full stop in another (Shaw, 1987). Once a correct exposure has been obtained, the photographer has the capability to alternate any one of these parameters as needed. For example, an image obtained of a corneal lesion yields a correct exposure at 1/125 second (shutter speed), f/8 (aperture), and ISO 100. However, due to patient movement, the image is blurred. To compensate for motion, a faster shutter speed is necessary. A shutter speed of 1/250 second is chosen; however, to maintain correct exposure, the aperture should be stepped down one full stop, or the ISO setting decreased. This concept can be extended to incorporate moving in 1/2 or 1/3 stop increments as well. Thinking in terms of stops allows the photographer a great deal of creativity, while maintaining a correct exposure in the final image.

Shutter Speed (Exposure Time)

Most current cameras utilize a focal plane shutter. This consists of two overlapping curtains (slit or guillotine) located in front of the camera sensor (Adams & Baker, 2003). The shutter is responsible for controlling the amount of light that reaches the sensor by regulating the length of time it remains open. Shutter speeds may vary in increments (e.g., stops) ranging from thousandths of a second to minutes. Of note, however, is that most digital cameras today allow 1/2 to 1/3 stop increments to be performed as well, thereby providing the photographer with even greater flexibility. Alteration in the shutter speed allows the photographer the capability to halt motion and/or create blur, whichever is preferred. However, in the case of ophthalmic photography, the former is a priority. The shutter speed required to prevent motion blur is dictated by several factors, which may include the focal length of the lens, the working distance, and the direction of object movement (toward/away vs. side to side; Shaw, 2000). The focal length of the lens can impact the slowest shutter speed capable of maintaining a sharp image, specifically when the camera is handheld. As a rule of thumb, the shutter speed should be faster than the focal length of the lens being utilized. For example, when using a 105 mm lens, the shutter speed should exceed (e.g., be faster than) 1/100 second. The working distance and direction of object movements can impact shutter speeds as well, both affecting the speed at which the object moves across the sensor. At a shorter working distance, smaller movements either by the photographer or the object have a greater effect. Similarly, the direction of object movement can greatly impact image quality. Movements parallel to the sensor (e.g., globe movement) are more detrimental than back-and-forth movements, as the former reflect movement across the sensor to a greater degree.

Aperture (Intensity)

The aperture is the diameter of the lens opening, which regulates the intensity of light reaching the sensor at a point in time. This opening is formed by a series of overlapping blades within the lens (Fig. 13.1). It is defined by an f-number, which represents a fraction of the lens focal length. As such, the aperture (e.g., size of the opening) is a relative value. For example, an aperture of f/4 on a 60 mm lens represents a lens opening of $60/4 = 15$; however, f/4 on a 200 mm lens is $200/4 = 50$. Despite this, all lenses set to the same aperture (e.g., f/4), regardless of focal length, will transmit the same intensity of light to the camera sensor (Adams & Baker, 2003). As with shutter speed, aperture is altered in stop increments, which may vary by full, 1/2, or 1/3 stop increments. A change of one full stop is equivalent to twice (or half) the amount of



Figure 13.1 Image obtained from the rear lens of a Nikon 105 mm macro lens with aperture stopped down to f/8. Note the overlapping aperture blades regulating the diameter of the lens opening.

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light as its neighboring full stop. It is important to note when discussing aperture that an inverse relationship exists between the f-number and the size of the lens opening (e.g., light intensity). Smaller f-numbers equate to a larger lens opening and the transmission of more light. A simple way to think of this is "less is more." While it may seem logical to maintain the widest aperture possible, thereby allowing more light and permitting faster shutter speeds, aperture also plays a key role in controlling depth of field (DOF) as will be discussed shortly.

ISO (Sensitivity)

ISO is a numeric value that defines the sensitivity of the camera to light (Peterson, 2010). This value can range from 25 to > 6400 and may be defined in terms of relative speed: < 200 (slow), 400–800 (fast), and > 800 (very fast). Previously, the ISO value was determined by the film employed within the camera; however, using a digital camera this is now simply a matter of pressing a button. Altering the ISO varies the sensor's sensitivity to light, a process that occurs through amplification of the signals generated by the photosites within the sensor (Gulbins, 2008; Long, 2010c). Increasing the ISO setting translates into a greater light sensitivity. However, more important to our understanding of exposure, altering the ISO changes the *amount* of light required by the sensor. This latter point is inversely related to the ISO setting. For example, while increasing the ISO setting from 100 to 200 increases the sensor's sensitivity to light, it decreases the amount of light required for an exposure. By altering the ISO setting, the photographer has an additional tool by which to control exposure. Increasing the ISO reduces the amount of light required, thereby allowing faster shutter speeds and/or smaller apertures to be employed. The former may be required to reduce patient movement/blur, while the latter may be employed to increase DOF. However, it is always preferential to utilize an ISO setting as low as possible (e.g., < 400) to maintain maximum image quality (Olsen, 1979). Amplification of the signal generated by the photo sites may introduce digital noise (e.g., luminance or color) and degrade the final image. Luminance noise generates an overall graininess within the final image, while color noise creates a mottled color effect, particularly within shadowed regions of the image (Busch, 2004a; Long, 2010d).

Exposure Modes

Most digital cameras today offer a variety of exposure modes, each having their own advantages and disadvantages. Proper use of each requires a clear understanding of what is being controlled for by the camera and what possible limitations may exist. Common exposure modes include full auto, programmed auto, shutter priority, aperture priority, and manual exposure (Canon, 2009; Lowrie, 2007; Stansfield, 2010).

Fully Automatic

As the name would imply, while in this exposure mode the camera makes all decisions regarding exposure settings (e.g., shutter, aperture, ISO) and various other parameters (e.g., autofocus mode, white balance, color space). It allows the photographer to simply point and shoot. There is no flexibility or possible alteration of any major camera setting. While this mode often provides consistent results and requires very little in the way of understanding photographic principles, the final image may not be exposed correctly.

Program Mode

This exposure mode is similar to fully automatic in that it determines the shutter speed and aperture based on the scene; however, alteration in other settings such as ISO, white balance, metering modes, and so on is possible. This mode offers greater flexibility while still controlling some settings that dictate exposure.

Shutter Priority

This exposure mode is utilized when the photographer wishes to control the shutter speed, either to freeze motion and/or to create blur. Once the desired shutter speed is chosen, the camera then determines the appropriate aperture based on the brightness of the scene. Similar to the program mode, alteration of various other settings is possible.

Aperture Priority

This exposure mode is essentially the opposite of shutter priority, where the photographer determines the aperture and the camera determines the appropriate shutter speed. This mode is useful when wishing to determine and/or dictate the DOF present within the scene.

Manual Mode

As implied, within this exposure mode the photographer has complete control and dictates all exposure parameters (e.g., shutter speed, aperture, ISO). It affords the greatest amount of flexibility and is the preferred choice of the authors.

Focus

Obtaining the correct focus within the final image is fundamental, as it may be the difference between a good and an exceptional image. Several variables can affect focus, many of which have been discussed, including patient movement, shutter speed, and aperture selection. Aperture will be considered in more detail shortly as it pertains to DOF. There are several different methods for trying to obtain the correct focus; however, prior to this discussion an important point needs to be addressed. Simply put, the camera itself must be correctly focused for the refractive error of the photographer. This becomes extremely important when utilizing a manual mode and particularly relevant when multiple individuals

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operate the same camera. Adjusting for one's refractive error is easily performed by simply altering the dioptric control of the viewfinder. This is typically a small dial or knob located next to the viewfinder itself. Establishing the correct focus for the camera is comparable to adjusting a slit lamp, where attention is directed toward a series of points/marks (often focus points) located within the viewfinder. When proper focus has been obtained, these reference points will become sharp and crisp. However, while effective for most individuals, this dioptric adjustment may not be able to fully correct for one's refractive error if it is significant.

In general, one can use an automatic or manual approach to focus on the object of interest. Most current cameras in use today provide autofocus capabilities through a passive autofocus system, typically of the contrast detection type (Long, 2010d). These systems operate by focusing the lens until the image obtained demonstrates the greatest amount of contrast possible. A zone or spot is utilized to determine which part of the image will be analyzed for focusing purposes. These regions will beep or light up when focus has been obtained and can be varied as needed, either automatically or manually, based on the requirements of the photographer (e.g., if the object of interest is not centrally located). To activate the autofocus system (e.g., refocus), one simply needs to depress the shutter button halfway down. However, as the camera can only focus at one plane, it is important to pay attention to which zone/spot has achieved proper focus, as it may not coincide with the region of interest.

In addition to altering the zone/spot used for establishing focus, one may alter the autofocus mode. Several different modes are available on most cameras; each varies by the mechanism by which the camera identifies the object of interest. Modes commonly available include single shot, continuous (Al Servo), and automatic (Al Focus) modes (Canon, 2009; Lowrie, 2007). Single shot is typically used for still subjects, as once the shutter is depressed halfway the focus remains constant (unless released and redepressed). Continuous mode is utilized for moving subjects, since the autofocus system is constantly changing the plane of focus as it tracks the object of interest. Automatic mode is a combination of the former two and may be used for a variety of situations. A review of the instruction manual will determine which modes are available on your particular model. While these automatic focus modes are effective in a number of different situations, they can become confused under certain circumstances. One of these is low-light (low-contrast) situations, as passive contrast autofocus systems are largely dependent on the availability of light to operate correctly. One method by which the camera may try to compensate for this limitation is to provide a series of short bursts of light from the pop-up flash unit (pre-flash), thereby allowing the system sufficient light to establish proper focus (Canon, 2009). However, despite this, use of a manual focus mode may be required and is the preferred mode for the authors. Overriding the autofocus mode of the camera is performed by switching the AF/MF switch on the camera lens itself. This allows the photographer to set the focus plane by simply altering the focusing ring on the lens. An alternate approach, which is more applicable to ophthalmic photography, is to preset the plane of focus, based on the desired magnification and/or field of view, and to move to and from the object (e.g., globe) of interest. This provides the photographer complete control in determining which region of interest will be in perfect focus.

Depth of Field

Another fundamental concept in photography is DOF. Based on the optical principles of the imaging system, only one plane of an object can be in perfect focus at any given point in time (Shaw, 2000). However, there is a zone in front and behind this plane of focus which is considered to be acceptably sharp. This zone is referred to as the DOF. Several factors applicable to ophthalmic photography that may affect the DOF include aperture, lens focal length, and working distance (Adams & Baker, 2003; Davis, 2010). A brief summary of their effects on DOF is given in Table 13.1. Of these, aperture is likely to play the most significant role. However, additional considerations include magnification and the angle at which the plane of focus (angle of camera to object) is oriented. When imaging at higher magnifications, as is common in ophthalmic photography, DOF is significantly reduced. As such, positioning the camera slightly off axis can render portions of the image out of focus. Knowing and understanding these variables as they pertain to DOF can significantly improve the photographer's ability to control DOF and obtain the desired results.

DOF may be accessed directly, prior to obtaining an image, using the DOF preview button. This button is present on most high-end dSLR models, located on the front side of the camera body, and once depressed will stop down the aperture to the set f-number. This allows the photographer to preview

Table 13.1 Depth of field (DOF) and its relationship to aperture, lens focal length, and working distance.

Parameter	How to Increase DOF	Relationship to DOF
Aperture	Decrease	DOF inversely proportional to change in aperture; e.g., halving aperture doubles DOF
Focal length	Decrease	DOF inversely proportional to square of focal length
Working distance	Increase	DOF proportional to square of distance

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how the final image will appear through the viewfinder and assess the DOF. It is important to note, however, that DOF becomes increasingly difficult to assess through the viewfinder at higher f-numbers (smaller apertures) due to progressive light loss.

Lighting

Lighting is another fundamental aspect of photography, although a detailed discussion of light and its spectral properties is beyond the scope of this section (Hattersley, 1979). Light within the scene may be described in several different ways. Harsh light is a term used to describe light emanating from a distant concentrated light source (e.g., a flash). Soft light is used to indicate light emanating from a more diffuse light source (London et al., 2010b). A summary of the effects on the object within a scene is given in Table 13.2. Most light employed in ophthalmic photography is generated from a flash unit and is therefore considered to be harsh lighting; however, soft lighting may be obtained by using a diffuser over the flash unit and may be preferred under certain circumstances (Mandell et al., 1976). More relevant to ophthalmic photography is the direction of lighting. The placement and/or direction of the light source can drastically alter the final image, impact one's ability to visualize lesion(s) of interest, and/or result in the creation or placement of unwanted specular reflections. The direction of lighting as it pertains to ophthalmic photography can be characterized as follows: front lighting, side lighting (also known as tangential), and backlighting (e.g., retro illumination). Table 13.3 provides a summary of definitions, uses, and possible benefits.

Metering

A light meter is a device that determines the amount of light present within a scene. Metering plays a crucial role in determining ideal settings for a proper exposure. However, while most metering systems allow for good exposure, that exposure may not be correct. There are two general types of meters, incident and reflective. Most metering systems present within digital cameras are of the reflective metering type. A reflective meter determines the amount of light reflected from the object within the scene (e.g., luminance; London et al., 2010a; Long, 2010a). These systems are referred to as through the lens (TTL) metering systems, as light must first pass through the lens of the camera prior to reaching the meter. Several types of TTL metering system may be available on your digital camera, and it is important to understand and know how these vary. Common metering methods are summarized in Table 13.4 and may include matrix/evaluative, center-weighted, partial, and spot metering (Canon, 2009; Stansfield, 2010).

It is important to note, however, that color plays no direct role in metering a scene. In fact, these metering systems assume that everything within the scene has a reflectance of 18% light (e.g., neutral gray). It is because of this fact that some images may be over- or underexposed, despite proper metering. White objects in a scene typically reflect 36% of the light, while black ones reflect 9% of the light (Shaw, 2000). If there is a strong bias to either one of these in a scene, the metering system assumes a reflectance of 18%, which translates into an incorrect exposure. To compensate for this, underexposing for black objects or overexposing for white objects may be necessary due to the assumptions of the metering system.

Table 13.2 Comparison between harsh and soft lighting.

	Textural Definition	Contrast	Shadows	Color
Harsh light	Improved	Improved	Sharp edged	Vibrant
Soft light	Reduced	Reduced	Soft edged	Dull

Table 13.3 Comparison between front, side, and backlighting techniques.

	Front	Side	Back (Retro Illumination)
Light source	Pop-up flash and/or mounted accessory flash	Use of freely mobile accessory flash	Use of freely mobile accessory flash
Direction of lighting	Light strikes object straight on	Light strikes object from one side	Light almost coaxial with camera lens, reflecting from behind object of interest
Effects/ benefitzs	Flat effect; reduced contrast and textural detail	Improved contrast and textural detail	Silhouette effect
		Good contrast and delineation of object borders	Good contrast and delineation of object borders

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Table 13.4 Common metering modes: Methods of metering and their benefits.

Metering Mode	Matrix/Evaluative	Center Weighted	Partial	Spot
Method of metering	Divides scene into grid and meters each grid individually	Like matrix, with bias placed toward central 80% of the scene	Metering performed within the central 9% of the scene	Metering performed using extremely narrow angle of view (1–5 degrees)
	Final metering based on array of predetermined scenes programmed into camera, judging best fit	Metering based on assumption area of interest is in center scene		Provides very accurate metering of one specific spot in a scene
Benefits/ uses	Good for average scenes	Good for average scenes	Good for side or retro illuminated objects	Good for proper exposure of small object(s) within a scene

Flash

As previously mentioned, proper lighting is fundamental to photography and demands special consideration. In ophthalmic photography, lighting within the scene is generally provided by a flash unit, as room lighting is not recommended (Christopherson, 1982). Flash photography is a complex and often misunderstood aspect of photography. This following section should serve as a brief introduction. Careful review of your flash unit's manual is recommended to illustrate its full potential and any possible limitations.

The flash unit is simply a device that can generate short bursts (e.g., 1/1000 second) of artificial light at a color temperature around 6000 K (Canon, 2008; Guy, 2010). These units vary in their capabilities, from simple auxiliary light sources to complex and quite sophisticated devices. The amount and duration of light generated from these units may be controlled automatically via the camera's metering system (e.g., eTTL) or manually by the photographer. It is important to note, however, some fundamental concepts that pertain to flash photography. First, flash units and their effective area of coverage are dependent on the subject distance and obey the inverse square law (Guy, 2010). Simply put, doubling the subject distance translates into a reduction of light from the unit by a factor of 4. Second, due to the mechanics of the shutter, the maximum shutter speed obtainable is limited when the flash is employed. This maximum shutter speed is referred to as the flash sync speed, and is often about 1/200 to 1/250 second. Furthermore, while this is a difficult point to understand, the shutter speed does not limit the effective range of the flash; only the aperture and ISO do that (Guy, 2010). This is because the burst of light begins and ends while the shutter is open. Finally, metering of the flash unit may occur automatically (e.g., eTTL). However, the method by which this occurs differs from ambient light metering (e.g., evaluative metering). Metering of the flash is controlled by altering its light output, not by changing various exposure settings (e.g., aperture).

In ophthalmic photography, use of a flash unit will likely be the primary means of generating light within the scene, ensuring proper exposure. To improve the unit's ease of use and understand its benefits, some additional points should be considered. These include the flash range, recycle time, integration with the camera, and placement/mounting of the flash unit.

Flash Range

The flash range of a unit is described by its guide number (GN) and relates to the maximum subject distance that still maintains proper exposure. The GN is not a measure of the power of the flash; however, its value is dependent on sensitivity and angle of view (London et al., 2010b). While generally of little concern in ophthalmic photography due to small working distances, the GN will affect the range of apertures (and DOF) that may be utilized. Essentially, flash units with a low GN (e.g., pop-up flash) may not allow for the desired DOF in the final image. A GN of at least 40 (at an ISO of 25) is recommended for ophthalmic photography (Gutner, 1977).

Recycle Time

The recycle time of a flash unit is the duration needed to reach a full charge (e.g., maximum flash output). This time can range between tenths of a second to full seconds depending on the unit. Furthermore, these times are affected by the power setting of the flash (e.g., full vs. half) and the power supply (e.g., batteries vs. external power source) employed within the unit. As many of the patients imaged are not completely restrained/immobile (e.g., globes still freely mobile), rapid flash recycling time allows the greatest number of images to be obtained in the shortest amount of time.

Integration with the Camera

Many options and choices are available when it comes to selecting a flash unit; however, regardless of the unit chosen, it is important to ensure that it is compatible with the metering system of the camera. As previously mentioned, these metering systems differ from those involved with ambient light, with metering of light occurring once the shutter has been opened (Guy, 2010). Ensuring proper compatibility allows for automatic metering to occur, where flash output is

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regulated by the camera itself, based on predetermined exposure settings. Remember, automatic metering of the flash controls the flash output and does not alter exposure settings.

Placement of the Flash

This last point of consideration is probably the most important, as the best images of the globe and/or adnexal regions are obtained with a single, carefully placed light source (Olsen, 1979). Common flash units employed today include the pop-up flash, ring flash, and an accessory flash unit (which communicates via the hot shoe), the latter being the preferred choice of the authors. The pop-up flash, while convenient and present on every camera, offers minimal power (low GN), is fixed in its location, and provides only frontal lighting. The frontal light generated from these units typically results in flat images, with poor textural detail. Additionally, use of these units at higher magnifications and short working distances often results in a marked shadowing effect due to the camera lens and poor exposure. The ring flash is an alternative and mounts directly in front of the camera lens. While these units provide uniform illumination on the subject, their shadowless illumination impairs one's ability to assess depth in the final image. Furthermore, they generate centrally located specular reflections (flash artifact), which often obscure regions of interest in the final image (Mandell et al., 1976). The third choice is an accessory or external flash. These flash units communicate via the hot shoe of the camera and may be mounted directly to the camera or be freely positioned via wired or infrared (wireless) communication systems. The latter creates an endless number of possible locations and/or positions for the flash, whereby the flash may be mounted away from the camera via a bracket or handheld by the photographer. Moving the flash unit not only allows for control of how the subject is illuminated (e.g., side light), but also facilitates variation in the location of specular reflections created.

In summary, regardless of which flash unit is ultimately chosen, it should be of sufficient power, have controllable output, and not be obstructive in size or location (Gutner, 1977; Olsen, 1979).

Sensors and Generating the Image

Most digital cameras today house either a charge-coupled device (CCD) or a complementary metal oxide semiconductor (CMOS) sensor. Both are composed of a series of picture elements (e.g., pixels) in a grid-like fashion. While the method of generating the electrical signal differs between these sensors, the basic concept is similar (Long, 2010c). Following exposure to light, each pixel within this grid samples the amount of light received, analyzes it, and assigns a numeric value (e.g., bit). The range of numeric values that may be assigned is referred to as the bit depth and relates to the possible tonal range within the final image (Gulbins, 2008). Each pixel within the sensor is covered by a filter (color filter array). This filter is often devoted to the three primary colors (red, green, and blue), such that each color neighbors the remaining two (Busch, 2004b). This arrangement results in a series of color channels, each of which has its own bit depth (bit per channel), typically 8 bits or higher for each of the red, green, and blue channels. As such, the sensor creates three incomplete color images (color channels). The camera determines the true color of each pixel by analyzing information obtained within each adjacent pixel, a process referred to as demosaicing (Long, 2010c). Because of this process, each pixel in the final image is a combination of three primary color channels, each of which has its own bit depth (e.g., 8 bits). The sum of each of their bit depths (bits per channel) is represented as the bits per pixel and defines the final color tonal range. Thus, a single pixel typically consists of 24 bits of color information (8 bits per channel).

Finally, once this information has been obtained, it is amplified, then transferred to an analog–digital converter and onto the camera's processor, where a number of final adjustments occur (e.g., mapping into color space) to create the final image (Busch, 2004b).

Resolution, Image Size, File Size, and Image Quality

Several important concepts require a clear understanding when discussing photography, particularly in the digital realm, including resolution, image size, file size, and image quality. While these are all related, understanding their independent roles and how they are associated with one another is fundamental.

Resolution is used to describe the amount of detail an image holds. This is denoted by the effective pixel count (W × H) of the sensor and should not be confused with the actual pixel count (total number of pixels of the sensor; Busch, 2004b). The effective pixel count refers to the number of pixels that contribute to the final image. This count is lower than the actual pixel count, as several pixels are unused and/or utilized for shielding purposes (Long, 2010c). The effective pixel count is therefore considered to be a more accurate representation of the resolution of the sensor (pixel resolution) and is defined as the number of pixels per unit of measure (e.g., pixels per inch or ppi; Gulbins, 2008; Standardization Committee, 2005). While pixel resolution is of consideration when discussing the final image resolution, spatial resolution is of greater importance. It is a measure of how closely lines can be resolved in the final image and is dependent not only on the capabilities of the sensor, but on the optical properties of the imaging system itself.

Image size is simply the physical size in pixels of the final image and can be altered on most digital cameras (Busch, 2004b). Of note, however, is that reducing the image size will

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decrease the pixel resolution (e.g., the number of effective pixels) as well as the file size.

File size is the actual space or amount of memory the final image will take up on the storage medium. This is affected by the image size and the degree of file compression. The latter may occur within the camera or during postprocessing through selection of the file format. While its primary purpose is to improve storage capacity, increasing file compression may significantly degrade the final image quality. As such, it is always preferred to obtain an image utilizing the least amount of compression possible. Table 13.5 lists common file formats, demonstrating the relationship between file size, degree of on-camera processing, and compression (Gulbins, 2008; Long, 2010b).

Image quality is a term used to describe the perceived degradation present within the final image. As such, it is affected by the resolution of the imaging system itself, in addition to any artifacts introduced during on-board camera processing (e.g., amplification) and image compression. Furthermore, degradation of image quality may occur during postprocessing. While a detailed discussion of factors contributing to image quality is beyond the scope of this chapter, several of the factors describing image quality and relating to either the imaging system and/or postprocessing software programs may include sharpness, noise, dynamic range, contrast, and color balance.

White Balance

White balance is a function of the camera that is often overlooked and/or misunderstood, yet it can significantly affect the results in the final image. White balance refers to how the camera interprets light within a scene, based on its color temperature (Long, 2010d). Specifically, it is how the camera determines what should be white. Once established, all other colors are reproduced from this point of reference. As such, proper white balance is essential for accurate color renditions in the final image. White balance may be altered as needed to improve and/or correct for errors (e.g., blue color cast). All cameras have an automatic white balance function, in addition to several other preset configurations for various lighting conditions. Furthermore, several cameras offer the capability of creating a custom white balance, a function that may be useful or necessary for specific lighting conditions (e.g., infrared). Alteration of the white balance may also be conducted in a series of postproduction software programs when images are obtained in a RAW format (see below). A review of your camera's operating manual will identify which configurations are present and how to go about altering them.

Color Space

Color space and color management within the digital world are complex subjects and this section serves only as a brief introduction. The color space is the palate that provides the range of colors described by a particular color model (Kuehni, 2003). It is a mathematic model utilized by the camera and other reproduction devices to represent color. Most cameras today offer the choice of selecting between two common color spaces, sRBG and Adobe RGB. sRBG is a color space that encompasses only approximately 35% of the visible colors, according to the CIE (Commission Internationale de l'Eclairage, an international committee established to standardize colors). Its color gamut approximates that of most computer display devices and it is probably the most commonly utilized color space (Long, 2010c). Adobe RGB, on the other hand, encompasses approximately 50% of the visible colors according to the CIE. Its gamut provides an improvement within the cyangreens compared to sRGB (CIE, 2004). Regardless of which color space is utilized, proper selection is key to any color management system. By selecting the appropriate color space between devices, one ensures that the color values obtained from the original device (e.g., the camera) are accurately depicted by the reproducing device (e.g., the computer monitor).

Table 13.5 Common file formats and their impact pertaining to file size, degree of processing, compression, and quality.

File Format	RAW	TIFF	JPEG
File size	Large (less than TIFF)	Large	Variable
On-camera image processing	None	Yes	Yes
Compression	None	Minimal; compressed but information not discarded	Variable compression; low vs. high quality
			Low quality; high compression ratio (20:1)
			High quality; low compression ratio (4:1)
Image quality	High, preferred file format	High, good flexibility, free compression artifact	Variable, subject to compression artifacts

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Equipment Considerations

Digital Cameras for Ophthalmology

The best camera to take any photograph is the one that is available when needed, regardless of whether it is professional equipment or a cell phone (Jarvis, 2010). It is often less the camera that is important as much the expertise of the photographer. A good photographer can obtain an acceptable (and often excellent) image even with an inexpensive camera or a cell phone with limited options. Conversely, an expensive, feature-rich camera setup does not guarantee good image quality in the hands of someone who does not understand some basic principles of the art and science of photography. With the advent of digital photography and the explosion of various types of electronic camera systems, it has become much easier for most people to obtain acceptable ophthalmic images even on a limited budget. Nonetheless, there are equipment considerations that will facilitate acquisition of digital photographs in the veterinary clinical setting. This section will review our recommendations for external ophthalmic macrophotography at the time of publication. Although this is a rapidly changing field, most of the information will be applicable for the foreseeable future.

Digital Single Lens Reflex Cameras

The basic components of any digital camera (dSLR, mirrorless, compact, or smartphone) are a lens to focus incident light reflected from the subject (eye and adnexa) onto the "digital film"/sensor, a controllable aperture within the lens to control the amount of light reaching the sensor and to maximize the DOF, a shutter system to allow a highly controllable duration of exposure of light on the sensor, a light-tight enclosure (camera body) housing the sensor and electronic controls of the camera, a lens and a flash, and a means to view the subject (viewfinder or liquid crystal display [LCD] screen) and review the image (LCD screen).

The most versatile camera for ophthalmic macrophotography remains the dSLR. Although dSLR cameras are made with fixed built-in lenses, a dSLR with interchangeable lenses is more flexible. This enables attachment of a lens designed for close-up (macro) photography. The camera should have reasonably high sensor resolution (most of the cameras available commercially have at least 20 megapixel sensors). Full control over lens aperture is important to enable adequate DOF. Digital SLRs offer by far the best control of aperture in photographic mode aperture priority ("A" on Nikon and "Av" on Canon dSLR) or manual control ("M" mode on most cameras) of aperture and shutter speed. A small aperture is needed to achieve a good DOF for the eye and adnexa when working with high magnifications. Although one might assume that the aperture is controlled on the lens itself (as was the case using the aperture dial in the days before digital cameras), now the aperture is controlled electronically from the camera.

Two basic types of sensor are found existing in digital cameras: CCD and CMOS sensors. These differ in various ways that may affect image quality, signal noise, and energy use. Many camera manufacturers use sensors that are smaller than the traditional "full-frame" or 35 mm film size used previously in film SLR cameras. The commonest sensor sizes are full-frame (35 mm film), used by several Nikon and Canon cameras, and APS-C, with a crop factor of about 1.5×, used in various Nikon (DX format) cameras and those from other companies including Pentax, Sony, Samsung, and Fuji. Compact cameras have much smaller sensors and cell phones the smallest sensors of all. As the sensor size is reduced, the crop factor increases.

Lenses (including most macro lenses) designed for 35 mm sensors project a circle size at the sensor plane that would illuminate a full 35 mm frame. When using these lenses with a smaller sensor (for instance, the APS-C size sensor found in many dSLR cameras), the periphery of this circle of light falls beyond the edges of the CCD sensor. This means that the smaller sensor sizes effectively crop off the periphery of the image, introducing a crop factor dependent on the sensor size. The crop factor is the camera sensor's diagonal size relative to a 35 mm full-frame sensor. Most dedicated macro lenses are designed for full-frame sensor sizes. This results in a shift in the effective focal length of the lens when using a *smaller format sensor*. For example, a 100 mm macro lens used on a camera with a small sensor with a 1.5× crop factor is comparable to using a $1.5 \times 100 = 150$ mm macro lens. Practically, the longer focal length increases the working distance to the subject and reduces the size of the flash reflection on the cornea.

Whenever magnification is used in photography, there is a loss of DOF. Shallow DOF is sometimes needed to highlight part of an image (for instance, if the aim is to focus on a lesion in the cornea and blur deeper structures like the iris). In most situations, however, it is desirable to achieve good focus of ocular structures at different depths in the eye (lids, cornea, anterior chamber, iris), and a wide/deep DOF is needed, which in practice requires a small aperture (high f-stop) setting on the camera (Fig. 13.2). Routinely with the lenses mentioned here, an f-stop of f16 to f22 is recommended.

Although a small aperture will enable good depth of field, there are potentially two problems associated with this. At very small apertures, diffraction becomes an issue, causing a decline in image sharpness. In addition, longer exposures using a slower shutter speed (which is not good when shooting without a tripod) or a more sensitive film/sensor (higher ISO number) may be needed for any level of illumination. Usually, the exposure issue is negated in ophthalmic macrophotography by leaving a fast shutter speed (to avoid blur

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Figure 13.2 Two images of the same eye and adnexa taken with identical settings other than varying aperture: (**A**) at f/5.6 (large aperture), (**B**) at f/20 (small aperture). Note also that with the smaller aperture (**B**), the fluorescent light artifact is less noticeable.



Figure 13.3 Examples of Canon (EOS 5D Mk II with 100 mm lens) and Nikon (D90 and D700 with 105 mm lens) digital SLR cameras.

from animal or photographer movement) and low ISO (to maximize image quality) and using flash illumination.

Most digital cameras default to autofocus, which is very convenient for most uses other than macrophotography. It is important to have manual control over focus for ophthalmic photography of animals. The patient is likely to be moving, and using autofocus at high magnification and close range on a moving target (often with photographer movement added) will result in the autofocus continuously swinging on either side of sharp focus. It is much more efficient to set manual focus, then set the magnification on the lens and move the camera nearer or further from the subject. Another disadvantage of autofocus is that some in-lens focusing motors are noisy and may scare the animal, making the process even more difficult.

To achieve optimal exposures, dSLR cameras provide for exposure and/or flash compensation (to enable stepwise adjustments to exposure either manually or automatically over a sequence of images with exposure bracketing). This allows the user to set up a sequence of exposures where each time the shutter release is pressed, the exposure will vary from the calculated exposure by some fraction (often 0.3–0.5) of a f-stop (how much variance can be set ahead of time). This facilitates varying exposures without having to manually change ISO, aperture, or shutter speed.

Many dSLR cameras are now available from several manufacturers. However, we decided to consider only those from the two largest manufacturers, Canon and Nikon, in this chapter (Fig. 13.3). There are two reasons for this: first, these companies make very high-quality cameras with which we have most experience; and second – and this is quite important from the macrophotography perspective – both manufacturers make cameras, lenses, and flash systems that are fully compatible.

The exact model of dSLR is of less importance than the type of lens and flash equipment chosen for ophthalmic (and general) macrophotography. Table 13.6 lists currently available and recommended macro lenses and flash units from both Canon and Nikon. We have chosen cameras in the mid-price range for dSLRs.

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Table 13.6 Canon and Nikon digital SLR cameras (2020).

Digital SLRs (Body Price Only)	Features	Comments
Canon USA (http://usa.canon.com)		
EOS 5D Mark IV Estimated retail: $2,500	Full-frame CMOS 30.4 MP APS-H sensor Digic 6 image processor 100–32000+ ISO range, HD video, 3.2 in. clear view LCD, Canon EF lens compatible	Excellent choice in the mid-price range of Canon dSLRs CF card type I and II Only if you are prepared to buy prime lenses to take advantage of high resolution
EOS 5DS R DSLR Estimated retail: $3,699	Full-frame CMOS 50.6MP APS-H sensor. Digic 6 Image Processor 100–32000+ ISO Range, HD Video, 3.2 in. clear view LCD, Canon EF lens compatible	Excellent choice in the high-price range of Canon dSLRs. Dual card slots: SD and CF. Only if you are prepared to buy prime lenses to take advantage of high resolution
EOS 7D Mark II with Wi-Fi adapter kit Estimated retail: $1,399	Small frame CMOS 20.2 MP APS-C sensor Dual Digic 6 image processors 100–16000+ ISO range, HD video, 3.0 in. clear view LCD, Wi-fi adapter image transfer, Canon EF lens compatible	Excellent (slightly less expensive) choice in the mid-price range of Canon dSLRs CF card type I and II Wireless image transfer to phone or tablet
EOS 6d Estimated retail: $699 (used)	Small frame CMOS 20.2 MP APS-C sensor Digic 5 image processor 100–25600+ ISO range, HD video, 3.0 in. LCD, Canon EF lens compatible.	Excellent lower-price option SD/SDHC/SDXC card Built in Wi-Fi transmitter
EOS 6d Mark II Estimated retail: $1,339	Small-frame CMOS 26.2 MP APS-C sensor Digic 5 image processor 100–25600+ ISO Range, HD Video, 3.0 in. LCD, Canon EF lens compatible	Excellent lower-price option, SD/SDHC/SDXC card. Built-in Wi-Fi transmitter
Nikon USA (http://www.nikonusa.com/Nikon-Products/Digital-SLR-Cameras/index.page)		
D850 Estimated retail: $2,999	45.7 megapixel FX-format CMOS (full frame) sensor 64–25600+ ISO range 3.2 in. tilting LCD monitor	XQD and SD card (2 card slots) Only if you are prepared to buy prime lenses to take advantage of high resolution
D750 Estimated retail: $1,050	24.3 megapixel FX-format CMOS (full frame) sensor 100–12800+ ISO range 3.2 in. VGA monitor	SD card (2 card slots) Built-in Wi-Fi
D7500 Estimated retail: $599	20.9 megapixel DX format CMOS sensor 100–51200+ ISO range HD video 3.2 in. VGA tilting touch-sensitive LCD	DX (1.5x crop factor) sensor size SD/SDHC cards (2 slots) Built-in Wi-Fi
D5600 Estimated retail: $420	24.2 megapixel DX format CMOS sensor 100–25600+ ISO range HD video 3.2 in. vari-angle LCD	DX (1.5× crop factor) sensor size 1 SD/SDHC card Built-in Wi-Fi
D3300S Estimated retail: $400	24.2 megapixel DX format CMOS sensor 100–25600+ ISO range HD video 3.20 in. LCD	DX (1.5× crop factor) sensor size 1 SD/SDHC card

Depth of Field

Whenever magnification is used in photography, there is a loss of DOF. Shallow DOF is sometimes needed in highlighting part of an image (for instance, if the aim is to focus on a lesion in the cornea and blur deeper structures like the iris). In most situations, however, it is desirable to achieve good focus of ocular structures at different depths in the eye (lids, cornea, anterior chamber, iris) and a wide/deep DOF is needed; this in practice requires a small aperture (high f-stop) setting on the camera (Fig. 13.2). Routinely, with the lenses mentioned here, an f-stop of f16–f22 is recommended.

Although a small aperture will enable good depth of field, there are potentially two problems associated with this: a

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longer exposure (slower shutter speed, which is not good when shooting without a tripod) and/or more sensitive "film"/sensor (a higher ISO number may be needed for any particular level of illumination). Usually, the exposure issue is negated in ophthalmic macrophotography by leaving a fast shutter speed (to avoid blur from animal or photographer movement) and low ISO (to maximize image quality) and using flash illumination. Second, at very small apertures, diffraction becomes an issue, causing a decline in image sharpness.

The only other approach to achieving good focus of all parts of a subject (eyes) at different distances from the lens is to use the technique of "focus stacking." This involves combining several photographs of the same eye taken at very slightly different focus points – sequentially points at different depths in the object are in focus – and then combining the images in an editing application (Adobe Photoshop or Helicon Focus from Helicon Soft, Kharkiv, Ukraine) so that in the combined image all levels appear in focus. This is not practical for clinical photography in live moving animals, since the perspective in each image needs to be the same and requires that the camera and subject be relatively fixed. This can be achieved in two situations in ophthalmic practice: photographing an eye in an anesthetized patient with ocular fixation and for gross pathologic specimens of eyes. In both situations, it is possible to mount the camera on a tripod or operating microscope and fix the position of the eye being photographed.

Lenses for dSLR Cameras

The lens chosen is often more important than the camera. A high-quality lens, which allows focusing as close to a 1:1 magnification as possible, is ideal. Although this may be built in with a compact camera, the best options come as interchangeable lenses with dSLR systems. Prime macro lenses are optically some of the best lenses made. These lenses have a wide range of apertures, which is important to maximize DOF. Cameras with dedicated macro lenses (from the same manufacturer as the camera or with lenses designed for the particular camera) are recommended. A lens with a fixed focal length of about 100 mm is recommended for clinical photographs of companion animals. Shorter focal length macro lenses (e.g., 60 mm) can be used, but the working distance (camera to subject) is reduced.

Lenses for macro use should be able to focus and provide a 1:1 life-size image or larger. These are usually prime lenses (fixed focal length). These lenses tend to be higher quality, lower weight, and smaller in size. Prime macro lenses are highly corrected for optical aberrations that could occur when focused close up. This is achieved by a very specific design feature of the lens elements in the prime macro lens, which is missing in zoom lenses. The prime macro lenses mentioned here are some of the sharpest types of lens available and well worth the price for the quality of the images achieved.

Alternatives are zoom lenses, which comprise more than one lens element that move relative to one another, are larger and heavier, tend to be of lower quality, and introduce more chromatic and spherical aberration at larger aperture sizes, which may not be a big issue for macro work since we tend to use high f-stops (smaller apertures). These lenses rarely approach a 1:2 reproduction ratio (many are nearer 1:4 or more). The macro zooms that do achieve a 1:1 ratio may only do so at certain focusing distances; generally, these are simply lenses with a fairly close focus ability. The image sharpness is usually less for macro zooms compared with true prime macro lenses. Both Canon and Nikon make excellent 50–105 mm prime macro lenses (Table 13.7). Generally,

Table 13.7 Canon and Nikon macro lenses for digital SLRs.

	Features	Comments
Canon		
EF 100 mm f/2.8 macro USM Estimated retail: $600	Life size (1:1) with 5.9 in. working distance (minimum focus distance sensor plane to subject 12 in.)	Excellent 100 mm macro lens and reasonable price Auto focus not useful for ophthalmic imaging benefits, lost at high magnification
EF 100 mm f/2.8L macro IS USM Estimated retail: $749	Same lens with image stabilization	Little need for image stabilization for macro – benefits of image stabilization lost at high magnification
EF-S 60 mm f/2.8 macro USM Estimated retail: $350	Life size (1:1) with 4 in. working distance (minimum focus distance sensor plane to subject 12 in.)	Good choice for small sensor cameras
Nikon		
AF-S VR Micro-Nikko 105 mm f/2.8 G IF-ED Estimated retail: $810	Life size (1:1) with 12 in. minimum focus distance (sensor plane to subject)	Excellent 100 mm macro lens and reasonable price Sold as FX (full-frame lens) Best Nikon lens for ophthalmic macro Little need for vibration reduction for macro – benefits of vibration reduction lost at high magnification
AF-S Micro Nikkor 60 mm f/2.8 G ED Estimated retail: $600	Life size (1:1) with 7.2 in minimum focus distance (sensor plane to subject)	Excellent 60 mm macro lens FX (full frame) compatible
AF-S DX Micro Nikkor 85 mm f/3.5 G ED VR Estimated retail: $560	Life size (1:1) with 10.8 in minimum focus distance (sensor plane to subject)	Excellent 85 mm macro lens DX (1.5× crop factor camera) compatible

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less costly macro lenses for both makes of camera are made by other manufacturers (Tokina, Tamron, and Sigma).

Flash Illumination

Lighting is an extremely important aspect of the macrophotography system, as it is generally in photography. Regardless of how many features the camera has or the quality of the lens, if the lighting is wrong, the image will suffer. Unfortunately, it is also the part of the "macro equation" that can be most difficult to control. Natural lighting does not work well for ophthalmic macrophotography (see some of the artifacts discussed later).

Flash is inevitably used in ophthalmic photography; ambient lighting is really not an option for ophthalmic work. Most eye photographs are taken in very reduced ambient lighting to avoid lighting artifacts; hence the need for flash. Even with flash lighting, it is still possible to introduce artifacts, which interfere with the quality of the image.

A flash strobe with complete control over output intensity and direction of incident light on the subject (possible with most dSLR cameras; more difficult with compact and cell phone cameras) is the best choice. Proprietary flash units, designed specifically to work with the particular make of camera, are best. This will enable synchronization of the flash and TTL autoexposure (iTTL or eTTL), which considerably facilitates photography in the clinical setting.

The in-camera pop-up flash present in many dSLR cameras (and almost all compact cameras and smartphones) is often a poor choice for macro illumination, especially if using a short working distance from camera to subject. Larger flash units attached to the camera hot shoe also do not fare much better. If using either pop-up flash or one of the regular hot shoe flash units (as opposed to a macro flash unit), problems arise with either the flash reflex on the cornea interfering with the image or the camera lens actually being in the light path of the flash and causing a shadow of the lens on the subject. Flash units positioned near the end of the lens provide better illumination of the eye being photographed. This can be avoided with hot shoe regular flash units if handheld near the end of the lens or mounted on a flash bracket controlled from the camera, either wirelessly or with a cord connecting the flash to the hot shoe of the camera. This is one area where using a digital zoom lens may be beneficial, since it allows a longer working distance. Although the resulting image is small in the frame, with the high resolution available in most cameras the image can be cropped to concentrate on the area of interest: eye and adnexa.

Macro Lighting Systems

The best option for ophthalmic macrophotography is to use the proprietary macro flash units for name-brand cameras (Canon's Macro Twin Lite MT-24EX and Nikon's R1C1 Wireless Close-Up Speedlight System). Although these units are expensive, they are definitely worth the cost. They utilize TTL metering to make exposure simple (iTTL for Nikon and eTTL for Canon). These systems allow for variable control of the light output from each strobe unit; operation off the lens ring to enable more creative effects and reduce the rather flat lighting achieved with most ring flash units; diffusion of the incident light to reduce the effect of corneal flash reflexes; and, in the case of the Nikon R1C1, wireless control of the flash units (Fig. 13.4).

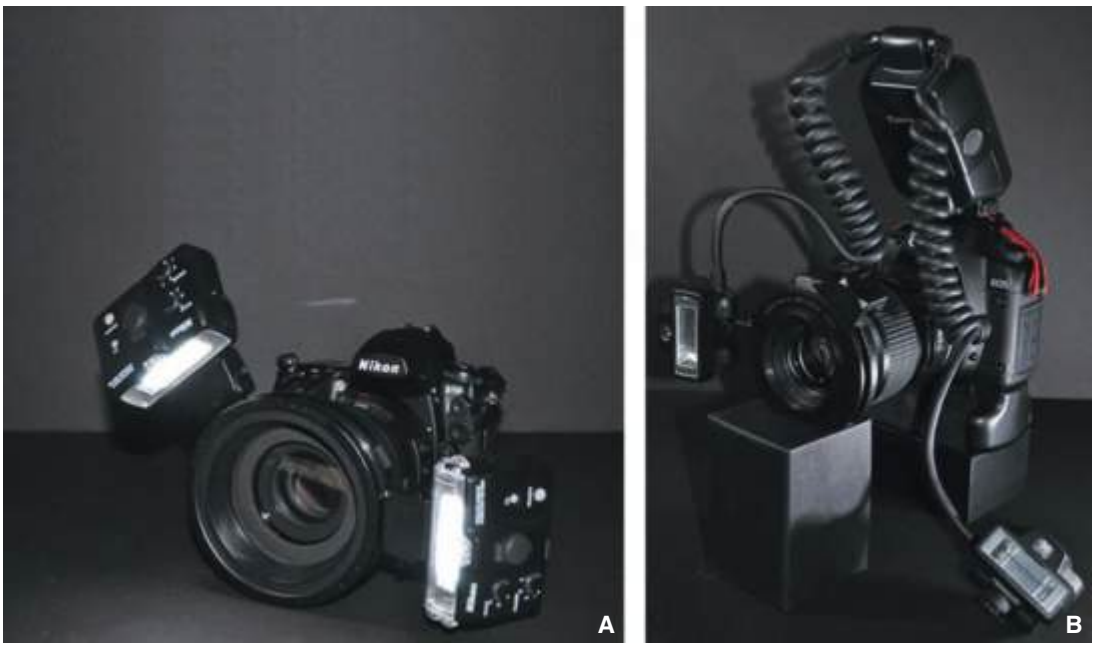


Figure 13.4 **A**. Nikon R1C1 Speedlight. **B**. Canon Macro Twin Lite MT-24EX.

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Both units have at least two strobe units (Nikon allows several units to be controlled wirelessly) that can be detached from the camera; Nikon is an even better option here, since the strobes are wirelessly controlled and can be positioned anywhere in relation to the camera and subject. The ratio of light output of each flash strobe can be independently varied. This allows the flash intensity from one direction to be less or more than that from another direction. Moving the flash unit further from the lens and eye both provides for a smaller flash reflex on the cornea and increases the depth and appearance of contour and texture in the image (Table 13.8). Flash units that can be removed from the camera to allow for variable direction of the incident light can aid in giving more depth to the image. Macrophotography and macro lenses tend to result in rather flat images, with limited DOF and little contour detail seen. Apart from increasing the depth of field via reducing lens aperture, flat-looking images can also be avoided by aiming the incident light from an angle to the subject–sensor axis. This happens to some degree even with a ring flash attached to the lens, since the flash strobe is a few degrees to the side of the lens–subject axis. This effect can be minimized by removing the flash from the camera and holding it to one side, at more of an angle.

Table 13.8 Macro flash units for Nikon and Canon digital SLRs.

	Features	Comments
Canon		
Macro Twin Lite MT-24EX Estimated retail: $990	Fits all Canon macro lenses Flash heads can be rotated around the eye, and angled for varied illumination depending on the working distance Can hold each flash strobe off camera Output of each flash head can be independently varied Incandescent focusing lights	Best option for Canon cameras Focusing lights ideal for ophthalmic photography in darkened room Flash head arrangement avoids "flat," featureless images seen with traditional ring flash
Canon MR-14EX Macro Ring Lite Estimated retail: $550	Fits all Canon macro lenses Can hold entire ring off camera for directional lighting	Reasonable option for Canon lenses and cameras (if you like a ring flash)
Nikon		
R1C1 Wireless Close-Up Speedlight System Estimated retail: $710	Fits all Nikon macro lenses Individual strobes can be detached from the lens ring to allow for convenient positioning to maximize detail and contour	Best option for Nikon cameras without wireless control built into the camera (otherwise use R1)
R1 Wireless Close-Up Speedlight System Estimated retail: $460	Same as R1C1 but without the C1 wireless controller Can use with any dSLR with wireless Speedlight control built into the camera	Best option for Nikon cameras with wireless control built into the camera

The Canon and Nikon macro flash units mentioned here incorporate a modeling light(s) in the flash strobes. This is of benefit for ophthalmic photography, which is usually performed in darkened rooms – the modeling lights provide adequate light to enable focusing on the subject, as well as showing the exact direction of the incident light, so the flash strobes can be oriented to illuminate the subject adequately when the flash actually discharges.

Diffusers can be placed in front of the flash strobe (the Nikon R1C1 system comes with diffusers) to reduce the harshness of the flash reflex on the cornea. Various third-party flash diffusers are available to use with the Nikon and Canon macro flash lights. In general, the ophthalmologist will need to experiment with the flash direction and diffusers to determine what works best in any situation.

Ring Flash Units

Many ring flash designs are available for macro work. The main problem with most of these is that the flash reflex in the cornea can be quite intrusive, obscuring lesions being photographed. Additionally, having two flash strobes on either side (or as a continuous ring around the flash unit) renders rather a flat-looking image. Not all third-party ring flash units work with the camera "TTL metering" for autoexposure. If this is the case, it is necessary to use manual mode and adjust the aperture and shutter speed settings, and then bracket exposures widely to obtain the results you would like; this is often not a realistic option in a clinical setting with a nervous animal and owner present and time at a premium.

Some ring flash units (for instance the Sigma Flash Macro Ring EM-140 DG) are available for Canon, Nikon, Pentax, Sigma, and Sony dSLR cameras and lenses. Although the results with the Sigma unit may not be quite as good as the macro flash units from Nikon and Canon (which only work with their respective dSLRs), the Sigma unit costs less and is a reasonable alternative.

Pop-Up Flash

For macrophotography, using the camera's built-in pop-up flash is rarely a good option, mainly because the lighting is too far off axis from the macro lens to provide even illumination at the close-up working distance used. The macro lens itself will often cast a shadow of the macro lens over part of the image when using pop-up flash at a close working distance.

However, there are times when a pop-up flash will be the only option available. In this situation, the working distance from the camera to the patient should be increased to avoid

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lens shadowing. Additionally, a light diffuser can be placed around the end of the macro lens. This will provide better lighting (the image will not look as flat), and the lens shadow will not be an issue. An inexpensive diffuser can be made from white, light-transmitting plastic.

TTL flash autoexposure is available on any camera for which there is a compatible flash unit produced by the same manufacturer (for instance, Nikon iTTL and Canon eTTL) and for some flash units made by third-party manufacturers but with specifications for use with a particular manufacturer's cameras (for instance Sigma ring-flash units). When the shutter release is pressed, the flash unit will produce a rapid pre-flash (small flash output from the unit). Light reflected into the camera "through the lens" is measured, and the amount of light needed for the actual flash during exposure of the sensor is calculated, then the flash fires again as the shutter opens.

For ophthalmic macrophotography with flash, it is best to set the camera to "front-curtain-flash" mode. In "rear-curtain mode," the flash fires at the end of the exposure (just before shutter closes); if using a low shutter speed, this could result in a pupillary light reflex or reactive movement of the animal before the main flash occurs. Using cameras with a nondedicated flash unit, it may be necessary to make numerous exposures at varying shutter speeds or ISOs (keeping high-stop/small aperture for good DOF) to achieve an optimally exposed image – rarely an option in clinical practice with nervous animals. The pre-flash output can be a problem in some situations, causing a blink reflex before the exposing flash/shutter opening occurs; this will require the lids to be held open in many situations. Some species of animal may be able to react and actually move out of the frame between the pre-flash and the exposure occurring, hence the need for good restraint.

Camera Settings

Familiarity with the camera manual, although often difficult to read, is recommended to gain familiarity with the specific settings available for the camera, which vary by manufacturer. See Table 13.9.

For the shooting mode, aperture priority ("Av" on Canon cameras and "A" on Nikon cameras) is the best choice for macro, since it allows for the best control over DOF. Apertures recommended for ophthalmic macrophotography are in the range of f/16–f/22. Even at these settings, there may be some introduction of reduced sharpness due to diffraction. Practically, this rarely matters for our images; it is more important to be able to quickly render decent DOF on the anterior segment in a potentially moving subject (for use printed small or viewed on screen), rather than an image which will be exceptionally well focused when made into a very large print.

When using flash (as is usually the case with ophthalmic photography), the shutter speed should be relatively fast (1/120 second) to help freeze animal or photographer movement. As a rule of thumb, the shutter speed should match or be faster than the focal length of the lens – for 100 macro, use 1/120 second or faster.

The best ISO (or sensor "speed") setting is usually about 200 when using flash. This effectively provides for excellent image resolution and sharpness and minimal noise.

The color space chosen may differ depending on image use: sRGB for patient records, prints, Microsoft PowerPoint,

Table 13.9 Manufacturers and supplier websites for equipment used in digital and macrophotography.

Manufacturer/ Supplier	Website	Comments
Adorama	www.adorama.com	Reliable source for all camera equipment
Amazon.com	www.amazon.com	Reliable source for all camera equipment
B&H	www.bhphotovideo.com	Reliable source for all camera equipment
Canon-USA	www.usa.canon.com	Manufacturer of very high-quality dSLR, compact point and shoot, lenses, and dedicated flash units
Kolari Vision	www.kolarivision.com	Digital camera infrared conversion services
Life Pixel	www.lifepixel.com	Digital camera infrared conversion services and infrared photography resource
Nikon-USA	www.nikonusa.com	Manufacturer of very high-quality dSLR, compact point and shoot, lenses, and dedicated flash units
Ricoh	www.us.ricoh-imaging.com	Manufacturer of Pentax K-5 dSLR cameras, macro lenses, and macro flash
Sigma	www.sigmaphoto.com	Manufacturer of Sigma dSLR cameras, and lenses/flash compatible with Nikon and Canon dSLR cameras
Sony	www.store.sony.com	Manufacturer of Sony dSLR cameras, macro lenses, and macro flash
Tamron	www.tamron.com	Manufacturer of 60 mm prime macro lens for Nikon, Canon, and Sony dSLR cameras
Tokina	www.tokinalens.com	Manufacturer of 100 mm prime macro lens for Nikon and Canon dSLR cameras

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Apple Keynote, or web use. For publication and research, Adobe RGB may be a better choice. The white balance needs to be set at flash or auto settings.

The exposure metering mode chosen may vary with the luminance of the subject (part of eye, pupil color, iris color, periocular skin color) and may require some trial and error to get the area of the eye of interest adequately exposed. For instance, if the skin color is black and the setting is for matrix, which assesses the light needed to expose the entire frame, the light output may be higher than necessary for the central area of the image. This may result in blown highlights in the white conjunctiva or tapetal reflection in the pupil. Generally, matrix metering works well for most situations, and this is the preferred setting. Occasionally, there will be a need to experiment with center-weighted and, rarely, spot metering.

If an image appears too bright or dark in the LCD review (or on the computer screen if tethered), the exposure can be adjusted (exposure compensation) in various f-stop increments (usually ± 0.3–0.5 to either darken or brighten the image, respectively). Flash compensation can also be used to achieve a similar effect. The histogram (see later discussion) is a useful way to assess whether to use exposure compensation.

Incremental fractions of an f-stop on either side of the iTTL/eTTL-determined "correct" exposure allow a series of images (three or five) to be taken with automatic predetermined changes in the exposure for each image (exposure bracketing setting). This is particularly beneficial when photographing animals in the clinic, since it speeds up the process of taking a series of images.

It is a good idea to use the superimposed histogram in the post-image review, since it is often difficult to be sure of the adequacy of exposure, even on a 3 in. LCD screen on the camera, or on a tethered laptop, where the intensity settings of the screen may affect the distribution of brightness. The histogram allows a quick check that there is a good distribution of tones over the darks, midtones, and highlights.

Autofocus should be turned off; use manual focusing. Generally, use the focusing ring to change the magnification and then move closer or further from the eye until adequate focus is appreciated, and then take the photograph. This is much more easily achieved with dSLR using the viewfinder than using the LCD.

RAW or JPEG files (or occasionally, RAW and JPEG recorded simultaneously) are the best file type options to record in the camera. The image quality should be fine and the image size large. If the resulting images have too much data, some can be discarded (for instance, to compress files for use on the web). Conversely, low-quality images cannot be improved in editing software.

A list of valuable resources regarding photographic equipment, software reviews, and digital photography training (websites and printed resources) can be found in Table 13.10.

Compact Point and Shoot Cameras

Although lacking the flexibility and user control of dSLR cameras, most current point and shoot cameras can produce good-quality macro images. However, ophthalmic macrophotography with these cameras will rarely achieve the same results obtained with a dSLR camera/lens/flash system. Compact point and shoot cameras (CPAS) do have an inherent advantage for macro work due to the small sensor size and short focal length of the lens, which results in a wide DOF, but this is offset by several details of design and function

CPAS are a good choice for work in the field with large animals, where it is convenient to carry a small camera tucked away in a pocket. For large eyes (horses and cattle), photographs can be taken at a longer working distance. CPAS cameras can also be convenient for surgical or histopathologic images taken through a microscope.

Limitations of CPAS

CPAS cameras do, however, have some disadvantages. Of significance for clinical photography is that the shutter lag (time from when the shutter release button is fully depressed until when the image is captured) can be a problem. The shutter lag is considerably longer on a CPAS than a dSLR. Although a shutter lag of 0.5 second may seem short, it is 10 times slower than many dSLR cameras. To reduce shutter lag, always depress the shutter halfway to refocus – a rectangle appears on the LCD, which will change color (green on the Canon compact) when the subject area is in focus – then fully depress the shutter button. This may reduce shutter lag to about 0.1 second on some compact cameras.

A parallax effect may be seen due to the offset between the viewfinder (if available) and the lens; the area centered in the viewfinder may be off center in the resulting image. This is not a problem if using the LCD screen to frame the subject and to focus the camera.

Focusing on particular lesions of interest, using the LCD to frame the image on a compact camera can be difficult if the autofocus does not "choose" the area you want in best focus. Focusing can also be more difficult: a camera which allows manual focusing as well as autofocus (as with macro on a dSLR) may make it easier to achieve focus on the area/lesion of interest. Autofocus can be a problem with any digital camera due to continual refocusing because of unavoidable subject and photographer movement. The CPAS camera does have the advantage compared to a dSLR/macro lens combination in this regard, however, because the inherent greater DOF with a CPAS camera allows more structures to be in reasonable focus at any time. The highest f-stop/smallest aperture available on compact cameras does not compare with a dSLR. DOF on these cameras is usually good, nevertheless, due to the very small sensor size and relatively wide-angle lens.

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Table 13.10 Websites and books providing equipment, software reviews, photographic training, and information about digital and ophthalmic photography.

Name	Website	Comments
LinkedIn Learning	www.linkedin.com/learning	A subscription-based site providing in-depth (the best) video tutorials on a wide range of software, photographic equipment, and technique Excellent resource for learning Lightroom, Photoshop, Photos, and much more Able to subscribe monthly ($25) Perhaps the best photography learning site on the web – highly recommended
Adobe	www.adobe.com	Useful free tutorials and white papers on Adobe products
Digital Photography Review	www.dpreview.com	Reviews of cameras, lenses, and flashes from the major manufacturers Objective and useful reviews Recommended
Imaging Resource	www.imaging-resource.com	Reviews of cameras, lenses, and flashes from the major manufacturers Objective and useful reviews
Ken Rockwell	www.kenrockwell.com	General photographic equipment review site – has reviews of most current Nikon and Canon dSLRs
Digital Photography School	www.digital-photography-school.com	Interesting articles and forums for all aspects of photography
Photo.net	www.photo.net	Articles, forums, and reviews of equipment
The Digital Camera Resource Page	www.dcresource.com	Reviews of cameras, lenses, and flashes from the major manufacturers
The-Digital-Picture.com	www.the-digital-picture.com	Reviews of cameras, lenses, and flashes from the major manufacturers
The Lightroom Queen	www.lightroomqueen.com	Victoria Brampton's site – everything Lightroom, including books to download on Lightroom Classic and Lightroom CC
Cambridge in Colour	www.cambridgeincolour.com	Interesting articles and tutorials on digital and macrophotography
Focus Photo School	www.focusphotoschool.com	A site with free tutorials and forums (and much other information) relevant to using Lightroom Notably recommends using an external hard drive for mobile catalogue access

Macrophotography and Digital Asset Management Books

Victoria Brampton (2015) *Adobe Photoshop Lightroom CC/6: The Missing FAQ: Real Answers to Real Questions Asked by Lightroom Users*. Isle of Wight: LRQ Publishing.

Victoria Brampton (2018) *Adobe Photoshop Lightroom Classic CC: The Missing FAQ (Version 7/2018 Release): Real Answers to Real Questions Asked by Lightroom Users*. Isle of Wight: LRQ Publishing.

Martin Evening (2017) *The Adobe Photoshop Lightroom Classic CC Book: The Complete Guide for Photographers*. San Francisco, CA: Adobe Press.

Fil Hunter, Steven Biver, & Paul Fuqua (2007) *Light Science & Magic*, 3rd ed. Waltham, MA: Elsevier (Focal Press).

Peter Krogh (2009) *The DAM Book*. Sebastopol, CA: O'Reilly.

Peter Krogh (2018) *The DAM Book 3.0*, available as PDF or CD, http://thedambook.com/the-dam-book.

Bryan Peterson (2009) *Understanding Photography Field Guide*. New York: Amphoto Books.

Bryan Peterson (2010) *Understanding Exposure*, 3rd ed. New York: Amphoto Books.

If using a CPAS camera very close to the subject, lighting from the offset flash location can be very uneven, resulting in marked shadowing of the side of the image furthest from the flash. Achieving optimum exposure with flash can be more difficult with CPAS than dSLR, especially if focusing close to the subject. Photographing from an increased distance helps reduce this. The lack of a focusing light on a CPAS camera requires that photos be taken with some ambient lighting to enable focus on the lesion – lighting artifacts will then become more of a problem.

Camera Settings for CPAS Cameras

Auto, program, or aperture priority shooting modes can be used with the camera set to "macro." Matrix and center-weighted

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exposure modes are suitable (some degree of trial and error may be needed here to get the best exposure) and focus mode should be set to autofocus (which works quite well with CPAS cameras) or manual focus (Fig. 13.5).

Autofocus aims an infrared beam at the subject and then determines the focus of the closest point when used in macro mode. When photographing animals, which tend to be moving targets even with good restraint, it is important that you use a camera with both a rapid autofocus mechanism and a short shutter lag. Autofocus works well with larger objects (equine eyes for instance) where the camera can be held slightly further from the eye and still fill a large area of the viewfinder/LCD. In most of the CPAS cameras, a focusing indicator appears on the LCD (white rectangular box on Canon cameras), which will turn green when the shutter release button is slightly depressed if the image is focused; then, the shutter can be fully depressed, and the photograph taken. Optical zoom should not be used with autofocus in macro mode, because the autofocus will usually only function when using the lens at a wide angle.

It is important not to get too close to the subject with the CPAS; the autofocus mechanism will work, but only part of the image will be illuminated due to the offset position of the flash strobe (Fig. 13.6). It is better to take the image from further away to ensure good even lighting of the entire subject, and then use the zoom in playback to enlarge the image; when processing, the image can be cropped to remove extraneous adnexal tissues. Avoid using optical or digital zoom; the wide-angle lens setting works best with autofocus. The minimum focus distance in macro mode will be found in the camera manual and, in most cases, macro with flash will work best at a greater distance than the minimum.



Figure 13.5 A compact point and shoot should not be held too close to the subject to avoid large flash reflexes, but the user should also avoid using optical zoom to ensure accurate autofocus.



Figure 13.6 Uneven illumination with a compact point and shoot camera (especially underexposed at lower left of image). This is avoided by increasing the working distance between the camera and the eye.

Since most of the images will be recorded in a darkened room, it may be necessary to illuminate the subject with a transilluminator or light from a slit lamp if using manual focusing to be able to see that the eye is in focus. With autofocus, this may still be needed to allow for rapid positioning of the camera to take the photograph before the patient moves. Focal illumination may also acclimate the patient to the light and thus elicit less of a reaction when the flash fires.

Smartphone Photography

What the smartphone camera lacks in flexibility and user control of settings, it makes up for with ever-improving image quality and immediate accessibility. The image quality obtained from smartphone cameras is inferior to that obtained using dSLRs. However, there are many instances when the images obtained are superior based on the fact that using a dSLR in some situations is much more time-consuming (Fig. 13.7). Even so, ophthalmic macrophotography with these cameras will rarely achieve the same results obtained with a dSLR camera/lens/flash system. Smartphone cameras can take images that complement those taken with a dSLR in conjunction, resulting in more accurate case documentation.

Smartphone cameras are a good choice for work in the field, especially with large animals where it is convenient to carry a small camera tucked away in a pocket. For large eyes (horses and cattle), photographs can be taken at a longer working distance using a modeling light without a flash to improve cooperation from the animal (Fig. 13.8). Since exposure lag time has become a thing of the past, obtaining good-quality images in rapid succession can be expected. Smartphone cameras can also be used to obtain handheld slit

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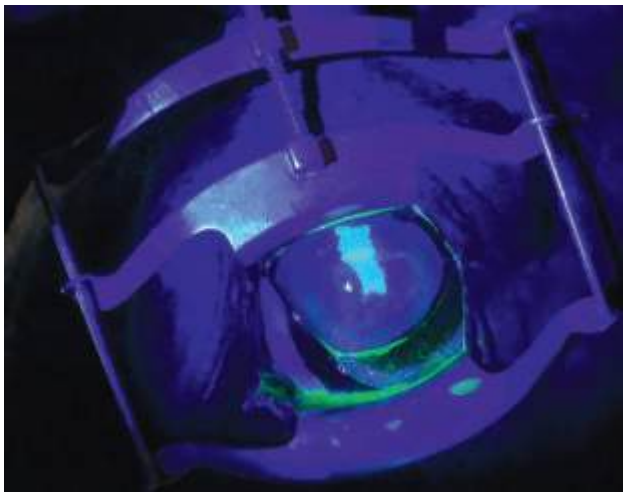


Figure 13.7 Cobalt blue filter illumination of a fluorescein-positive superficial corneal ulcer resulting from an improperly placed subpalpebral lavage system in a young Thoroughbred gelding. This image was taken 3 days after initial presentation.

lamp, surgical, or histopathologic images taken through a microscope (Fig. 13.9, Fig. 13.10, and Fig. 13.11).

Smartphone Camera Limitations and Advantages

Limitations such as shutter lag (the time from when the shutter release button is fully depressed until when the image is captured) or focusing on a particular lesion/area of interest can be a problem. However, these minor inconveniences can be readily overcome with just a little practice. The speed and quality of modern smartphone cameras have allowed them to slowly become the "camera of choice" for most day-to-day situations.

Focusing on particular lesions of interest, using the large smartphone screen is very straightforward and readily achieved merely by pressing the area of interest (on the screen) with your fingertip. Autofocus actually works quite well on most modern smartphones, being both fast and silent. The greater inherent DOF with a smartphone camera allows more structures to be in reasonable focus at any time. DOF on these cameras is usually good, due to the small sensor size and relatively wide-angle lens.

Lighting from the internal smartphone camera flash can result in significant overexposure when used for ophthalmic photography. This can be partially offset by applying a piece of transparent medical tape over the flash to decrease the intensity. However, because modern smartphones function very well in low-light situations, good-quality images can be obtained when using modeling or head-mounted lights, without the need for the smartphone flash.

Because using a smartphone camera is very intuitive, it will rapidly become an integral part of your everyday case documentation process. Images of a procedure or diagnostic test can be rapidly obtained, even when assistance is limited. Since these cameras have a wider field of view than dSLRs with a mounted macro lens, rapid procedure overview images can be obtained using a smartphone camera, without having to switch out your macro lens. Not only are such lens changes time con-



Figure 13.8 **A.** Overview of upper eyelid location of tubing from a subpalpebral lavage (SPL) system that resulted in a large geographic superficial corneal ulcer in a young Thoroughbred gelding. This image was taken during the initial presentation (same horse as in Fig. 13.7). **B**. Footplate of the SPL tubing is visible approximately 12–15 mm proximal to the upper eyelid margin. Note the faintly fluorescein-stained superficial corneal ulcer in the dorsal cornea.

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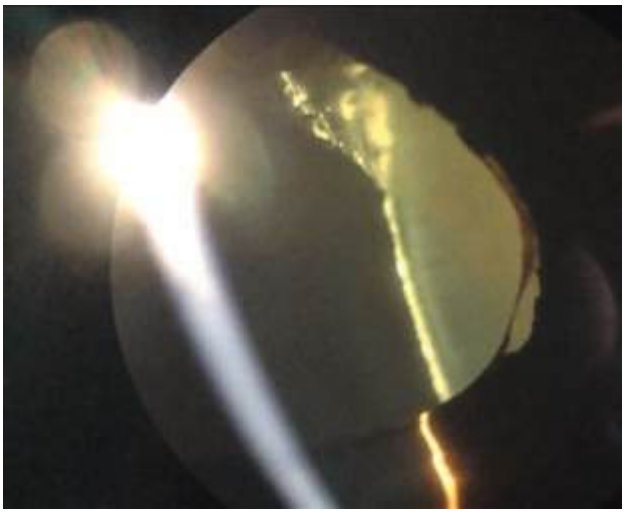


Figure 13.9 Slit lamp image of a subluxated lens with vitreal prolapse and peripupillary iris atrophy in a 9-year-old Quarter Horse gelding. The image was captured using an iPhone X held up to the ocular of a Kowa SL-17 handheld slit lamp.



Figure 13.10 Postoperative image of a corneoconjunctival transposition to surgically treat a descemetocele in a young English Bulldog. This image was taken using an iPhone X held up to the ocular of a Zeiss operating microscope.

suming, they result in many images not being obtained due to personnel limitations, especially during examinations or surgery. Your smartphone camera will keep you from missing many of those shots in the future (Fig. 13.12).

Clinical Studio and Practical Aspects of Image Acquisition

The "clinical studio" requires reduced ambient lighting (no overhead lighting and any ambient lighting in the exam room

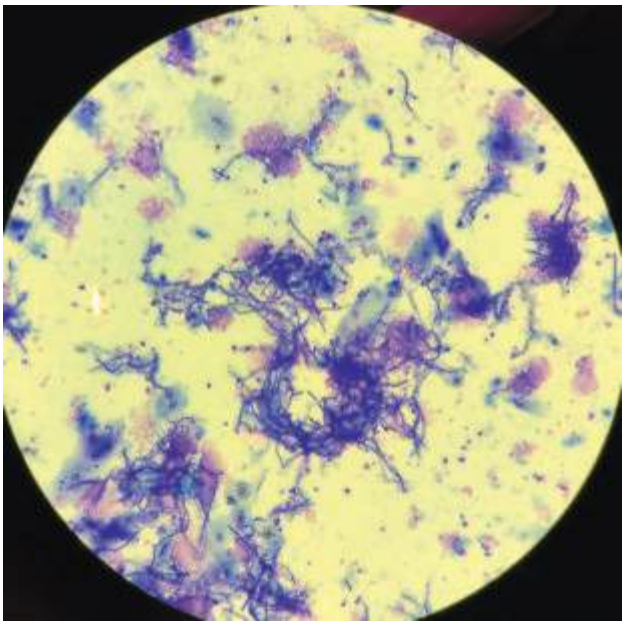


Figure 13.11 Cytology sample from an infected corneal ulcer in a 15-year-old Missouri Foxtrotting Horse gelding. Multiple linear and branching fungal hyphae can be readily observed in this image taken with an iPhone X held up to the ocular of a microscope.



Figure 13.12 This image of an intrastromal injection of voriconazole for the treatment of superficial keratomycosis was taken with an iPhone X.

should be at floor level). Photographs taken in brightly lit exam rooms (especially with overhead fluorescent tube lighting) or stalls or outdoors will usually have lighting artifacts and especially reflections from other light sources on the cornea. This necessitates the use of some form of modeling light on the flash unit or handheld light (Finoff transilluminator or slit-lamp biomicroscope) to provide enough illumination of the subject to allow for focusing.

In the clinical setting, it is rarely possible to use tripods to steady the camera: the patient tends to be a moving target

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and, unlike in human photography, commands to avoid movement do not work. It cannot be emphasized enough that apart from the equipment and some knowledge of how to use it, successful clinical macrophotography depends on having helpers who can provide excellent restraint of the subject. Patience is essential from both the photographer and the helpers involved.

Some practical suggestions will help in acquiring good-quality images (Fig. 13.13). Avoid photographing ophthalmic subjects outdoor or without flash illumination (Fig. 13.14), especially if wearing light-colored clothing (white lab coats particularly).

The patient should be well restrained. If restraining a small animal on a table, the holder should ideally be braced against the table with the animal's head held against the body or, if possible, resting both arms on the examination room table. The photographer should also brace against the table or rest the elbows on the table, and use the elbows as a hinge point about which to move forward or backward to achieve adequate focus. For large animals, sedation is ideal (although not reasonable purely for taking photographs) and often will be required for the clinical examination *per se*. Support and relative immobilization of the head on a stack of hay bales work well. The photographer should not use one hand to hold the animal's head or to open the eyelids (hands, arms, and fingers will appear reflected in the cornea; Fig. 13.15). The eyelids should be opened by the person providing restraint, by bringing the fingers over and under the head from the opposite side to the eye being photographed and placing the fingers above and below the eyelids. A third helper may be needed to provide modeling light to achieve focus.

Although photographing eye lesions can occur at the time of anesthesia and surgery (in cases undergoing surgery to treat the disease), rotation of the eye may make it difficult to gain access to the lesions of interest. Additionally, some lesions may not be as evident in the anesthetized animal (for instance entropion), and the normal appearance of ocular structures relative to one another may be affected. Clinical photography should ideally be carried out on the awake animal whenever this is possible.

Avoid taking photographs with ring flash units at very close working distances, to prevent the flash strobe reflection(s) appearing large on the corneal surface (Fig. 13.16). It is better to take the photograph from a slightly greater distance and then zoom into the image and crop as needed. Photographing from a slightly greater distance is also usually less stressful for the patient.

Clinical photographs should not be performed immediately before animals undergo testing of retinal function, due to the photo pigment bleaching effects on the retinal photoreceptors. Electroretinography (ERG) should precede clinical photography; otherwise, ERG should be performed at least 60 minutes after photography (see Chapter 10, Part 4; Tuntivanich et al., 2005).



Figure 13.13 **A**. Avoid use of fluorescent overhead lighting. **B**. Use a darkened examination room with any ambient lighting at floor level, not above the patient.

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Figure 13.14 Avoid photographing ophthalmic subjects outdoors or without flash illumination, to prevent loss of subject detail and appearance of artifactual reflections in the cornea.



Figure 13.15 The photographer should not use one hand to hold the animal's head or to open the eyelids (or hands, arms, and fingers will appear reflected in the cornea).

Photographic Techniques

External Macrophotography

Macrophotography allows the photographer to capture detailed images of very small objects (e.g., lesions) and is an essential tool for the veterinary ophthalmologist. While it is possible to obtain usable and even relatively high-quality images with different types of lenses, dedicated macro lenses allow even extremely small lesions to be visualized in detail.

Most traditional macrophotography is done with the camera mounted on a tripod for stability, because even the slightest movement can result in motion blur. While tripod-mounted shooting is possible for many different subjects and types of macrophotography, it is generally not feasible to routinely utilize a tripod when photographing animal eyes. As a result, most macrophotography performed in veterinary ophthalmology is done with the photographer stabilizing the camera in his or her hands and arms. This "handheld" method of camera stabilization requires a good deal of practice and patience before the technique is mastered. In addition to normal breathing and muscle movement from the photographer, subject movement also heavily influences the ability to capture a well-focused image.

While most modern lenses, including macro lenses, have quick and relatively quiet autofocus motors, one will achieve better and more consistent results if the lens is manually focused. Once the lens is set to the appropriate focal distance to capture the area of interest within the frame, subtle movement, toward or away from the subject, is all that is necessary to adjust, or fine-focus, the image.

External Light Sources

For most macro images taken of the adnexal and ocular structures, an external light source is essential. Since flash options

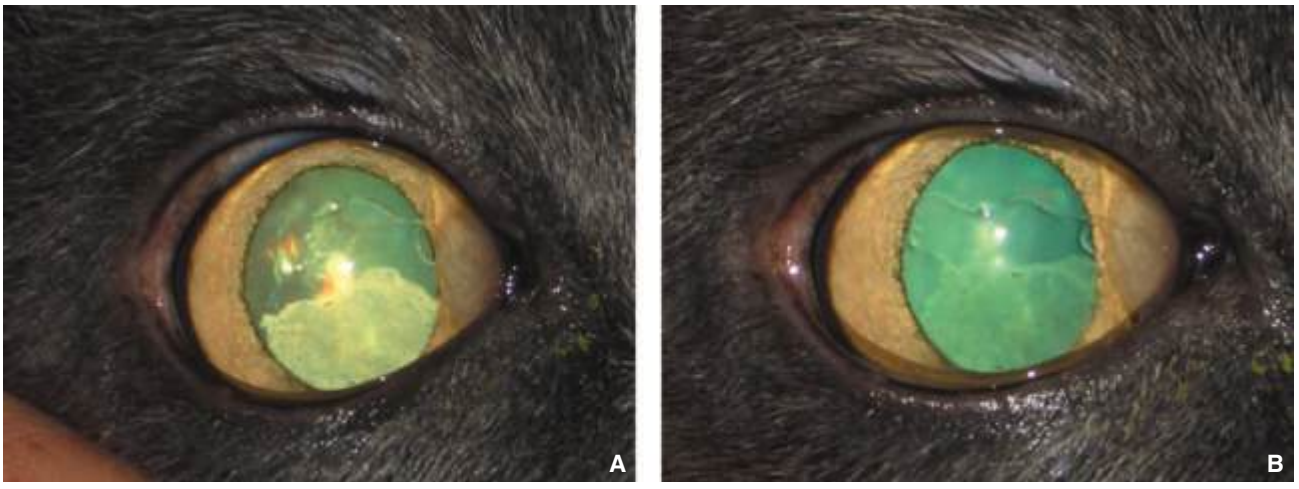


Figure 13.16 The size of the corneal flash artifact and its effect on the image (**A**) can be minimized by photographing the eye from a slightly greater distance (**B**).

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were discussed earlier in the chapter, in this section we will focus on the effect of certain types and angles of external light that can be utilized to help highlight a lesion. While a table-mounted slit lamp is the instrument of choice for the human ophthalmic photographer, most veterinary ophthalmologists do not possess or have access to this piece of equipment. Table-mounted slit lamp cameras are generally reserved for research or teaching purposes in an academic setting (Fig. 13.17). This does not, however, mean that one cannot capture informative, high-quality handheld slit lamp images.

In addition to adequate manual restraint, a bright, handheld light source (e.g., a Finoff transilluminator) can be very useful, providing adequate illumination for the photographer to appropriately focus on the tissue or lesion to be photographed (Fig. 13.18). A transilluminator is bright enough to provide decent diffuse illumination and can be used as the sole light source to offer tangential (oblique) lighting. With a few minimal adjustments to the camera settings, clear, well-focused handheld images may be obtained. The sensor's sensitivity to light (ISO) should be increased, the aperture size



Figure 13.17 Canine patient being manually restrained and positioned by a technician for table-mounted slit lamp photography. (Courtesy of NC State University.)



Figure 13.18 A Finoff transilluminator is directed obliquely at the right eye in this horse to provide diffuse illumination. This improves the photographer's visibility, and their ability to obtain a sharply focused image of the specific lesion of interest. (Courtesy of NC State University.)

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increased (a smaller f-number represents a larger-diameter aperture), and the shutter speed decreased (motion blur is more likely). Once the settings have been appropriately adjusted, it is essential that the camera (and the subject) is kept as still as possible to facilitate capture of a well-focused image of the intended lesion or structure (Fig. 13.19). The graininess of the resulting image will depend on the ISO level, and motion blur can easily creep into the image due to even subtle movements from the subject, the camera, or both.

A handheld slit lamp can be utilized to provide diffuse tangential lighting, as well as giving the photographer a means for obtaining handheld slit lamp images of the anterior segment (Fig. 13.20). This technique generally requires the help of at least one assistant (to restrain the animal and to steady the slit lamp), but the resulting images allow for more accurate documentation of many pathologic processes (Fig. 13.21). This can be especially useful when consulting with colleagues via email. Alternatively, a smartphone can be held up or mounted to the slit lamp biomicroscope to obtain an image through the ocular. This method also requires the help of an assistant, but can result in some very useful images (Fig. 13.22).

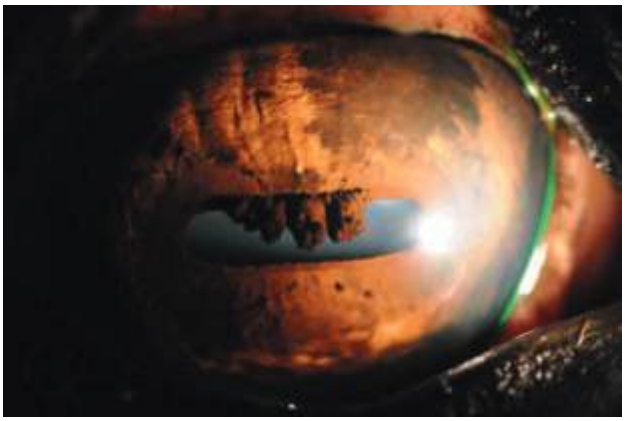


Figure 13.19 Oblique lighting from the Finoff transilluminator provided the sole source of illumination in this image and highlights the topographic features of the iris.



Figure 13.20 A Kowa SL-14 handheld slit lamp and a dSLR equipped with a macro lens are being used to capture handheld slit lamp images in a dog. (Courtesy of NC State University.)

Forms of Illumination

Diffuse Illumination

Diffuse illumination is frequently utilized to accurately focus on the subject being photographed (Mártonyi et al., 1984a, 1984b). While it helps with visualization of the lesion or area of interest, the light is rarely seen in the image due to the intensity of the flash. Frontal lighting provides diffuse, uniform illumination (Nicholl, 1985). While this is typically the most commonly utilized technique given the convenience of the pop-up flash, the images generated are flat, lack depth, and generally include marked specular reflections, some of which may obscure regions of interest.

Direct Focal Illumination with a Wide Beam

This technique is utilized frequently during the ophthalmic examination and is essential for localizing lesions within specific ocular tissues (Fig. 13.23). Two types of direct focal illumination, with a wide beam and with a narrow slit (optic section), are strategically implemented to highlight lesions within different tissues and various depths. Direct focal illumination with a wide beam of light helps to identify the limitations of the lesion being photographed, as well as putting the lesion into context with relation to its surrounding tissue. Additionally, the slit beam improves the examiner's (and photographer's) ability to determine the depth of a specific lesion within the cornea (Fig. 13.24) or lens (Fig. 13.25). Direct focal illumination may also be applied tangentially (Fig. 13.26) to provide visualization of the anterior chamber or iris through a cloudy cornea, or to highlight the topography of the iris and iridocorneal angle (ICA; Fig. 13.27).

Direct Focal Illumination with a Narrow Slit

This technique allows for precise identification of the depth of a specific lesion within the light-refracting tissue (cornea and lens) of the eye. Due to the differences in refraction at the anterior and posterior aspects of the cornea and lens, one can highlight a section of tissue using a narrow beam of light (optic section), which allows the examiner to determine the lesion's depth based on its position relative to the anterior and posterior aspects of the tissue being evaluated (Fig. 13.28).

Direct Focal Illumination Applied Tangentially

A focal light source can be directed at the eye from the nasal or temporal aspect of the globe and held roughly par-

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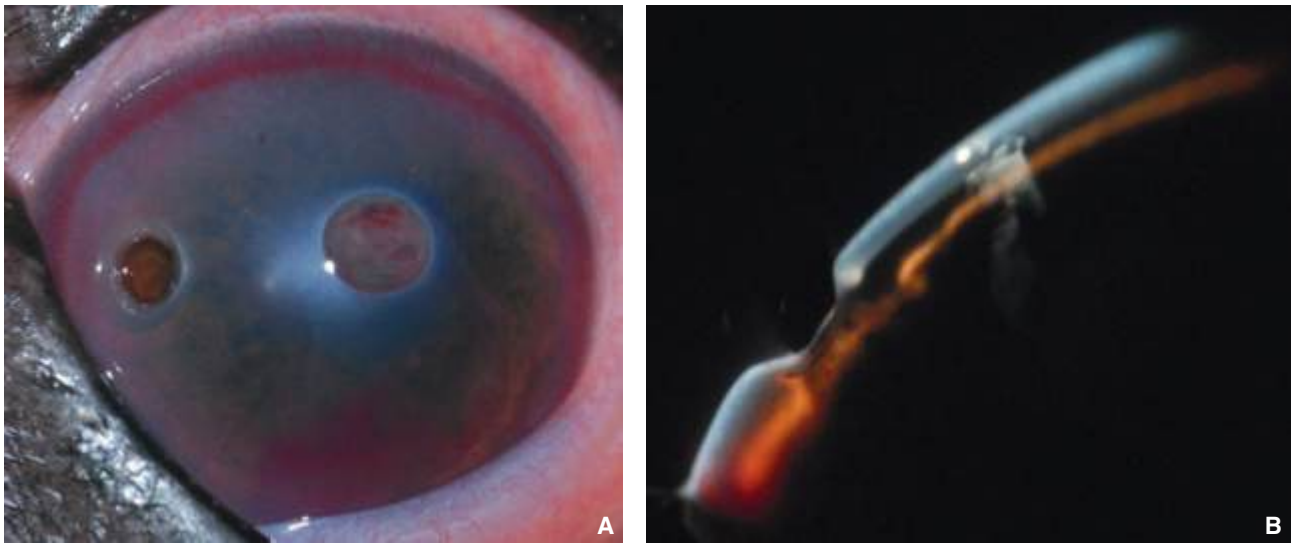


Figure 13.21 **A**. In this canine cornea, two circular lesions (medial descemetocele and axial corneal perforation plugged with fibrin) are readily visible. Mild corneal edema surrounds both lesions. Peripheral corneal vascularization and conjunctival hyperemia are prominent, and hyphema is present within the inferior anterior chamber. Anterior chamber depth is difficult to accurately determine in this conventional image. **B**. This handheld slit lamp image from the medial cornea in the same eye reveals the loss of corneal tissue down to the level of Descemet's membrane and a collapsed anterior chamber.

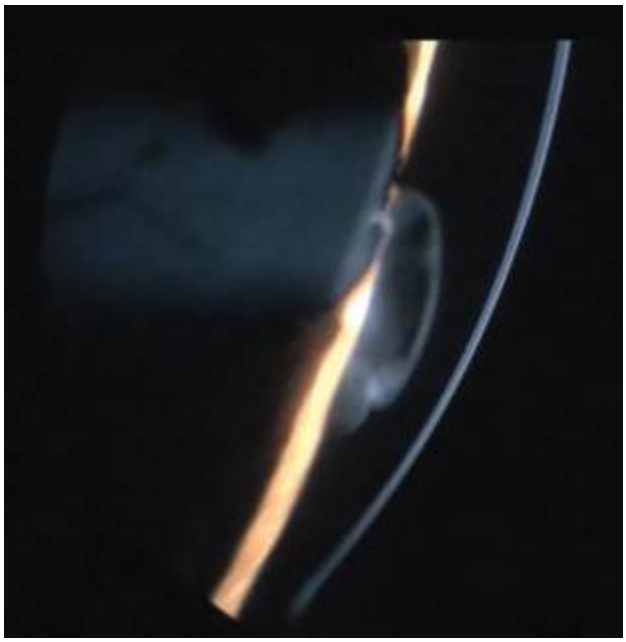


Figure 13.22 Slit lamp image of temporal vitreal prolapse in a horse obtained by holding an iPhone X up to the ocular of a Kowa SL-17 handheld slit lamp.

allel to the surface of the iris. This method of illumination allows for a greater appreciation of the topography of the iris in the case of a clear cornea, and for indirect evaluation of the anterior chamber contents, even in the case of a cloudy cornea (Fig. 13.29). Diffuse, side illumination relies on the passage of light through a transparent media while observing scattered light from a dark background

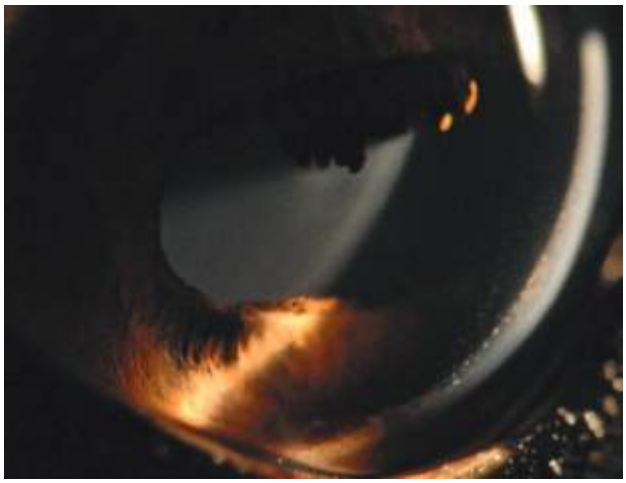


Figure 13.23 Wide slit beam (parallelepiped) of light used to illuminate multifocal, punctate corneal endothelial opacities via direct retro illumination.

(Christopherson, 1982). Under pathologic conditions, however, scattering within the corneal tissue may occur and is often best illustrated using a very oblique light source (Blaker, 1989; Mártonyi et al., 1984a). This type of lighting provides topographic information, yet fails to demonstrate the depth of a lesion. Demonstration of depth requires narrowing of the light source (as with use of a slit lamp), such that an optical section is created. This technique may be performed utilizing a dSLR camera and a handheld slit lamp as the primary light source; however, due to reduced lighting intensity, increased ISO settings (e.g., 800 and above) are often required.

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Figure 13.24 Note the brightly illuminated, punctate lesions along the posterior aspect of the optic section, localizing the lesions to the corneal endothelium. Lesion depth is precisely determined using the narrowest slit diaphragm (optic section) on the slit lamp.

Pinpoint Illumination (Tyndall Effect)

This highly specific form of illumination is utilized to help identify particulate/cellular matter within the aqueous humor, which may be otherwise invisible or very difficult to visualize (Fig. 13.30). The result of cellular accumulation within the aqueous humor is referred to as "aqueous flare" and is indicative of the presence of intraocular inflammation. It may be the only visible sign that the eye is actively inflamed and may be very subtle.

Retro Illumination

This method of illumination is possible due to corneal transparency and is divided into direct and indirect retro illumination. For simplicity, however, we will limit the discussion to direct retro illumination. Here, the light source must be coaxial (or close to it) with the imaging system, such that light reflecting from behind the lesion of interest is captured. Since the tapetum is present in most species examined, it often serves as the major reflecting structure. While this technique provides no information regarding depth, the silhouette effect created helps delineate extent and may provide information regarding the characteristics (e.g., obstructive vs. respersive) of the lesion(s).

Infrared Macrophotography

Most of the same principles as pertain to conventional macrophotography also apply to infrared macrophotography. Therefore, this section will cover specific points of consideration unique to infrared macrophotography.

Digital cameras can be readily converted for infrared image capture (www.lifepixel.com; www.maxmax.com). Following conversion, digital infrared images can be obtained in the same manner as conventional color images. Following the recommended white balance calibration using green grass, the infrared converted camera is ready to use. When shooting in manual mode, aperture, shutter speed, and ISO can be readily adjusted, and the captured image is visible on the camera's LCD viewing screen, similarly to that seen using a digital color camera (Fig. 13.31). A detailed description of the conversion process can be viewed at www.lifepixel.com. Briefly, the camera's normal sensor, which contains filters to block out ultraviolet (UV) and infrared waves of light, enhancing the sensitivity to light within the visible spectrum,

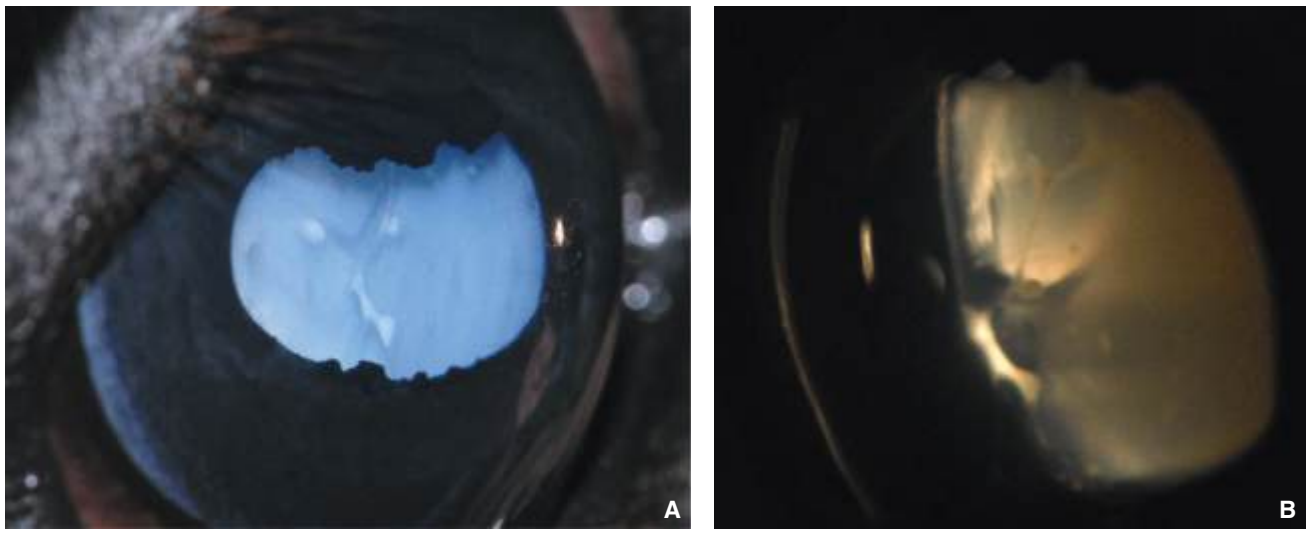


Figure 13.25 **A**. Note the multifocal, bright white, circular to linear opacities within the pupil margin in this horse's eye. Additionally, a diffuse and dense, white cataract is present. **B**. This handheld slit lamp image from the same eye clearly demonstrates that the bright white, circular to linear opacities are located along the lens capsule epithelium, whereas the dense, white lens opacity involves the nucleus, but not the complete cortex. In the center of the image, clefting of the anterior lens sutures is readily visible.

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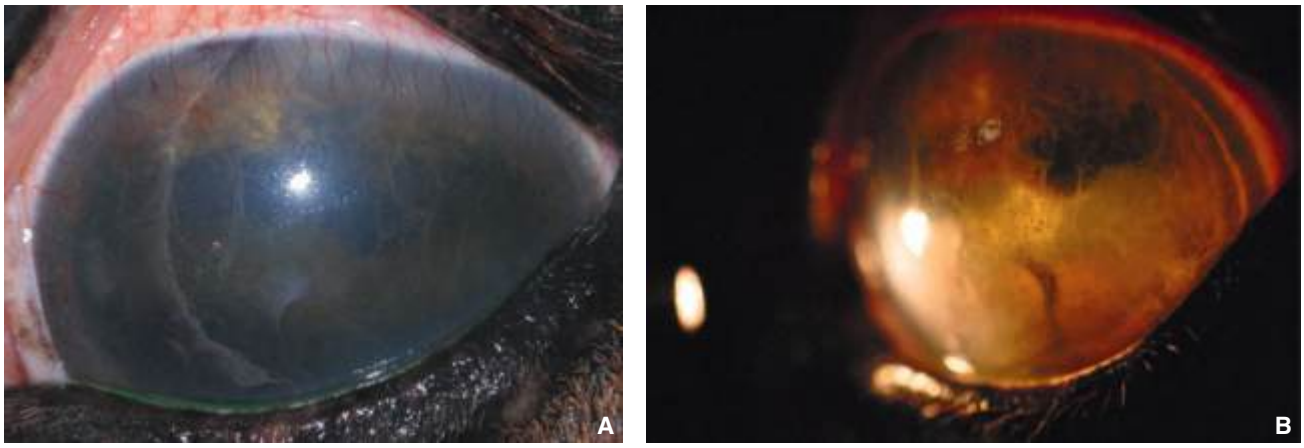


Figure 13.26 **A**. Conventional anterior segment image of an equine eye with chronic, nonulcerated keratitis and concomitant anterior uveitis. **B**. Tangential light is utilized as the sole source of illumination to highlight the changes within the anterior chamber in the same horse's eye. Diffuse, dark, punctate to linear opacifications representing corneal endothelial pigment deposition and diffuse fibrin accumulation (network of pale strands) are highlighted within the anterior chamber.

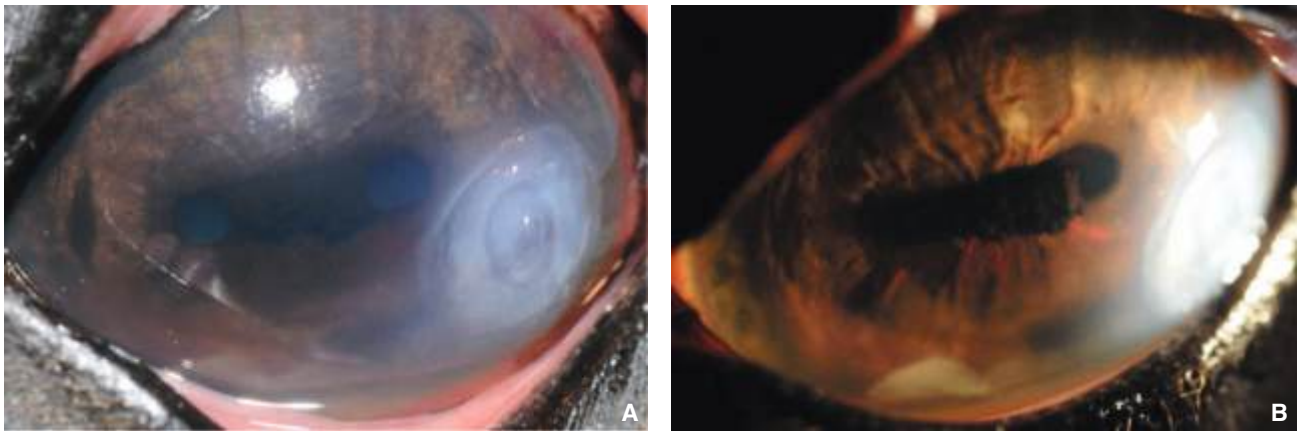


Figure 13.27 **A**. Conventional image of the left eye of a horse with a circular, inferior-temporal area of corneal malacia, chronic peripheral corneal vascularization, and miosis associated with secondary anterior uveitis. **B**. Tangential lighting of the anterior segment of the same eye highlights the anterior surface of the iris and structures within the anterior chamber. Note the obvious presence of vessels along the surface of the inferior iris, just below the granula iridicae.

is removed and replaced with a sensor that contains filters for visible and UV waves of light, allowing infrared wavelengths to pass undisturbed. Since the captured image can be visualized on the camera's LCD screen, immediate adjustments can be made to enhance its quality.

Because of its longer wavelength compared to light within the visible spectrum, infrared light is less susceptible to scatter. This characteristic makes digital infrared photography an ideal means of visualizing the intraocular structures of the anterior segment (e.g., iris, lens) through a cloudy or opaque cornea (McMullen et al., 2009; Fig. 13.32). Additionally, because of the ability of infrared light to pass through areas of edematous or fibrotic corneal tissue, essentially rendering them transparent, foci of cellular infiltrate can be made visible within these types of cornea lesions. This provides important information regarding a cornea's response to medical therapy, as well as postoperative lesion progression (Fig. 13.33).

Infrared light is also absorbed by pigmented tissue, making it an ideal means for identifying small, often indiscernible areas of hyperpigmentation of the iris, even in animals with darkly pigmented (i.e., brown) irides (Fig. 13.34). Infrared photography of the iris provides a means of tracking the progression of pigmented lesions or masses (i.e., uveal melanocytomas/melanomas), as these areas of iridal hyperpigmentation are readily discernable from the surrounding, heavily pigmented, normal iris. This makes even subtle areas of hyperpigmentation along the lesion's borders readily identifiable (Fig. 13.35). In diseases associated with pigment dispersion within the anterior chamber (e.g., pigmentary uveitis in the Golden Retriever) and iridal depigmentation resulting in corneal endothelial pigment

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Figure 13.28 This handheld slit lamp image localizes these corneal opacities (diffuse, multifocal keratic precipitates in a 12-year-old Rat Terrier with chronic lens-induced uveitis) to the corneal endothelium. Both direct (over the surface of the inferior iris) and indirect (over the pupil) retro illumination highlights the keratic precipitates located away from the optic section.

deposition (Fig. 13.36), infrared macrophotography may be useful in identifying subtle pigment changes present early in the disease process (Fig. 13.37).

Similar lighting principles apply to digital infrared macrophotography as apply to digital color macrophotography. A Finoff transilluminator is used as a modeling light and allows the photographer to focus on the iris, while an external flash provides sufficient illumination to utilize moderate camera settings (e.g., ISO 200, f/16, and 1/250 shutter speed; Fig. 13.38). Alternatively, a Finoff transilluminator can be utilized to provide the sole source of illumination. This is especially useful for highlighting changes within the anterior segment using tangential illumination (Fig. 13.39).

Plane of focus is important when shooting in infrared. Without using an external light source to illuminate intraocular structures (anterior chamber masses, iris, lens), the specific lesion or tissue structure to be photographed will likely be out of focus if the camera lens is parallel to the visual axis. Oblique infrared photographs taken medially or laterally at approximately 45<line>degree angles from the globe allow the portion of the cornea closest to the lens as well as the iris and anterior lens surface to remain more in focus (Fig. 13.40). Using an external light source allows direct visualization of the specific tissue and structure(s) to be photographed, ensuring that the desired plane of focus is achieved.

Slit Lamp Photography

Table-mounted slit lamp photography, while irreplaceable in human ophthalmology, is limited to research and academic settings in veterinary ophthalmology. Although there are several challenges to overcome, with a systematic approach and meticulous attention to detail it is possible to obtain handheld slit lamp images that provide useful additional information as well as enhancing case documentation. Therefore, in this section we will discuss some techniques that will enable documentation of both subtle and not so subtle changes in the anterior chamber using a dSLR and a handheld, portable slit-lamp biomicroscope. Additionally, it is possible to obtain

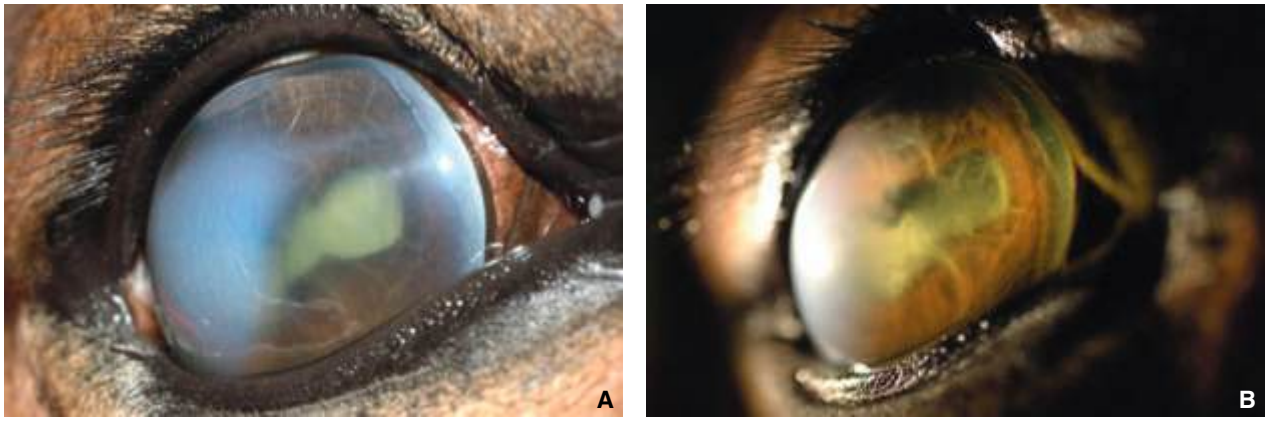


Figure 13.29 **A**. Conventional image of an 11-year-old Quarter Horse's left eye following blunt force trauma. Temporal corneal edema, superior and medial areas of anterior synechiae, and a cataract are readily visible. Also note the mild accumulation of fibrin in the anterior chamber. **B**. Using tangential illumination of the anterior chamber, medial iris dialysis is readily visible. The mild fibrin accumulation identified in (**A**) is revealed to be more severe (moderate accumulation).

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Figure 13.30 A thin slit beam of light is used to highlight the appearance of proteinaceous or cellular accumulation within the anterior chamber. Clinically this is referred to as aqueous flare and is a hallmark sign associated with anterior uveitis.



Figure 13.31 Color image of the back of an infrared (IR) converted Nikon D200 with a black-and-white IR image on the LCD screen.

slit lamp images using a smartphone camera held up to or mounted to the ocular of the handheld slit lamp.

While it is possible for the same individual to manage both the slit lamp and a dSLR, it is usually much more beneficial for an assistant to focus the slit lamp independently of the photographer (Fig. 13.41). This allows both the slit lamp and the camera to be individually stabilized and allows for greater control of the slit beam. Begin with the widest slit beam of light and with the camera in the manual mode of operation. Good settings to start with are aperture f/11, shutter speed 1/640 of a second, and ISO 640, but these will constantly need to be adjusted based on the appearance of the image on the on-camera LCD screen. If the image is overexposed (too bright), it may be necessary to decrease the aperture size (larger f-stop number) and increase shutter speed, while at the same time decreasing the ISO. If the image is underexposed (too dark), adjustments in the opposite direction will be necessary: increase aperture size (smaller f-stop number), decrease shutter speed, and increase ISO.

The thickest slit beam of light will provide the most illumination, but will also offer the least amount of information pertaining to lesion depth (Fig. 13.42). By decreasing the size of the slit beam, the ability to assess lesion depth increases; however, it will also be necessary to increase the ISO, increase aperture size, and decrease shutter speed, due to the decreased illumination. It may be necessary to set the ISO at 1250, the aperture at f/4.5–5.6, and the shutter speed to between 1/80 and 1/200 of a second. This will lead to a grainier image with a shallow DOF, and it becomes increasingly more difficult to obtain a sharply focused image, due to motion blur (Fig. 13.43). Image stabilizers within the lens or camera significantly reduce the effects of motion blur, which results in well-focused handheld images when using the previously described settings.

Common artifacts associated with handheld slit lamp photography are reflections from the slit lamp or from surrounding objects or people, especially in a relatively clear, healthy cornea (Fig. 13.44). To prevent or minimize these artifacts, turn off all unnecessary overhead lights and cover all windows. Reflections from the light source (white slit lamp) can be more difficult to eliminate because of the proximity and angle of incident light necessary to illuminate the lesion or tissue for imaging. If this reflection cannot be completely avoided, try to confine the reflection to an area where it will have the least impact on the final image.

Goniophotography

Many of the lighting and focusing challenges associated with handheld slit lamp photography are similarly encountered in goniophotography, due to the necessity of keeping the goniolens and the camera aligned while trying to simultaneously provide illumination with an external light source.

With currently available handheld retinal cameras, it is possible to obtain acceptable gonio images. Using the Kowa Genesis-D fundus camera set at a high flash output, the illumination is adequate to obtain diagnostically useful images of the ICA – notably the width of the anterior border of the cleft, presence of normal or dysplastic pectinate ligaments, or the presence of goniodysgenesis with sheets or partial sheets of mesenchyme across the face of the ICA. As with gonioscopy using any form of light source, the most easily imaged areas of the ICA are in the ventromedial, ventrolateral, and,

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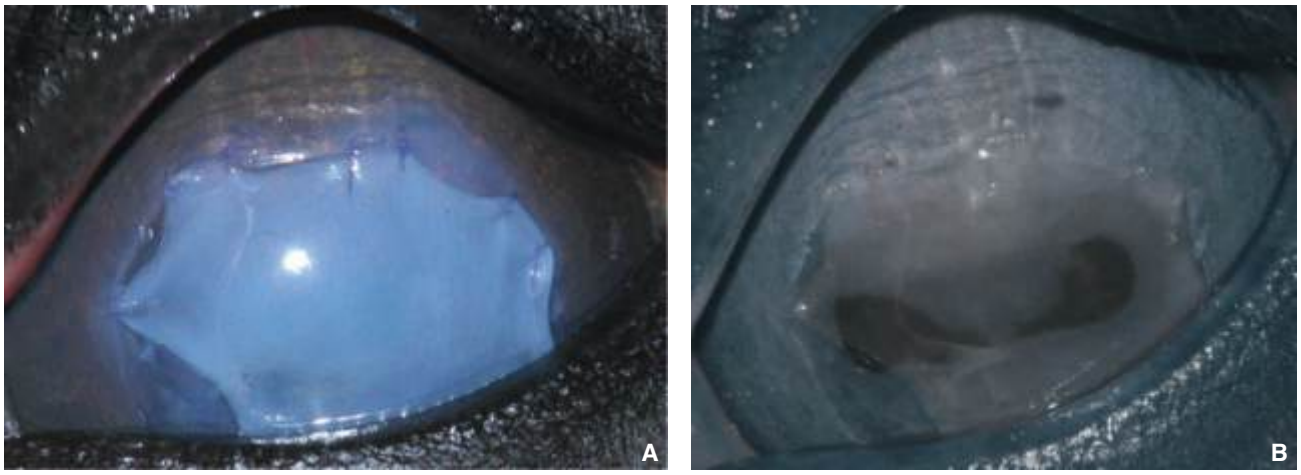


Figure 13.32 **A**. In this conventional image of an equine eye with an axial amniotic membrane transplant (AMT), the pupil is not visible. **B**. Infrared photography of the same eye allows direct visualization of the pupil through an opaque cornea, or in this case through the AMT.

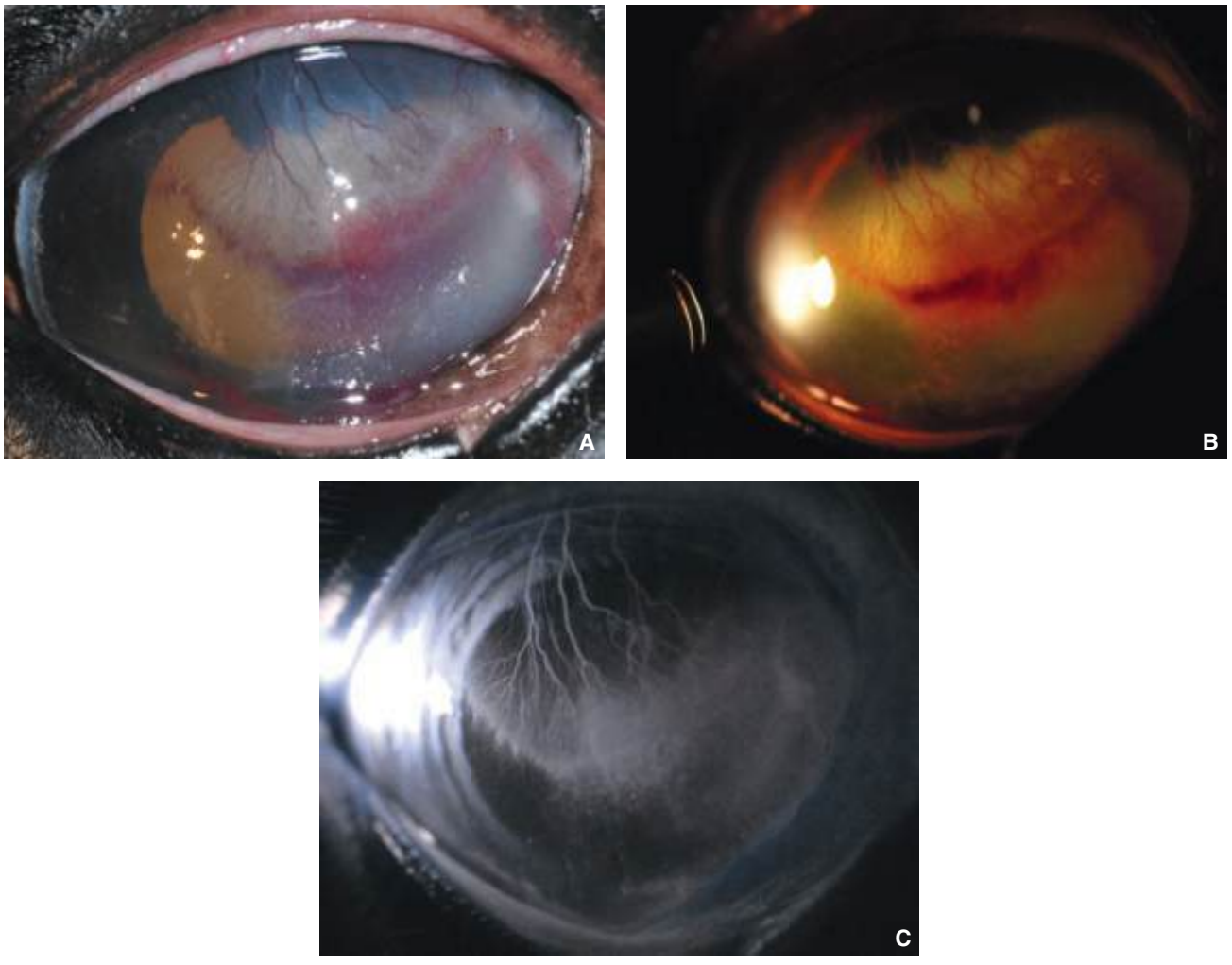


Figure 13.33 **A**. Conventional color image of an equine eye with chronic, ulcerative keratomycosis. **B**. Tangential illumination of the same eye. Note the enhanced visualization of the corneal vessels. **C**. Tangentially illuminated infrared image of the same eye. In addition to the dense area of cellular infiltration within the angle where the corneal vessels converge medially (3 o'clock position), there is also diffuse punctate cellular infiltrate within the cornea, axial to the superior corneal vessel terminations.

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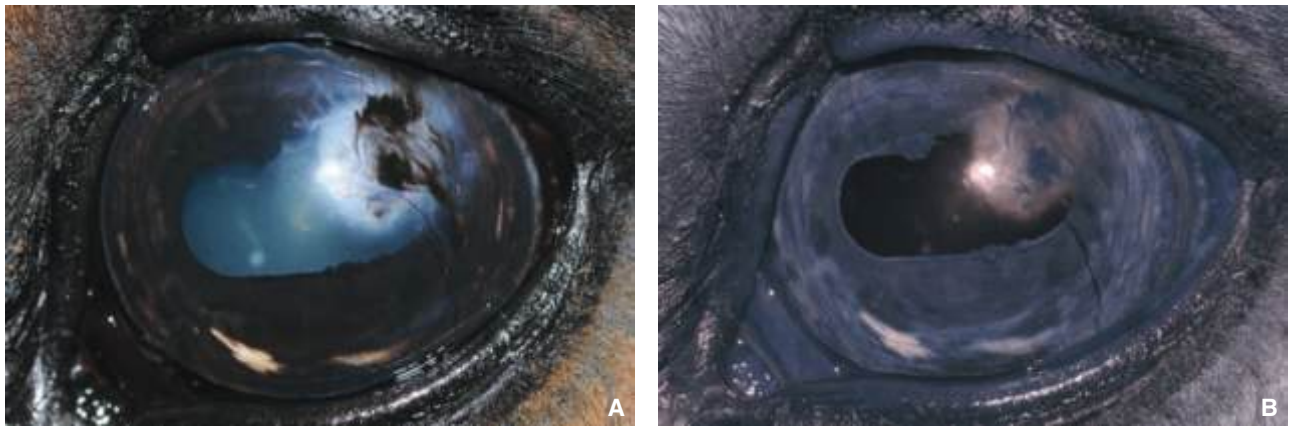


Figure 13.34 **A**. Conventional color image of the left eye of a 19-year-old Cleveland Bay gelding 3 months following posterior lamellar keratoplasty. **B**. Digital infrared image of the same eye. Note the improved contrast within the darkly pigmented iris (e.g., granula iridicae) and the cornea. The notch defect in the medial aspect of the superior palpebral, which can be easily overlooked in the color image, is readily identifiable in the infrared image.



Figure 13.35 **A**. Color image of the right eye of a 9-year old, gray Quarter Horse gelding with multiple areas of iridal hyperpigmentation (1, 5, 6, and 9 o'clock positions), roughly halfway between the limbus and pupil margin. **B**. Digital infrared image from the same eye in which the described areas of hyperpigmentation are readily distinguished from the surrounding iris, despite its inherent level of pigmentation. The area of hyperpigmentation at the 5 o'clock position is raised from the surface (see the oblique view in Fig. 13.34), suggestive of an iris melanocytoma/melanoma.

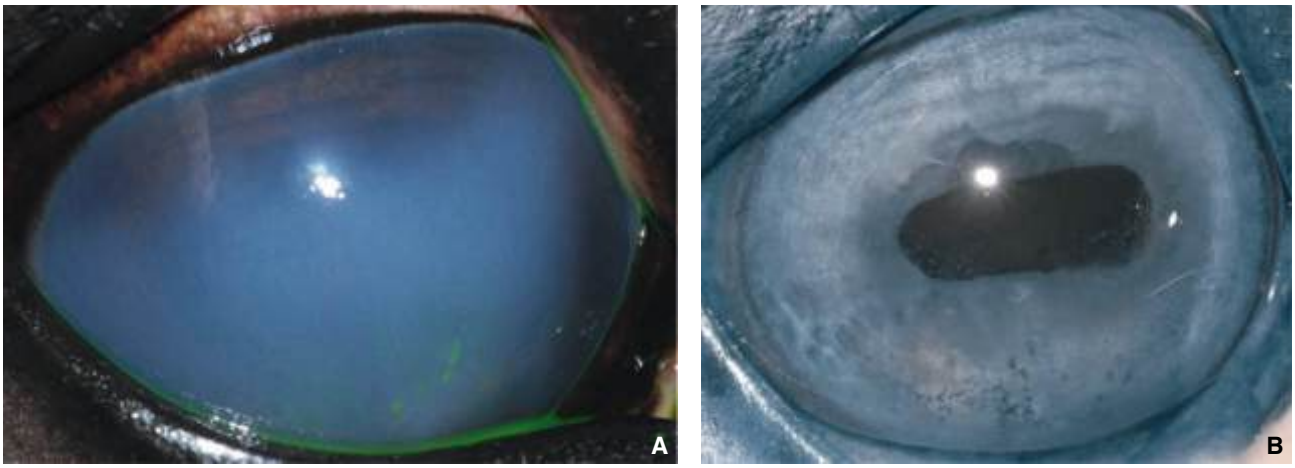


Figure 13.36 **A**. Color image of the right eye of an 11-year-old Quarter Horse mare with diffuse corneal edema and multifocal areas of superficial corneal ulceration associated with corneal bullae (e.g., small areas of fluorescein stain uptake). **B**. Digital infrared image from the same eye reveals diffuse punctate pigment deposition along the axial and inferior corneal endothelium. Infrared wavelengths of light pass through corneal edema with minimal scatter, allowing for a relatively clear view of the anterior segment despite a significant degree of opacification.

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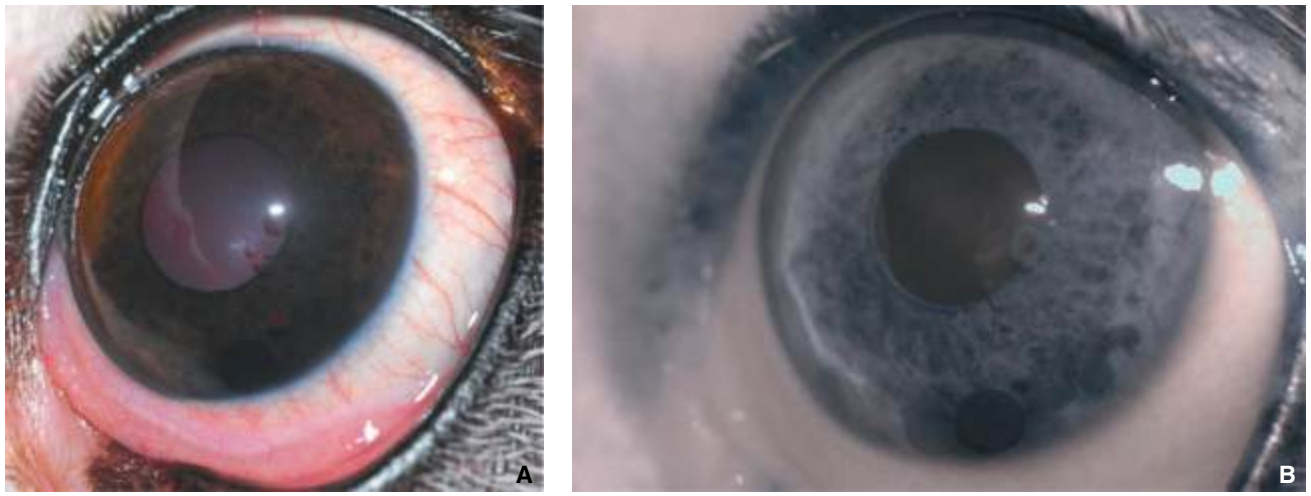


Figure 13.37 **A**. Color image of the left eye of an 8-year-old male castrated Boston Terrier. A small translucent uveal cyst can be seen at the 3 o'clock position within the pupil margin (partially obscured by the flash reflection) and a larger, more heavily pigmented cyst can be seen within the inferior anterior chamber (5 o'clock position). A thin, interrupted line of hyphema can be seen spanning the distance between the two cysts. **B**. Digital infrared image of the same eye. Note that the translucent cyst seen at the 3 o'clock position within the pupil margin is closer to the cornea than to the iris (the pupil margin can be seen within the center of the cyst, and a curvilinear shadow from the cyst is being cast on the surface of the iris). Also, note the two additional uveal cysts medial and temporal to the larger cyst within the inferior aspect of the anterior chamber.

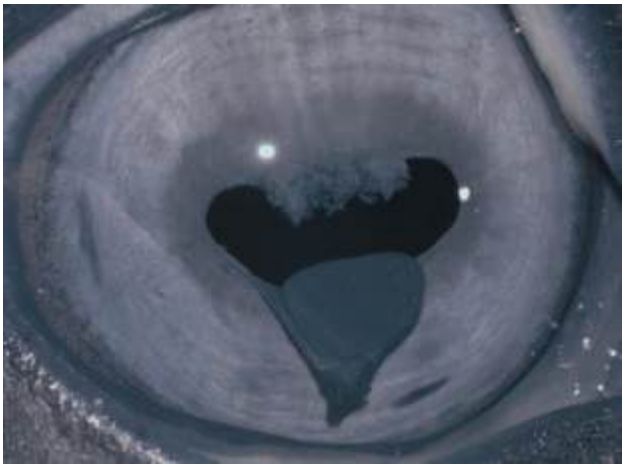


Figure 13.38 Digital infrared image taken with direct flash illumination. Note the presence of the large uveal cyst extending from the inferior pupil margin.



Figure 13.39 Digital infrared image taken with tangential illumination. This is the same eye as in Figure 13.38. Note the increased surface detail of the iris and the three-dimensional effect achieved by the creation of shadows within the anterior chamber. It is clear in this image that the uveal cyst has adhered to the corneal endothelium inferiorly (anterior synechia), and that there is a relatively large space between the cyst and the surface of the iris.

to a lesser extent, dorsomedial quadrants. The view of the dorsolateral quadrant can be more difficult due to the difficulty in positioning the head in such a way that the nose does not interfere with the positioning of the camera (Fig. 13.45).

A Koeppe goniolens is applied to the topically anesthetized cornea using a viscous coupling solution (GonioGeL, Aurolab, Tamil Nadu, India) and held in place on the eye with the operator's finger lightly applied to the top of the lens, which allows the lens to be moved over the cornea to obtain the best view of the ICA. A combination of the small movements of the lens and the camera itself will allow the ICA to be scanned.

As with retinal photography, it is essential that the prism on the front of the camera is positioned as close to the goniolens (2–3 mm) as possible, to avoid a bright flash reflection artifact that will totally obscure the ICA. This is easily achieved with practice. Resting the camera against the hand holding the goniolens allows you to move with any small movements the animal may make (Fig. 13.46).

A photograph is taken in each quadrant when the ICA appears at its widest extent. ICA photographs are taken

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Figure 13.40 Oblique digital infrared image of the same eye as in Figure 13.35. Images taken from this perspective help to create a three-dimensional impression of any lesions present. In this image, it can be appreciated that the inferior-medial area of hyperpigmentation is slightly raised above the surface of the iris. A small shadow is cast behind the lesion, suggesting elevation. Tangential illumination, as in Figure 13.39, can be used to further emphasize changes in surface elevation, as the shadows created are much more dramatic.



Figure 13.41 Handheld slit lamp and oblique positioned dSLR utilized to obtain slit lamp images of the anterior segment in the horse. Note that the slit lamp and camera are being focused independently by separate individuals. (Courtesy of Silas Zee, Auburn University.)

before mydriasis and using the Genesis-D camera, with a reasonably bright focusing light intensity and flash strobe set at about 12. Usually the flash intensity must be bracketed widely, depending on the extent of pigmentation in the anterior segment of the individual eye (Fig. 13.47).

Surgical Photography

Peri- or intraoperative ophthalmic photography follows many of the same principles as macrophotography described earlier. One major difference is that the surgery suite is often



Figure 13.42 Handheld slit lamp set to the largest diaphragm setting, being demonstrated in a horse. (Courtesy of NC State University.)

relatively dark to minimize glare while the surgeon is working under the microscope. This requires that adjustments be made to the camera settings. Images taken during microsurgery can be obtained both with and without a flash. Illumination from the microscope is sufficient to obtain photographs highlighting specific procedural steps. However, these images are generally a bit darker and lack some of the detail that can be achieved with a flash (Fig. 13.48). Intraoperative flash photography readily provides the foundation for well-focused, interpretive images representing the real-time appearance of the subject. Both color and infrared digital images can be obtained peri- or intraoperatively with only minimal (if any) changes to the camera settings used for external photography (Fig. 13.49).

Fundus Photography

Most of the fundus photography performed in veterinary ophthalmology is obtained with specialized fundus cameras. One of the greatest disadvantages associated with digital fundus photography is the comparatively low image quality when compared to dSLR images. The dated technology of the currently available digital handheld, portable fundus cameras (e.g., the Kowa Genesis is a 2 megapixel camera) and the limited number of readily available, and affordable, fundus cameras that can obtain quality images contribute to this dilemma.

Fundic images can be obtained with a dSLR and a condensing lens, but the results are inconsistent. Because it is extremely difficult (if not just about impossible) to visualize the exact portion of the fundus that is to be photographed while capturing the image in this manner, there are many necessary camera adjustments that must be made, and constant repositioning is necessary to obtain high-quality images. The inherent difficulty associated with this technique, in addition to the relatively unpredictable results, generally

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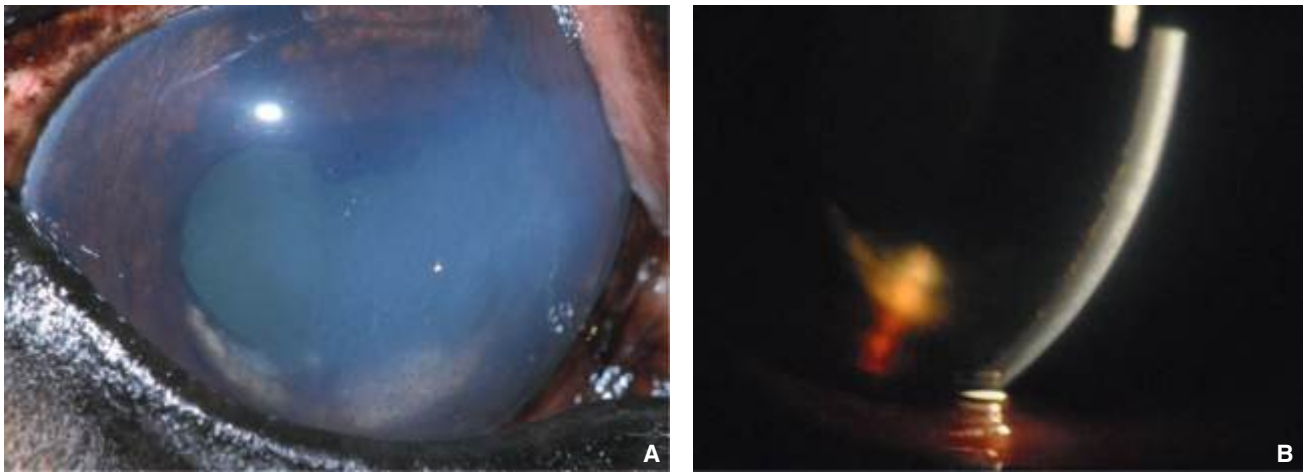


Figure 13.43 **A**. Color image of the right eye of a 23-year-old Hanoverian Warmblood gelding with endotheliitis and anterior uveitis associated with pigment dispersion. **B**. Handheld slit lamp image from the same eye. The camera settings were adjusted to allow for image capture using the slit lamp as the sole source of illumination (ISO 1250, f/5.6 and 1/80 of a second). A relatively grainy image is to be expected.

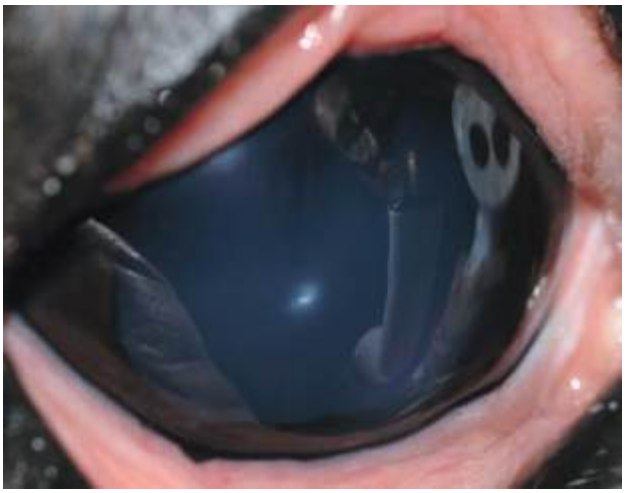


Figure 13.44 Note the reflection of the white, handheld slit lamp, as well as the person holding the instrument, in this horse's cornea. This can be minimized or avoided by using a Finoff transilluminator as a modeling light for focusing, and by having the assistant stand on the opposite side of the animal.

results in very few fundic images being obtained with this method. This practice has been all but superseded by dedicated handheld fundus cameras or smartphones. Although the image quality is inferior to those obtained with a dSLR, the availability of smartphones and the relative ease by which fundus images can be obtained has made this approach more feasible in a busy practice or even specialty referral center. However, while fundus images obtained in this manner are of acceptable quality for basic documentation and client education, they often lack detail and cannot be used to highlight subtle retinal lesions. Specific, digital handheld fundus cameras, such as the Smartscope (Optomed, Oulu, Finland) and ClearView (Optibrand, Fort Collins, CO, USA), have been utilized in an attempt to bridge the gap in fundus photography that has resulted due to the decreased use of more sophisticated handheld fundus cameras in human ophthalmology. While the overall expense associated with the Smartscope and ClearView fundus cameras can be considered reasonable, the image quality does not rival that once obtained using film-based handheld fundus cameras. That fact, coupled with the ever-improving quality of smartphone cameras, has resulted in a general lack of dedicated, high-quality (i.e., publishable image quality) digital fundus cameras for routine use in veterinary ophthalmology.

Recently, a prototype lens adapter has been developed that allows exceptional fundic images to be obtained when mounted to a dSLR (Pirie & Pizzirani, 2011a). Imaging of the posterior segment using this adapter relies on the principles of indirect ophthalmoscopy. This system utilizes an indirect ophthalmic lens, common to the examiner, which is secured in front of a camera lens. The indirect ophthalmic lens forms a real, inverted aerial image at the object plane of the camera lens, which then forms the final image for the camera sensor. Alteration of the indirect lens is possible, allowing for alterations in magnification and field of view. Using lenses ranging from 28 to 90 D, an approximate magnification range between 1× and 4× and an approximate field of view range between 30 and 95 degrees (horizontal axis) are possible when imaging the canine eye (Pirie & Pizzirani, 2011b).

The ClearView must be connected to a computer or laptop, where the images are automatically downloaded to a "ClearViewImages" folder and organized in subfolders labeled with the animal owner's last name. Individual patient folders contain subfolders for each examination, organized by date of acquisition. Once the ClearView

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Figure 13.45 Photographing the iridocorneal angle and pectinate ligaments using a Genesis D fundus camera.



Figure 13.46 Goniophotography using a Genesis D fundus camera. The hand holding the camera is rested against the animal's head. The iridocorneal angle is brought into focus by moving the camera and the goniolens on the cornea using the finger of the opposite hand, and rotating the focusing dial on the camera.

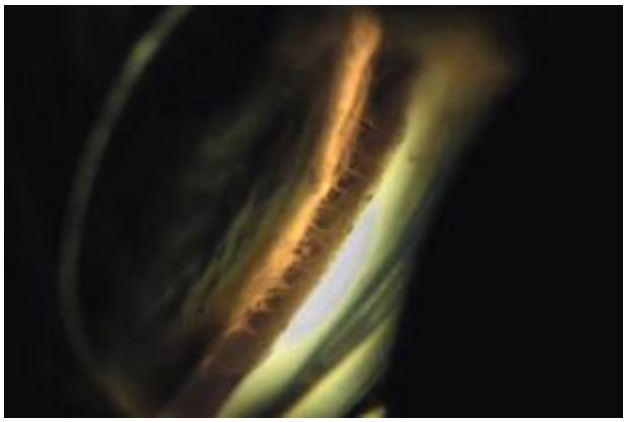


Figure 13.47 Goniophotograph of a normal, open iridocorneal angle of a 6-year-old male neutered mixed-breed dog.

camera is attached to the laptop/computer and the software application is opened, the images are readily obtained in a "burst" fashion. The shutter release button (located on the side of the camera) is depressed and held down to obtain a short burst of four sequential images. The camera is held up to the animal's eye in a noncontact manner while the person obtaining the images confirms the correct location and focus by viewing the computer screen (Fig. 13.50). There is a short learning curve associated with this camera, but it does not take long to become comfortable using it. The ability (or necessity) to view the image directly on the computer screen makes this camera useful for teaching and client education purposes. The ClearView focuses automatically on the retina of the animal being examined and the diopters cannot be manually adjusted (Fig. 13.51). As a result, the fundus cannot be accurately imaged in an aphakic or pseudophakic eye.

The SmartScope/SmartscopePro is a self-contained, nonmydriatic handheld unit with a 40 degree field of view. The camera has 5 megapixels of resolution and is capable of capturing color, red-free, and infrared, still and video images. It has 8 GB of memory. Image transfer from the camera to a computer can be achieved via USB or over Wi-Fi. The camera back is fitted with a 2.4 in. LCD display that provides the photographer the ability to visualize the fundus in his or her line of site, thus allowing for direct control of the image focus. The SmartScope has autofocus, as well as allowing for manual diopter adjustments within a range of −20 D to +20 D.

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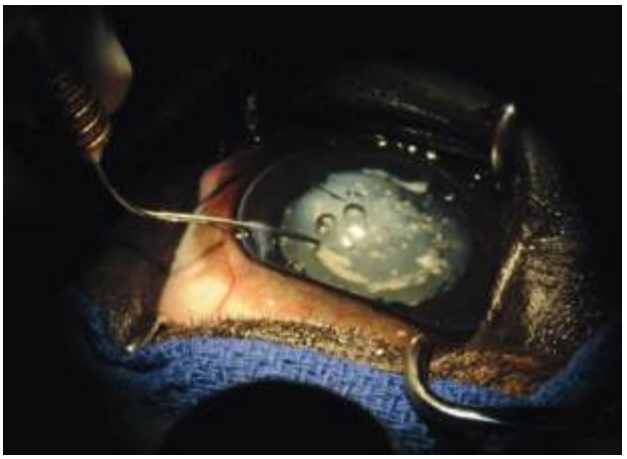


Figure 13.48 Intraoperative image using only the light from the operating microscope. High-frequency diathermy is being used to perform an anterior capsulotomy in a 2-year-old Quarter Horse mare.



Figure 13.50 ClearView camera being used to image the fundus of a 7-year-old Icelandic Horse mare. The image is captured via a laptop connected via a USB cable (computer not shown).

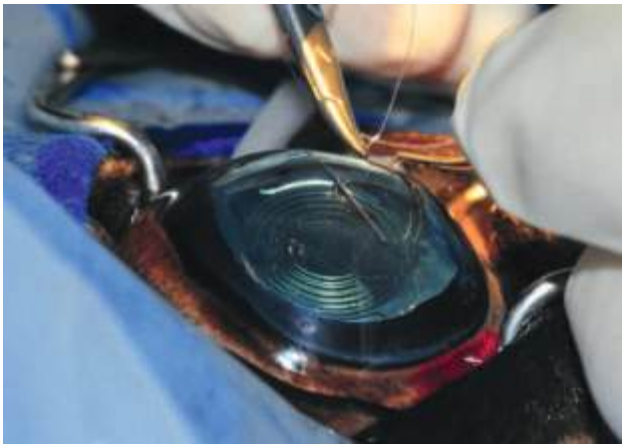


Figure 13.49 An external flash was utilized to capture this intraoperative image following intraocular lens implantation in an adult horse. Some corneal artifacts may be present (instrument reflection in the cornea) if the light from the operating microscope is not momentarily blocked while the image is being taken.

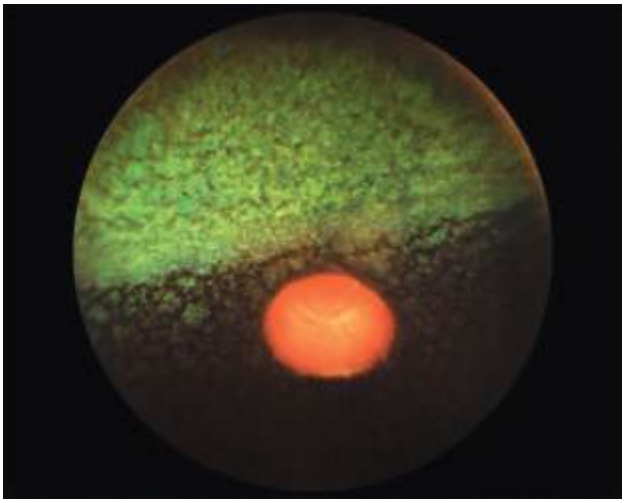


Figure 13.51 ClearView fundus image of the right eye of a 10-year-old American Paint Horse gelding with equine motor neuron disease. Note the reticulated pattern of pigment clumping that is a consistent ocular finding in affected horses.

Over the past decade there has been increasing popularity, availability, and use of smartphones in clinical ophthalmology. These devices offer important and expanding diagnostic capabilities, allowing the user a fully embedded imaging system, capable of acquiring, storing, and transferring images wirelessly. Several ophthalmic applications are available for different examinations that can assess visual acuity, color vision, astigmatism, and pupil size, to name a few. More importantly, in conjunction with the use of various adaptors and apps, these devices are capable of imaging the posterior segment in a variety of species (Haddock et al., 2013; Kanemaki et al., 2017). They offer the user a more cost-effective means to capture images of the fundus.

Most smartphone fundus cameras and photoadaptors rely on the principle of indirect ophthalmoscopy. Accessory lens(es) employed may be mounted in a specific housing and/or held freehand. Various lens configurations have been assessed utilizing a number of different smartphone models/suppliers and have been shown to produce a field of view comparable to that of conventional fundus cameras (Ludwig et al., 2016). The imaging technique is detailed in a recent report (Haddock et al., 2013) and it is generally accepted that increased image quality is acquired with continued practice and patience.

While these low-cost smartphone systems offer the user a more affordable alternative, good image quality is a prerequisite for their diagnostic utility. In physician-based medicine, comparative studies have demonstrated conflicting results pertaining to image quality. In one report, smartphone-based

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imaging generated images of low quality, compared to a standard fundus camera (Darma et al., 2015). An alternative report demonstrated no statistically significant difference (Adam et al., 2015). To date, no comparable study has been performed in veterinary medicine.

An additional point of consideration is the photobiologic safety of conducting fundoscopy using these smartphone-based systems. The light safety limits for ophthalmic instruments are set by the ISO (ISO 15004-2.2) and it has been recommended that spectral irradiance on the retina be weighted separately for both thermal and photochemical hazards. To date, only one safety study has been performed, comparing retinal exposure levels of a smartphone-based imaging system to those of conventional indirect ophthalmoscopy (Kim et al., 2012). Based on this report, retinal exposure from a smartphone was one order of magnitude less than that of indirect ophthalmoscopy and within the ISO safety limits of thermal and photochemical hazards. Currently, it can only be assumed that the light intensity and energy levels generated by other, newer smartphone-based systems are comparable. Similar light safety evaluations have not been conducted for other smartphone models.

Fundus photography is difficult not only for the reasons listed, but also since even when utilizing a specialized fundus camera, many minor camera adjustments must be made to obtain consistent images, even from the same location within an individual eye. Depending on which part of the fundus is being photographed, several adjustments may be necessary from one image to the next. Often, it is necessary to frequently alternate lighting adjustments even at the same location within the fundus from the same eye, to obtain a well-illuminated and sharply focused image.

The following section is based on obtaining fundus images with the Kowa Genesis-D digital fundus camera (Kowa Optimed, Torrance, CA, USA; Fig. 13.52). Prior to obtaining fundus images, ensure that the camera is properly set up and focused for use. There are focusing mirrors within each ocular (similar to most handheld portable slit-lamp biomicroscopes). Adjust the oculars so that two sharply focused sets of lines are visible in each (rotate oculars clockwise or counterclockwise to focus). Once the camera has been focused, start with the flash level set to medium and the intensity level at 3 or 4 (right dial) when photographing a dog, or 4–5 when photographing a horse (for cats, set the flash level to low and the intensity level at 0.3 or 0.4 to start with), with the optic nerve head in the center of the image. The left dial on the base adjusts the amount of incident light, which allows the photographer to visualize and focus on the fundus. In order to make the imaging process easier, decrease this light intensity to as low as possible while still allowing visualization of the fundus. This will minimize resistance from the animal due to excessive light stimulation. If this light is kept as low as possible, most animals will tolerate the flash relatively well.



Figure 13.52 Kowa Genesis-D camera, assembled and ready for use. (Courtesy of NC State University.)

There is a significant learning curve associated with using a handheld fundus camera because of operator movement caused by triggering the on-camera shutter, the delay associated with the foot pedal, and retraction of the globe by the animal. To trigger image capture on camera, it is necessary to activate a horizontal green lever, located on the grip, after ensuring that the image is in focus (manual adjustments can be made by adjusting the focusing wheel toward the front of the camera).

To avoid the common flash artifact associated with images taken with this camera, the lens needs to be very close to the cornea (within 2–3 mm). This requires quite a bit of practice and a steady hand. Generally, this is achieved by resting the camera against the first finger (from the opposite hand) that is being used to hold the eyelids open. That ensures that you are always aware of where the camera is, and you can readily reposition following the regular breaks that are necessary to ensure that the cornea remains hydrated. Periodically, your view of the fundus will go from being in focus to blurry without any adjustments on the part of the photographer. This is generally associated with active globe retraction and movement of the nictitating membrane. Remain patient and do not make any major adjustments during this period. Instead, give the animal a short break and resume. Once the fundus has been brought into focus, only minor adjustments should be necessary.

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When photographing the tapetal portion of the fundus, the light intensity should be decreased incrementally to prevent overexposure. Light intensity will need to be increased accordingly to prevent underexposure when photographing the nontapetum (Fig. 13.53). As with any method of photography, regular use and critical evaluation of one's techniques and settings are necessary to become proficient in obtaining high-quality fundic images.

Photography of Specific Lesions

Adnexal Lesions

Accurate representation and depiction of adnexal lesions often require forethought and technical considerations on the part of the photographer. Composition of the final image(s) should always be planned from the beginning, with special attention given to the placement of the flash (Olsen, 1979). When imaging the adnexa, it is important first to obtain an overall representation of the lesion(s) such that a story is created. This entails imaging not only from several viewpoints, but also at varying magnifications. By doing so, the viewer obtains a greater appreciation of the "big picture." Simply obtaining a close-up image of an upper eyelid mass leaves the viewer with no perspective for comparison. One recommendation is to obtain at least two images (often several), one of low and one of high magnification (Christopherson, 1982; Fig. 13.54). Imaging at low magnification is performed to obtain an overall perspective of the lesion/abnormality that is being depicted. This is generally obtained by imaging the animal initially straight on using a front light source, with the plane of focus being the animal's eyes. This method of illumination allows for uniform lighting (Mandell et al., 1976). From here, alteration in the point of view and/or angle of illumination (e.g., 45 degrees) may be performed to better relay information regarding depth and/or variations in profile. Magnifications typically employed for this purpose are approximately 1:8 to 1:5, utilizing an aperture setting of f/11–22 (Gutner, 1977; Mandell et al., 1976; Olsen, 1979). From here, imaging of the region of interest should be conducted at higher magnification(s). These images may involve a series of incremental increases in magnification and are obtained to more accurately depict pathologic changes of the lesion(s) of interest. Use of side lighting is preferred here as it creates shadows, improving textural detail and depth within the image. The specific location of the light source (e.g., left vs. right side) may vary, depending on the desired effect and specific location of the lesion. Magnifications typically employed will vary depending on the size of the lesion, typically ranging between 1:4 and 1:2 (Christopherson, 1982; Olsen, 1979). However, one must always bear in mind the effects of increasing magnification and DOF. As such, higher aperture settings (e.g., f/32) may be required to ensure the maximum amount of DOF within the image.

Some potential artifacts present in the final image while photographing adnexal lesions often relate to the light source. As previously mentioned, use of a point light source (e.g., flash) often results in harsh lighting, which generates pronounced specular reflections. Use of a diffuser may be of benefit while working at lower magnifications (Mandell et al., 1976). A diffuser will not only decrease the intensity of these reflections, but also provide more uniform illumination.

Corneal Lesions

Imaging the cornea creates some additional considerations, as the goal may be not only to illustrate the presence, size, depth, and/or morphology of a particular lesion, but also to demonstrate its transparency. The latter point is of the greatest difficulty, but is achievable with careful placement of the light source.

Two methods often employed to photograph the cornea include utilizing a standard camera (e.g., dSLR) and/or a slit-lamp biomicroscope. However, the latter produces a limited DOF, due to the optical design of the system (Tate & Safir, 1980). Regardless of which modality is employed, the concepts and methods are comparable.

When composing the final image, the lesion of interest should be centrally located, demonstrating its size, topography, and relationship with surrounding tissues (e.g., conjunctiva, sclera, and eyelids). Magnifications required for this purpose typically range from 1:1 to 2:1, utilizing an aperture around f/22–32 (Gutner, 1977; Olsen, 1979). A 1:1 magnification ratio will allow for the globe and surrounding tissues to be imaged (small animal), while a 2:1 ratio will result in the cornea filling the image (Christopherson, 1982). Most available macro lenses will allow for a 1:1 ratio to be obtained; however, going beyond this (e.g., 2:1) requires some modification. Several methods may be employed for this purpose and include the use of extension tubes, teleconverters, close-up lenses, and/or reversing lenses. While each has its own advantages and disadvantages, it is the authors' preference to utilize extension tubes, if needed. Table 13.3 provides a brief summary. One additional point of consideration is proper alignment between the corneal lesion and the camera lens as magnification increases (and DOF decreases). The axis of the lesion should be oriented perpendicular to the camera lens (e.g., sensor), thereby maximizing focus. This nevertheless becomes somewhat difficult with unrestricted ocular movements.

Due to the spectral properties of the cornea, a number of lighting techniques may be employed, each revealing often dramatically different features/properties of the lesion(s). These may include frontal, side, and retro illumination lighting techniques. Figure 13.55 provides examples of these

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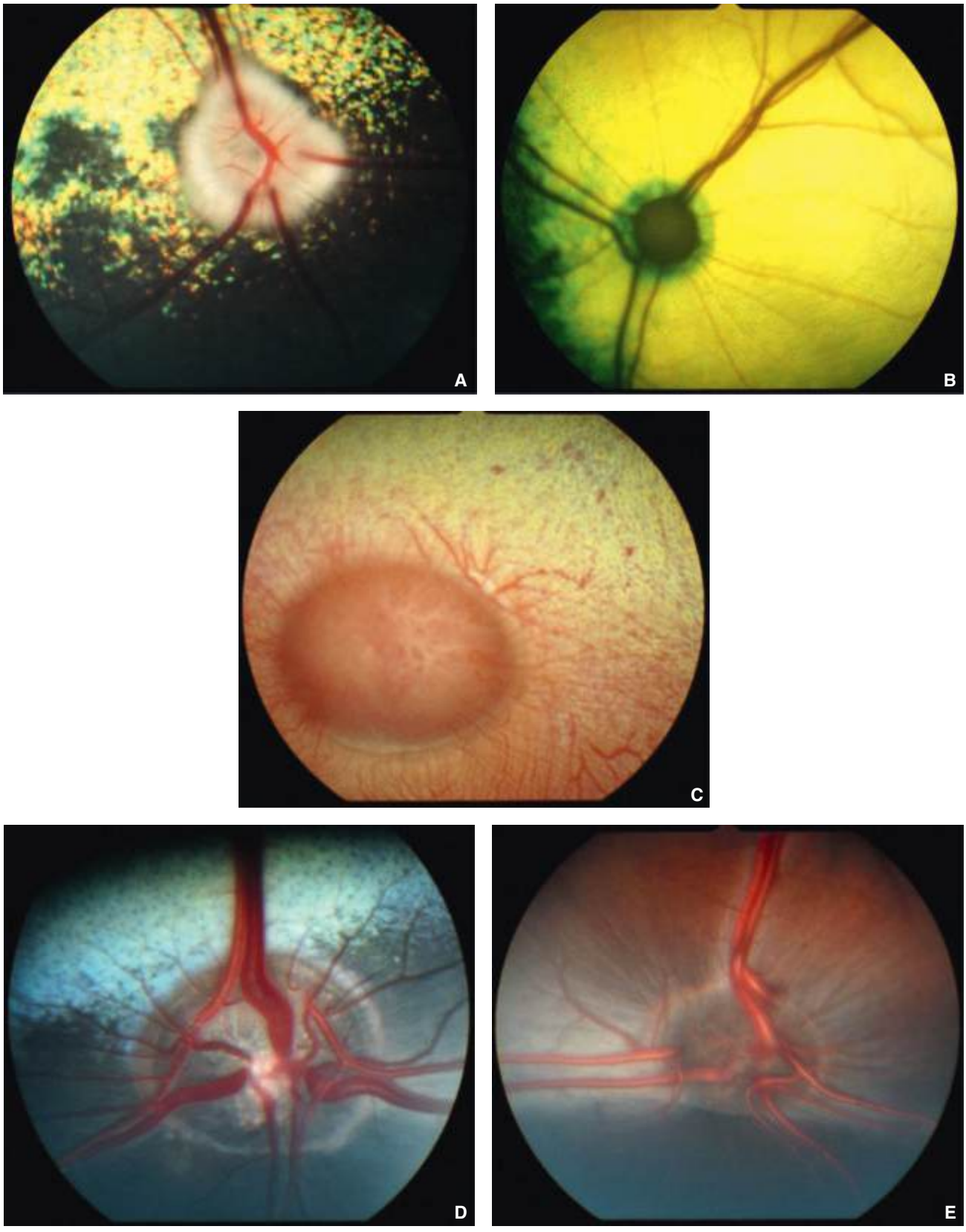


Figure 13.53 Normal fundic images from (**A**) canine, (**B**) feline, (**C**) color-dilute equine, (**D**) bovine, and (**E**) camelid (alpaca).

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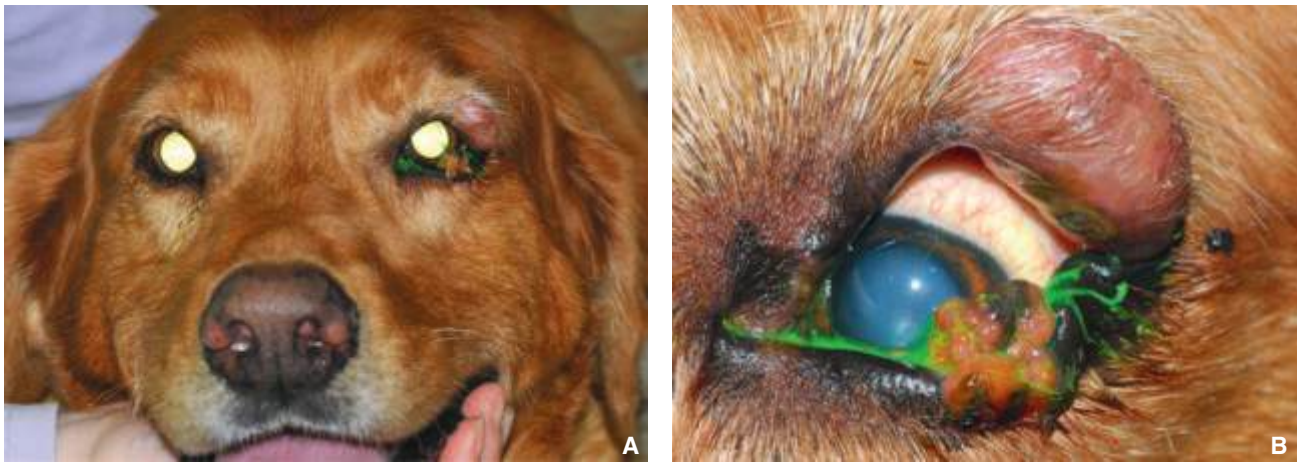


Figure 13.54 **A**. A 12-year-old Golden Retriever with upper and lower eyelid masses of the left palpebrae. **B**. Close-up of left eye. The smooth upper eyelid mass involving approximately 50% of the upper eyelid can be readily distinguished from the multilobulated pink to partially pigmented mass affecting the central and lateral aspect of the inferior palpebra, extending into and involving the lateral canthus.

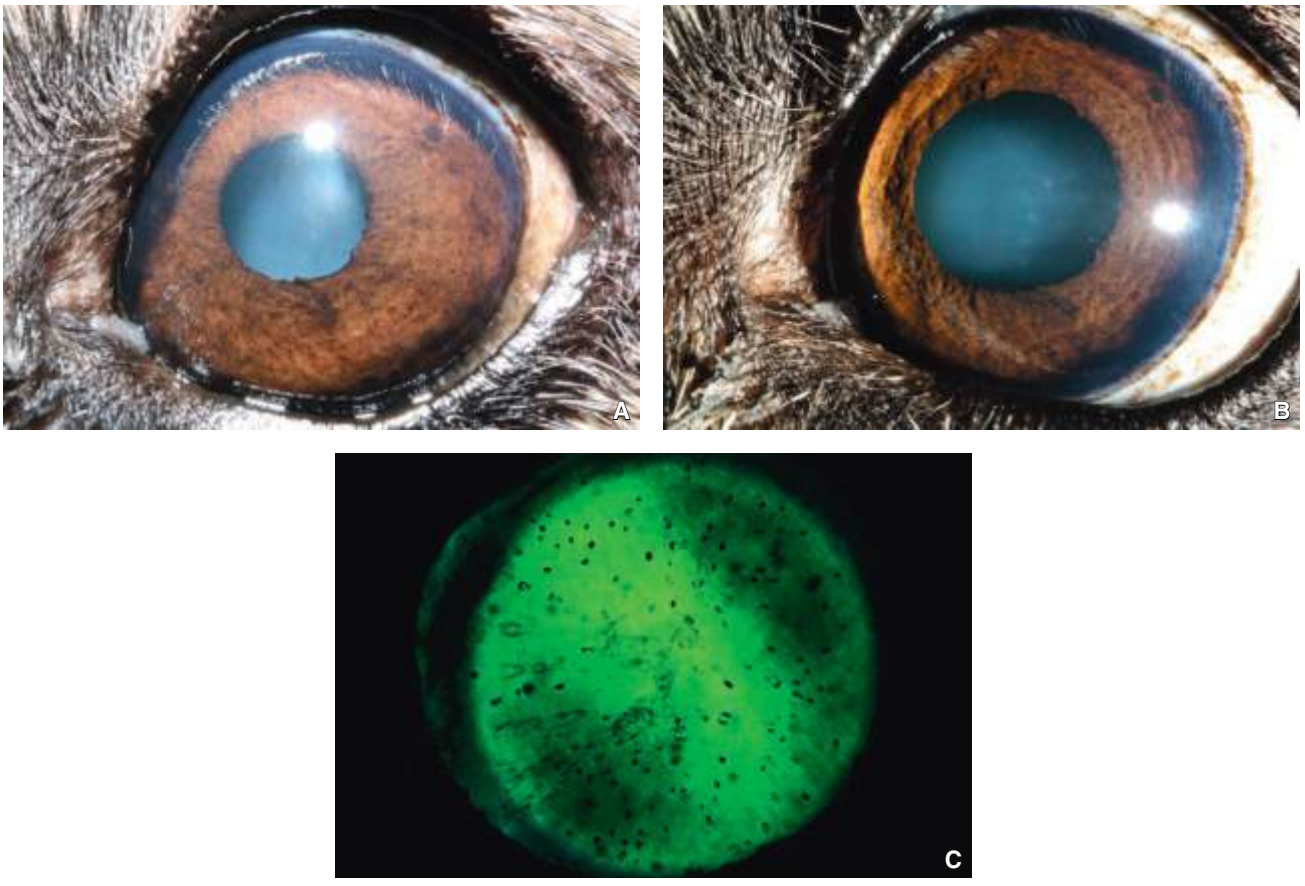


Figure 13.55 Images obtained from the same patient demonstrating the effects of different lighting techniques. While the following series illustrates changes involving the lens, similar effects are noted with corneal lesions as well: frontal lighting (**A**), side lighting (**B**), and retro illumination (**C**). Note in (**A**) the lack of detail, marked flash artifact, and poor illustration of regions of interest (e.g., cataracts). Using side lighting (**B**), displacement of the flash artifact and the direction of light allow for improved visualization and depth. In (**C**), improved visualization and illustration of more subtle details are clear.

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lighting techniques, illustrating their primary effects. To capture a sharply focused image of a corneal surface lesion, ensure that the first Purkinje–Sanson image (reflection from precorneal tear film or corneal epithelial surface) is in focus. The source of the Purkinje–Sanson image may originate from incidental light, a handheld light source, or the focusing light emitted by the camera. It is generally helpful to turn off any overhead lights when photographing an animal's eyes, as this will eliminate unwanted reflections in the cornea. A clear, healthy cornea has an extremely reflective surface. Overhead or natural light shining onto the cornea results in the reflection of surrounding objects appearing on the corneal surface of the final image (Fig. 13.56). White objects will reflect strongly from the corneal surface, and a conscious effort must be made to prevent capturing the reflection from the slit lamp or bystanders wearing light-colored clothes in the final image (see Fig. 13.44).

As discussed, imaging the cornea typically involves a magnification ratio of 1:1 or above (Gutner, 1977; Olsen, 1979). At these magnifications, DOF is limited and may be compensated to some extent by reducing the aperture size (e.g., increasing f-number). However, as the magnification of the image increases, so does the magnification of any movement. This movement may be on the part of the photographer and/or the patient. As such, some general guidelines should be employed in an effect to maintain a sharp image and minimize motion artifacts. First, always ensure that you, as the photographer, are stable. This may require leaning on the examination table or wall to prevent body movements or hand tremors. Second, proper animal restraint is important; while preventing ocular movement is not often possible, limiting head movement can be of great benefit. Last and generally speaking, the shutter speed should be no slower than the focal length of the lens being used. This is true while working at low magnifications and becomes of increasing consideration at high magnifications. Another artifact, in addition to motion artifact, is specular reflections involving the cornea, some of which may obscure regions of interest. These reflections (e.g., flash artifact) simply demonstrate the ability of the cornea to act like a convex mirror. As such, it is important to pay particular attention to the location of the flash (and subsequent artifact), as simply relocating its position may largely reduce these reflections. Similarly, it is important to instruct the person restraining not to peer over the animal's head, since reflections of this individual's face (or anyone in close proximity) may be reflected in the cornea. These reflections, however, can largely be eliminated through the use of specialized equipment and/or cross-polarization (Fariza et al., 1989; Pirie & Pizzirani, 2011a; Shun-Shin et al., 1992), the latter being a relatively simple technique that utilizes two linear polarizers, one over the light source (e.g., flash unit) and the other over the camera lens, as demonstrated in Figure 13.57. It should be pointed out that while specular reflections often obscure details of interest, they may serve some purpose in the determination of refractive indices, measurement of binocular misalignment, and corneal diameter (Howland, 1980; Quick & Boothe, 1992; Robinson et al., 1989).



Figure 13.56 This image was taken of a horse's left eye in an open stall. The blue sky, with clouds as well as surrounding pine trees, can be seen within the pupil. Additionally, there is a very bright flash artifact on the cornea, over the temporal iris. Due to the amount of incidental light, the lashes and vibrissae also cast their reflection onto the cornea. (Courtesy of Erin Matheson-Barr.)

Anterior Uveal (Iris) Lesions

The iris is a unique structure within the eye, in that it is a well-textured surface in an array of colors (Fig. 13.58). Typical magnifications required to image the iris are comparable to those for the cornea and include magnification ratios of 1:1 and above. Recall, however, that DOF is significantly reduced at these magnifications. This creates an additional challenge when imaging the iris, due to its normal convex profile. Therefore, to ensure proper focus within the final image, it is imperative to ensure correct alignment of the camera lens to the iris plane. When composing the final image, the iris should fill the frame within the viewfinder, placing the pupil centrally. The final image obtained should provide the viewer with an overall representation of the lesion as it pertains to the iris itself, and any surrounding tissue(s). Higher magnification, focusing on the lesion of interest, may then be obtained to provide greater pathologic detail.

The iris is best illuminated using either side lighting (tangential lighting) and/or retro illumination techniques. As previously discussed, side lighting creates sharp-edged shadows, improving on textural detail and depth perception within the final image. This method of illumination is particularly useful when demonstrating topographic changes

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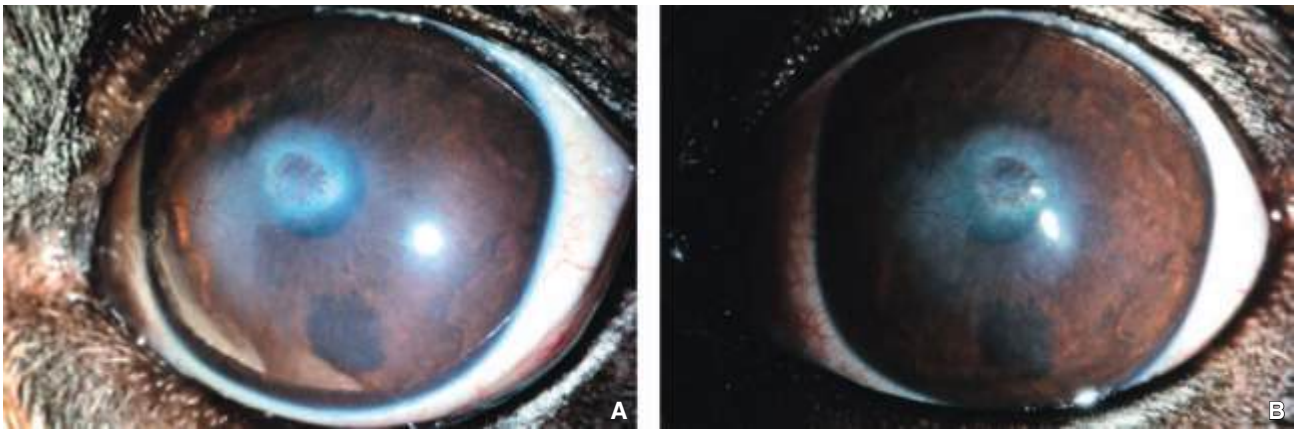


Figure 13.57 Images obtained from the same patient demonstrating the effects of nonpolarized (**A**) and polarized lighting (**B**). Note the improved detail within (**B**) due to a significant reduction of corneal specular reflections (e.g., no reflection of palpebral conjunctiva, reduced flash artifact, etc.).

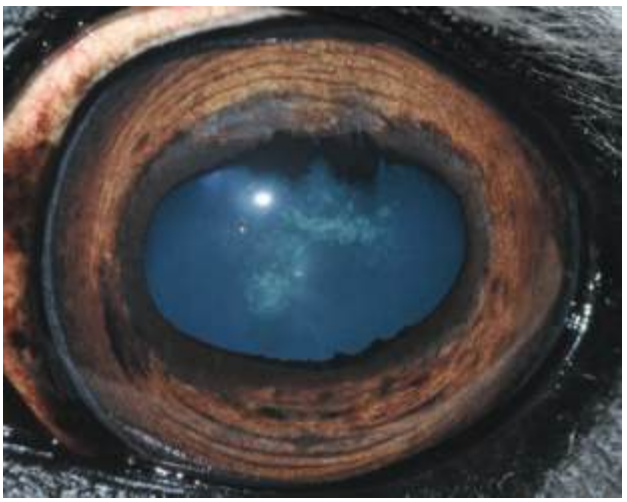


Figure 13.58 Conventional image of a horse's iris with adjusted camera settings (f/13; 1/160 second; ISO 640) to better visualize the details of this darkly pigmented tissue using an external flash.

(e.g., raised anterior uveal melanoma), and also allows visualization of the anterior chamber and surface of the iris through an opaque cornea (Fig. 13.59). Although the specific location of the light source will vary based on the location of the lesion, it is important to pay attention to specular reflections generated on the corneal surface, as these may obscure regions of interest. An external, handheld light source used to illuminate the globe from the side generally requires a slower shutter speed and larger aperture to ensure adequate illumination of the subject (Fig. 13.60). Alternatively, camera settings routinely utilized for photographing the anterior iris (i.e., f/16 and 1/250 exposure) are selected, while an off-camera flash positioned nasally or temporally from the globe provides the appropriate illumination to capture a similar image (Fig. 13.61).

Retro illumination may be useful instead, relying on light reflecting from the fundus (e.g., tapetum). While not a transparent tissue, this illumination technique may demonstrate both structural and pathologic abnormalities of the anterior uvea

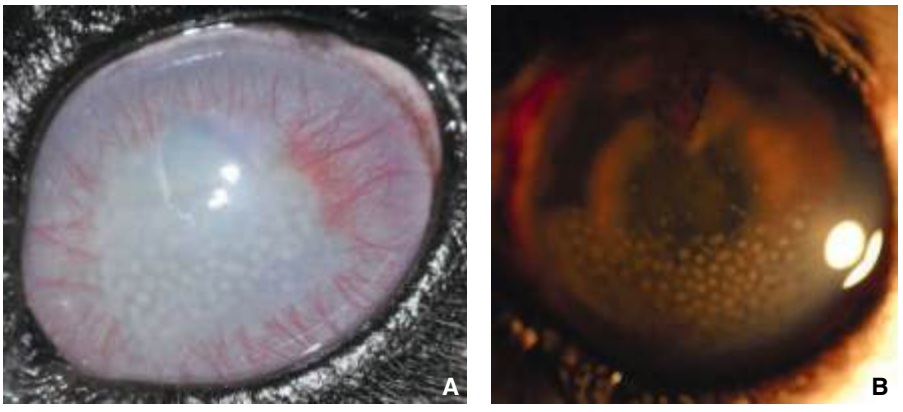


Figure 13.59 **A**. This image was taken using an external flash, an aperture setting of f/20, and a shutter speed of 1/200 second. **B**. This image of the same eye was taken without a flash and with the aperture set to f/5.6 and the shutter speed reduced to 1/200 second. Tangential illumination allowed for direct visualization into the anterior chamber.

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Figure 13.60 A Finoff transilluminator is shown providing tangential illumination as the sole source of lighting in this canine patient. (Courtesy of Silas Zee, Auburn University.)



Figure 13.61 Tangential lighting is provided with an off-camera flash held temporally to this horse's eye. This technique is useful in highlighting changes on the surface of the iris. (Courtesy of NC State University.)



Figure 13.62 Retro illumination image of the left eye of a 14-year-old Paint Horse gelding. The red fundic reflex is due to the lack of tapetum and pigment in the retinal pigmented epithelium. The areas of increased transparency within the iris are due to a lack of iridal pigment (heterochromia irides) and subsequent iris atrophy. The dark curvilinear band that is visible midway between the ventral edge of the pupil and the lower eyelid margin represents the ventral aspect of the lens. This structure is not normally visible.

(Fig. 13.62). It requires some considerations, including the position of the light source and pupil size. For light to pass first through the pupil and onto the reflective surface (e.g., fundus), it must be positioned as close to the camera lens as possible (or be coaxial to it). Furthermore, the pupil must be of sufficient size to allow enough light to pass. While pupillary dilation allows a greater amount of light to be transmitted, less iris tissue is visualized due to peripheral displacement. As such, the preferred time to conduct this imaging technique is shortly after the instillation of a dilating agent, prior to its maximum effect. This provides a balance between the pupil size and degree of iridal tissue still visualized and thus capable of being retro illuminated. Additional imaging techniques may rely on altering the illumination source and/or use of special filters (e.g., red free; Fig. 13.63). Furthermore, advanced imaging techniques, such as fluorescein angiography, may be conducted to assess the iris vasculature (Fig. 13.64; Alario et al., 2012).

Lens Lesions

The lens is normally a biconvex transparent structure located behind the anterior uvea. Under various disease states, alteration in its transparency and/or position may occur and can

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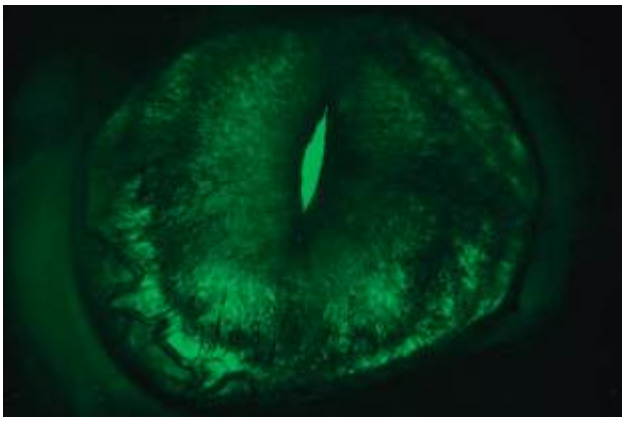


Figure 13.63 Red-free image of the feline iris.

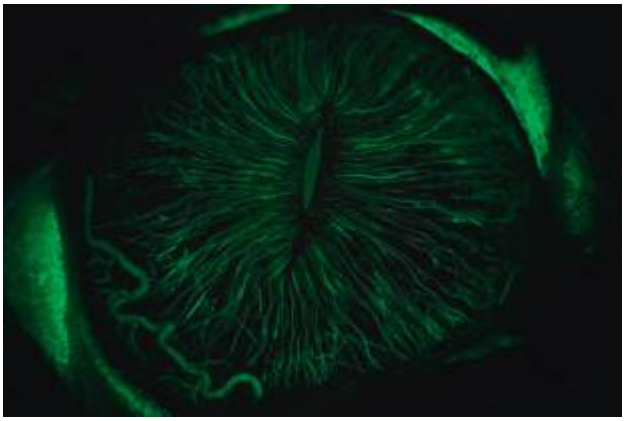


Figure 13.64 Image demonstrating anterior segment fluorescein angiography of the feline iris (same eye as Fig. 13.63) during the early venous phase. Note the clear visualization of the major arterial circle, iris arterioles, and venules.

be documented photographically. This may be performed utilizing either direct and/or retro illumination techniques. Direct illumination may be conducted using either front or side lighting, with the latter being preferred. Utilizing this method of illumination, light is either refracted or scattered within the lens. The former often results in the overall bluish appearance typically seen with nuclear sclerosis, while the latter causes opacities (e.g., cataracts) to appear white. Retro illumination, on the other hand, is not subject to refraction, only obstruction, and results in lenticular opacities appearing dark/black (depending on the density of the lesion). This method of illumination provides improved visualization of subtle changes in lens transparency (Fig. 13.65).

Magnifications typically employed to image the lens are comparable to those required for both the cornea and the iris. However, due to its biconvex nature, only a small plane of focus is maintained within the final image. As such, it is imperative to maximize the DOF (e.g., smaller apertures) where possible. Of final note is that when specifically imaging

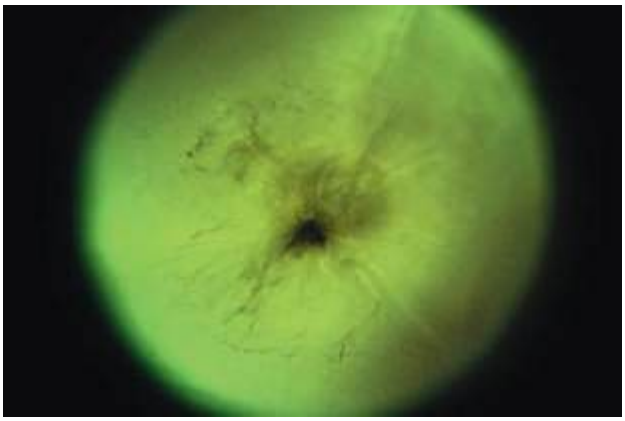


Figure 13.65 Image of a posterior cortical cataract in a dog via retro illumination. Note the subtle detail and improved visualization of lens involvement obtainable using retro illumination.

the lens, maximum pupillary dilation (unless contraindicated) is recommended. This will limit any masking effect by the anterior uvea and improve the photographer's ability to retro illuminate the lens.

Retinal Lesions

Imaging of the retina typically relies on the use of a devoted fundus camera; however, newer alternatives are becoming increasingly available (Chalam et al., 2009; Guyomard et al., 2008; Pirie & Pizzirani, 2011a). Conventional fundus cameras are based on the principle of reflex-free indirect ophthalmoscopy (Gullstand, 1910). Magnifications and fields of view that may be obtained are dependent on the imaging system and may range from 2× (low magnification) to 5× (high magnification; Allen, 1964). Some units are fixed and do not allow for any such variation. Similarly, flash settings available will vary depending on the power of the flash unit within the system. As such, it is important to review the manual of the system being used to ensure a clear understanding of these parameters.

Prior to attempting to image the posterior segment, it is important to ensure the fundus camera has been correctly focused for the photographer. This procedure is like that required for use of a slit lamp and relies on the presence of crosshairs/lines within the objective of the camera. Once proper focus of the camera has been obtained, the photographer is now ready to image the posterior segment. If utilizing a portable unit, this process involves axial movement of the system toward the patient until proper focus of the retina has been obtained, a technique like direct ophthalmoscopy. Fine-tuning using the dioptric adjustment on the unit may be required due to the refractive error of the patient. Alternatively, because of the inherent shallow DOF provided by these units, changing the plane of focus may be needed depending on the lesion of interest.

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The final image obtained should ideally be sharply focused, evenly illuminated, and deeply saturated in color (Leutwein & Littmann, 1980). While these imaging systems can obtain high-quality images, it is important to acknowledge that the globe itself plays a vital role in the quality of the final result. As such, any alteration in the normal transparency of the cornea, lens, and/or vitreous may significantly reduce image quality. The final image should provide an overall representation of the lesion(s) of interest and include the optic nerve head as a point of reference (Nicholl, 1985). If illustrating changes in topography (e.g., swollen optic nerve head), it is common practice to obtain the initial image(s) at the most elevated surface within the field, followed by a series of images altering the depth of field as needed. Additional photos, varying the field of view and/or magnification, may then be obtained. Several techniques have been recommended whereby a series of standardized overlapping images are obtained to describe fundus abnormalities (Diabetic Retinopathy Study, 1981). Furthermore, with the use of a digital-based imaging system, these standardized approaches may allow for the creation of collages via several imaging software programs (Hackel & Saine, 2005; Mahurkar et al., 1996; Fig. 13.66).

Common artifacts that may be noted in the final image of the fundus generally relate to incorrect axial positioning of the camera and/or misalignment. If the camera is too close to the eye, a bright bluish-white reflection will occur within the center of the image (Fig. 13.67). If the camera is too far away, the image obtained will be poorly saturated and contain a bluish-gray ring around its periphery. If the camera is misaligned, an orange crescent will result within the final image. Correction of this artifact requires movement of the camera in the opposite direction from the side of the crescent (Justice, 1982).

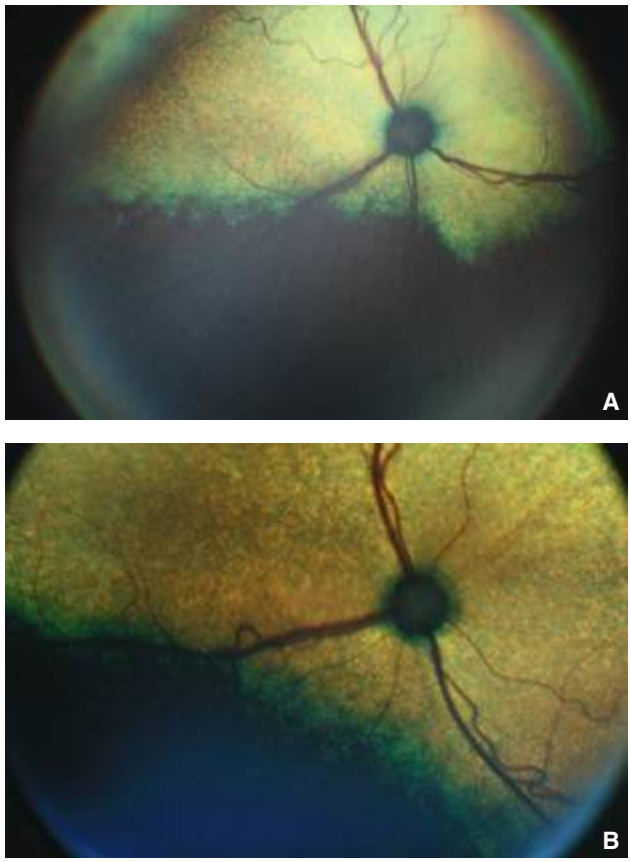


Figure 13.67 Fundus images demonstrating the effects of improper positioning. Imaging system too close (**A**) and too far (**B**) from the patient.

Image Capture, Storage, Archiving, and Retrieval

Digital Darkroom

The cataloguing, processing, and output of images in a digital environment require various considerations relating to the computer system chosen. Most image cataloguing and editing applications are best used on computers with a fast-central processing unit (multicore processors) and large amounts of high-quality random-access memory (RAM). High-quality graphics cards are recommended for image processing applications.

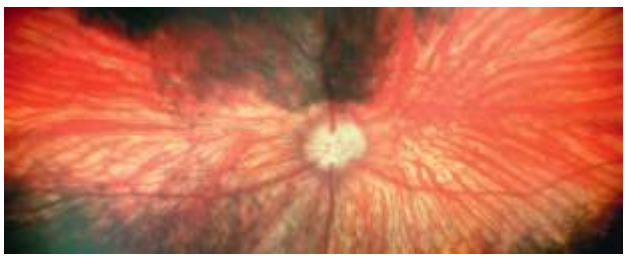


Figure 13.66 Fundus montage of a heterochromic canine eye. This image was generated from a series of five images and blended using Adobe Photoshop CS4.

Hard drives need to be of high capacity and have speeds of 7200 rpm or more. Internal connections with serial advanced technology attachment (SATA) provide fast processing, although these may be replaced by faster serial-attached (SAS) small computer system interface (SCSI) drives. In the future, we may expect to see more use of solid-state drives (SSDs) for the operating system and applications in desktop computers, with data (including image) storage on other (SATA or SAS) internal and/or external hard drives. External hard drives used for accessing imaging collections should at least aim to use eSATA or USB 3 connections for speed of access.

For imaging processing on laptops or connecting to multiple computers, external hard drives can be used and should have eSATA or USB 3 connections. Laptops with SSDs are fast enough for the cataloguing/editing software, although the actual image collection (which may become large) is

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better housed on an external hard drive. Laptops should ideally have two external hard drives connected so that images can be mirrored on both drives in case of drive failure.

A high-quality monitor (or monitors) is required, generally light-emitting diode (LED) backlit with at least 12 bit color depth and internal calibration ability. A monitor profiler (X-Rite i1Display Pro, www.xrite.com, or Data Color S5P100 Spyder 5PRO Elite, spyder.datacolor.com) can be used to ensure that the colors seen on the monitor are as close to reality as possible.

File Types

For most veterinary ophthalmologists, the easiest and most easily managed files are JPEG – these have the advantage of a relatively small file size and yet adequate quality (data retention) for storage in medical records, publications, or use in slideshow presentations. This is a lossy format (data are discarded at the time the photograph is taken), and the downside to the format occurs if you plan further pixel editing (e.g., in Photoshop), which will further degrade the image. If any editing is done on virtual images in parametric image editing applications (e.g., Lightroom), this is not an issue since the imported master images are not "damaged" in the editing process (and all edits are easily reversible).

If you plan on creative editing with images, some form of RAW file format would be preferable for capture in the camera – for Canon files, the file name ends with .CR2, and for Nikon, .NEF. These files are ideal if you intend to open the files in Photoshop (which requires conversion in Photoshop or Lightroom to a PSD or TIFF format) and to make significant adjustments. These RAW files have the disadvantage of being large and consuming a lot of space on a hard drive. The other concern is that these formats are proprietary to particular companies and potentially might change or not be supported in the future. Regardless, if you want the best data that the camera can capture, use RAW files and convert or view in Lightroom. If file size and hard drive space are a concern and you are more interested in a convenient image of a case that can be stored with a patient record, printed, used in slide presentations, or uploaded to a web album, JPEGs are quite adequate.

One additional alternative to the proprietary RAW file formats is the Adobe DNG (digital negative) file type. This is comparable to the basic RAW file, but is an open source format and is thus less susceptible to individual camera company vagaries and more likely to be supported in the future. It offers the benefits of a RAW file, but with more peace of mind for the future. One option is to take photographs in both RAW and JPEG formats in the camera, storing them on the CompactFlash (CF) or Secure Digital (SD) card, and then to back up the RAW files to archival optical media (DVD discs) and import into Lightroom as DNG files. DNG files are optimal for use in the Adobe applications Bridge and Lightroom.

In summary, for most uses in ophthalmology (patient files, PowerPoint, storage), the highest-quality JPEGs are adequate. To use in publications where submission to a publisher or journal is involved, the best options are TIFFs, portable network graphics (PNG) files, or high-quality JPEGs. If you plan to use the images for creative or artistic purposes, RAW files are recommended. These can be backed up to retain a master copy of the original data, and a second set can be converted to DNG for any further processing in an editing process. If in doubt about how images may eventually be used, it is best to capture them as RAW files. Many cameras now enable each image to be recorded as both RAW and JPEG files.

File Naming Conventions

Maintain the original file name as part of any conversion. This is most important when you capture the image in more than one format (RAW and JPEG), or if you keep master copies (RAW) but also make DNG copies for use in the cataloguing database (you may even end up with RAW + DNG + JPEG copies of your images). If the original file name is always maintained, it is possible to revert to the original RAW file if needed (if the JPEGs are lost or corrupted, for instance). So, a RAW Canon image file imported as MG_5409.cr2 might be changed to Smith_Freddy_10687_MG_5409.DNG or .CR2 or converted to Smith_Freddy_10687_MG_5409.JPG (case name/hospital case number/original file name/number/file format).

Professional media photographers often catalogue based on the date the photo was taken. For instance, vacation shots might be catalogued by year_month_location: 2012_1_Naples_Carnival. The date has less value for ophthalmology file naming, since that information can be recorded as part of the metadata in the cataloguing software. Of more importance in locating images are the patient's name and hospital case number. For all other aspects of file identification, one can rely on the metadata. It rarely makes sense to include the diagnosis in the file name, since that is more than adequately covered in the keyword tag applied to the photographs. In fact, the information contained in metadata is so complete that one could dispense with any change in file name at import and simply include all of the patient information in the metadata. The disadvantage to this approach, however, is that you end up with a very bloated set of keywords, which includes patient name and reference numbers that may only ever be applied to a single small group of patient photos.

Image Cataloguing and Organization: Digital Asset Management

Digital imaging allows a photographer to capture a large number of photographs easily and inexpensively (compared to film). Just as with film imaging, it is possible to end up with a large image collection, but then to have little time to be

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able to organize and easily locate specific photos in the future. The approach taken to organizing and retrieving images will depend on how the images will be used. The process has been referred to as digital asset management (DAM).

One option is to store the image collection on one hard drive (hopefully with at least a second drive as a backup copy) in a folder arrangement accessible via a browser application such as Windows Explorer, Mac Finder, or Adobe Bridge. Folders for an ophthalmology collection might cover species, anatomic parts of the eye, and disease processes, with file naming based on the patient name with or without the ocular condition. This would allow the database to be searched by a browser based on the file or folder name criteria. However, this can be limiting when it comes to locating particular images.

Adobe Bridge works well to connect different types of files in the various applications found in the Adobe Creative suite. These might be graphics, website design, and photography, audio, and video applications. These can all be browsed in Bridge, which supports many more file types than the parametric image editing (PIE) applications. In any network situation where multiple users might need to access the same files for particular projects, Bridge works very well. Lightroom can only be accessed by one user at a time (catalogues cannot presently be used on a network).

PIE applications such as Lightroom are better organization applications than Bridge for photographers, because they allow you to do all the things that you need to within the DAM application. However, if you use other applications for multimedia presentations (e.g., website design in Adobe Dreamweaver, illustration in Adobe Illustrator), you might *also* access images from within Bridge to integrate them into the file formats of these other applications. Bridge is included with purchases of Adobe Photoshop.

In the clinical setting, it may be adequate to import images into whichever practice management and electronic medical record (EMR) software is used. This will attach images to patient files and visits, which is ideal to be able to follow the progression of an ophthalmic case photographically. In most practice management software applications, it is possible to tag or keyword images to facilitate retrieval of conditions later. Image editing is less often supported in practice management software, partly because of the need to preserve the original data and avoid issues of falsification where a record could be unethically changed. This issue is complicated by differences in both human and veterinary medicine and the country where the patient lives. Veterinary medicine in the United States follows the human Health Insurance Portability and Accountability Act (HIPAA) guidelines, which specify privacy and accuracy requirements for medical records. Any editing of images should take place outside the medical record itself to avoid the charge of record falsification.

One approach to image organization, retrieval, and backup in the clinical setting is to store images in both the practice management software and in a separate DAM application with more extensive organizational and editing features. This allows for not only easy access in the clinic when reviewing cases, but also considerable flexibility for the use of images in other software applications.

When the photograph is taken, it should be added to the dated visit for the patient in the medical record; this may simply require that the image is printed for inclusion in a paper medical record or preferably appended as a JPEG to the patient/visit in an EMR. Concurrently, the image can be copied to at least one other separate hard drive (and preferably two for an extra backup) for access by one of the cataloguing applications discussed here. The images accessed or referenced by the cataloguing application are then available for editing, grouping by disease process by tagging or keywording, and output for use in publications, presentations, or online, within the guidelines for the ethical use of medical images (see later in this chapter).

DAM applications have various common features. Most notable is the concept that the actual image files and the application files are separate entities. There is a catalogue or library folder of files with information about the images that is separate from the image files themselves. Changes to the information (which can include any editing of the images) happen in the catalogue/library files and reference the image files, but do not change the image file data.

Image capture or taking the photograph is obviously the first step. The actual processing on images also begins in the camera with the proprietary programs built in. These will take the digital data and store it in a format that is specific to the camera and manufacturer (the RAW data file). The camera software may also (depending on the file acquisition settings chosen) process the raw data and store the image in a format that can be read by most software applications (JPEG). At the time an image is taken, it is essential to identify and record the subject in some way. A simple approach is to photograph the patient information/case number from the physical, paper record as the first photograph in the sequence pertaining to the case.

Some DAM applications (including Lightroom) enable the simultaneous capture of images to the camera and a computer or laptop. This can be achieved with either a wired (usually USB) or wireless connection between the camera and computer (which depends on the camera). This is useful for macrophotography, where it is often difficult to assess focus on the small LCD screen on the camera, and removes the additional step of taking photographs and having to download the images to the computer later (Fig. 13.68). Tethered capture starts the image organization process the moment the photograph is taken, and avoids the accumulation of disorganized images that is commonly seen with digital photograph collections. Ideally with tethered capture the file naming is established, keywords assigned, and a destination folder specified in the catalogue before the images are

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Figure 13.68 Tethered capture setup. Camera is connected via USB or wirelessly to laptop computer with Lightroom and catalogue files installed on the internal hard drive. Images are directly transferred as acquired to a folder on one external hard drive. The second hard drive backs up both the internal drive Lightroom catalogue and the images on the first external drive.

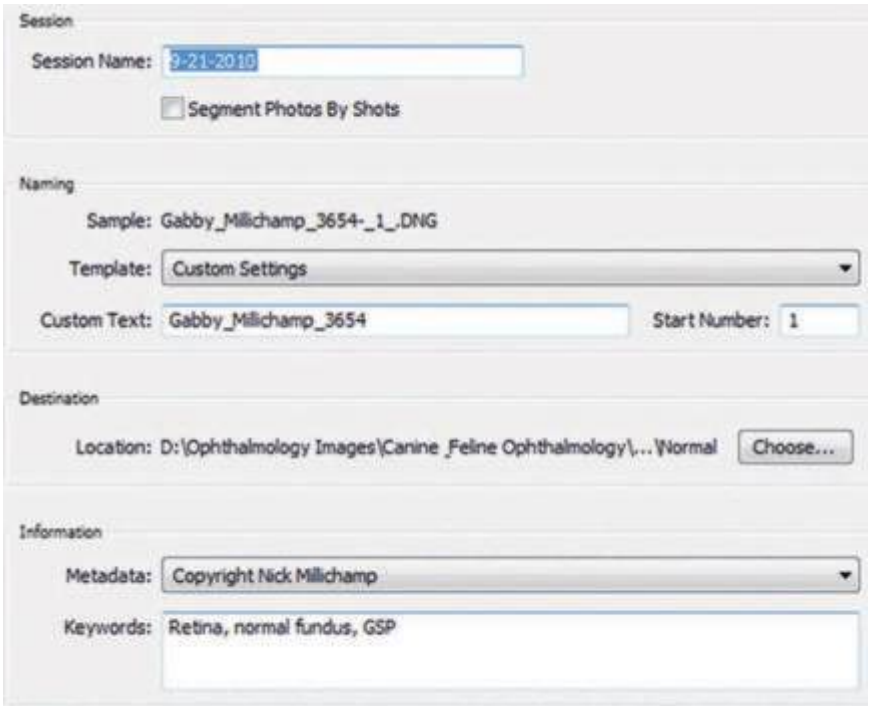


Figure 13.69 Tethered capture settings in Lightroom. Files can be renamed, have metadata applied, and be imported to a folder on the hard drive. (Adobe product screen shot reprinted with permission from Adobe Systems Incorporated.)

taken; each is identified by a file name with an appended sequence number as they are imported (Fig. 13.69).

Importing images into the catalogue/library database happens either as the photograph is taken via tethered capture, or later when image files are copied from the camera to a computer hard drive. In either case, the term "import" implies that the image is copied to a location of your choosing on the hard drive and an entry generated in the DAM database that references the master image file. The image *per se* is not "in the database," although, depending on the

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application, the "master" image may be stored within the application file (for instance, as a managed image in Aperture) or anywhere else on the hard drive (a referenced image in Aperture).

The proprietary camera file names (for instance DSC or MG on Nikon or Canon cameras, respectively) are changed to something meaningful for your cataloguing system. Metadata (information about the image) are added. Metadata include keywords to facilitate retrieval and organization by subject, copyright information, and ways to group or rate images by color coding or on a numeric scale. At the same time, files can be copied or rearranged into whatever organizational arrangement (for instance, by anatomic location or disease process) is preferred. For the DAM application to keep track of the individual images, it is essential that any rearrangement of the image files on the hard drive be done from within the DAM software.

Although it is best to rename files and add metadata when images are copied from the camera to the hard drive and imported to the DAM catalogue, this may not always be practical. If images from many different cases are imported at the same time, making changes to filenames and assigning keywords at that time does not easily work, since the information will be different for the groups of images pertaining to each case. In this instance, use the DAM software to copy to a folder identified by the date on which the images were taken and import all images to the catalogue/library. Later, these images can be keyworded and moved to a more logical folder-based organizational structure (based on species/location of lesion/specific disease).

Images can be backed up to another location (a separate external hard drive is a good option) at the time of transfer from the storage card in the camera, to protect against accidental loss from the card or primary image location directory. Again, ideally, if images can undergo renaming and addition of metadata *before* the initial backup, there is less chance of getting confused between the backup of the downloaded images and any subsequent backups of the archival images that will be accessed by the DAM software. For additional backup protection of images, a copy of the "virgin" (RAW and/or JPEG) files can be made directly from the camera to another hard drive or optical medium before any renaming is done.

Once images are in the cataloguing application, they can be quickly reviewed. Poor images (out of focus, poor DOF, severely over- or underexposed, or otherwise deemed inadequate) are rejected and deleted from the catalogue (and hard disk drive).

Organization of images within the catalogue can occur at import or later (or both), and this is easily done from within the DAM application (in fact, resist the temptation to do any organization from outside the DAM application). For instance, photographers might import initially into a folder system that is based on the date the image was taken and then organize into the folder system (species, anatomic location, disease process) later. Alternatively, images might be imported directly into a destination folder at import (or immediately when captured via tethering).

DAM applications use various systems for organizing images, including dated albums, tree or hierarchy-based lists of folders and albums, geotagged locations or places, and facial recognition (little used for ophthalmology libraries). Many applications utilize smart albums/collections, which automatically add images to albums or collections as they are imported based on predetermined criteria. For instance, all images keyworded with "iris atrophy" would automatically move into the "uveal diseases" or "iris atrophy" folder on import. Taking time to set up smart albums or collections can make it much faster to organize images into the relevant folder in the catalogue.

Metadata (and especially keywords) applied to every image in a catalogue or library enable numerous ways to retrieve images from within a collection. For instance, if every image is keyworded on import by breed and disease process and the better photographs are given a numeric rating as to quality, it becomes easy to search the catalogue for the best examples of breeds with specific diseases. Most cataloguing programs enable some degree of image editing. The extent of image editing in which you should engage is very much determined by the subsequent use of the image (see ethical considerations in image editing below). Editing may be very rudimentary – for instance, changes in brightness, fill light, contrast, color hue, and saturation (this is the case with programs such as Apple Photos) – or done in a program that allows for considerable control (such as Lightroom). Automated (manufacturer-embedded programming instructions) editing options are available in most programs, and although these quickly and easily change images, they are of limited value and often result in an edit that does not bring out the feature you may want to emphasize in the photograph.

The most important consideration here is that any image editing should be nondestructive (this excludes Adobe Photoshop, which makes changes to the actual pixels in the image). This means that the original image data are left untouched and edits are simply written as separate files within the cataloguing program, which reference the original image. This is referred to as PIE. In some DAM applications, *copies* of the original images can be made before any image editing is applied (which is easily done in PIE applications). For instance, in Lightroom, virtual copies of images can be created for further editing, and then the edited images can be compared back to the original images.

After image organization and any further editing in the software, the files should again be backed up on a regular basis. This entails backup of both the original/archival image files and the catalogue index files (the files that refer to the original data, contain metadata and keywords or tags, and have instructions about image edits that have been applied).

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Most applications enable direct output as slideshows of images, the ability to print images within the program (or send online to a printing facility), reproduce images in slideshow applications such as PowerPoint or Keynote, publish images to web galleries, export images to other applications such as email, blogs, messaging, and telemedicine, and upload images to social networking sites.

Cataloguing, Image Organization, and Parametric Image Editing Software

Several DAM applications are available to catalogue and organize images. Applications such as Apple Photos and Google Photos are consumer products, whereas Adobe (Photoshop) Lightroom is intended for the more serious or professional photographer. The DAM application reviewed here is Lightroom, due to its popularity with professional photographers. Other DAM applications that have many of the same features are also mentioned to provide the spectrum from inexpensive but functional software up to the best applications available. Lightroom creates a database of small file size previews and metadata, which reference the master image files and may reside anywhere (on either a connected or a disconnected drive or even on a DVD).

Lightroom is a DAM and PIE database (referred to as a library or catalogue, respectively) which contain all the information about your images. The database (which can only be accessed by single users as no networking is available) stores the name, hard drive location, and all information (metadata, editing, all versions, and thumbnail previews of the master image).

File information is stored using the Extensible Metadata Platform (XMP) for all file formats supported by Lightroom (JPEG, TIFF, PSD, and DNG). XMP metadata are written into the files in the location where the images are stored. For RAW files, the data are written into "sidecar" files, which are associated with the individual RAW image files.

The application allows users to have multiple databases (for instance, to group images related to diagnosis, research project, species, breed), although only one can be in use at any one time. The program allows the master image files to be stored either within the program database or at any other location (files can even be referenced on a different hard drive or even other storage media). Nondestructive editing of images is possible (master files are never altered), and multiple versions of any image (for instance, with different edits applied to each) can exist in the database. With all the power of the most recent versions of this application, there is now little need to edit images in Photoshop (unless interested in creative and artistic use).

Adobe Photoshop Lightroom

Lightroom was originally a desktop application (it cannot be run on a network), but recently Adobe has moved to a subscription format for its photography applications. The Adobe Creative Cloud Photography Plan includes Lightroom for local use (now called Lightroom Classic CC) as well as a more recent addition of the cloud-based Lightroom CC (which is only compatible with more recent versions of Windows). Photoshop CC and Bridge are also included in the photography plan.

The two versions of Lightroom (Lightroom Classic and Lightroom CC) are different in several respects. Lightroom Classic is essentially the same version of the application that has been available for some years, but as part of the subscription undergoes periodic updates.

Lightroom Classic CC

Lightroom Classic CC is a versatile and powerful cataloguing and imaging application that can be used on either Mac or Windows platforms.

Lightroom initially was a cataloguing and organization application, but each version has added more parametric image editing features. In the latest versions the editing options are powerful enough to be sufficient for most photographers without the need to further edit images in Photoshop. Some features present in Photoshop are currently absent in Lightroom (for instance, the ability to use layers when compositing and editing images).

Lightroom is designed to follow the photographer's workflow using modules (*Library* for image importation cataloguing and organization, *Develop* for advanced image editing, *Map* for image geotagging, *Book* for publishing images, *Slideshow* to allow grouping and presentation of images in a slideshow format, *Print* to set up printing options, and *Web* where images are grouped and published as web albums (Fig. 13.70).

The interface is divided into a central pane (2 in Fig. 13.70), which can either show a grid of photograph previews or enlarged views of individual or groups of images for examination and editing, two side panels (1 and 3), the content of which changes depending on the module in use, and a filmstrip at the bottom of the interface (4), which allows selection of the images to be worked on in any of the modules. The side panels contain information about the images (keywords, camera, and capture data) and commands to perform functions in the different modules as you progress through the workflow (for instance, editing changes in the Develop module; Fig. 13.71). The left side panel (1) is for navigation in Lightroom Classic (based on the existing folder structure). The right side panel (3) contains information about a highlighted image (histogram, metadata including keywords) and image editing options (either quick develop in the Library module for basic editing or the more comprehensive editing options of the Develop module). The menu bar at the top of the interface (5) has the modules, which follow a typical workflow from left to right.

In the Library module, the navigation panel on the left allows the user to see the organizational structure of the library in a folder format (as might already exist on the hard

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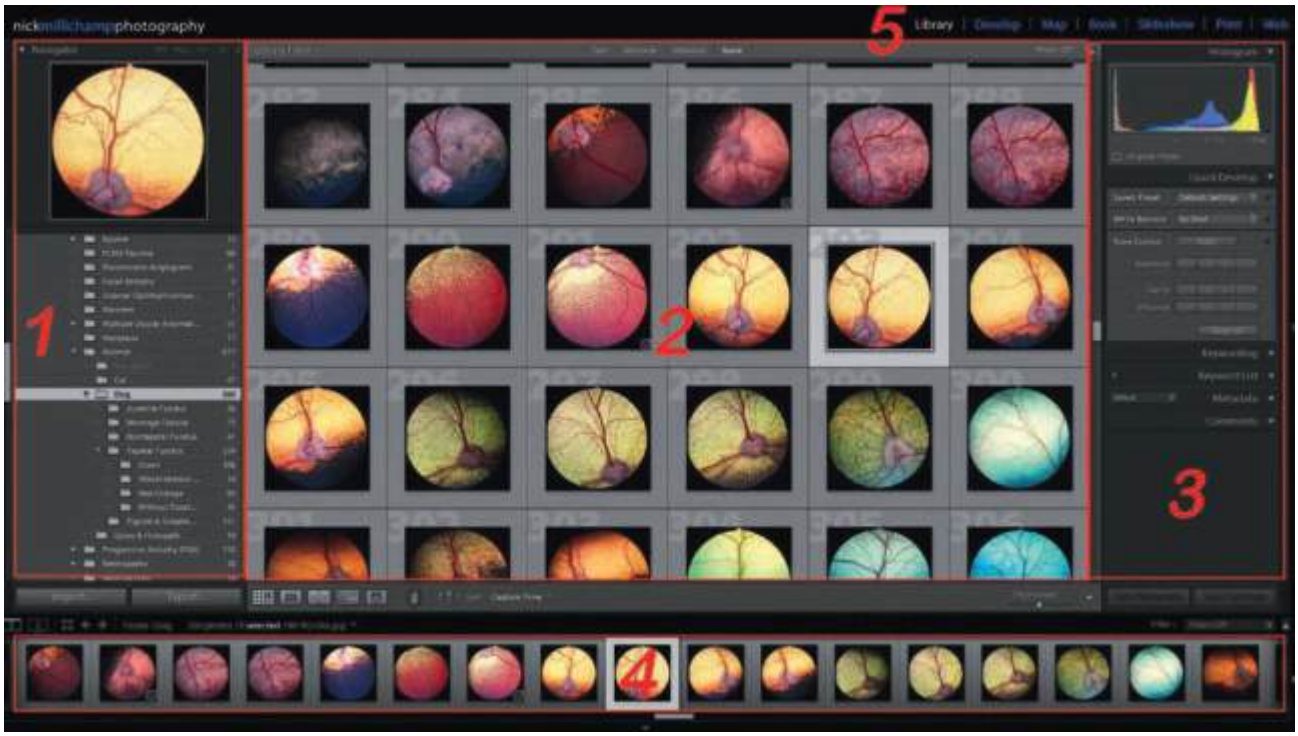


Figure 13.70 Lightroom interface. The areas of the interface (1–5) are described in the text. (Adobe product screen shots reprinted with permission from Adobe Systems Incorporated.)



Figure 13.71 In Lightroom Classic CC, images follow a photographic workflow through modules to organize, modify, and output to print, slideshow, or the web. (Adobe product screen shots reprinted with permission from Adobe Systems Incorporated.)

drive; Fig. 13.72). Images could all be in a single large folder if preferred, and can still be found utilizing the powerful metadata search options in the application. Most users will probably adopt a folder format, particularly if importing images into the database from previous organizational structures based on folders (in which case the actual location of the drive does not change). An advantage of Lightroom is that it is possible to move images and folders within the application and change their location on the hard drive and still have Lightroom keep track of the changes. Lightroom's reliance on accessing the actual location of the image file does, however, mean that moving image files from outside of the program (e.g., in Explorer) will cause problems with the database being able to find the moved image on the hard drive. In other words, all rearranging of image files on the hard drive should be done inside Lightroom.

Importation of images in Lightroom can occur from existing locations on an internal or external hard drive, from a memory card in a digital camera, or directly as the photograph is taken (in tethered or wireless mode). The importation process occurs in the Library module. Options allow for copying of images to a specific location on the internal or external hard drive. Images already on the hard drive in a folder structure can simply be added to the Lightroom catalogue at their present location in the existing folder-based organization (Fig. 13.73).

Images can be imported as RAW (NEF or CR2), JPEG, TIFF, PSD (native Photoshop format), or even CMYK. At import, images can optionally be converted to DNG files. Alternatively, RAW images can be viewed and processed in the Develop module (which is essentially the Adobe Camera Raw application). After an initial backup of the virgin files from the camera in RAW or JPEG format, conversion of RAW files to DNG in Lightroom is a good option to consider (smaller files, embedded metadata, file verification).

In the large center pane (2 in Fig. 13.70), all images in a folder or collection can be viewed in a grid, or individual images can be enlarged in loupe view (single image on screen) or arranged in pairs or small groups for comparison when grading. The panels around the central pane can all be

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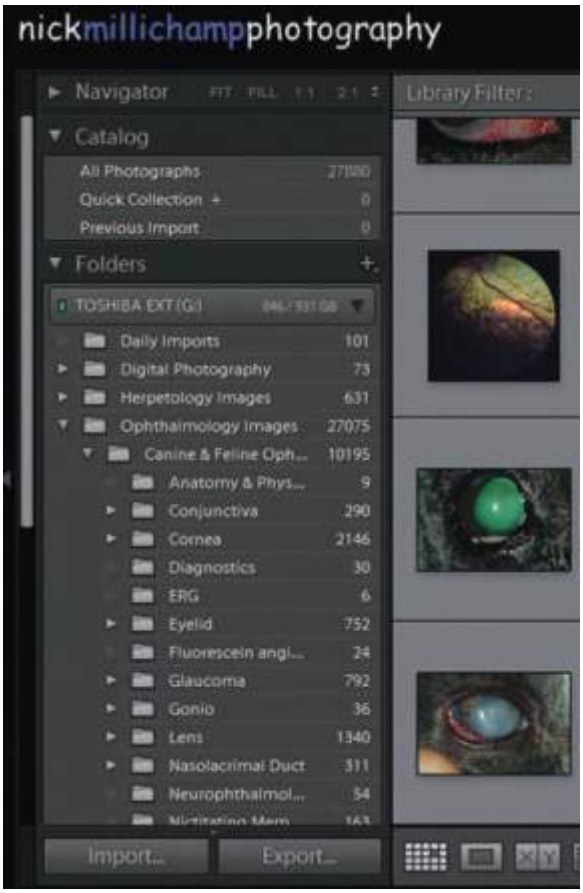


Figure 13.72 Lightroom Library Module – the navigation panel is where images are organized and rearranged in the catalogue and physically in folders on the hard drive. (Adobe product screen shot reprinted with permission from Adobe Systems Incorporated.)

viewed or hidden to show images in full-screen mode. At this stage, the images are either flagged as picks to keep or rejected from the catalogue (and hard drive if of poor quality), and then can be further ranked on a 1–5 star system or color coded into groups if so desired. Basic editing can also occur in the Library module, and this is often more than sufficient for most editing needs.

The power of applications such as Lightroom Classic lies in their ability to organize images in numerous ways and to be able to find images wherever they are located (hard drives, optical media, etc.) by tagging images with metadata. Some of the metadata (IPTC) is applied automatically in the camera when the photograph is taken, while other metadata (keywords, and preset information such as your copyright and contact information) is added either at the time of importation (best practice) or later when working on images in the library.

The keywording option in Lightroom Classic is the most powerful feature for a collection of ophthalmology images. It is possible to tag images by species, breed, age, sex, part of the eye, and type of disease process involved (or any other keyword combinations you choose). Groups of keywords (sets) likely to be used for particular diseases (e.g., a glaucoma set of keywords could include epistler injection, corneal edema, mydriasis, optic nerve cupping, lens luxation, etc.) speed up the process of applying groups of keywords to single files or groups of images. Using metadata tags in combination with renaming on import to identify by patient name and hospital case number allows for fast and easy retrieval of any image (Fig. 13.74).

Apart from the organization of images into folders within the catalogue, separate collections of images can also be generated from the master image files (the location of the master images is not altered, but rather "virtual" copies of the master images are created in the separate collections). Individual images (which can only reside in one folder) can be referenced in multiple collections. For instance, when putting together a talk requiring numerous images, the images can be put into a collection for temporary access while preparing the presentation without affecting their original location.

Smart collections can be populated by images based on predetermined metadata criteria. In this way, collections of images can be automatically generated as images are imported to the catalogue.

Lightroom's Develop module is the area where all detailed editing occurs. The editing capabilities of the Develop module are adequate for almost all the editing needs of the photographer, without the need to further edit in Photoshop or other pixel editing software. Various editing options are available using parametric nondestructive changes, and the histogram-oriented level adjustments, tone curves, and hue and saturation of the editing options offered here are well beyond the needs of the ophthalmic photographer (Fig. 13.75).

Versions of the images (virtual copies) can be created for editing and can be grouped into collections (e.g., all images of a particular topic might be selected and grouped into a collection for export and use in presentation or published to a web gallery to be shared). These "copies" are much smaller than the copies that would be generated in a nonparametric image editor (such as Photoshop), and therefore creating multiple virtual copies take up very little space on the hard drive. Apart from straight collections you create to house groups of images, the Library module also can contain user-generated "smart collections." These are automatically generated based on criteria you specify. For instance, you might set up a smart collection for iris melanoma – any image added to the catalogue that has iris and melanoma in the filename or keywords is automatically added to your smart collection. You choose the type of metadata to filter with (keywords, date image taken, camera used, aperture used, etc.), and then specify conditions for the metadata (e.g., all images with keyword phaco shot at aperture f/22). See Table 13.11.

Output options in Lightroom include the Slideshow, Web, and Print modules. Although the slideshow module is helpful in generating slideshows that will present a group of

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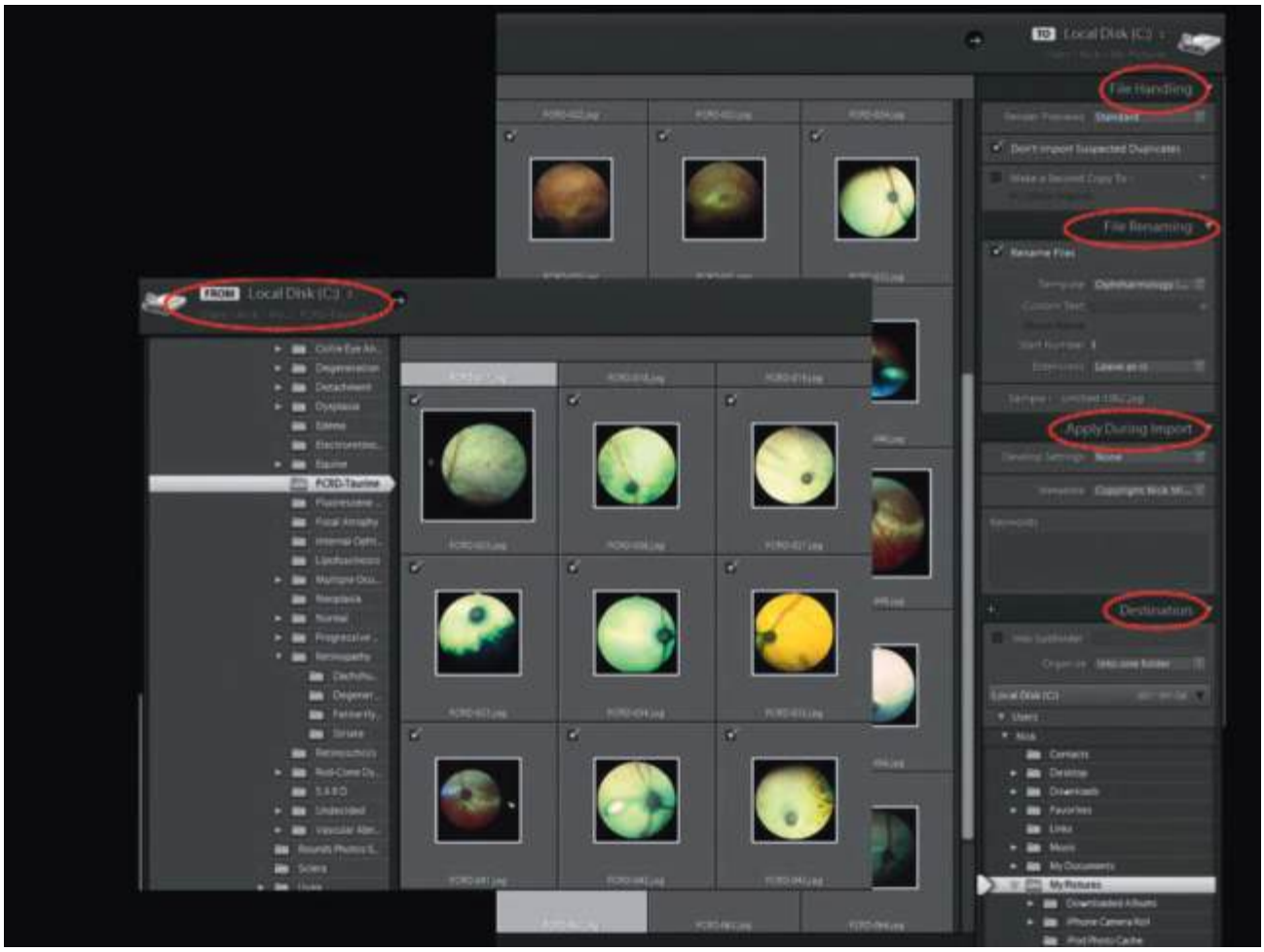


Figure 13.73 Lightroom images are imported (and copied) from a digital camera to the hard drive or can be added to the image catalogue without moving if already located on the hard drive. Images are renamed, tagged with metadata, and the location of the copied files is specified. (Adobe product screen shots reprinted with permission from Adobe Systems Incorporated.)

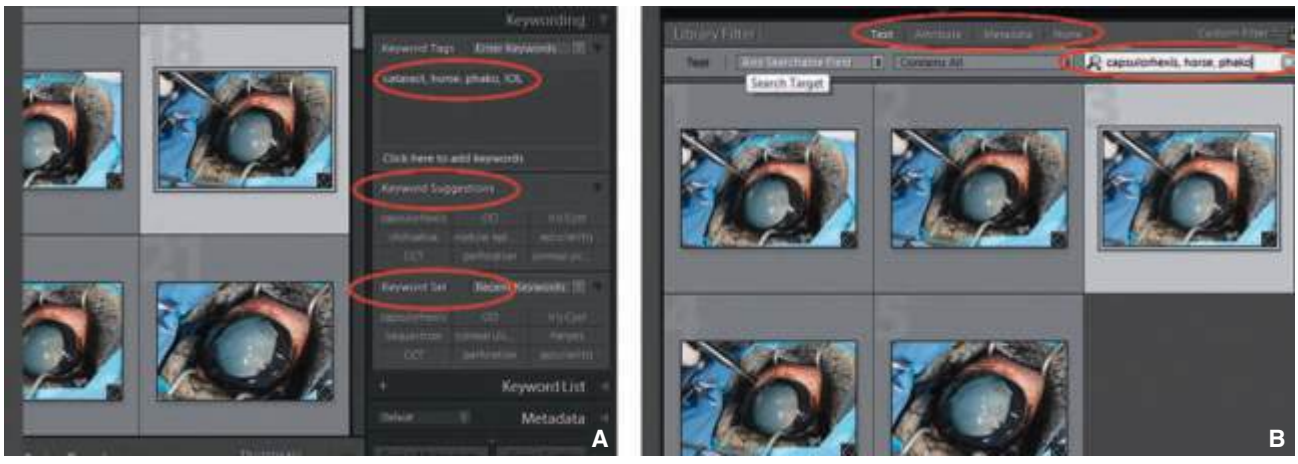


Figure 13.74 The Lightroom Keywording panel (**A**) is where keywords are added to images. This is facilitated with keyword suggestions and groups (sets) for frequently used keyword combinations. The catalogue is searched (**B**) using filenames, keyword combinations, ratings, or metadata. (Adobe product screen shots reprinted with permission from Adobe Systems Incorporated.)

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Figure 13.75 Lightroom's Develop module provides several means to edit images and apply corrections for specific lenses. (Adobe product screen shots reprinted with permission from Adobe Systems Incorporated.)

Table 13.11 Organizational summary for Adobe Lightroom Classic CC.

Catalogues (Ophthalmology, Veterinary, Family, Travel, etc.)
Folders: Ophthalmology by species (Dog, cat, horse, exotics, etc.)
• **Subfolders**: Part of eye (Orbit, Eyelids, and Cornea, etc.)
• **Subfolders:** Normal, type of disease – congenital/acquired, etc. or disease type (developmental uvea, uveitis, neoplasia, etc.)
Collections: groups of images you are working with, for instance to put in book chapter or into slideshow for PowerPoint or Keynote. You can have multiple virtual copies of the master images to edit or manipulate.
Smart collections: predetermined collections that auto-populate based on specified criteria. For example, every time you add a photo with the word "cyst" in the filename or metadata keyword tag, the image will also appear (as a copy in the catalogue) in the smart collection for cysts – even if the image was imported to a file location/folder for uveal cysts or elsewhere in the library.

images in a variety of formats that may be useful for professional and commercial photographers, most ophthalmologists will be more interested in utilizing images in applications such as PowerPoint and Keynote. Drag and drop is possible from Lightroom on Mac into either Keynote or PowerPoint for Mac, but at present this is not possible when using Lightroom on a Windows platform. On either Mac or Windows, images can be exported as a JPEG slideshow and then inserted into PowerPoint slides.

Lightroom CC

The more recent version of Lightroom, now called Lightroom CC, is quite different to the existing Lightroom Classic. This is a cloud-based application that imports and stores all of the images (including RAW files) in the cloud (local copies can and should also be stored on a local hard drive). This does have the benefit of providing an immediate cloud-based backup of images rather than the user having to do this as a separate step in Lightroom Classic.

Whereas Lightroom Classic imports and will use a conventional folder structure, Lightroom CC imports based on the date and time of the import. Images are stored in albums that can be further organized into folders and subfolders (although these have to be set up manually in the navigation pane; Fig. 13.76). Metadata cannot be added during the import of images and it is not possible to specify the destination of images with the same specificity in Lightroom CC (basically to the cloud rather than specific folders on the local hard drive).

The ability to keyword images is also not available in Lightroom CC, the "find" feature being replaced by a search box that utilizes artificial intelligence to locate specific features of the image. At this time, this is not a useful feature for a collection of ophthalmology images – whereas the search feature might find all images with dogs or cats, it will not locate (for example) any images with hypopon or retinal hemorrhage as the search criteria (at least as yet; Fig. 13.77).

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Figure 13.76 Lightroom CC main window with folder structure and grid view. (Adobe product screen shot reprinted with permission from Adobe Systems Incorporated.)

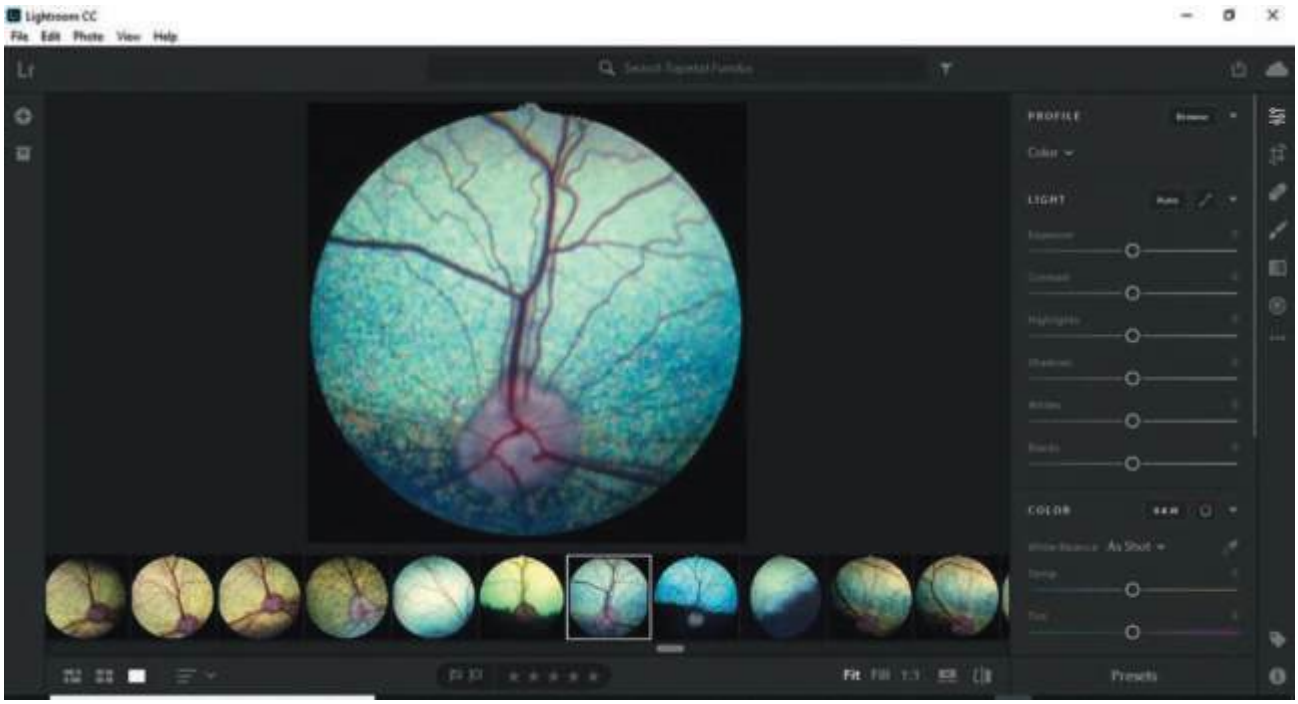


Figure 13.77 Lightroom CC window with artificial intelligence–based search box and edit panel. (Adobe product screen shot reprinted with permission from Adobe Systems Incorporated.)

The editing options in Lightroom CC are also far more limited than in Lightroom Classic and are more typical of the simple editing options available in other applications such as Apple Photos and Google Photos (Fig. 13.77).

It has for some time been possible in some previous versions of desktop-based Lightroom to synchronize a collection of images to a mobile application, to view images on a tablet or cell phone. This has been taken much further in Lightroom

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CC and it is a definite advantage of this version. Since the images are all uploaded to the cloud-based servers, they are readily accessible to any mobile platform, not just for viewing but also to be edited and distributed. The downside to this approach is found with a very large collection of images, which will require more investment in online storage capacity with Adobe, and hence higher cost than when storing images on a local drive.

Several other DAM applications are available as alternatioves to Lightroom. These vary from free or low-cost consumer applications such as Apple Photos and Google Photos to more advanced professional applications. A web search will reveal numerous applications that can perform in a similar way to Lightroom. However, it should be remembered that Adobe Photoshop and Lightroom have been present for a long time and hopefully the company will continue innovating and improving its products. The same cannot always be said for smaller, less-established companies in the digital imaging field.

Image and Catalogue Storage Options, Imaging Workflow, and Data Backup

Original Image (Master) Storage and Catalogue Backup

Most photographic images will be stored primarily on a hard drive – often the main drive in a computer. Hard drives are prone to eventual failure and can have bad sectors on the disc, which may adversely affect the image collection. It is therefore important to have some form of backup system in place to ensure that images are not lost or corrupted.

There are numerous approaches that can be taken to image backup, which vary in complexity and reliability. For a comprehensive review of best backup practices, see *The DAM Book 3.0* (2017; http://thedambook.com/the-dam-book). There is no "right way" of image cataloguing, editing, and backup. Images on an internal hard drive with a backup copy on an external hard drive is the minimum backup recommended. More redundancy in the system can be achieved with multiple backups both onsite and offsite, with permanent backup on optical media.

Two data backups are needed with PIE applications – one for the actual image files (RAW, JPEG, PNG, etc.) and the other for the cataloguing software data files (the database). It is important to recognize that while the cataloguing software application usually has a built-in feature for backing up the catalogue files, this does not necessarily back up the actual image files. Backup of the original or master image files (in "virgin" form) may require other actions and software. In Lightroom, a backup, which can be set to occur every time the catalogue is closed, only applies to the catalogue files, not the individual image files.

Backup of images can start in the camera. There are several cameras that include a slot for a second memory card and an option built into the camera software to use this second card (which should be same capacity of card) for an exact backup copy of the original image (this protects against failure of one or other card).

Images should be copied (not moved) to a computer hard drive as soon as possible after they are recorded on the memory card to avoid accidental deletion. Images should not be "moved" from card to hard drive in case errors occur during the transfer. No images should be deleted from the memory card until they are transferred to the hard drive, and preferably not until an additional backup has been made. A decision must now be made as to whether to back up the "virgin" images (to a hard drive or optical medium) or wait until the files have been imported into Lightroom and have undergone metadata additions and filename changes.

Images can be simply copied to a folder on the hard drive in Mac Finder or Windows Explorer. There is a small risk of errors during the transfer and no way to verify that the transfer occurred without error using this approach. Alternatively, copy and verify software can be used to ensure that the copied files are identical to those on the memory card. Once on the hard drive, the images can be imported (without necessarily changing the location on disc) into the DAM application.

If a small number of images are to be transferred from camera to hard drive on a frequent basis (possibly nightly or weekly), they may be copied into the final location on the hard drive using whatever organizational/folder structure is chosen using the DAM application (e.g., Lightroom), creating an entry in the catalogue with a changed filename, and adding keywords as necessary. For instance, feline uveal cyst images are renamed, keyworded as "uvea," "cyst," and "feline," and imported to a "subfolder: cyst" in the "subfolder: uvea" or the "folder: feline ophthalmology."

One hour spent each week performing this task is more efficient, less exhausting, and less likely to cause data loss than infrequent downloads of vast numbers of patient images.

If, however, images are only downloaded infrequently or when the memory card is nearly full (hence large numbers of images of many different cases and diseases), with the intent to return to them later and make the metadata/filename changes, an alternative option is to use Lightroom to copy the original camera files to a *dated download folder* on the internal hard drive. The copied files are identified in the download folder in the Lightroom catalogue by subject and year, with subfolders to identify the month (e.g., into a folder called "Ophthalmology 2020" with subfolders for the month "Ophthalmology 3–12"). These files are then backed up to an external hard drive or optical medium. When time permits, the images in the dated folders are renamed and metadata applied, and then they are moved in Lightroom to a permanent folder on the internal hard drive more relevant to the subject (remember that this *must* be done in Lightroom and not in Windows Explorer or Mac Finder). Individual images can be identified from the camera by including a photograph

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of the patient file information or a card with the patient's information. Renaming the image files and adding keywords can then be done at a later date.

If importing RAW files into Lightroom, this is the time to convert them to DNG if that is the preferred file format. One of the benefits of using DNG format for your image files inside Lightroom is that a validation code is embedded in the DNG file. The DNG file has a source image that never changes (regardless of other edits or changes to the metadata). Any future backups of the DNG file will automatically enable data verification.

Once images have had renaming/keywording changes made, they are again backed up as a finished/archival file. Several applications are available for backup of the image files to either additional external hard drives, optical media, or online (e.g., Acronis True Image, Acronis, Schaffhausen, Switzerland, or Nova Backup Pro, NovaStor, Agoura Hills, CA, USA). Although it is more convenient simply to use backup software to make compressed image backups, a better approach is to make exact copies of the image files to the backup location with backup or file synchronization and verification software; this ensures that the copies in the backup are indeed identical to the original images, with no errors detected in the backup or copy process.

Any further work on these image files will be parametric in Lightroom for either JPEG or RAW images (i.e., no changes to the archival/master file, only edits in the Lightroom catalogue file). The DAM application will also make a backup of the catalogue/library file that is separate from the actual image collection.

If any RAW file from the archive is subsequently changed in a pixel editing program like Photoshop, the edited version should be saved as a *separate copy* with the same file name, plus a designation to indicate that it is a copy that has been edited (e.g., Heidi_Snooks_MG6705_editcopy.PSD). To keep any copies edited in Photoshop organized in the Lightroom catalogue, the editing should be initiated in Lightroom and then saved back to the catalogue as an edited image.

It is good practice to store the archival images on optical media once they have been renamed (this is not a copy of the Lightroom catalogue file, but simply the renamed master images, the same as will be in the archive) so that one additional copy exists on a different medium. At present, the most convenient optical backup is DVD (4.3 GB). With increasing digital image file size in high-resolution dSLR cameras, it is now only practical to use DVD storage, and certainly so if shooting RAW or RAW + JPEG files. CDs may be a reasonable option for collections of JPEG images, although if shooting 4 MB images a CD will accommodate fewer than 200 images. For archiving purposes only, use "R" (read-only) discs to avoid inadvertent overcopying of data. We have little reliable data on the longevity of optic media – estimates of a 50- to 100-year storage life seem optimistic. In general, it seems that at present, DVD-R discs with silver or gold reflective coatings may be the most stable. Companies with archival quality DVD-Rs popular with photographers include MAM-A (Colorado Springs, CO, USA). Soon it seems likely that Blu-Ray will start to replace CDs and DVDs for image archiving due to the higher storage capacity (up to 50 GB at present and expected to rise in the future).

If backing up to a laptop or computer hard drive, it is fast and easy to attach an external hard drive and immediately make an exact copy (mirror) of the files to the external drive. At this stage of the workflow, the images should be copied to the external drive as an *additive backup*. This simply requires adding the new files from the memory card to the existing files on the internal and/or external drive. One way to organize these additions is to place each data transfer of new files in a dated folder on the hard drive. The same organizational structure should then be copied to any other external drives or optical media. An even better practice is to back up the original files to two external drives set up in a RAID 1 configuration. Various external hard drives that facilitate this are available (Fig. 13.78).

It is possible to copy the images and validate that the copied files are identical using software such as ViceVersa (TGRMN Software, Fullarton, Australia) or SyncBack (2BrightSparks, Singapore) on Windows, and ChronoSync (Econ Technologies, Winter Springs, FL, USA) on Mac.

It is also good practice periodically to copy one other backup of the original master files to another external drive that is maintained offsite at another location to avoid the possibility of data loss from theft, fires, and so on. In the clinical setting, an additional backup may occur if the patient images are also copied into the patient record in the practice management software.

Ideally, as much as possible of the subsequent image transfer and modification should be handled from within the imaging software. It is important not to move or edit images outside of the catalogue application or the images will not be referenced correctly in the catalogue.

Catalogue and Image Library Configurations

The simplest arrangement for any image collection is on the primary hard drive of the laptop or computer. In this configuration, both the catalogue files and the image library files are on the same drive (as well as the operating system and other applications and documents). The main drawback with this arrangement is that image collections can easily become so large that they fill up the entire drive. Various other configurations are possible, however, with most parametric cataloguing and imaging software.

The most reliable, stable, and easily organized approach is to use one computer as the imaging workstation – a good option is to have two to four hard drives in the tower as well

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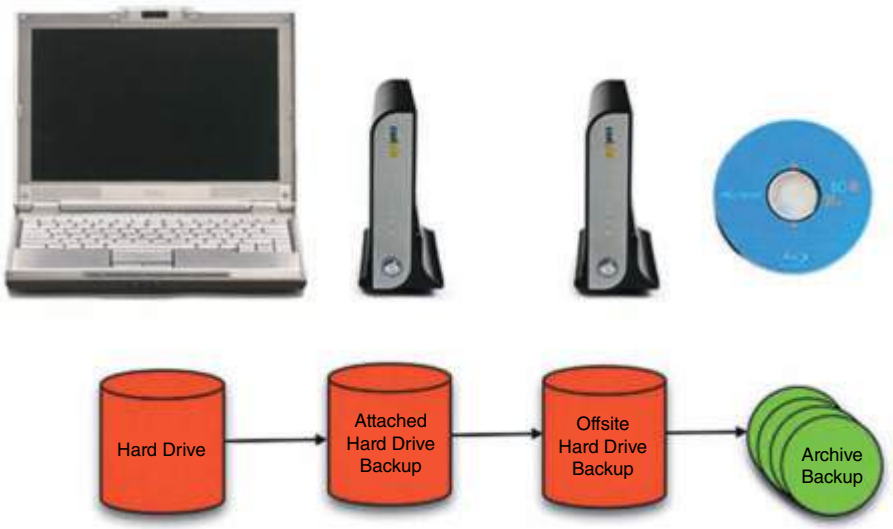


Figure 13.78 Simple backup configuration for one computer imaging system. (Reproduced with permission from *The DAM Book*, Peter Krogh, O'Reilly, 2009.)

as USB or Firewire connections for external backup hard drives, and an internal DVD-RW drive (or even an internal Blu-Ray drive) for optical backup.

If most of the imaging workflow is done on one desktop computer, the primary drive houses all the usual application software, including the Lightroom catalogue. This can either be a regular hard disk drive (HDD) or a solid state drive (SSD). The master image collection is then located on a separate internal hard drive (usually a HDD drive, since this allows for a large volume of images at lower cost than SSD). Using internal drives for the catalogue and the image collection additionally has the advantage of speed of processing. Both the catalogue/library and the master image collection need to be backed up regularly to external hard drives.

The simplest recommended organization and backup configuration for one computer use is shown in Figure 12.74. Images are imported onto the laptop or PC hard drive (the catalogue is kept here as well). The entire drive is cloned to two separate external drives – one remains online, and backups are continuous; the other is updated on a regular schedule (weekly or monthly) and then taken and kept at a different location (home or work). Separate periodic optical drive backups of the image collection and the catalogue are also recommended. Essentially, all the parametric imaging is done in the DAM catalogue on the internal drive, and backup of the catalogue and image collection to the external hard drives occurs on a regular schedule. Backup is all about ensuring redundancy – that is, multiple backups of images – so that if the worst happens and the primary collection of images and the DAM catalogue are lost, destroyed, or corrupted, they can be restored intact.

Offsite backup can be achieved using the cloud. The first time a large collection of image masters is backed up to the cloud it can take some considerable time, but subsequent continuous backup ensures an additional offsite set of images. Various cloud backup and synchronization applications are available, including CrashPlan (Code42 Software, Minneapolis, MN, USA), Backblaze (San Mateo, CA, USA), and Carbonite (Boston, MA, USA). All charge a monthly fee for storage space, certainly worth the peace of mind of an additional offsite backup in case of failure of the primary system. These cloud systems in no way guarantee your data if lost and should never be used as the primary backup system for original image (or any other) files.

One further option for local backup is network access storage (NAS). Images and catalogues (and any other files you like) are kept on a NAS drive that can be accessed online. An example would be the Synology DiskStation (Synology, New Taipei City, Taiwan), which has replaceable SATA hard drives in an external network-connected enclosure. This can be accessed anywhere online for image and catalogue access and backup, and is effectively a personal cloud backup.

Multiple Computers for Catalogue and Image Library

If images are viewed and edited on more than one computer (e.g., on a laptop at home or when traveling and a computer at work), a different storage arrangement is needed to avoid errors of synchronization between the catalogues of each computer.

One way to achieve this is to keep the primary copy of the catalogue and the image collection (masters) on an external hard drive (preferably with a Firewire, USB 3.0, or Thunderbolt interface) rather than on the internal drive of

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one of the computers used. The external drive is moved from computer to computer, where the DAM application (Lightroom) is installed on internal drives. The main drawback is that accessing the catalogue and the image collection on an external drive tends to be slower than using internal drives. Other issues that have been noted are problems when using USB connections to external hard drives on a Mac and the risk of major file corruption if USB drives are inadvertently disconnected from the computer or laptop. It may be necessary to ensure that the drive letter and path are the same for the external drive when used on different computers for the Lightroom library to function normally. Multiple backups are recommended if a traveling external hard drive is used for the images and the catalogue.

A better and simpler approach if using Lightroom Classic CC is to set up the catalogue either on Dropbox (www.dropbox.com) or in the Adobe Creative Cloud folder, which is automatically added to Windows Explorer or Mac Finder when you install the Creative Cloud Photographer's Plan. This enables a single Lightroom Classic catalogue to be viewed across multiple devices (computer, tablet, cellphone) in much the same way as can be achieved with Lightroom CC, but using Creative Cloud also has the benefits of all the additional features of Lightroom Classic (editing and keywording) that are valuable for an ophthalmology collection. Large collections need more storage space on either Dropbox or Adobe Creative Cloud, but the benefits may outweigh the additional cost.

Ethics of Editing and Use of Images

The need may arise to edit images that are of slightly poor quality (mostly inadequate exposure, or occasionally to do with focus and sharpness) and attempt to improve on the camera's output. With applications such as Photoshop and Adobe Fireworks, it is possible to make many adjustments to the image, but it is important to remember that this is changing the pixels themselves (vs. the parametric image editing performed by Lightroom).

In the interest of scientific honesty, it is generally accepted that photographic editing should be limited, in order not to use the editing process rather than the actual captured image as a basis for interpretation of results in experimental studies. However, the change to digital imaging has not significantly affected the way image editing and output have historically been used to illustrate (and possibly in some instances falsify) research findings. Even subtle changes in the exposures used for printing and techniques such as burning and dodging have been available ever since photography was first invented. It is easier now to make editing adjustments to final images because of computer technology, but overall nothing has changed with the advent of digital imaging.

It should also be remembered that image editing can be very valuable in enabling interpretation of scientific and diagnostic images that would be difficult if these techniques were not applied.

There are some rules that should be adopted when considering image editing (also known as enhancement or manipulation). Simple adjustments to the *entire image* are generally acceptable. For documentation in a medical record, there should be very limited if any image enhancement, no more than changes to exposure applied to the entire image. *All enhancements must be made to a copy of the unprocessed original image and saved in the record along with the original (unedited) image.*

For illustration purposes, it is acceptable to enhance images. For instance, in teaching ophthalmology, enhancement may be used to bring out certain aspects of pathology that might be difficult to illustrate otherwise. This can easily be done in applications such as Lightroom on a desktop or laptop to illustrate lesions to students or clients. Applications exist for tablet use, which enable photo enhancement for illustrative purposes. Depth of focus using focus stacking techniques and high dynamic range processing can be especially useful in illustrating lesions recorded in gross histopathology images of the eye, where multiple images can be captured with a camera mounted to a photo table or tripod.

For image documentation of scientific research, enhancements are only acceptable if exact details are included with the images of what adjustments were made. Ideally, a copy of the original image should accompany the edited/enhanced version of the image, or a statement be made that particular edits have been applied to the image. Individual publishers and journals vary in what image manipulation they will accept. These are usually detailed in the author guidelines for each publisher.

Images of the same subject that will be compared from one to another (e.g., to determine changes in pathology over time) should be acquired and processed identically each time (this can be difficult to achieve in the clinical setting).

Images collected as RAW data will need to be processed for publication; generally it is recommended that for publication images are submitted as TIFF or EPS, and that lossy compression techniques (e.g., JPEG) that change pixel data are avoided. JPEG images should never be edited and resaved; each time this happens, more data are lost.

Several types of image manipulation are not permitted in publications or research presentations. Combining different images to portray a single case or experimental result is definitely prohibited. Changes should not be selectively made to the brightness or contrast of *selected* areas of an image. Concealing, cropping, or adding data to an image (e.g., using layers and cloning and healing tools in Photoshop) that affects the interpretation of the image is considered unethical, particularly if the image is to be used to support research findings.

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Generally, all image manipulation for publication should be used as little as possible, relying instead on good photographic technique to record important details of the case pathology or experimental results.

Image Use and Publication

Although privacy issues about use of images and medical data may not be as restrictive and regressive in veterinary versus human medicine, it is recommended that before taking photographs of ophthalmic cases, permission is obtained to acquire and use patient images. This is easily done by including a permission statement to be signed at the time of the patient's admission to the hospital. The statement should assign all rights to use images in a way that does not identify the patient (necessarily), but also enables use in various print and online media. Privacy rules in veterinary medical records obviously still must apply.

An example of permission to acquire and use patient images is as follows:

> I consent for medical photographs to be made of my pet(s) by XYZ Veterinary Hospital. I understand that these images may be used in the medical record, for purposes of medical teaching, research into animal eye disease, publication in books or journals and electronically online. I understand that I will not receive payment from XYZ Veterinary Hospital or any other individual or entity for photographs taken of my pet(s).

The statement should be signed and dated and kept on the patient's medical record.

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Section IIIA

Canine Ophthalmology

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14

Diseases and Surgery of the Canine Orbit

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Orbital diseases are not uncommon in the dog. The close vicinity of the oral and nasal cavity, tooth roots, and paranasal sinuses renders orbital structures susceptible to disease processes extending from any of these structures through the orbital wall. The dog has an incomplete bony orbit. The orbital rim consists of bone for approximately four-fifths of its circumference and is completed by the orbital ligament. The rest of the orbit is enclosed by bone only on the dorsomedial and cranioventral sides. The rest of the roof and floor and the lateral wall of the orbit are formed by the temporal, masseter, and medial pterygoid muscles of mastication and by the zygomatic salivary gland (Murphy et al., 2012). As a result, the orbital contents are relatively susceptible to penetrating trauma through the surrounding soft tissues (Fig. 14.1).

The orbit can be divided into an intraconal and an extraconal space, separated from each other by the fascial sheets that envelop the extraocular muscles and fuse with Tenon's capsule anteriorly, and with the periorbita around the annulus of Zinn at the orbital apex. The orbital muscle cone contains the extraocular muscles, such as the four rectus muscles, the two oblique muscles, and the retractor bulbi muscles, CN II through VI, the internal ophthalmic artery, the anastomotic branch of the external ophthalmic artery, and the orbital venous plexus. The extraconal space is enclosed by the periorbita, which is a fascial layer covering the osseous and soft tissue walls of the orbit. Certain structures that cross the caudal orbital floor area are of major significance and are to be avoided during surgery, including the maxillary artery and nerve, the pterygopalatine ganglion, and the associated parasympathetic, sympathetic, and somatic nerves. Unoccupied spaces within the orbit are filled with fat, which cushions the globe and other susceptible intraorbital structures.

Clinical Signs/Examination

A full history, obtained from the patient caregiver, needs to include information on the duration, onset, and progression of the disease, any signs of pain and systemic disease, a possible history of trauma, any initiated treatments, the response to those treatments, and the results of any diagnostic tests that have been performed.

Clinical signs of orbital disease are relatively nonspecific with regard to etiology. Orbital diseases result in altered orbital volume, impaired function of orbital structures, or both. Changes in orbital volume manifest as exophthalmos or enophthalmos, depending on whether the orbital volume has increased or decreased, and depending on the location of a volume change within the orbit. Diffuse orbital volume increases, or intraconal mass lesions located inside the muscle cone behind the globe, typically displace the globe in an anterior and axial direction. Focal lesions outside the muscle cone in a more nasal, temporal, inferior, or superior position in relation to the globe will displace or rotate the globe off-axis into a direction opposite the mass lesion (Fig. 14.2). These changes can be quite subtle, but they can help localize the lesion within the orbit and help plan an approach for biopsy acquisition and surgical exploration. Careful evaluation of any asymmetries or aberrations in axis orientation of both eyes needs to be performed by observing both pupils at an arm's-length distance. The degree of exophthalmos or enophthalmos is usually estimated by determining the position of the axial cornea relative to the orbital ligament and the other eye, both from a distance and from above (Fig. 14.3). It can also be measured directly with a Luedde or Hertel exophthalmometer (McCalla & Moore, 1989; Musch et al., 1985). A bilateral orbital volume decrease and subsequent enophthalmos can be caused by a trigeminal neuropathy or

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Figure 14.1 Canine skull demonstrating the lack of an osseous orbital floor, rendering the orbital contents susceptible to penetrating trauma through the roof of the mouth.

cachexia, or age-related orbital fat and masticatory muscle atrophy (Fig. 14.4). Unilateral masticatory muscle atrophy and enophthalmos are typically caused by dysfunction of the mandibular branch of the trigeminal motor nerve. Secondary entropion can occur (Fig. 14.5).

Nictitating membrane protrusion also typically accompanies orbital volume changes. An extraconal volume increase displaces the nictitans anteriorly, causing protrusion as well (Fig. 14.6), whereas an intraconal volume increase typically does not cause nictitans protrusion. With a volume decrease, passive nictitans protrusion occurs due to enophthalmos.

The orbital contents can be palpated both caudal to the orbital ligament and from the oral cavity through the pterygoid muscle. The immediate retrobulbar tissues can be palpated by retropulsion of the globe. In normal mesaticephalic and dolichocephalic dogs, the globe can be displaced caudally for some distance. This is usually not possible in brachycephalic breeds. In the presence of space-occupying orbital lesions, retropulsion of the globe will be restricted or impossible, and may also be painful.

The bony rim of the orbit and the walls of the nasal cavity and paranasal sinuses should be carefully palpated and evaluated for the presence of any asymmetry. Percussion of the paranasal sinuses can be helpful to determine the presence of sinus-occupying inflammatory or neoplastic material. The presence of a symmetric flow of air through both nostrils should be evaluated, as sinonasal tumors can cause tumor invasion of the orbit.

The oral cavity is routinely inspected, because disease processes from the oral cavity or teeth may adversely affect the orbit and its contents (Ramsey et al., 1996). Conversely, orbital diseases may affect, or be visualized through observation of, adjacent structures, such as the oral cavity, for instance pterygopalatine fossa swelling behind the last upper molar tooth. Restrictive myopathies, like masticatory muscle myositis, can cause restrictions or even an inability to open the mouth. The degree to which the mouth can be opened should be recorded during the initial and follow-up examinations in such cases.

Inflammatory changes within the orbit are usually accompanied by pain, especially upon globe retropulsion and when opening the mouth. Movement of the vertical ramus of the mandible into the orbital space upon opening the mouth increases pressure on the orbital contents. Most dogs with orbital pain will therefore display difficulties with, or will vocalize during, some activities requiring jaw movement: chewing and eating (especially dry food, rawhides, bones), playing with balls and sticks, barking, or yawning. Thorough inspection of the oral cavity needs general anesthesia in these patients. Inflammatory changes in the orbit (cellulitis, abscess formation), which cause tissue edema, can be accompanied by conjunctival chemosis and periocular swelling.

Impaired function of orbital structures manifests as reduced ocular motility, strabismus, abnormal globe position, anisocoria, blindness, and increased or reduced tear production. These signs can be caused by mechanical entrapment, pressure atrophy, loss of nerve function, and neural stimulation of affected tissues.

Congestion of episcleral vessels is caused by a decreased venous return, which is due to increased orbital tissue and intravenous pressure.

In more extreme cases of exophthalmos, lagophthalmos ensues due to a decreased ability to close the eyelids. This quickly results in exposure keratitis, ulceration, and potential loss of the eye.

Indentation of the globe can be observed by ultrasound or ophthalmoscopically as an area of fundus elevation and altered reflectivity due to the altered angles of incident and reflected light. This indented fundus area should be observed during spontaneous eye movements. The indentation will not change position if it is caused by a mass attached to the globe, whereas unattached masses will cause an indentation that shifts position during globe movement. The presence of retinal detachments secondary to orbital mass lesions has been described (Attali-Soussay et al., 2001).

Even with marked deformation of the globe, the intraocular pressure usually remains within the normal range (Spiess et al., 1995). However, in dogs with a relatively short palpebral fissure, the globe can be pressed against the lids by a space-occupying lesion, elevating the intraocular pressure.

In rare cases of pulsating or intermittent exophthalmos associated with arteriovenous fistula or varix, auscultation of the orbit may be useful.

Ancillary Diagnostic Tests

Because the orbit cannot be visualized directly, thorough general physical, ophthalmic, and neuroophthalmic examinations must be followed by a variety of diagnostic tests.

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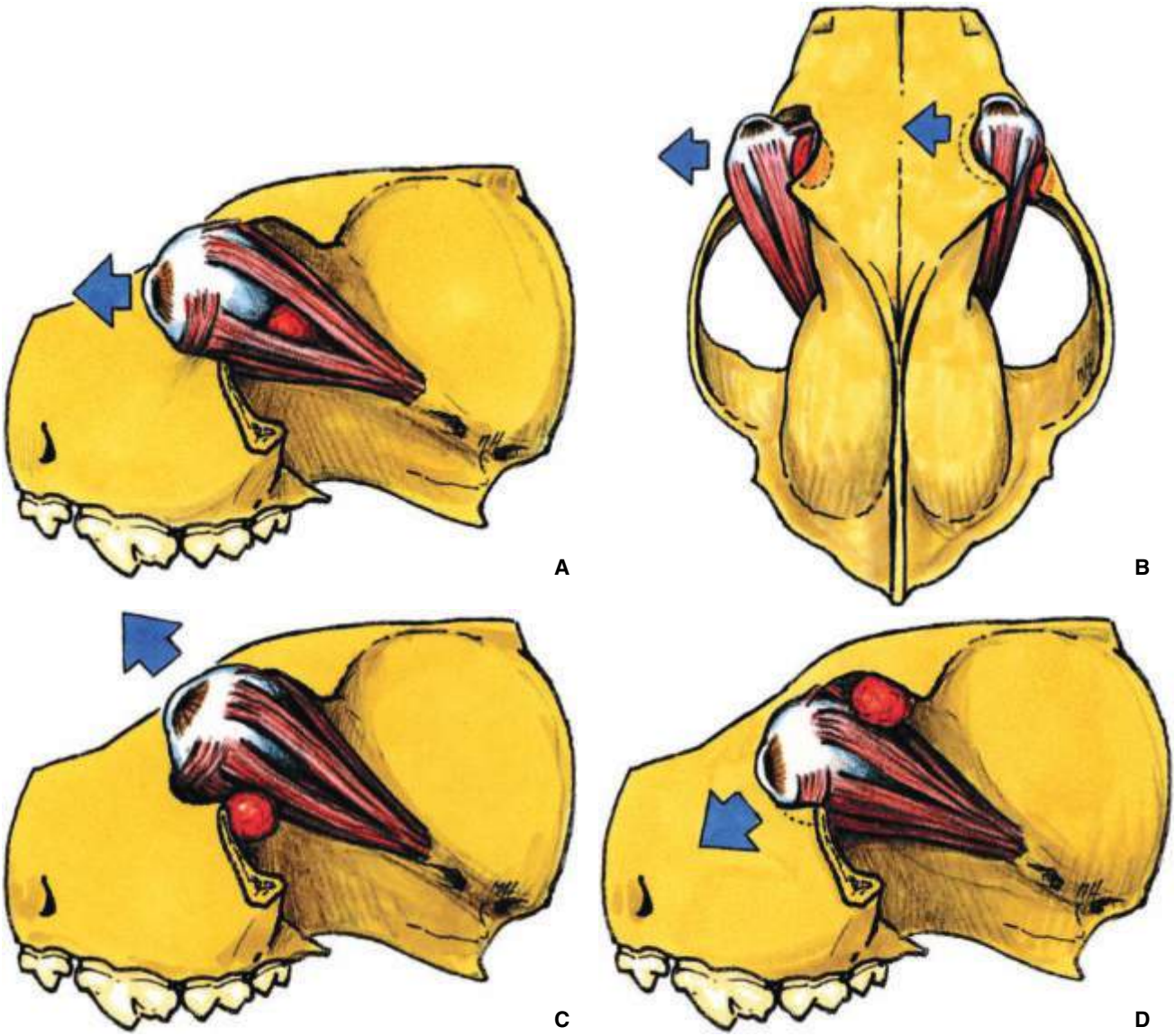


Figure 14.2 Globe displacement caused by focal mass lesions in the orbit. **A**. Localized inside the muscle cone. **B**, **C**, and **D**. Localized outside the muscle cone, in a more nasal or temporal (**B**), inferior (**C**), or superior (**D**) position in relation to the globe. (*Source:* Adapted with permission from Miller, P.E. (2008) Orbit. In: *Slatter's Fundamentals of Veterinary Ophthalmology* (ed. Maggs, D.J., Miller, P.E., & Ofri, R.), 4th ed., pp. 352–373. St. Louis, MO: Saunders.)

A combination of diagnostic imaging and cytology/biopsy sample acquisition is usually employed to localize and identify orbital pathologies. Although almost always available, x-ray films are not the modality of choice for ocular disease. Nevertheless, in cases of orbital disease it may serve as a first survey modality. The limitations are the same as for any other part of the skull. Soft tissue swelling with depiction of the lesion center will be possible. Also, changes in the bony structures, such as periosteal reactions, fractures in cases of trauma, aggressive bone lesions causing osseous proliferation or destruction, and lesions containing radiopaque material will be depicted (Fig. 14.7; Dennis, 2000; Johnston & Feeney, 1980; Ruehli & Spiess, 1995a). Still, we have to consider that changes visible on films are usually rather advanced. Being confronted with such lesions, a decision to continue or not may be taken with the owners. Contrast radiography of orbital tissues, such as pneumoorbitography, orbitography, orbital arteriography, venography, optic nerve thecography, and sialography, has frequently been used to diagnose orbital diseases (Ackerman & Munger, 1979; Gelatt et al., 1970; Johnston & Feeney, 1980; LeCouteur et al., 1982b; McCalla & Moore, 1989). However, these methods have largely been displaced by more recent cross-sectional imaging techniques, including orbital ultrasonography

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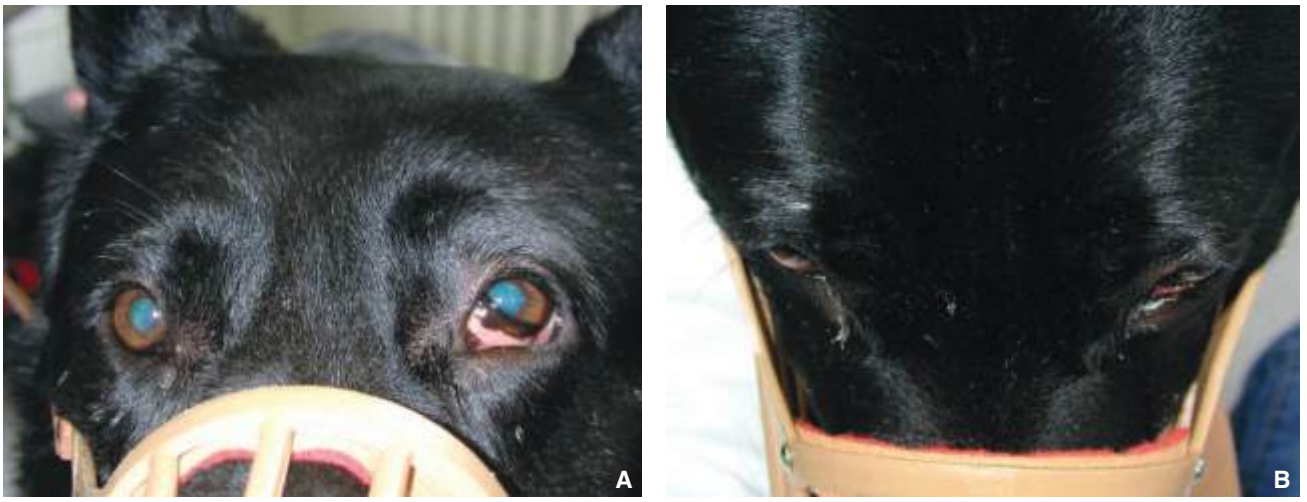


Figure 14.3 Exophthalmos of the left eye (OS) caused by orbital neoplasia. **A**. Frontal view, demonstrating left-sided nictitans membrane protrusion and a slight "off-axis" position OS. **B**. Dorsal view showing a mild degree of forward displacement OS.



Figure 14.4 Age-related loss of retrobulbar fat and marked muscle atrophy in both eyes.



Figure 14.5 Unilateral cranial nerve V lesion leading to marked unilateral masticatory muscle atrophy and enophthalmos.

(Cottrill et al., 1989; Dziezyc & Hager, 1988; Dziezyc et al., 1987; Schmid & Murisier, 1996), computed tomography (CT; LeCouteur et al., 1982a), and magnetic resonance imaging (MRI; Grahn & Wolfer, 1993).

Diagnostic Ultrasound

The basic principles of diagnostic ultrasound have been described in Chapter 10, Part 2. Various approaches for B-mode ultrasonography of the orbit exist. The ultrasound probe can be placed:

1) On the anesthetized corneoconjunctival surface for a direct corneoconjunctival contact approach, which eliminates attenuation of the ultrasound beam by the skin and decreases potential reverberation artifacts due to air trapping between the probe and the skin.
2) On the upper eyelid skin with the eyelids closed for a transpalpebral approach, which can decrease patient discomfort.
3) Caudal to the orbital ligament for a temporal approach, which allows visualization of the deeper orbital structures, including the optic canal and orbital fissure (Stuhr & Scagliotti, 1996).
4) On the oral mucosa behind the last upper molar, directed toward the orbit, for a transoral approach (Fig. 14.8), which is useful for fine needle aspirate (FNA) guidance and foreign body searches in retrobulbar abscess or cellulitis suspects.

Two scanning planes should routinely be obtained. For the corneoconjunctival and transpalpebral approaches, a vertical and horizontal axial scan should be obtained to gain an overview of the globe, optic nerve head, optic

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Figure 14.6 Bilateral orbital disease causing exophthalmos and nictitans protrusion in both eyes. (Courtesy of the University of Wisconsin-Madison Comparative Ophthalmology Service.)

nerve, extraocular muscles, orbital fat, and bony orbital walls. Scans in additional planes can be obtained depending on the localization of the lesion of interest. In human patients a transverse and longitudinal/paraxial probe orientation is used for a more detailed evaluation of the extraocular muscle bellies (Byrne & Green, 2002). When using a temporal or transoral approach, the probe is oriented along the longitudinal and transverse planes of the orbit. Scanning along the craniocaudal axis of the orbit yields the best results when evaluating the optic nerve and deeper parts of the orbit. Both eyes should be imaged routinely to compare the normal and abnormal sides and to identify or rule out the presence of bilateral disease.

Ultrasound is a useful technique to image the orbit, especially for an initial screening for the presence of lesions. The normal orbit is characterized by a relative hypoechogenicity of the extraocular muscles and optic nerve, compared to the orbital fat (Fig. 14.9). The bony orbital wall presents as an uninterrupted reflecting interface, which can be scanned for surface irregularities and defects. In the presence of lesions, the normal ultrasound anatomy of the orbit is usually altered or absent. Ultrasound characteristics of inflammatory and neoplastic lesions have been described in specialized texts (Byrne & Green, 2002; Nyland & Mattoon, 2002; Spaulding, 2008). In cases of orbital lesions, when the exact location and tissue of origin of a lesion need to be defined, as well as the extension (including bony involvement) and the nature of the lesion (benign vs. malignant), ultrasonography has many limitations. In situations in which these questions need to be answered, cross-sectional imaging techniques (CT and MRI) are indicated.

In cases of cellulitis, either a generalized loss of contrast between the orbital contents or no ultrasonographic abnormalities are observed (Dennis, 2000). Abscesses are identified as lesions with a well-demarcated echogenic wall, hypoechogenic corpuscular contents, and signal enhancement distal to the lesion. Cavitary lesions with a fluctuant center are found in dogs with cystic lesions and orbital abscesses, but are also identified in more than 10% of neoplasms (Boroffka et al., 2007; Mason et al., 2001). Cavitary lesions are described as typical lesions in orbital myxosarcoma in dogs (Dennis, 2008). When the suspicion of a retrobulbar abscess or cellulitis is high and the presence of a foreign body needs to be determined, ultrasound seems to be a relatively sensitive diagnostic tool (Boroffka et al., 2007). Foreign bodies are often identified as hyperechogenic linear structures with distal signal attenuation (shadowing). However, old wooden foreign bodies do not necessarily cause distal shadowing and can be difficult to identify. CT or MRI studies are indicated for an evaluation of the size, number, and exact localization of retrobulbar foreign bodies (Dennis, 2000; Hartley et al., 2007). Sometimes both modalities, CT/MRI and ultrasonography, may be complementary, as cases exist where ultrasound depicts the foreign body and CT/MRI does not, and vice versa (Fig. 14.10 and Fig. 14.11).

Neoplastic lesions were most commonly hypoechoic and homogenous, and globe indentation was identified more often than with inflammatory lesions (Fig. 14.12). However, these features are by no means distinctive. Orbital bone defects and tissue mineralization were almost exclusively seen in neoplastic lesions (Boroffka et al., 2007; Mason et al., 2001). In one study, the sharper delineation of lesion margins was the most discriminating feature of neoplasms compared to inflammatory lesions, with both ultrasound and CT (Boroffka et al., 2007). Color Doppler ultrasound used to characterize orbital blood flow can be useful for the differentiation of orbital lesions (Byrne & Green, 2002; Gelatt-Nicholson et al., 1999).

The advantages of ultrasound over some of the more advanced imaging techniques are its relatively low costs, general accessibility in practice, the fact that general anesthesia is usually unnecessary, and its use for real-time guidance during FNA or tissue biopsy acquisition.

Ultrasound can be used to evaluate the intraorbital extension and localization of disease, but more accurate tools are available for this purpose. Another limitation of ultrasound is the inability to image beyond the bony orbital wall, precluding the evaluation of extraorbital lesion extension and the evaluation of adjacent structures in general (Richter et al., 2003).

Computed Tomography and Magnetic Resonance Imaging

Both CT and MRI allow multiplanar imaging, and therefore complete assessment of the anatomic structures of interest beyond the bony margins (nasal and cranial cavities) can be readily achieved (Fig. 14.13). When we need to decide which of these two modalities we should use, the

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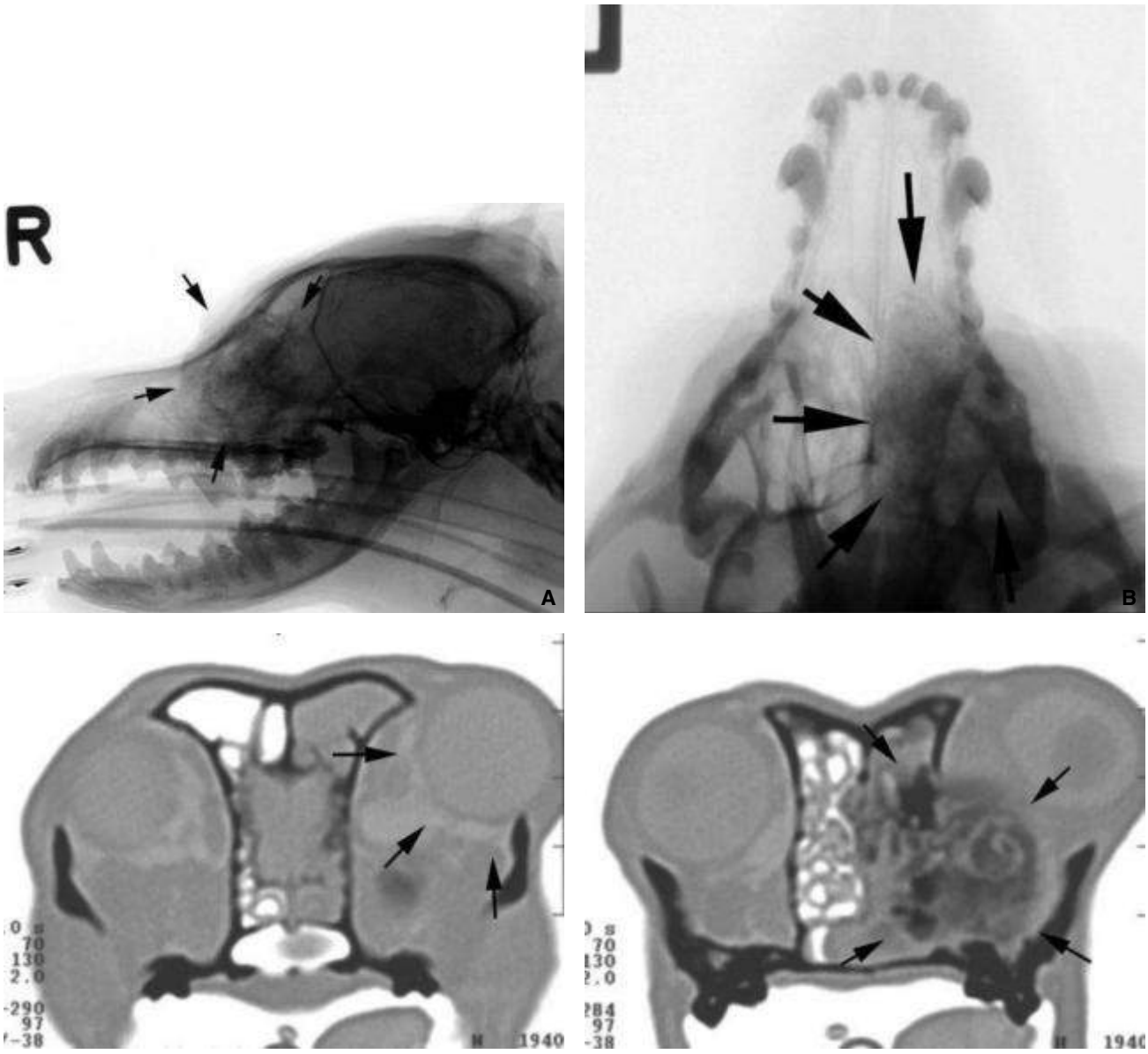


Figure 14.7 **A**, **B**. Mineralized space-occupying lesion right nasal cavity: laterolateral view (**A**) and ventrodorsal view (**B**). Note the marked, well-defined, inhomogenously mineralized space-occupying lesion visible on the radiographs (white arrows). With these findings, a suspicion of an aggressive neoplastic lesion can be raised, preparing a discussion on how to proceed with the patient. Only if continuation and therapy are planned is further imaging, such as computed tomography (CT), necessary. **C**, **D**. Transverse CT images of the region, indicating the exophthalmus (white arrows in **C**), the osteolysis, and the large mineralized space-occupying lesion (white arrows in **D**).

advantages and disadvantages of both techniques must be considered. CT is fast, thus requires less time under general anesthesia, and it offers very good bony detail. The main disadvantages are the use of ionizing radiation and poor soft tissue contrast. In contrast, MRI obtains an excellent soft tissue contrast, and characterization of the lesions (hemorrhagic, cystic, necrotic, mineralized) can be performed with exquisite detail thanks to different sequences. The main disadvantages of MRI are that it is less available, more expensive, and slower than CT, requiring longer general anesthesia times.

The basic principles of CT and MRI have been described in Chapter 10 Part 2 and will not be repeated in this chapter. The normal anatomy of the orbit in CT and MRI studies has been described (Boroffka & Voorhout, 1999; Boroffka et al., 2008; Joslyn et al., 2014; Morgan et al., 1994). Reference values for normal canine eyes have been published (Chiwitt et al., 2017; Salguero et al., 2015). Globe size was correlated

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Figure 14.8 Ultrasound probe placement for a transoral approach to the orbit.

with weight and showed significant differences between small, medium, and large-breed dogs (Chiwitt et al., 2017). Periorbital length was equal across brachycephalic, mesaticephalic, and dolichocephalic dog breeds and was positively correlated with both bodyweight and cranial length (Klaumann et al., 2017). Some characteristics of CT and MRI in respect to specific orbital pathologies will be highlighted here.

Due to the natural contrast between bone, soft tissues, air, and fat, CT has superior contrast resolution qualities, enabling excellent visualization of orbital structures, especially bone. MRI provides better soft tissue contrast resolution compared to CT. MRI scans are therefore superior to CT scans in cases in which an exact evaluation of soft tissue tumor extension into the surrounding soft tissues, including intracranial extension (Fig. 14.14), is needed (Dennis, 2000). An MRI scan is recommended for patients that show neurologic signs indicating central nervous system involvement. Cysts and abscesses are also more easily identified with MRI. Despite the fact that osseous changes can be evaluated on MRI scans (cortical bone presents as a signal void on MRI; see Fig. 14.14), CT is the modality of choice for the evaluation of traumatic injury, osseous changes, and the visualization of foreign bodies (especially metallic ones, where MRI is contraindicated; Boroffka et al., 2011; Malhotra et al., 2011). Tissue perfusion can be assessed using both imaging modalities by comparing pre- and postcontrast studies. Well-perfused tissues (most tumors, granulomatous lesions, abscess walls, tissue reactions surrounding foreign bodies, vascular lesions) will contrast enhance after contrast injection (Hoyt et al., 2009).

As with other imaging modalities, due to a lack of specificity neither CT nor MRI is straightforward for distinguishing between inflammatory and neoplastic processes when mass lesions are identified. As with any rule there exist exceptions,

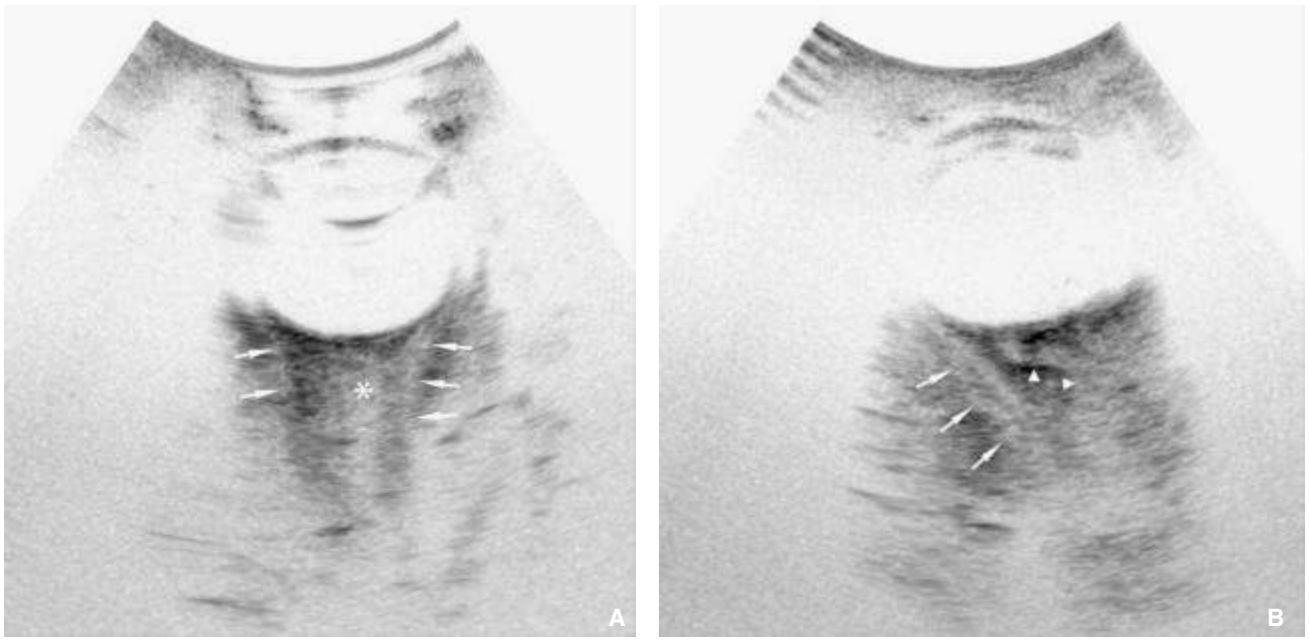


Figure 14.9 Ultrasound images of a normal canine orbit. **A**. Axial scan: the optic nerve (asterisk) and extraocular muscle bellies (arrows) are hypoechogenic compared to the surrounding orbital fat. **B**. Paraxial scan facilitating examination of the extraocular muscles (arrows). The optic nerve can be seen as an S-shaped hypoechogenicity (arrowheads). Note that the lens is not visible in this probe orientation. (Courtesy of M. Dennler.)

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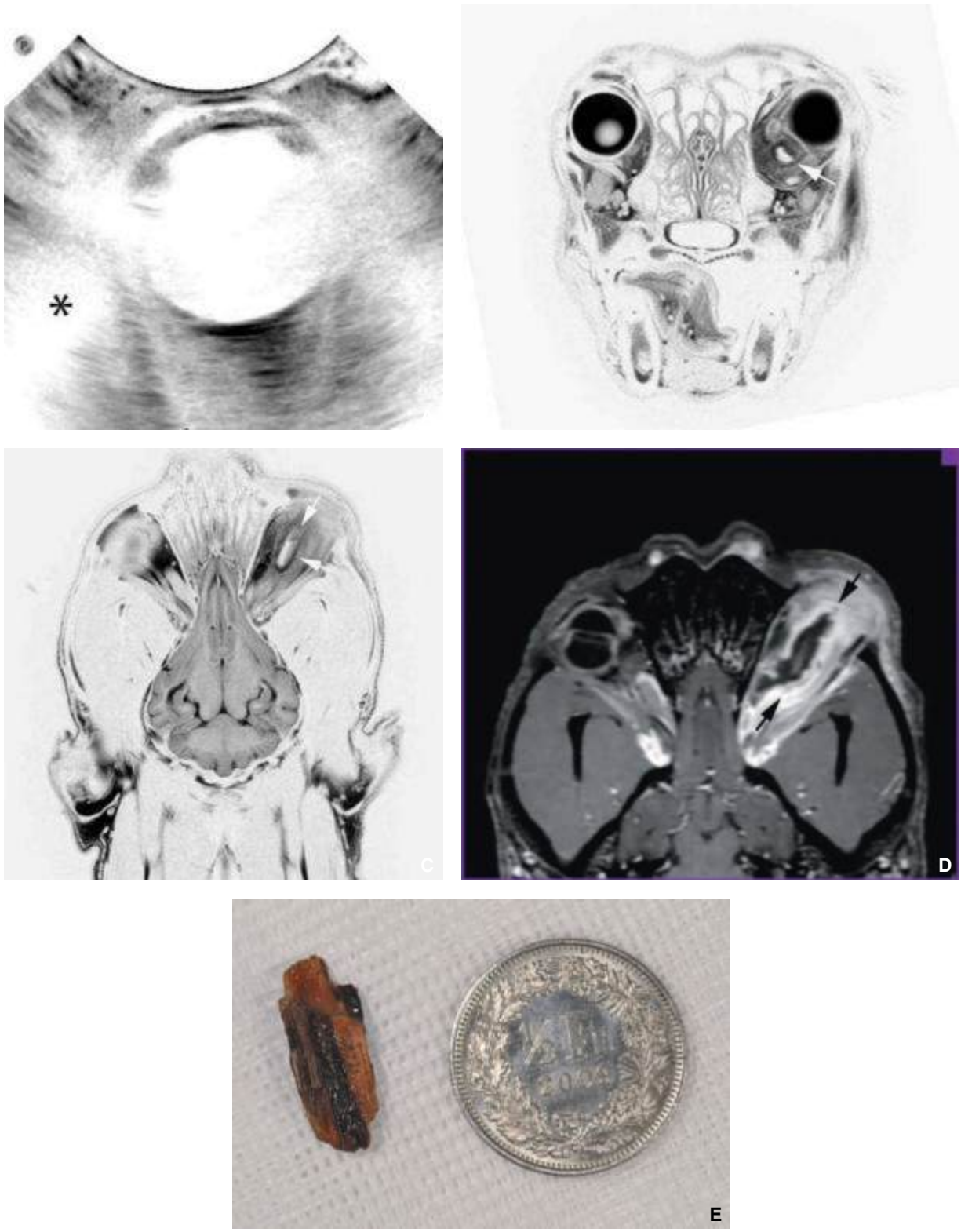


Figure 14.10 Orbital foreign body in a 5.5-year-old Eurasier dog. **A**. Ultrasound demonstrated a clean shadow in the deeper part of the orbit (asterisk). A definitive distinction between a shadow caused by a foreign body or by the normal bony contours of the skull was not possible. **B**–**D**. Magnetic resonance imaging (MRI): transverse, dorsal, and oblique T1-weighed postcontrast planes show a linear signal void surrounded by marked contrast uptake (black arrows). This was identified as a foreign body. In this case MRI confirmed the diagnosis. **E**. A wooden foreign body was delivered via modified lateral orbitotomy.

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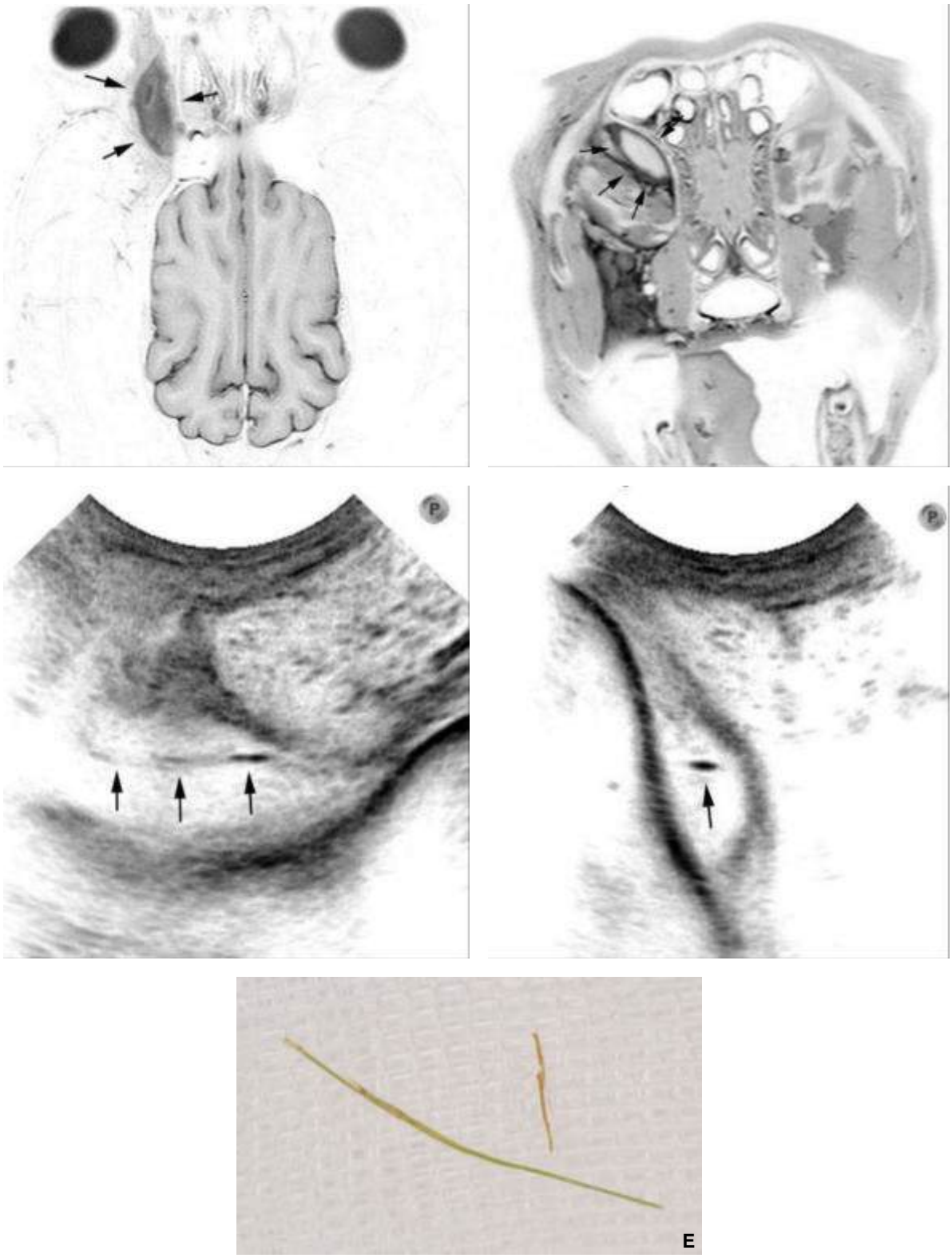


Figure 14.11 Orbital abscess due to a foreign body in a German Shepherd dog. **A**. T2-weighed dorsal plane. **B**. T1-weighed postcontrast transverse plane of the abscess with T2 hyperintense and T1 hypointense content with marked rim enhancement (white arrows). A foreign body could not be identified in these sequences. **C**, **D**. Ultrasound images of the abscess. In the center of the cavity a hyperintense linear structure is visible (white arrows) representing the foreign body. In this case ultrasound confirmed the diagnosis. **E**. A piece of grass was extracted during surgery.

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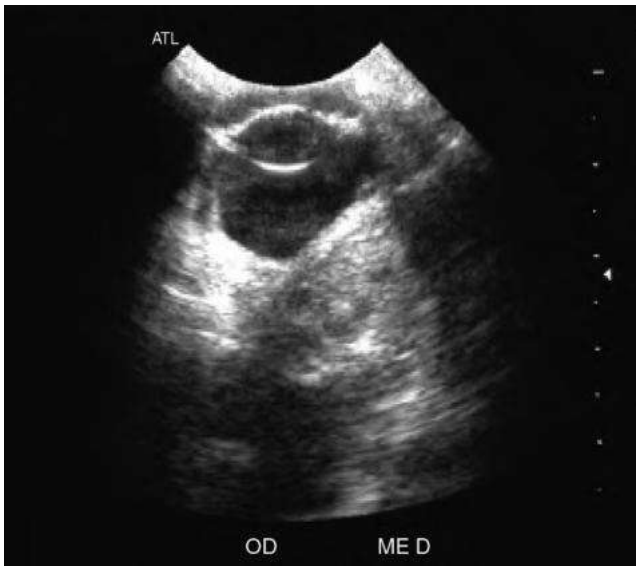


Figure 14.12 Ultrasonography of an orbital neoplasm (meningioma) in a 10-year-old Collie. Note the marked indentation of the caudonasal globe.

such as melanotic tumors, which are almost pathognomonic in MRI: intraocular melanomas have a unique signal behavior of T1 hyper- and T2 hypointensity. Sensitivity and specificity for the detection of optic nerve and intracranial lesions are high in MRI.

In a study evaluating CT signs associated with inflammatory and neoplastic orbital conditions, Lederer et al. (2015) identified increased attenuation of orbital fat (fat-stranding) to be associated with inflammatory and bone defects with neoplastic lesions. Osteolysis is typically interpreted as a sign of neoplastic disease, which is supported by most publications describing and comparing orbital imaging techniques (Boroffka et al., 2007; Calia et al., 1994; Dennis, 2000). Winer et al. (2018) identified both osteolysis and new bone formation to be highly associated with neoplasia. However, in endemic areas fungal granulomas, causing clinical symptoms and displaying imaging characteristics similar to those of neoplastic lesions, need to be considered as a differential diagnosis (Baron et al., 2011; Hecht et al., 2011; Fig. 14.15).

In general, MRI scans require more time than CT scans, but allow the acquisition of images in various planes, without the need for repositioning the patient. CT imaging allows the acquisition of guided biopsies, through the acquisition of short scans ascertaining the correct placement of the biopsy needle. This is a possible advantage of CT over MRI imaging. A diagnostic scan should be performed prior to needle placement and aspiration, to ensure that tissue changes (e.g., hemorrhage) or the introduction of air into the biopsy area does not interfere with the results of the scan. Also, if radiation therapy is part of the therapeutic plan, a diagnostic CT scan can be used for radiation planning as well (Boston, 2010). A recent paper described the three-dimensional printing of orbital and periorbital masses using CT scans to facilitate surgical planning (Dorbandt et al., 2017). Whether CT or MRI is used for further diagnostics often depends on various factors, including suspected diagnosis, therapy planning purposes, machine availability, costs, and clinician preference.

Future applications of MRI could include the use of microcoil-assisted MRI for high-resolution imaging of the cranial orbit and globe (Ivan et al., 2019; Lavaud et al., 2019; Fig. 14.16). Table 14.1 lists the clinical value of various diagnostic imaging modalities in various situations (Gonzalez et al., 2001; Morgan, 1989; Penninck et al., 2001).

Fine Needle Aspiration and Tissue Biopsy

Biopsy specimens can be obtained via the oral cavity, through bulbar conjunctiva, or through the skin caudal to the orbital ligament, with or without the use of ultrasound or CT guidance (Boydell, 1991). With the advent of modern imaging techniques, diagnostic orbitotomies have become almost obsolete. Some publications providing data on the diagnostic sensitivity of FNAs and tissue biopsies show that an FNA yields diagnostic results in approximately 50% of cases, whereas tissue biopsies provide a definitive diagnosis in approximately 75% of cases (Armour et al., 2011; Attali-Soussay et al., 2001; Gilger et al., 1992). In a study by Hendrix and Gelatt (2000) a definitive diagnosis was derived from 49% of the cytologies, 56% of the nonsurgical biopsies (trephine, biopsy needle), and 100% of the surgical biopsies performed. When cytology and a nonsurgical biopsy were both performed, the diagnostic yield increased to 79%. Sufficient amounts of tissue can be obtained with an ultrasound-guided tru-cut core biopsy technique, which was found to be of equal diagnostic value compared to excisional biopsies in lesions with a maximum diameter of 25–38.5 mm (Cirla et al., 2016). FNAs were found to be less likely to yield a definitive diagnosis when performed on mesenchymal tumors, likely due to the fibrous and cell-poor nature of these masses (Attali-Soussay et al., 2001). A recent study showed that tumor diagnosis based on core needle and surgical biopsy samples was superior to FNAs. A discordance between cytologic and histopathologic diagnosis was reported in 53% of cases (Flaherty et al., 2020). The use of special stains and immunohistochemical markers can increase diagnostic accuracy (Dubielzig et al., 2010; Giudice et al., 2005).

Congenital Anomalies of the Orbit and Globe

Anophthalmos

Complete absence of the eye, or anophthalmos, is very rare. In most cases, some remnants of ocular tissue can be identified histologically (Kern, 1991).

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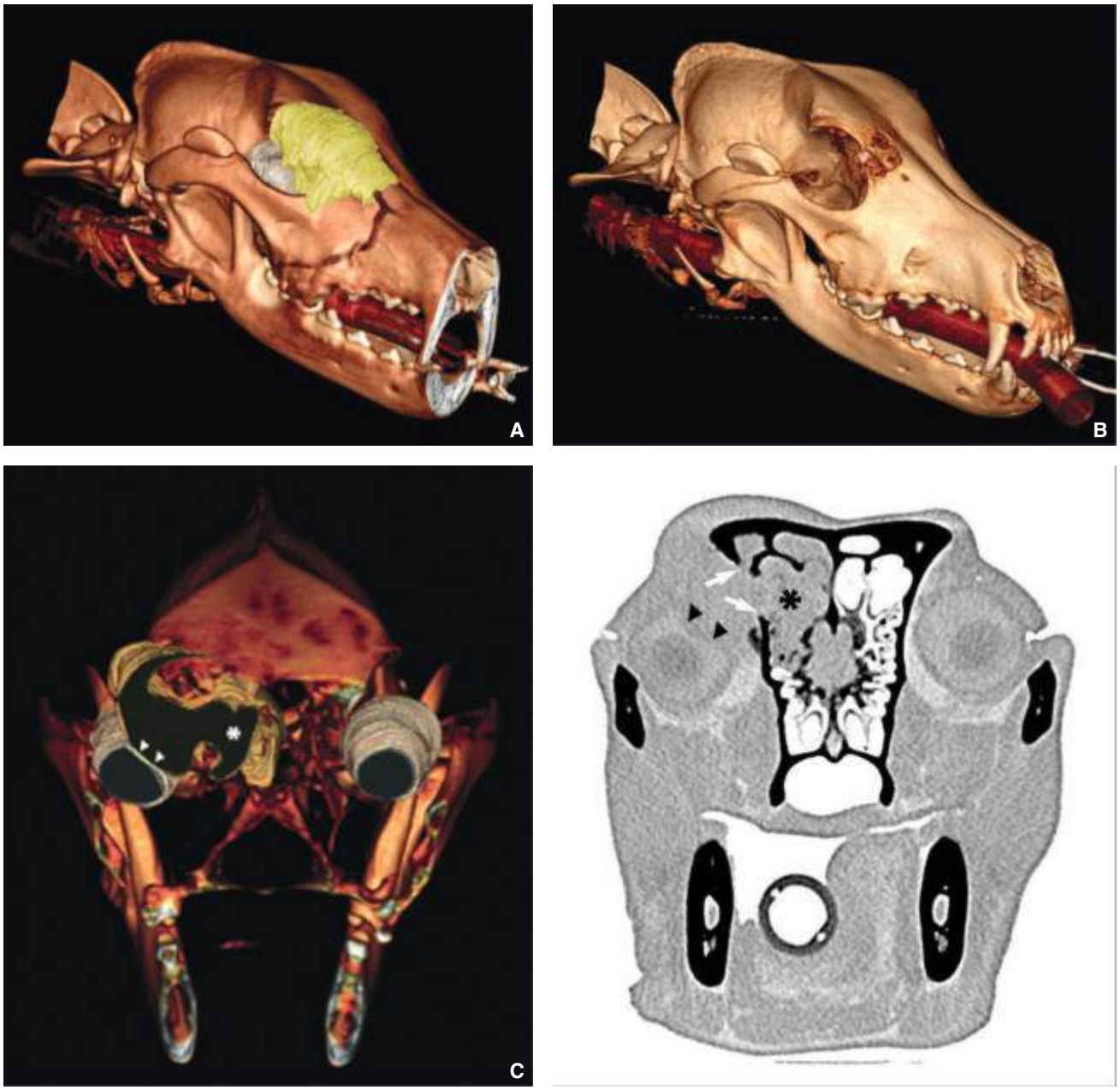


Figure 14.13 Computed tomography study of a squamous cell carcinoma invading the dorsocranial orbit and nasal cavity. **A**, **B**. Three-dimensional (3D) reconstructions outlining the tumor (yellow) in relation to the skull and eye (white). Osteolysis is evident underneath the tumor mass. **C**, **D**. Cross-section of 3D reconstruction and transverse bone window demonstrating the enophthalmos and globe indentation (arrowheads) due to the tumor mass effect. Osteolysis (arrows) and nasal involvement (asterisk) are clearly identified in **D**. (Courtesy of M. Dennler.)

Cystic Eye, Microphthalmia, and Nanophthalmia

If remnants of ocular tissue are present histologically, a diagnosis of either a cystic eye or microphthalmia can be made. Cystic eyes are structures that consist of an outer mesenchymal layer, lined internally with a single layer of undifferentiated neuroectoderm. In these cases, development has been arrested at the optic vesicle stage.

In true microphthalmia the globe contains evidence of the presence of surface ectoderm (lens), neural crest migration, and neuroectodermal differentiation (Grahn & Peiffer, 2007). Microphthalmia therefore presents as an abnormally small globe, with various other ocular anomalies involving the cornea, lens, uvea, vitreous, and retina (Slatter, 1990). Vision may be normal, reduced, or absent. In contrast, a small but otherwise normal globe is called nanophthalmia.

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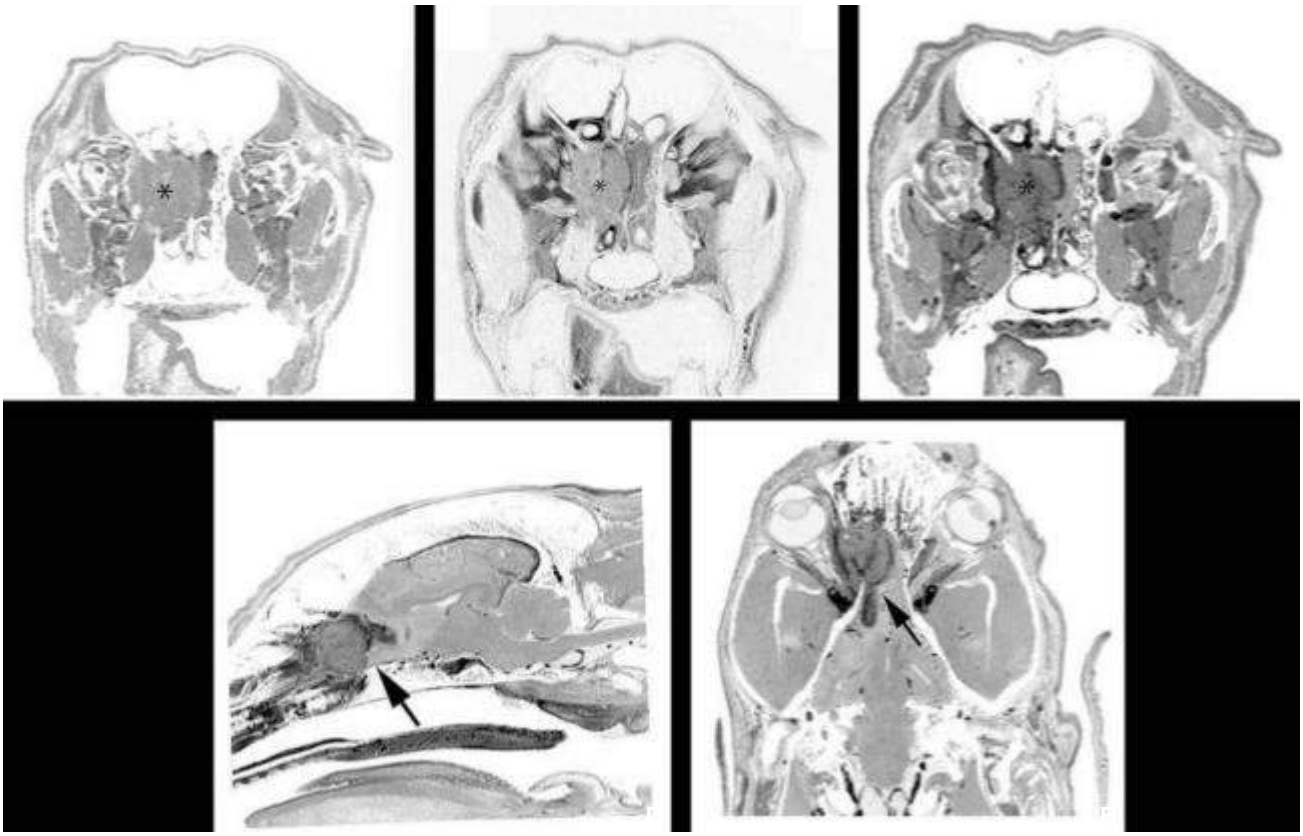


Figure 14.14 **A**–**C**. Magnetic resonance imaging (MRI), transverse plane, T1-weighed precontrast (**A**), T2-weighed (**B**), and T1-weighed postcontrast (**C**) sequence: exophthalmos caused by a nasal adenocarcinoma (asterisk) with orbital and intracranial tumor extension. **D**, **E**. MRI T1-weighed postcontrast reconstructions in the (**D**) sagittal and (**E**) dorsal plane. The tumor is highlighted by marked contrast uptake (white arrow) and shows invasion into the neurocranium and also into the retrobulbar space, where the nasal bone, observed as a clear signal void on the contralateral side, is almost completely destroyed.

In the Doberman Pinscher, microphthalmia is associated with anterior segment and retinal dysplasia (Arnbjerg & Jensen, 1982). The cause of this anomaly remains unknown, but a genetic trait is suspected (Lewis et al., 1986). Congenital cataracts and microphthalmia in the Miniature Schnauzer (Gelatt et al., 1983; Shastry & Reddy, 1994; Zhang et al., 1991) and microphthalmia in the Australian Shepherd (Gelatt & McGill, 1973; Gelatt et al., 1981) are recessively inherited. In the Australian Shepherd dog, microphthalmia is associated with equatorial staphylomas, persistent pupillary membranes, and retinal dysplasia (Gelatt & Veith, 1970). Poorly pigmented animals are most affected (Bertram et al., 1984). Collies and Shetland Sheepdogs with Collie eye anomaly often exhibit variable degrees of microphthalmia (Kern, 1991); this is especially true for merles. Microphthalmia has also been observed in the Beagle (Saunders & Rubin, 1975), Akita (Laratta et al., 1985), Chow Chow (Collins et al., 1992), Cavalier King Charles Spaniel (Narfström & Dubielzig, 1984), Irish Wolfhound (Kern, 1981), and a number of other breeds of dog (Bayon et al., 2001; Boroffka et al., 1998).

Vascular Anomalies

Orbital varices and arteriovenous fistulas are very rare orbital anomalies with few reported cases. Varices can be congenital (Adkins et al., 2005) as well as acquired. In humans, they are often a sequel of head trauma (Troost & Glaser, 1995), which has also been suspected in orbital varix (Millichamp & Spencer, 1991) and arteriovenous fistulation cases in dogs (Tidwell et al., 1997). In contrast to humans, dogs typically present with a nonpainful, pulsating, or intermittent exophthalmos (Komar & Schuster, 1967; Ruehli & Spiess, 1995b). A decrease in venous return from the head can influence the extent of exophthalmos if an orbital varix is present, with the exophthalmos worsening when the head is kept low or pressure applied to the jugular vein region (Adkins et al., 2005). In arteriovenous fistula cases, not varices (Millichamp & Spencer, 1991), a systolic murmur ("bruit") can be auscultated in the orbital region (McCalla & Moore, 1989; Rubin & Patterson, 1965).

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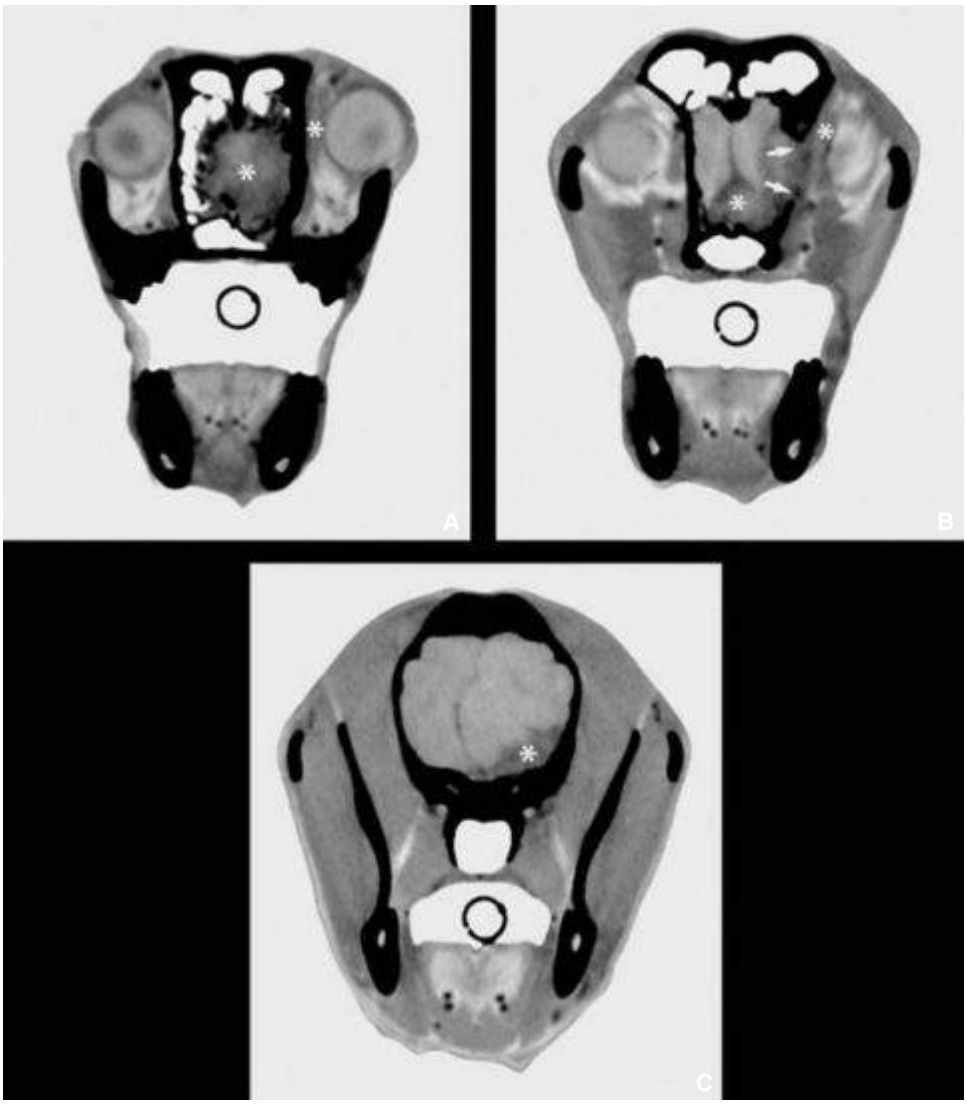


Figure 14.15 Postcontrast computed tomography (CT) study, transverse plane, soft tissue window: extensive osteolysis (**B**; arrows) and a mass lesion (asterisks) extending into the nasal cavity (**A**), orbit (**A**, **B**), and cranial vault (**B**, **C**). Based on the nasal extension of the mass, identified on this CT examination, tissue samples were acquired via rhinoscopy. Histologic examination yielded a diagnosis of blastomycosis. (Courtesy of R. Drees.)

The diagnosis of these vascular anomalies is made on the basis of clinical signs and results of diagnostic imaging, including dynamic contrast CT imaging and magnetic resonance angiography (Tidwell et al., 1997).

Treatment can be difficult and the prognosis is guarded. Ligation of orbital vessels can cause massive hemorrhage, necessitating enucleation of the globe and/or ligation of the common carotid artery. Orbital exenteration and careful hemostasis should be curative. The successful use of guided coil embolization with or without subsequent application of intravenous sclerosing foam has been described in dogs with an orbital varix (Adkins et al., 2005; Saunders et al., 2018).

Table 14.2 lists the most important differential diagnoses for exophthalmos.

Orbital Cysts

A retrobulbar dermoid cyst (Walde, 1997), microphthalmia-associated orbital cysts of neural tissue (Regnier et al., 2008), and medial canthal cysts originating from lacrimal glandular or nasolacrimal ductal tissue in young dogs (Ota et al., 2009) have been reported. Surgical excision is recommended. Intralesional injection of a sclerosing agent (1% polidocanol) was recently reported to be successful in resolving a suspected nasolacrimal duct cyst in a dog (Zimmerman et al., 2019).

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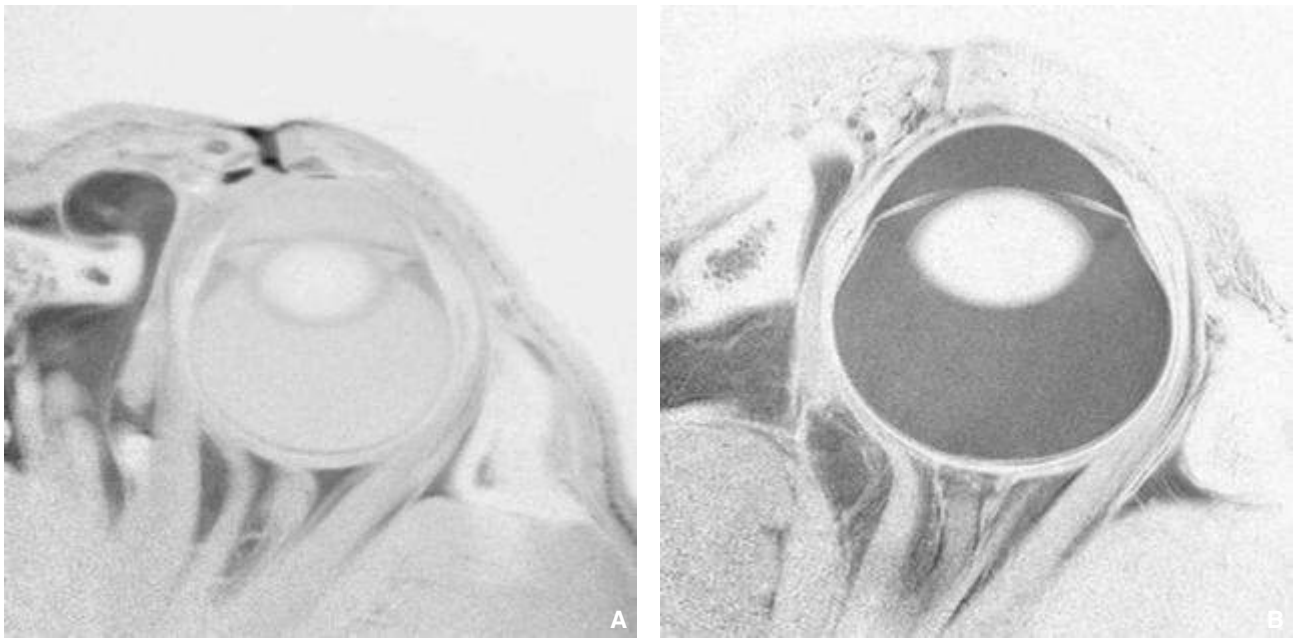


Figure 14.16 High-resolution magnetic resonance imaging in a healthy, 8-year-old Beagle dog: T1 (**A**) and T2-weighed (**B**) images. Note the detailed depiction of the ocular and cranial orbital structures.

Table 14.1 Diagnostic imaging: Added value beyond clinical examination/indications.

	Radiography	Ultrasound	Computed Tomography (CT)	Magnetic Resonance Imaging (MRI)
Cellulitis	–	+/–	+	++
Abscess	–	+	++	++
Foreign body				
Metallic	++	+	++	X[a]
Bone	+	+	++	++
Glass/plastic	–	+/–	++	++
Plant (grass awn/wood)	–	+/–	+	+
Salivary cyst	–	+	+	++
Neoplasia				
Intraorbital	+/– (mineralization)	+	++	++
Affecting bone	+/– (size, location)	+/– (location)	++	+
Extraorbital extension	+/–	+/–[b]	++	++
Intracranial extension	–	+/–[b]	+	++
Biopsy/aspirate guidance	–	+[c]	+[d]	–
Three-dimensional reconstruction	–	+	++	++

–, No added clinical value beyond what can already be deduced based on clinical examination findings; +, of added diagnostic value; ++, significant addition of diagnostic information.
[a] An MRI is contraindicated in the presence of a metallic foreign body, as those can possibly dislodge under influence of the strong magnetic field.
[b] In cases where major bone lysis has taken place, extraorbital structures may become visible on ultrasound. In such cases the suspicion of involvement can be raised.
[c] Aspirates and biopsies can be guided in real time (or as the needle is being advanced) with ultrasound assistance.
[d] Real-time guidance is not possible with CT assistance. Rather, the needle will be placed and its position assessed with a quick scan. Needle position can then be adjusted and reassessed as needed. Delineation of the lesion, on the other hand, is much more precise with CT compared to ultrasound.
Source: Information from Armour et al. (2011); Attali-Soussay et al. (2001); Boroffka et al. (2007); Byrne & Green (2002); Calia et al. (1994); Dennis (2000, 2008); Drees et al. (2009); Gonzalez et al. (2001); Grahn et al. (1993); Hendrix & Gelatt (2000); Malhotra et al. (2011); Mason et al. (2001); Morgan (1989); Penninck et al. (2001); Stuhr & Scagliotti (1996).

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Table 14.2 Causes of exophthalmos.

Vascular anomalies
Orbital varix
Orbital arteriovenous fistula
Cystic lesions
Salivary retention cyst and mucocele
Inflammatory lesions
Abscess
Cellulitis
Granuloma
Extraocular muscle myositis
Masticatory muscle myositis
Neoplasia
Primary orbital
Metastatic or primary multifocal
Locally invasive tumor invading orbit
Traumatic causes
Orbital fracture
Hematoma
Emphysema
Miscellaneous
Craniomandibular osteopathy

Acquired Orbital Diseases

Inflammatory Lesions: Orbital Cellulitis/Abscess

In contrast to large animals, orbital inflammatory diseases are rather common in small animals, especially in dogs. According to most studies, dogs presenting with non-neoplastic orbital diseases are significantly younger than dogs presenting with neoplastic diseases. In one representative study, dogs presented with orbital abscesses at a mean age of 4 years, whereas the mean age of tumor patients was 9.5 years (Boroffka et al., 2007; Dennis, 2000; Ruehli & Spiess, 1995b). Other studies showed no significant age difference between these two groups of patients (Calia et al., 1994; Mason et al., 2001).

Typically, dogs present with acute, unilateral exophthalmos (Fig. 14.17), protrusion of the nictitating membrane, conjunctival hyperemia and chemosis, episcleral venous congestion, periocular swelling, serous to mucopurulent ocular discharge, and pain. The globe itself is generally normal and normotensive. Affected dogs are usually febrile and inappetent, although in one study none of the 12 animals with orbital cellulitis presented with these signs (Armour et al., 2011). This underlines the potential inaccuracy of a diagnosis based on clinical symptoms alone. A white blood cell count usually reveals neutrophilia.

The underlying cause often remains unidentified (Koch, 1980), but foreign material is sometimes encountered (Grahn & Wolfer, 1993; Ruehli & Spiess, 1995b; Stades et al., 2003). The point of entry of such foreign bodies is not always easily identified. Foreign bodies may enter the orbit from the oral cavity, percutaneously, or through the conjunctival sac. Hematogenous infection of orbital tissues has been suspected as well. Microorganisms may invade from the oral cavity, sinuses, or tooth roots, notably the caudal roots of the upper fourth premolar and the roots of the upper first and second molar teeth (Grahn et al., 1995a; Hakanson, 1994; Ramsey et al., 1996). The presence of a swelling or fistula on the surface of the maxillary bone (Fig. 14.18) anterior to the orbital margin is a typical sign of an apical tooth root infection. Overly aggressive or improper dental extraction techniques can result in inadvertent penetration of, and introduction of an infection into, the orbit and potentially even the globe (Ramsey et al., 1996; Smith et al., 2003). Infections of the zygomatic gland may present as orbital cellulitis or abscess (Simison, 1993), and in these cases a swollen excretory duct may be seen lateral to the second molar tooth. In another study the majority of dogs with zygomatic sialadenitis were male and of medium or large breeds. The disease was unilateral in 9/11 dogs and a sialocele formed in 7/11 dogs. Both MRI and CT were excellent diagnostic methods to identify sialadenitis. Medical treatment with antimicrobials and anti-inflammatory drugs resolved clinical signs within 3 weeks in most dogs (Cannon et al., 2011). Significant inflammatory diseases of the globe itself (panophthalmitis, scleritis) can also cause orbital cellulitis. Ultrasound can be useful in confirming typical globe abnormalities in combination with signs of cellulitis, including retrobulbar fluid accumulation (Fig. 14.19).

Wang et al. (2009) identified extension from adjacent structures, exogenous trauma, and foreign bodies as the most common causes of infectious orbital disease. *Staphylococcus* spp. were isolated in 25%, E. coli in 16.7%, *Pasteurella multocida* in 8.3%, and anaerobic bacteria (mostly *Bacteroides* and *Clostridium* spp.) in 30.5% of the canine patients in this study. In another study, *Pasteurella* spp. were the most common isolates from orbital abscesses (Ruehli & Spiess, 1995b). Fungal organisms are an uncommon cause of orbital disease (Baron et al., 2011; Bruchim et al., 2006; Dubielzig et al., 2010; Roberts & Thompson, 1969) and the clinical signs are usually pathognomonic for orbital inflammatory diseases. Onchocercosis seems to be an emerging disease in the southwestern United States and south-central Europe. In chronic cases, the worms are incorporated in

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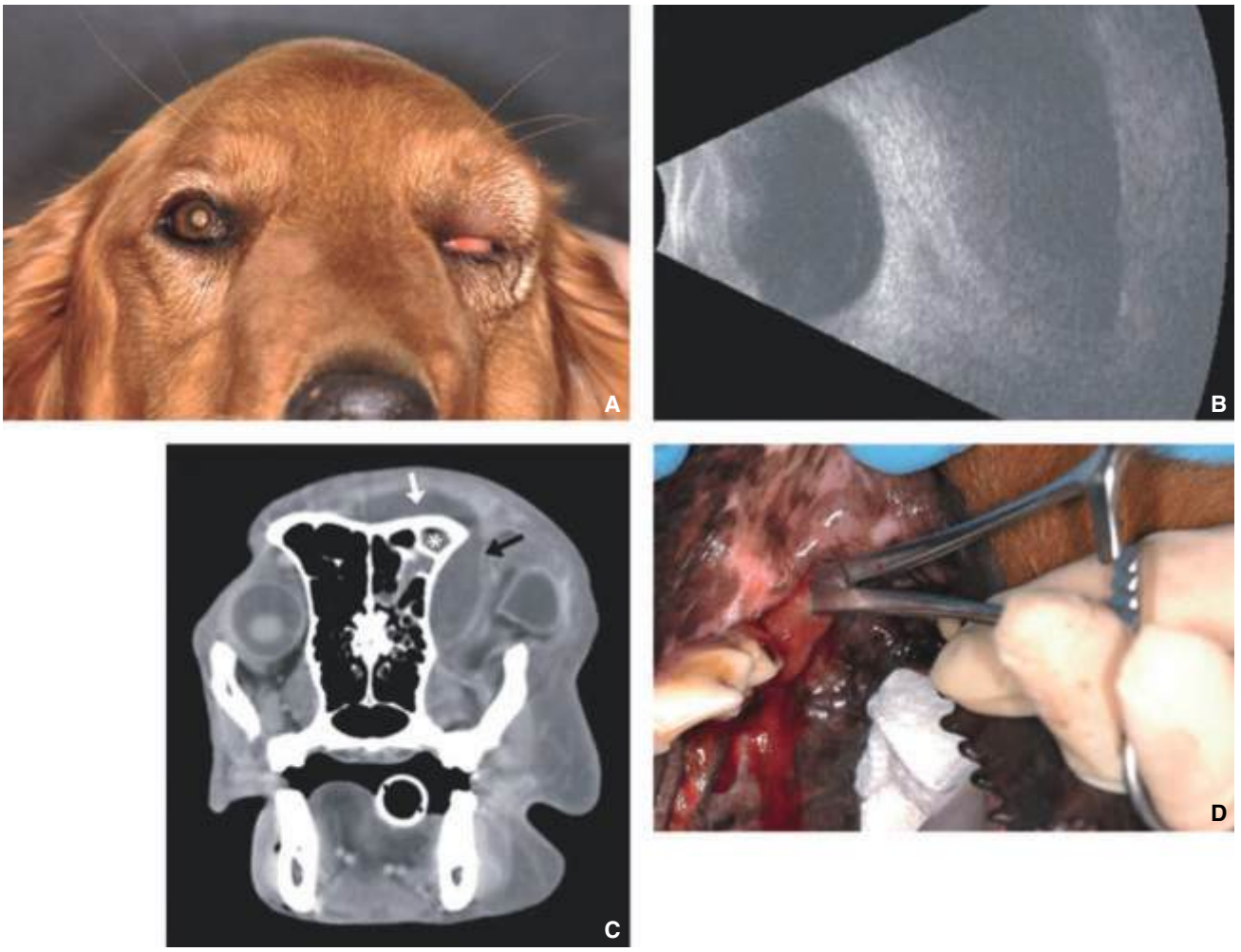


Figure 14.17 **A**. Clinical presentation of a 2-year-old dog presenting with a sudden, painful exophthalmos of the left eye. **B**. Ultrasound of the left retrobulbar space, occupied by a large hypoechoic lesion with a relatively well-defined cranial border and demonstrating a loss of orbital tissue contrast. **C**. Postcontrast computed tomographic study revealing lesion extent: generalized swelling and hypoattenuation of the soft tissues along the left side of the face, and an abscess with hypoattenuating center (white arrow) and contrast-enhancing capsule (black arrow) is identified along the dorsal and lateral surfaces of the frontal bone. Sinus involvement (asterisk) is seen (intracranial extension was present on other slices), the peribulbar area is compartmentalized, and the globe itself severely compressed. **D**. Abscess drainage caudal to the last upper molar. All images represent the same patient. (Courtesy of the University of Wisconsin-Madison Comparative Ophthalmology Service.)

subconjunctival, episcleral, and orbital granulomas, causing corresponding clinical symptoms. Treatment consists of surgical excision and the postoperative use of macrofilaricid drugs (Dubielzig et al., 2010; Komnenou et al., 2002; Sreter & Szell, 2008). Other parasites are rarely identified in orbital disease (Laus et al., 2003).

Ultrasonography is a cost-effective method to determine the presence of a drainable retrobulbar abscess and to screen for the presence of a foreign body (see Fig. 14.17B). The type of foreign body material dictates which imaging modality is most useful for identification. Most foreign bodies are not recognized on plain radiographs, but metallic foreign bodies are easily demonstrated. MRI scans are contraindicated when a suspicion for a metallic FB exists, due to the risk of FB displacement under the influence of the strong magnetic field (Malhotra et al., 2011). Low-field (0.4 Tesla) MRI tends to overestimate the presence of foreign bodies, according to a recent publication (Fischer et al., 2019). A CT scan can directly pick up foreign bodies that are sufficiently dense (metal, glass, bone). Foreign bodies of lower density (plant material, wood, plastic, porcupine quills) may be identified in postcontrast studies as a filling defect with a contrast-enhancing rim of reactive tissue (Boroffka et al., 2011). In patients that show clinical signs consistent with extraorbital involvement, CT or MRI studies to evaluate the extent of periorbital tissue involvement and to determine the prognosis are indicated (see Fig. 14.17C; Kneissl et al., 2007). Intracranial extension of

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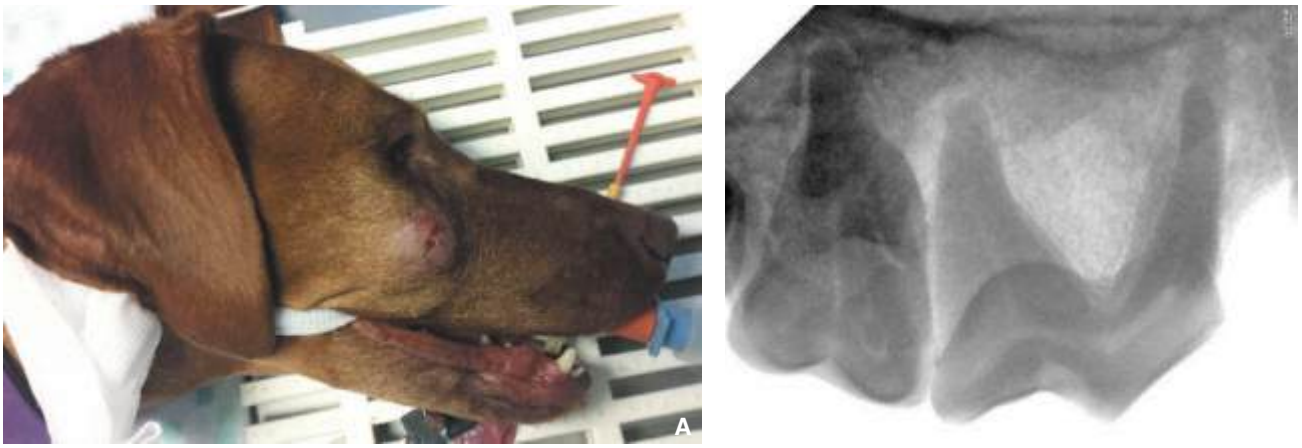


Figure 14.18 Clinical appearance of a suborbital fistula (**A**) originating from a tooth root abscess of P4 with apical alveolar bone lysis (**B**). (Courtesy of S. Grundmann.)

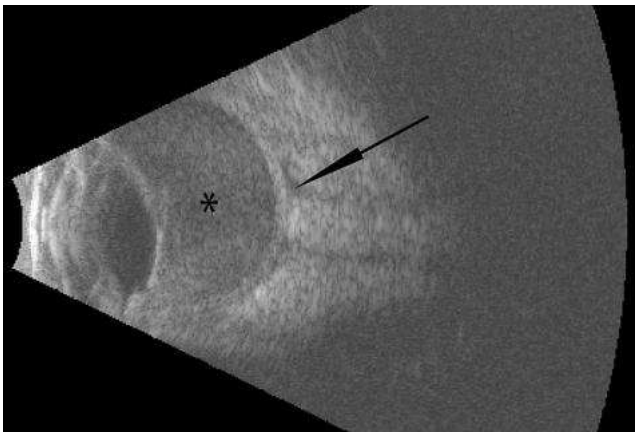


Figure 14.19 Ultrasound B-scan image of a patient with blastomycosis panophthalmitis and secondary orbital cellulitis. Note the hyperechogenicity of the vitreous (asterisk), the lack of contrast between the orbital tissues, and the fact that the outer contour of the sclera and optic nerve is visible due to retrobulbar fluid accumulation (thin black arrow). (Courtesy of the University of Wisconsin-Madison Comparative Ophthalmology Service.)



Figure 14.20 Postcontrast computed tomography study, transverse plane of a dog with orbital cellulitis: mild exophthalmos and a loss of definition of orbital structures. (Courtesy of M. Dennler.)

fungal and bacterial orbital disease is possible and significantly decreases the prognosis for survival (Baron et al., 2011; Hecht et al., 2011; Oliver et al., 2009). As with ultrasound, a loss of definition of orbital structures, increased attenuation of orbital fat, and a diffuse, poorly defined mass effect are the typical feature of orbital cellulitis on CT and MRI images (Fig. 14.20; Armour et al., 2011; Lederer et al., 2015).

Obtaining samples for cytology and culture/sensitivity assays is an important step in the diagnostic process. FNAs and tissue biopsies can be used for these purposes. A surprisingly high number of submitted cultures yield negative results, however (Armour et al., 2011; Wang et al., 2009).

The first and most important step in treating an orbital abscess is drainage, which is performed in general anesthesia with protection of the airways through intubation and tube cuffing. The oral mucosa behind the last upper molar tooth, which may show a fluctuating swelling, is incised. A closed hemostat is advanced through the pterygoid muscle (Fig. 14.21) and then opened and withdrawn without closing (see Fig. 14.17D). The hemostat is advanced in a blind fashion into an area richly supplied by blood vessels and nerves, but complications are rarely encountered. However, damage

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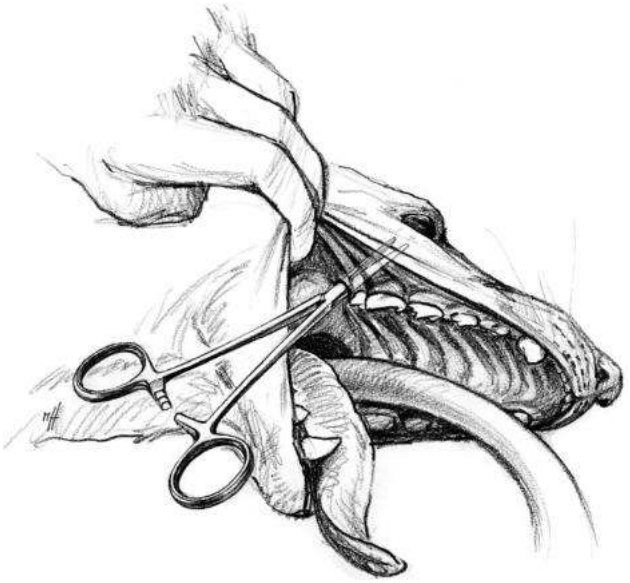


Figure 14.21 Transoral abscess drainage technique.

to the optic and ciliary nerves has been observed (Kern, 1991; Ruehli & Spiess, 1995a, 1995b). Irrigation of the retrobulbar area is a controversial issue. Exacerbation of the exophthalmos and spreading of infectious organisms are potential complications. On the other hand, irrigation with crystalline penicillin has been beneficial (Slatter, 1990). When orbital ultrasonography fails to reveal an abscess, drainage of the orbit may be postponed, and systemic antibiotic therapy instituted instead. Most orbital inflammations respond within 2–3 days with systemic antibiotic therapy.

Systemic antibiotic therapy using broad-spectrum antibiotics is usually indicated pending the results of bacterial culture and sensitivity testing. A relatively high incidence of mixed aerobic/anaerobic and pure anaerobic bacterial infections has been reported (Jang et al., 1997; Wang et al., 2009). Use of cephalosporins, extended-spectrum penicillins (e.g., ticarcillin), potentiated penicillins (e.g., amoxycillin-clavulanic acid), and carbapenems was therefore recommended based on aerobic and anaerobic culture sensitivity results in these and other studies. Additionally, if no contraindications exist, these patients are usually treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Hot packs also are beneficial and well tolerated by most dogs (Ruehli & Spiess, 1995a, 1995b).

The globe itself must be treated symptomatically. In cases of lagophthalmos, lubrication of the ocular surface is important. The degree of exophthalmos often increases temporarily after drainage, and a temporary tarsorrhaphy may be necessary. Soft food should be offered until the globe is back in its normal position.

The prognosis is usually good. In a series of 17 cases, 15 healed within a week, one healed after one recurrence, and one was lost to follow-up (Ruehli & Spiess, 1995a, 1995b). In most cases, the exophthalmos regresses within 36–48 hours, and the general condition of the animal markedly improves. Long-term ophthalmic pathology was observed in 30% of dogs following retrobulbar cellulitis and abscessation in a recent retrospective study, with 5/41 dogs suffering permanent blindness due to suspected optic nerve compression. This highlights the need for initial ophthalmic assessment and follow-up examinations (Fischer et al., 2018). If foreign material is retained in the orbit, recurrences are to be expected. An attempt to identify and localize a potential foreign body via ultrasound, CT, or MRI is warranted in such cases. Surgical retrieval of an identified foreign body can be performed via abscess drainage or any of the orbitotomy techniques described later in this chapter. Surgical exploration via orbitotomy and flushing of the retrobulbar space was effective in curing patients with recurrent retrobulbar abscesses in one case series (Tremolada et al., 2015). Patients presenting with chronic purulent ocular discharge should be checked for the presence of a conjunctival fistulous tract, along which foreign body material may be retrieved via surgical exploration (Fig. 14.22; Stades et al., 2003).

Salivary Retention Cysts and Mucoceles (Sialoceles)

Cystic structures in the orbit or periorbital tissues can arise from any glandular or epithelial tissue, including lacrimal, third eyelid, and salivary glands, and conjunctival or paranasal sinus mucosa. The main clinical signs relate to the mass effect created by the volume and location of the cyst.

Mucoceles (or sialoceles) usually result from trauma to the head, with or without skull fractures (Knecht et al., 1969; Schmidt & Betts, 1978). In a mucocele, leakage of saliva from the zygomatic gland or its excretory duct causes inflammation and tissue fibrosis (Slatter & Basher, 2003), resulting in a thick fibrous capsule, but no true epithelium, surrounding the cavitary lesion. A mucocele is therefore not a true cystic lesion (Dubielzig et al., 2010). Mucoceles must be distinguished from salivary retention cysts, caused by inflammation and ulceration of the oral mucosa and obstruction of salivary outflow, with subsequent cyst formation (Bartels, 1990; Nell & Walde, 1994).

Salivary retention cysts are true cysts, which are lined with a true epithelium when viewed histologically (Dubielzig et al., 2010). These cysts are caused by obstruction of the salivary duct, typically due to sialoliths or inflammation of the oral mucosa. The reaction of tissues surrounding the cysts is minimal. A distended excretory duct of the zygomatic gland can sometimes be seen in the oral mucosa. The clinical distinction is not always possible, since the clinical signs of retention cysts and mucoceles are similar: a fluctuating swelling with a variable position within the orbit and possible conjunctival or oral presentation. Exophthalmos and

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Figure 14.22 Orbital foreign body in a 6-year-old dog. **A**. Initial presentation with chronic purulent discharge from the right eye. **B**. Fistulous tract in the dorsal conjunctival fornix. **C**. Surgical exploration of the fistulous tract. **D**. Foreign material (wood) retrieved from the orbit.

protrusion of the nictitating membrane are usually present, and pain on opening the mouth or palpation of the globe is variable, but usually minimal. In one case, strabismus and secondary iritis were observed (Nell & Walde, 1994).

The diagnosis is made on the basis of clinical signs and results of orbital ultrasonography, CT. and/or MRI. Tissue characteristics identified via MRI can assist with disease differentiation (Boland et al., 2013). Aspiration of a yellowish and slightly tenacious fluid with variable amounts of blood is typical for mucoceles (Schmidt & Betts, 1978). True cysts usually yield clear to mucoid fluid.

Mucoceles are best treated by surgical excision of the cystic cavity and associated gland (Slatter & Basher, 2003). In cases of salivary retention cysts, treatment of the oral mucosal disease is essential; at the same time, the cyst can be drained from the oral cavity, similar to an orbital abscess. Successful use of sclerotherapy after aspiration of cyst contents has been described (Stuckey et al., 2012). The prognosis appears to be favorable. In most reported cases, healing occurred within a short time following surgical and medical therapy.

Myositis

Because of the absence of a temporal bony orbital wall, swelling or atrophy of the muscles of mastication will displace the globe (Fig. 14.23A). Eosinophilic myositis of the muscles of mastication, or masticatory muscle myositis (MMM), predominantly affects young German Shepherds and Weimaraners, but has also been described in Labrador Retrievers and Golden Retrievers (Koch, 1980). MMM is an immune-mediated inflammatory myopathy targeting the temporalis, masseter, and pterygoid muscles of mastication. These muscles contain type 2M myofibers, which are composed of myosin heavy and light chains unique to the masticatory muscles. This unique myofiber-type composition provides the basis for the preferential susceptibility of masticatory muscles to myositis (Orvis & Cardinet, 1981). Type

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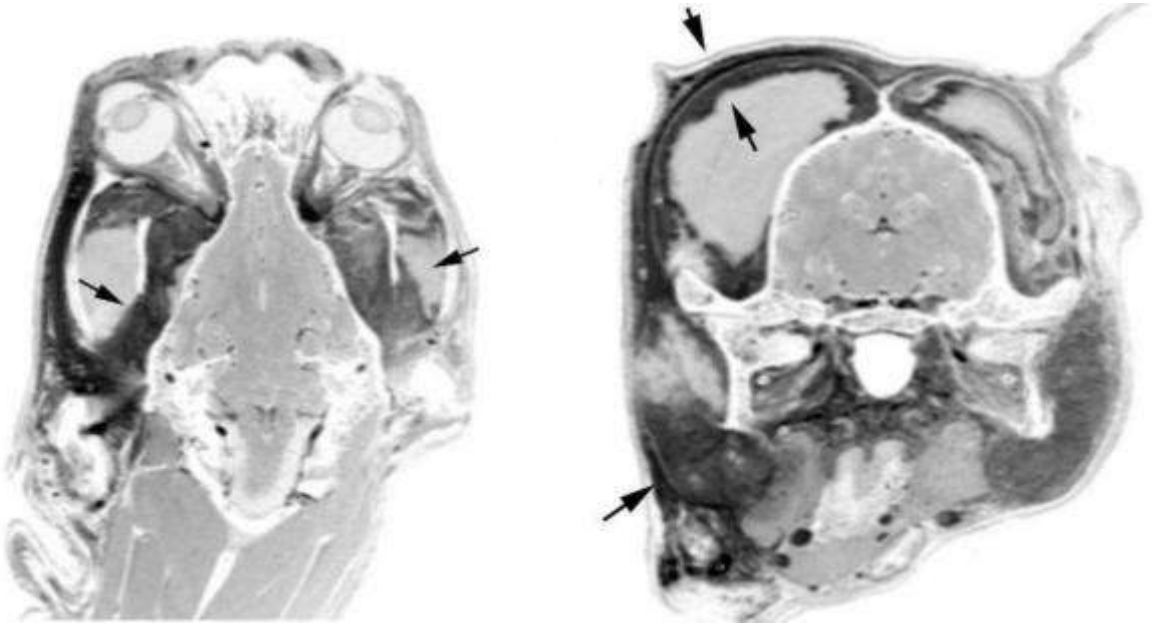


Figure 14.23 **A**. Masticatory muscle myositis in a German Shepherd. There is marked swelling of the masticatory muscles and bilateral exophthalmos, which is more marked in the left eye. (Courtesy of I. Walde.) **B**, **C**. Postcontrast magnetic resonance imaging T1-weighed study of a different patient, dorsal (**B**) and transverse (**C**) planes: note the marked irregular contrast enhancement of the inflamed muscle bellies (white arrows) accentuated in the peripheral muscle areas.

2M fiber-specific autoantibodies against masticatory muscle myosin heavy and light chains are routinely found in dogs with MMM, but not in dogs with polymyositis, using immunoblotting and enzyme-linked immunosorbent assay (ELISA; Shelton, 2007; Shelton et al., 1987). A major target for autoantibodies in canine MMM has been identified and named masticatory myosin binding protein-C (Wu et al., 2007). In acute myositis, a leukocytosis with peripheral eosinophilia, elevated serum levels of creatine phosphokinase, and a positive 2M antibody test are typically present. Histopathology of temporal muscle biopsies reveals degeneration of muscle fibers as well as neutrophilic and eosinophilic infiltration (Carter, 1981). The digastricus muscle does not contain type 2M fibers (Bubb & Sims, 1986), which likely explains the results of a study describing CT findings in dogs with MMM, in which abnormalities were identified in the temporalis, masseter, and pterygoid muscles of mastication, but not in the digastricus muscle (Reiter & Schwarz, 2007).

MMM is usually an acute disease accompanied by fever, lethargy, anorexia, and weight loss. Pain and swelling of the masseter and temporal and pterygoid muscles causes painful and restricted jaw movements and exophthalmos, respectively. Optic neuritis and subsequent blindness have been described in association with acute MMM (Lescure,

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1985). Despite the fact that this is a bilateral disease, symptoms of bilateral muscle involvement are not always appreciable clinically. Without treatment, inflammatory episodes persist for 1–3 weeks (Carter, 1981). Acute myositis must be differentiated from orbital cellulitis or abscesses, temporomandibular joint disease, and (extraocular) polymyositis. Cross-sectional imaging (ultrasound, CT, MRI) can assist with an early diagnosis of MMM (Fig. 14.23B, C). Changes in size, signal attenuation, and inhomogenous contrast enhancement have been identified via CT in the masticatory muscles of dogs with MMM (Czerwinski et al., 2015; Reiter & Schwarz, 2007). Masticatory muscles were swollen and hyperintense on T2-weighted and gradient echo short tau inversion recovery (GE STIR) sequences in MRI, indicating inflammation-induced muscle edema (Cauduro et al., 2013).

Fibrosis of the muscles of mastication causes muscle atrophy, enophthalmos, and an inability to open the mouth in chronic cases. Muscle fibrosis without inflammatory infiltrates is evident histologically, and leucocyte, creatine phosphokinase, and 2M antibody levels are unlikely to be elevated. This situation must be differentiated from neurogenic and steroid-induced muscle atrophy, and from atrophy secondary to endocrine diseases. Difficulties in opening the mouth can handicap a dog and negatively impact its quality of life. Severe enophthalmos causes secondary entropion and may impair vision in combination with nictitans protrusion. In some cases, muscle fibrosis and atrophy occur without clinically detectable antecedent inflammation (Kern, 1991; Whitney, 1970).

Extraocular polymyositis has been described in 37 dogs, of which 29 were female and 21 were Golden Retrievers (Williams, 2008; Fig. 14.24). Affected dogs are typically young. Bilateral exophthalmos with anterior globe displacement, retraction of the upper eyelid without protrusion of the nictitating membrane, and congestion of episcleral vessels are common presenting signs. A predominantly CD3+ lymphocytic infiltrate dominates the muscle histopathology (Dubielzig et al., 2010). In chronic cases, fibrosis of the extraocular muscles can cause mild enophthalmos and strabismus. In contrast to Graves' disease in humans, extraocular polymyositis is not associated with either hyper- or hypothyroidism (Carpenter et al., 1989). Ultrasonography, CT, or MRI will reveal swollen extraocular muscles in cases of extraocular polymyositis (Fig. 14.25).



Figure 14.24 Bilateral extraocular polymyositis in an 8-month-old Golden Retriever. Note the bilateral symmetric exophthalmos without nictitans membrane protrusion.

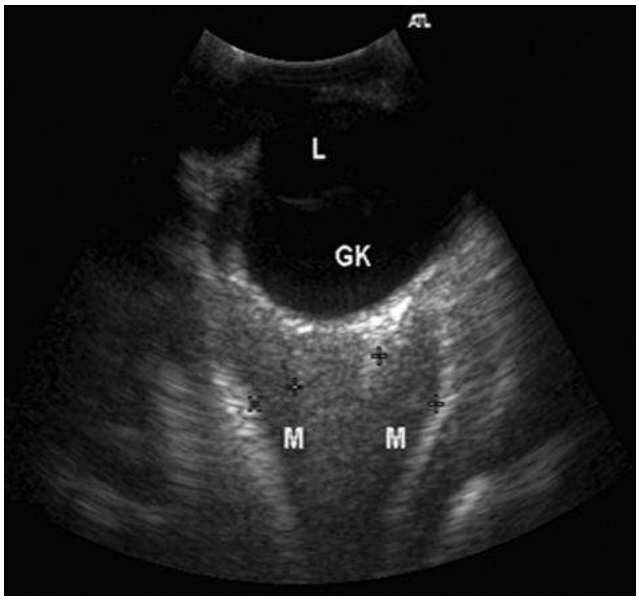


Figure 14.25 Ultrasonographic image of the swollen rectus muscles (outlined by asterisks) in a 5-year-old Great Dane with extraocular polymyositis.

Restrictive nasoventral strabismus has been described as a uni- or bilateral (Fig. 14.26), progressive esotropia in young dogs, which can lead to blindness within a few weeks (Allgoewer et al., 2000). Extraocular muscle fibrosis was histologically diagnosed in all specimens in this case series, and signs of either acute or chronic lymphocytic inflammation (extraocular muscle myositis) were present in most cases. Radical surgical transection of the affected muscles resulted in a central eye position in 9/12 treated eyes, although most eyes remained enophthalmic. Three of the treated eyes returned to the original preoperative position following surgical correction.

In the acute stages, myositides respond well to immunosuppressive doses of oral corticosteroids over 3–4 weeks. Azathioprine can be given at a dose of 1–2 mg/kg body weight for 10–14 days and then tapered off. The prognosis is guarded. Recurrence rates have traditionally been reported to be quite low (Koch, 1980), but relapses may occur (Kern, 1991). Uncontrolled myositis will invariably lead to atrophy of the affected muscles. Advanced muscle atrophy and fibrosis cannot be influenced medically. Silicone or glass beads

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Figure 14.26 Bilateral esotropia in an 18-month-old field trial Labrador Retriever. Clinically, this patient demonstrated limited spontaneous abduction of both eyes (OU) and forced duction toward the temporal side was restricted OU. A slight posterior movement of the globe was noticed while rotating the globe in a temporal direction. A nasal rotation of the superior retinal veins was observed OU. This was interpreted as evidence of dorsal oblique and medial rectus muscle shortening and likely fibrosis. (Courtesy of the University of Wisconsin-Madison Comparative Ophthalmology Service.)

have been implanted in the orbit to correct the enophthalmos, but migration of these implants has been a major problem in both humans and animals (Helms et al., 1987).

Neospora caninum has been associated with extraocular polymyositis in a litter of German Shorthaired Pointers (Dubey et al., 1990). Infectious causes of myositis, like neosporosis, toxoplasmosis, leishmaniasis (Naranjo et al., 2010), and lyme borreliosis (Raya et al., 2010), need to be considered as a differential diagnosis for masticatory and extraocular muscle myositis.

Orbital Neoplasia

Tumors represent the most common group of orbital diseases. Primary tumors can arise from any orbital tissue, and secondary neoplasms either invade the orbit from adjacent structures or metastasize to the orbit from distant sites. In general, orbital neoplasms occur in older animals (Attali-Soussay et al., 2001; Boroffka et al., 2007; Calia et al., 1994; Cirla et al., 2016; Dennis, 2000; Mason et al., 2001; Ruehli & Spiess, 1995a).

Depending on the localization, orbital tumors cause slowly progressive, unilateral exophthalmos or enophthalmos, with variable displacement and indentation of the globe (Slatter & Basher, 2003). Nictitans protrusion is present and retropulsion of the globe is decreased or impossible. Bilateral orbital neoplasia appears to be extremely rare. In contrast to orbital inflammatory diseases, neoplasms tend not to be painful. However, a diagnosis of orbital neoplasia cannot reliably be made based on clinical signs alone. In a retrospective study of 44 dogs with orbital neoplasia, Hendrix and Gelatt (2000) found that one-third of patients with neoplastic disease showed acute symptoms of pain, purulent inflammation on cytology, and/or a favorable initial response to antibiotics. Osteolytic processes are usually associated with pain as well. Vision can be retained even in chronic cases, depending on the level of pressure or tension on the optic nerve. Tumors arising from the optic nerve or its meninges will cause blindness at an early stage (Spiess et al., 1995). On top of the clinical signs already described, nasosinal tumors can cause epistaxis, altered percussion tones, and pain upon palpation and/or percussion of the nasosinal cavities, and a decreased or absent airflow through the nose.

The frequency of occurrence of the various types of orbital tumors in dogs, as diagnosed in some larger case series, is listed in Table 14.3 (Armour et al., 2011; Attali-Soussay et al., 2001; Boroffka et al., 2007; Calia et al., 1994; Cirla et al., 2016; Dennis, 2000; Flaherty et al., 2020; Gilger et al., 1992; Hendrix & Gelatt, 2000; Kern, 1985; Mason et al., 2001; O'Brien et al., 1996; Ruehli & Spiess, 1995a). According to these studies, the most common orbital tumors in dogs are:

1) Tumors of mesenchymal origin (osteosarcoma, fibrosarcoma, multilobular osteochondrosarcoma).
2) Tumors of epithelial origin (mostly adenocarcinoma, among which primary nasosinal tumors were common).
3) Miscellaneous (peripheral nerve sheath tumor, orbital meningioma, mastocytoma).

Most of these tumors are of primary orbital origin, with the exception of nasal and paranasal sinus tumors. All of the tumors listed above are malignant.

A complete general physical exavmination, including evaluation of regional and distant lymph nodes, and a search for possible metastases via thoracic and abdominal imaging are part of a routine workup.

Characteristics of orbital neoplasia, identifiable with the various imaging modalities, have been described in "Ancillary Diagnostic Tests" (see Fig. 14.7, Fig. 14.12, Fig. 14.13, and Fig. 14.14). MRI characteristics of some major tumor types (carcinoma, sarcoma, lymphoma) have been described in detail (Armour et al., 2011).

After localization of the lesion, an FNA or tissue biopsy is obtained. The diagnostic sensitivity of the various sampling procedures is discussed in "Ancillary Diagnostic Tests". On cytology, lymphoma can sometimes be difficult to distinguish from a benign reactive proliferation of lymphocytes. In such cases, a polymerase chain reaction assay for antigen receptor rearrangement (PARR) can be used to determine the clonal origins of lymphocyte populations. Since clonal lymphocyte replication is a hallmark of neoplasia, this test can confirm the monoclonal origin (and thus tumorous nature) of lymphocytes. The test can be performed on blood, FNA, biopsy, and aqueocentesis samples (Burnett et al., 2003; Pate et al., 2011).

Unfortunately, many orbital neoplasms are discovered in an advanced stage at which euthanasia or palliative surgery

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Table 14.3 Neoplastic orbital diseases.

	Tumor Frequency		References[a]
1	2	3	
Nasal adenocarcinoma 14/112	Osteosarcoma 12/112	Anaplastic/undifferentiated sarcoma 11/112	Flaherty et al. (2020)
B-cell lymphoma 10/23	Fibrosarcoma 5/23	Soft tissue sarcoma 3/23	Cirla et al. (2016)
Carcinoma 13/53[b]	Sarcoma 8/53	Peripheral nerve sheath tumor 5/53	Armour et al. (2011)
Nasosinal tumor 9/29	Sarcoma 8/29	Carcinoma (not nasosinal) 6/29	Boroffka et al. (2007)
Adenocarcinoma 3/13	Osteosarcoma 2/13	Various 1/13 each	Attali-Soussay et al. (2001)
Nasosinal tumor 14/26	Sarcoma 6/26	Various 2/26 each	Mason et al. (2001)
Osteosarcoma 6/44	Fibrosarcoma 5/44	Nasosinal tumor 5/44	Hendrix & Gelatt (2000)
Adenocarcinoma 4/12[c]	Fibrosarcoma 2/12	Various 1/12 each	Dennis (2000)
Multilobular osteochondrosarcoma 10/24	Fibrosarcoma 4/24	Osteosarcoma 3/24	O'Brien et al. (1996)[d]
Meningioma 4/19	Mesenchymal mass 4/19	Fibrosarcoma 3/19	Ruehli & Spiess (1995a)
Nasosinal tumor 3/13	Various 1/13 each		Calia et al. (1994)
Osteosarcoma 6/23	Mastocytoma 4/23	Reticulum cell sarcoma 3/23	Kern (1985)
Squamous cell carcinoma 8/21	(Adeno-)carcinoma 5/21	Malignant lymphoma 3/21	Gilger et al. (1992)[e]

[a] Cats were excluded from this table for all but the last reference.
[b] Of these carcinomas, eight were suspected to be of nasosinal origin.
[c] Three of these four adenocarcinomas showed (para-)nasal involvement. The fourth was a recurrence of a previously incompletely removed third eyelid adenocarcinoma.
[d] A population bias exists in this study, since these patients were all candidates for orbitectomy surgery.
[e] This reference was incorporated for comparison: 21 cases of orbital neoplasia in cats.
Note: Top-tier orbital tumors in dogs:

- Tumors of mesenchymal origin (osteosarcoma, fibrosarcoma, multilobular osteochondrosarcoma)
- Tumors of epithelial origin (mostly adenocarcinoma, among which primary nasosinal tumors were common)
- Miscellaneous (peripheral nerve sheath tumor, orbital meningioma, mastocytoma)

is the only option. Osteolysis is a poor prognostic indicator and is associated with a significant decrease in survival time (Hendrix & Gelatt, 2000). Localized neoplasms without evident distant metastasis may be surgically removed via orbitotomy or orbitectomy and reconstruction procedures while preserving the globe and, possibly, the animal's vision. If preservation of the globe is not possible, exenteration of the globe or radical orbitectomy must be considered (for references, see "Orbitotomy and Orbitectomy"). Surgical management of orbital neoplasia can be combined with radiation therapy, chemotherapy, or both. For some tumor types, including nasosinal tumors, irradiation yields favorable results when used as monotherapy.

Nasosinal tumors are graded on a scale from 1 to 4, based on local tumor extension. Tumors involving the orbit are minimally classified as Stage 3. The median survival time after cobalt irradiation is significantly decreased for Stage 3 and 4 tumors (315 days), compared to Stage 1 and 2 tumors (745 days; Adams et al., 1998). A diagnostic CT scan can be used for radiation planning and was considered to be superior to MRI for nasal tumor staging (Drees et al., 2009). It is therefore important for treatment planning and prognostic purposes to include a CT scan in the diagnostic workup of a patient suspected of having a nasal tumor. Helical tomotherapy and modern linear accelerators with sophisticated treatment planning are different from older irradiation devices, like cobalt units, in that the avoidance of critical structures within the treatment field is an achievable treatment goal (Deveau et al., 2010). The use of such image-guided intensity-modulated radiation therapy modalities has resulted in survival times comparable to those attained using older methods, while massively reducing the occurrence of severe ocular side effects, including cataracts, retinal degeneration, keratoconjunctivitis sicca, and blindness (Lawrence et al., 2010; Pinard et al., 2012). Recently, canine sinonasal tumors were treated using image-guided intensity-modulated radiation therapy with an integrated boost technique in which the gross tumor volume was exposed to 20% additional irradiation. Only mild ocular side effects were observed during the first 3 months after treatment (Soukup et al., 2018). The tolerability of the simultaneously integrated boost technique for canine sinonasal tumors using image-guided intensity-modulated radiation therapy and improved local tumor control is predicted based on theoretical calculations (Gutierrez et al., 2007).

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Canine lobular orbital adenomas are benign tumors of lacrimal or salivary gland origin, consisting of multiple individual friable lobular units dispersed into the orbital connective tissues. Dogs typically present with painless eyelid and nictitating membrane swelling and anterior orbital involvement. Metastasis has not been reported. The risk for recurrence after surgical excision is high, unless the tumor is completely resected, which potentially requires orbital exenteration (Headrick et al., 2004).

Orbital myxosarcoma is a rare, slowly progressive neoplasm in dogs. Typically, large fluid-filled cavities are seen in the orbit and along fascial planes. The main differential diagnosis is zygomatic sialocele. Advanced cross-sectional imaging identified involvement of the temporomandibular joint in 6/7 cases in two studies. Osteolytic changes to the temporomandibular joint were identified on standard radiographs in two dogs. These tumors usually are not amenable to resection, but also typically show a slow and largely pain-free progression (Dennis, 2008; Parslow et al., 2016).

Benign orbital hibernomas are rare neoplasms of brown adipose tissue occurring in older dogs. Surgical excision should be curative (Ravi et al., 2014).

Canine orbital rhabdomyosarcoma is a malignant neoplasm predominantly of young dogs. Surgical resection had a favorable prognosis in older dogs in a recent case series (4/4 dogs alive 8–13 months after diagnosis), whereas the majority of younger dogs (9/11) were euthanized within 6 months (median 2.5 months) after diagnosis (Scott et al., 2016).

In most cases of orbital neoplasia, the prognosis is guarded at best. In one study of 12 cats and 13 dogs with retrobulbar tumors, the overall average survival time was 8.6 months, with a range of 1 month to 3 years. The average survival time was 1 month in cats and 13 months in dogs (Attali-Soussay et al., 2001). Most dogs with orbital neoplasms are euthanized shortly after diagnosis. With early diagnosis and surgical therapy, however, the survival time increases to several months to years (Kern, 1985; Lawrence et al., 2010; O'Brien et al., 1996; Spiess et al., 1995). Hendrix and Gelatt (2000) showed that, of the dogs that either died or were euthanized within 6 months of diagnosis, 78% (14/18 dogs) did not receive treatment. Of the dogs that survived for longer than 6 months, 86% (12/14 dogs) did undergo some form of therapy.

Traumatic Lesions

Orbital Fractures and Hematomas

Orbital fractures and hematomas usually result from road accidents. The frontal, temporal, and zygomatic bones are most commonly involved, and clinical signs include skin lacerations, pain, facial asymmetry, lacrimation, exophthalmos or enophthalmos, strabismus, proptosis, lagophthalmos, and secondary xerophthalmia. Contusions of the globe are often associated with lens luxation, intraocular hemorrhage, and retinal detachment. In severe cases, scleral ruptures, usually extending from the lamina cribrosa, may occur (Rampazzo et al., 2006). Fractures involving the paranasal sinuses may cause orbital or subcutaneous emphysema with crepitus (Ruehli & Spiess, 1995a; Slatter & Basher, 2003).

Animals with orbital fractures should be kept quiet to prevent further swelling and hemorrhage, and cold compresses should be administered. The eye must be cleansed immediately and kept lubricated.

Local and systemic antibiotics and systemic corticosteroids should be given. Topical steroids are administered if the corneal epithelium is intact. NSAIDs may increase the risk of further hemorrhages. Topical application of atropine sulfate is controversial, because secondary glaucoma may be a complication of marked hyphema.

As soon as the overall condition of the patient is stable, the eyes and orbit need to be further evaluated. CT is the fastest and most comprehensive imaging modality when dealing with trauma patients: an exact evaluation of fracture topography, a reliable assessment of globe integrity, and a complete evaluation of the entire head are possible. MRI would be the most useful imaging modality if intracranial changes are suspected. Ultrasonography of the globe may be indicated when hyphema prevents examination of the posterior segment. The reader is referred to "Ancillary Diagnostic Tests" for references.

Small, nondisplaced fractures stabilize spontaneously and do not require surgical reduction and fixation. Small, displaced, and offending bone fragments need to be removed surgically and large, unstable fractures may require internal fixation. Entrapment of extraocular muscle bellies is a possible complicating factor. A strabismus may be present and eye movements can be restricted, as are forced ductions in the opposite direction. Chronic entrapment can result in permanent loss of muscle function and even fibrosis, leading to a persistence of clinical signs. In cases of muscle entrapment, surgical therapy is indicated. Orbital fractures can induce an oculocardiac reflex in dogs, as evidenced by bradycardia and an atrioventricular block (Selk Ghaffari et al., 2009). To prevent serious exposure keratitis, a third eyelid flap or a temporary tarsorrhaphy is indicated. In cases with extensive trauma to the globe, the prognosis for long-term comfort is poor, phthisis bulbi is a common sequel, and enucleation is usually recommended.

Spontaneous orbital hematoma formation can occur as a result of rodenticide ingestion. Conjunctival or subcutaneous hematomas, exophthalmos, orbital pain, and typical clinical pathologic abnormalities (prolonged prothrombin time, normal to prolonged partial thromboplastin time, and normal to decreased platelets) are suggestive of the diagnosis. A favorable response to vitamin K1 treatment is typically quick and complete (Griggs et al., 2016).

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Orbital Emphysema

Orbital emphysema is usually a complication of enucleation. Brachycephalic dogs appear to be predisposed. This may result from increased pressure in the nasal cavity of such dogs during expiration. Air is pressed into the orbit via the nasolacrimal duct. Fractures of the paranasal sinuses may also cause orbital emphysema (Barros et al., 1984; Bedford, 1979; Martin, 1971; Slatter & Basher, 2003).

The soft swelling of an orbital emphysema often reveals crepitus when palpated. If clinical signs are equivocal, plain radiographs will show air in the orbit and, at the same time, may demonstrate orbital fractures. Orbital emphysema resolves spontaneously in most cases. If an emphysema persists or occurs later after enucleation, the proximal end of the nasolacrimal duct must be identified and ligated (Gornik et al., 2015; Slatter & Basher, 2003). In brachycephalic breeds, prophylactic ligation of the nasolacrimal duct at the time of enucleation could be considered.

Proptosis

Proptosis results from a sudden, forward displacement of the globe with simultaneous entrapment of the eyelids behind the equator (Gilger et al., 1995). This entrapment prohibits spontaneous repositioning of the globe (Fig. 14.27). Proptosis must be differentiated from exophthalmos, in which the lid margins remain in a physiologic position. Proptosis of the globe is a true ophthalmic emergency, which requires rapid assessment of the situation as well as immediate medical and surgical therapy. Even if vision cannot be preserved, the globes can often be salvaged for cosmetic purposes by early and correct management.

Though proptosis is usually the result of some traumatic incident, trauma may be minimal in brachycephalic breeds. In one series of 29 dogs, 14 dogs were brachycephalic (Fritsche et al., 1996). In dolichocephalic breeds, greater trauma is necessary to cause proptosis.

The diagnosis of proptosis is relatively easy to make. Determination of the prognosis, as well as the appropriate medical and surgical management, may be more difficult. The prognosis for vision is guarded to poor in general and depends on the extent of (peri-)ocular tissue damage. As an approximation, only 20% of proptosed globes regain some functional vision (Fritsche et al., 1996; Gilger et al., 1995). Hence, prognosis refers to the possibility of salvaging the globe for cosmetic purposes, as opposed to enucleation. Salvaged globes must be free of discomfort to the dog and cosmetically acceptable to the owner.

The degree of proptosis may provide some idea regarding the amount of extraocular muscle damage. Usually, the medial rectus muscle is the first to be avulsed. If more than two rectus muscles are avulsed, the vascular supply and innervation to the anterior segment are compromised due to the extensive tissue trauma, and the globe should be enucleated (Fig. 14.28; Fritsche et al., 1996; Gilger et al., 1995). Scleral ruptures are often associated with intraocular hemorrhage and loss of shape and turgor of the globe. Enucleation is recommended in these cases (Rampazzo et al., 2006).

Globes with intraocular hemorrhage, especially if combined with avulsion of more than one extraocular muscle, have a guarded prognosis. Such eyes may still be repositioned. If an acceptable status does not result, enucleation can be performed at a later date.

Keratitis sicca and neurotrophic keratitis due to corneal desensitization are common sequelae and may be difficult to



Figure 14.27 Proptosis of the right globe in a young Golden Retriever. There is entrapment of the eyelids as well as severe swelling and hyperemia of the bulbar conjunctiva. The cornea has already been protected with an ointment.



Figure 14.28 Severe proptosis with avulsion of the optic nerve and several extraocular muscles in an American Cocker Spaniel. Despite the clear and intact anterior segment, enucleation was inevitable.

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manage. The long-term prognosis must be discussed with the owner in such cases. Some owners may prefer enucleation rather than a blind eye that is salvaged, but requires constant attention for many years.

Eyes with only a minor or moderate degree of proptosis and with avulsion of no more than one muscle and either no or minor intraocular hemorrhage have a better prognosis for salvaging the globe. Usually, such eyes remain blind.

Size of the pupil itself is no indicator for prognosis. Eyes that have direct or indirect pupillary light reflexes and vision on initial examination have a better long-term prognosis for vision. Positive direct and indirect pupillary light reflexes as well as assessment and operation performed by a veterinary ophthalmologist were the sole factors correlated with a favorable prognosis in a recent study (Pe'er et al., 2020).

Proptosed eyes should be repositioned under general anesthesia as soon as possible. Until anesthesia is induced, proptosed globes must be kept lubricated with a viscous gel or ointment. The globe is cleansed with sodium chloride solution, and the eyelids are engaged with strabismus hooks or Allis forceps and pulled both up and away from the globe. Gentle pressure will cause the globe to settle back into the orbit. A lateral canthotomy may be necessary. Orbital hemorrhage and tissue swelling usually prevent the eye from returning to an absolutely normal position; therefore, a temporary tarsorrhaphy must be performed using 4-0 to 2-0 (depending on the size of the animal) monofilament nonabsorbable suture material. Two or three horizontal mattress sutures with stents are usually required. At the medial canthus, a small opening should be left to facilitate topical medication. Immediately after completing the temporary tarsorrhaphy, a cold pack is applied to the eye to decrease swelling until the animal recovers from anesthesia. Postoperative care is identical to that given to orbital fracture and hematoma patients. Depending on the amount of orbital swelling and degree of exophthalmos, all sutures should remain in place for at least 1 week and are then removed one at a time, starting medially, on subsequent visits and dependent on the return of a healthy blink.

Long-term sequelae of proptosis include blindness, strabismus, mild exophthalmos, lagophthalmos, sensory deficits of the cornea, keratoconjunctivitis sicca, exposure keratitis, glaucoma, and phthisis bulbi (Fritsche et al., 1996; Gilger et al., 1995). Exotropia is a common sequel resulting from avulsion of the medial rectus muscle, the shortest of the four rectus muscles (Fig. 14.29). Globe position often returns to near normal over the course of several months. With the brachycephalic breeds, bilateral medial or lateral canthoplasty in order to shorten the palpebral fissure and thus prevent future proptosis should be discussed with the owner at the time of repositioning the proptosed globe.



Figure 14.29 Exotropia following proptosis of the right globe and medial rectus muscle avulsion in a Shih Tzu. Due to the medial rectus avulsion, the globe now lacks a force rotating the globe in a nasal and pulling it in a posterior direction. The result is a subtle exophthalmos and chronic erosion on the nasal (now central and most protruding) part of the cornea. (Courtesy of the University of Wisconsin-Madison Comparative Ophthalmology Service.)

Miscellaneous Lesions

Orbital Fat Prolapse

Prolapse of orbital fat is uncommon in dogs; only a few cases have been described (Boydell et al., 1996; Grahn et al., 1993). Orbital fat is separated from the subconjunctival space by Tenon's capsule. In humans, senile weaknesses of Tenon's capsule are responsible for herniation of orbital fat within the eyelids. The cause of orbital fat prolapse in the dog is unknown.

Prolapsed fat presents as a subconjunctival swelling (Fig. 14.30). Inflammatory reactions and ocular discharge are lacking. The swelling is easily movable and usually nonprogressive, but enophthalmos and protrusion of the nictitating membrane can be present. FNA is typically diagnostic.

If necessary, orbital fat prolapse can be treated surgically, by excision of the prolapsed fatty tissue and suturing the conjunctiva to the episcleral tissue or orbital rim to prevent recurrences (Boydell et al., 1996). Excessive removal of orbital fat should be avoided, as enophthalmos could ensue. The prognosis is good, and recurrences have not been described.

Craniomandibular Osteopathy

Craniomandibular osteopathy is a non-neoplastic, proliferative bone disease that predominantly affects Scottish Terriers and West Highland White Terriers at the age of 3–6 months. Other breeds can also be affected.

Affected pups are often lethargic, inappetent, and slightly febrile. The mandibular lymph nodes are enlarged, and the temporal muscles may be atrophied. Because of their inability to open the mouth, affected dogs salivate profusely, have difficulty eating and drinking, and are often dehydrated and

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Figure 14.30 Orbital fat prolapse in a dog. A soft mass that was not attached to the globe caused significant swelling of the ventral bulbar conjunctiva. (Courtesy of B.M. Spiess.)

emaciated (Manley & Amundson Romich, 1993). The orbit is rarely involved, but exophthalmos has been described (Mould, 1993). The etiology is unknown, but hereditary factors are suspected to play a role (LaFond et al., 2002; Padgett & Mostosky, 1986).

The diagnosis is made on the basis of plain radiographs or CT images of the skull showing typical periosteal lesions of the mandible and temporal bone. In severe cases, the temporomandibular joint can be damaged. Recently, MRI was used to diagnose craniomandibular osteopathy (Matiasovic et al., 2016).

The disease is self-limiting. However, supportive therapy during the active stage of the disease is important. In many cases, administration of analgesic drugs suffices. In severe cases, nutrients and fluids need to be administered parenterally (Slatter & Wolf, 1993). The prognosis is good, except in cases affecting the temporomandibular joint, in which food intake may permanently be problematic.

Due to the clinical and pathologic similarities between the two diseases, it seems likely that craniomandibular osteopathy and calvarial hyperostosis are manifestations of the same disease with different predilection sites (Fig. 14.31; Mathes et al., 2012; McConnell et al., 2006; Thompson et al., 2011).

Surgery of the Globe and the Orbit

Surgical Preparation

For all orbital surgeries, the periorbital skin and eyelids are clipped, shaved, and prepared for aseptic surgery in a routine manner. The ocular surface and conjunctival sac are copiously flushed with sterile saline solution; a 1:50 aqueous povidone-iodine solution can also be used as part of the chemical preparation of the eye for surgery.

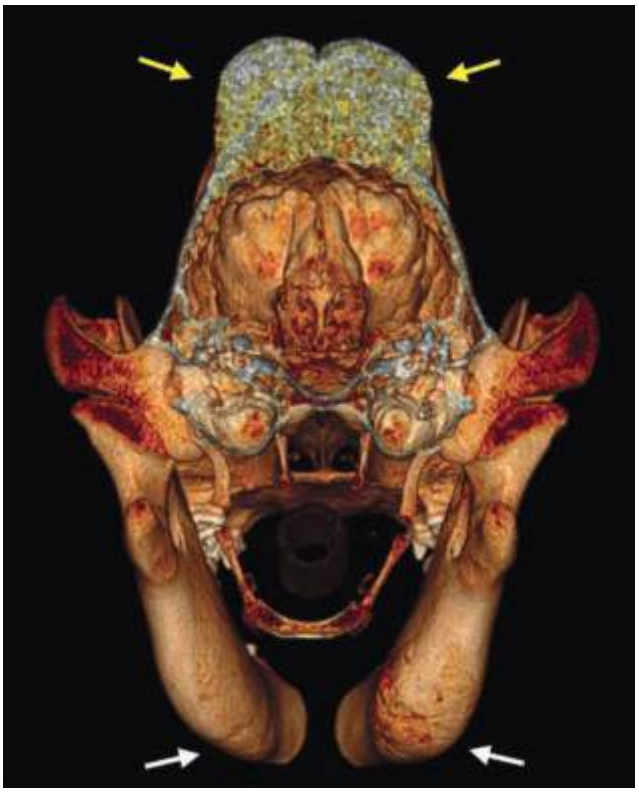


Figure 14.31 Three-dimensional computed tomographic reconstruction of a dog with craniomandibular osteopathy (white arrows) and calvarial hyperostosis (yellow arrows pointing at cross-sectioned temporal bones, caudal view). (Courtesy of M. Dennler.)

Local and Regional Anesthesia

A preoperative retrobulbar block with a sodium channel blocker (bupivacaine, lidocaine, etc.), with or without adrenaline, improves perioperative analgesia and reduces the need for additional postoperative analgesics (Myrna et al., 2010). The inferior-temporal palpebral (ITP) route has been shown to give the most consistent intraconal drug placement. A ~4 cm, 22-gauge spinal needle is bent at the midpoint in an approximate 20° angle. The needle is positioned at the inferior orbital rim and inserted through the inferior lid; it is advanced 1–2 cm in total, depending on patient size and the depth of the orbit, until a slight popping sensation is detected, which indicates piercing of the orbital fascia. The needle is then directed slightly dorsally and nasally toward the apex of the orbit (Fig. 14.32). After drawing on the syringe plunger, the medication is slowly injected.

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Figure 14.32 Frozen skull, sectioned through the eye and orbit. Needle placement for a retrobulbar injection via the inferotemporal palpebral route is demonstrated. (Reproduced with permission from Accola, P.J., Bentley, E., Smith, L.J., et al. (2006) Development of a retrobulbar injection technique for ocular surgery and analgesia in dogs. *Journal of the American Veterinary Medical Association*, **229**(2), 220–225.)

There should be no resistance and the eye should move forward slightly and rotate centrally while the pupil dilates (Accola et al., 2006).

A supratemporal approach for retrobulbar anesthesia has recently been evaluated in canine cadavers and appears to be a valid alternative to the ITP approach (Fig. 14.33A; Chiavaccini et al., 2017). A canine cadaver study demonstrated that retrobulbar anesthesia provided marginally better injectate volume distribution compared to peribulbar anesthesia (Fig. 14.33B). However, the study predicted an inadequately reliable success rate of 40%–60% even for the retrobulbar technique (Shilo-Benjamini et al., 2017). In a later study, the same authors demonstrated that peribulbar injection produced notable anesthesia more reliably than retrobulbar injection (Shilo-Benjamini et al., 2019).

To avoid the risks associated with retrobulbar blocks, intraoperative bupivacaine splash blocks and intraorbital lidocaine-bupivacaine–infused absorbable gelatin sponges have been evaluated and demonstrated similar pain control efficacy compared to retrobulbar blocks with bupivacaine

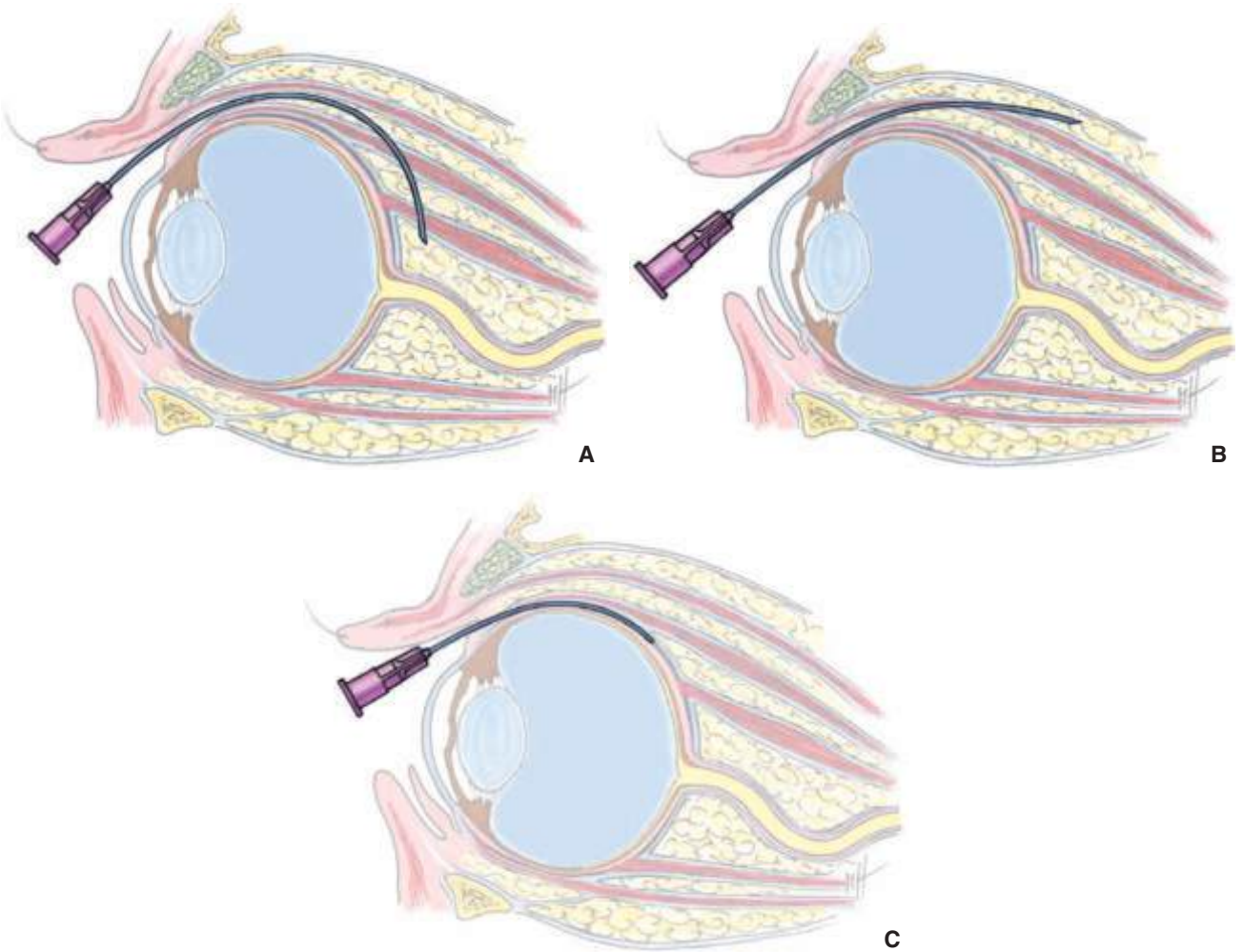


Figure 14.33 Needle position for retrobulbar anesthesia (**A**), peribulbar anesthesia (**B**), and sub-Tenon's anesthesia (**C**).

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(Chow et al., 2015; Ploog et al., 2014). However, a recent study demonstrated that a preoperative retrobulbar bupivacaine block is more effective than an intraoperative bupivacaine splash block at controlling intraoperative and postoperative pain perception in dogs undergoing enucleation (Zibura et al., 2020).

Vezina-Audette et al. (2019) demonstrated that an oculocardiac reflex occurred less frequently in animals receiving retrobulbar nerve blocks compared to animals without such blocks.

An ultrasound-guided posterior extraconal block was demonstrated *ex vivo* to successfully deliver contrast close to the main nerves that provide sensory and motor innervation to the eye (Viscasillas et al., 2019).

A sub-Tenon's capsule injection of lidocaine resulted in mydriasis and extraocular muscle akinesia and intraoperative analgesia, thus providing an alternative to retrobulbar blocks in certain surgeries (Fig. 14.33C; Ahn et al., 2013a, 2013b, 2013c).

In a recent review, Shilo-Benjamini (2019) concluded that there is little evidence for choosing one ophthalmic regional anesthesia technique over another, due to a lack of controlled clinical trials and adverse events reported in the veterinary literature.

Enucleation

Enucleation is the most common orbital surgery performed in animals. Removal of the globe is indicated in any case involving blind, painful eyes (e.g., uncontrollable glaucoma, endophthalmitis, severe ocular trauma with hemorrhage, and so on). It is also indicated for treatment of intraocular tumors not amenable to other forms of surgical or medical treatment.

The most commonly used surgical technique is the subconjunctival approach (Fig. 14.34; Kuhns, 1976; Slatter & Basher, 2003). The main objectives are to remove the globe, nictitating membrane, conjunctival sac, and lid margins, while leaving as much soft tissue behind as possible to minimize postoperative depression of skin over the orbit. A lateral canthotomy is performed to facilitate exposure of the globe, and a lid retractor is inserted. Beginning in the dorsal quadrant, the bulbar conjunctiva is incised approximately 5 mm posterior to the limbus. The conjunctiva and Tenon's capsule are bluntly dissected from the globe, and the extraocular muscles are identified and transected close to their scleral insertion. Dissection of these muscles allows the globe to be mobilized and displaced in an anterior direction. Undue traction on the extraocular muscles is better avoided due to the risk of inducing an oculocardiac reflex, which is a well-known phenomenon in pediatric strabismus surgery in humans (Choi et al., 2009). The retractor bulbi muscle is then identified and dissected in a similar fashion. Medial rotation of the globe will expose the optic nerve, which is clamped with curved hemostats and then transected a few millimeters behind the globe. The surgeon must avoid tension on the optic nerve, so as not to damage contralateral optic nerve fibers at the crossover point in the optic chiasm (Stiles et al., 1993). Blunt dissection of soft tissue and transection of the muscles close to the sclera will minimize hemorrhage. Once the globe is removed, the orbit is packed with gauze sponges to control diffuse hemorrhage, and the nictitating membrane is grasped with forceps and dissected at its base (to include the gland of the third eyelid). The lacrimal gland is usually not removed. In addition, 3–5 mm of eyelid margin are removed with scissors. The conjunctival sac is removed as thoroughly as possible. After removal of the gauze package, the periorbital/deep fascial layers and subcutis are sutured with 4-0 absorbable suture material in a continuous pattern. The skin is closed with simple continuous or interrupted sutures using 4-0 nonabsorbable monofilament suture material. Postoperative care is symptomatic, and sutures are removed after 10–14 days. Owners should be informed that serosanguinous secretions from the ipsilateral nostril may occur over the first few postoperative days, until the nasolacrimal duct is obliterated.

An alternate technique is the transpalpebral approach in which the eyelids are sutured together in a continuous suture pattern (Fig. 14.35; Wolf, 1990). Two elliptical incisions approximately 5 mm behind the lid margins are joined near the medial and lateral canthus. Deep dissection will identify the bulbar conjunctiva. After transection of the medial and lateral canthal ligaments, forward traction of the eyelids will help with dissection of the conjunctiva, until the sclera is encountered at the limbus. Further dissection, globe removal, and wound closure are the same as for the subconjunctival approach. The globe, conjunctival sac, nictitans, and lid margins are removed *en bloc*.

The transpalpebral approach has the advantage of minimizing exposure of the orbit to contaminants from the ocular surface. This method is therefore employed in cases of ocular surface infection.

The most common postoperative complication is hemorrhage within the first few hours after surgery, which results in swelling of the surgical site and serous discharge from the suture line. Cold compresses, pressure bandages, and sedation of the patient are usually sufficient to control hemorrhage. Icing the wound between wound closure and recovery may help to reduce swelling. Warm compresses applied to the orbit during the days following surgery can also help to reduce swelling.

Draining fistulas from the orbit can result from incomplete removal of the caruncle at the medial canthus or of the remaining secretory tissues (e.g., conjunctival goblet cells, third eyelid gland) within the orbit. Postoperative orbital

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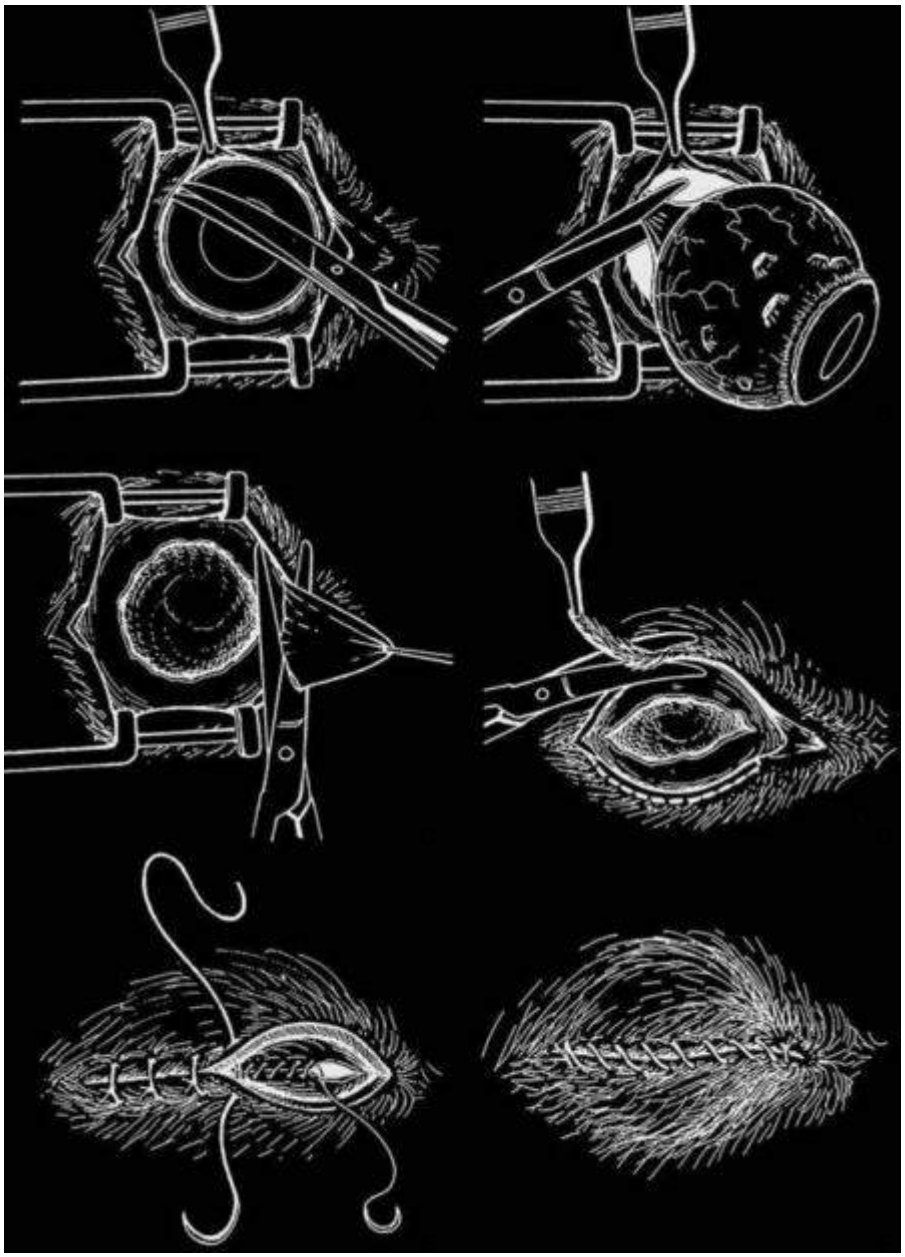


Figure 14.34 Enucleation: subconjunctival approach. **A**. Incision of the bulbar conjunctiva. **B**. After transection of the extraocular muscles close to their scleral attachments, the optic nerve is clamped and severed. **C**. The orbit is packed with a gauze sponge and the nictitating membrane resected. **D**. Excision of the lid margins. **E**, **F**. Closure of the periorbital and deep fascial layers with a continuous suture pattern, after removal of the gauze sponge. Skin closure with simple interrupted or continuous sutures. (Adapted with permission from Slatter, D.H. & Basher, T. (2003) Orbit. In: *Textbook of Small Animal Surgery* (ed. Slatter, D.H.), 3rd ed., pp. 1430–1454. Philadelphia, PA: W.B. Saunders, Figure 95-25.)

infection is a rare complication. In brachycephalic breeds, orbital emphysema may also be a complication of enucleation. Orbital sialoceles have been reported as a complication of enucleation surgery associated with prior parotid duct transposition, for which parotid duct transposition reversal has been described and proposed as a preventive measure (Guinan et al., 2007; Young et al., 2018). A recent comparative study identified carprofen as a more effective postoperative pain treatment than tramadol (Delgado et al., 2014).

A recent evaluation of owner perceptions and satisfaction following bilateral enucleation demonstrated that 90% of owners were satisfied with the procedure, perceived their dogs to have a good quality of life, and would consent to the procedure again (Hamzianpour et al., 2019).

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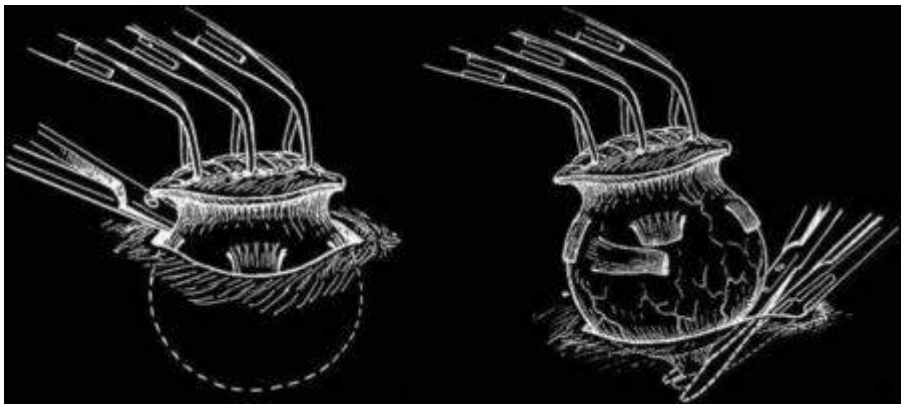


Figure 14.35 Enucleation: transpalpebral approach. **A**. The eyelids are sutured or clamped together and an elliptical incision is made around the lid margins. **B**. After transection of the extraocular muscles close to their scleral attachments, the optic nerve is clamped and severed. The globe, conjunctival sac, nictitans, and lid margins are removed *en bloc*. Bilayered closure of the orbit is identical to that during subconjunctival enucleation (Fig. 14.34E, F). (Adapted with permission from Slatter, D.H. & Basher, T. (2003) Orbit. In: *Textbook of Small Animal Surgery* (ed. Slatter, D.H.), 3rd ed., pp. 1430–1454. Philadelphia, PA: W.B. Saunders, Figure 95-27.)

Exenteration

Exenteration involves removal of the conjunctiva, periorbita, extraocular muscles, and globe. In case of an orbital tumor, exenteration may be extended to involve all orbital contents. A transpalpebral approach is used, in which the eyelids are sutured together in a continuous pattern. An incision is made around the palpebral fissure and approximately 5 mm from the lid margins. Dissection is then advanced caudally through the orbicularis oculi and orbital fascia toward the orbital rim, involving all extraocular muscles, the globe, conjunctiva, nictitating membrane, and lacrimal gland (Slatter & Basher, 2003). If necessary, the remaining orbital connective tissues and fat can be excised. Closure of the subcutis and skin is routine, as described for enucleation. The orbital depression is more marked following exenteration than following enucleation, and a prolene or Dacron mesh can be anchored to the orbital rim to avoid an unsightly depression. A novel surgical approach for an extensive orbital exenteration was described in detail in a recent publication (Berggren & Wallin-Hakansson, 2019).

Orbital Prosthesis

To improve the postoperative cosmetic appearance of enucleation or exenteration surgery, silicone or methyl methacrylate spheres may be implanted (Hamor et al., 1993; Moore, 1990; Nasisse et al., 1988; Oria et al., 2016). This reduces the extent of the depression of skin over the orbit, commonly seen after enucleation surgery.

Silicone spheres are most commonly used today. The size of the implant is selected according to the size of the orbital space to be filled; the diameters in dogs vary between 12 and 28 mm. These implants are placed into the orbit after hemostasis has been achieved. To improve the cosmetic appearance and avoid rotation of the implant, the anterior quarter of the sphere is removed using scalpel blades and Mayo scissors, until a flat, anterior surface with smooth, rounded edges is produced. After placement, the sphere should snugly fit into the orbit without causing undue compression of orbital tissues and the anterior surface of the sphere should not protrude from the orbital rim. The wound is then closed in a routine manner.

Postoperative care is the same as for enucleation and exenteration. Possible complications include traumatic dislocation and rotation of the implant, orbital seroma formation, and infection. The latter can result in wound dehiscence and extrusion of the implant (Hamor et al., 1994; Nasisse et al., 1988). Contraindications to the placement of an orbital prosthesis include the presence of neoplasia or infection in the orbit, or extraorbital sources of a systemic bacteremia.

Evisceration and Implantation of Intrascleral Prostheses

Evisceration involves replacing the intraocular contents with an appropriately sized silicone sphere, leaving only the fibrous tunic. The diameter of the silicone sphere should equal the horizontal diameter of the opposite healthy cornea (Ruoss et al., 1997), or be 1 to 2 mm larger (Wilkie et al., 1994). Blind and painful eyes of an approximately normal size, without septic endophthalmitis or intraocular neoplasia, are candidates for evisceration and implantation of a silicone prosthesis (McLaughlin, 1990; Ruoss et al., 1997). A blind eye with early phthisis bulbi can be fitted with an intrascleral prosthesis to prevent further globe shrinkage and secondary adnexal problems (Lettow, 1987).

Animals are premedicated with systemic flunixin meglumine and antibiotics. After routine preparation and draping

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of the eye for intraocular surgery, a lateral canthotomy is performed (Fig. 14.36). A 5–8 mm, 120°, limbal-based flap of bulbar conjunctiva and Tenon's capsule or, alternatively, a fornix-based flap of equal size is then prepared. The sclera is incised parallel to and 5 mm behind the limbus with a #64 Beaver blade over a length of 2–3 mm. Care is taken not to incise the uveal tract. Up to this point, no aqueous humor should escape. A cyclodialysis spatula is then inserted between the uvea and sclera and carefully advanced into the anterior chamber. At this point some aqueous humor will escape. Alternatively, a lens loop can be used, which necessitates a slightly larger scleral incision. While avoiding the corneal endothelium, careful rotating movements of the spatula are used to bluntly separate the uveal tract from its scleral attachments, except for its attachment at the optic papilla. The scleral incision is enlarged with scissors to a length 1–2 mm larger than the diameter of the prosthesis. The uveal tract is then grasped with forceps and removed in one piece by slow, gentle, continuous traction. Vitreous and retina are usually removed together with the uvea. Transection at the optic nerve head may be necessary to release the uvea and retina. A lens loop is used to remove the lens, and the scleral shell is irrigated with lactated Ringer's solution and inspected for residual uveal tissue. The prosthesis is inserted into the globe using a special sphere introducer. Some hemorrhaging will occur during evisceration, and blood will usually fill the space between the sclera or cornea and the silicone sphere. The scleral incision is closed with 6-0 absorbable suture material in a simple interrupted pattern. Tenon's capsule and the limbal-based conjunctival flap are sutured with the same suture material in a continuous pattern. The canthotomy is closed with 4-0 nonabsorbable suture material.

Complications, including regrowth of unidentified intraocular neoplasms, scleral wound dehiscence, and postoperative intrascleral infections, have been reported to occur in 10% of cases (Hamor et al., 1994; Koch, 1981). Corneal erosions and septic keratitis were identified as the most common postoperative complications in 9/20 patients in a retrospective study (Lin et al., 2007).

In general, corneal integrity is a prerequisite for implantation of a prosthesis, but such devices have been used to

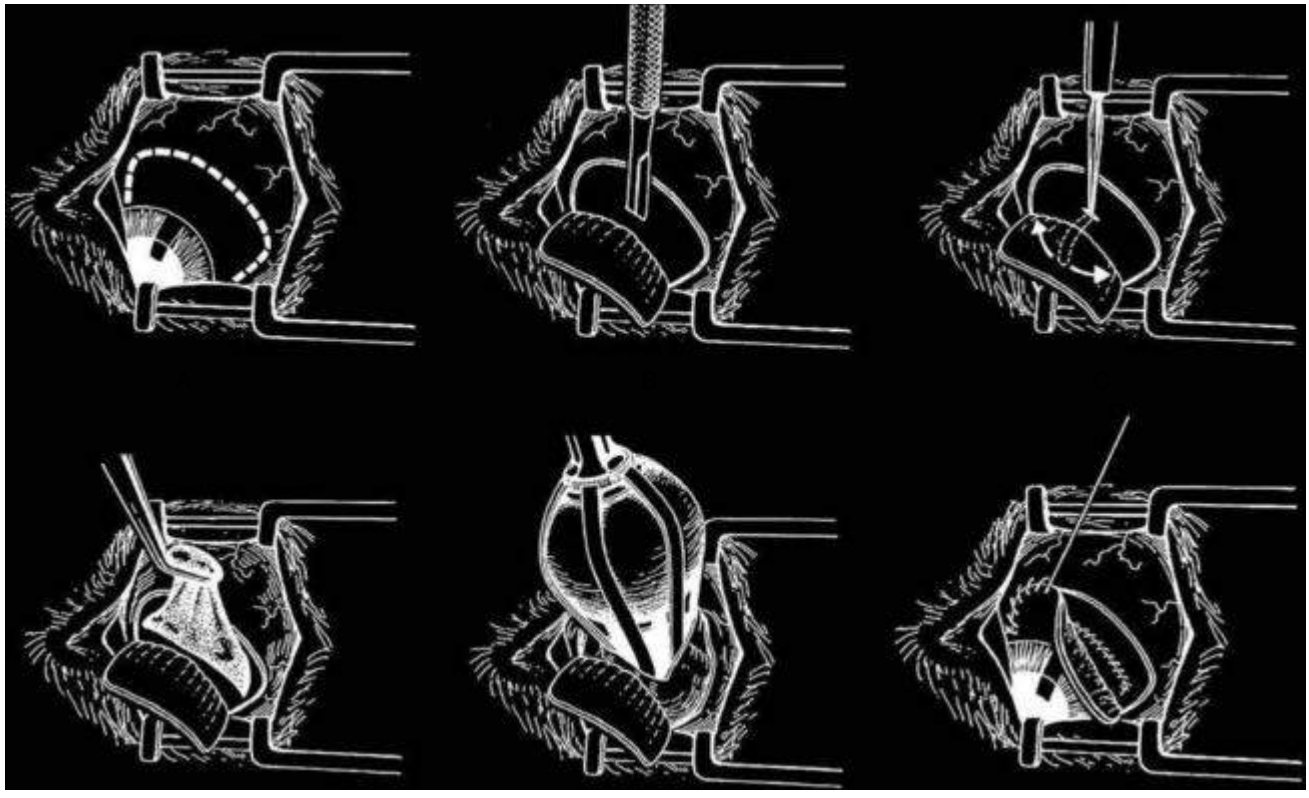


Figure 14.36 Evisceration and implantation of an intrascleral silicone prosthesis. **A**. Outline of the limbal-based conjunctival flap. **B**. The sclera is incised down to the uveal tract. **C**. A cyclodialysis spatula is inserted between sclera and uvea and advanced into the anterior chamber. The uveal tract is separated from its scleral attachments with sweeping movements of the spatula. **D**. After enlargement of the scleral incision, the uvea is grasped with serrated forceps and removed by slow, continuous traction. **E**. After irrigation of the globe, an appropriately sized silicone prosthesis is inserted using a Carter sphere inserter. **F**. The scleral and conjunctival wounds are closed with 6-0 absorbable suture material.

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salvage globes with corneal lacerations (Riggs & Whitley, 1990). Also, intraocular neoplasms have to be carefully ruled out prior to evisceration and implantation of a silicone prosthesis. However, a report of nine cases with intraocular neoplasia suggests that such tumors may not be an absolute contraindication to placement of an intrascleral prosthesis (McLaughlin et al., 1995). The cosmetic results are usually acceptable (Fig. 14.37). In a retrospective study, most clients were satisfied with the result (Ruoss et al., 1997).

Extrascleral Prosthesis

Extrascleral prostheses are more commonly used in horses than in small animals. Such devices are acrylic or porcelain shells designed to fit into the conjunctival sac and cover a noninfected blind and phthisic eye, an intrascleral or orbital implant, or an empty socket (Gilger et al., 2003; Hamor et al., 1992; Lavach & Severin, 1984; Romkes & Eule, 2012; Slatter & Wolf, 1993). Pegged extrascleral prosthesis systems, in which a peg anchored to an orbital implant protrudes through the conjunctiva and couples the orbital implant to an extrascleral prosthesis, facilitate statistically, but not clinically, significant movement of the prosthetic shell (Yi et al., 2009). The use of such pegged implants in dogs should be discouraged, since the physician-based literature contains evidence that patients receiving pegged implants have a high risk of experiencing complications unique to pegging, and therefore a significantly higher rate of complications overall when compared with patients who received a nonpegged implant (Fahim et al., 2007). Species-related problems with hygiene and potential self-trauma would likely influence the postoperative complication rate that is to be expected in dogs.

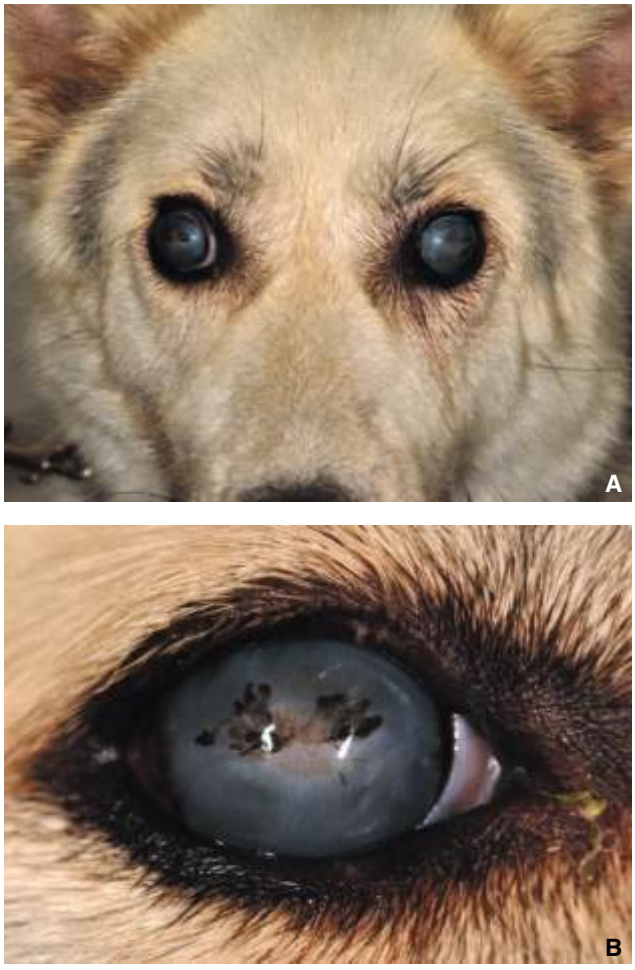


Figure 14.37 **A**. Portrait of a dog bearing intrascleral silicone prostheses in both eyes, 5 months postoperatively. **B**. Close-up of the right eye, demonstrating mild neovascularization, fibrosis, and pigmentation of the cornea.

Orbitotomy and Orbitectomy

Several approaches to the orbit are possible, depending on lesion localization (Gelatt & Gelatt, 2011). A transconjunctival approach will provide access to lesions anterior to the equator of the globe (Slatter & Basher, 2003). Dorsal, ventral, nasal, or temporal approaches can be chosen (Williams & Haggett, 2006). Masses within the extraocular muscle cone necessitate transection of the respective rectus and oblique muscles. Even then, visualization is limited using this route (Fig. 14.38). Ventral transpalpebral anterior orbitotomy was described as alternative means to gain moderate access to space-occupying lesions in the ventral anterior orbit. Tissue dissection was minimal and postoperative complications were few (McDonald et al., 2016).

A wider access to the orbit is gained through a lateral approach, with transection of the lateral orbital ligament. If deep orbital structures such as the zygomatic salivary gland must be accessed, a portion of the zygomatic arch can be removed with a rongeur (Bistner et al., 1977).

Removal of localized orbital neoplasms usually requires a more radical approach. Three-dimensional printing to create a model of the surgical site might become a useful surgical planning tool (Dorbandt et al., 2017). Adequate access to the ventral and caudal aspects of the orbit can be gained by lateral orbitotomy with resection of the zygomatic arch (Fig. 14.39A, B; Slatter & Abdelbaki, 1979). This technique has been used to remove orbital tumors and, at the same time, retain both the globe and vision (Spiess et al., 1995). In a modification of this technique, the orbital ligament is transected and the zygomatic arch deflected ventrally after osteotomy. Extensive tissue dissection of the temporal muscle is prevented, thus decreasing closure time and sparing and safeguarding the palpebral branch of the facial nerve (Fig. 14.39C, D; Gilger et al., 1994). Another advantage of this modified lateral approach is the fact that the zygomatic arch remains attached to the masseter muscle, leaving the blood supply intact. The modified lateral orbitotomy

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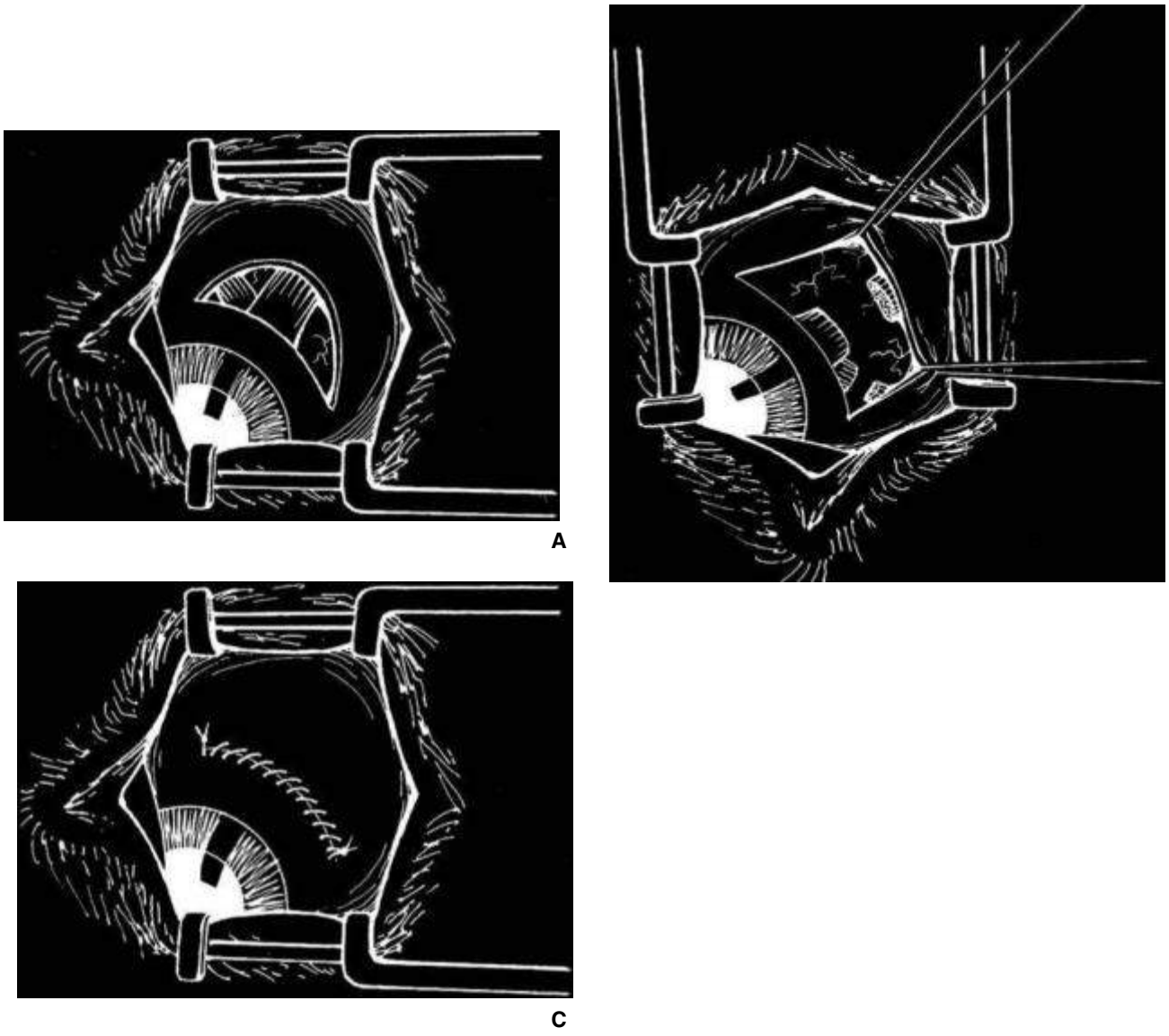


Figure 14.38 Transconjunctival orbitotomy. **A**. The conjunctiva and Tenon's capsule are incised in the desired quadrant, and the extraocular muscles are identified. **B**. Transection of the extraocular muscles allows limited visualization of the anterior orbit. **C**. After the transected muscles are sutured, the conjunctiva is closed with resorbable suture material in a continuous pattern. (Adapted with permission from Slatter, D.H. & Basher, T. (2003) Orbit. In: *Textbook of Small Animal Surgery* (ed. Slatter, D.H.), 3rd ed., pp. 1430–1454. Philadelphia, PA: W.B. Saunders, Figure 95-28.)

currently seems to be the most widely used technique to gain access to the orbit (Barnes et al., 2010; Bartoe et al., 2007; Gelatt & Gelatt, 2011; Hartley et al., 2007; Lassaline et al., 2005). An adaptable three-step procedure to gain access to almost the entire orbit, called transfrontal orbitotomy, has been described (Fig. 14.39E, F; (Håkansson & Håkansson, 2010). Surgical exposure was excellent and postoperative recovery uneventful in 9/9 patients.

Possible complications of orbitotomies include hemorrhage, transient lagophthalmos, postoperative swelling and infection, enophthalmos, and strabismus (O'Brien et al., 1996; Slatter & Abdelbaki, 1979; Spiess et al., 1995).

In cases with local extraorbital tumor extension and/or bone involvement, extensive and aggressive tumor resection, in the form of partial or total orbitectomy (Fig. 14.40), is indicated. These are invasive surgical procedures that involve opening of the (para-)nasal sinuses, calvarium, and/or oral cavity, up to complete resection of the orbit, including its osseous delineation (orbital rim, frontal bone, maxillary bone including last molar(s), zygomatic arch, etc.). The main intraoperative risk is profuse bleeding from the maxillary artery or one of its tributaries when working in the ventral orbit. These arteries need to be ligated if they are (to be) severed. If they cannot be identified, the ipsilateral carotid

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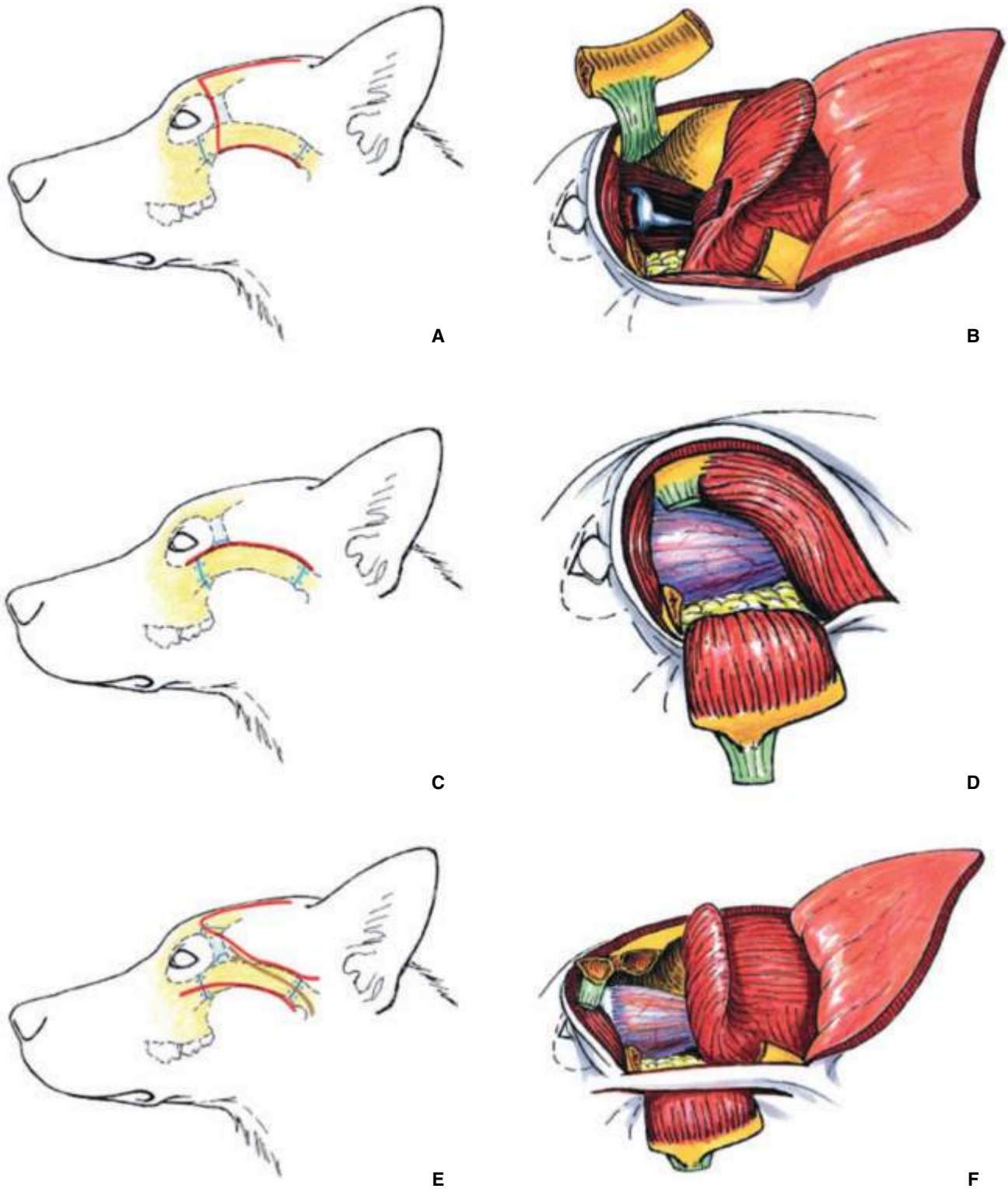


Figure 14.39 Orbitotomy techniques. **A**, **C**, **E**. Skin incisions are indicated in red, and cerclage hole, osteotomy, and orbital ligament transection sites are indicated in blue. **B**, **D**, **F**. Demonstrating surgical exposure after tissue reflection and retraction. Lateral orbitotomy (Slatter & Abdelbaki, 1979): **A**. The skin incision is made along the ventral rim of the zygomatic arch and is continued along the orbital ligament and sagittal crest. After preplacing cerclage holes, an osteotomy is performed rostrally and caudally to the orbital ligament. **B**. The skin, fascia, and temporal muscle are reflected caudally and the zygomatic arch is reflected dorsally, exposing the orbital fascia and muscle cone. The retractor bulbi muscles, optic nerve, and caudal globe are exposed by incising the orbital fascia and transecting the lateral rectus muscle. This approach necessitates the sacrifice of the palpebral branch of the facial nerve, leading to postoperative lagophthalmos. Modified lateral orbitotomy (Gilger et al., 1994): **C**. The skin incision runs along the dorsal rim of the zygomatic arch. The subcutaneous palpebral branch of the facial nerve is preserved by blunt dissection from the surface of the temporal muscle and dorsal retraction together with the skin. **D**. After transection of the orbital ligament and the temporal muscle aponeurosis, an osteotomy is performed and the zygomatic arch is deflected ventrally. Transfrontal orbitotomy (Håkansson & Håkansson, 2010): **E**, **F**. The skin is incised along the ventrolateral zygomatic arch, followed by a modified lateral orbitotomy, as described by Gilger et al. (1994). A second skin incision follows the course of the palpebral branch of the facial nerve, to preserve a strip of skin protecting that nerve (outlined in yellow in **E**). This incision is then continued to facilitate elevation and caudal retraction of the temporal muscle from the orbital ligament and sagittal crest. In order to maximize exposure of, and room for surgical manipulation in, the cranial and ventromedial orbit, an osteotomy and cranial reflection of the zygomatic process of the frontal bone are finally performed.

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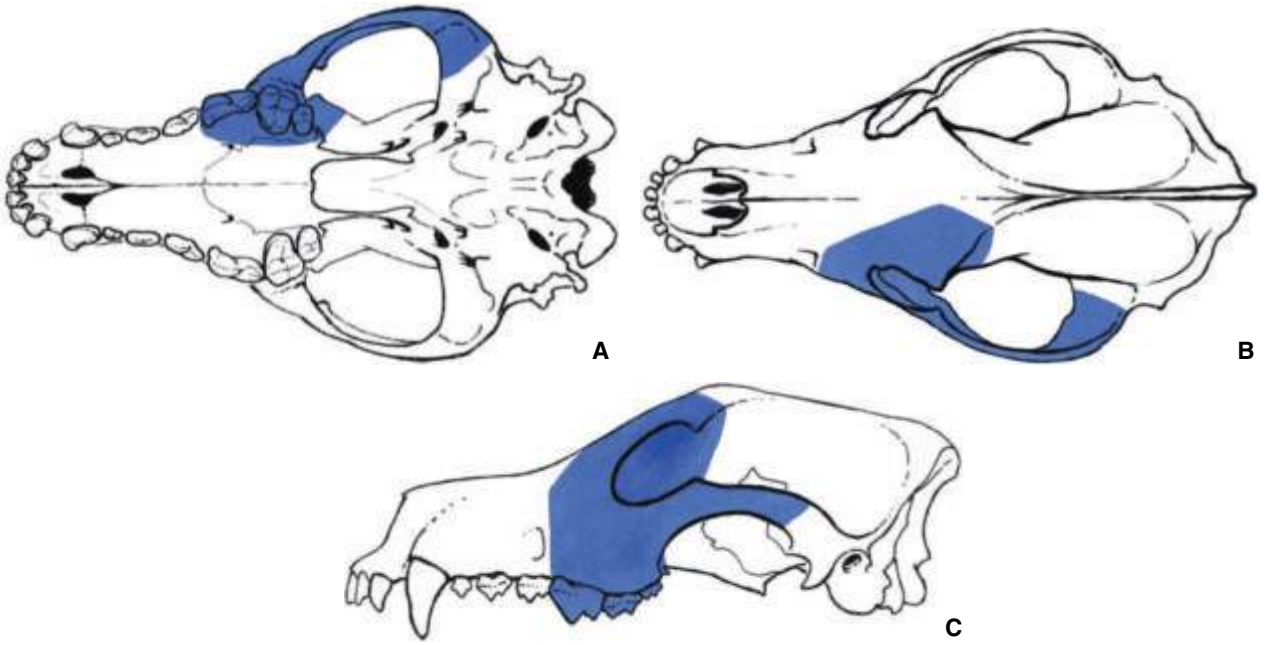


Figure 14.40 Illustration of surgical margins observed when performing a total orbitectomy. (Adapted with permission from O'Brien, M.G., Withrow, S.J., Straw, R.C., et al. (1996) Total and partial orbitectomy for the treatment of periorbital tumors in 24 dogs and 6 cats: A retrospective study. Veterinary Surgery, 25, 471–479.)

artery may need to be occluded to control hemorrhage and obtain a bloodless surgical field (Slatter & Basher, 2003). In a case series of 30 orbitectomies, the postoperative complications were relatively minor in most patients (O'Brien et al., 1996).

When partial orbitectomy is performed, the globe will be sacrificed if a neoplastic process involves the globe or structures that are critical to globe survival. A superior orbitectomy involving the soft tissue structures dorsal to the eye (including eyelid) usually warrants eye removal. Loss of the inferior eyelid can be remedied using a lip-to-lid procedure, as described by Pavletic et al. (1982).

Wound closure can be routine if no large skin defects were created during tumor resection. In those cases no special care needs to be taken to close the nasal or frontal sinuses (Boston, 2010; O'Brien et al., 1996). Reconstructive techniques are indicated in cases where calvarial bone was resected and the brain is relatively unprotected, or where large skin defects were created during tumor resection. A temporalis muscle flap can be used to reconstruct the calvarial wall or reconstruct nasal and paranasal cavities and the orbital rim (Bentley, 1991). Caudal auricular axial pattern flaps can be used to close large skin defects in the head and neck region (Stiles et al., 2003). A masseter muscle flap was used to stabilize the ventral orbit and support the globe after caudal maxillectomy and ventral orbitectomy (Sivagurunathan et al., 2014). Another technique to support and maintain the eye in a normal position following ventral orbitectomy involved the use of a temporalis fascia transposition flap (Dent et al., 2019). An adaptable three-step method for the reconstruction of bone and soft tissue defects resulting from partial orbitectomy procedures not involving structures critical to globe survival was described in a recent case series. The authors reported excellent tectonic, functional, and cosmetic results, with mild postoperative complications. Step one involved the reconstruction of the orbital rim and facial contours with cerclage wires. A prolene mesh covering the wires and reestablishing the inner orbital and outer facial contours was placed in step two. A collagen sheet was placed over the mesh followed by subcutis and skin closure over the construct in step three (Fig. 14.41; Wallin-Hakansson & Berggren, 2017).

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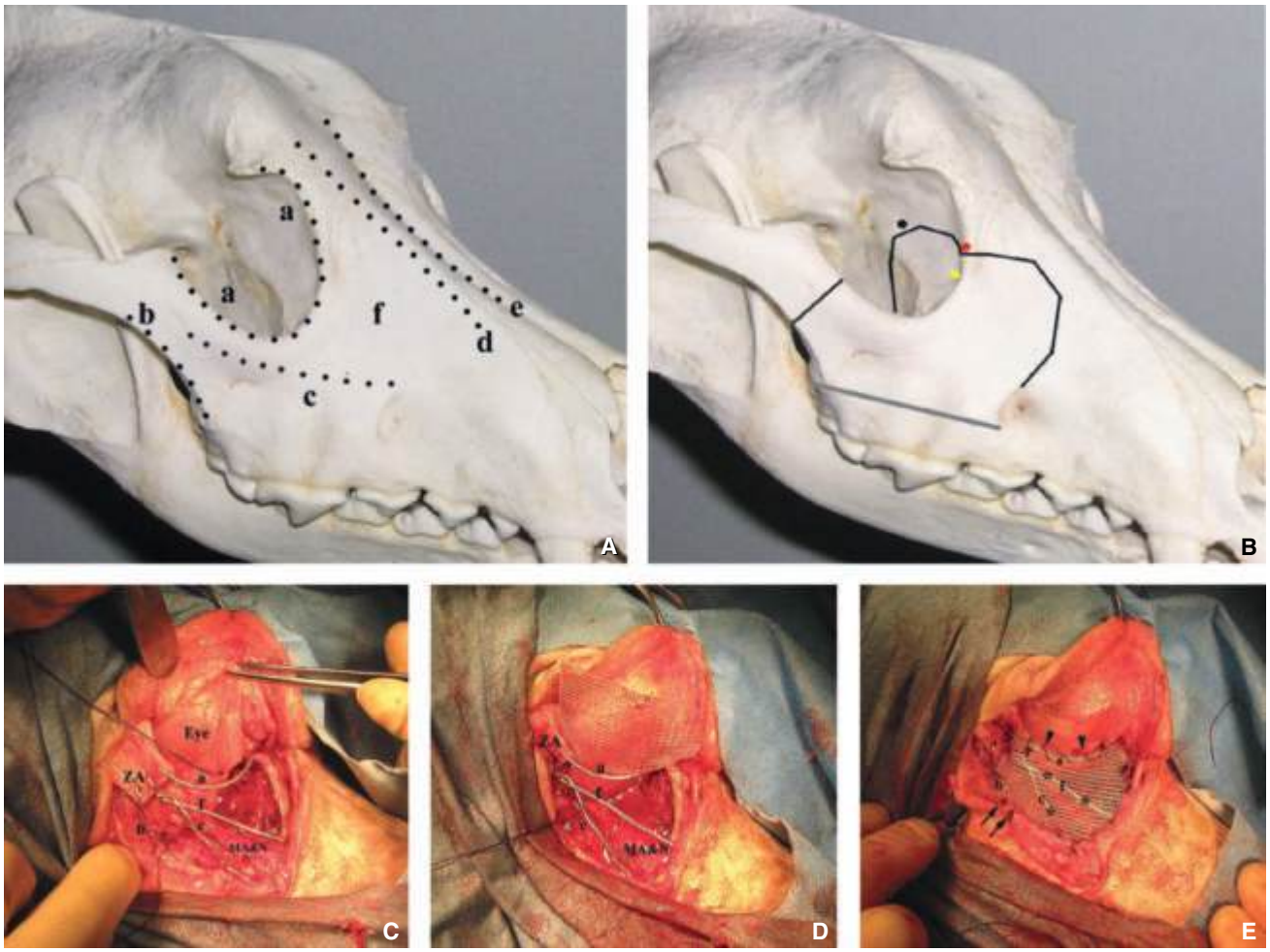


Figure 14.41 Reconstruction of orbital and facial features. **A**. Facial features to be reconstructed: a, orbital rim; b, ventral edge of zygomatic arch; c, facial crest overlying maxillary canal; d, dorsolateral ridge of nasal bridge; e, midline of nasal bridge; f, flat area of maxilla. **B**. Schematic representation of ostectomy. **C**. Intraoperative view after placement of cerclage wires: a, b, c, f, cerclage wires at facial features indicated in **A**; MA&N, maxillary artery and nerve; ZA, posterior cut end of zygomatic arch. **D**. View after placement of prolene mesh inside orbit. **E**. View after prolene mesh has been folded down over the facial bone defect, trimmed, and sutured. (Reproduced with permission from Wallin-Hakanson, N. & Berggren, K. (2017) Orbital reconstruction in the dog, cat, and horse. *Veterinary Ophthalmology*, **20**(4), 316–328.)

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15

Diseases and Surgery of the Canine Eyelid

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The primary function of the eyelids is the protection of the globe. The eyelids cover the orbit and globe, and surround the palpebral fissure through which the globe contacts the environment. When the palpebral fissure is fully open in the normal adult dog and the eye is looking forward, the eyelid margins should just cover the dorsal and ventral external limbi. It is normal for the lateral limbus and sclera to be exposed, and when the globe is deviated laterally, the medial sclera is seen. The hairless margins of the lids should be well aligned to the curvature of the cornea and should move smoothly across the globe. The inside of the lids is covered by the very loose (except the area over the Meibomian glands–tarsal "plate") palpebral conjunctival mucosa connecting to the corneal limbus and allowing movements of the globe behind the lids.

Compared to other species, eyelid diseases in dogs are frequent, of considerable significance, and represent an important part of the practitioner's and eye specialist's ophthalmic case load. The initial diagnosis of lid disease is not usually difficult; however, determining the inciting cause of deterioration in the subtle interactions of conjunctiva, muscles, ligaments, hairs, and folds may be less simple.

The eyelid diseases can be divided into congenital-developmental and hereditary, trauma, inflammatory, immune-mediated and others, and neoplastic disorders. Clinical management of most of the eyelid diseases, except for the inflammatory and immune-mediated types, is primarily surgical. Lid surgery can be challenging. The selection of the surgical technique for a particular condition may be influenced not only by the most effective procedure, but also by the experience of the surgeon, the surgical instrumentation available, the quality (3–5× magnification) of the operating loupe or operation microscope (5–20× magnification), the timing of the surgical intervention, and the optimal surgical procedure, all of which are critical for the final result.

Most of the small animal eyelid surgical procedures were adapted from techniques performed in humans, such as the Celsus procedure for entropion (Celsus, cited by Zeis, 1839; Patel & Anderson, 1996). In older dogs, eyelid neoplasms are much more common than in other companion animals. The majority of neoplasms can be excised by reasonably simple surgical procedures when performed at an early stage. Surgical procedures for the canine eyelids have been reported in several comprehensive chapters and reviews in the veterinary literature in recent years (Aquino, 2007, 2008; Gelatt & Gelatt, 2011; Hamilton et al., 2000; Lackner, 2001; Martin, 2005; Moore, 2000; Moore & Constantinescu, 1997; Slatter, 2001; Stades et al., 1998; van der Woerdt, 2004; Wyman, 1979, 1990).

In this chapter, we describe the procedures available in both Europe and America, those with which we have personal experience and success, and those that the veterinary ophthalmologist would be expected to perform.

Structure and Function

The anatomy of the eye is covered in detail in Chapter 2. Here, the more clinical and functional aspects are discussed (Fig. 15.1), especially as they relate to lid surgery (Gelatt & Gelatt, 2011; Stades et al., 1998). The eyelids are composed of skin, palpebral conjunctiva, collagen, muscle, and glandular tissue. They can be divided into the larger, 2–5 mm longer, and more mobile dorsal, superior, or upper eyelid; and the ventral, inferior, or lower eyelid. The circular muscle surrounding the palpebral fissure is the orbicularis oculi muscle. However, the eyelids do not close by circular contraction. Because of the subcutaneous tissues and a ligament in the medial canthus attached to the nasal bones and the retractor anguli lateralis muscle plus a lateral palpebral ligament in the lateral canthus, it narrows to a horizontal slit. This lateral ligament may contribute to eyelid distortion, particularly in mesocephalic breeds (Robertson & Roberts, 1995a, 1995b).

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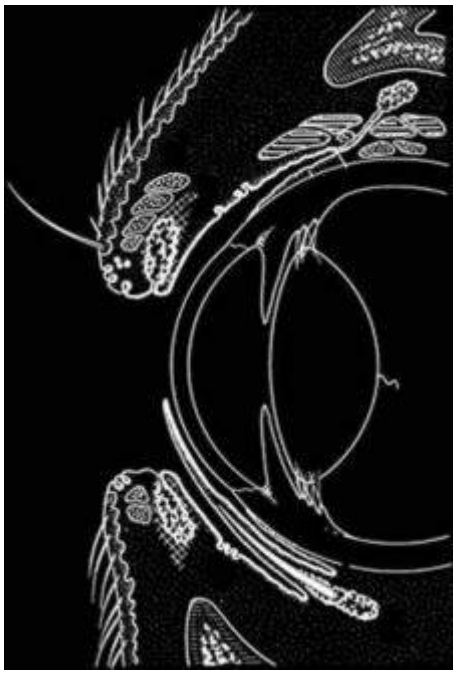


Figure 15.1 Cross-section through the canine lid: 1. eyelash-like hair on the lateral part of the upper lid; 2. Zeis/Moll glands; 3. Meibomian gland; 4. mucus cells conjunctiva; 5. fornix; 6. scleral conjunctiva; 7. nictitating membrane gland; 8. orbicularis oculi muscle; and 9. tarsal "plate." Copyright Frans C. Stades.

The average length of the palpebral fissure when stretched by calipers is approximately 33 mm in most medium to large breeds of dogs. In breeds with a distinct lack of contact of the lower lid to the globe, the palpebral fissure length is usually over 39 mm (Fig. 15.2; Stades et al., 1992). The orbicularis oculi muscle enables the closing phase of blinking, a movement in which the upper eyelid plays the most important part. During closure there is a lateral-to-medial zipper-like movement, bringing the tear surplus to the lacrimal puncta. The levator palpebrae (innervated by the oculomotor nerve), levator anguli oculi medialis (Müller's muscle), and other superficial facial muscles help open the upper eyelid, thus maintaining the precorneal tear film. The malaris muscle opens the lower eyelid (Fig. 15.3).

Skin and Cilia

The eyelids are thin and of pliable skin, enabling blinking and following the corneal surface smoothly. Fine and short hairs normally cover the eyelid skin. In dogs, the borderline of the "eyelash" hairs and regular hairs in the upper lid begins about 1 mm away from the free lid margin (and not at the outer free rim of the edge itself, as in human eyelashes). In the lower lid, hairs start about 2 mm away from the free margin. Cilia or eyelashes occur primarily on the lateral part of the upper eyelid, usually in two or four irregular rows. These cilia are normally the same color as the adjacent eyelid hair coat. Long tactile hairs (pili supraorbitales or vibrissae) appear as a tuft along the dorsomedial orbital margin.



Figure 15.2 Lid length measurement using unsharpened calipers in a St. Bernard. The stretched lid fissure in this St. Bernard is almost 45 mm. Courtesy of Frans C. Stades.

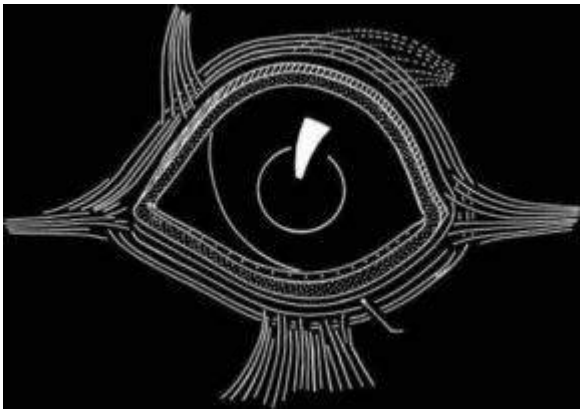


Figure 15.3 Muscles of the lids of the left eye: 1. orbicular oculi muscle; 2. lateral palpebral ligament or retractor anguli oculi lateralis; 3. medial palpebral ligament; 4. malaris muscle; 5. levator palpebrae muscle; and 6. levator anguli oculi medialis muscle. Copyright Frans C. Stades.

Margin

The free margins (*margo intermarginales*) of the eyelids are generally pigmented (usually nonpigmented if the skin around the eye is nonpigmented, for example in the area of a white spot around the eye), and they are hairless. Furthermore, the margins are smooth, glossy, and fatty, but dry. Some 30–40 orifices of the Meibomian glands open into the free lid margin in a fine groove, also named the "gray line." This groove and the openings are important surgical landmarks used to reappose lid margins in surgical procedures. In case of doubt, pressure by anatomic forceps on the lid margin will produce sebaceous

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material, revealing their position. On the conjunctival surface of the lid margin, the Meibomian glands are visible, below the conjunctiva, as 3 to 4 mm long, whitish yellow lines running perpendicular to the margin. Just outside the groove are the even smaller orifices of the glands of Zeis and Moll (modified sweat glands). The oily material secreted by these three glands coats the margin of the lid with a lipid layer, preventing the tear fluid from flowing across it. Meibometers to measure the delivery rate of lipids on the lid margin are available for use in humans, but the precision in dogs is still questionable (Benz et al., 2008). The Meibomian gland secretion of dogs is biochemically very similar to that of humans (Butovich et al., 2011). This secretion also forms an extremely thin oily film on the watery tear fluid, thereby reducing evaporation.

The eyelids of humans are quite similar to those in dogs, with one major difference. In humans, the tarsal layer consists of a distinct cartilaginous plate that provides internal support for the eyelids. In domestic animals, the tarsal plate consists of a thinner and more flexible fibrous tarsus, but it does provide a surface for muscle attachment.

Canthus

Both canthi are composed of the lid margins converging together in the medial canthus, leaving 3–5 mm of skin, which continues into the conjunctiva in a minor eminence at the base of the nictitating membrane, called the lacrimal caruncle. The hair growth in the area is short and soft. The hairs point outward medially. In the lateral canthus over 2–3 mm, there are no Meibomian glands or tarsal "plates."

Lid Sensation

The main sensation of the canine eyelids is provided by several branches of the trigeminal (V) nerve. Sensation of the lateral two-thirds of the upper eyelids is provided by the trigeminal nerve. The medial canthus and medial aspects of the upper eyelids are also served by the largest branch of the ophthalmic nerve. The sensation for the entire lower eyelid is provided by the maxillary division of the trigeminal nerve. This concentration of trigeminal nerve endings around the palpebral fissure guarantees an extreme sensitivity to stimuli and provides the afferent limbs of the palpebral reflex that stimulate the orbicularis oculi to close the lids when touched.

The palpebral branch of the facial (VII) nerve innervates the majority of the muscles (e.g., orbicularis oculi) that control the palpebral fissure size, except for the levator palpebral superioris muscle, which is innervated by the oculomotor (III) cranial nerve. The levator anguli oculi medialis is under sympathetic control as loss of sympathetic innervation in Horner's syndrome results also in ptosis of the medial upper lid.

Blood Supply and Lymphatic Drainage

The blood supply to the eyelids primarily originates from the medial and lateral palpebral arteries. Additional blood supply to the lateral canthus and upper and lower eyelid is derived from branches from the external ethmoidal artery. The medial aspects of the canine eyelids are also supplied by branches of the malaris artery, a branch of the infraorbital artery, which anastomose with the inferior palpebral and transverse facial arteries and branches of the external ophthalmic artery. Limited blood supply to the eyelids originates from the deeper orbital blood vessels. All these together provide a profuse vascular supply of the lids and result in marked hyperemia and edema in inflammatory reactions.

The lymphatic drainage from the eyelids converges at the medial and lateral canthal areas. Lymphatic drainage is mainly to the parotid lymph node as well as to the mandibular lymph nodes. Both lymph nodes need to be examined if regional metastases from eyelid neoplasia are suspected.

Lid Functions

The functions of the eyelids include the following:

- The direct protection of the eye and the active blink reflex to tactile stimuli applied to the cornea, conjunctiva, or nictitating membranes, or following a strong light and/or loud stimuli, all resulting in protection of the globe. When direct stimuli are applied to the eyelids, conjunctival, and corneal surfaces, the eyelids blink. This reflex is subcortical, involving the ophthalmic division of the trigeminal nerve (afferent portion) and palpebral division of the facial nerve (efferent portion). In domestic animals, eyelid closure may be very powerful, particularly when the animal is in pain (blepharospasm). Both enophthalmos and microphthalmos may result in reduced support for the lid margin, allowing the lid to turn in toward the globe (secondary entropion), producing pain and thus contraction of the orbicularis oculi.
- Entrapment and removal of material from the conjunctival sac and cornea to the medial canthus.
- Production of glandular secretions by the tarsal glands, keeping the lid margin fatty, and reduction of evaporation of the tear film.
- Distribution of the tear film and the removal of tears toward the lacrimal puncta.

Principles of Lid Surgery

Exactly how lid surgery is conducted may vary somewhat among ophthalmologists, but the general principles are similar.

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Anesthesia

In general, sedation and local anesthesia are insufficient for lid surgery, especially because sufficient muscle relaxation is needed for the correct estimation of, for example, the lid fissure length, the amount of tissue to be removed, or the degree of correction necessary. However, in geriatric or debilitated patients, light sedation plus local 2% lidocaine infiltration anesthesia may be useful for minor procedures (Giuliano, 2008; Swinger & Carastro, 2006).

Preparation of the Operative Field

The lid skin is usually shaved or clipped by very small hair clippers. The last row of eyelash hairs may be cut by scissors, with some ointment on the blades so that the cut hairs will stick to the ointment. Afterward, the conjunctival sac and the skin are washed copiously with hand-warm saline. Diluted baby shampoo (1 part diluted with 20 parts water) can be used to clean the eyelids if excessive dirt is present. The skin is then dried with gauze sponges. Starting at the margins, the lids are penciled by the standard water-based surgical povidone-iodine solution. Care should be taken not to allow iodine to reach the conjunctival sac or the other eye. An alternative method prepares the eyelid surface with 1 : 50 aqueous povidone-iodine solution, which is not toxic if corneoconjunctival contact occurs.

Positioning

For lid surgery, the lid fissure has to be positioned more or less horizontally and the medial canthus lower than the forehead. The positioning of the head is best carried out by using a vacuum pillow. In lid surgery, the surgeon works in a sitting position, at the ventral side of the head, with the hands resting, as much as possible, on the animal's head, thus preventing the risk of uncontrolled movements and minimizing tremor. The lid fissure can be stretched by closed Castroviejo forceps and stretched ventrally, or dorsally, by a finger of the surgeon. Also, special lid plates or spatulas (Jaeger or Gränitz) can be used to support the lid. However, undesired cutting onto a lid plate, resulting in perforation of the conjunctiva, is possible.

Draping

Special ocular drapes with an opening for the eye, or disposable drapes with a preexisting hole or a hole cut during surgery, can be used for eye surgery. The drapes may be fixed by towel clamps (Jones or Scheadel). During surgery, the drapes are secured below the head; otherwise, they may be pulled downward by the knees of the surgeon, thus influencing the shape of the lid fissure or position of the eye. Adherent (windows) sheets are less desirable in lid surgery because they place traction on the lids, influencing the position.

Magnification Equipment and Light

One of the most important factors for eyelid surgery is good magnification; 3× to 5× magnification is sufficient in most cases. Powerful, well-focused operating lights, a head-mounted light, or operating microscope lights are essential during surgery.

Surgical Instruments

These may include the Kalt, Arruga, or Castroviejo needle holders, strong modified (teeth shortened to 0.3 mm) Castroviejo's suture, cilia and Graefe fixation forceps, calipers, chalazion and Stades nictitating membrane and small towel clamps, short-beaked Stevens tenotomy scissors, electroepilator, and lid plate/spoon (Jaeger or Gränitz). Cutting by rounded scalpel blade easily causes folding of tissues. Using a pointed scalpel blade from the inside to the outside provides a more precise incision. Cutting by scissors causes crushing of the tissues and nonperpendicular incision edges (Fig. 15.4).

Suture Material

For eye (lid) surgery, atraumatic suture material is always used. However, the surgeon must be aware that the introduction opening of the needle is always approximately double

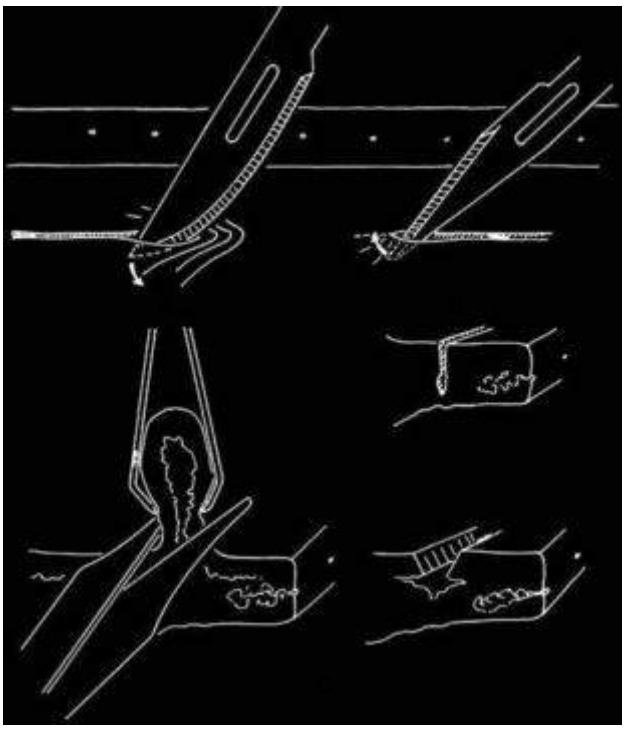


Figure 15.4 **A**. Cutting by rounded scalpel blade, causing folding. **B**. Cutting from inside out by pointed scalpel blade. Both methods result in perpendicular wound edges. **C**. Fold cutting by scissors results in nonperpendicular wound edges. Copyright Frans C. Stades.

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the size necessary for the suture material. For lid skin, which may be extremely leathery, 10–16 mm, 3/8–1/2 circle, extra-sharp-pointed round, micropointed, or extra-fine-cutting needles are used. Their behavior in tissues is illustrated in Fig. 15.5. If there is any likelihood of postsurgical irritation of the cornea by the suture material (e.g., recurrence of entropion), soft material such as silk is advised. If strength is important, 5-0 or 6-0 monofilament nylon can be used. For difficult-to-handle animals, absorbable material, such as polyglactin 910 or polyglycol acid, can be used, eliminating the need for suture removal. However, these materials and their ends are more abrasive and can irritate the cornea in case of contact. Also, the resorption process can cause more reaction of the surrounding tissues. If there is a higher risk of infection, monofilament nylon 6-0 is used (blepharoplasties). The needle should be handled at its flattened middle area. Capturing the conic tip of the needle with the hardened beak of the needle holder will roughen its surface and badly hamper skin passage. Handling the rounded back part of the needle, where the suture material is clamped/glued in, may result in uncontrolled rotation of the needle and unwanted trauma by its tip.

Suturing

Wound edges must be closed very precisely (Fig. 15.6). As eyelids are moving continuously, the knots of the suture must be well secure. The surgical knot consists of a double throw, closed by a square knot (Fig. 15.8). Suture ends are left long to allow easy removal and thus hang downward, or they are gathered together in the upper lid or canthi (Fig. 15.7); short ends may "brush-irritate" the cornea. If wounds are unequal in length (e.g., in the Celsus–Hotz or Stades procedures), the longer wound edge has to be "smuggled" away over the total

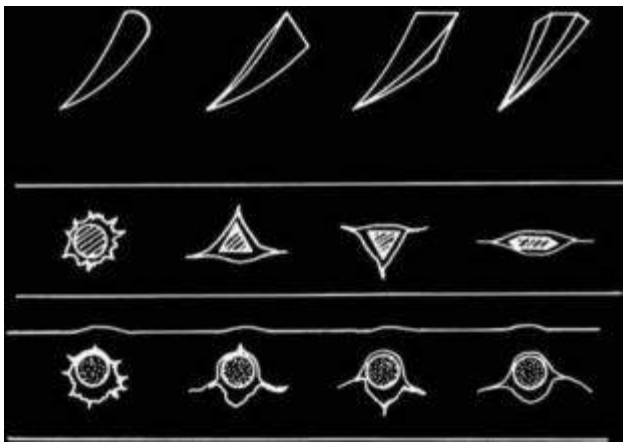


Figure 15.5 Surgical needles (**A** and **B**) and monofilament suture material (**C**) and their behavior in tissues. Left to right: round, cutting, reversed cutting, and spatula needle sections. C2 is especially hazardous in thin covering layers like the free lid margin. Copyright Frans C. Stades.

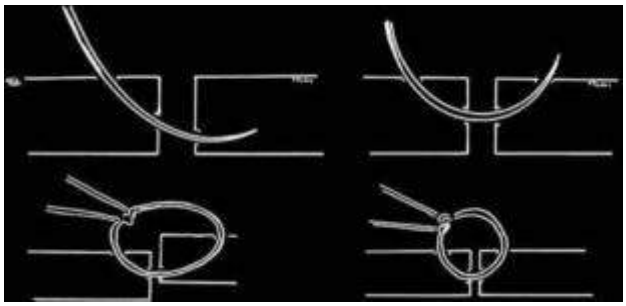


Figure 15.6 **A**. Asymmetric suture. After suturing, the wound levels will not be equal, resulting in delayed and scarring wound healing. **B**. Symmetric suture, resulting in exact apposition. Copyright Frans C. Stades.

(also see later Fig. 15.22, Fig. 15.28, and Fig. 15.8C), thus preventing folding on either side of the wound (dog-ears). Special attention is necessary to appose the edges of eyelid margin defects (Fig. 15.8 and Fig. 15.9). Sliding flaps should be pulled into the defect and bulge within the contour of the lid margin. If there is traction on the flaps or sliding grafts, it should be gradually minimized by the direction of the sutures and/or traction sutures (Fig. 15.11A and B). The posterior aspect of the skin graft postsurgically will be covered by conjunctival cells spontaneously, or it can be lined with mucosa from adjacent palpebral conjunctiva, buccal mucosa, or an island graft from bulbar conjunctiva of the opposite eye. However, the latter methods are more time-consuming and may lead to unwanted traction bands and secondary graft edge entropion.

A single-layer wound closure (starting at the eyelid margin with a figure-of-eight or horizontal mattress suture with nonabsorbable or absorbable suture material and the remaining wound by single, interrupted sutures) was compared to a two-layered wound closure (starting by apposing the deeper tarsoconjunctival layer with a simple continuous suture or one horizontal mattress suture, with buried knots of an absorbable suture material, and further closure as described in the first method). No significant difference was present in wound recovery, eyelid structure, and function after wound healing (Romkes et al., 2014).

Hemostasis

Hemostasis is usually achieved by direct pressure. Excessive hemorrhage can also be stopped by (bipolar) electrocoagulation. For hemorrhages of very fine vessels, special ophthalmic (battery) disposable microcautery units are available. Cautery of vessels will cause a local area of necrosis, and for this reason cauterization should not be done too quickly or excessively. Diffuse hemorrhages during lid surgery will usually clot spontaneously. To avoid delay caused by waiting for the hemorrhage to stop spontaneously, cutting by scalpel should be done from the lowest to the highest point.

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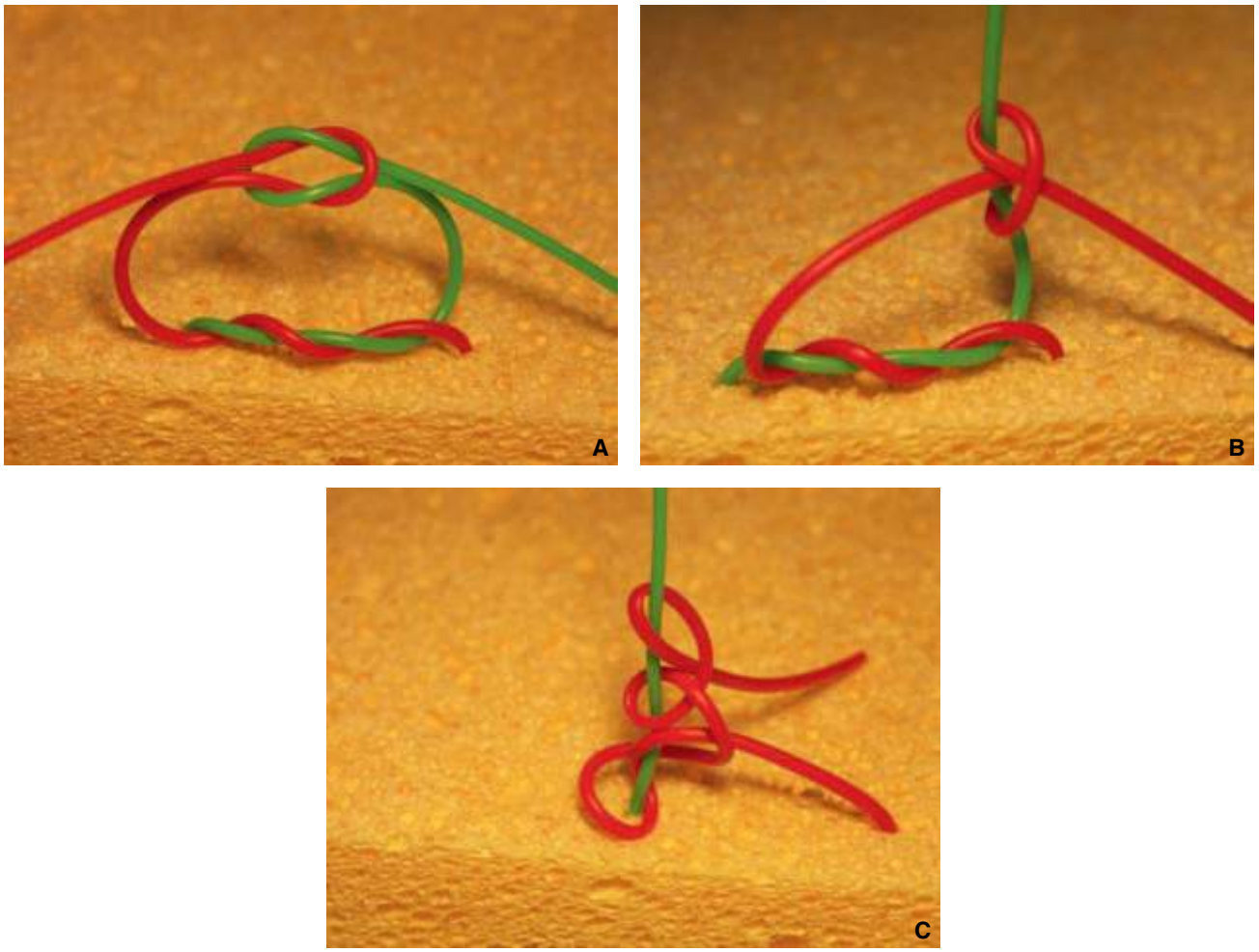


Figure 15.7 **A**. The surgical knot consists of a double throw, closed by a square knot. **B**, **C**. Both ends of the knot should be pulled equally, avoiding capsizing or spilling of the knot that would result in a potentially slipping knot. Courtesy of Frans C. Stades.

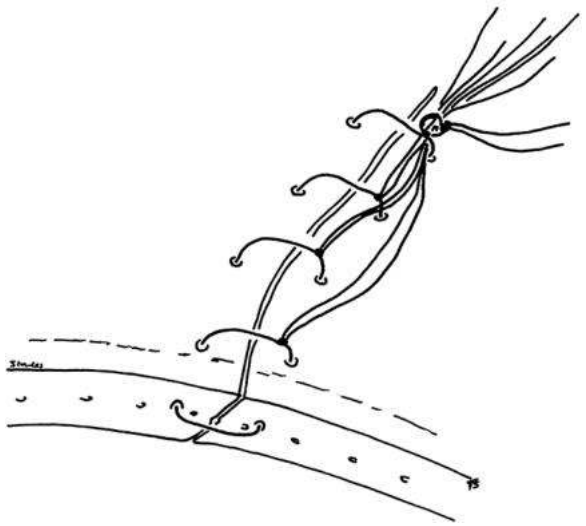


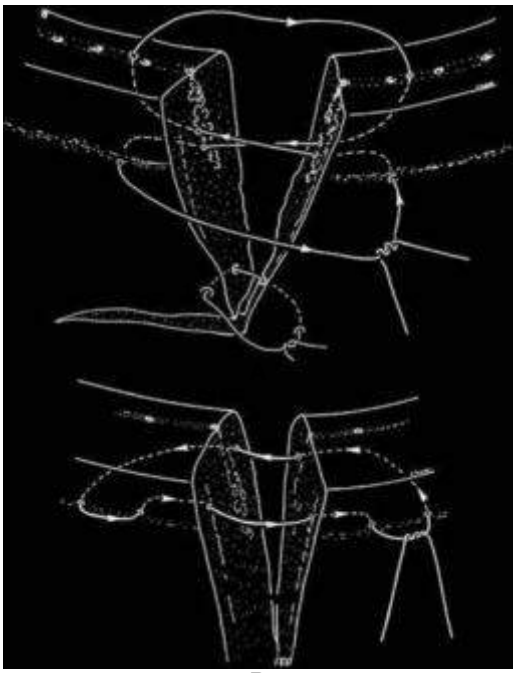
Figure 15.8 The ends of upper lid or lateral canthus sutures can be caught or linked together in an outer-placed suture to prevent irritation of the cornea. Copyright Frans C. Stades.

Diffuse hemorrhages during lid surgery will generally result in swelling of the weakest adjacent tissue. In entropion and ectropion correction, the area of swelling is usually the conjunctiva behind the skin wound. In entropion, the conjunctival swelling may displace the lid margin beneficially away from the often painful cornea, which may appear as an overcorrection initially. However, in ectropion and macroblepharon corrections, this swelling may result in recurrent ectropion. Therefore, in the latter procedures, more thorough hemostasis should be achieved before the final closure of the wound, or a small drain must be placed, especially following extensive blepharoplasties.

Cryosurgery

In cryosurgery, the destructive effect of freezing the intracellular water ruptures the cell membrane in unwanted tissues. In general, two cycles of rapid freezing and slow, spontaneous thawing are used. The tissues are frozen to at

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B

Figure 15.9 Suturing of a free lid margin wound. Methods of suturing using a figure-of-eight-like (**A**) or a U-form (**B**) suture. The conspicuous points of the wound are sutured first (1). The remaining wound is sutured by halving the intervals. Copyright Frans C. Stades.

least −25 °C, but no more than −30 °C (possible necrosis), by the use of carbon dioxide or nitrous oxide.

Cryosurgery may be of use for the destruction of hair follicles, the destruction of reactive granulation, or several types of neoplasia. The main advantages of cryosurgery are the relative simplicity and repeatability of the method. Potential disadvantages are severe postoperative swelling; depigmentation, which may be permanent; and the unwanted loss of normal tissue.

Postoperative Care

During recovery from general anesthesia or later during unsupervised moments, the patient may loosen or lose stitches, or worse, tissues, resulting in wound dehiscence and infections. Routine use of an Elizabethan or E-collar may prevent such complications.

Congenital and Presumed Hereditary Structural Abnormalities

Ankyloblepharon: Physiologic

The canine palpebral fissure is sealed at birth. A pinhole-sized patency at the medial canthus may be the earliest indication of the later separation. This period of natural ankyloblepharon is required in the dog because of the relative immaturity of the ocular and adnexal tissues at parturition. The bridge of tissue in the palpebral fissure between the already developed margins of the eyelid normally regresses at 10–14 days postpartum. Because the canine and feline palpebral fissure is not patent at birth, the term congenital with reference to disease in these animals should apply for a period of approximately 6–8 weeks after birth, until the main structures of the eye have developed.

Premature opening of the palpebral fissure is usually accompanied by exposure keratoconjunctivitis and severe corneal ulceration; globe perforation and uveitis are possible complications. In such cases, wetting ointments or gels must be used to protect the ocular surfaces. On occasion, temporary tarsorrhaphy with long and adjustable sutures may be necessary, particularly if the palpebral fissure opens within the first few days postpartum. When surgical closure proves to be necessary, mattress sutures are used to appose the lid margins for approximately 10–14 days, and it may prove necessary to maintain topical wetting therapy for several days after the sutures are removed. If the condition is accompanied with a tear film deficiency, prognosis is less favorable.

Ankyloblepharon: Pathologic

Ankyloblepharon is delayed or complete failure of opening of the palpebral fissure. Even though little is known about the cause of this regressive defect, some epidermal growth factor must be involved. The anomaly occurs infrequently and is usually bilateral. Conjunctivitis or ophthalmia neonatorum must be considered in the differential diagnosis, but in this condition the closed eyelids will bulge as a result of the exudate that accumulates behind the adhered eyelids. This often staphylococcal keratoconjunctivitis may result from an intrauterine infection or from the dam's genital tract during partum. The bacteria enter the conjunctival sac, presumably via the patent opening in the medial canthus. The first indication of its presence may be a bead of purulent material at the medial canthus and the bulging lids (Fig. 15.12). The lid fissure should be carefully opened without delay; otherwise, the lacrimal gland, cornea, and even the whole globe can be irreversibly damaged.

Therapy

Treatment consists of gently massaging the fissure cautiously until it opens. If this fails, mechanical spreading with mosquito forceps in the spontaneous first opening and/or into the groove of the future fissure starting in the medial canthus will open the fissure. Sometimes, an incision at the medial canthus with a pointed scalpel is necessary. Care is required to follow the line of separation between the two lid margins accurately, using Stevens scissors, and to avoid any contact with the cornea. The conjunctival sac can be swabbed to determine the cause of infection

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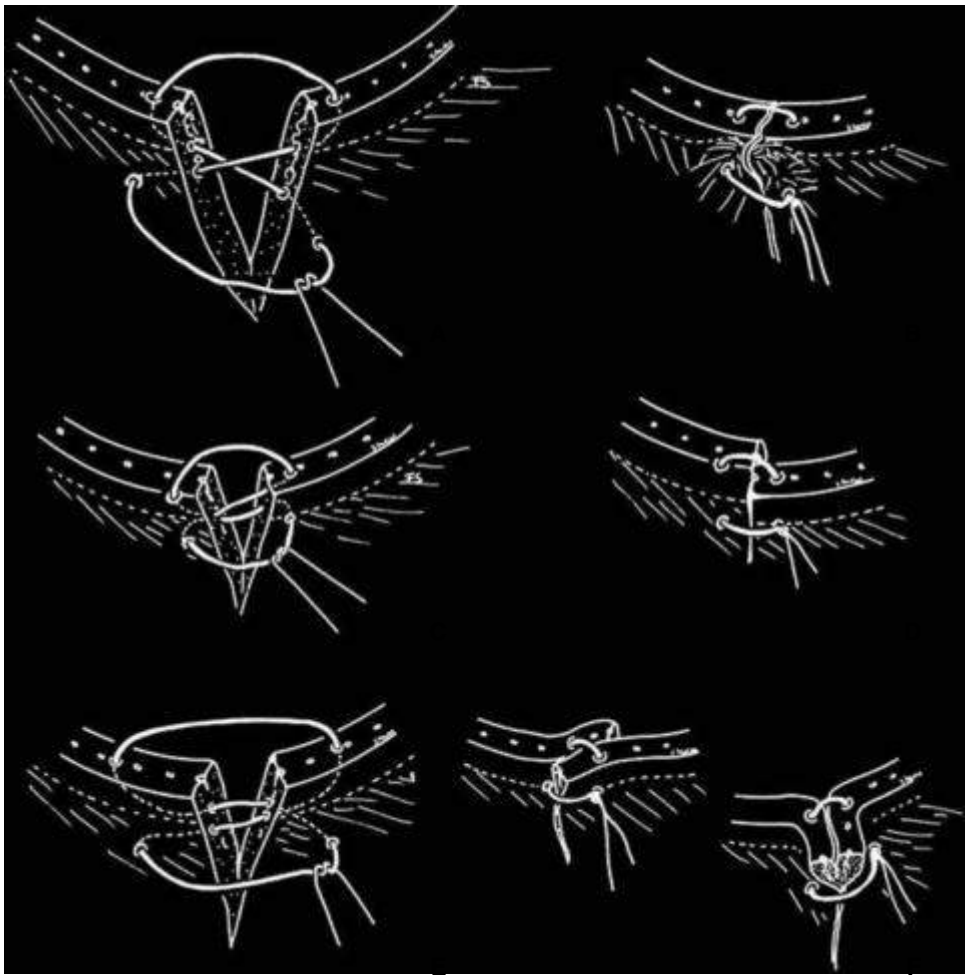


Figure 15.10 Suturing of a free lid margin wound as it should *not* be done. Suturing at unequal intervals and too far away from the margin's first figure-of-eight suture (**A**) and the result (**B**). Incongruous suture: at the left side, 1 mm outside of the margin; at the right side, in the line of the Meibomian gland openings or gray line (**C**) and its result (**D**). Suture located in the line of the Meibomian gland openings but too far away from the wound (**E**) and its possible results (**F**). Copyright Frans C. Stades.

and to establish antibiotic sensitivity. The conjunctival sac may be irrigated with 10% acetyl cysteine. All debris is removed using sterile saline or a 1:50 povidone-iodine aqueous solution. The eye is examined for corneal damage, and a broad-spectrum topical antibiotic is applied four to six times per day for as long as necessary. Specific antibiosis can be substituted once the sensitivity has been established.

Prognosis

The prognosis is favorable. There are no known means of preventing this condition.

Eyelid Coloboma or Aplasia

In eyelid coloboma or aplasia palpebrae, or lid agenesis, the lid margin and the lid itself are completely or partly undeveloped. This rare anomaly is congenital, presumed hereditary, usually bilateral, and in the canine affecting the lateral part of the lower eyelid; the condition is not infrequent in cats. Eyelid coloboma is often associated with other congenital anomalies such as microphthalmia, absence of the lacrimal gland, keratoconjunctivitis sicca, persistent pupillary membrane, cataract, retinal dysplasia, and optic nerve head colobomata. The pups are often born with the palpebral fissure partly or fully open. Sometimes, the margin of the eyelid is developed but without Meibomian glands.

Therapy

If the margin of the eyelid is developed without Meibomian glands, no surgical therapy is necessary. If there are ectopic hairs in the area, they should be removed. If the cornea is only slightly irritated, administration of topical lubricants, to effect, on a daily basis will be sufficient. If the lesions are larger, a substitute eyelid should

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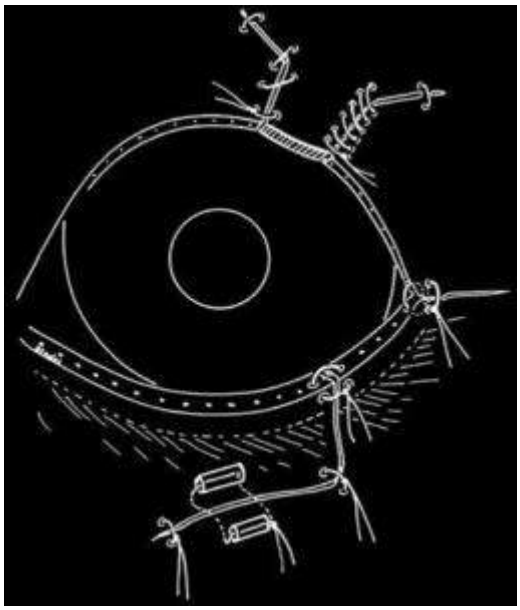


Figure 15.11 Surgical correction of wounds and the order of suturing (1–3). If there is traction on the wound, U-figure relaxation sutures can be used; silicon or infusion tubing prevents sutures from cutting into the skin (**A**). If flaps are to be positioned (**B**), the sutures should pull the flap into the defect (B, 1, 2), relieving traction on the leading edge of the graft. The leading wound edge (**C**), to be the new lid margin, should bulge slightly within the lid margin contour, resulting in a continuous lid margin line after cicatrization. Copyright Frans C. Stades.

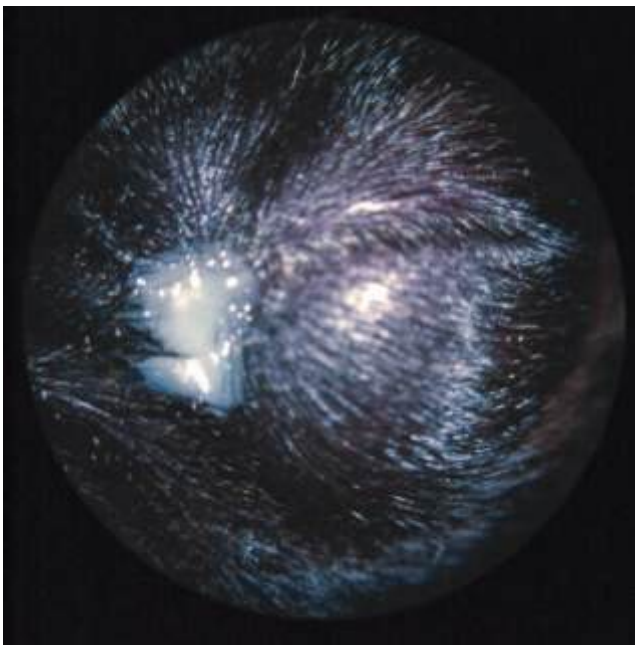


Figure 15.12 Pathologic ankyloblepharon. Delayed eyelid opening in a puppy has resulted in ophthalmia neonatorum with pus extruding from the medial canthus. Courtesy of Frans C. Stades.

be created by blepharoplasty. Many methods have been described, using skin, skin with orbicularis and tarsus, and, in the more sophisticated but also more complicated procedures, skin posteriorly lined with adjacent conjunctiva or homologous conjunctiva/mucosa from elsewhere (see reconstructive blepharoplasties, later Fig. 15.75, Fig. 15.77, and Fig. 15.83, and Chapter 28, "Feline Ophthalmology").

Prognosis and Prevention

In cases of minor defects, the prognosis is favorable. In larger lesions, the substitute eyelid can function reasonably well. In some cases, lifelong administration of topical lubricants will be necessary. In case of failing lacrimation, prognosis is less favorable. If there are other congenital anomalies, they should be considered in the prognosis.

Osteoma Cutis Eyelid Deformation

Osteoma cutis is a rare ossification within the deep dermis. Osteoma cutis in the eyelid may be cause trichiasis, keratitis, and even strabismus (Hindley et al., 2016).

Therapy

Local resection of the abnormal tissue appears to be curative.

Dermoids and Dysplasia Palpebrae

Dermoids or choristomas of the lids are ectopic and abnormally developed islands of skin in or at the margin of the eyelid, frequently associated with some dysplastic deformities of the adjacent conjunctiva. They are rare, possibly hereditary, anomalies, usually of the lower lid near the lateral canthus (Fig. 15.13). Genetic predisposition exists in the French Bulldog, Shih Tzu (Badanes & Ledbetter, 2019), German Shepherd, Wirehaired Dachshund, Dalmatian, and St. Bernard, with the latter breed demonstrating a familial relationship between lower eyelid coloboma and dermoid formation (Brandsch & Schmidt, 1982).

An island or fold of skin often disrupts the lid margin and is continuous with the conjunctiva. The fissure length itself is sufficient in most cases. Blinking is abnormal, and hairs generally grow toward the cornea, causing chronic irritation and resulting in edema, vascularization, and pigmentation.

Therapy

Treatment consists of removal of the abnormal parts of the eyelid and conjunctiva, and especially the hair follicles in the involved area. Thereafter, the lid margin wound is closed with extreme care. Blepharoplasties are necessary when the lid margin has insufficient length. If a normal upper lid is available, the stretched lid margin length can be measured by calipers. If the normal part of the lower lid

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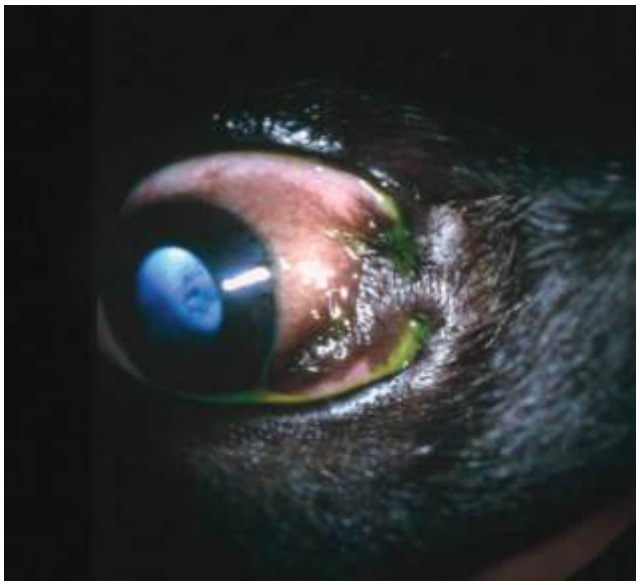


Figure 15.13 Dermoid and eyelid dysplasia of the lateral canthus and conjunctiva in a 6-month-old French Bulldog. Courtesy of Frans C. Stades.

margin is 2–3 mm too short, the defect can be closed directly. Otherwise, the defect can be closed using a sliding (graft) procedure. If the condition does not produce overt corneal disease, the operation is often delayed until 10–12 weeks of age, when anesthesia risks are lower. For patients with severe defects, it may be best to operate soon. Postoperative treatment consists of topical initial choice, antibiotic eye ointment, or lubricating solutions four times daily for 10–14 days.

Prognosis and Prevention

The prognosis is favorable. Parents and littermates should also be examined. Affected animals and, ideally, also members of their immediate family should not be used for breeding.

Distichiasis and Conjunctival Ectopic Cilia

Distichiasis refers to single or multiple hairs arising from the free lid margin. They usually arise singly or with two or more hairs from the Meibomian duct openings (Fig. 15.14). The follicle itself is located 4–6 mm behind the margin of the lid in the posterior distal tarsal "plate," in or near the base of the Meibomian glands. The Meibomian glands are modified hair follicles, and distichiae develop from undifferentiated mesenchymal gland tissue and are not associated with histologic changes of the tarsal glands (Raymond-Letron et al., 2012). Both lids can be affected, and the condition usually demonstrates a bilateral presence (Bedford, 1971; Gelatt, 1969; Halliwell, 1967; Schmidt, 1980). In dogs affected with soft distichiae, directed away from the cornea, the condition appears to have limited clinical significance. Hairs floating on the corneal surface in the precorneal tear film in humans are known to irritate significantly. Stiff hairs that rub the cornea can irritate and cause injury (Bedford, 1971). This type of cilia may be coated with some mucin. Irritation leads to increased lacrimation, blepharospasm, and epiphora. Distichiasis may also act as a wick, resulting in an overflow of tears over the lower lid margin, moistening the margin and the exterior skin of the eyelid.

Occasionally, corneal ulceration will present with distichiasis, and though the cilia may be directly responsible for loss of epithelium, self-trauma may also be involved. Secondary entropion may be present, or in primary entropion distichiasis may cause severe irritation, resulting in a vicious circle.

Although distichiasis is considered to be inherited, the exact mode of transmission is unknown. It occurs frequently, and predisposed breeds (1995–2000, 27,087 pure-bred dogs) include the American (69%) and English (49%) Cocker Spaniels; Welsh Springer (48%) and Cavalier King Charles Spaniels (24%); Flat-Coated Retriever (31%); Boxer, English Bulldog, Havanese, and Shetland Sheepdog (25%); Shih Tzu, Pekingese, and Tibetan Terrier; and Spaniel, Dachshunds, Poodles, and Jack Russell Terrier. Distichiasis may be present in puppies during litter screening at 6 weeks of age. Dogs with distichiasis are prone to having ectopic cilia in the conjunctiva. Breed predispositions to ectopic cilia are as for distichiasis in the Flat-Coated Retriever, Pekingese, Shih Tzu, English Cocker Spaniel, Boxer, English Bulldog, Poodle, and Jack Russell Terrier.

Irritation caused by distichiae leads to variable degrees of frequent blinking, moisture on the margins of the lower eyelid, and corresponding corneal lesions such as edema, vascularization, ulceration, and pigmentation. Distichiae may be difficult to detect without magnifying glasses and strong focal illumination. A common sign of distichiasis is the mucin that adheres to the hairs, revealing their presence. The mucus can effectively mask, but on the other hand betray, their existence. Straight, tough hairs, directed toward the cornea, however, can cause trigeminal irritation, as witnessed by excessive lacrimation, blepharospasm, mild conjunctivitis, and superficial keratitis. Trichiasis and entropion must be considered in the differential diagnosis, but in these conditions no hairs arise from the free lid margin.

Therapy

The simplest treatment is manual epilation by rounded-tip epilation forceps at regular intervals (4–5 weeks). The advantages of this method are that it allows detection of irritation caused by the hairs, it needs no anesthesia, and, if there are only a few hairs, it can be performed by skillful owners themselves. Manual epilation may also be used to confirm that the clinical signs are related, in fact, to the distichiae.

For permanent treatment of distichiasis, the hair follicle is destructed, removed, or redirected. The methods vary from

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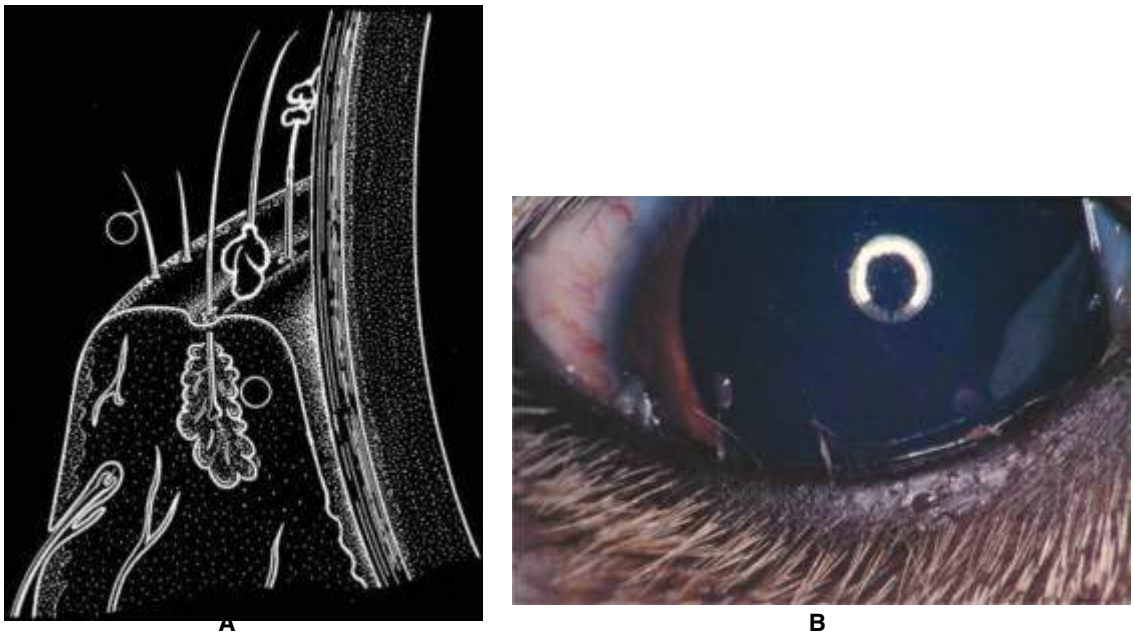


Figure 15.14 **A**. Distichiasis (hairs in or on the lid margin) emerging from the Meibomian (1), Zeis, or Moll (2) gland openings; 3. tear film; 4. cornea. **B**. Distichiasis of the lower lid in a dog. Mucus adheres to several of the distichiae, revealing their presence and proving their corneal contact and irritation. Copyright Frans C. Stades.

diathermy-electroepilation to electrocautery, high-frequency radiohyperthermia, electrolysis, cryotherapy, partial resection of the distal tarsal "plate," eyelid split, transpalpebral conjunctival dissection, and Celsus–Hotz repositioning, but all have various limitations. All these methods require general anesthesia and, more important, adequate magnification (5–10×) to detect the orifice of the hair and the follicle (Halliwell, 1967).

In electrocautery, the hair follicle is destroyed by coagulation. A simple battery-powered device is the Perma Tweez (Stades et al., 1998). A very thin, stiff steel wire, mounted on a fragile spring, is introduced along the hair about 3 to 5 mm deep (not deeper!) into the lid margin to the follicle. If incorrectly positioned, the wire will move backward because of the spring instead of into the root of the hair follicle (Fig. 15.15A). It is disadvantageous that destruction of the follicle must be assumed rather than observed. The tip is rotated slightly in each follicle for at least 15 seconds, and when the tip is retracted the hair ideally should adhere to the steel wire. When the hair is removed by an epilation forceps, it should provide no resistance. Otherwise, the procedure has to be repeated, or it has to be combined with another method, such as the destruction of the follicle via the conjunctiva.

Electrocautery and high-frequency radiohyperthermia units for hemostasis, provided with a needle, are usually too powerful and will easily lead to destruction of the free edge of the lid margin and result in nasty distortion and scarring (Fig. 15.15B), often without destroying the follicle. Bipolar electrolysis apparatus, as advocated to destroy "mustache" hairs in humans, are usually not powerful enough for the destruction of the more deeply located hair follicle in distichiasis.

Cryosurgery is a popular technique. It is performed through the conjunctival surface directly over the follicle, 3–4 mm behind the free margin of the lid (Chambers & Slatter, 1984; Wheeler & Severin, 1984). The lid margin is stabilized and everted, using a Von Graefe forceps or Desmarres eyelid clamp (Fig. 15.16). A double freeze–thaw cycle using (nitrous oxide) specific probes produces a −25 °C freeze, which can destroy the follicles but spare the adjacent eyelid tissue. Because temperatures below −30 °C will easily produce necrosis and eyelid distortion, the use of thermocouple needles may ensure that tissue temperature does not fall below −25 °C. A 60-second freeze is followed by a brief thawing period and then a second freeze for 30 seconds. The immediate postoperative effect is considerable swelling of the cryosurgery site, sometimes so much that blinking is impaired. Preoperative systemic nonsteroidals or postoperative topical treatment with corticosteroid initial choice antibiotic eye ointment is helpful. The swelling usually lasts no more than 2–4 days. Depigmentation of the frozen areas occurs within 72 hours. Repigmentation usually takes up to 6 months to complete. Permanent depigmentation, scarring, and distortion are possible complications.

Two variations of lid splitting can be effective in patients with substantial eyelid thickness and if the cilia are more localized (Bedford, 1973, 1979; Campbell, 1977; Long, 1991).

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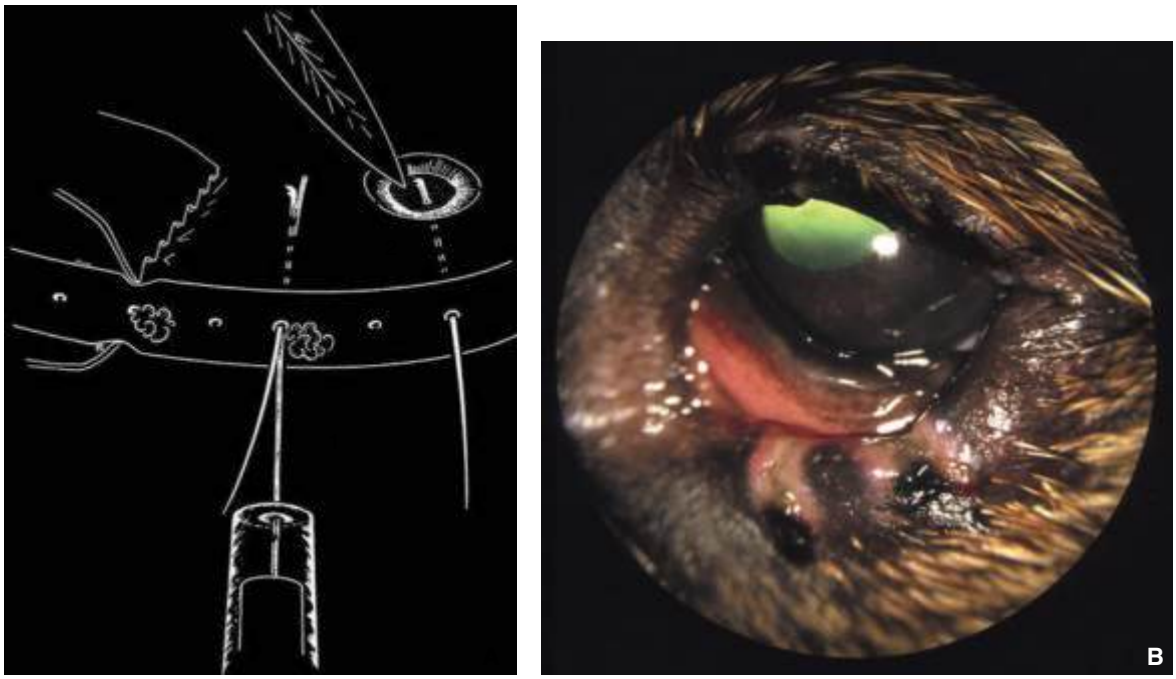


Figure 15.15 **A**. Distichiasis. Destruction of a single hair follicle by battery-powered needle coagulator (Perma Tweez) via the opening of the gland (1) or by electrocautery (cutting) via the conjunctiva–tarsal "plate" (2). Alternatively, cryodestruction can be done at the same location. **B**. Lid margin damage after distichiasis-hair follicle destruction using an overpowered needle cautery. Specific blank tip-isolated shaft needles do exist for follicle destruction, but the diameter is less fine than the Perma Tweez. Copyright Frans C. Stades.



Figure 15.16 Cryodestruction of multiple distichiae in the conjunctiva–tarsal "plate" in a dog. Courtesy of Frans C. Stades.

The eyelid "wedge" removal requires a special lid clamp, and the free lid margin is damaged. Very precise parallel incisions, approximately 5 mm deep, are made anterior and posterior to the involved Meibomian ducts. A wedge of tarsal tissue is removed together with the hair follicles; however, the location of the follicle must be assumed rather than observed. The posterior eyelid margin is left intact; thus, postoperative eyelid distortion is avoided. In the removal of the involved tarsal "plate," including the Meibomian glands, very precise incisions, approximately 4 mm deep, are made outside the involved Meibomian ducts and just behind the base of the glands, and the tarsal "plate" removed (Bedford, 1979).

In both procedures the wounds are allowed to heal by granulation, and the partial loss of Meibomian function seems to have no demonstrable effect on the stability of the precorneal tear film. These techniques should not be attempted in breeds with relatively thin eyelids because of the risk of cicatricial distortion or distortion of the entire length of the lids. In the removal of a tarsal "plate" strip, including the base of the Meibomian glands, the palpebral conjunctiva is incised 2 mm behind and parallel to the free lid margin over the involved area. A second incision, 4 mm behind and parallel to the first incision, allows removal of a strip of tarsoconjunctival tissue, with the assumed distichia follicles. If performed over most of the length of the eyelids, postoperative cicatrization may cause secondary entropion. A sliding tarsoconjunctival graft may be incorporated to prevent this complication (Long, 1991).

A simpler method to remove the root of the distichia is to use an electric knife or electrocautery pen, 3–4 mm behind the location of a distichia into the tarsal "plate" until the follicle is visualized and destroyed (Stades et al., 1998). These methods can also be combined with the Perma Tweez method when the destruction of the follicle is uncertain. The defect will be refilled by secondary granulation and be re-epithelized after 10 days.

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Alternatively, a transconjunctival strip involving the area between 2 and 4–5 mm from the free lid margin bearing the ciliae can be resected (Gómez et al., 2020). The wound closes by secondary intention. Appearance of new distichiae occurred in 14/30 eyes (46.3%). Recurrence of distichiae only occurred in one eye (3.3%). Postoperative complications included trichiasis and cicatricial entropion, which developed in two eyes (6.6%).

The Celsus–Hotz procedure can also be used to evert the lid margin with distichiae involving nearly all of the eyelid margin, to break the corneal contact and relieve the clinical signs. However, the necessary eyelid eversion may prove to be unacceptable and the distichiae remain in place.

The Stades forced granulation procedure (Stades, 1987b) can be used both to remove the hair follicles and to evert the lid margin (see later Fig. 15.58), but it will result in a marked scar formation just outside the lid margin, which may or may not pigment.

Ectopic Cilia

Dogs with distichiasis are predisposed to having ectopic cilia in the conjunctiva as the same hair follicles are involved. Here, one or multiple cilia emerge through the palpebral conjunctiva and impinge directly on the cornea, causing severe corneal irritation (Bellhorn, 1965; Gwin et al., 1976a, 1976b; Helper & Magrane, 1970; Playter & Ellett, 1972). They are usually pigmented in the same color as the rest of the hairs of the dog and located in a small, pigmented spot of conjunctiva (Fig. 15.17). Predisposed breeds (also for distichiasis) are Flat-Coated Retriever, Pekingese, Shih Tzu, Cavalier King Charles Spaniel, Boxer, English Bulldog, English Cocker Spaniel, Poodle, and Jack Russell Terrier. The upper eyelid is primarily involved. Single, multiple ciliae, bundles (Shih Tzu), or knots of hairs (Poodle) emerge through the conjunctiva, approximately 4 mm behind the free lid margin. The condition is usually in the young dog, accompanied by acute, intense blepharospasm and lacrimation, and may resemble a foreign body. It easily results in a superficial, rounded (no scratch) corneal defect, without undermined edges, and is accompanied by vessels. The clock-hour position of the corneal defect usually reveals the position of the cilia in the corresponding tarsal conjunctiva. Sufficient cooperation of the patient, light, and magnification are important factors for diagnosis.



Figure 15.17 Ectopic cilia in the middle of the upper eyelid in a dog. Therapy is to excise or destroy the cilia follicles by cautery or cryothermy. Courtesy of Kirk N. Gelatt.

Therapy

In treatment, the lid is everted by Von Graefe's forceps, a chalazion, or an eyelid clamp. From the palpebral conjunctival surface, using an electric knife, the covering conjunctiva is removed until the hair follicle is visualized and then destroyed. Alternatively, the assumed follicle area is excised *en bloc* by scalpel, by a dermal biopsy punch (D'Anna et al., 2007), or destroyed by cryosurgery. In the latter method, the cilia have to be removed by epilation afterward. Manual epilation may work in very easy-to-handle dogs (Park & Beckwith-Cohen, 2015). However, much more thorough inspection is possible under general anesthesia as multiple ectopic cilia are common, and permanent destruction of the aberrant hair follicle is preferable. Aftercare consists of topical initial choice antibiotic ointment 4 times daily for 7 days.

Prognosis and Prevention

The prognosis is favorable; however, the owner should be informed that other adjacent hair follicles may be invisible at the first session or, when not visualized, the germinal bud may not be destroyed and the hair shaft may regrow. The prevalence of distichiasis in 799 English Cocker spaniels from Denmark, examined between 2004 and 2013, was shown to be 49.31%. The relative risk of developing the disease was 1.3 and 1.8 for offspring of one or two affected parents, respectively. This, together with the moderate to high heritability (0.22 to 0.51) of the condition, indicates that selective breeding can be used to reduce the incidence of distichiasis (Petersen et al., 2015). Affected animals, even with "only" one or two distichiae, should not be used for breeding, especially for breeds in which the percentage of affected dogs is still low.

Entropion

Entropion is the inversion of all or part of the eyelid margin, such that the free rim of the lid margin or the outer skin contacts the conjunctival or corneal surface, or both. The degree of entropion is considered to be mild when the margin is tilted by about 45°, moderate when it is tilted by about 90°, and severe when the margin is turned inward by about 180° (Fig. 15.18). Entropion may be lateral, medial, angular, or total, and may affect the lower or upper lid, or both. Entropion can be divided into categories: primary, such as congenital or developmental entropion; and secondary or

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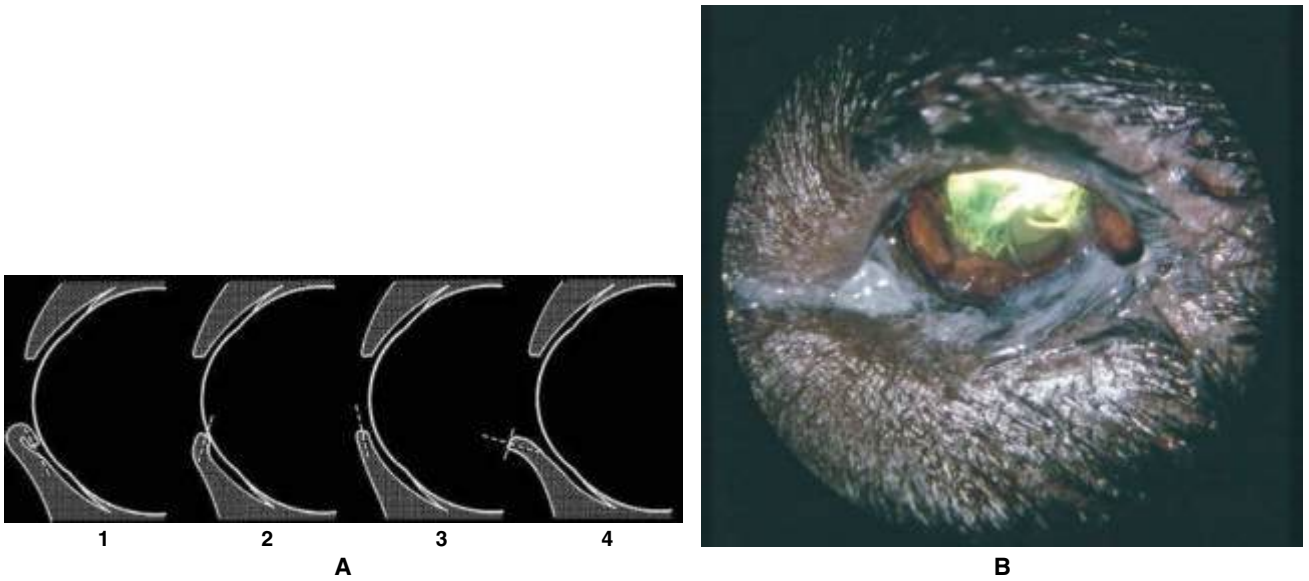


Figure 15.18 **A**. Positions of the lid margin: 1. severe entropion; 2. mild entropion; 3. normal position; and 4. ectropion. **B**. Severe, high-degree lower lid entropion, masked by exudate in a Rottweiler. Copyright Frans C. Stades.

acquired, such as spastic and cicatricial entropion. Entropion may result from a difference in tension between the orbicularis oculi muscle and the malaris muscle (lower lid entropion) and is influenced by multiple conditions such as the length of the lid fissure, conformation of the skull, the orbital anatomy, gender, and the extensiveness of folds of facial skin around the eyes.

Epidemiology

Primary, congenital, or developmental entropion is a common condition in pure-bred dogs. A hereditary defect is common, but the genetic basis is not well understood. It is commonly present in one or two littermates, with sound parents, excluding simple, dominant inheritance. It is more likely polygenic, but a dominant inheritance with incomplete penetrance or a recessive trait is not impossible.

Severe entropion of the entire lower lid (Fig. 15.18B and Fig. 15.19A) occurs in breeds including the Chow Chow, Shar Pei, Bouvier des Flandres, Neapolitan Mastiff (Guandalini et al., 2016), and Rottweiler. In these breeds, the lid fissure is usually relatively short. In hunting breeds like the German Pointer, Labrador, Golden Retriever, and others, the lateral three-fourths of the lower lids are commonly involved. In large or giant breeds, such as the Great Dane, St. Bernard, and Leonberger, entropion is often associated with an oversized palpebral fissure length, and is commonly found in the lateral half of the lower lid and the lateral canthus (see later Fig. 15.44A). Upper eyelid entropion (Fig. 15.19B) (usually in combination with trichiasis; see also later Fig. 15.59A) occurs in the Bloodhound, Chow Chow, and Shar Pei, and in the older English Cocker Spaniel and Basset Hounds, in which the looseness of the circum orbital skin, the presence of loose facial folds (see later Fig. 15.65A), and the long and heavy ears contribute to upper lid distortion.

Medial entropion occurs frequently in the Pekingese, Shih Tzu, Pug, Toy and Miniature Poodle, Cavalier King Charles Spaniel, and English Bulldog. In breeds like the Shar Pei and Chow Chow, the lower and upper eyelid entropion can be present as early as 2–6 weeks of age. In the other breeds, the onset of entropion is usually at 4–7 months. However, sudden onset of entropion, also unilateral, in 4- to 6-year-old or even older dogs, possibly initiated by secondary spasm caused by minor trauma, is also possible.

Infrequently, the entropion is secondary or acquired as a result of severe (corneal) pain, such as occurs in primary corneal ulceration. It can also be secondary to a loss of lid support (e.g., in microphthalmos, phthisis bulbi, retrobulbar fat resorption, or muscle atrophy secondary to chronic myositis). In rare cases, conjunctival and skin scarring (caused by wounds or surgery) may cause traction to the lid margin and cause secondary cicatricial entropion, trichiasis, or both.

Clinical Signs

The inverted position of the lid margin against the palpebral conjunctiva of the nictitating membrane and the bulbar conjunctiva and cornea results in irritation, excessive lacrimation, mucopurulent discharge, and blepharospasm. There is increased conjunctival vascularity and signs of chronic irritation of the cornea such as edema, vascularization, granulation, pigmentation, and even ulceration. The margin and exterior surface of the eyelid are moist, often discolored, and there may be mucopurulent discharge

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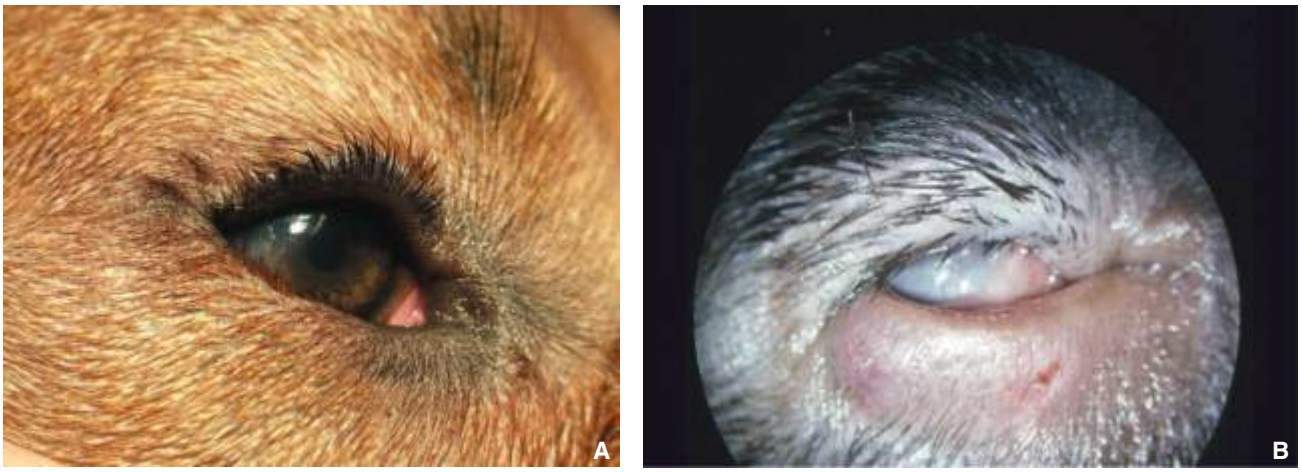


Figure 15.19 **A**. High-degree, entire lower lid entropion with secondary corneal ulceration in an Rhodesian Ridgeback. **B**. High-degree upper lid entropion in a German hunting dog. Courtesy of Frans C. Stades.

dependent on the severity of the inversion and degree of irritation. Where hairs contact the cornea, corneal defects are common. Because of the trigeminal irritation, the patient will be in constant pain, resulting in excessive lacrimation, enophthalmos, a loss of support of the lid margin, and subsequently a further increase of the entropion. Moreover, self-trauma in an attempt to relieve pain will contribute to the overall damage. This leads to a vicious circle that can be resolved only by surgical correction of the entropion. The corneal lesions may be filled by granulation tissue or they may deepen until perforation occurs. The final stage is the formation of scar tissue and pigmentation or, sometimes, loss of the eye.

Diagnosis

Diagnosis is based on clinical signs, history, and breed. The patient should be observed without restraint to determine the degree of entropion. After the evaluation has been done at a distance, during closer examination the animal should not be held too tightly by the nape of the neck, because traction on the skin may evert the entropion. In case of doubt (e.g., when only the outside of the eyelid margin is moist), an entropion provocation test should be performed. For this purpose, a small skin fold, approximately 10 mm below the lower lid margin, is retracted slightly so that the lid margin inverts and the outer edge lies against the cornea. This inversion should be corrected by a single blink, and its persistence indicates (habitual) entropion. The instillation of a topical anesthetic is another diagnostic method to differentiate the structural component from the secondary spastic or pain contribution of the entropion.

Trichiasis, distichiasis, and eyelid coloboma must be considered in the differential diagnosis, but in these conditions the cilia and the free lid margin, or absence of lid margin, can be visualized.

Therapy

In mild entropion, the cornea may be protected by a topical lubricant. It is usually best to postpone surgical correction until the head has grown to full size (1.5–2 years of age). However, if there are signs of distinct conjunctival or corneal irritation, surgical intervention is certainly indicated.

Tacking Lids or Stay Sutures

In puppies (mainly Shar Pei and Chow Chow) less than 12 weeks old (when the anesthesia risk is relatively high) with severe entropion, temporary retraction sutures ("tacking"; Fig. 15.20; Johnson et al., 1988; Lenarduzzi, 1983) can be placed to gather up the skin of the lid and thereby evert the lid, thus preventing corneal lesions. Alternative staple or skin-crushing methods are considered unpredictable, irritating, and animal-unfriendly methods. Usually, two to four 5-0 to 6-0 nonabsorbable or absorbable (but they last for less time) tacking sutures are placed adjacent to the involved lid margin. Simple, interrupted (needle direction away from the cornea, thus less risk for corneal trauma) mattress sutures or interrupted, vertical mattress sutures are placed in the lower and less frequently in the upper eyelids. The "bites" are about 5 mm long to ensure adequate retraction and tissue holding occur. Often, the sutures are left long to permit multiple adjustments.

When the sutures are removed (4–6 weeks) or lost, the surrounding "scar tunnel" will remain, thus still causing correcting traction on the lid margin. Therefore, this procedure must be considered a surgical intervention for entropion and the patient so identified. In some cases, the entropion will not need further correction. Persistent entropion requires further surgery.

The tacking procedure is also indicated in adult dogs to treat spastic entropion or to prevent secondary trichiasis-entropion of the upper lid to the lower lid after lower lid

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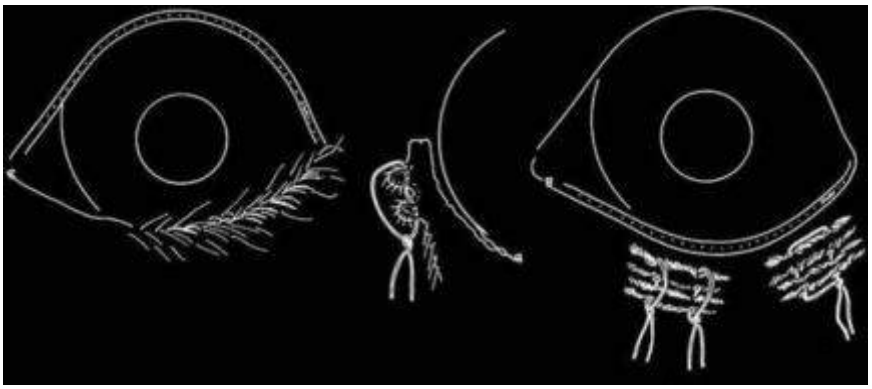


Figure 15.20 Entropion correction by retraction sutures (tacking). The sutures can be maintained for at least 2–3 weeks. The scar tissue "tube" formed around the suture material will result in moderate permanent correction. **A.** Simple interrupted sutures. **B.** U-figure suture, with the disadvantage that the needle also points in the direction of the cornea during suturing. Copyright Frans C. Stades.

entropion correction. Severe entropion should be corrected when there are corneal lesions, even in very young animals. Special care must be taken to avoid overcorrection, particularly in very young animals. Before operating, the entropion is evaluated before and after application of a topical anesthetic to determine the extent and degree of entropion. In long-standing lesions, the entropic lid hairs are coated with a mucoid material that appears whitish tan and gives the surgeon an indication of the amount of eversion necessary to correct the defect.

Quickert–Rathbun Procedure

As reported by Williams (2004), the Quickert–Rathbun technique can be used in dogs for lower lid entropion using fornix-based sutures. This technique may be an alternate procedure to the tacking method in young puppies (especially those where entropion recurs after tacking) or may be employed in older dogs. In this procedure, double-ended 4-0 absorbable suture is positioned from the deep fornix to exit externally 1–2 mm from the eyelid margin, immediately everting the lid margin and entropion (Fig. 15.21). The tension by the sutures can be varied to effect normalcy or slight ectropion. Further work is necessary to evaluate the long-term success. The use in the upper lid, as done in humans, may be harmful to the lacrimal gland ductuli.

Many methods and variations are available for the correction of entropion (Veenendaal, 1936). There is no "cookbook" method to fit every patient. Complicated entropion cases, such as combinations of upper and lower lid entropion, medial entropion, and combinations with severe corneal lesions (e.g., ulcer, corneal pigmentation), require more surgical skills and experience.

Surgical Procedures

Entropion correction was described by Celsus in the first century AD as a technique by which only skin was removed and the skin wound sutured (Zeis, 1839). Hotz improved the

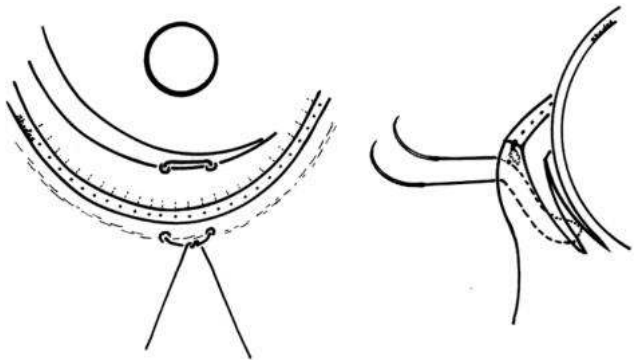


Figure 15.21 In the Quickert–Rathbun technique, a double-ended 4-0 absorbable suture is extended from the deep fornix to exit just in front of the lower lid margin, immediately everting the lid margin and entropion. The tension by the sutures can be varied to effect normalcy or slight ectropion. Disadvantage: less predictable after removal of the suture. Copyright Frans C. Stades.

procedure to include removing a strip of the orbicular oculi muscle and closing the wound with simple, interrupted sutures anchored in the remaining muscle (Hotz, 1879). In the veterinary literature, the excision of a somewhat circular section of skin to effect correction of entropion was described by Fröhner around 1900 (Fröhner, 1900). At least three different surgical procedures were described and illustrated for entropion for animals by Nicholas (1914). The excision of an oval portion of skin involving the lateral lower eyelid and lateral canthus for entropion was referred to as the Berlin–Mégnin method. A simple method to repair entropion in the dog was reported by Veenendaal (1936). The excision of an arrowhead-shaped section of lateral canthus skin for the treatment of entropion has been referred to as the Schleich method (Carter, 1967; Dixon, 1948; Halliwell, 1965; Menges, 1946; Miller & Albert, 1988; Mitchell, 1931).

The Celsus–Hotz procedure and its modifications are currently the basic surgical techniques for the treatment of most types of entropion. This procedure and its modifications

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provide consistent and beneficial results. Others claim the Celsus method alone to be sufficient for correction (Martin, 2005). Lid procedures in dogs must consider that this species lacks a cartilage tarsal plate and a well-developed lateral canthal ligament that are present in humans. Often the presence of enophthalmos can further complicate the correction of entropion.

Surgical correction is begun with an incision 2–2.5 mm from and parallel to the margin of the lid (where the pigmentation of the skin ceases and the first eyelid hair begins; Fig. 15.22), extending at least 1 mm medial and lateral to the entropic part of the lid. The lid may be stretched by closed forceps in the lateral canthus and a fingertip adjacent to the area of entropion, or by an entropion clamp, or it can be held taut and the eye protected by, for example, a Jaeger or Gränitz lid plate. If the first incision is too close to the margin, there will not be enough tissue for suturing, and there is a greater possibility of the sutures touching the

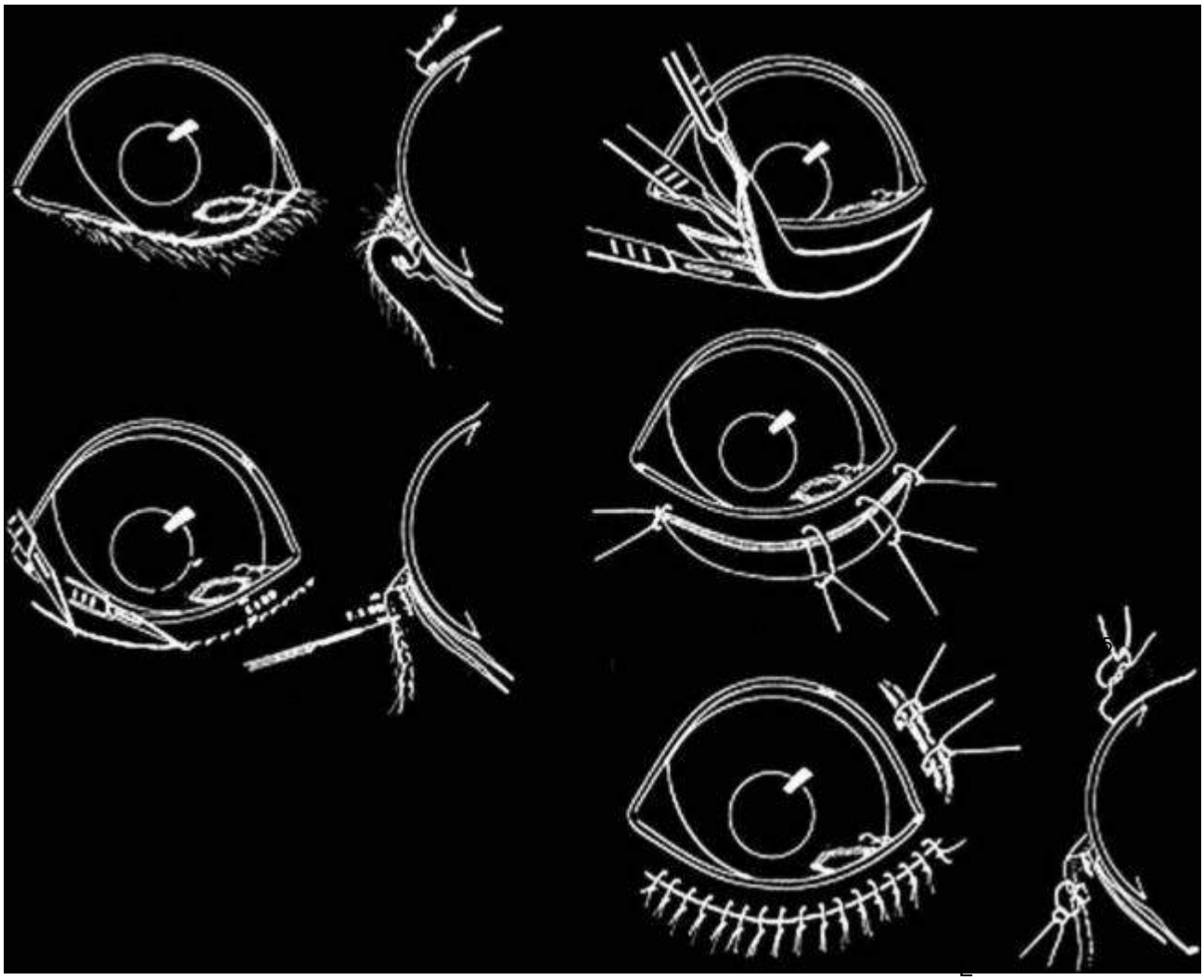


Figure 15.22 Celsus–Hotz procedure for the correction of severe lower lid entropion with corneal ulceration. **A**. The skin is incised at about 2.5 mm (as near as possible to the margin for better prediction of the entropion correction, but with enough space for skin suturing) from and parallel to the lid margin (**B**). **C**. The skin plus orbicularis muscle are excised; not deeper: canaliculus and (sub-) conjunctival tissues should not be damaged. The lid margin should no longer show spontaneous intention of inward rolling. **D**. The skin is sutured with material not exceeding 5-0 (e.g., nonabsorbable or absorbable, especially in difficult-to-handle animals, mono- or polyfilament), using a fine, round-body needle with or without a micropoint. Continuous sutures alone are not used because of the risk of rupture of the suture material when rubbed, resulting in dehiscence of the entire wound. The first sutures are placed at the medial and lateral ends, and the rest of the wound is closed by halving the intervals in the following order: 1, 2, 3, 4, and so on. The distance between sutures is 2–2.5 mm. Alternatively, the intervals of the simple interrupted sutures can be made at about 4 mm, and thereafter the remaining wound intervals closed by a continuous suture. **E**. Secondary upper eyelid trichiasis to the lower, caused by postoperative lower lid conjunctival swelling, can be prevented by tacking of the upper lid (5). Copyright Frans C. Stades.

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cornea. If the first incision is too far from the margin, the lid may not evert sufficiently, and the result will be less than anticipated. Overcorrection may cause ectropion, which may result in additional, less predictable surgery. Therefore, correctly estimating the amount of tissue to be removed is most important. The following methods can be used as an aid:

- The most entropic part of the skin that lies against the cornea before surgery can be marked. The eyelid is replaced in its entropion position after the first incision has been made (Fig. 15.23). Using forceps, a small amount of blood is applied to mark the margin of the skin of the inverted lid. The second or external, elliptical-shaped incision is then made just along the edge of this mark (Stades et al., 1996).
- The rule-of-thumb technique (Fig. 15.24) is performed by placing digital pressure on the lid skin adjacent to the entropic margin and pulling down until the free lid margin is exposed. The distance the thumb moves to evert the lid is the widest portion of the lid skin excised. The second incision is made in an elliptical fashion, joining the two ends of the primary incision (Wyman, 1979, 1990).



B

Figure 15.23 Entropion correction estimation: blood-staining method (Stades). After the primary incision parallel to the lid margin, the lid is replaced in the entropion position. Using forceps, blood is applied to mark the skin at the line where the lid rolls inward. The second incision is made just along the edge of this mark. Advantages: simple, proper estimation of necessary correction. Copyright Frans C. Stades.

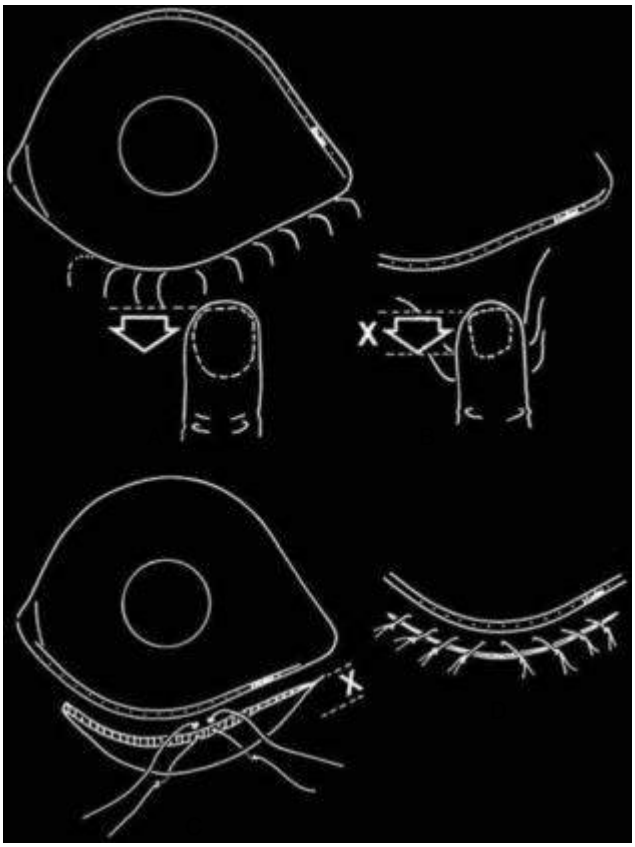


Figure 15.24 Entropion correction estimation: rule-of-thumb method (Wyman). **A**. Correction is accomplished by placing digital pressure on the lid skin adjacent to the entropic margin and pulling down until the free lid margin is exposed. **B**. The distance the thumb moves to evert the lid is the widest portion of the lid skin excised. **C**. An "arrow pattern" of suturing can be used, starting in the middle of the wound. The first two sutures are placed at an angle of 45°, pointing to the pupil. Disadvantage: the wound may not perfectly appose in between. **D**. The remaining sutures are placed parallel to each of the first two on the corresponding sides. Advantage: simple, moderate estimation of necessary correction. Copyright Frans C. Stades.

- Sufficient skin can be grasped with Allis forceps, for example, until the eyelid returns to its normal position (Fig. 15.25). The resulting fold of skin is removed by cutting with scissors (Miller & Albert, 1988).

The part of the skin around which the incisions have been made is further excised with a scalpel or with scissors ("fold" method), including a superficial strip of the orbicularis muscle (see Fig. 15.22 and Fig. 15.25). The palpebral conjunctival sac should not be perforated. After removal, the remaining lid margin should conform to the corneal surface and not tend to invert. Hemorrhage is usually minor and occurs from the lateral and medial ends of the incisions. Temporary clamping of the larger blood vessels by hemostats or digital pressure is usually sufficient. Thermocautery (or ligatures) of these bleeders is seldom necessary and may cause local fibrosis in the lid.

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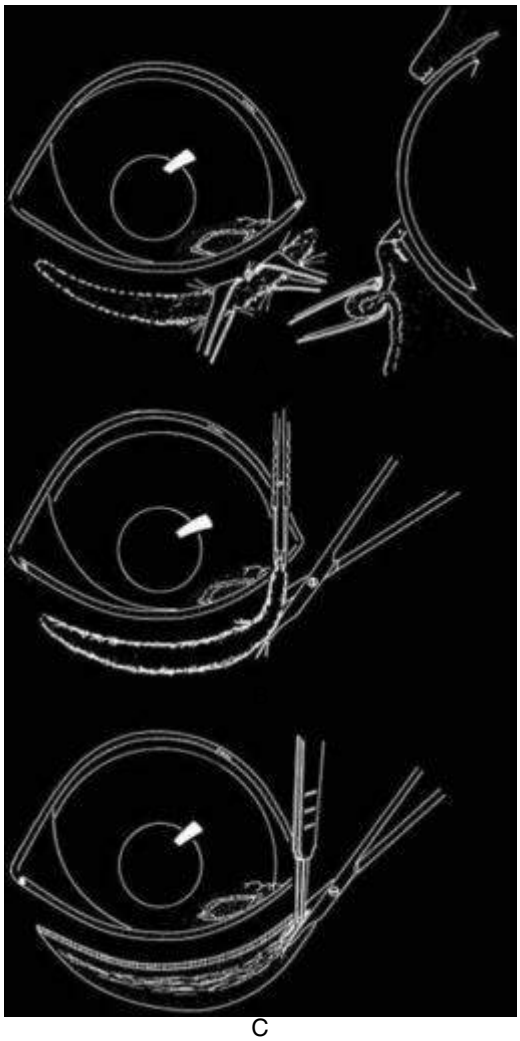


Figure 15.25 Entropion correction estimation: fold-grasping method. **A**. Sufficient skin can be grasped, for instance with an Allis forceps (not a hemostat), until the eyelid returns to its normal position. **B**. The resulting fold of skin is removed by cutting with scissors. **C**. A strip of the orbicular oculi muscle is removed. Advantage: simple, moderate estimation of necessary correction. Disadvantage: imprecise, nonperpendicular wound edges due to cutting with scissors. Copyright Frans C. Stades.

The wound is closed with interrupted sutures of material that will effectively reappose the wound edges and should be 5-0 or 6-0 (e.g., absorbable or nonabsorbable mono- or polyfilament), using a fine, round-body needle with or without a micropoint (see Fig. 15.22 and Fig. 15.24). The sutures are placed at intervals of not more than 2 mm. Alternatively, the intervals of the simple interrupted sutures can be made at about 4 mm, and thereafter the remaining wound intervals closed by a continuous suture. Continuous sutures alone are not recommended because of the risk of dehiscence of the entire wound when it is rubbed. Placement of the sutures must accommodate the shorter eyelid margin wound and the longer distal incision. The first sutures are placed at the medial and lateral ends, and then the rest of the wound is closed by halving. In lateral canthal entropion, the first suture is positioned at the lateral canthus. Some surgeons advocate an arrow pattern starting in the middle of the wound. The first two sutures are placed at an angle of 45° to each other, pointing to the eye. However, this may result in less perfect wound apposition between those stitches. The remaining sutures are placed parallel to each of the first two on the corresponding sides. They should be spaced as described previously. The edges of the wound should be joined together carefully so that no parts of the edge remain visible. Some postoperative swelling of the conjunctiva is normal and even desirable because it keeps the eyelid margin off the cornea, which is often still painful, thus allowing the cornea to heal quickly.

Surgery for Central Entropion

In the orbicularis pedicle traction strip or Wyman procedure, the central tarsal pedicle is combined with the Celsus–Hotz procedure to treat central lower entropion (Fig. 15.26; Wyman & Wilkie, 1988). The technique involves construction

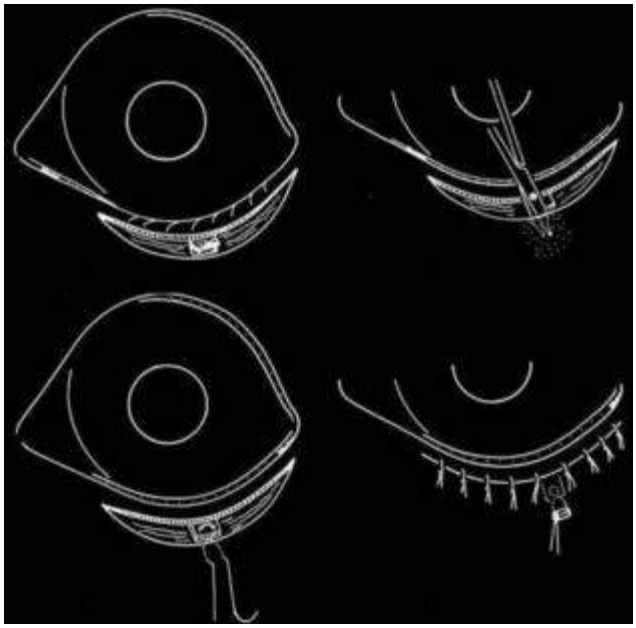


Figure 15.26 The central tarsal pedicle procedure for entropion (Wyman procedure). **A**. A tarsal pedicle anchored at the eyelid margin is combined with the Celsus procedure. The initial skin incision is performed about 2.5 mm from the eyelid margin. A tarsal pedicle is constructed by scalpel, with its base at the eyelid margin of the most extensive entropion. The second skin incision of the Celsus method is performed, and the section of skin is removed using tenotomy scissors. The width of the surgical wound varies with the extent of the entropion. **B**. A subcutaneous tunnel is made below the pedicle. **C**. Through the tunnel, a 5-0 cruciate suture attached to the tarsal pedicle is secured with a stent or silicone or infusion tubing below the surgical wound. **D**. The skin wound, to correct the remainder of the entropion, is apposed with simple interrupted, 5-0 to 6-0 sutures. Disadvantage: complicated and less predictable results. Copyright Frans C. Stades.

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of a pedicle of tarsus to evert the eyelid margin. The pedicle is secured in the subcutaneous tissues. This procedure is mainly recommended for severe and previously operated, recurrent entropion.

To correct mild central entropion of the upper and lower eyelids, the Wharton–Jones or Y to V method (not to be confused with the V to Y method for ectropion) has been advocated. The initial Y incision is made, starting from just below the eyelid margin, including eyelid skin and orbicularis oculi layers (Fig. 15.27). The tip of the flap is sutured outward, thus everting the lid margin outward. The procedure is traumatic to the orbicularis muscle, and because the middle of the flap does not control traction to the margin optimally, the result is difficult to predict.

Surgery for Medial Entropion

In cases of medial entropion, a little more of the skin can be removed to counteract any tendency to develop nasal folds, and without the risk of overcorrection. The Celsus–Hotz procedure may be modified for medial entropion and epiphora in miniature breeds of dogs. The objective of the technique is to evert the medial lower eyelid margin enough to assist the lower lacrimal punctum to conduct tears to its orifice (Peiffer et al., 1978a, 1978b). The extent of the lower eyelid skin–orbicularis oculi muscle to be excised is determined preoperatively by estimating the millimeters of correction to evert the medial lower eyelid. The incision should not be deeper than the orbicularis oculi muscle to avoid damage to the lower lacrimal punctum and canaliculus. Alternatively, pads of skin plus muscle can be removed by trephining.

Medial canthus entropion combined with relative oversize of the lid fissure and caruncle trichiasis, as in breeds such as the Pekingese or Shih Tzu, should be corrected by medial canthoplasty (see "Trichiasis"). Alternative methods such as the Bigelbach and Stades Diabolo procedures also can be used in the medial canthus, but are more complicated, less predictable, and do not remove the caruncle trichiasis.

Surgery for Entropion and Macro- and Microblepharon

In many large and giant-breed patients with lateral lower lid entropion, the palpebral fissure is oversized. In these dogs, the stretched fissure length often varies from 40 to 50 mm. If the lid fissure is shortened in these patients, the lateral entropion usually disappears without specific correction. For additional details, see "Ectropion and Oversized Palpebral Fissure (Macro- or Euryblepharon"). In miniature breeds with microblepharon, this abnormality is usually accompanied by upper lid entropion. When the lid fissure is lengthened in these patients, the entropion disappears without specific correction. For additional details, see "Microblepharon, Blepharophimosis, or Blepharostenosis."



Figure 15.27 The Y to V plasty (Wharton–Jones) for entropion may be used for mild entropion of the central to lateral portion of the lower lid. **A**. The initial incision of the lid skin and orbicularis oculi muscle layers starts about 1–2 mm from the eyelid margin. The lower part of the incision will determine the extent of the lid eversion. **B**. A triangular section of skin and orbicularis oculi muscle, based at the eyelid margin, is dissected from the underlying tarsus by tenotomy scissors. **C**. The tip of the skin–muscle flap is apposed in a V shape to effect eversion of the eyelid margin with simple interrupted, 5-0 to 6-0 sutures. Disadvantage: unpredictable results. Copyright Frans C. Stades.

Surgery for Lateral Canthal Entropion

The Celsus–Hotz procedure may be adapted for entropion of the lateral one-third of the upper and lower eyelids and the lateral canthus (Fig. 15.28). This modification is recommended when the palpebral fissure size is normal and an additional

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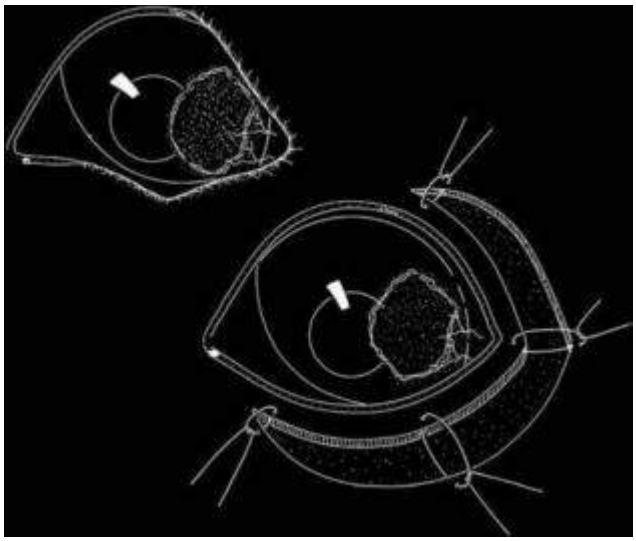


Figure 15.28 Arrowhead Celsus–Hotz surgical correction of lateral angular entropion with a secondary corneal ulcer and the order of suturing (1–4). The correction does not change the size of the palpebral fissure. Advantage: predictable. Disadvantage: no lateral traction to the lateral canthus. Copyright Frans C. Stades.

enlargement of the palpebral fissure is not necessary. It has been proposed that transection of lateral palpebral ligament band or transconjunctival lateral canthal tenonectomy will reveal the true dimension of the palpebral fissure, and that a combination of this technique with the more conventional blepharoplasties offers a much better approach to correction of lateral canthus entropion (Robertson & Roberts, 1995a, 1995b).

In the lateral canthoplasty procedure by Wyman (Fig. 15.29A–D), the lateral canthoplasty and construction of a lateral canthal ligament can be useful for large and giant breeds with minor central ectropion and lateral entropion of the lower and upper lids and the lateral canthus (Wyman, 1971). In this method, two strips of lateral canthal orbicular muscle are sutured to the zygomatic arch periosteum to retract the lateral canthus outward.

The latter method can be modified, using one, or preferably two, nonabsorbable traction sutures attaching the lateral canthus to the periosteum of the zygomatic arch (Fig. 15.29E), thus stabilizing the lateral canthus (Peiffer et al., 1978a, 1978b). This reduces the time for surgery, and with less tissue dissection the postoperative wound swelling is reduced. An alternative method is to use a section of frozen scleral homograft.

The lateral canthal tendonectomy procedure (Robertson's procedure) is to treat lateral canthal entropion that releases the tension in large and giant breeds of dogs by transection of the lateral canthal tendon (Robertson & Roberts, 1995b). The lateral canthus is everted by forceps to expose the palpebral conjunctiva. With curved Stevens or tenotomy scissors, the palpebral conjunctiva is separated from the deeper tarsus in a 9 mm arc. The fibrous band is located by blunt dissection that extends from the lateral canthus to the orbital ligaments and zygomatic arch, and a wedge of the tendon excised near its base. An alternative technique is to sever the tendon (tendonotomy) by scissors midway between its original and the insertion. The conjunctival wound is not apposed by sutures. Other entropion techniques may be combined with this method.

In macroblepharon combined with lateral entropion, a lateral canthoplasty may be indicated (Grussendorf, 2004; see later Fig. 15.51; Gutbrod & Tietz, 1993; see later Fig. 15.31). In these procedures, the newly created lateral canthus is more or less anchored to the lateral ligament.

Surgery for Entropion Combined with Shortening of the Lower Lid

In the partial Celsus–Hotz full-thickness lateral wedge resection procedure of Read and Broun (Fig. 15.30), the entropion is corrected by a combination of a Celsus–Hotz procedure and a lateral lid margin shortening of 20%–30% using a wedge resection, directly adjacent to the lateral canthus. The crescent of skin and the underlying orbicularis muscle of the partial Celsus–Hotz procedure and the full-thickness wedge are removed. The partial Celsus–Hotz wound is closed using simple interrupted, rapidly absorbable sutures. The wedge is closed double-layered, with a figure-of-eight suture at the margin. The success rate was 94% and especially effective in breeds with macroblepharon. Mild entropion recurrence was present in 6% of dogs. Recurrences were most common in breeds with short to average-sized stretched palpebral fissure length. The advantage of a more time-consuming and less easy to estimate method including lid shortening was not clarified (Read & Broun, 2007).

In the lateral canthoplasty Gutbrod and Tietz (1993) procedure (Fig. 15.31), the lower lid is shortened over 2–6 mm, and a full-thickness triangular area, including the lateral canthus, is removed, inducing lateral traction on the lateral canthus. The canthus is closed using 4-0 absorbable material. The conjunctiva, the orbicularis oculi muscle plus subcutaneous layers, and the skin wound are separately apposed by simple interrupted sutures of the same material. The method appeared to have good results, mainly in the correction of entropion in a variety of breeds. The procedure has also been used for the correction of ectropion-macroblepharon.

Postoperative Management

Aftercare for entropion correction consists of applying topical initial choice antibiotic ointment (more lubricating than drops) at least 4 times daily for 14 days. Systemic antibiotics may be indicated in lateral canthoplasty techniques when surgical time and trauma are more excessive. If corneal ulceration is present, appropriate mediations are instilled. Even when sutured with great care, a protective E-collar is recommended to prevent self-trauma and possible wound dehiscence. The sutures are removed between 10 (especially silk) and 14 (monofilament, nonabsorbable) days after surgery.

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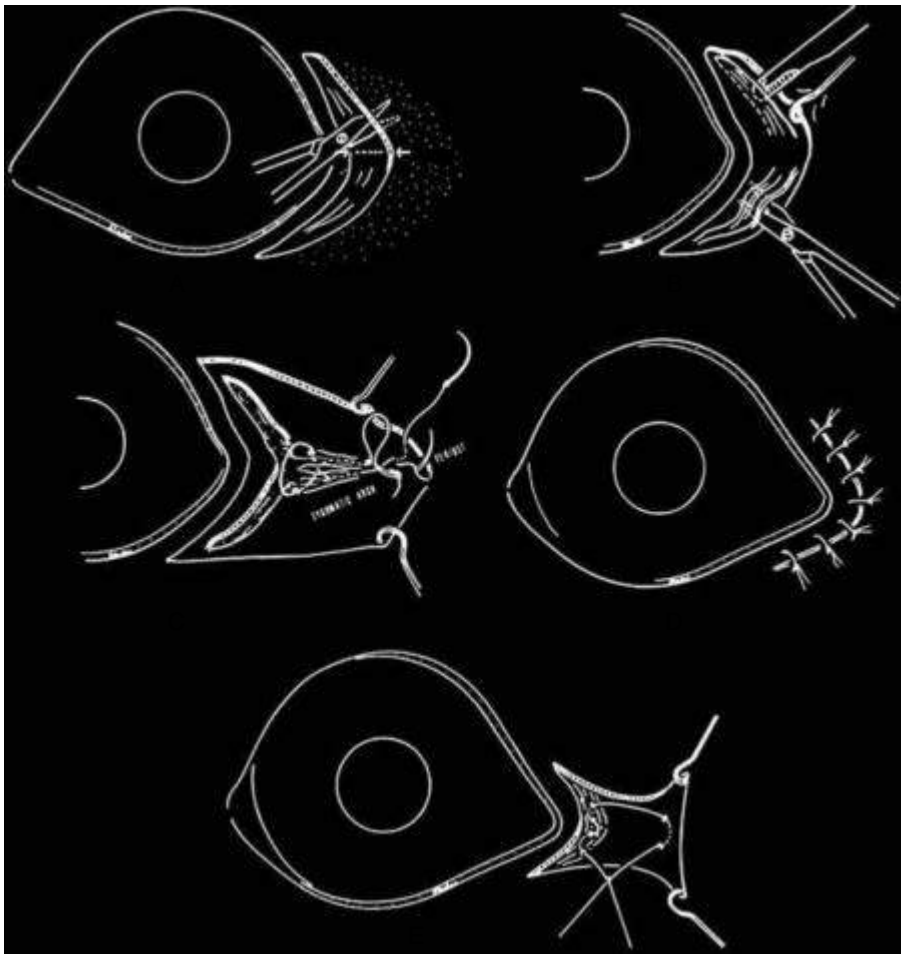


Figure 15.29 The lateral canthoplasty and construction of a lateral canthal ligament by Wyman can be useful for large and giant breeds with central ectropion and lateral entropion of the upper and lower lid and the lateral canthus. **A**. An arrowhead of skin is removed at the lateral canthus over 3–5 mm. The width of the surgical wound should approximate the amount to effect correction of the entropion. **B**. Two myotomies are performed with their bases at the lateral canthus. These strips of muscle will form the new lateral canthal ligament. **C**. After subcutaneous dissection by tenotomy scissors, the pedicle of orbicularis oculi is secured by a cruciate suture to the periosteum of the zygomatic arch by a simple interrupted, 5-0 nonabsorbable suture. **D**. The skin layers are apposed by simple interrupted, 5-0 to 6-0 sutures. **E**. As an alternative to the pedicle of orbicularis oculi muscles in the lateral canthoplasty procedure, one or preferably two sutures or a section of frozen scleral homograft can be used to attach the lateral canthus to the periosteum of the zygomatic arch and stabilize the lateral canthus. Advantages: both methods provide sufficient traction on the lateral canthus; the Wyman procedure is more complicated but stronger because of the tissue bridge. Anticipate postoperative lid swelling. Copyright Frans C. Stades.

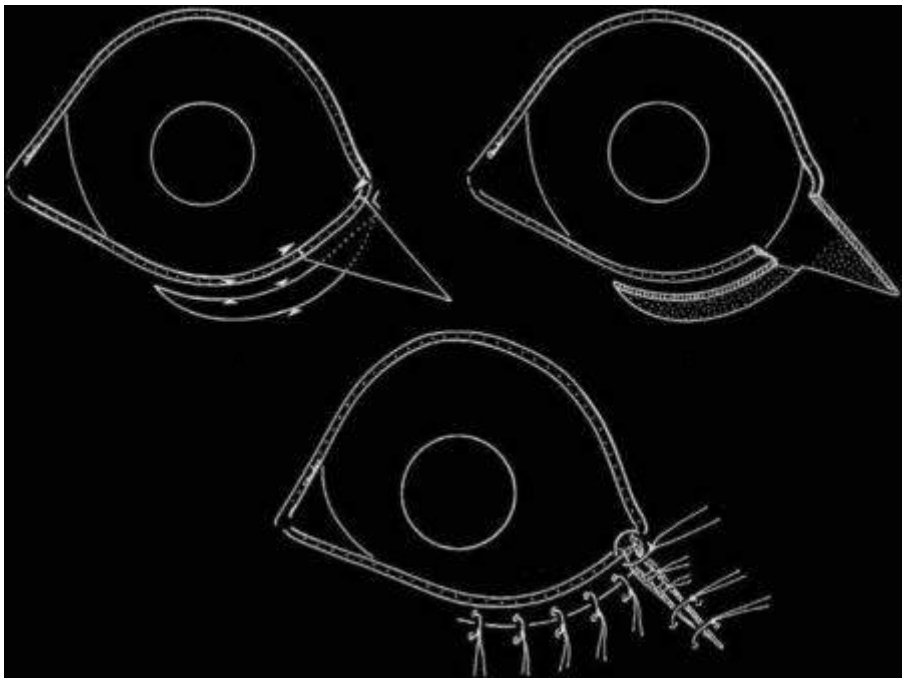
Absorbable materials will not absorb very quickly in the skin, and the dissolution process causes more reaction and irritation, but removal is avoided, which is especially useful in uncooperative and/or anesthesia-risk patients.

Complications

The primary goal of these procedures is a functional, nonirritating eyelid, and a secondary goal is cosmetic acceptability. Complications with all of these procedures are often associated with overcorrection or undercorrection and undesired scar formation, leading to extensive and complicated repair surgery. Recurrent wound dehiscence in entropion correction has been described due to sebaceous adenitis (Carmack et al., 2010). Directly after lower lid entropion correction, there will be wound swelling, mainly of the more elastic conjunctiva, enabling the upper lid cilia to irritate the lower lid margin and/or conjunctiva during blinking. This temporary trichiasis phenomenon can be prevented by tacking the lateral upper lid (Stades et al., 2007, p. 82) until the lower lid conjunctival swelling has resolved (see Fig. 15.22, E5).

Large and giant breeds of dogs with entropion and enophthalmos present additional challenges because the globe–lower eyelid contact is often absent and entropion repair is less predictable. Breeds with excessive forehead skin folds also complicate entropion surgery that may require concurrent excision of large amounts of the forehead skin, which is

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Figure 15.30 The Celsus–Hotz full-thickness lateral wedge resection by Read and Broun can be useful in entropion combined with an oversized lower lid, shortening the lower lateral lid margin over 20%–30%. **A**. The lateral lower lid is grasped and retracted laterally to establish how much the lid can be shortened. The partial Celsus–Hotz procedure and the lateral wedge resection incisions are made. **B**. The lateral incision of the wedge is 10–20 mm long and placed directly adjacent to the lateral canthus and perpendicular to the lid margin. The medial incision is run obliquely to meet the end of the lateral incision, resulting in a rectangular triangle. Using scissors, the crescent of skin (at the widest point 3–7 mm wide) and the underlying orbicularis muscle of the partial Celsus–Hotz procedure are removed from the tarsus. **C**. Finally, the full-thickness wedge is removed. The partial Celsus–Hotz wound is closed using simple interrupted, rapidly absorbable sutures. The wedge is closed double-layered, with a figure-of-eight suture at the margin. Advantage: lid shortening in oversized lid fissures. Disadvantage: entropion recurrences in breeds with short to average-sized stretched palpebral fissure length, more time-consuming, and possible leakage of the full-thickness wedge wound. Copyright Frans C. Stades.

in the direct interest of the dog, but will affect the dog's appearance (see "Upper Eyelid Trichiasis" and "Redundant Skin Folds around the Eye").

Prognosis and Prevention

The prognosis for entropion correction is good when the surgical procedure is performed correctly. In cases of deep corneal damage, corneal scarring may remain. Parents and siblings should also be examined. Affected animals should not be used for breeding. Breeding schemes should aim for dogs with lids with fissures of normal length. It would be advantageous to have the breed, name, tattoo or microchip, and pedigree number of affected animals registered centrally, and to persuade owners to report such information to the breed association.

Other Methods

Excision using CO_2 laser including a superficial part of the orbicularis oculi muscle without bleeding and without suturing has been described. The wounds were left to heal by secondary intention (Serrano & Rodríguez, 2014). Electrocautery of the skin and superficial aspects of the orbicularis oculi muscle have been used to stimulate the formation of scar tissue and thus correction of the entropion. The predictability of the ectropionizing effect is low.

Several nonsurgical methods to treat entropion in small animals have been used. Subcutaneous injections of antibiotics, paraffin, mineral oil, hyaluronic acid (McDonald & Knollinger, 2019), and silicones have been used to provide temporary or permanent eyelid margin eversion and relief from the trichiasis and blepharospasm. The larger the volume of the injection, the greater the extent of the eversion of the eyelid margin. These methods have been generally replaced by the different lid surgeries because of the low predictability of the correction, and, more important, the injected agents such as silicones may cause severe necrosis, granuloma formation, and scarring. Hyaluronic acid is well tolerated and can be of use in elderly animals or poor anesthetic candidates, but long-term tolerance has not been documented.

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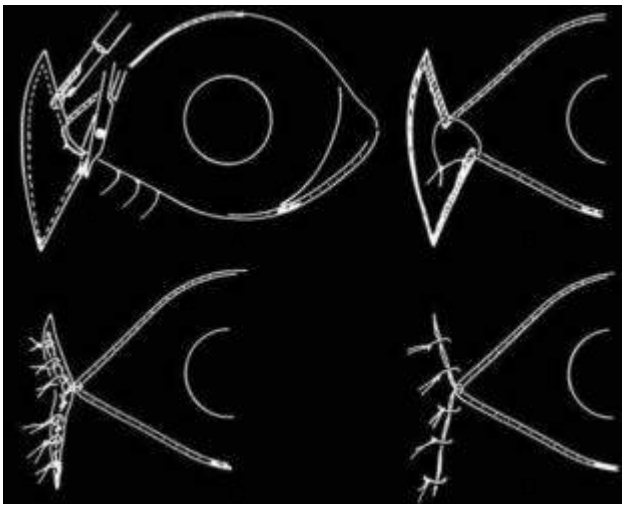


Figure 15.31 Lateral canthoplasty, Gutbrod and Tietz procedure. In this procedure, the lower lid is shortened over 2–6 mm and removed full-thickness, including the lateral canthus over an area, with the appearance of an orange piece (**A**). The lateral canthus (d) is apposed to the lower lid margin (a) and closed, using 4-0 absorbable material (**B**). The conjunctiva, the orbicularis muscle plus subcutis layers, and the skin wound are separately apposed by simple interrupted sutures of the same material (**C**, **D**). The method appeared to have good results in the correction of mainly entropion in a variety of breeds (see text). The type of entropion was not specified. The procedure has also been used for the correction of ectropion-macroblepharon. Disadvantage: unpredictable results. Copyright Frans C. Stades.

Ectropion and Oversized Palpebral Fissure (Macro- or Euryblepharon)

Ectropion is an eversion of the lid margin, usually of the lower eyelid (Fig. 15.32A and later Fig. 15.35A), but cicatricial eversion of the upper lid may occur. It is readily recognized because the orifices of the Meibomian glands are visible in the everted margin. In the dog, it is usually accompanied by an oversized palpebral fissure, and the lower lid is not adjacent to the globe. It is not always easy to differentiate between the two entities. In an oversized fissure, the lid margin is distinctly longer (stretched 5–15 mm) than the normal 33–35 mm necessary to cover the sclera in the opened eye.

When the lower eyelid is not appropriately apposed to the globe over a distance of 1–10 mm or more, a funnel or sac is formed in the lower eyelid. The lids, blink reflex, and tears cannot perform their normal function of cleaning, shielding, and lubricating the eye. The conjunctival sac becomes chronically inflamed as a result of its permanent exposure to air, dust, bacteria, and stagnant tears. In more severe cases (e.g., Bloodhound, St. Bernard, Leonberger, Corso dog, Clumber Spaniel, or Pug; Krecny et al., 2015), when the middle portion of the lid is everted, there is often some inversion near both canthi (Fig. 15.32B and later Fig. 15.44A), or laterally there is distinct entropion, which may result in a chronic purulent conjunctivitis and corneal irritation.

Most forms of ectropion and oversized palpebral fissure are primary or congenital and breed related or presumed hereditary. The genetic transmission is most likely polygenic. The breeds of dogs frequently affected with lower lid ectropion/macroblepharon include the Bloodhound, St. Bernard, Great Dane, Newfoundland, Mastiff, and several spaniel and French hunting breeds. Some owners, dog fanciers, and breeders believe ectropion and oversized palpebral fissure to be normal, and some even encourage the "diamond"-appearing palpebral fissures and the everted lower eyelids (which give the dog a "devoted and sad expression"). Moreover, some breed standards tolerate or even promote these conditions. Breed prescriptions vary from "showing little, if any, haw," to "Acceptable to have some haw showing but without excess," "the haw may sometimes show without excess," "appear slightly sunken beneath thick eyelid, the lower lid shows a certain looseness," "lower lids a little slack so that a little haw is visible are nevertheless tolerated," and "a small angular fold on the lower lids with the haws only slightly visible as well as a small fold on the upper lids are permitted." The country of origin prescribes the text of the breed standards. The UK has made a start, adding "Free from obvious eye problems" for all descriptions, and "Never protruding, exaggerated or showing white when looking straight ahead."

The additions of "normally fitting around the eye-ball" and "at no time should the eye-lashes touch or interfere with the eyes" are not yet optimal, but hopeful. It is important to influence Kennel Clubs to revise the breed descriptions and recommend adding a general line, such as "exaggerated facial conformation is undesired." Strangely enough, many Kennel Clubs do not accept breeding from entropion- or ectropion-affected dogs in their breed standards.

Excessive facial skin folds, heavy ears, long eyelids (especially the lower lid), and unstable lateral canthus result in a sagging lower lid and an inverted upper and lower lateral canthus. Weakness of the lateral retractor muscle may lead to further instability of the lateral canthus. A poorly developed lateral canthal ligament or excessive tension from this structure and variable enophthalmos are other complicating disorders.

The acquired or secondary forms of ectropion are fortunately rare. They may be associated with cicatrix formation, trauma, neurologic, and postoperative causes, such as overcorrection of an entropion. Ectropion and oversized palpebral fissure are rare in other species.

Clinical Signs

Signs of ectropion or oversized palpebral fissure are as follows: the lower lid margin is rotated outward (the openings of the Meibomian glands are visible in the free margin); the fissure is often diamond or pagoda shaped; and the conjunctiva is red, swollen, and folded, resulting in increased tear and mucus production and purulent exudate. There is a

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slight enophthalmos, which increases the distance between the lid margin and the globe. When the animal is more active than usual, as at dog shows or on the veterinarian's examination table, and whenever it is held tightly by the nape of the neck, the ectropion or oversized palpebral fissure may almost disappear, but then too much sclera will be visible on the lateral side. Diseases associated with microphthalmos, phthisis, or enophthalmos (Horner's syndrome, uveitis) must be considered in the differential diagnosis.

Therapy

If the defect is slight, no treatment is required apart from irrigating the eyes upon returning from walks and applying a neutral, lubricating ophthalmic ointment or solution, particularly in young dogs whose heads have not yet reached adult size. Surgical correction of ectropion is recommended when chronic or severe secondary ophthalmic disease results. In more severe lesions, corrective measures may be taken, but usually not before age 2–2.5 years, when the skull is full sized and orbital fat is present. Surgery should attempt to provide a relatively normal lower eyelid length and an adequate apposition to the cornea. Overcorrection should be avoided, because entropion may result and can cause potentially more damage to the cornea and conjunctiva than the ectropion might cause. Also, excessive scar formation should be avoided because it may result in focal contractions and be unsightly to the owner.

The methods vary from influencing the lower lid position to shortening the lid fissure, restoring it to the actual size of the globe and repositioning lateral canthus laterally. Because in most dogs there is a combination of ectropion and an oversized lid fissure, the different ectropion surgical procedures primarily shorten and strengthen the lid. Because the medial canthus is relatively fixed and more complicated by the presence of the lacrimal ducts and the nictitating membrane, most surgical procedures for ectropion and macroblepharon involve the lateral lower eyelid and canthus. Moreover, the lid excision is better performed at the lateral canthus to avoid the possible development of an irritating notch in the middle of the visual axis, or an unsightly postoperative eyelid margin defect or notch. In general, it is the authors' preference to use the Blaskovics or similar procedures for moderate to severe ectropion of the lower lid only, and the simple lid fissure reduction permanent tarsorrhaphy procedures for distinct, oversized palpebral fissures.

Evolution of Ectropion Surgery

Like the surgical correction of entropion in humans and animals, reports of different surgical procedures for the treatment of the various types of ectropion have spanned nearly 150 years. Often, these surgical procedures were refined by other surgeons, whose names were added to the basic surgical procedure. In veterinary ophthalmology, several of these procedures have been adapted for use in animals. Of all of these techniques, the Kuhnt–Szymanowski (K-S) procedure forms the basis for the surgical procedure for ectropion in humans (Bedford, 1999a, 1999b; Fox, 1976; Stades et al., 1998).

In 1883, Kuhnt reported the lid-splitting technique revived from Antyllus' (Greek surgeon, ca. 150 AD) lid-splitting surgery and added a tarsoconjunctival triangular resection (or wedge). He revised this procedure a few years later to include an additional resection of the outer skin and muscle of the eyelids (Fox, 1976). Szymanowski, in 1870, reported his initial technique, which was improved further by Kuhnt. It is now utilized as the K-S procedure (Kuhnt & Szymanowski, 1976). Blaskovics, in 1938 and later, reported modifications of the K-S procedure, avoiding splitting of the lid margin, for both medial and lateral ectropion (Blaskovics, 1959, 1976). Fox and Smith modified the K-S–Blaskovics procedure further by placing the skin incision closer to the lid margin and preserved the lid margin with a full-thickness eyelid resection laterally (Fox, 1976; Stades et al., 1998). This procedure was reported by Munger and Carter (1984) in the dog.

Influencing the Lower Lid Position in Primary Ectropion, Not Shortening the Fissure

Shortening the lower palpebral conjunctiva is one method to treat pure ectropion but not lid length. Where there is normal fissure length, only slight correction could be achieved by removing an elliptical part of the conjunctiva and suturing together (basting) the ventral palpebral conjunctiva with a continuous, subconjunctival absorbable suture. In the dog, the procedure is rarely used and easily leads to unwanted conjunctival traction bands.

The V to Y or Wharton–Jones procedure (Fig. 15.33) offers another approach. This method induces scar tissue below the margin of the eyelid, which supports and pushes up the lower margin. It may be indicated to treat mild (e.g., cicatricial) ectropion (Bedford, 1999a, 1999b). The method, however, is only reliable when ectropion is not combined with an overlong palpebral fissure, and therefore it is useful solely in exceptional cases. It has been shown to be advantageous in cases of scarring dermatopathies resulting in extensive cicatricial upper and lower lid–lateral canthus ectropion (Donaldson et al., 2005).

Homologous and Prosthetic Lateral Canthal Ligament Construction

In these procedures, the lateral canthus is adjusted laterally, stretching the palpebral fissure, and resulting in lifting the lower lid. It does not influence the length of the fissure, which limits the indications. The lateral canthoplasty and construction of a lateral canthal ligament by Wyman (Fig. 15.29) can be useful for large and giant breeds with minor central ectropion and lateral entropion of the lower and upper lids and the lateral canthus. In this method, two strips of canthal orbicular muscle are sutured

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Figure 15.32 **A**. Pronounced lower lid macroblepharon-ectropion in a Clumber Spaniel. The stretched fissure length was 51 mm. There is additional upper eyelid trichiasis. The lower lid ectropion results in chronic exposure and secondary conjunctivitis. **B**. Pronounced macroblepharon-ectropion (diamond-shaped fissure) in a Bloodhound. The stretched fissure length was 48 mm. There is also some medial and lateral entropion and a notch or kink in the lower lid margin. Note that the lower lid hangs in the middle about 15 mm away from the third eyelid–cornea and is not really everted in an ectropion position. This all results in chronic exposure and secondary conjunctivitis. Courtesy of Frans C. Stades.

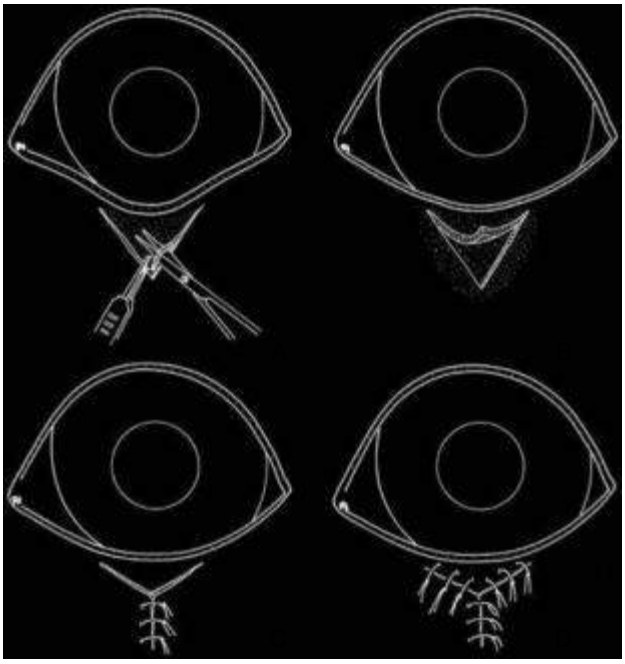


Figure 15.33 The V to Y plasty may be used to treat mild (e.g., cicatricial) ectropion. **A**. Converging skin incisions are made by the scalpel blade starting 1–2 mm from the eyelid margin. **B**. The V-shaped skin flap is separated from the underlying tissues, and present scar tissue is excised. **C**, **D**. The skin flap is apposed by simple interrupted, 5-0 to 6-0 sutures as a Y-shaped closure, lifting the lid margin upward. Disadvantage: unpredictable results. Copyright Frans C. Stades.

to the zygomatic arch periosteum to retract the lateral canthus outward (Wyman, 1971, 1979).

In the prosthetic lateral canthal ligament construction, an access incision is made 10–20 mm lateral to the lateral canthus. A 4-0 nonresorbable suture is placed through the incision, penetrating the dermis (not epidermal) at the canthus, and returns to the incision subcutaneously. There it is tied inverted, adjusting the position of the canthus by tension on the suture (Peiffer et al., 1978a, 1978b). This method may be combined with lid fissure shortening, as is done in the Grussendorf procedure (Grussendorf, 2004).

Pedicle Grafts, Z-Plasties, and Free Transplants for Severe (Cicatricial) Pure Ectropion

Cicatricial pure ectropion is fortunately rare. It is usually caused by the overcorrection of entropion. When the entropion correction is made too far away from the lid margin, the wound is made too deep, or suture material is too heavy, irregular scar formation can retract the lower lid downward and away from the globe as far as 10–15 mm. After the lower lid margin has been freed and the undesired scar tissue removed, the missing tissue to bring the lid margin back to its normal position can be estimated. Similar tissue from elsewhere has to be found to fill the defect (e.g., by a pedicle graft or Z-plasty; Fig. 15.34). Preferably, upper lid skin is used. If upper lid skin is unavailable, other adjacent skin or skin from elsewhere (free transplant), with the same hair growth and flexibility, must be found (Fig. 15.35). A temporary tarsorrhaphy is made to prevent distortion of the lid margin caused by postoperative conjunctival swelling and scarring.

Ectropion-Macroblepharon Correction Procedures to Shorten the Lower Lid Margin

In most instances of ectropion, the lower eyelid margin or both the upper and lower eyelid margins are oversized. Methods aimed at reduction either around the defect in the margin or at the lateral canthus yield the best results. These methods require critical judgment on the part of the surgeon. Scars from previous faulty operations may

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complicate future surgeries. Before surgery, the lid fissure is stretched and measured by calipers. The fissure should be shortened to approximately 33–35 mm (Stades et al., 1992).

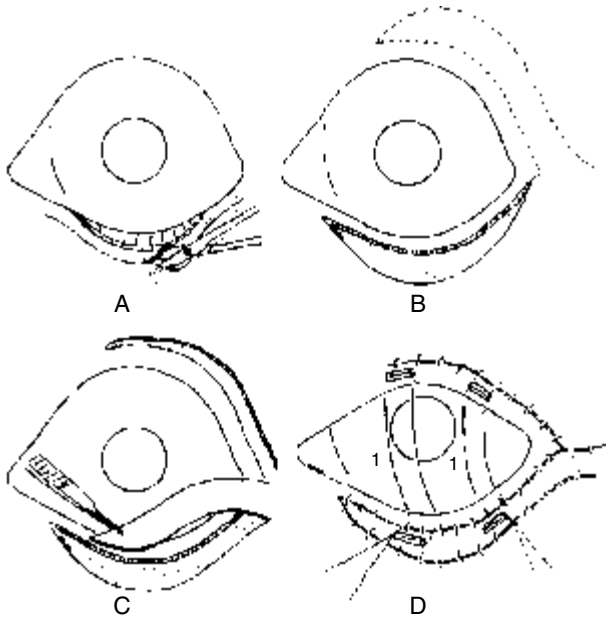


Figure 15.34 Pedicle graft from the upper to lower lid may be used to correct, for example, severe cicatricial ectropion (Z-plasty principle). **A**. The skin is incised 2.5 mm from the lid margin. The wound is bluntly dissected by tenotomy scissors, and the scar tissue is removed. **B**. The remaining defect can be filled by either a large skin pedicle from the upper lid or a free transplant of thin skin grafted from elsewhere in the body, preferably with the same type of hair and placed in the same direction (see also Fig. 15.35). **C**. The pedicle is transposed to the lower wound. **D**. The wounds are closed by simple interrupted, 6-0 monofilament sutures. A temporary tarsorrhaphy (1) is placed for 10–14 days. Copyright Frans C. Stades.

Lateral Eyelid Wedge Excision

A full-thickness triangular lower lid section, immediately next to the lateral canthus, is excised (Fig. 15.36). The surgical defect is apposed by one or two layers of sutures. The method is the most simple, but it does not have the benefit of the double-layered staggered wound preventing leakage, and it has a greater chance of eventual wound dehiscence and atrophy of the eyelid margin.

General Considerations for Double-Layered, Staggered Wound Creation in Shortening the Lid Margin (Nonsplitting vs. Lid Margin Splitting)

When the lower lid overlength is not excessive, procedures for shortening only the lower lid may be sufficient. These procedures effectively shorten the lower eyelid, give some support of the lateral lower lid by the scar tissue between the double layers, and cause moderate traction laterally (Fig. 15.37, Fig. 15.38, Fig. 15.39, Fig. 15.40, and Fig. 15.41).

In the Kuhnt–Szymanowski–Helmbold procedure, the lid margin (and deeper parts) are split. The lid margin is incised in the line of the Meibomian gland openings or "gray line" over the desired length plus 1–2 mm. The skin plus muscle is separated from the tarsoconjunctival tissues by blunt dissection to a depth of 10–15 mm. The Meibomian glands are damaged over the operated distance. Although there is no direct proof of problems caused by the missing glands, it is preferable to leave the lid margin intact as much as possible. Moreover, the suturing and healing of the two layers of free lid margin easily lead to notches and other deformities in the "new" lid margin. Neither procedure addresses overlength of the upper eyelid (Bedford, 1999a, 1999b; Kuhnt & Szymanowski, 1976; Patel & Anderson, 1996).

In the K-S modified by Blaskovics lateral canthoplasty and ectropion procedure (Fig. 15.40), reported in 1938, the lower lid is shortened, and splitting of the lid margin is avoided.



Figure 15.35 **A**. Severe cicatricial lower lid ectropion caused by massive overcorrection of an entropion in a young Dutch hunting dog. The lower lid margin is retracted by scar tissue to the zygomatic arch. **B**. The postoperative result in the same dog. The skin was incised 2.5 mm from the lid margin and all scar tissue removed, resulting in an approximately 10 mm broad defect. This remaining defect was filled using a free transplant of thin skin from the abdomen of the same dog (note that there is less hair on the transplanted skin). Courtesy of Frans C. Stades.

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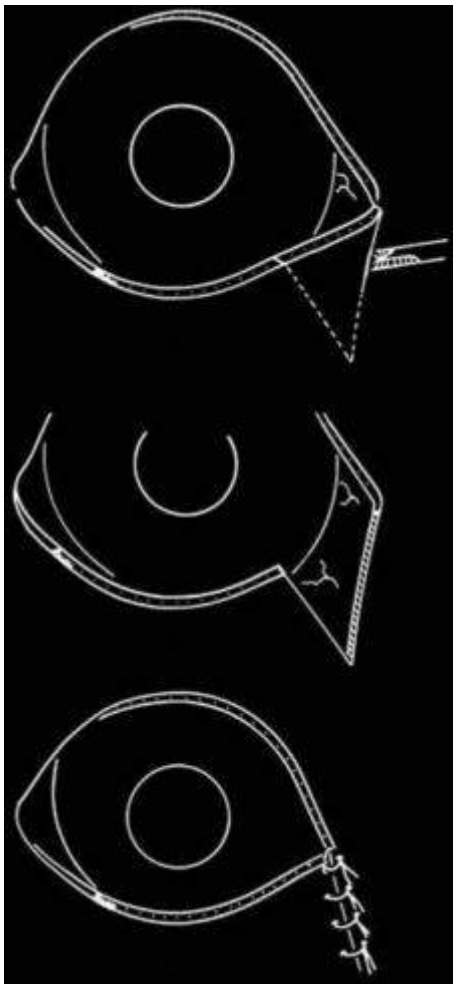


Figure 15.36 The lateral wedge excision procedure for shortening the lower eyelid in ectropion-macroblepharon. Before surgery, the lid fissure is stretched and measured by calipers. The fissure should be shortened to approximately 33–35 mm in medium and large breeds of dogs. **A**, **B**. A full-thickness triangular section of lower lid is excised by scalpel and scissors. The surgical defect is apposed by one or two layers of sutures. **C**. The tarsoconjunctival layers can be apposed with a simple continuous, 8-0 absorbable suture. The skin–muscle layers are apposed with 5-0 to 6-0, figure-of-eight suture at the margin and further with simple interrupted sutures. Advantage: simple. Disadvantage: no staggering closure preventing leakage and wound dehiscence. Copyright Frans C. Stades.

The lid margin and tarsal "plate" stay intact. The double-layered, staggered wound, preventing leakage and wound dehiscence, starts below the lid margin (Blaskovics, 1959, 1976). Smith modified further the Blaskovics procedure by placing the upper skin incision closer to the lid margin (Fox, 1976). This procedure was described in the veterinary literature by Munger and Carter (1984).

Removal of a Deformed Notch and Shortening of the Lid Margin

In breeds such as the St. Bernard, the ectropion notch, approximately in the middle of the oversized upper and

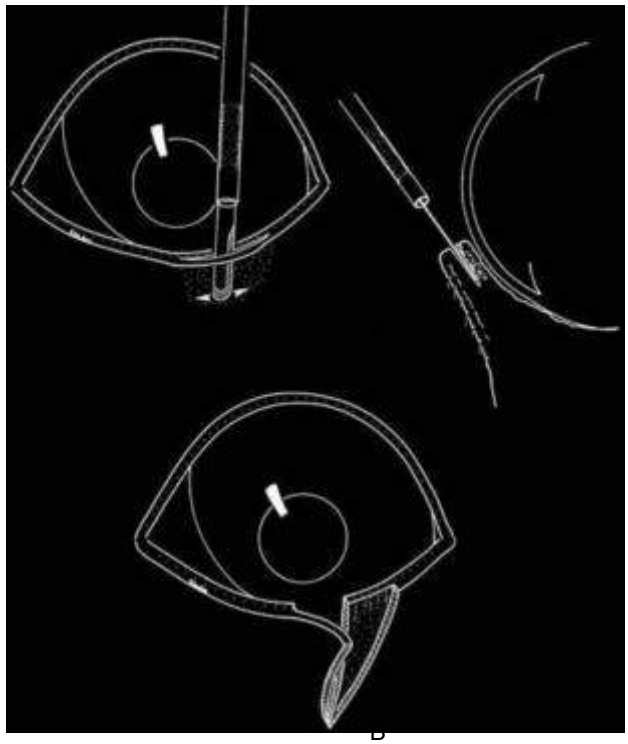


Figure 15.37 Principle of shortening of the lower lid margin using lid splitting according to Kuhnt–Szymanowski. **A**. The lid margin is incised in the line of the Meibomian gland openings or "gray line" over the desired length plus 1–2 mm. **B**. The skin plus muscle is split from the tarsoconjunctival tissues by blunt dissection to a depth of 10–15 mm. A desired part of the tarsoconjunctiva is removed. The oversized skin–muscle outside the lid rim is shortened over the same distance. Advantage: the resulting wound is in two different levels (staggering wound), preventing leakage and wound dehiscence. Disadvantage: the lid margin, including the Meibomian glands, is damaged over the operated distance. Copyright Frans C. Stades.

lower lid, is usually so deformed that even after shortening, or shortening and lateral traction, these notches will not totally disappear. In these cases, the removal of that area itself and shortening of the lid margin may be advantageous (Fig. 15.39). The disadvantages are that the procedure has to be done in both upper and lower lids, it is time-consuming, and there is no further traction laterally toward the lateral canthus.

Kuhnt–Szymanowski Blaskovic's Modification (Further Modified by Fox and Smith): Procedure for Oversized Lower Lid Margin and Ectropion

This procedure was first described in dogs by Munger and Carter (1984). The skin incision is made 2–2.5 mm from and parallel to the margin of the lid, starting a few millimeters medial of the worst area of ectropion and ending 5–10 mm lateral to the lateral canthus and from there downward (Fig. 14.40). The entire skin–orbicular oculi flap is loosened. A wedge-shaped part of the tarsoconjunctiva is excised in

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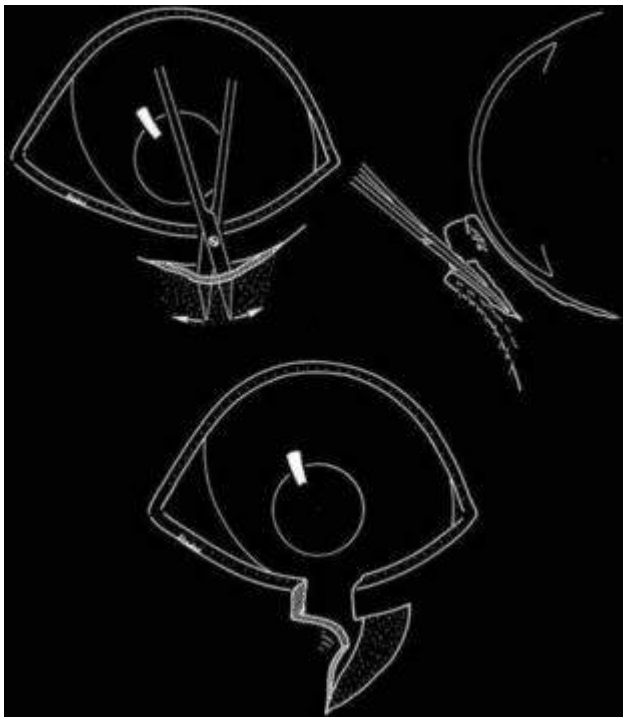


Figure 15.38 Principle of shortening of the lower lid margin according to Kuhnt–Szymanowski, modified by Blaskovics to avoid splitting the lid margin. **A**. The skin is incised 2.5 mm (as near as possible to the margin for better prediction of the area of ectropion or deformity to be corrected, but leaving enough space for lid margin suturing) from and parallel to the lid margin. The skin is divided from the muscle–conjunctiva by blunt dissection to a depth of 10–12 mm. A desired part of the lid edge plus a wedge of muscle–conjunctiva is removed. The oversized skin flap is shortened over the same distance. **B**. Advantage: the resulting wounds are in two different levels (staggering wound), preventing leakage and wound dehiscence. Copyright Frans C. Stades.

the worst area of ectropion. A similarly sized wedge of skin–orbicular oculi is excised laterally, thus shortening the flap. This method shortens the eyelid margin to the desired length and draws it upward and laterally. The double-layered, staggered wound prevents leakage and wound dehiscence.

Kuhnt–Szymanowski and Helmbold Procedures for Oversized Lower Lid Margin and Ectropion

These procedures predate the newer and improved procedures in use. The K-S procedure differs from Blaskovic's method in that the incision is not below the margin of the eyelid but in the margin itself (lid splitting), in the line of the orifices of the Meibomian glands or gray line (Fox, 1976). The Meibomian glands are damaged and/or destroyed in the whole lid margin wound, and the procedure is more time-consuming than the Blaskovics method.

The Kuhnt–Szymanowski–Helmbold procedure (Fig. 15.41) shortens the lower lid by removing two wedge sections from the outer and inner layers at different areas of the lid, thereby

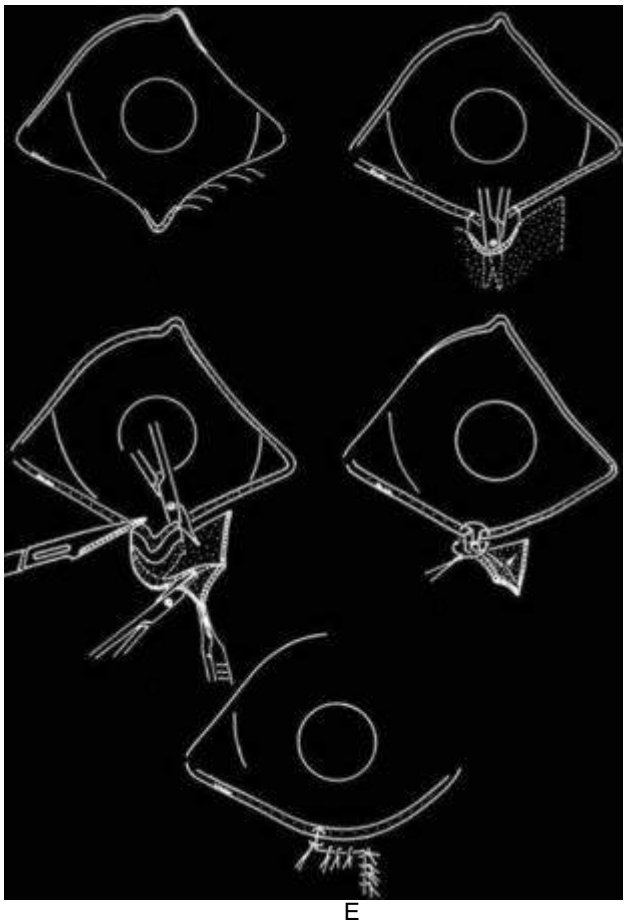


Figure 15.39 **A**. Removal of a deformed notch and thereby shortening the lower lid in, for example, a St. Bernard can be done by a Blaskovics plasty. **B**. The skin is incised 2.5 mm from and parallel to the lid margin. The skin is separated from the muscle–conjunctiva by blunt dissection to a depth of 10–12 mm. The deformed part of the lid margin plus a wedge of muscle–conjunctiva is removed. **C**. The oversized skin flap is shortened over the same distance. **D**. The lid margin wound is apposed by a figure-of-eight, 6-0 monofilament nylon suture. **E**. The skin flap is sutured by simple interrupted sutures. Advantages: staggering wound and removal of the deformed notch. Disadvantage: more time-consuming. Copyright Frans C. Stades.

avoiding a full-thickness lid wound (Bedford, 1999a, 1999b; Fox, 1976). Like the K-S method, the eyelid margin incision for the Kuhnt–Helmbold procedure is along the Meibomian gland ducts and causes damage to these vital structures.

Macroblepharon-Ectropion Correction, Reducing Lower and Upper Lid Length

Because the medial canthus is relatively fixed and more complicated by the presence of the lacrimal ducts and the nictitating membrane, surgical procedures just to change the size of the palpebral fissure usually involve the lateral canthus. Surgical reduction of the medial canthus is usually restricted to the smaller breeds, such as Pekingese and

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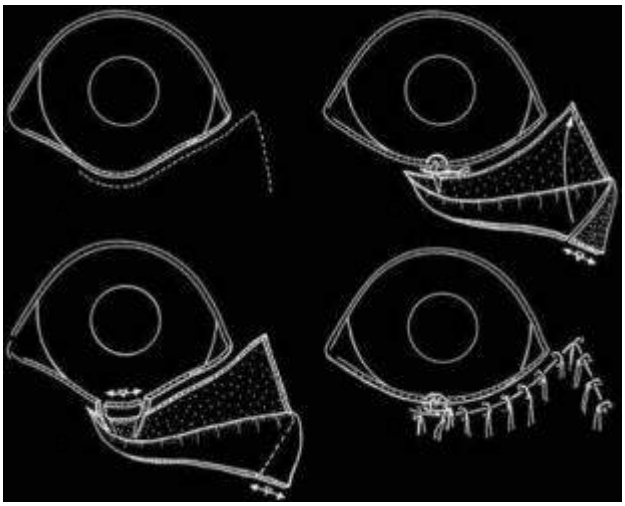
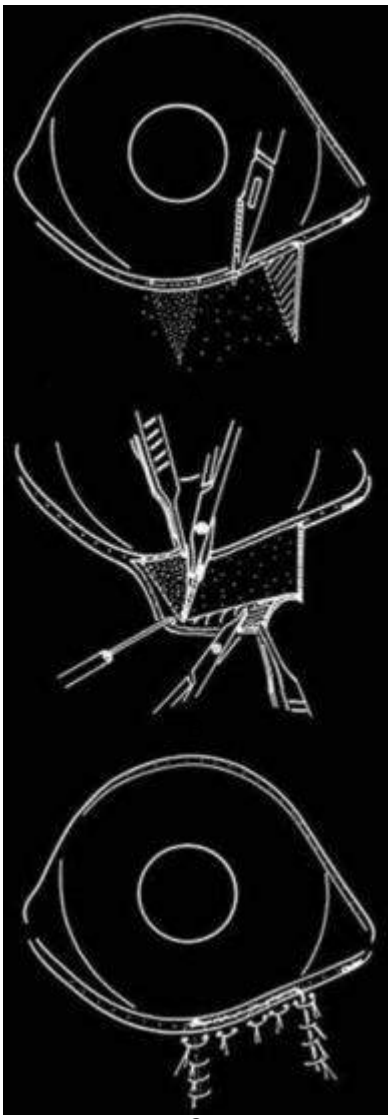


Figure 15.40 Kuhnt–Szymanowski procedure, modified by Blaskovics and further by Fox and Smith for ectropion-macroblepharon to avoid splitting the lid margin. Use in the dog was first described by Munger and Carter. **A**. The skin incision is 2–2.5 mm below the eyelid margin and extends 5–10 mm beyond the lateral canthus. The skin flap is dissected from its deeper muscle layers. All bleeding has to be arrested. **B**. Equal-sized wedges, one of lid margin conjunctiva and one of skin, are excised by scissors. **C**. The lid margin is apposed by a figure-of-eight or U-figure 5-0 to 6-0 suture. If desired, the conjunctival wound can be sutured by a subconjunctival, simple continuous, 8-0 absorbable suture. **D**. The skin defect is apposed by simple interrupted, 5-0 to 6-0 sutures. Advantages: staggering wound, less damaging to the lid margin. Disadvantage: shortens only the lower lid. Copyright Frans C. Stades.

Shih Tzu, with medial entropion, nasal folds, and caruncle trichiasis. In these breeds, the palpebral fissure measures some millimeters longer than the average 33 mm, thus easily allowing the globe to luxate but preventing spontaneous repositioning. Therefore, moderate lid shortening combined with a canthoplasty in the medial canthus is indicated (see also trichiasis of the medial canthus).

The lateral canthus is most accessible, but surgical sites in this area are more apt to atrophy with time. The lack of stability and the increased movements of the lateral canthal region may also complicate these surgical procedures by causing greater short-term stress on the suture line and long-term tension of the apposed eyelid tissues. For both the medial and lateral canthoplasty procedures, the goals are to reduce the stretched palpebral fissure to 33–35 mm and to provide some overlap of the tissues of the eyelids, thereby enhancing its strength.



C

Figure 15.41 Kuhnt–Szymanowski–Helmbold procedure for ectropion. **A**. The lower eyelid is split at the gray line into tarsoconjunctival and skin–orbicularis oculi muscle layers to a depth of 10–15 mm. **B**. Identical wedges of tarsoconjunctiva and of skin–muscle are excised. **C**. The tarsoconjunctival defect is apposed with simple interrupted, 5-0 to 6-0 absorbable sutures. The skin–muscle layer is apposed with simple interrupted, 5-0 to 6-0 sutures. The lid margin wound is apposed with through-and-through interrupted, 6-0 mattress sutures. Advantage: staggering wound. Disadvantages: the lid margin, including the Meibomian glands, is damaged over the operated distance; procedure shortens only the lower lid and therefore is rarely used. Copyright Frans C. Stades.

Simple, Permanent Lateral Palpebral Fissure Reduction Tarsorrhaphy

In general, the stretched lid fissure in macroblepharon-ectropion measures over 40 mm. An average lid fissure measures 33–35 mm. The fissure can be shortened over the surplus distance. The free outer lid margin and the tarsal "plate," including the Meibomian glands, are removed over the measured distance (Fig. 15.42 and Fig. 15.43). Closure is more secure if the conjunctiva is sutured separately (Fig. 15.33D). The method is the most simple, but it lacks the

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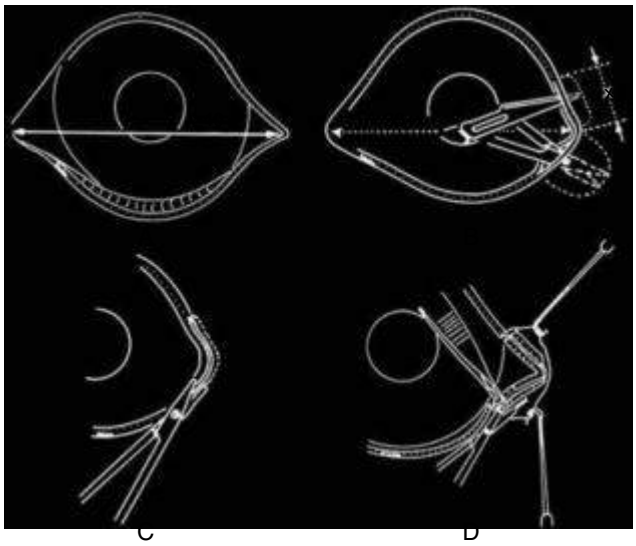


Figure 15.42 Simple lateral (or medial) permanent tarsorrhaphy for macroblepharon-ectropion correction. **A**. In general, the stretched lid fissure in macroblepharon measures more than 40 mm. **B**. An average lid fissure measures 33–35 mm. The fissure can be shortened over the surplus distance (X). The lid margin is split by scalpel, and a pocket is made by tenotomy scissors to a depth of 3–5 mm. If the procedure is performed in the medial canthus, the lacrimal canaliculi and punctae must be avoided. **C**. The pigmented outside of the upper and lower lid margins is excised. **D**. Thereafter, the inside upper and lower margins with their Meibomian glands are excised. Advantage: removal of Meibomian glands and outer free rim of the lid margin. Copyright Frans C. Stades.

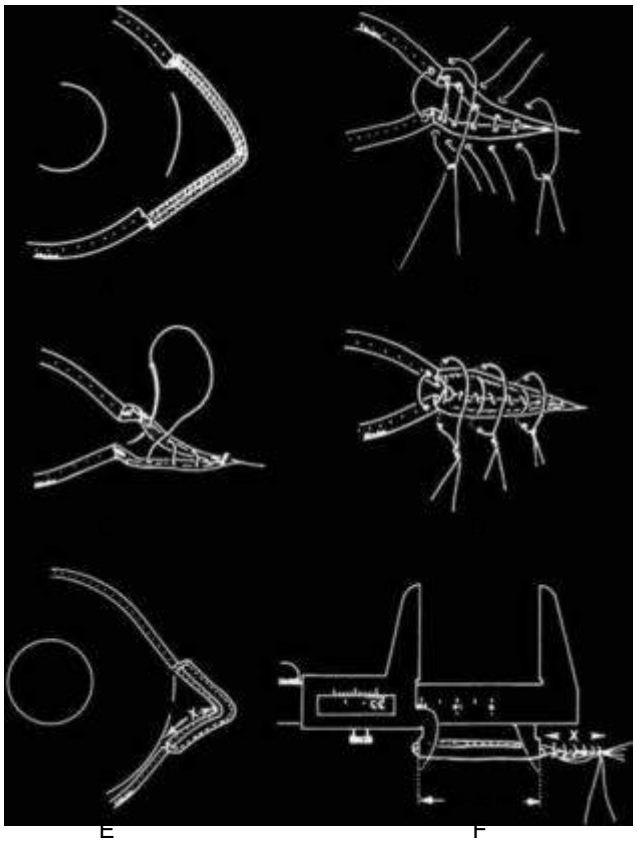


Figure 15.43 Simple lateral or (medial) lower plus upper lid fissure length reduction or permanent tarsorrhaphy for macroblepharon-ectropion correction. Suturing methods. **A**. Wounds after removal of the outside lid margin and the inside margin plus Meibomian glands. **B**. Apposition of the new lateral canthus by a (1) figure-of-eight, 5-0 to 6-0 suture and further closure by simple interrupted sutures (2, 3). The ends of the sutures can be linked or gathered together in the outer-placed suture to prevent irritation of the cornea (see also Fig. 15.8). **C**. The conjunctiva can be apposed by a simple continuous, 6-0 to 8-0 absorbable suture. **C**, **D.** The new lateral canthus and the remaining skin wound can be closed as shown in **B** or **D**. If the lid fissure length is shortened over X mm, the lid fissure after suturing should measure approximately 33–35 mm. **E**, **F**. Advantages: simple and effective; shortens both upper and lower lid margins. Disadvantages: no staggering wound, no extra lateral traction/anchoring. Copyright Frans C. Stades.

double-layered, staggered wound, which prevents leakage and wound dehiscence. The procedure is possible, but less desirable in the medial canthus.

Permanent Lateral Palpebral Fissure Reduction Plasty (Modified Roberts–Jensen Pocket Procedure)

The original procedure by Jensen (1979) was described for the medial canthus; however, it may also be employed for the lateral canthus. The procedure starts with the removal of the medial or lateral upper lid margin and the inside margin plus Meibomian glands, as described in the simple palpebral fissure reduction tarsorrhaphy (Fig. 15.45). If performed in the medial canthus, the upper punctum is lost during the procedure. A flap of upper conjunctiva is pulled downward into the pocket in the lower lid between the conjunctiva and muscle–skin layers and anchored. The method is simple, provides a double-layered, staggered wound, and prevents leakage and wound dehiscence.

The procedure, as described by Jensen, is used in the medial canthus and also results in loss of the upper lacrimal punctum. It has the advantage of concurrent correction of medial lower entropion and protection from nasal folds in Pekingese, Shih Tzu, Pug, and similar breeds. It has the disadvantages of being more complicated and of the loss of the upper punctum. However, as the functioning of the tear ducts in these short-nosed breeds is questionable, the loss generally does not result in (more) epiphora.

Permanent Lateral Palpebral Fissure Reduction Plasty, Fuchs Procedure

The lateral canthoplasty, modified from Fuchs, provides a strong, permanent union at the lateral canthus by rotating a section of lower eyelid skin and orbicularis oculi muscle into a lateral upper lid defect (Kuhnt & Szymanowski, 1976;

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Figure 15.44 **A**. Pronounced lower lid macroblepharon-ectropion (diamond-shaped fissure) in a German Dog (Great Dane). The stretched fissure length was 49 mm. There is also severe medial and lateral entropion and a notch or kink in the lower lid margin. **B**. The postoperative result in the same dog. The stretched fissure length was shortened over 16 mm to 33 mm. There is some swelling of the lower lid conjunctiva, and the "notch" appeared to be a kink and did stretch nicely. Courtesy of Frans C. Stades.

Fig. 15.46). The larger surgical surface area provides a stronger union for the permanent lateral canthoplasty. The procedure starts with the removal of the outside lid margin and the inside margin plus Meibomian glands, as described in the simple palpebral fissure reduction tarsorrhaphy. The procedure is possible but less desirable in the medial canthus.

Permanent Lateral Palpebral Fissure Reduction Plasty, Wyman and Kaswan Procedure

The procedure starts with the removal of the outside lid margin and the inside margin plus Meibomian glands, as described by Kaswan et al. (1988) in the simple palpebral fissure reduction tarsorrhaphy (Fig. 15.47). A double-layered, staggered wound is made. In contrast to the Fuchs method, the inner conjunctiva layers, in the modified Wyman and Kaswan method, are closed by a simple, continuous, absorbable suture. This method creates a double-layered, staggered wound, preventing leakage and wound dehiscence. The procedure is possible but less desirable in the medial canthus.

Permanent Lateral Palpebral Fissure Reduction Plasty, Kuhnt–Szymanowski Procedure

In this procedure, modified by Bedford (1998), the desired length of reduction is removed in the lateral lower and upper lid instead of reducing the lower lid length in the area of the most extensive ectropion in the middle (Fig. 15.48). The lateral lower skin flap provides further lifting and lateral fixation. Results from a series of 22 dogs collected over a period of 6 years demonstrated an overall improvement, but 5 of the dogs required further resection of redundant forehead skin.

Permanent Lateral Palpebral Fissure Reduction Plasty and Stabilizing the Lateral Canthus Procedure

This procedure, in which the lower lid is shortened over 2–6 mm and the lateral canthus area is removed full-thickness, has been described mainly for the correction of entropion, but it has also been advocated for the correction of ectropion-macroblepharon. For more details, see "Surgery for Entropion Combined with Shortening of the Lower Lid" (Gutbrod & Tietz, 1993; see Fig. 15.31).

Macroblepharon-Ectropion and Entropion Correction, Reducing Lower and Upper Lid Length plus Repositioning and Fixation of the Lateral Canthus Laterally

In combined macroblepharon-ectropion-entropion, the procedures for correction of lateral entropion may be insufficient, because they stabilize the lateral canthus but do not reduce the palpebral fissure and/or do not fixate the lateral canthus laterally, as required, for example, in the diamond-shaped lid fissures of the giant breeds of dogs. These more recently developed surgeries shorten the lid fissure and attempt to stabilize the lateral canthus laterally, thereby correcting the lateral entropion.

In the Bigelbach (1996) procedure, the lower and upper eyelids can be shortened 20%–25% and attempts made to correct entropion and stabilize the lateral or medial canthus (Fig. 15.49). A trapezoid-shaped section of skin and orbicularis oculi muscle is excised from the lateral canthus. Interrupted sutures anchor to the deep fascia–lateral ligament, thus fixing the lateral canthus. The procedure has been recommended in large and giant breeds of dogs and in principle is possible in the medial canthus.

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Figure 15.45 The Roberts–Jensen pocket method for lid fissure length reduction by permanent medial or lateral tarsorrhaphy. **A**. The procedure starts with the removal of the outside lid margin and the inside margin plus Meibomian glands. If performed in the medial canthus, the upper lacrimal punctum is incised in the procedure. **B**. A flap of upper conjunctiva is pulled downward into the pocket in the lower lid between the conjunctiva and muscle–skin layers and anchored through the muscle–skin by a simple interrupted, 5-0 suture. **C**. Apposition of the new lateral or medial canthus by a figure-of-eight, 5-0 to 6-0 suture, and further closure by simple interrupted sutures. Advantage: effective, especially in Pekingese, Shih Tzu, Pug, and similar breeds. Disadvantages: more complicated; loss of upper punctum if performed medially, although the functioning of the tear ducts in these short-nosed breeds is questionable. Copyright Frans C. Stades.

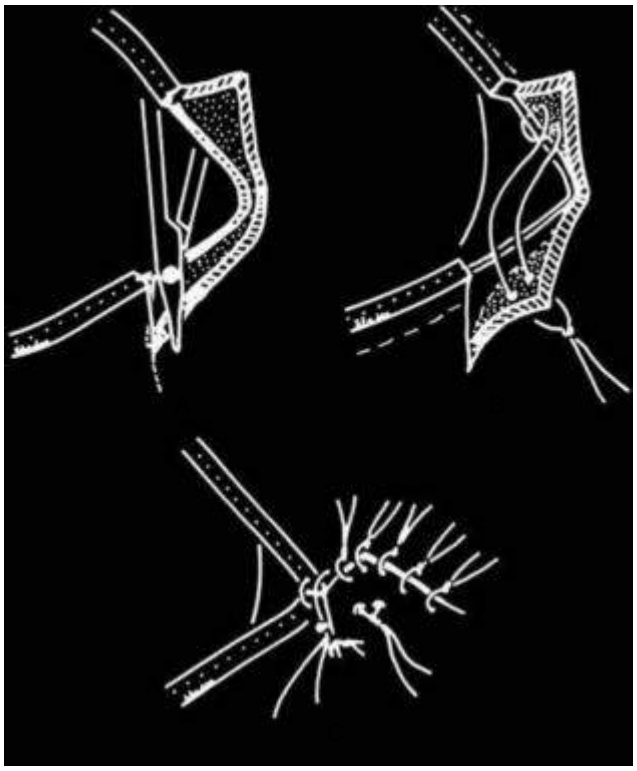


Figure 15.46 Lateral canthoplasty (Fuchs modification) method for lid fissure length reduction by permanent lateral tarsorrhaphy. The procedure starts with the removal of the outside lid margin and the inside margin plus Meibomian glands, as described in Fig. 15.42. **A**. A triangular flap of muscle–skin of 5–7 mm wide is removed. The lower lid skin–muscle is incised over 5–7 mm. **B**. The lower flap is sutured to the upper conjunctiva by a simple interrupted, 6-0 suture. **C**. Apposition of the new lateral canthus by a figure-of-eight, 5-0 to 6-0 suture and further closure by simple interrupted sutures. Advantage: shortens both upper and lower lid margins. Disadvantages: no extra lateral traction/anchoring; less effective and more complicated. Copyright Frans C. Stades.

Reduction of Lower and Upper Lid Length plus Repositioning and Fixation of the Lateral Canthus Laterally: Stades Procedure

In this technique, two full-thickness wedges (approximating the length of the required lid fissure shortening) are excised, and the new lateral canthus is apposed by a figure-of-eight, 5-0 to 6-0 absorbable suture anchored laterally in the lateral ligament and skin (Fig. 15.50).

Reduction of Lower and Upper Lid Length plus Repositioning and Fixation, by Traction Suture of the Lateral Canthus Laterally

This procedure is especially suitable for palpebral fissure length reduction and lateral canthus replacement in giant breeds (Grussendorf, 2004). The redundant length of lid margin is removed, up to a third of the lid length (as shown in Fig. 15.51). An additional lateral skin incision is made

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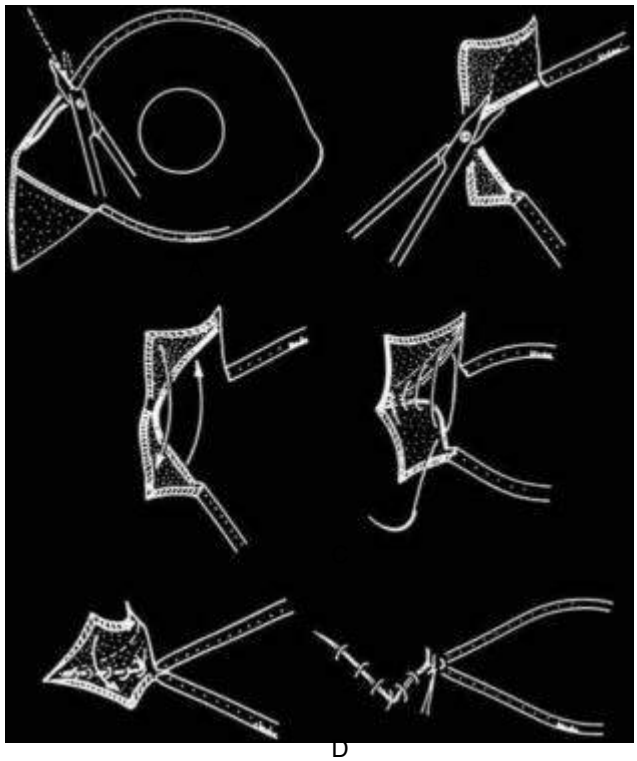


Figure 15.47 Lateral canthoplasty (Wyman and Kaswan modification) procedure for lid fissure length reduction by permanent lateral tarsorrhaphy. The procedure starts with the removal of the outside lid margin and the inside margin plus Meibomian glands. **A**. A triangle of skin–muscle 5–7 mm deep is removed. The opposite lid skin–muscle is incised over 5–7 mm. **B**. Below that area, the conjunctiva is excised. **C**. The lower and upper conjunctivae are apposed by a simple continuous, 6-0 to 8-0 absorbable suture (knot, subconjunctivally). **D**. The skin–muscle flap is apposed in the new lateral canthus by a figure-of-eight, 5-0 to 6-0 suture and further closed by simple interrupted sutures. Advantage: shortens both upper and lower lid margin. Disadvantages: no extra lateral traction/anchoring; less effective and more complicated. Copyright Frans C. Stades.

some 2 mm behind the orbital ligament. The new canthus is created using a figure-of-eight suture. A nonabsorbable traction suture connected to the orbital ligament replaces the lateral canthus until the lid fissure reaches a normal appearance. The surplus skin triangles are then removed.

Postoperative Treatment

Therapy after ectropion-oversized lid fissure procedures consists of applying topical initial choice antibiotic ointment (more lubricating than drops) four times daily for 14 days. Systemic antibiotics may be indicated for extensive procedures. An Elizabethan collar is used routinely to prevent the patient from rubbing the surgical site and producing local irritation and even suture loss. The sutures are removed 12–16 days after surgery. The end result can be judged only after cicatrization, about 6–8 weeks after surgery.

Prognosis and Prevention

The prognosis for correction of ectropion-oversized palpebral fissure, although dependent on the cause, is usually good. Parents and siblings should also be examined, and affected animals should not be used for breeding. Breeding should aim for closed lids with fissures of normal length and also for ears of normal weight and placement.

Microblepharon, Blepharophimosis, or Blepharostenosis

An abnormally small or narrowed palpebral fissure, which is referred to as microblepharon, blepharophimosis, or blepharostenosis, is not only seen particularly in miniature breeds like the Miniature Pinscher and Shetland Sheepdog, but also in larger breeds such as the English Bull Terrier, Chow Chow, Kerry Blue Terrier, and both Rough and Smooth Collies (Fig. 15.52).

The entity should not be confused with a spasm of the orbicular muscle caused by entropion or other chronic corneal pain. Before enlarging the fissure in such patients, the stretched palpebral fissure should be measured using calipers after topical anesthesia, or for best results under general anesthesia.

In microblepharon, the globe is usually of normal size, but it may accompany microphthalmos. The stretched palpebral fissure is usually 5–10 mm shorter than the normal fellow eye or the normal eye of a sibling. Microblepharon is often accompanied by upper lid entropion. However, if the lid fissure is surgically lengthened in these patients, the entropion disappears without further specific correction. The condition has no direct significance to the patient unless it predisposes to entropion and associated ocular surface disease. Patients with microblepharon and related dogs should not be used for breeding.

Therapy

Correction is achieved by a lateral augmentation canthoplasty that increases the functional length of the palpebral fissure (Fig. 15.53). The stretched palpebral fissure is measured by calipers. A 5 to 10 mm long lateral canthotomy is created using tenotomy scissors. Two small arrowhead skin resections will achieve a more gradual transition to the newly created lid "margin."

Trichiasis

Trichiasis is the presence of normally located but abnormally directed hairs that irritate the opposite lid margin, the globe, conjunctiva, or both. The chronic corneal irritation results in extra lacrimation, blepharospasm, and mucopurulent conjunctival discharge. When hairs contact the cornea, corneal disease is common. The lesions are often healed by granulation tissue, but they may also deepen until

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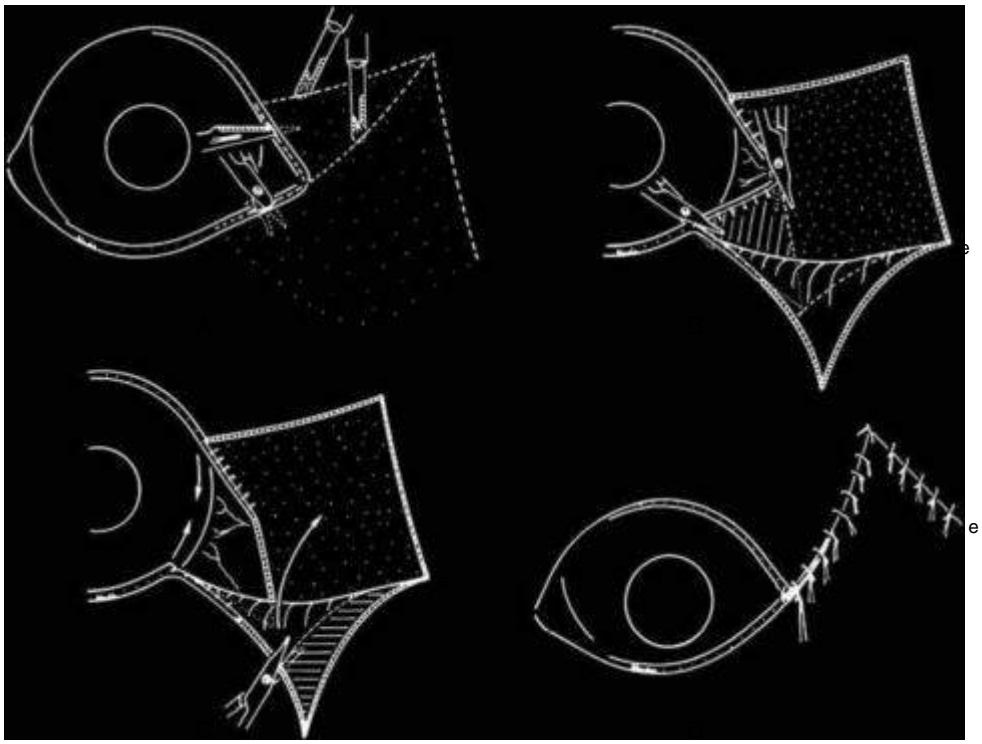


Figure 15.48 Lateral canthoplasty (Kuhnt–Szymanowski modified by Bedford) procedure for lid fissure length reduction by permanent lateral tarsorrhaphy. **A**. A lid split (a–f) is made, and following the curvature of the lower eyelid, a skin incision is constructed to (d) and downward to (e). This outer lid margin skin–muscle flap is bluntly dissected by tenotomy scissors from its underlying tarsoconjunctival–subcutaneous tissues. **B**. A triangle of lower eyelid margin–tarsoconjunctiva is excised for a distance that approximates the length of the desired lid shortening. The outer lid margin (a–f) is not removed. **C**. The skin flap is shortened (c–e), using scissors, over the same length. **D**. Apposition of the new lateral canthus by a figure-of-eight, 5-0 to 6-0 suture and further closure by simple interrupted sutures. Advantages: shortens both upper and lower lid margin; provides lateral anchoring. Disadvantages: no extra lateral traction; more complicated. Copyright Frans C. Stades.

perforation occurs. The final stage is the formation of scar tissue and pigmentation, or sometimes even the loss of the eye (Stades et al., 1993).

Trichiasis is usually corrected surgically. Trichiasis occurs mainly in (1) nasal folds; (2) the upper eyelid, usually dorsolaterally; and (3) in combination with entropion in the same area (Fig. 15.54). In brachycephalic breeds with exophthalmia, such as the Pekingese, Shih Tzu, and Lhasa Apso with exophthalmic eyes, the caruncle hairs may also irritate the globe and contribute to epiphora. Less frequent hairs in nonpredilection locations around the lid fissure (e.g., in dysplasia or lid colobomata) are misdirected and irritate the globe. Also, poorly healed lid lacerations or blepharoplasties may result in trichiasis.

Trichiasis occurs in several dog breeds as a hereditary, most likely polygenic entity and is a desired characteristic in some breed standards.

Nasal Fold Trichiasis

Because of breed standards and fashions that disregard the animals' health but are nevertheless supported by breeders, judges, and buyers alike, almost all eyes of prominent-eyed breeds (e.g., Pekingese, Shih Tzu, and Lhasa Apso) are chronically irritated, have corneal disease, and are predisposed to proptosis or luxation. For example, breed standards, which most veterinarians do not agree with, require that the Pekingese should have a short muzzle with a marked stop and heavily wrinkled skin with long and straight hairs, and also that it should have large and protruding eyes. In most patients, it is found in combination with medial entropion, caruncle trichiasis, a slightly oversized lid fissure, and lagophthalmos. Dogs with nasal folds were nearly 5 times more likely to be affected by corneal ulcers than those without, and brachycephalic dogs (craniofacial ratio < 0.5) were 20 times more likely to be affected than nonbrachycephalic dogs. A 10% increase in relative eyelid aperture width more than tripled the ulcer risk. Exposed eye-white was associated with a nearly three times increased risk (Packer et al., 2015).

These breeds often develop recurrent mediocentral corneal ulcerations that have the potential to progress and even perforate. The blink reflex may be weak and incomplete, resulting in a thin precorneal tear film on the center of the cornea and increased risk of epithelial loss.

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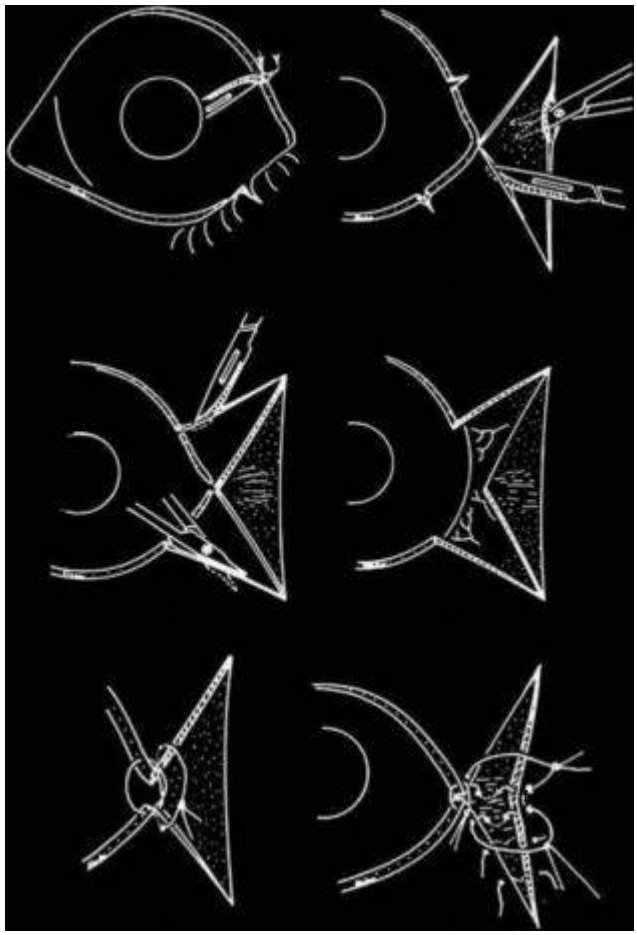


Figure 15.49 Lateral canthoplasty, Bigelbach procedure, for lid fissure length reduction and lateral entropion correction by permanent lateral tarsorrhaphy. In this lateral tarsorrhaphy-canthoplasty method, a trapezoid-shaped section of skin and orbicularis muscle is excised from the lateral canthus. **A**. Two 2 mm scalpel incisions (a, b) are made perpendicular to the upper and lower eyelid margins. They mark the extent of the lid shortening. **B**. A curved skin incision is extended from the lateral canthus following the curvature of the lower eyelid to (d). Similarly, a skin incision is performed from the lateral canthus following the curvature of the upper eyelid to (e). An additional skin incision is made between (d) and (e). This skin triangle is excised. **C**. Two upper and a lower lid, full-thickness triangles of *adc* and *bec* are excised. **D**. A trapezoid area remains. **E**. The new lateral canthus is apposed by a figure-of-eight, 5-0 to 6-0 nonabsorbable suture. **F**. Further closure is by interrupted sutures anchored in the deep fascia–lateral ligament. Advantages: shortens both upper and lower lid margin; provides lateral anchoring. Disadvantages: no extra lateral traction; more complicated. Copyright Frans C. Stades.

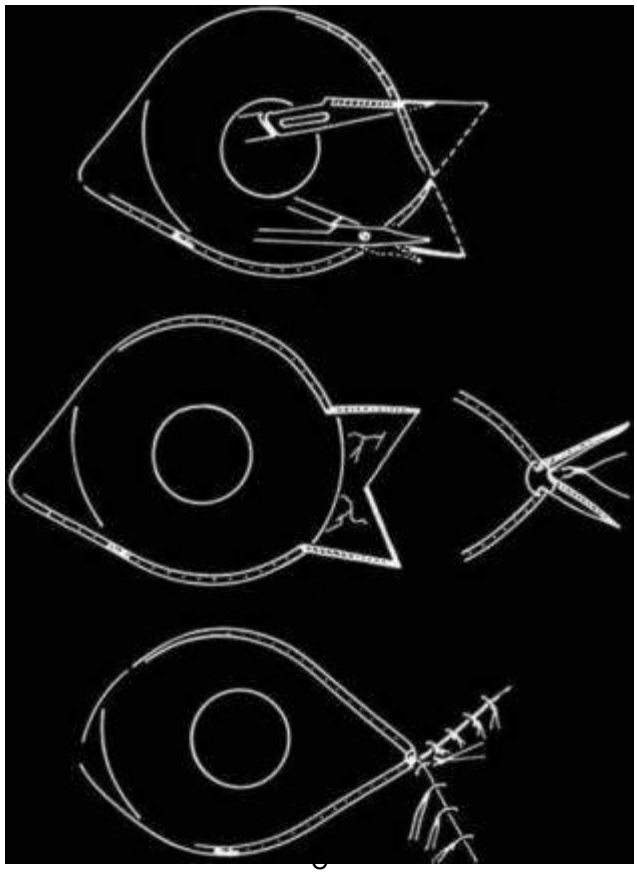


Figure 15.50 Lateral canthoplasty (Stades Diabolo) method for lid fissure length reduction by permanent lateral tarsorrhaphy. **A**. Two full-thickness lid wedges (approximating the length of the required lid fissure shortening) are excised. **B**. The new lateral canthus is apposed by a figure-of-eight, 5-0 to 6-0 absorbable suture anchored in the lateral ligament–skin. **C**. Further closure of the wound by simple interrupted sutures. Advantages: shortens both upper and lower lid margin; provides lateral anchoring. Disadvantages: no extra lateral traction; more complicated. Copyright Frans C. Stades.

The hairs on the nasal fold, the caruncles, and the medial entropion are potential sources of irritation to the conjunctiva, including the nictitating membrane and the medial quadrant of the cornea, resulting in excessive lacrimation, slight blepharospasm, corneal edema, vascularization, pigmentation, and other corneal defects. The final stage is medial pannus formation with accompanying pigmentation, which may ultimately cover the entire cornea. Additionally, the prominent eyes and associated lagophthalmos result in drying of the axial cornea and erosion of the epithelium. Some of these dogs sleep with the central cornea exposed. Ulcers (rounded, craterlike) in these breeds resulting from this insult (without being noticed by the owner) often become lytic and progress to descemetocele within 24 hours. They may rupture during excitation, which results in pain reactions like whining and moaning and is often interpreted by the owner as trauma caused by a cat or dog fight. Traumatic defects, however, are usually scratch shaped. Finally, they may end in severe central corneal scarring, often with anterior synechia or even the loss of the eye. The retention of topical rose Bengal by the central cornea suggests this region is at risk for ulceration and confirms the lagophthalmos.

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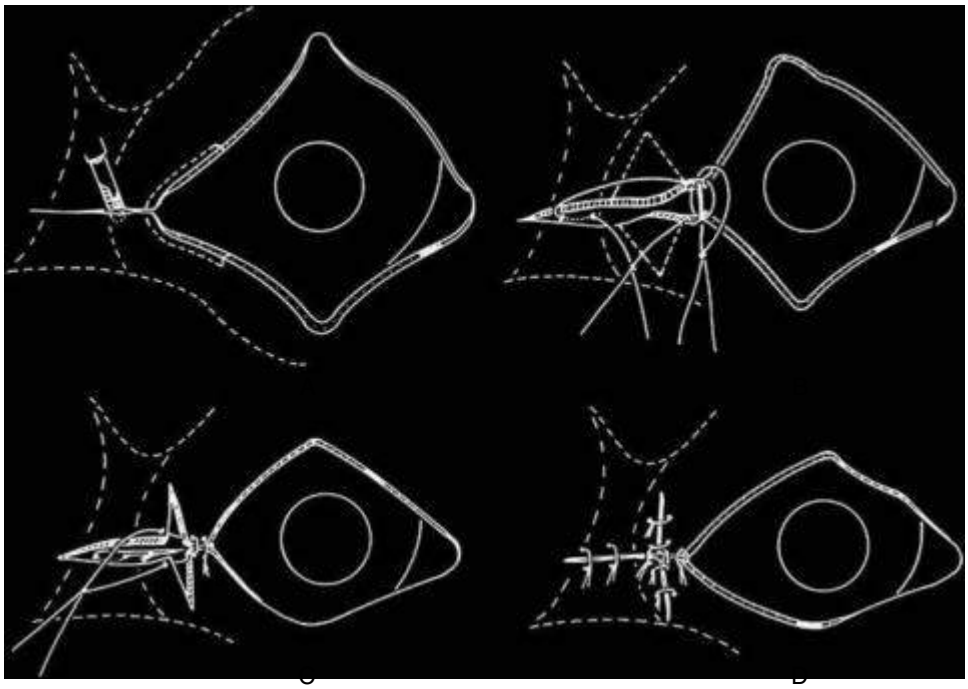


Figure 15.51 Lateral canthoplasty, Grussendorf procedure for lid fissure length reduction including lateral entropion, mainly in giant breeds, by permanent lateral tarsorrhaphy and lateral canthus repositioning by a traction suture. The redundant length of lid margin, up to one-third of the lid length, is removed. **A**. A further lateral skin incision is made some 2 mm behind the orbital ligament. **B**. The new canthus is created, using a figure-of-eight suture. A nonabsorbable traction suture connects the lateral canthus to the orbital ligament until the lid fissure reaches a normal appearance. The surplus triangles of skin (*acd* and *bef*) are removed. **C**. The four wound angles are sutured together using a U-figure suture. **D**. Further closure of wounds by simple interrupted sutures. Advantages: effective in diamond-shaped eyes; shortens both upper and lower lid margins; provides lateral anchoring and extra lateral traction as required. Disadvantages: more complicated; stretches but does not remove lid notches in breeds like the St. Bernard. Copyright Frans C. Stades.

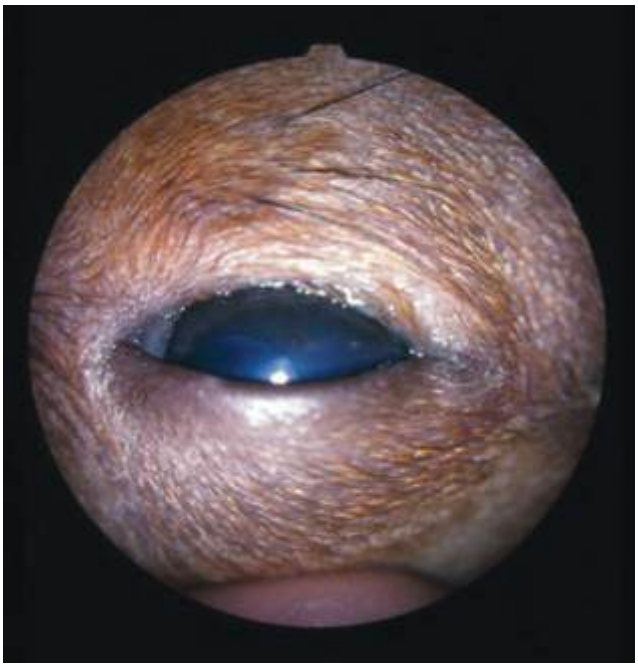


Figure 15.52 Microblepharon or blepharophimosis in a Miniature Pinscher puppy. The upper lid shows a high degree of entropion. Courtesy of Frans C. Stades.

Therapy

In cases of minor corneal disease, therapy can be started with an initial choice antibiotic and lubricating ointments, every 6 hours. If the corneal defects have healed after 10 days, the cornea may be protected by oil or a neutral ointment 2–4 times daily, adhering the hairs together, but this alone seldom resolves the problem.

Removal of part or all of the nasal folds is possible, but usually is not sufficient to deal with the other deformities in these breeds. Removing the medial canthus and caruncle hairs, repositioning the medial canthus more laterally, and reducing the normal or sub-oversized palpebral fissures may be indicated in the brachycephalic breeds with nasal fold trichiasis and exophthalmia, such as the Pekingese, Shih Tzu, and Lhaso Apso. The surgical reduction in the size of the palpebral fissure will decrease corneal exposure, the possibility for recurrent corneal ulcerations, and the risk for proptosis or luxation of the globe.

Removal of Nasal Folds

Nasal folds (partial upper or complete) can simply be removed. In this operation, the fold is lifted and excised with large scissors, and the wound is closed with 5-0 absorbable sutures (Fig. 15.55). However, this operation does not correct

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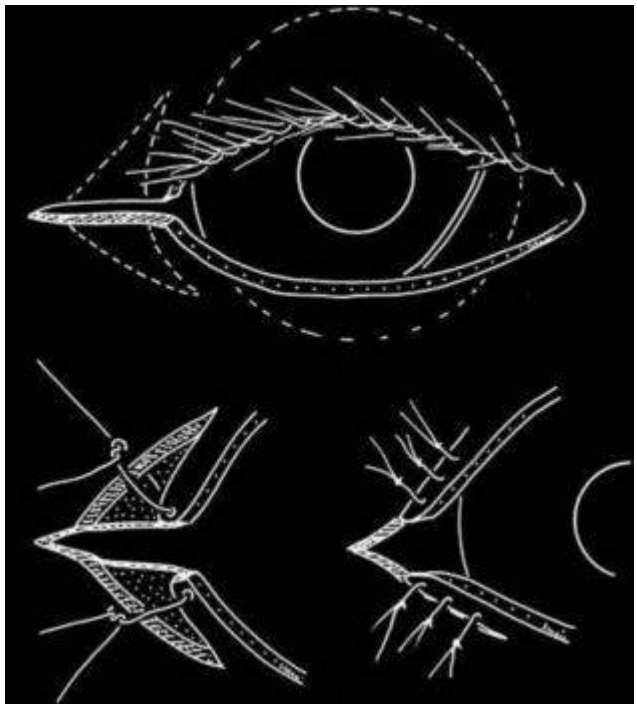


Figure 15.53 Microblepharon or blepharophimosis correction. **A**. Often a microblepharon is combined with entropion of the upper lid. A full-thickness lateral canthotomy is performed. The entropion will then usually correct spontaneously. Two triangles of skin, 2 mm lateral to the lateral canthus, are removed. **B**. The lateral canthus skin is sutured to the middle of the opposite skin wound edge, and the rest of the wounds are closed by simple interrupted, 5-0 to 6-0 sutures. The remaining canthotomy wounds of skin and conjunctiva are left to heal by secondary healing. Advantage: simple and effective. Copyright Frans C. Stades.

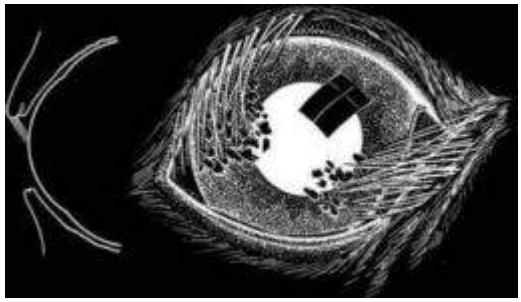


Figure 15.54 An eye with the two main locations of trichiasis. **A**. Dorsolateral eyelash hairs drooping into the lower conjunctival sac and on the cornea. **B**. Nasal fold hairs irritating the ventromedial quadrant of the cornea. Copyright Frans C. Stades.

the associated medial entropion or the caruncle trichiasis, and does not reduce the palpebral fissure length.

Medial Canthoplasties

Many of the surgical techniques that address ectropion-oversized palpebral fissure as well as the combination of entropion and ectropion also decrease the size of the



B

Figure 15.55 For the treatment of nasal fold trichiasis, the nasal folds can be excised. **A**. The nasal folds are clamped and carefully excised by curved Mayo scissors. **B**. The wound edges are apposed with simple interrupted, 5-0 to 6-0 sutures. The first sutures are placed at the upper and lower ends and at the medial canthus, then the rest of the wounds are closed by halving the intervals. Advantage: simple. Disadvantage: ineffective. Copyright Frans C. Stades.

palpebral fissure and can be used in nasal fold trichiasis. However, these procedures do not specifically remove the caruncle hairs and may be more complicated to perform in the medial canthus, with its deep "stop" of the muzzle of these breeds.

Medial Canthoplasties for Brachycephalic Dog Breeds and Dogs with Medial Canthus Hair Irritation

Medial canthoplasty procedures reduce the size of the palpebral fissure, remove the caruncle hairs, and replace the medial canthus laterally, away from the nasal folds (Fig. 15.56; Stades & Boevé, 1986) and prevent medial canthal hair irritation of the conjunctiva and globe. The lacrimal puncta and canaliculi should be identified and protected during surgery. A diamond-shaped area of skin, upper and lower lid margin, and outer conjunctiva of the nictitating membrane, including the caruncle hairs, are removed. A slightly more simplified technique has been described by

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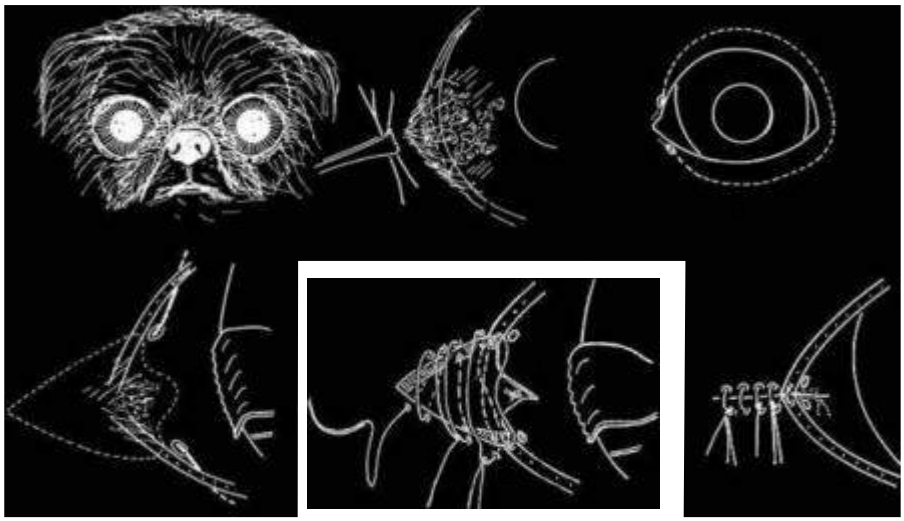


Figure 15.56 Medial canthoplasty procedure for the correction of nasal fold trichiasis. **A**. This technique turns the medial lid margin outward and, replacing it approximately 7 mm laterally, eradicates caruncle trichiasis and reduces the size of the palpebral fissure, which practically precludes luxation of the globe and lagophthalmic complications. **B**. To prevent surgical damage to the lacrimal apparatus, a well-recognizable, 00 to 2-0 monofilament blue Prolene suture with heat-rounded tips may be positioned from the upper to the lower lacrimal punctum-canaliculus via the cul-de-sac. **C**. An arrowhead-shaped skin and medial caruncle conjunctiva area is circumcised with a scalpel. The lid margins are cleaved just before, at, or lateral to the punctae, depending on the estimated required shortening of the lid fissure. The skin and conjunctiva are bluntly dissected by tenotomy scissors. **D**. The remaining wound is either apposed by 1–2 single subconjunctival 6-0 absorbable sutures (1) closing the palpebral conjunctiva, a figure-of-eight suture (2) closing the lid margins, and a continuous suture (3) closing the remaining skin wound; or is apposed by one continuous suture, starting deep, subconjunctivally. Special care should be taken that the suture ends do not enter the conjunctival sac and that the lid margin wounds appose perfectly. **E**. The sutures end medially in the skin. Advantage: simple and effective, especially in Pekingese, Shih Tzu, Pug, and similar breeds. Disadvantage: if more length is required, it is possible but more difficult to prevent damage to the puncta. However, the functioning of the tear ducts in these short-nosed breeds is questionable. Copyright Frans C. Stades.

Yi et al. (2006) primarily for the treatment of epiphora in dogs, in which the medial canthus upper and lower lid margins up to just 1 mm medial of the punctae, plus the haired mucosa of the caruncle, are removed (Fig. 15.57). The medial canthus is thereafter closed with a figure-of-eight suture and nasally an additional simple interrupted suture.

Also skin cauterization and hair follicle destruction around the medial canthus in a figure of an arrowhead using a radiofrequency hyperthermia unit have been described by Lieberknecht et al. (2010), resulting in a hairless medial canthus and a lid position correction.

Postoperative treatment after a medial canthoplasty consists of topical, initial choice, antibiotic ointment 4 times daily for 14 days. As a result of this operation, the medial canthus is turned outward, emerges from behind the nasal folds, and is replaced 6–10 mm laterally. Additional benefits are the removal of the caruncle hairs and the shortening of the palpebral fissure by 6–8 mm, which practically precludes luxation of the globe and diminishes lagophthalmic complications.

Upper Eyelid Trichiasis

In this condition, the eyelash hairs of the lateral upper eyelid or hairs on skin folds above the eyes, in combination with upper eye lid entropion, irritate the eye. These hairs droop over the eyes, irritating the lower conjunctiva and the cornea. Particularly in breeds such as the Bloodhound, Chow Chow, and Shar Pei (and less severely in the elderly English Cocker Spaniel and Basset Hounds), these hairs may cause serious lesions of the cornea. In these breeds, the excessive masses of frontal wrinkles press the margin of the upper eyelid inwardly onto the globe. In the Bloodhound, Basset Hound, and English Cocker Spaniel, this pressure is increased by the heavy weight of the ears when the head is turned toward the ground.

The irritation results in extra lacrimation and blepharospasm, which may worsen the condition. The hairs on the upper eyelid are dark and moist, and the upper lid margin is entropic. The conjunctiva is red and swollen, and the corneal epithelium is damaged, resulting in ulceration, mainly of the upper lateral part of the cornea, and, in rare cases, the condition also leads to perforation. Finally, it often results in scarring and pigmentation.

Therapy

In cases of minor irritation, the cornea may be protected by an indifferent topical ointment, oil, artificial tears, or petrolatum 2–4 times daily, but this measure alone seldom

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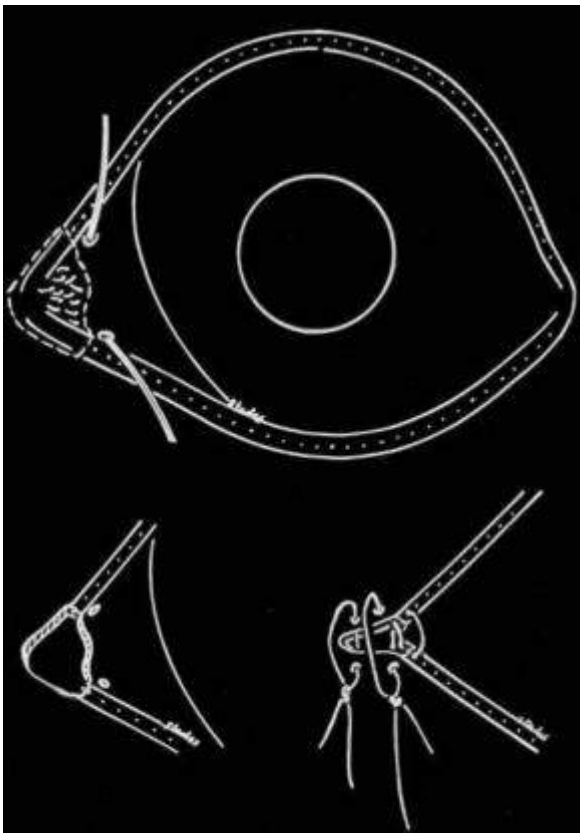


Figure 15.57 Medial canthoplasty procedure for the prevention of medial canthal hair irritation of the conjunctiva and globe by Yi et al. (2006). **A**. The lacrimal puncta and canaliculi are identified and protected during surgery. **B**. The medial canthus upper and lower lid margins up to just 1 mm medial of the punctae, plus the haired mucosa of the caruncle, are removed. **C**. The medial canthus is thereafter closed with a figure-of-eight suture and nasally an additional simple interrupted suture. Copyright Frans C. Stades.

resolves the problem. A simple Celsus–Hotz entropion correction, as described previously, is possible although rarely sufficient.

Radical excision of the upper lid skin, including the irritating, eyelash-like hairs, and forced healing by secondary granulation (Stades method) is most useful in these cases (Fig. 15.58; Allgoewer, 2011; Stades, 1987a, 1987b; Stades & Boevé, 1987).

Skin directly above the free rim of the upper eyelid margin (removing all hair follicles), up to 25 mm in width, is circumcised in the form of a "clown's eyebrow" and superficially removed. Up to 5 interrupted 6-0 absorbable presutures are used to divide and appose the much longer dorsal wound edge to the base of the Meibomian glands–tarsal "plate." A continuous suture over it apposes the outer wound edge completely at that line. The remaining open part of the wound is forced to heal by secondary granulation (the owner must be warned of this before surgery). This results in an upper lid covered over approximately 5 mm with scar tissue, preventing redundant folds from reaching the globe (Fig. 15.59). Infection in the open wound has not been reported.

The brow-sling procedures (see "Redundant Skin Folds around the Eye") can be successful in those breeds in which excessive skin folds are distorting the eyelid function (Bedford, 1990; Blogg, 1980; Kása & Kása, 1979; Kirschner, 1995; Krahwinkel & Merkley, 1976; McCallum & Welser, 2004; Stuhr et al., 1997).

The removal of upper and dorsolateral folds or frontal skin or a brow-sling procedure takes away the pressure on the lids and canthi, but has less effect on the lid margin entropion itself. It usually produces less satisfactory long-term results because it does not eliminate the lash-type hairs that cause the direct trichiasis irritation.

The degree of correction requires a skilled hand. Recurrences, infections around the sutures and implants, and undesired scarring may cause complications.

Prognosis and Prevention

The prognosis is usually favorable. Affected animals should not be used for breeding. Parents and siblings should also be examined. The desire of breeders and judges, supported by buyers, for very short noses, a marked stop, and heavily wrinkled and abundant skin should be discouraged. Breed standards should be corrected.

Caruncle Trichiasis

The caruncle normally has some short, soft hairs directed outward nasally. In brachycephalic breeds with exophthalmia, such as the Pekingese, Shih Tzu, and Lhasa Apso, the caruncle hairs may irritate the globe, resulting in medial, limbal pigmentation of the cornea and even epiphora. In rare cases, some of the caruncle hairs grow up to 10–15 mm long and irritate the cornea (Fig. 15.60).

For therapy in the brachycephalic breeds, see "Nasal Fold Trichiasis." In the other cases, the hairs can be epilated first to be sure they are the cause of the irritation. They can be removed permanently by destroying the hair follicles using electro-, laser-, or cryodestruction. See the therapy section under "Distichiasis and Conjunctival Ectopic Cilia."

Trichiasis in Other Locations

Infrequently, hairs in nonpredilection locations around the lid fissure or in dysplastic areas are misdirected and irritate the conjunctiva, globe, or both. For therapy, the hairs can be epilated first to make certain they are the cause of the irritation. If the area is more than 2–3 mm away from the lid margin, the area can be circumcised and removed, and the wound closed by one or two sutures. If the hair follicles are located within 2 mm of the free rim of the lid margin, the Celsus–Hotz principle will usually result in recurrent

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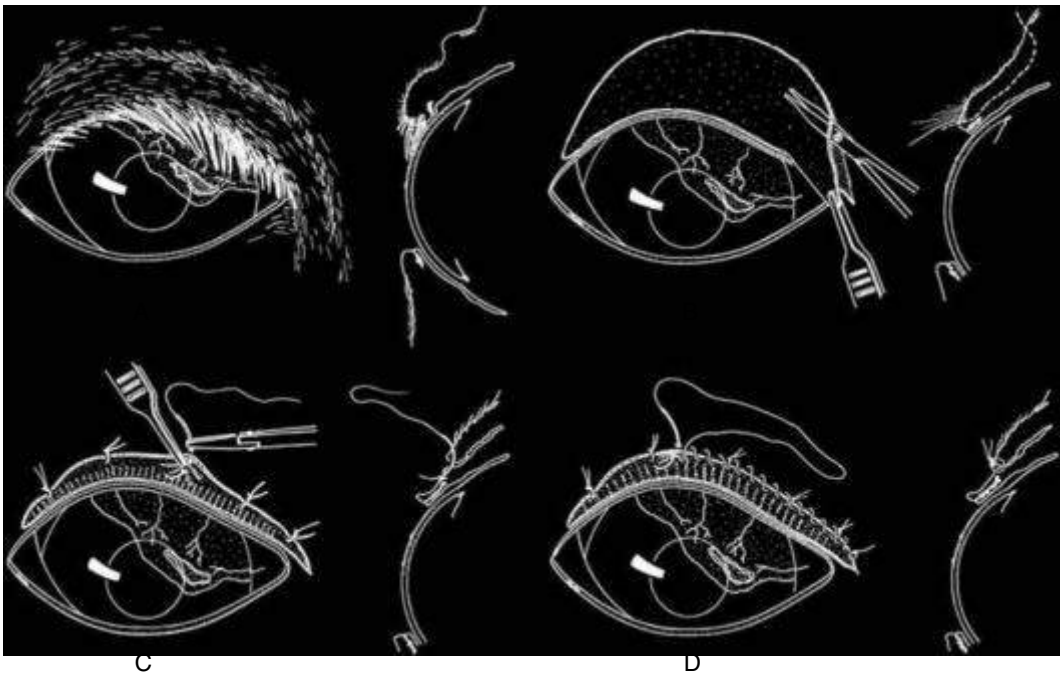


Figure 15.58 **A**. Upper eyelid trichiasis-entropion and redundant skin folds: Stades forced granulation procedure. **B**. The first incision is located 0.5 mm from and parallel to the margin of the eyelid, care being taken not to injure the Meibomian glands. A piece of skin up to 25 mm (usually where the first fold above the eye ends in a sulcus) in width is circumcised in the form of a "clown's eyebrow" and superficially removed by blunt dissection. If the trichiasis is combined with distichiasis, the now visible follicles should be scraped away or destroyed by cautery. **C**. The dorsal edge of the wound is reattached at a distance of 4–5 mm from the margin of the eyelid by three to five simple interrupted sutures (absorbable 6-0, round-body needle), at the base of the Meibomian glands–tarsal "plate" (and *not* closer to the lid margin). **D**. A continuous suture apposes the outer wound edge completely at that line, forces the remaining open wound to heal by secondary granulation (the owner must be warned of this before surgery), and rotates the lid margin upward. After further scarring, the upper lid is covered by hairless scar tissue, which becomes pigmented after a few months. Advantages: simple and very effective. Disadvantages: no effect on the medial canthus; open wound directly after surgery; visible scar. Copyright Frans C. Stades.

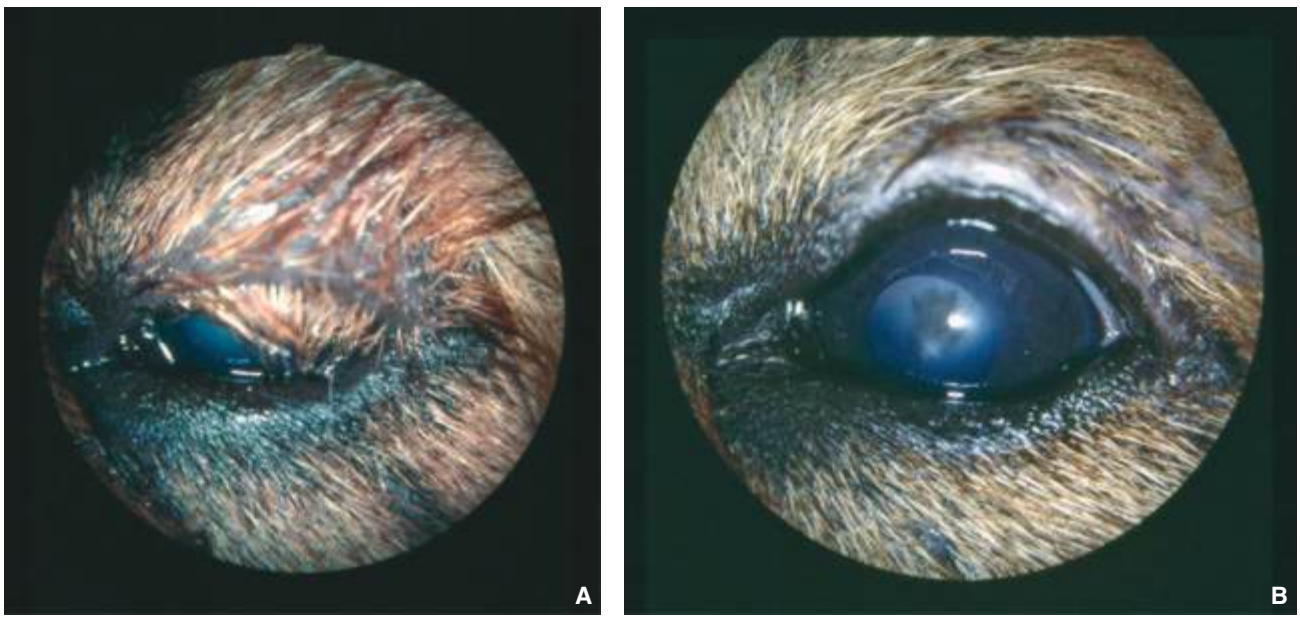


Figure 15.59 **A**. Preoperative appearance of a 6-week-old Chow Chow puppy with upper eyelid trichiasis-entropion and redundant skin folds. **B**. Postoperative appearance of the same Chow Chow puppy, 3 weeks after a Stades forced granulation procedure. The wound has healed by secondary granulation. The upper lid skin can no longer reach the conjunctiva or globe. Courtesy of Frans C. Stades.

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Figure 15.60 Elongated caruncle hairs in the medial canthus of a dog. Courtesy of Frans C. Stades.

trichiasis. In this case, the Stades (1987a, 1987b) forced granulation procedure (Fig. 15.61 and Fig. 15.62), electro-, laser-, or cryodestruction, is indicated for therapy. See also the therapy section under "Distichiasis and Conjunctival Ectopic Cilia."

Secondary Trichiasis

Poorly healed lid lacerations and blepharoplasties that involve reconstruction of the lid margin may result in trichiasis. Usually, one or more hair follicles are misdirected because of scarring. In blepharoplasties, the leading edge of pedicles can easily be inverted by traction of the faster-healing conjunctiva on the inside and on the nonprecise apposed and sutured transition of the graft to the normal lid margin. This should be prevented by cutting the free edge in a nonundermining way, preventing any traction on the leading edge, the use of relaxation sutures, and having the leading edge of the graft bulge slightly within the lid margin contour. The hair follicles can be destroyed (e.g., by cryodestruction), or the scarring notch with the hair follicles must be removed and the wound closed with great care. In severe cases, more extensive blepharoplasty has to be performed.

Trichomegaly

Trichomegaly refers to abnormally elongated eyelid cilia and is most commonly observed in American Cocker Spaniels. It has no clinical significance as long as the hairs do not touch the conjunctiva or cornea.

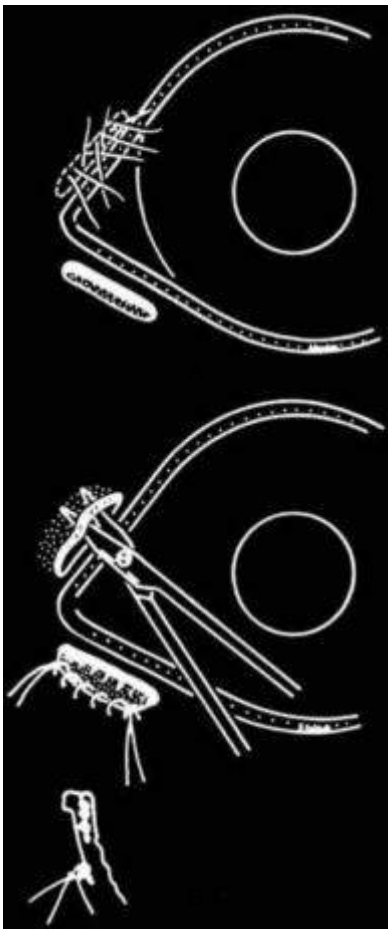


Figure 15.61 Medial canthus or any other displaced trichiasis hairs very near the lid margin (no space for Celsus–Hotz procedure) can also be removed or repositioned by the Stades forced granulation procedure. **A**. The trichiasis area is circumcised and removed. **B**. The outer wound edge is dissected over 3–5 mm and anchored to the subdermal muscular layers by a simple continuous, 6-0 absorbable suture. Advantages: simple and very effective. Disadvantages: open wound directly after surgery; visible scar. Copyright Frans C. Stades.

Redundant Skin Folds around the Eye

Redundant skin folds around the eye, complicated by heavy ears, usually do not directly irritate the eye, but cause pressure on the lid margins and canthi, resulting in medial and upper lid entropion and trichiasis. In breeds such as the Bloodhound, Chow Chow, and Shar Pei, the elderly English Cocker Spaniel, Basset Hound, English Bulldog, and Pug, the wrinkles may cause serious eye problems. In the Bloodhound, Basset Hound, and English Cocker Spaniel, the problem is worsened by the heavy weight of the ear pinnae when the head is turned toward the ground. The palpebral fissure droops and masks the globe, affecting sight. There is usually entropion of both the upper and lower eyelids at the lateral canthus as well as ectropion of the central part of the lower eyelid. The nictitating membrane and the lower

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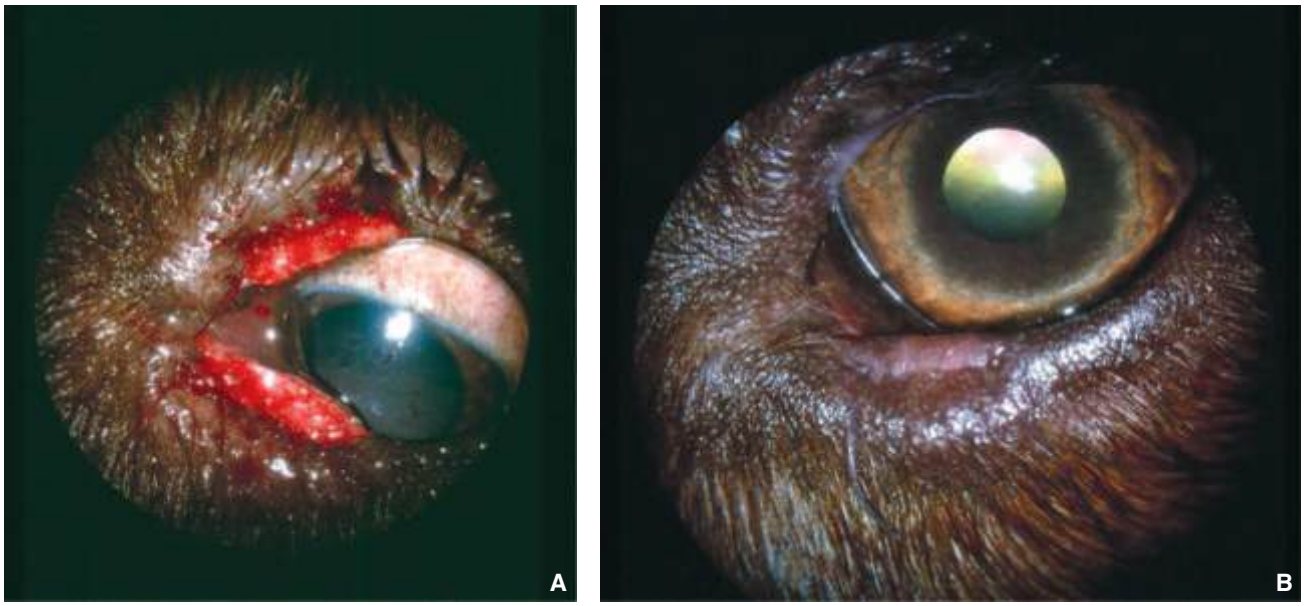


Figure 15.62 **A**. Operative appearance of an English Springer Spaniel with trichiasis near the medial canthus. **B**. Postoperative appearance (about 3 weeks) of the same dog after a Stades forced granulation procedure. Courtesy of Frans C. Stades.

palpebral conjunctiva are exposed, and there is impaired tear film drainage and ocular surface disease.

The irritation results in extra lacrimation and blepharospasm, which may worsen the situation. The hairs on the upper eyelid are dark and moist, and the upper lid margin is entropic. The conjunctiva is red and swollen, and the corneal epithelium is damaged, resulting in ulceration, mainly of the upper lateral part of the cornea, and in rare cases the condition also leads to perforation. Finally, it often results in scarring and pigmentation.

In cases of minor irritation, the cornea may be protected from the trichiasis by an indifferent topical ointment, artificial tears, oil, or petrolatum 2–4 times daily, but this measure alone seldom Courtesy of Frans C. Stades. resolves the problem. A simple Celsus–Hotz entropion correction is rarely sufficient. In breeds such as the Pekingese, Shih Tzu, English Bulldog, and Pug, the removal of the nasal folds will relieve pressure on the medial canthus, but in most patients surgical correction by medial canthoplasty of the medial canthus is much more likely to produce an effective and durable result, and such correction should be attempted as the first option.

Surgical correction of trichiasis prevents further direct irritation (Stades procedure and medial canthoplasty). However, in some cases the pressure on the direct eye adnexa still has to be relieved.

The brow-sling procedure (Fig. 15.63) in breeds like the Shar Pei can be successful (Cairó et al., 2018; McCallum & Welser, 2004; Stuhr et al., 1997; Willis et al, 1999). Recurrences, infections around the sutures, and undesired scarring may cause complications. Furthermore, entropion-trichiasis of the lid margins superior and or inferior generally still have to be corrected additionally. The removal of the upper lateral folds is simple, relieves direct pressure on the dorsolateral part of the eye, and "opens" the face of the patient (Fig. 15.64 and Fig. 15.65).

Removal of 15–20 cm frontal skin, as in Bloodhounds and as advocated by Blogg (1980), can prevent the major wrinkles disturbing the eye. The removal of an elliptical area of skin on the forehead (rhytidectomy) running from the medial canthi to the nuchal crest, as in the elderly English Cocker Spaniel and as described by Bedford (1990), or dorsolaterally of the eye in the Neapolitan Mastiff as described by Steinmetz (2015), does "open" the face (see Fig. 15.65A). Attempts to anchor facial skin to the nuchal crest do not enjoy long-term success. Major "facelifts" can be performed in severe cases, as described by Kása and Kása (1979), although the trichiasis-entropion of the upper lid margin itself still has to be corrected.

The latter four methods do not stop further drooping during the remaining life and do not eliminate the direct trichiasis significantly. Thus, in most patients, surgical procedures directly influencing the palpebral fissure are more likely to produce an effective and durable result, and such correction should be attempted as the first option.

Lid Trauma

Trauma to the lids can be caused by materials contacting or penetrating the lid skin or directly disrupting the lids. Contact trauma to the lids (and deeper structures) may be caused by chemicals such as alkaline and acids such as

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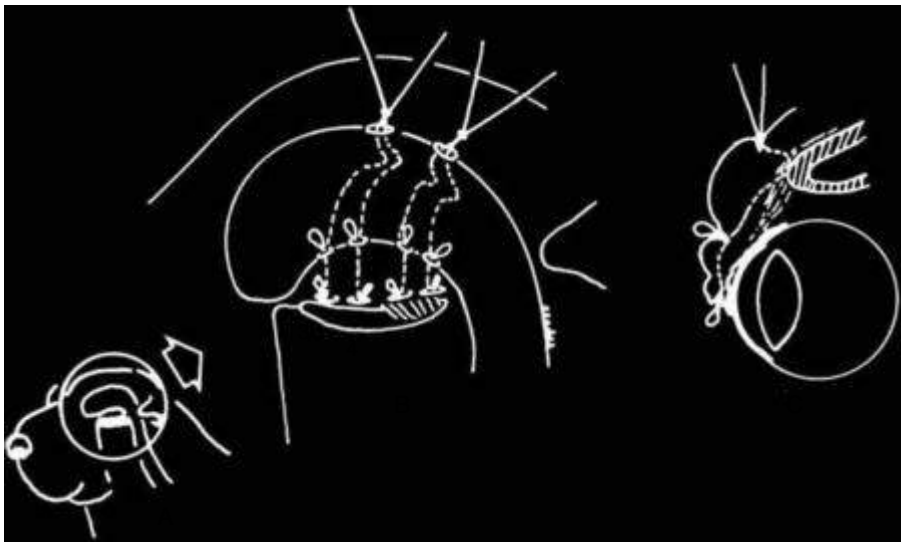


Figure 15.63 **A**. Redundant folds can be lifted utilizing two mersilene strip slings fixed to the temporal bone periosteum (procedure developed by Willis, Martin, Stiles, and Kirschner). Five stab incisions are made above the eye (more or less in the interfold sulci). **B**, **C**. A strip of mersilene on a straight needle is passed from incision 1, via incision 2, to the upper lid stab (3) and parallel to the lid margin to stab (4) back upward via 5, and finally is anchored in the temporal bone periosteum. Advantages: simple and effective. Disadvantages: no effect on the medial canthus; contamination may cause infection around the sling, and overcorrection may cause lagophthalmos; introduction of foreign material. Copyright Frans C. Stades.

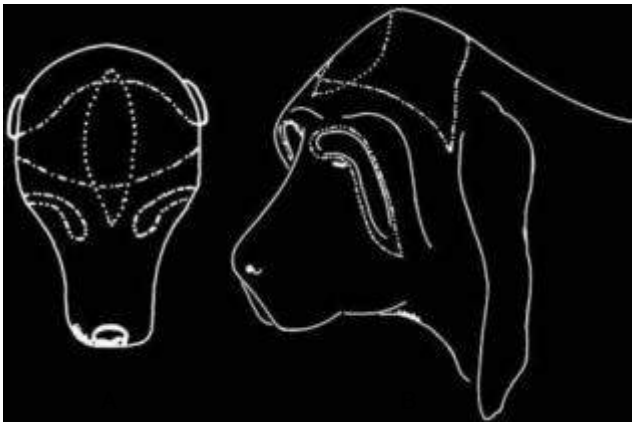


Figure 15.64 Redundant fold correction by removal of (**A**) an elliptic area of the dorsum (Stellate rhytidectomy procedures; Bedford procedure; approximately 5 × 10 cm, dotted line, e.g., in English Cocker Spaniel) of the frontal skin (Blogg procedure; 15 × 20 cm, in Bloodhounds, dot-stripe line), or (**B**) the primary folds dorsolateral of the eye (dot-dot-stripe line), stops the drooping of the skin folds above the eyes. Advantage: simple. Disadvantages: does not prevent direct trichiasis-entropion of the upper lid margin itself; disastrous wound appearance in cases of wound dehiscence. Copyright Frans C. Stades.

battery acid, detergents, and quicklime, caterpillar hairs, and snake bite poison.

Alkaline and acids can cause very severe defects. Acids are slightly less dangerous because they cause precipitation of protein, which hinders a deeper penetration. Alkalis penetrate quickly and cause more severe damage. There is profuse, diffuse edema and there may be hemorrhagic defects and depigmentation (Busse et al., 2015).

The owner must irrigate the eye immediately, preferably with liberal amounts of lukewarm tap water, or any other water available. The first seconds/minutes are by far the most important. In the case of a distinct alkali burn, vinegar or boric acid solutions may be useful. After local anesthesia, the veterinarian can then irrigate the eye for 5–10 minutes with lukewarm 0.9% sodium chloride solution (1–2 L). The conjunctival sac should be examined for possible residues of the injurious material. Aftercare consists of initial choice antibiotics and topical anti-inflammatory agents. Parenteral antiprostaglandins and corticosteroids may be necessary.

In caterpillar trauma, the removal of the hairs by saline hydropulsion and medical treatment by anti-inflammatory drugs was successful in almost all cases (Costa et al., 2016).

In snake bite trauma, blepharoedema, blepharospasm, chemosis, and conjunctival hyperemia occurred in all cases, regardless of the bite location (periocular or ocular). In most cases the clinical signs resolved quickly with symptomatic topical medications and antivenin therapy. However, severe complications such as blindness did occur (Martins et al., 2016).

Disrupting eyelid lacerations caused by dog bites, cat claws, barbed wire, and so on are frequent in young smaller dogs and require surgical repair. Eyelid lacerations may be divided into partial and full-thickness, marginal and nonmarginal, and may include the lacrimal canaliculi. Eyelid and conjunctival sac wounds are often right-angled. Because eyelids are highly vascular, they will usually bleed heavily. The extensive vascularity also protects

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Figure 15.65 **A**. Preoperative appearance of a Chow Chow with a redundant lateral facial fold. **B**. Postoperative appearance of the same Chow Chow after removal of these folds. Courtesy of Frans C. Stades.

against tissue ischemia and necrosis. If the lid edge is transected, the defect will enlarge spontaneously in the lid via contraction of the orbicularis oculi muscle. Lid healing by secondary intention may result in considerable fibrosis and distortion of the eyelids and lid margin, which may eventually require surgical correction. Injuries at a 90° angle to the eyelid margin have a greater potential to affect eyelid function and cosmesis than do injuries parallel to the lid margin.

Wounds in the eyelid should therefore always be sutured directly, even if they are more than 8 hours old. Hair along the wound edges can be clipped. Both the wound in the lid and the wound in the conjunctival sac must be very thoroughly irrigated. A water pick is an excellent method of providing irrigation and wound debridement. Mechanical wound debridement should be kept to a minimum. Loose parts (over 1 mm), especially of the lid margin, should not be excised but used to fill the defect. Reapposition of severely traumatized eyelids usually yields better postoperative results than the excision of still attached but lacerated lid tissues and subsequent reconstructive blepharoplastic surgical procedures.

Sutures at the eyelid margin should have their knots external to the free rim of the lid margin to avoid contact with the cornea. Two layers of sutures may be used in sterile wounds. In contaminated wounds, conjunctival drainage is desirable. The deeper palpebral conjunctiva and tarsus can be closed by simple continuous, 6-0 to 8-0 absorbable suture. Knots should be avoided or placed beneath the conjunctiva. The skin, together with the orbicularis oculi muscle, is closed using simple interrupted, 5-0 to 6-0 nonabsorbable monofilament sutures. Absorbable material may be used in aggressive or anesthesia-risk patients.

The wound in the eyelid margin must be apposed very precisely with a figure-of-eight or mattress (only in thick lid margins) suture. The Meibomian gland openings or gray line are used as a guideline for precise realignment. Horizontal or vertical mismatching (see Fig. 15.9 and Fig. 15.10) of the two parts of the lid margin is unacceptable. Small defects in the conjunctiva rarely have to be sutured. After the lid margin has been closed, the most conspicuous points of the wound (e.g., angles) are brought together with simple interrupted sutures. The remaining parts of the wound are then closed by dividing into halves. The maximal distance between sutures should not be more than 2 mm.

Lacerations of the Medial Canthus, Including the Lacrimal Canaliculus

Lacerations of the medial canthus are rare. They are usually in the lower lid and are accompanied by laceration of the lower lacrimal duct. The canaliculi are located in the swollen wound by intubation and injecting sterile saline and/or air. An S-shaped 000 probe or Worst pigtail probe, preferably with an eye in the tip, is introduced via the upper punctum into the wound (see Chapter 16). A 0.7–1.3 mm diameter circular silicone tubing is used to appose the edges of the canaliculus wounds. The skin wound is closed as described previously. The tubing is left in place for at least 2–4 weeks.

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Lacerations with Loss of Tissue

When there is loss of tissue at the margin of the lid, retraction will enlarge the defect even more. If reconstructive blepharoplasty cannot be performed directly, one or two relaxation sutures should be inserted. Cutting into the tissue by the sutures should be prevented by the use of pieces of silicone or infusion tube. If possible, a blepharoplasty should be performed directly. The house-inverted triangle method is appropriate for closure of a small but deeper defect. Broad, shallow defects should be corrected by an H-plasty. Even larger defects can be closed by rotating, sliding, Z-, or other blepharoplasties.

Aftercare

After surgical repair, the aftercare consists of topical initial choice antibiotic ointment onto the eye and the wound. Some clinicians avoid topical therapy and administer antibiotics only parenterally, and some do both. If contamination is evident and concern about bacterial infection is present, culture and sensitivity tests are indicated. The progression of healing should be evaluated and treatment modified as necessary.

Ptosis

Ptosis is the drooping of the upper eyelid. It may be a consequence of disorders of the third nerve or sympathetic innervation, as in, for example, Horner's syndrome. The cause of the lagophthalmos should be determined and, if possible, treated.

Lagophthalmos

Lagophthalmos is an inability to close the eyelids completely. It may be a consequence of disorders of the facial nerve that lead to paralysis of the orbicularis oculi muscle, or it may be congenital in the prominent-eyed breeds (Pekingese, Shih Tzu, Lhasa Apso, Pug, French Bulldog, and other breeds), as previously described. If lagophthalmos persists, it predisposes to exposure corneal desiccation, resulting in vascularization, granulation, pigmentation, and recurrent ulcerations. Lagophthalmos should be treated medically as a keratoconjunctivitis sicca or by temporary tarsorrhaphy (see "Miscellaneous Eyelid Procedures") until the cause of the lagophthalmos is found and, if possible, cured. If it is evident that temporary therapy is not sufficient, the lid fissure can be shortened permanently (see "Trichiasis," "Medial Canthoplasties"). Medical stimulation of tear formation may also be helpful.

Inflammation

Inflammation of the eyelids may be restricted to one eye or both or may be associated with a generalized dermatologic disease. They may involve only certain glands of the eyelids or involve the entire lid surfaces. Eyelid margins without macroscopic evidence of ocular disease may frequently show histopathologic signs of inflammation, for example blepharitis, meibomitis, or perifolliculitis (64.6%), or even of developing adenomas and melanocytomas (6.4%). The clinical relevance of these changes is not yet understood (Eule et al., 2010).

Generalized Blepharitis

Blepharitis covers a number of inflammatory conditions of the eyelid, often the primary cause being masked to some extent by possible secondary complications. The inflammation may be focal or diffuse with variable involvement of all four eyelids or one or both eyes. Because the eyelids are highly vascular structures, hyperemia and edema are usually marked. Pain is indicated by blepharospasm and excessive lacrimation with epiphora, which may be worsened by self-induced trauma. In addition, there may be exudate, evidence of self-trauma, alopecia, erosion, and scaliness.

Chronic inflammation can lead to eyelid distortion, with both entropion and ectropion resulting from cicatrix formation and secondary corneal and conjunctival diseases. The causes of generalized blepharitis include sebaceous overproduction, bacteria, parasites (especially demodex and scabies), leishmania, fungi, flies, and ticks.

Bacterial Blepharitis

In puppies, a purulent blepharitis occurs as part of juvenile pyoderma or puppy "strangles." The entire skin of the head may be involved with multiple abscesses, usually caused by *Staphylococci* spp. Pain and complicating self-trauma to the face may require an Elizabethan collar. High levels of systemic antibiotics (based on culture and sensitivity) and corticosteroids usually resolve the condition. Topical initial choice or sensitivity test–based specific antibiotics are used to help lubricate and protect the cornea.

Staphylococci and *Streptococci* spp. are most commonly involved in bacterial blepharitis in adult patients (Fig. 15.66). Bacterial blepharitis may be presented as a diffuse superficial lid inflammation, pyogranulomas of the lid subcutaneous tissues, and meibomianitis (discussed later in this section). Acute diffuse blepharitis is characterized by hyperemia, lid swelling, and crusting. Over several weeks, ulceration of the eyelid skin and margins, alopecia, and fibrosis with the development of entropion, ectropion, or a combination of both develop. Abscessation and impaction of the Meibomian glands may also occur. Systemic and topical

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Figure 15.66 Chronic staphylococcal blepharitis in an adult dog. Courtesy of Kirk N. Gelatt.



Figure 15.67 Eyelid pyogranulomas of the upper lid and lateral canthus in a Miniature Poodle. Courtesy of Kirk N. Gelatt.

ophthalmic antibiotics (applied directly to the eyelid skin) based on culture and sensitivity are indicated.

Staphylococcal infections may also involve the deeper parts of the lids and present as single or multiple pyogranulomas (Fig. 15.67; Barrie & Parshall, 1979; Chambers & Severin, 1984; Sansom et al., 2000). Diagnosis is established by histopathologic examination, which reveals microabscesses. Pyogranulomatous blepharitis is treated with systemic and intralesional antibiotics. Because staphylococcal toxins may have a necrotizing effect, topical corticosteroids may be beneficial. Autogenous vaccine can be effective in chronic and seemingly resistant staphylococcal infections (Chambers & Severin, 1984).

Mycotic Blepharitis

Blepharomycosis is uncommon, but infection with *Microsporum* and *Trichophyton* spp. is seen as part of a generalized problem in young dogs. Expanding alopecia, scaling, and hyperemia are the clinical features, and diagnosis is confirmed by staining skin scrapings with either Gram's or Giemsa stain or culturing the organisms on Sabouraud's agar. Effective antifungal therapy may include povidone-iodine scrubs together with topical miconazole nitrate (preferably combined with chlorhexidine). Clotrimazole creams are effective for superficial infection, but care should be taken to avoid corneal contact. Persistent and deep-seated infection may be treated by additionally using itraconazole or terbinafine (Moriello et al., 2017).

Malassezia spp. found on the skin of dogs have been associated with blepharitis, mucoid or mucopurulent ocular discharge, or dogs that were administered topical aqueous-based ophthalmic medications (Newbold et al., 2014).

Parasitic Blepharitis

Both demodectic and sarcoptic mange can include the eyelids, the lesions being characterized by hyperemia, alopecia, and pruritus, and often complicated by secondary bacterial infection and self-trauma (Mueller, 2004; Shipstone, 2000). *Demodex canis* is considered to be a normal inhabitant of hair follicles, sebaceous glands, and sweat glands, and disease may develop only when large numbers of the parasite are present in the presence of immunosuppression or possible inherited T-cell deficiency. In young dogs, the disease tends to be restricted to the face, and eyelid involvement is common (Fig. 15.68). Spontaneous regression is expected, but topical rotenone ointment or isofluorophate ophthalmic ointment can be used to good effect. In older dogs, a more generalized disease is seen, which often proves resistant to treatment. *Sarcoptes scabiei* var. *canis* infection causes intense pruritus, several parts of the body being classically involved in addition to the eyelids. Oral treatment with fluralaner or spot-on treatment with imidacloprid/moxidectin is currently considered as a highly effective initial choice therapy.

Cuterebra infestation has been reported in the conjunctiva of a puppy (Rosenthal, 1975). *Cuterebra* spp., order *Diptera*, family *Cuterebridae*, is a larva of the rabbit or rodent bot fly. Larva involving the lid probably enters the conjunctiva or lid surface; wounds can facilitate penetration. Larva requires about 4 weeks to develop with black cuticular spines, often within a thick-walled abscess and an identifying entry hole. Eventually, the larva pupates and exits the host. Presence of a drainage tract should alert the client to the possibility of *Cuterebra* infestation. Therapy is larva removal, and topical and systemic antibiotics.

Leishmania Blepharitis

Systemic leishmaniasis, a chronic and potentially fatal disease, is endemic in countries around the Mediterranean Sea as well in India and Central and South America. In the Mediterranean region, the protozoan *Leishmania infantum*

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Figure 15.68 Superficial blepharitis associated with demodex infestation in a young dog. Courtesy of Kirk N. Gelatt.

is carried by sand flies (*Phlebotomus* spp.). The clinical signs of leishmaniasis are quite variable, but the eyelids are frequently involved (Di Pietro et al., 2016; Koutinas et al., 1999; Pena et al., 2000; Slappendel & Ferrer, 1998).

In one report, one-fourth of all leishmania cases had ocular or periocular disease. The eyelid lesions may vary from a dry dermatitis with alopecia, diffuse edema, and cutaneous ulcerations, to discrete nodular granuloma formations. Diagnosis is by cytologic or histopathologic examination, serology, or polymerase chain reaction testing. Antileishmania therapy includes subcutaneous *N*-methylglucamine antimoniate (80 mg/kg daily for a minimum of 30 days) and allopurinol orally (10 mg/kg every 12 hours for 6–12 months). Local treatment often includes antibiotics and corticosteroids.

Immune-Mediated Blepharitis

Several autoimmune and immune-mediated phenomena can involve the canine eyelid, either in isolation or in association with systemic clinical features, but are fortunately rare diseases (Ackerman, 1985; Halliwell, 1980; Ihrke et al., 1985; Manning et al., 1980; Marsella, 2000; Olivry & Chan, 2001; Scott et al., 1980, 1982; Walton et al., 1981; White et al., 1992).

The pemphigus group of vesiculobullous epidermal diseases can involve mucocutaneous junctions, with inflammation and ulceration of eyelid tissue being commonly seen. In both pemphigus foliaceus, which is more common, and pemphigus erythematosus, the facial lesions usually involve the eyelids. Pemphigus vulgaris and bullous pemphigoid are more severe but uncommon types of autoimmune dermatoses, and may involve the oral cavity, nail beds, and skin in addition to ulcerative lesions of the eyelids, lips, external nares, and ears. Whereas in pemphigus the lesions are the result of autoantibody production against the intercellular matrix of the epidermis, in bullous pemphigoid these antibodies are directed against the epidermal basement membrane. Hence, the resultant blister formation is observed intradermally or subepidermally, respectively, which can be confirmed by means of dermatohistopathology of skin biopsies or the finding of so-called acantholytic cells at cytology (pemphigus only). The treatment of this disease complex requires long-term systemic and topical corticosteroid therapy. Occasionally, the cicatricial entropion from these diseases may require corrective blepharoplasty. It is also recommended to refer such cases to a dermatologist.

Medial canthal ulcerative blepharitis represents a juxtapalpebral disorder, usually affecting the medial canthus (Fig. 15.69). Breeds most often affected include the German Shepherd, Long-Haired Dachshund, and Toy and Miniature Poodle. In the German Shepherd, the medial canthal blepharitis may be concurrent with pannus (chronic superficial keratitis) and the immune-mediated plasma cell infiltration (plasmocytoma) of the nictitating membrane. In the Long-Haired Dachshund, medial canthal blepharitis may occur concurrent with superficial punctate keratitis. The condition is usually bilateral. Biopsy reveals both lymphocytic and plasma cell infiltration; sebaceous glandular hyperplasia may also be present. Epithelial cell antibodies have been demonstrated in selected cases and may suggest a relation to pemphigus. The condition usually responds to topical ophthalmic antibiotics and corticosteroids.

Vogt–Koyanagi–Harada (VKH), or uveodermatologic syndrome, is another immune-mediated disease that can affect the eyelids and can be presented to veterinary ophthalmologists (Herrera & Duchene, 1998; Morgan, 1989). Often, the loss of pigmentation of the nose and eyelids is the primary clinical sign recognized by the owner and is the basis for the initial examination. Breed predisposition may be important; affected breeds include Akita, Siberian Husky, Golden Retriever, Samoyed, Rottweiler, Chow Chow, Shetland



Figure 15.69 Immune-mediated medial canthal blepharitis in an adult mongrel German hunting dog. The dog also has bilateral chronic superficial keratitis. Courtesy of Frans C. Stades.

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Sheepdog, and others. Because the uveal component of VKH dominates the ophthalmic disease clinically, and the eyelid signs are a minor aspect, the reader should consult Chapter 21 for additional details.

Chalazion

Chalazion is a firm, nonpainful swelling of the Meibomian gland caused by accumulation of secretion that results in chronic inflammation and a granulomatous reaction. The inflammation may predispose to a staphylococcal infection and thus hordeolum formation. Treatment is by scalpel incision along the granuloma with curettage. The incision is allowed to heal by secondary intention. Topical initial choice antibiotic ointment is administered for 7–10 days after curettage.

Hordeolum or Stye

An external hordeolum or stye is caused by suppurative infection of the Zeis or Moll glands and manifests itself as either single or multiple abscess formation along the anterior aspect of the eyelid. External hordeolum affects mainly young dogs; an individual dog may exhibit these lesions over several weeks. Affected lids are usually swollen and painful; focal abscesses occur on the eyelid surface. Treatment consists of hot compresses and topical and systemic antibiotics. During therapy, these abscesses usually rupture. Focal abscesses can be opened by scalpel or cannula incision along the swelling with curettage.

In the hordeolum internum, the eyelid is also swollen and painful. The localized infection can be directly observed within the tarsal "plate," distending the palpebral conjunctiva when the eyelid is everted. Treatment is by scalpel or cannula incision along the swelling, parallel to the margin of the lid, with curettage. The incision is allowed to heal by secondary intention. Topical initial choice antibiotic ointment is administered for 7–10 days.

Focal Blepharitis, Blepharitis Adenomatosa, Meibomianitis, and External Hordeolum

Meibomianitis is inflammation of the Meibomian glands; either or both eyelids can be involved, and the condition may be unilateral or bilateral. The lid is usually swollen and somewhat painful with blepharospasm (Fig. 15.70). Eversion of the affected eyelid permits direct observation of the swollen and often enlarged Meibomian glands. Pressure on the inflamed glands frequently causes expression of exudate from the gland's ducts along the eyelid margin. With persistent meibomianitis, bacterial culture followed by sensitivity tests and cytologic examination may guide the optimal choice of topical and systemic antibiotics. Chronic meibomianitis may result in thickened and fibrotic eyelids with either entropion or ectropion that may require later surgical correction. Chronic meibomianitis can also result in reduction or loss of the lipid layer of the precorneal tear film and a qualitative tear deficiency with normal levels of aqueous tear formation (as measured by the Schirmer's tear test), but an accelerated tear film breakup time with topical fluorescein application. Treatment includes application of hot compresses, possible manual expression of the lesions under topical analgesia, and the use of both topical and systemic antibiotics. Topical and sometimes systemic, sensitivity-tested antibiotics and corticosteroids are administered for 14–21 days.



Figure 15.70 Diffuse meibomianitis of the eyelid in a Miniature Pinscher. Courtesy of Frans C. Stades.

OTHER EYELID DISEASES

Marginal Meibomian cysts are single to multiple small cystic structures that may develop along the eyelid margin. These cysts may occur more frequently in older than in younger dogs and may or may not be associated with Meibomian tumor formation. They can cause local corneal irritation. Therapy consists of manual rupture and topical antibiotics and steroids for 5–7 days.

An allergic blepharitis (Fig. 15.71) is usually characterized by an acute-onset edema and hyperemia, and may be caused by local exposure to a contact allergen or occur as part of a generalized response. Swelling of the eyelids and muzzle will be seen following insect bites (ants, ticks, fleas) and as postvaccinal reaction. Topically applied drugs may be responsible for contact allergy, with neomycin being most commonly involved. Seasonal or nonseasonal reaction to environmental allergens is seen in atopy, in which there is an inherited predisposition to immunoglobin E antibody production (Bedford, 1999a, 1999b; Marsella, 2000; Olivry & Chan, 2001). Several breeds are involved, with the West Highland White Terrier demonstrating especially high incidence. Clinical signs are manifest in young dogs usually from the age of 1 year, and

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Figure 15.71 Allergic, likely parasitic, blepharitis in a Labrador Retriever. The lesions resolved after treatment with systemic corticosteroids for 1 month. Courtesy of Frans C. Stades.

periocular hyperemia, facial pruritus, and conjunctivitis are common. Identification of the specific allergen and desensitization are rarely possible, with treatment relying upon the use of topical and systemic corticosteroids and antihistamines.

Food allergies and systemic drug reactions can cause periocular dermatitis and blepharitis, with the avoidance of the allergen or cessation of the drug therapy being the obvious lines of treatment.

Eyelid Masses and Neoplasia

Inflammatory Masses

Inflammatory masses or pseudotumors of the eyelids are infrequent in dogs and tend to occur in certain breeds. Eosinophilic granuloma is a more frequent condition in cats, but is also described in dogs (Vercelli et al., 2005). This may present as slow progressing granulomatous nodules or plaques, sometimes with yellow-white detritus on them. It is mostly localized not only in the oral cavity but also at the lid margin, or in cats on the cornea. Complete remission usually can be achieved with topical glucocorticoid eye ointment or oral glucocorticoid treatment.

Histocytosis of the Bernese Mountain Dog is a systemic and familial disorder that affects males more often than females (Collins et al., 1992; Moore, 1984; Radgett et al., 1995; Rosin & Moore, 1986; Scherlie et al., 1992). The condition has also occurred in the Rottweiler, Golden Retriever, Labrador Retriever, and Flat-Coated Retriever. This disease manifests in two different forms: (1) a generally slow, cutaneous form; and (2) an aggressive or malignant cutaneous form with eventual multiorgan involvement of the lymph nodes, spleen, and bone marrow. The eyelids are often involved and present as recurrent or persistent nodules, papules, or plaques of upper and lower eyelids. Their surface may be alopecic to ulcerated, and subsequent recurrences tend to be more severe. Biopsy of the masses is usually diagnostic. This disease is unfortunately progressive and fatal.

Nodular fasciitis occurs rarely in the dog and may be most frequent in the Collie and similar breeds (Gwin et al., 1971). In the Collie, the condition affects the eyelids, conjunctiva, episclera, and peripheral cornea. Microscopically, the lesions are characterized as a subcutaneous mass with abundant fibroblasts, variable ground substance, and fiber formation. Inflammatory cells consist of lymphocytes and mononuclear cells, with occasional giant cells. Therapy consists of surgical excision, cryotherapy, and for dogs heavier than 10 kg, oral administration of niacinamide (500 mg every 8 hours) and tetracycline (500 mg every 8 hours), with therapy gradually tapered.

Mesenchymal hamartoma may be found in the eyelid as a benign eyelid mass. A subcutaneous, firm, lobular soft tissue growth ranging in diameter from 0.6 to 3 cm can be found, which in some cases can be adherent to the underlying orbital rim, or be freely palpable between the skin and conjunctiva of the eyelid. The lateral canthus is predisposed. It should be included in the differential diagnoses of benign eyelid masses in dogs. Fine needle aspiration may easily be inconclusive. Therapeutically, it has to be bluntly dissected, which may lead to large defects, necessitating blepharoplasties (Kafarnik et al., 2010).

Lid Neoplasia

In contrast to cats, horses, and cattle, the dog eyelids exhibit a large number of different neoplasms that are fortunately, for the most part, locally minimally invasive and respond to fairly conservative surgical procedures. Distinct metastasis from eyelid neoplasms in dogs has not been reported. Eyelid tumors must be distinguished from conjunctival neoplasms, which tend to be locally invasive, often recur after attempts at surgical excision, and may metastasize.

At least two reports on canine eyelid neoplasms have been published and indicate similar results (Table 15.1; Krehbiel & Langham, 1975; Roberts et al., 1986). Benign neoplasms outnumber malignant tumors by a ratio of about 3 : 1. The epithelial tumors outnumber the mesenchymal tumors by a ratio of about 5 : 1. Most eyelid tumors occur primarily in dogs over 10 years old, and no gender predisposition has been reported. The upper lid is affected slightly more often than the lower lid. Breeds reported as having increased prevalence of lid tumors include the Beagle, Siberian Husky, and English Setter in one report, while Bedford in the UK reports the Toy and Miniature Poodle, Labrador Retriever, and Golden Retriever as overrepresented (Bedford, 1999a, 1999b). However, these numbers were not corrected for the frequencies of the

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Table 15.1 Histologic classification and frequency of canine eyelid neoplasms.

Tumor Classification	N = 202 (%)	N = 200 (%)
Sebaceous adenoma	28.7	60
Squamous papilloma	17.3	10.6
Sebaceous adenocarcinoma	15.3	2.0
Benign melanoma	12.9	17.6
Malignant melanoma	7.9	2.8
Histiocytoma	3.5	1.6
Mastocytoma	2.5	1
Basal cell carcinoma	2.5	1.2
Squamous cell carcinoma	2	1
Fibroma	2.1	–
Fibropapilloma	1	–
Lipoma	1	–
All others (less than 1% individually)	3	1
Undetermined	0.5	1.2
Benign	73.3	87.8
Malignant	26.7	8.2

Source: Data from Krehbiel & Langham (1975) and Roberts et al. (1986).

breed in the population. The largest group of neoplasia arising from the Meibomian glands are the adenomas and adenocarcinomas (Barron, 1962; Buyukmihci & Karpinski, 1975; Krehbiel & Langham, 1975; Roberts et al., 1986). These tumors are first noticed erupting through the eyelid margin or the palpebral conjunctiva just behind the eyelid margin (Fig. 15.72A). They may be pink or have varying degrees of pigmentation and may appear as multiple lobes. With exposure, advanced Meibomian adenomas or adenocarcinomas may ulcerate and even hemorrhage. They can cause local irritation resulting in blepharospasm, epiphora, conjunctival hyperemia, corneal vascularization, and pigmentation.

Melanocytic neoplasias of the eyelid are the second-largest group of tumors and appear as two distinct types (Gwin et al., 1976a, 1976b, 1982; Wang & Kern, 2015). One type arises from the eyelid skin and is usually a single or multiple pigmented mass, which can generally be excised with low recurrence rates. The second type arises from the pigmented eyelid margin and tends to expand to both directions (Fig. 15.73). These tumors are more aggressive locally, and their removal involves the eyelid margin, which must then be restored. Again, these melanomas behave more benignly than melanomas in the conjunctiva, mouth, or other sites and can be treated successfully by one or more attempts at surgical excision. The surgery site may also be treated by cryosurgery following excisional surgical biopsy.

Fibromas and fibrosarcomas are less prevalent but can be locally invasive. They appear as gradually enlarging subcutaneous masses. Other masses affecting the lid subcutaneous tissues are mastocytoma, or mast cell sarcoma, and lipomas. Squamous cell carcinoma rarely affects the canine eyelid; it appears as either a surface proliferative or ulcerative lesion (Barrie et al., 1982). Histiocytomas affect mainly young dogs, appearing often as rapidly proliferative masses. These tumors may spontaneously regress over a few weeks.

Firm masses with swollen hyperemic lids and ulcerated skin overlying the mass, extending from the palpebral conjunctiva to the eyelid margin at the medial canthus, may be identified as granular cell tumors (Lu & Dubielzig, 2012).

Papillomas represent about 10%–20% of lid tumors, and if combined with oral papillomatosis affect young dogs. These tumors may have a viral origin, but autogenous vaccines have been of limited value. These lid tumors often regress with time and are removed only when tumor-induced corneal contact and irritation result. In rare cases they may transform into malignant squama cell carcinomas (Wiggans et al., 2013). Surgical excision followed by cryosurgery decreases recurrence (Barrie et al., 1982; Gwin et al., 1976a, 1976b).

Therapy

Therapies for the canine lid tumors include surgical excision, debulking plus cryosurgery (Zibura et al., 2019), cryosurgery, or a combination of these. Most veterinary ophthalmologists prefer surgery. Recurrence rates after surgery (15%) and cryosurgery (11%) were not significantly different in one study, but the time for recurrence after surgery was 28.3 months compared to 7.4 months after cryosurgery (Collins & Collins, 1994; Holmberg, 1980).

Surgical procedures depend on the size and site of the eyelid mass and the involvement of the lid margin (Aquino, 2007; Blogg & Turner, 1994; Bussieres et al., 2005; Carter, 1970; Esson, 2001; Gelatt & Blogg, 1969; Gwin, 1980; Hamilton et al., 1999; Lewin, 2003; Munger & Gourley, 1981; Mustardé, 1981; Pavletic et al., 1982; Peiffer, 1979; Pellicane et al., 1994; Poinsard et al., 2019; Stades, 1987a, 1987b; Szentimrey, 1998). In general, eyelid neoplasia are best removed early, when the resultant surgical defect is small. Larger masses result in more extensive defects that require greater reconstruction. Lid masses removed at surgery should be submitted for histopathologic examination and the surgical margins closely examined for the possible tumor. Masses that involve the medial canthus, lacrimal puncta, or both can be excised, but with greater difficulty.

In high risk cutaneous malignancies, such as on suspicion of a mast cell tumor, narrow removal and direct histopathology (Mow's micrographic surgery) enable identification of the tumor type and the margins. This allows an optimal surgical margin assessment, blepharoplasty method, and provides the lowest recurrence rate (Bernstein et al., 2013).

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Figure 15.72 **A**. Preoperative appearance of an adenoma in the lateral upper eyelid in a 9-year-old Dalmatian. **B**. Postoperative appearance in the same dog after a four-sided wedge or "house-shaped" removal of the tumor. Courtesy of Frans C. Stades.



Figure 15.73 Multiple melanomas of the lower lid margin in a mixed-breed dog. Courtesy of Frans C. Stades.

Hyperthermia, cryotherapy, and carbon dioxide laser therapy have been reported for canine lid tumors. Cryosurgery is best monitored with thermal couples within and adjacent to the mass to measure the extent of freezing (Collins & Collins, 1994; Grier et al., 1980; Holmberg, 1980). Laser ablation can successfully treat Meibomian gland adenomas, but because lid margin loss occurs often, apposition of the wound post laser is recommended (Bussieres et al., 2005; Swinger & Carastro, 2006).

When the surgical defect approaches or exceeds 50% of the upper eyelid, a semicircular skin flap can be constructed to permit medial movement to increase the size of the resultant palpebral fissure. When 60%–90% of the eyelid is involved with neoplasia, more extensive blepharoplastic procedures are required for successful treatment (presented in the subsequent section).

The usual postoperative treatment after the excision of small lid masses is topical antibiotics, eventually combined with topical corticosteroids. The Elizabethan collar or other protective devices (e.g., Optivizor) are useful to prevent the patient from rubbing and possibly interrupting the surgical wound. The most frequent result after these procedures is the development of an obvious V notch at the eyelid margin. This can usually be avoided by use of the four-sided procedure.

Reconstructive Blepharoplasty

Reconstructive blepharoplasty includes the different surgical procedures to restore the lids after extensive defects resulting from congenital defects or abnormalities, trauma, or the removal of scar tissues and neoplasia (Blogg & Turner, 1994; Carter, 1970; Esson, 2001; Gelatt & Blogg, 1969; Gwin, 1980; Hamilton et al., 1999; Lewin, 2003; Munger & Gourley, 1981; Mustardé, 1981; Pavletic et al., 1982; Pellicane et al., 1994; Stades, 1987a, 1987b; Szentimrey, 1998). The limits of these surgical procedures depend on the skill and imagination of the surgeon. The basic blepharoplastic procedures include sliding skin and pedicle grafts, tarsoconjunctival grafts, pedicle skin or skin and muscle grafts, full-thickness eyelid grafts – also called the bucket-handle or Beard–Cutler technique (Cutler & Beard, 1955); see also "Tarsoconjunctival Grafts and Whole Lid Grafts" – and full-thickness grafts from the upper to lower lid. All of these procedures, with occasional modifications, are applicable to all animal species.

These procedures have several general principles. The upper lid is more mobile than the lower lid, is the most important lid to cover the cornea, and is essential for most of the blink reflex. The upper lid is also larger than the lower lid and a potential donor of autogenous tarsoconjunctiva, myocutaneous, or full-thickness lid tissues. Only the lateral

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upper lid margin of the dog contains eyelashes or cilia; transplantation of these cilia follicles from the same or fellow upper eyelid has not been described, but is technologically simple with insertion of a strip of cilia follicles into a V-shaped furrow about 5 mm deep in the recipient upper lid. Lid surgeries involving the medial canthus must consider the upper and lower lacrimal puncta; if a punctum is to be sacrificed, the lower carries the majority of the tears into the nasolacrimal system and should be spared if possible. The lid margin is the most important in blepharoplasty and is sometimes the most difficult area to restore. Fibrotic eyelid margins can cause considerable corneal and conjunctival discomfort and damage. The posterior aspects of the skin graft may be lined by conjunctival cells spontaneously, possibly with more scarring, or can be lined with mucosa from adjacent palpebral conjunctiva, buccal mucosa, or an island graft from bulbar conjunctiva of the opposite eye. However, these methods are more time-consuming and may result in traction bands (also in the area where the graft is harvested) and secondary leading-edge entropion.

The lower conjunctival fornix is critical to tear collection and movement to the lacrimal punctum. Adequate blunt dissection and tissue undermining are important to reduce tension on sutures, but should be minimized to reduce trauma and postoperative swelling, and possibly comprising blood supply to the lid. Lid flaps and grafts should be handled minimally during surgery because they rapidly swell. They tend to contract postoperatively, and should always be constructed slightly larger than the defect to allow for shrinkage. Immediate postoperative dressings can be used to apply limited pressure to fresh grafts and reduce the swelling, hemorrhage, and serum accumulation. An E-collar is necessary when eyelid dressing and sutures are in place to prevent self-damage to the surgical site. Most blepharoplastic procedures can restore adequate lid function following large congenital, traumatic, and surgery defects, but they may not completely restore the lid appearance to normalcy.

"House-Inverted-Triangle" or "Triangle-Triangle" Blepharoplasty

The most simple and effective procedure is the "triangle-triangle," or more precisely "house-inverted-triangle," blepharoplasty for the correction of smaller but relatively deeper lid margin defects (e.g., after removal of an adenoma), leaving an intact lid margin in the center of the eye (besides the scar) and an artificial lid margin (A to B) laterally. When the stretched lid fissure reaches less than 33 mm after closing of the defect, this is the first-choice method to add some lid margin length (Fig. 15.74).

Depending on the lid laxity, eyelid masses involving up to 25% of the eyelid length may be excised by scalpel or scissors as a wedge of full-thickness lid, shaped either as a V or as a four-sided defect (Gelatt & Blogg, 1969; Gwin, 1980; Hamilton et al., 1999). The V (thus cutting some Meibomian glands obliquely) or four-sided (house shape, cutting the lid margin in a rectangular-shaped excision) wedge excision is performed by scissors and/or scalpel and should be at least one Meibomian gland or 1 mm beyond the tumor margins (Fig. 15.74). Closure is by one (or two) layers. The deeper tarsoconjunctival layer can be apposed by simple continuous, 6-0 to 8-0 absorbable sutures with the knots buried. The eyelid margin is apposed with a figure-of-eight or U-figure suture (see Fig. 15.9), using 5-0 or 6-0 monofilament or

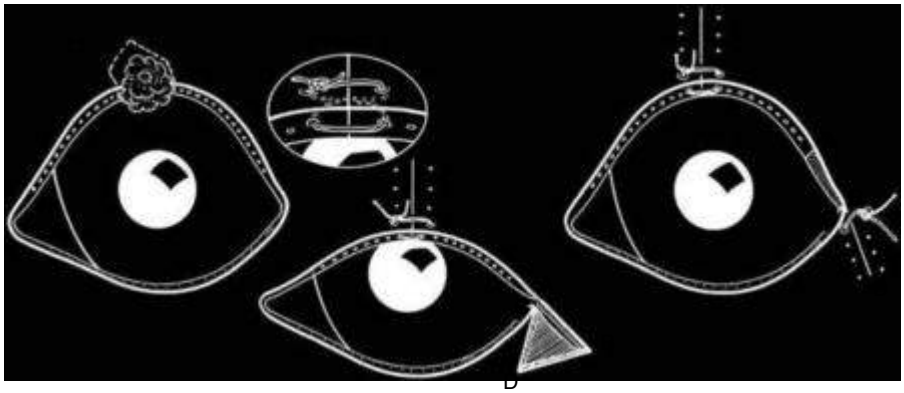


Figure 15.74 "Triangle-triangle," or more precisely "house-inverted-triangle," blepharoplasty for the correction of smaller but relatively deeper lid margin defects (e.g., after removal of an adenoma), leaving an intact lid margin in the center of the eye (besides the scar) and an artificial lid margin (A-B) laterally. When the stretched lid fissure reaches less than 33 mm after closing of the defect, this is the first-choice method to add some lid margin length. The "house"-formed defect after the tumor removal is sutured by a figure-of-eight suture at the free rim and further by simple interrupted, 5-0 to 6-0 monofilament nylon sutures. If the defect is in the upper lid, the suture ends are tied together, thus preventing corneal irritation. After removal of the skin triangle *CDB* (always pointing in the opposite direction to the defect), B is apposed to C. Note that the canthotomy wound *AB* is full-thickness, follows a continuous lid margin line, and is left open to become an artificial lid margin. Advantages: simple, effective, no scarred new lid margin at the tumor removal site. Disadvantage: small, open wound laterally directly after surgery. Copyright Frans C. Stades.

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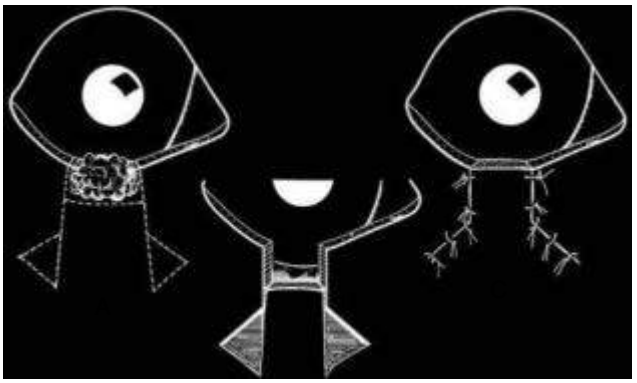
polyfilament absorbable or nonabsorbable suture material, sometimes including the upper eyelid for extra support. The lid margin is most important because the greatest tension occurs at this single suture. For this reason, the use of a round-body needle, at the least in the lid margin, is preferred over a triangular or spatula cutting needle. The remaining muscle–skin lid is apposed with simple interrupted, 5-0 to 6-0 (non-)absorbable mono- or polyfilament sutures. The four-sided wedge technique offers the advantage of accommodating a larger surgical approach, and all of the muscle–skin sutures share equally in the wound tension and prevent an obvious notch postoperatively. As in the simple V-wedge technique, closure is in one or two layers. Depending on the affected lid laxity after these wedge procedures, a permanent relief lateral canthotomy may be necessary.

Sliding Skin Graft or H-Figure Plasty

The sliding skin graft, consisting of the thin lid skin and limited depths of the orbicularis oculi muscle, is the most basic blepharoplastic procedure. The technique can be applied to the entire lower and upper lids and lateral canthus, and can restore the lid length to preoperative size. Pedicle rather than sliding grafts are used for medial canthal defects because tissues in this area are very firmly attached to the deeper tissues. Sliding skin grafts generally are used for full-thickness lid defects, but can also be used to replace the outer lid tissue layers following extensive trauma or removal of a superficial neoplasm (Fig. 15.75). The adjacent deeper layers of the orbicularis oculi are separated from the sliding skin graft to permit movement of the graft into the surgical defect. If this tissue dissection is incomplete, contract of the graft may occur, resulting in postgraft ectropion, trichiasis, and distortion of the lid margin. The sliding skin incision should be larger than the surgical defect to accommodate tissue shrinkage; small triangles of skin (Burow's triangles) are excised to prevent puckering of the graft's base (Fig. 15.75B). The posterior aspects of the skin graft may be lined by conjunctival cells spontaneously, or can be lined with mucosa from adjacent palpebral conjunctiva. If the available local conjunctiva is inadequate, free-hand conjunctival grafts from the fellow eye or mucosal grafts from the mouth may be used. The skin graft is positioned slightly higher than the adjacent lid margins to accommodate graft contraction (Fig. 15.75C and Fig. 15.76). Sutures attaching the conjunctiva to the sliding skin graft should not touch the cornea; interrupted mattress sutures are often used, especially at the lid margin. Counterpressure with a partial to complete temporary tarsorrhaphy is sometimes indicated to maintain the opposite lid sliding skin graft in position and ensure the best postoperative results.

Sliding Skin and Myocutaneous Grafts

When an eyelid surgical defect approaches one-third or more of the eyelid length, a rotation skin graft, rotation skin graft



B

Figure 15.75 H-figure sliding graft for broader defects: after full-thickness excision of the eyelid neoplasm. **A**. Two slightly diverging skin incisions are continued from the base of the wound. These skin incisions should be 1.5–2 times the length of the defect's height. **B**. Two equal-sized triangles (Burow's triangles) of skin are excised to facilitate shifting the graft into the surgical wound. **C**. After careful subcutaneous dissection under the skin graft, the flap is moved into the wound. The leading edge of the skin graft should be 0.5–1.0 mm bulging into the contour of the adjacent eyelid margin. The skin graft is secured by simple interrupted, 5-0 to 6-0 nonabsorbable monofilament sutures starting at the angled area. The sutures should pull the flap forward to the lid margin (1–2). Advantages: simple and effective. Disadvantages: small, open wound directly after surgery; scarred new lid margin. The posterior aspects of the skin graft can be overgrown by conjunctival cells spontaneously or can be lined with mucosa from adjacent palpebral conjunctiva, buccal mucosa, or an island graft from bulbar conjunctiva of the opposite eye. However, these methods are more time-consuming and may result in traction bands (also in the area where the graft is harvested) and secondary leading-edge entropion. Copyright Frans C. Stades.

(Mustardé procedure), sliding outer lid margin (Landolt) graft, or caudal auricular axial pattern flap may be used to close the defect (Fig. 15.76, Fig. 15.77, Fig. 15.78, Fig. 15.79, Fig. 15.80, Fig. 15.81, and Fig. 15.82; Degner, 2007; Esson, 2001; Jacobi et al., 2008a, 2008b; Munger & Gourley, 1981; Mustardé, 1981; Pavletic et al., 1982; Pellicane et al., 1994; Stades, 1987a, 1987b; Stanley et al., 2010; Stiles et al., 2003). In the semicircular flap procedure, a curved skin–orbicular oculi incision is extended laterally, and the flap is separated from its deeper tissues. The flap is then shifted medially to appose the lid defect. Conjunctival mucosa may be used to line the deeper flap's surface. Surgery results appear promising.

Sliding Z-Plasty

A modified sliding myocutaneous graft for the upper eyelid at the lateral canthus is the sliding Z-plasty (Gelatt & Blogg, 1969; Gwin, 1980). In this procedure, after *en bloc* excision of the neoplasm involving the lateral aspects of the upper eyelid, incisions including skin and some orbicularis oculi muscles are made in the form of triangles, which are then excised (Fig. 15.83). The Z-graft is then advanced to replace the missing eyelid margin. The posterior aspects of the skin

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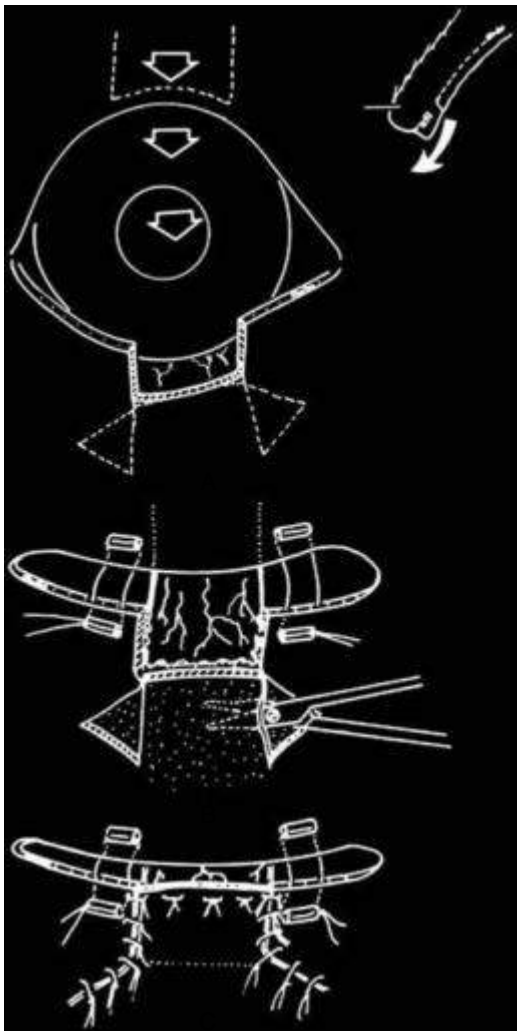


Figure 15.76 A sliding skin graft involving one eyelid may be combined with tarsoconjunctival grafts from the upper eyelid or vice versa. **A**. The lower eyelid neoplasm has been excised full-thickness. The upper tarsoconjunctival graft is constructed to be slightly larger than the lower lid defect. About 2 mm above the eyelid margin, a palpebral conjunctiva and tarsus pedicle graft is prepared by tenotomy scissors. **B**. The tarsoconjunctival graft is secured in the lower lid defect by simple continuous, or interrupted, 5-0 to 6-0 absorbable suture(s). **C**. The lower lid sliding skin graft is prepared. A temporary complete tarsorrhaphy is performed to immobilize the graft sites. The skin sutures are removed in 10–14 days. The tarsorrhaphy sutures are removed in 3–4 weeks, and the base of the tarsoconjunctival graft is transected by tenotomy scissors. The upper tarsoconjunctival defect is allowed to heal by secondary intention. Disadvantages: much more time-consuming and complicated, two-step procedure than alternative methods; open wound directly after surgery; scarred new lid margin. Copyright Frans C. Stades.

graft may be lined by conjunctival cells spontaneously or can be lined with adjacent conjunctival mucosa.

Tarsoconjunctival Grafts and Whole Lid Grafts

Tarsoconjunctival grafts are similar to sliding skin grafts, but are the deep aspects of the lid. Combinations of the sliding

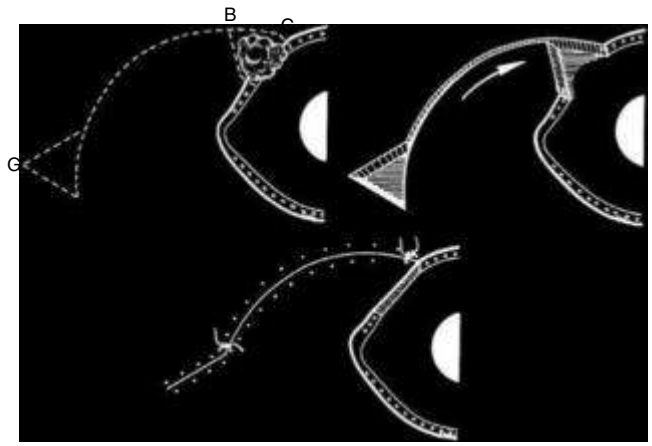


Figure 15.77 Rotation skin graft for larger defects in the lid margin. The radius of the circle must be twice the length of the lid margin defect. After careful subcutaneous dissection under the skin graft, the flap is moved into the wound. The leading edge of the skin graft should be 0.5–1.0 mm bulging into the contour of the adjacent eyelid margin. The skin graft is secured by simple interrupted, 5-0 to 6-0 nonabsorbable monofilament sutures starting at F–H, thus relieving tension on the flap. Further interval sutures should pull the flap into the direction of the lid margin. The posterior aspects of the skin graft may be lined by conjunctival cells spontaneously, or can be lined with mucosa from adjacent palpebral conjunctiva, buccal mucosa, or an island graft from bulbar conjunctiva of the opposite eye. However, these methods are more time-consuming and may result in traction bands (also in the area where the graft is harvested) and secondary leading-edge entropion. Advantage: effective. Disadvantages: more time-consuming; open wound directly after surgery; scarred new lid margin. Copyright Frans C. Stades.

skin and tarsoconjunctival grafts include the entire lid thickness and most often involve transplantation of part of the upper lid to lower lid defects (Fig. 15.84). A 5–7 mm strip of the upper lid margin is avoided during upper to lower lid transplantation to ensure upper lid function and cosmesis. This procedure is referred to as the bucket-handle or Beard–Cutler technique.

Recently, a human Hübner's tarso-conjunctivo-marginal graft technique has been described in dogs for repairing eyelid margin defects after tumor resection involving between one-quarter and two-thirds of the length of the eyelid (Poinsard et al., 2019). Harvesting of the graft with a length of half the length of the tumor, including its free margins, was performed via a full-thickness incision on the ipsilateral healthy eyelid. The cutaneous layer and all of the muscle fibers of the transplant were meticulously removed except for a 3 mm strip along the free lid margin. A full-thickness tumor excision was then performed. The graft was sutured at the level of the defect to be reconstructed. A sliding H flap was generated. The resulting nourishing myocutaneous flap was then sutured along the free margin of the tarso-conjunctivo-marginal graft. The lateral edges of the advancement flap were sutured to the edges of the receiving sites, resulting in a stretched lid fissure length that was shortened by 7–11 mm. This tarsomarginal

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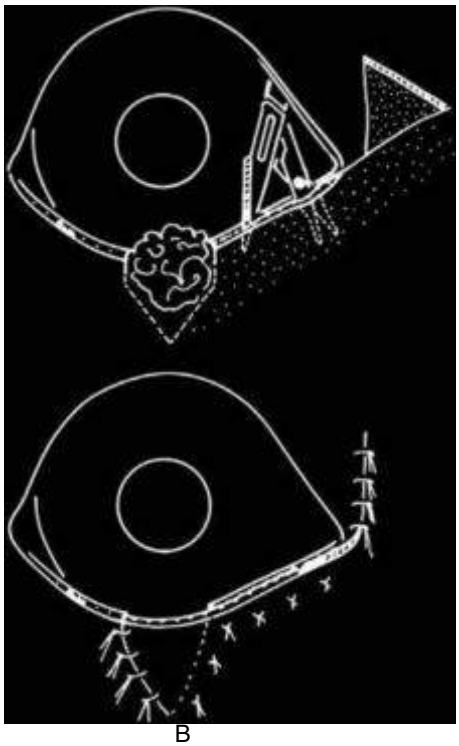


Figure 15.78 Sliding skin–outer lid margin flap (Landolt) for larger, deeper defects. **A**. After lid splitting, a large flap of 10 to 15 mm depth is dissected, and a relaxation triangle is removed at the end of the wound. **B**. The sliding skin–outer lid margin flap is secured by simple interrupted, 5-0 to 6-0 nonabsorbable monofilament sutures. Advantage: effective. Disadvantages: more time-consuming; open wound directly after surgery; scarred new lid margin. Copyright Frans C. Stades.

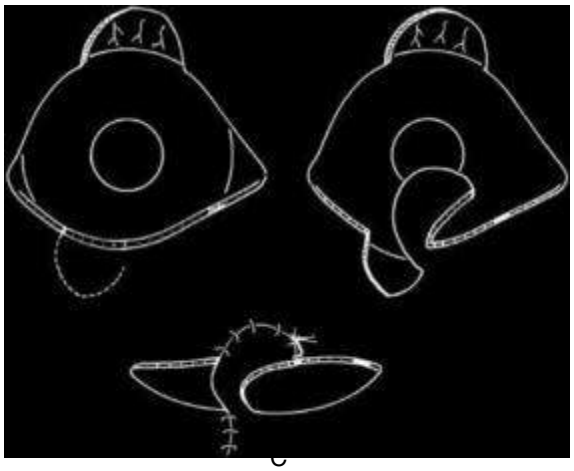


Figure 15.79 Rotation skin graft, Mustardé procedure in a central defect. **A**. Outline of the area to be used as donor tissue. **B**. Creation of a flap to fill the defect in the upper eyelid. **C**. Lower eyelid tissue sutured into upper eyelid defect. This procedure shortens the lid fissure, which later should be corrected by a canthoplasty procedure. A temporary tarsorrhaphy will prevent wound dehiscence. Disadvantages: time-consuming, two-step procedure; shortens lid fissure after enlargement; scarred new lid margin. Copyright Frans C. Stades.

grafting technique has yielded encouraging results in dogs. The few complications that were encountered were mainly the development of keratitis or suture dehiscence.

Miscellaneous Eyelid Procedures

In tarsorrhaphy procedures, portions of or the entire eyelids are apposed, either temporarily or permanently. In the partial procedures, only part (medial, central, or lateral) of the palpebral fissure is closed, thereby permitting vision by the patient, daily inspections by the veterinarian, and topical medication of the eye as well as keeping the eye in its orbit. If the indication was luxation or proptosis of the globe in brachycephalic breeds such as the Pekingese, after opening, a medial canthoplasty (tarsorrhaphy) must be considered as a preventive measure against recurrence.

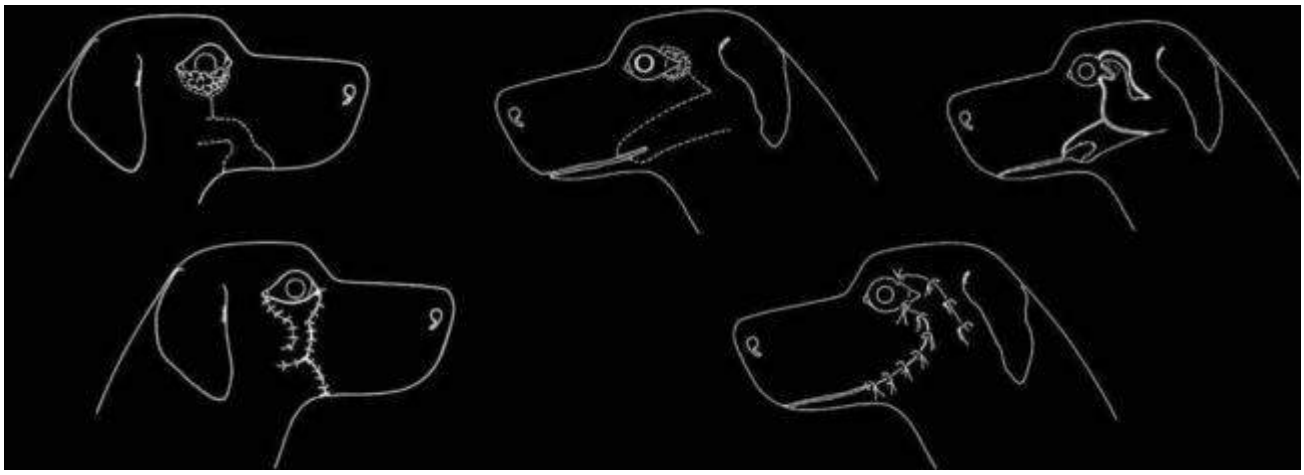
In permanent tarsorrhaphy procedures, all or parts of the eyelid margins of the upper and lower eyelids are excised; they grow together and remain sealed for extended periods of time or indefinitely. Partial permanent tarsorrhaphies are indicated to treat long-term ocular disorders, such as neuroparalytic keratitis, neurotropic keratitis, lagophthalmos, and chronic proptosis and exposure keratitis. Complete permanent tarsorrhaphies are part of the enucleation and exenteration procedures after removal of the eye and the orbital contents.

Temporary Tarsorrhaphy

The partial temporary tarsorrhaphy is used frequently after conjunctival and corneal surgery to reduce the eyelid trauma to the surgical site and provide some contact and pressure to fresh grafts or to keep contact lenses in place. The complete temporary tarsorrhaphy is indicated for the treatment of traumatic proptosis, after most orbitotomies, after many extensive eyelid procedures, after nictitating membrane flaps, after extensive conjunctival surgery, to treat premature opening of the eyelids, to help maintain collagen shields or soft contact lenses, and for the treatment of recurrent corneal erosions and other selected superficial corneal disorders. Complete temporary tarsorrhaphies are also indicated when upper eyelid function is impaired and the development of exposure keratitis is anticipated.

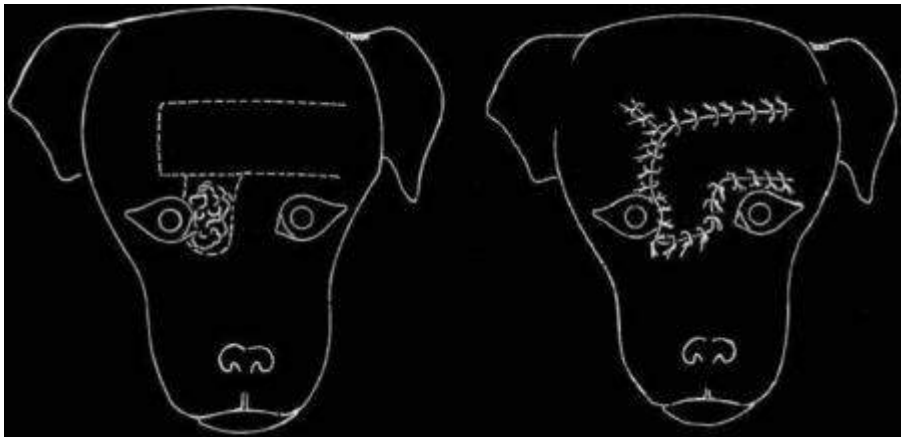
A temporary tarsorrhaphy is performed by placing 1–3 horizontal mattress sutures (5-0 or 6-0, cutting, micropoint, or round-body needle) on the required area, using, for example, silicone or infusion tubing to prevent the suture from cutting into the skin (Fig. 15.85). Mattress sutures are used to close the lid fissure. Sutures placed too far from the lid margin can cause entropion. Sutures placed through the conjunctiva may result in an "egg-slicing" effect of the suture to the cornea. After days or weeks, the sutures are removed (the medial first, if proptosis was the indication; if

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A B

Figure 15.80 **A**. Rotational graft using the dog's upper lip for large defects of the lower eyelid. Note that the pedicle has to be rotated 180° into the lower lid defect. **B**. Rotational graft using the dog's lip commissure for large defects of the lower eyelid and the lateral canthus, as described for the correction of aplasia or coloboma of the upper lid by Whittaker et al. (2010). Copyright Frans C. Stades.



A B

Figure 15.81 Caudal axial pattern flap for the reconstruction of medial eyelid defects, as described by Jacobi et al. (2008). **A**. A superficial axial pattern or transposition flap based on the opposite vascular pedicle is created and transposed into the defect. **B**. The subcutaneous tissues are apposed with several interrupted absorbable sutures, followed by a simple continuous pattern suture, and a drain is placed. Thereafter, the skin is closed. Copyright Frans C. Stades.

there is still an apparent tendency to luxation, the remaining suture is left in place for a longer period). The suture ends in the temporary tarsorrhaphies may be left long to facilitate occasional adjustment of the suture pressure as well as occasional loosening to open the tarsorrhaphy and inspect the eye.

Permanent Tarsorrhaphy

In permanent tarsorrhaphy procedures, all or parts of the eyelid margins of the upper and lower eyelids are excised and, after apposition by sutures, the "eyelids" grow together and remain sealed for extended periods of time or indefinitely. Medial or lateral partial, permanent tarsorrhaphies are indicated for diseases such as trichiasis, chronic exposure keratitis, and recurrent central corneal ulceration in the brachycephalic breeds (Fig. 15.86).

Aftercare consists of administration of an appropriate antibiotic ointment for 10 days. If the indication for the procedure has been healed, the tissue bridge can be transected. The wounds close spontaneously. Complete, temporary tarsorrhaphy constitutes a barrier to topical medication of an eye, but subpalpebral systems can be inserted in the dorsolateral or lateral conjunctival fornix at the conclusion of

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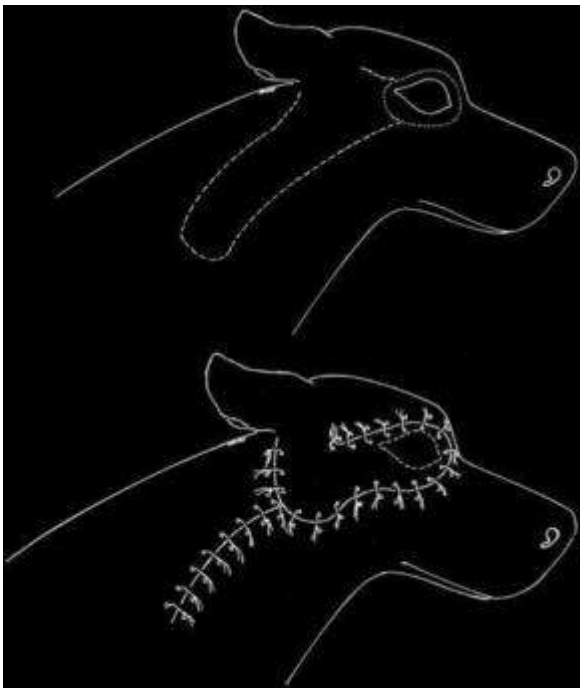


Figure 15.82 Caudal auricular axial pattern flap, as described for the closure of large defects, for example, after orbital exenteration by Stiles et al. (2003). **A**. The base of the flap was centered over the lateral aspect of the wing of the atlas. A flap of about 7 cm by 16 cm, including skin and the platysma muscle, is rotated ventrally into a bridging incision ventral to the ear, between the flap and the orbit, and sutured in place (**B**). As the exact course of the arterial supply varies, the distal portion of the flap is more vulnerable to avascular necrosis. Copyright Frans C. Stades.

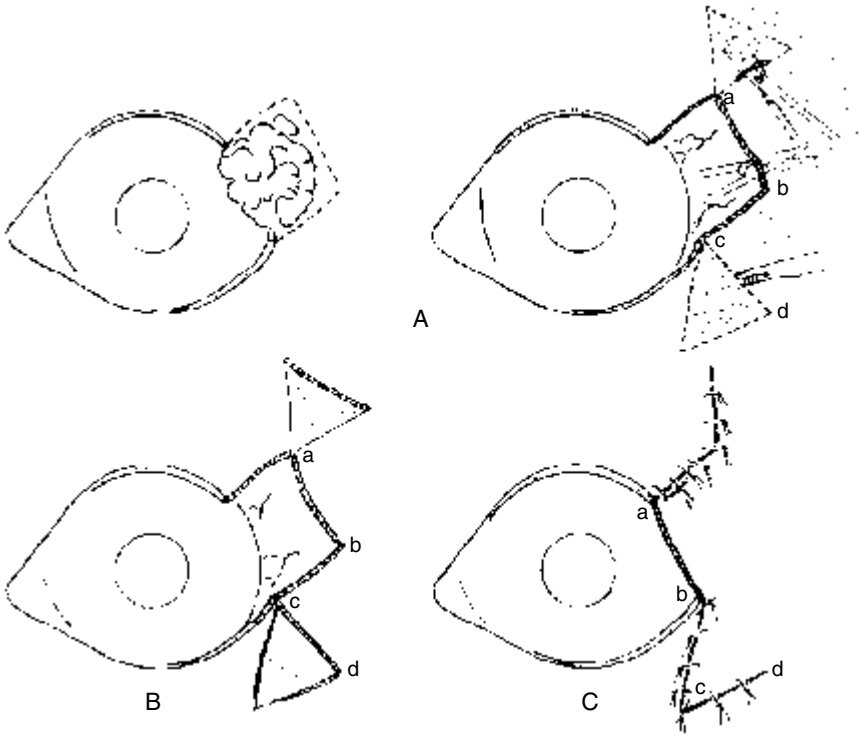


Figure 15.83 The Z-plasty procedure is a modified sliding skin graft for lateral canthal defects. **A**. After removal (full-thickness) of the mass by tenotomy scissors from the lateral portion of the upper eyelid, the subcutaneous tissues in the lateral canthus are dissected bluntly and two equal-size triangles of skin are excised. **B**. The skin flaps are slid into position. Note that both *ab* and *cd* can be used as the leading edge of the graft, depending on the availability of skin dorsally or laterally. **C**. The flaps are secured by simple interrupted, 5-0 to 6-0 nonabsorbable monofilament sutures. Advantage: effective. Disadvantages: time-consuming; open wound directly after surgery; scarred new lid margin. The posterior aspects of the skin graft may be overgrown by conjunctival cells spontaneously or can be lined with mucosa from adjacent palpebral conjunctiva, buccal mucosa, or an island graft from bulbar conjunctiva of the opposite eye. These latter methods may result in traction bands (also in the area where the graft is harvested) and secondary leading-edge entropion. Copyright Frans C. Stades.

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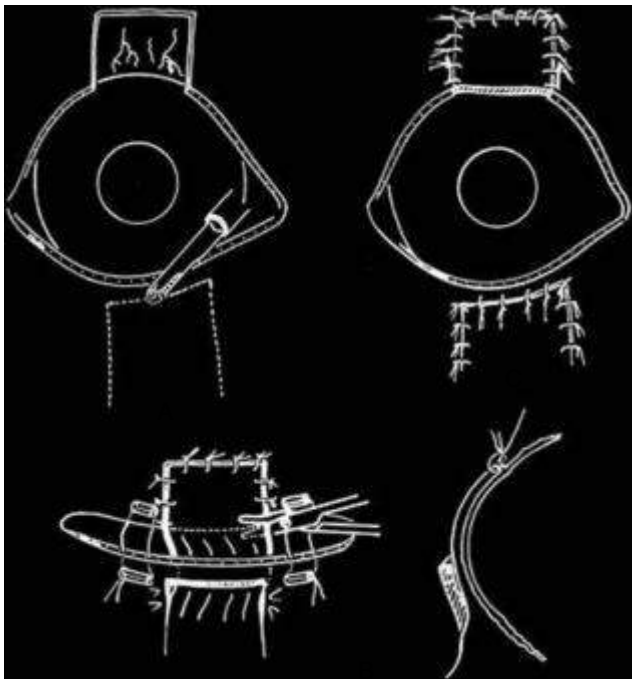


Figure 15.84 For full-thickness eyelid (bucket-handle or Cutler–Beard technique) grafts, either the lower or upper eyelid may be used as the donor. **A**. The full-thickness lid graft is constructed about 4 mm from the eyelid margin and should be 0.5–1 mm larger than the surgical wound. **B**. The lower lid graft is positioned under (deep to) the strip of remaining lower lid margin and secured in the upper lid defect by two layers of sutures. The tarsoconjunctival layers are apposed by a simple continuous, 5-0 to 6-0 absorbable suture. The skin–orbicularis oculi layer is apposed by simple interrupted, 5-0 to 6-0 nonabsorbable sutures. A complete temporary tarsorrhaphy is performed to stabilize the graft site. After 3–4 weeks, all the skin and tarsorrhaphy sutures are removed, and the base of the full-thickness lid graft is transected (1). **C**. The upper lid edges are reapposed by simple interrupted, nonabsorbable 4-0 to 6-0 sutures. Advantage: effective. Disadvantages: very time-consuming, complicated, two-step procedure; open wound directly after surgery. Copyright Frans C. Stades.

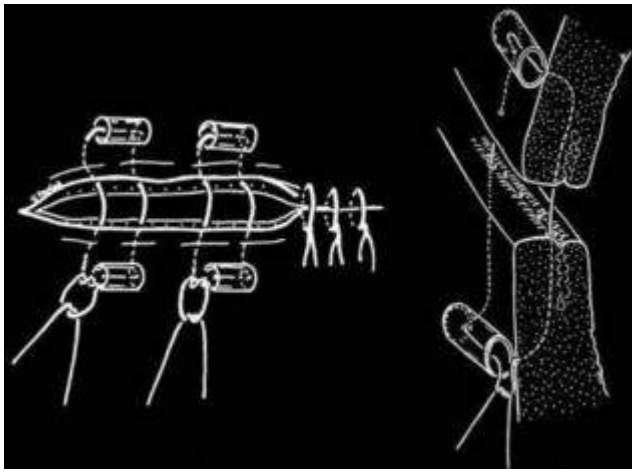


Figure 15.85 Temporary tarsorrhaphy. After, for example, a canthotomy and repositioning of a luxated or proptosed globe, a temporary tarsorrhaphy can be performed, seen from the front (**A**) and in section (**B**). The lid fissure is closed by two or three U-figure sutures, prevented from cutting into the skin by, for example, infusion tubing. Copyright Frans C. Stades.

surgery to ensure delivery of ophthalmic solutions. The apposed eyelids may also retain the topical solutions in contact with the cornea for longer periods of time, thereby increasing their effectiveness.

Postoperative Care and Complications after Tarsorrhaphy

The most frequent complications immediately after temporary tarsorrhaphy techniques are variable swelling of the eyelids and suture contact with the cornea. Thus, patients should be examined daily or every other day. If the sutures become too tight, local eyelid necrosis and irritation result. If the sutures become too loose, "egg-slicing" suture contact to the cornea may occur. Routine use of a protective E-collar postoperatively in small animals is important and effectively prevents self-trauma to the surgical site.

The most frequent postoperative complications after permanent tarsorrhaphy are related to excessive tension on the lid sutures for the short term and wound failure for the long term. Chronic tension may result in gradual weakening and atrophy of the surgical apposition site. Dehiscence within the first few weeks postoperatively is usually repaired by debriding the wound edges and apposition with additional sutures.

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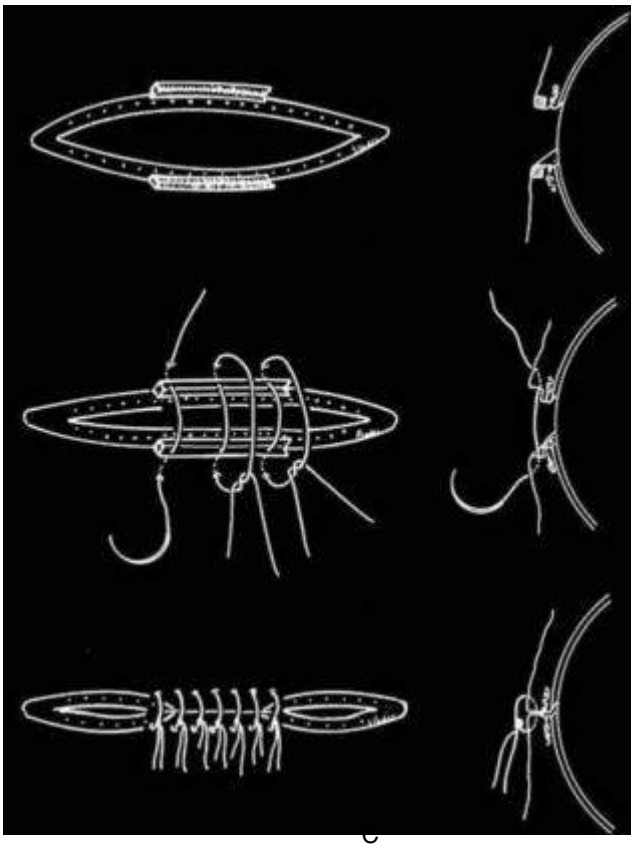


Figure 15.86 Permanent central tarsorrhaphy, seen from the front and in section, for long-term closure of the lid fissure. In the center of the lid, over 10–15 mm, the outer free rim of the margin of upper and lower lids is incised by scalpel and removed by tenotomy scissors (**A**). The opposite skin wounds are apposed by simple interrupted, 5-0 to 6-0 sutures (**B**), forming a bridge of skin over the intact free inner rims of the upper and lower lids (**C**). Copyright Frans C. Stades.

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Diseases and Surgery of the Canine Nasolacrimal System

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Introduction

The nasolacrimal duct system of the dog is similar to that of most domestic animals. It is a thin-walled conduit that drains the tear film from the eye into the nasal passages. This chapter reviews the embryology, anatomy, physiology, and diagnostic procedures of the canine nasolacrimal system. The clinical manifestations for both congenital, developmental, and acquired diseases and the appropriate medical and surgical management of each disorder are described.

Embryology

The nasolacrimal duct system develops from surface ectoderm within the nasolacrimal groove (i.e., furrow), which separates the lateral nasal fold and the maxillary process (Fig. 16.1A) (Arey, 1974). Ectodermal cells grow along this groove, sink into mesenchyme, and become buried. These cells form a cord as the maxillary process fuses with the lateral nasal fold between days 22 and 26 of gestation in the dog (Fig. 16.1B) (Noden & de Lahunta, 1985). The ectodermal cords grow toward the nasal cavity and the eye, and eventually, they extend from the eyelid to the inferior nasal passage (Noden & de Lahunta, 1985). The upper end of this cord develops two buds, which grow into the upper and lower eyelid near the medial canthus (Fig. 16.1C) and develop into the superior and inferior canaliculi and puncta. The cord becomes a duct through a process of canalization and normally is patent at birth (Noden & de Lahunta, 1985).

Anatomy

The superior and inferior puncta are oval to slit-like openings that measure approximately 1 mm by 0.3 mm, with their long axis parallel to the lid margin (Evans, 1993; Getty, 1975). They are located on the palpebral conjunctiva at the edge of the upper and lower eyelids 2–5 mm from the medial canthus, approximately where the tarsal glands end (Fig. 16.2A). The puncta are the openings to the superior and inferior canaliculi. The canaliculi are approximately 4–7 mm in length and 0.5–1.0 mm in diameter (Getty, 1975). They extend through the orbicularis oculi muscle, and they join together ventral to the medial canthus to form the lacrimal sac, which lies within a slight depression (i.e., the lacrimal fossa) in the lacrimal bone. The lacrimal sac is poorly developed in the dog; it is simply a slight dilation at the beginning of the nasolacrimal duct (Evans, 1993). The nasolacrimal duct itself is constricted as it traverses the lacrimal bone (Lavach, 1993), and the constricted region is important in retention of foreign bodies and development of dacryocystitis in the dog. The duct then passes through a canal on the medial surface of the maxillary bone and ends in a nasal punctum. The nasal puncta are usually located in the ventral lateral nasal meatus, opening approximately 1 cm inside the external nares (Fig. 16.2B). In approximately 50% of dogs, the nasolacrimal duct has a second opening in the oral mucosa of the central hard palate, behind the incisors at the level of the canine teeth (Severin, 1995). The nasolacrimal duct is approximately 1 mm in diameter, and the length varies considerably between brachycephalic, mesocephalic, and dolichocephalic dogs (Gelatt & Gelatt, 2011). Brachycephalic breeds often have short nasolacrimal ducts and they often drain the tears into the pharynx. The nasolacrimal ducts are lined with tall, pseudostratified columnar epithelium (Fawcett, 1994).

Physiology

The sole purpose of the nasolacrimal duct system is to drain tears from the surface of the eye to the nasal passages. Evaporation, which varies with environmental conditions, removes a significant portion (approximately 25%) of tears

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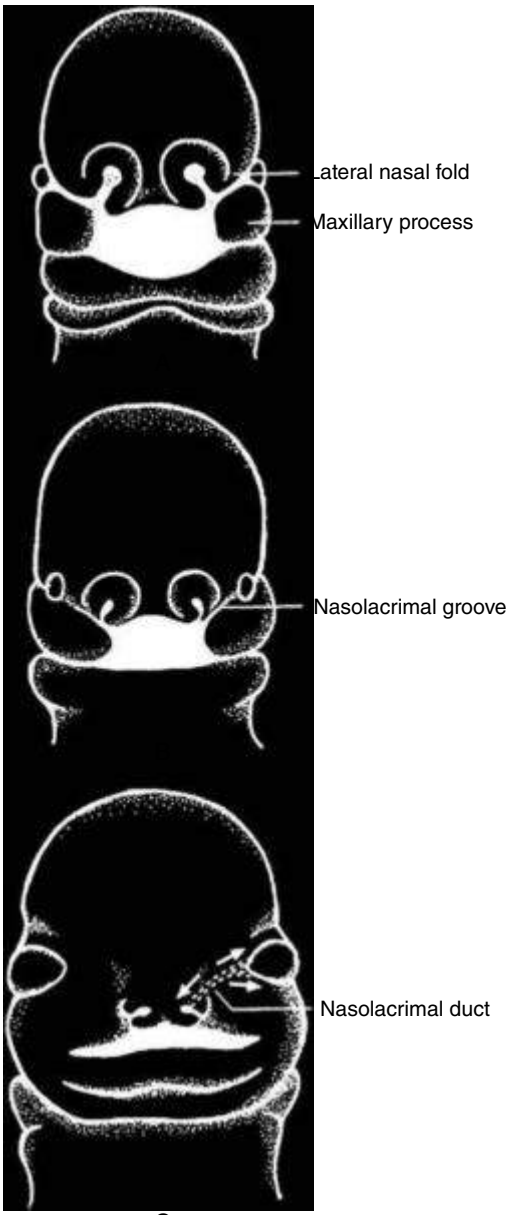


Figure 16.1 Embryologic development of the canine nasolacrimal system. **A.** Note the nasolacrimal groove between the lateral nasal fold and the maxillary process at approximately day 21 of development in the dog. **B.** The lateral nasal fold fuses with the maxillary process between days 22 and 26. This fusion buries the surface ectoderm cells, which will grow and form the nasolacrimal duct system. **C.** The ectodermal cells form a cord with two proximal processes that extend toward the medial upper and lower eyelid, whereas the distal end grows toward the nostril. This ectodermal cord canalizes and becomes a duct and canaliculi shortly after birth.

from the ocular surface before drainage can occur (Lemp & Wolfley, 1992). Drainage through the nasolacrimal system occurs as a result of multiple forces. Most (at least 60%) of the tear volume is normally drained through the inferior puncta

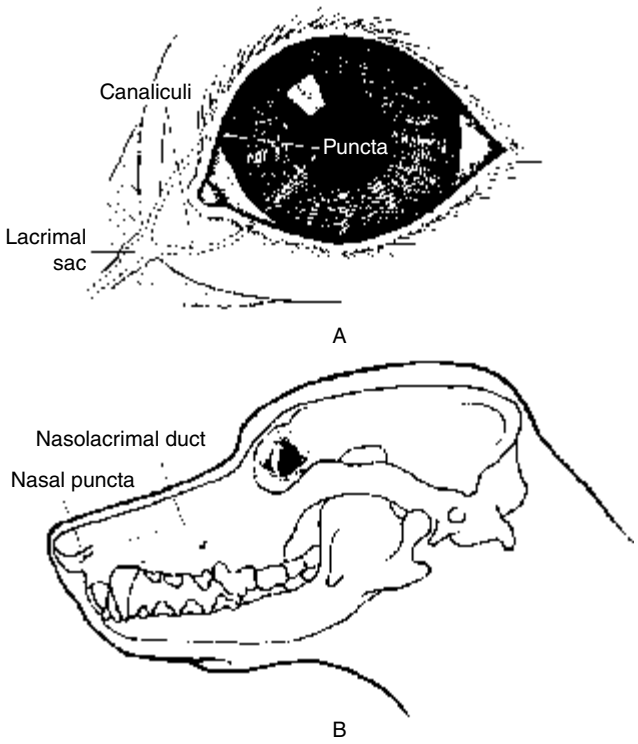


Figure 16.2 **A, B.** Gross anatomy of the canine nasolacrimal duct system. Note the relationship of the eyelids, puncta, canaliculi, lacrimal sac, nasolacrimal duct, and nasal puncta.

and canaliculi (Lemp & Wolfley, 1992). Tears flow ventrally in response to gravity and they are pulled into the canaliculi during eyelid closure because of reduced intracanalicular pressure (Doane, 1981). This reduced pressure develops as these thin-walled ducts are compressed by contraction of the orbicularis oculi muscle. In addition, capillary action and siphon effect from the lacrimal sac pull tears through the canaliculi and duct (Doane, 1981; Gelatt, 1991b; Gelatt & Gwin, 1981; Hill et al., 1974a, 1974b; Lemp & Wolfley, 1992).

Mucosa-associated lymphoid tissue has been reported in human nasolacrimal drainage systems (Knop & Knop, 2001). This lacrimal drainage-associated lymphoid tissue is part of the common mucosal immune system, and T cells, B cells, and plasma cells were confirmed with immunohistochemistry within the walls of the nasolacrimal ducts and canaliculi (Knop & Knop, 2001). In addition, basal mucous glands were associated with the lacrimal canaliculi (Knop & Knop, 2001). It is hypothesized that the main and accessory lacrimal glands, conjunctiva, and lacrimal drainage system are an integrated system and that the mucosal-associated lymphoid tissues in these are connected, and recirculation of lymphocytes within this system is likely (Knop & Knop, 2001). In addition, the lacrimal drainage mucosal-associated lymphoid tissue may be connected to the ocular surface and lacrimal glands via a neural reflex arc that may influence ocular surface integrity (Knop & Knop, 2001). The nasolacrimal

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ducts have also been reported to produce natural peptide antibiotics, which may have a therapeutic benefit in dacryocystitis; however, they may also be detrimental because they induce scarring and dacryostenosis (Paulsen et al., 2001). Mucosa-associated lymphoid tissue and production of natural peptide antibiotics has not been reported in the dog, but they are likely present in animals.

Clinical Manifestations of Nasolacrimal Disease

Disorders of the nasolacrimal duct system in the dog may be congenital, developmental, or acquired, and they are limited to a lack of patency or inflammation. The clinical manifestations of nasolacrimal system disease include: epiphora; mucopurulent punctal, conjunctival, and nasal discharge; swelling of the ventral medial canthal region; punctal foreign bodies; and draining fistula in the medial canthal region (Fig. 16.3, Fig. 16.4, and Fig. 16.5).

Epiphora is the most common clinical manifestation. Epiphora develops secondary to obstructions of tear flow through the nasolacrimal duct system (see Fig. 16.3 and Fig. 16.4) or to an overproduction of tears (i.e., lacrimation), in which the tear volume overwhelms the normal drainage system. Mucopurulent punctal and ocular discharge (Fig. 16.5), conjunctivitis, and draining fistulas from the duct system may develop secondary to nasolacrimal sac inflammation (i.e., dacryocystitis).

Diagnostic Procedures

Several diagnostic procedures allow clinicians to establish an accurate diagnosis of obstruction or inflammation of the nasolacrimal duct system or epiphora secondary to increased lacrimation. These include: the Schirmer tear test (Gelatt et al., 1975); slit-lamp biomicroscopy; cytology and microbial culture of punctal discharge (Lavach et al., 1977; Murphy, 1988); fluorescein dye passage test (Jones, 1961); normograde punctal and canalicular cannulation, and lavage (Gelatt, 1981, 1991a; Severin, 1972); nasal punctal cannulation and retrograde flushing (Gelatt, 1981, 1991b; Severin, 1972); endoscopy (Strom et al., 2018), dacryocystorhinography (DCG) (Gelatt et al., 1972;



Figure 16.3 A 12-week-old Papillon puppy with bilateral inferior punctal atresia, resulting in marked epiphora.



Figure 16.4 Tear-staining syndrome in a 10-month-old American Eskimo dog. The clinical manifestation was bilateral tear staining and epiphora. Abnormalities noted on biomicroscopic examination included medial caruncular trichiasis, subtle medial ventral entropion, tight medial canthal ligaments, and mild eyelid trichiasis.



Figure 16.5 A superior punctal and canalicular foreign body that was causing dacryocystitis in a 2-year-old Lhasa Apso. Note the mucopurulent ocular discharge and conjunctivitis.

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Yakely & Alexandra, 1971); ultrasonography (Alper et al., 1994; Barsotti et al., 2019; Jedrzynski & Bullock, 1994; Pavlidis et al., 2005); computed tomography (CT) (Divaris, 1995; Loftus et al., 1996; Massauld et al., 1993; Nykamp et al., 2004; Rached et al., 2011); magnetic resonance imaging (MRI) (Amrith et al., 2005; Goldberg et al., 1993; Hoffman et al., 1999; Kirchof et al., 2000; Manfre et al., 2000; Rahangdale et al., 1995; Rubin et al., 1994; Takehara et al., 2000); and lacrimal scintigraphy (Wearne et al., 1999).

Schirmer Tear Test

The Schirmer tear test should be the first diagnostic test completed during examination of a dog with epiphora. It estimates total reflex aqueous tear production; volumes from dogs in excess of 25 mm/min are consistent with the diagnosis of stimulated lacrimation. Lacrimation may overwhelm a functional nasolacrimal duct and result in epiphora. The causes of increased lacrimation vary, and they relate to diseases that cause red eye (e.g., conjunctivitis, keratitis, scleritis, uveitis, glaucoma, orbital cellulitis); the diagnoses of and therapy for those diseases are discussed elsewhere in this book.

Slit Lamp Biomicroscopy

Biomicroscopic examination of the superior and inferior puncta for patency, size, and location of the punctal openings is an essential component of the ocular examination. The puncta are normally oval to slit-like openings of 1 mm by 0.3 mm, with their long axis parallel to the lid margin (Evans, 1993; Getty, 1975). They are located on the palpebral conjunctiva at the edge of the upper and lower eyelids 2–5 mm from the medial canthus. Punctal atresia and micropunctum of the ventral punctum commonly cause epiphora in dogs. Misplacement of the ventral puncta and displacement caused by medial ventral entropion may also be associated with epiphora.

Cytology and Microbial Cultures

Cytology as well as both aerobic and anaerobic bacterial and fungal culture reveals inflammatory cells, foreign bodies, and microbial content of mucopurulent ocular discharge. These laboratory evaluations may be completed on the discharge expressed from puncta, canaliculi, and skin fistulae, or on that flushed from the nasolacrimal duct system of dogs with dacryocystitis, before application of topical anesthetics or stains. Bacterial opportunists, including *Staphylococcus* sp., *Streptococcus* sp., *Proteus* sp., and *Escherichia* sp., are often cultured from the nasolacrimal duct system of dogs with dacryocystitis (Lavach et al., 1984). Bacterial cultures from within the diseased nasolacrimal system often differ significantly from those taken from the conjunctiva around the punctum, thus prompting culture during surgery (Blicker & Buffam, 1993; MacEwen et al., 1994). Fungal dacryocystitis has been reported in humans (Arstenstein et al., 1993; Bessler et al., 1994; Purgason et al., 1992), but not in the dog.

Fluorescein Dye Passage

Fluorescein dye passage (i.e. Jones test) is the primary test of patency. It involves placing liquid fluorescein dye on the cornea and conjunctiva, and after several minutes have elapsed, both the nasal area (Fig. 16.6) and pharynx are examined with cobalt-filtered or ultraviolet light to confirm dye passage and duct patency. In a study evaluating fluorescein nasolacrimal transit times in normal dogs, transit times were highly variable, ranging from 2 to 840 seconds, with cephalic conformation, snout length, and reproductive status affecting the result. The test was found not to be of clinical use in brachycephalic dogs because most of these dogs did not show dye passage at the 30-minute test cut-off (Binder & Herring, 2010). Failure of passage to the nares may be an indication of physiologic or functional inadequacy of the nasolacrimal duct system. However, false negatives occur and a normograde nasolacrimal duct flush is frequently required to confirm patency.

Nasolacrimal Flushing

A 24-gauge intravenous catheter or nasolacrimal cannula (Fig. 16.7 and Fig. 16.8) is preplaced on a 3 mL syringe



Figure 16.6 A positive left- and negative right-nasal fluorescein dye passage test in a 1-year-old mixed-breed dog with right inferior punctal aplasia.

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Figure 16.7 A 24-gauge intravenous catheter inserted in the ventral punctum of a 1-year-old King Charles Cavalier Spaniel.

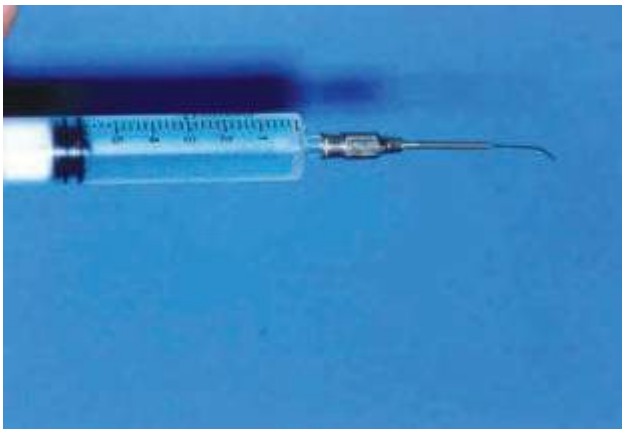


Figure 16.8 A 24-gauge nasolacrimal cannula, which may be used for punctal and canalicular cannulation in the dog. The soft, flexible nature of the intravenous catheter makes it ideal for punctal cannulation; however, small puncta in toy breeds may require the smaller diameter nasolacrimal cannula.

containing a commercial eye wash, and a drop of topical anesthetic is applied to the conjunctiva. The punctum and canaliculus are cannulated and a small volume of eye wash is injected while observing the contralateral punctum. When fluid passes through the opposite punctum, it is gently occluded with finger pressure, and continued injection into a normal nasolacrimal duct system will produce eye wash at the nostrils or induce swallowing as the solution flows into the pharynx. Retrograde nasolacrimal duct flushing is performed when a normograde flush is not successful. In most dogs, general anesthesia is required before cannulation of the nasal punctum and retrograde flushing can be completed. After anesthesia is induced, a nasal speculum is inserted into the nostril and is directed ventrally. Rhinoscopy may also be useful in locating the nasal punctum (Strom et al., 2018). The nasolacrimal duct punctum is located at the junction of the floor and lateral wall of the nare. Similar to anterograde flushing, a 24-gauge intravenous catheter preplaced on a 3 mL syringe is inserted and a small volume of eye wash is injected.

Radiographic and Other Imaging Examinations

Lateral and ventrodorsal open-mouth nasal radiographs are useful in evaluation of the nasal bones along which the nasolacrimal duct passes. The nasolacrimal ducts are vulnerable to traumatic laceration, erosion, or compression by infectious and neoplastic processes (Fig. 16.9).

Results of DCG will confirm nasolacrimal duct patency (Gelatt et al., 1972; Yakely & Alexandra, 1971). To perform DCG, the superior and inferior lacrimal canaliculi are cannulated using a 22-gauge catheter for large breed dogs and a 24-gauge catheter for small breed dogs. The catheters are sutured in place to ensure a tight seal in order to prevent leakage of the irritating contrast agent on the cornea. To protect the cornea further, lubricating corneal gels are applied at this time. Next, 2–4 mL of iodinated contrast media is injected. Radiographs are obtained as the dye passes through the nasolacrimal duct system (Fig. 16.10). Perforations or blockages of the nasolacrimal duct are readily detected on these images (Fig. 16.11).



Figure 16.9 Ventrodorsal, open-mouth radiograph of a dog showing increased density of the left nasal cavity and deviation of the nasal septum into the right nasal cavity. These radiographic signs are consistent with a diagnosis of a left nasal neoplasm. Results of endoscopic biopsies, light microscopy, and CT scan confirmed the diagnosis of nasal carcinoma with compression of the left nasolacrimal duct. Blockage of the duct resulted in left epiphora, which was the presenting clinical sign.

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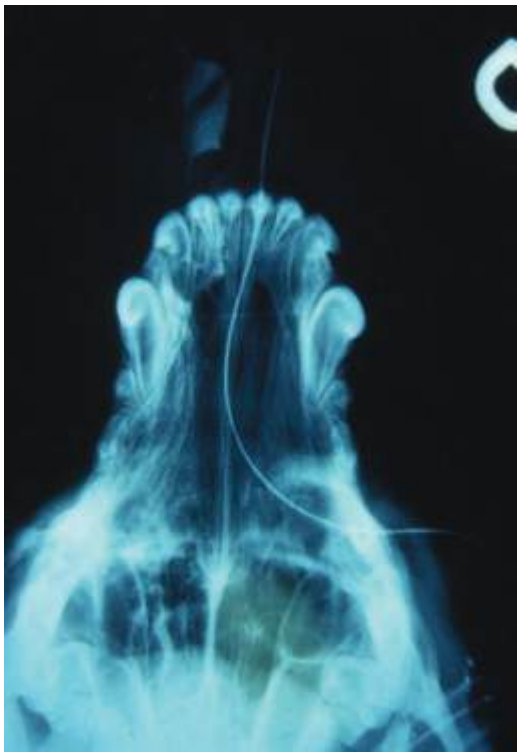


Figure 16.10 Dacryocystorhinogram of a normal dog. Note contrast media is visible throughout the nasolacrimal apparatus.

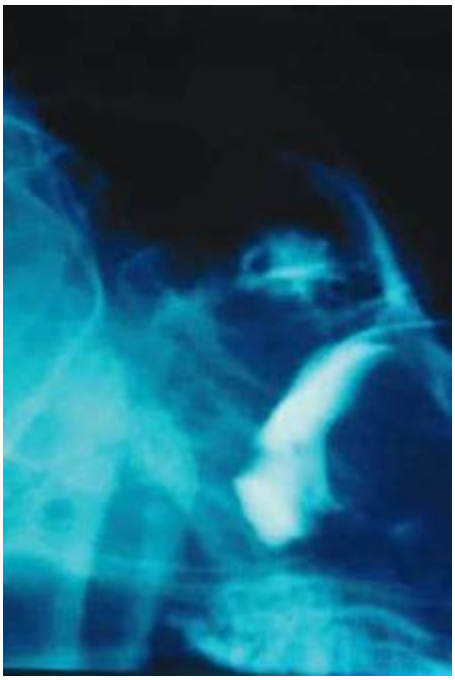


Figure 16.11 Dacryocystorhinograph of an obstructed nasolacrimal duct in a dog. Note the distended nasal lacrimal duct is filled with contrast media.

Advanced imaging studies (i.e., ultrasonography, CT, MRI, and scintigraphy) (Alper et al., 1994; Amrith et al., 2005; Barsotti et al., 2019; Divaris, 1995; Goldberg et al., 1993; Hoffman et al., 1999; Jedrzynski & Bullock, 1994; Kirchof et al., 2000; Loftus et al., 1996; Manfre et al., 2000; Massauld et al., 1993; Nykamp et al., 2004; Pavlidis et al., 2005; Rached et al., 2011; Rahangdale et al., 1995; Rubin et al., 1994; Takehara et al., 2000; Wearne et al., 1999) are also useful to confirm compression and occlusion of the nasolacrimal duct system. In addition, they are useful to determine the extent of primary disease in the nose and orbit (Fig. 16.12). Ultrasonography is not commonly utilized in evaluation of the nasolacrimal system but has been reported as a diagnostic modality in humans (Alper et al., 1994; Jedrzynski & Bullock, 1994; Pavlidis et al., 2005, Rached et al 2011). Ultrasonography of the medial canthus utilizing a multifrequency linear probe (8–14 MHz) was recently reported as useful for identification of foreign bodies in the lacrimal sac of dogs (Barsotti et al., 2019).

CT-DCG is reported in humans and dogs and is a superior imaging modality compared with conventional radiography (Divaris, 1995; Loftus et al., 1996; Massauld et al., 1993; Nykamp et al., 2004, Rached et al., 2011). CT-DCG provides information about bony tissue around the lacrimal sac and nasolacrimal duct. Smaller drainage structures, such as lacrimal canaliculi, are more consistently visualized com-

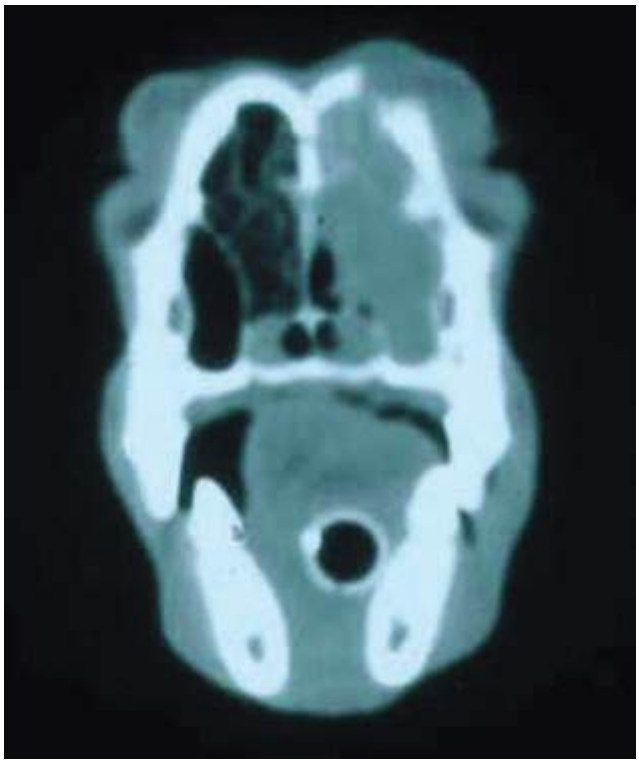


Figure 16.12 CT scan of a nasal carcinoma invading the anterior orbit through the maxillary bones.

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pared with conventional radiographic DCG. When combined with 3D reconstruction techniques CT-DCG provides detailed information regarding the anatomy of the nasolacrimal system and surrounding structures that is useful in diagnosis and in facilitation of preoperative planning. To perform CT-DCG, the superior lacrimal canaliculi are cannulated and iodinated contrast media is injected as for radiographic DCG. When detected at the nares, the injection is stopped and CT scans performed (Nykamp et al., 2004; Rached et al., 2011). Transverse beam projection orientation is reported to be superior to the oblique orientation for evaluation of inferior and superior canaliculi and the lacrimal sac (Rached et al., 2011).

Disadvantages of radiographic and CT-DCG include exposure of the eye to ionizing radiation, lack of detailed soft tissue imaging, and the required cannulation of the lacrimal canaliculi, which precludes functional evaluation of lacrimal drainage. Conventional and CT-DCG also require the use of iodinated contrast medium which may be irritating to the eye (Manfre et al., 2000; Rached et al., 2011). Magnetic resonance dacryocystography (MR-DCG) does not result in ocular exposure to ionizing radiation and has therefore been utilized with increasing frequency in humans but has not been reported in dogs. (Amrith et al., 2005; Goldberg et al., 1993; Hoffman et al., 1999; Kirchof et al., 2000; Manfre et al., 2000; Rahangdale et al., 1995; Rubin et al., 1994; Takehara et al., 2000). The technique is similar to CT-DCG, utilizing gadolinium as a contrast agent. Signal loss in the bony canal is a major disadvantage of MRI (Manfre et al., 2000). Although MRI is considered to be the technique of choice for evaluating periorbital soft tissues, CT-DCG depicts surrounding soft tissues reliably despite the limited contrast resolution (Nykamp et al., 2004; Rached et al., 2011).

Nasolacrimal scintigraphy (dacryoscintigraphy) involves the application of a radionucleotide (e.g. technetium-99) to the ocular surface, followed by imaging with a gamma camera (Lefebvre & Freitag, 2012). Images are obtained as the tracer passes through the lacrimal drainage system. This does not require forced injection of contrast into the nasolacrimal system thus allowing evaluation of physiological lacrimal outflow and is therefore more suitable for the study of physiologic or functional tear drainage than previously mentioned DCG techniques (Detorakis et al., 2014). Dacryoscintigraphy has been utilized to assess lacrimal drainage in humans but is not reported in dogs.

Endoscopy of the lacrimal drainage system (lacrimoscopy or dacryoendoscopy) is performed in humans using a small-diameter (0.9 mm) endoscope that can be passed through the punctum into the canaliculus for internal visualization of the drainage system. The technique is reported in humans and horses (Cassotis et al., 2000; Emmerich et al., 2000) and recently in dogs utilizing a miniature straightforward flexible telescope with a 0.5 mm outer diameter (Strom et al., 2018). Dacryoendoscopy has been utilized in humans to diagnose and surgically correct nasolacrimal duct obstruction (Sasaki, et al. 2005a, 2005b). In dogs, passage of the miniature endoscope was possible through the canaliculus and into, but not beyond, the lacrimal sac due to the high degree of flexibility which limited manual passage beyond this region (Strom et al., 2018). However, by passing an endoscope anterograde or retrograde through the lumen of a previously placed stent, observation of the entire nasolacrimal system was possible with gradual and simultaneous withdrawal of the stent and endoscope from the nasolacrimal system (Strom et al., 2018). There are several limitations to this modality in dogs, including the inability to provide insufflation or irrigation through an auxiliary channel due to the small diameter, as well as the high degree of flexibility which complicates manual passage (Strom et al., 2018). Further refinement of equipment and technique may improve the diagnostic practicality of endoscopy of the canine nasolacrimal system.

Congenital Diseases

Reported congenital anomalies of the nasolacrimal duct system include punctal atresia and micropuncta (Barnett, 1979); canalicular and nasal lacrimal duct atresia (Lavach, 1993; Severin, 1995); misplacement of the punctum and canaliculus (Gelatt & Gelatt, 2011; Gelatt & Gwin, 1981; Gelatt, 1991b); displacement of the punctum secondary to medial ventral entropion (Gelatt, 1991b; Gelatt & Gelatt, 2011; Gelatt & Gwin, 1981); dacryops (Grahn & Mason, 1995); and canaliculops (Gerding, 1991). Both the etiologies and incidence of these anomalies are unknown.

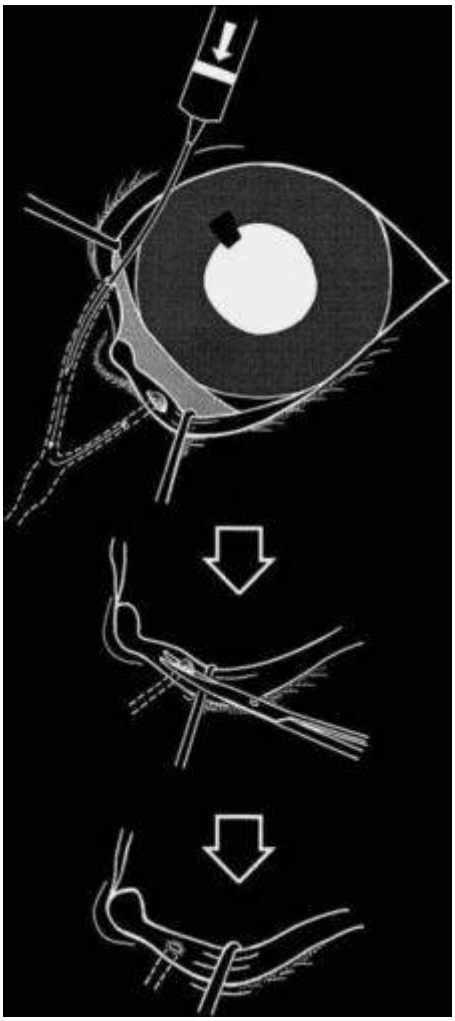
Lacrimal Punctal Atresia

Punctal atresia is the most frequently diagnosed congenital anomaly. It may affect the superior, inferior, or both puncta, and it may be either unilateral or bilateral. It occurs in numerous breeds and is commonly seen in American Cocker Spaniels, Bedlington Terriers, Golden Retrievers, Miniature and Toy Poodles, and Samoyeds (Genetics Committee of the American College of Veterinary Ophthalmologists, 1996; Grahn, 1999; Rubin, 1989).

The diagnosis is confirmed by biomicroscopic examination and normograde or retrograde nasolacrimal duct flushing. Superior punctal atresia is asymptomatic and is diagnosed incidentally during routine biomicroscopic examinations. Further diagnostic examinations are usually not completed with this condition; therefore, the presence of a superior canaliculus is not determined. When inferior punctal atresia is present, epiphora is usually present in puppies

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(see Fig. 16.3) and nasolacrimal flushing is warranted. The conjunctiva over the canaliculus will bulge during flushing. Ventral punctal atresia is treated by surgical excision of the ballooning conjunctiva (Fig. 16.13). The affected eye is then treated with topical antibiotic and corticosteroid solutions four times a day until reexamination in approximately 7 days; if the punctum is patent and epiphora no longer present, further therapy is not required. If the punctum has closed or significantly narrowed, it should be enlarged by the 1–2–3 snip technique (Fig. 16.14A–D) (Grahn & Mason, 1995; Lavach, 1993) or with a punctal dilator (Fig. 16.14E, F). The punctal dilator is inserted through the ballooning conjunctiva and down the canaliculus as the dilator is twisted (Fig. 16.14E, F). The enlarged punctum and canaliculus and nasolacrimal duct may then be cannulated with an indwelling silastic tube and then treated with an antibiotic–steroid solution for approximately 21 days to ensure patency. The silastic tube may be removed and the patency of the nasolacrimal duct should be reassessed after an additional 7 days of topical antibiotic–steroid therapy.



C

Figure 16.13 Ventral punctal aplasia. Note the ballooning of the conjunctiva over an aplastic puncta (**A**) during a normograde nasolacrimal flush through the superior puncta. The ballooning conjunctiva is excised with scissors (**B**) to create a new punctum (**C**).

Micropunctum

Incomplete development (i.e., micropunctum) or strictures of the ventral punctum causing epiphora may be enlarged with a punctal dilator (see Fig. 16.14E, F) or the 1–2–3 snip technique (see Fig. 16.14A–D) and catheterization (Barnett, 1979; Grahn, 1999). Punctal strictures in humans have also been treated successfully with cauterization (Fein, 1977) and the punctal pucker technique (Dolin & Hecht, 1986). These techniques are not reported in dogs; however, they may be useful. The punctal pucker technique involves a palpebral conjunctival incision through the ventral punctum and canaliculus (Fig. 16.15). Next, a horizontal mattress suture is placed from the edge of the incised ventral punctum and onto the medial canthus, and the suture is gently tightened; the tension puckers the skin and opens the punctum. The suture is left in place until the punctum heals. Punctal cauterization involves discrete placement of cautery burns around the ventral punctum and the cicatrization opens the ventral punctum (Fein, 1977).

Atresia of the Canaliculus, Nasolacrimal Sac, and Nasolacrimal Duct

Atresia of the canaliculus, nasolacrimal sac, or duct are rare (Lavach, 1993; Severin, 1995). Congenital anomalies of the nasolacrimal duct have been reported in cattle (Heider et al., 1975; van der Woerdt et al., 1996; Wilkie & Rings, 1990) and the horse (Latimer & Wyman, 1984; Lundvall & Carter, 1971), but not in the dog. When the ventral canaliculus, nasolacrimal sac, or nasolacrimal duct are missing, epiphora will be present, and the diagnosis is confirmed with a dacryocystorhinograph.

Therapeutic options are limited to surgery, and they include conjunctival rhinostomy (Blicker & Buffam, 1993; Covitz et al., 1977; Gelatt & Gelatt, 2011; Long, 1975), conjunctival maxillary sinusotomy (Gelatt & Gelatt, 2011), or conjunctival buccostomy (Fig. 16.16) (Gelatt & Gelatt, 2011). These procedures attempt to create a permanent fistula from the conjunctiva to the nasal turbinates, maxillary sinus, or mouth, respectively. The conjunctival rhinostomy is completed most commonly. A custom-made, 6-French polyethylene cannula is constructed either by estimating the total length from a preoperative radiograph for the conjunctival rhinostomy and conjunctival maxillary sinusotomy or by direct measurement on the patient for the conjunctival buccostomy. The distal end of the cannula is cut on an oblique

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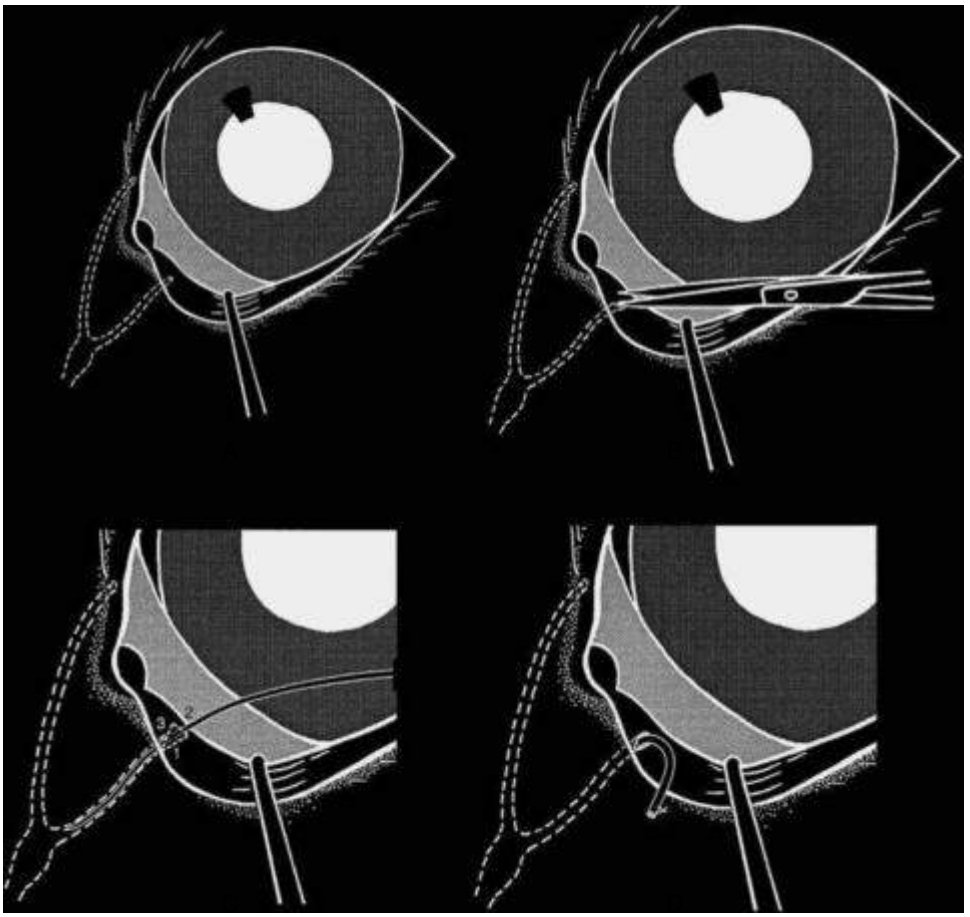






Figure 16.14 The 1–2–3 snip technique (**A**–**D**) using scissors for enlarging a micropunctum or stenotic punctum. The punctum and canaliculus are cannulated for approximately 3 weeks postsurgery. **E.** A photograph of a punctal dilator; note the two varied sized taper ends. **F.** The punctal dilator is inserted into the ventral micropuncta and twisted to enlarge the puncta and canaliculus.

taper, and the proximal end is cut so that two suture tabs are present, thus allowing it to be anchored to the medial canthus. Both ends are open flamed until they are smooth, and the cannula is autoclaved. The conjunctiva is surgically prepared with three lavages of dilute (1:25–1:50) aqueous iodine, and a 0.25-inch Steinmann pin is inserted in a Jacob's chuck. The pin is then drilled through the conjunctiva at the medial canthus and into the dorsal nares, maxillary sinus, or buccal cavity (Fig. 16.16A). The custom-made cannula is inserted through the tract, and the tabs are sutured into the medial canthus with simple, interrupted, 5-0 nonabsorbable monofilament suture (Fig. 16.16B, C). The cannula is left in

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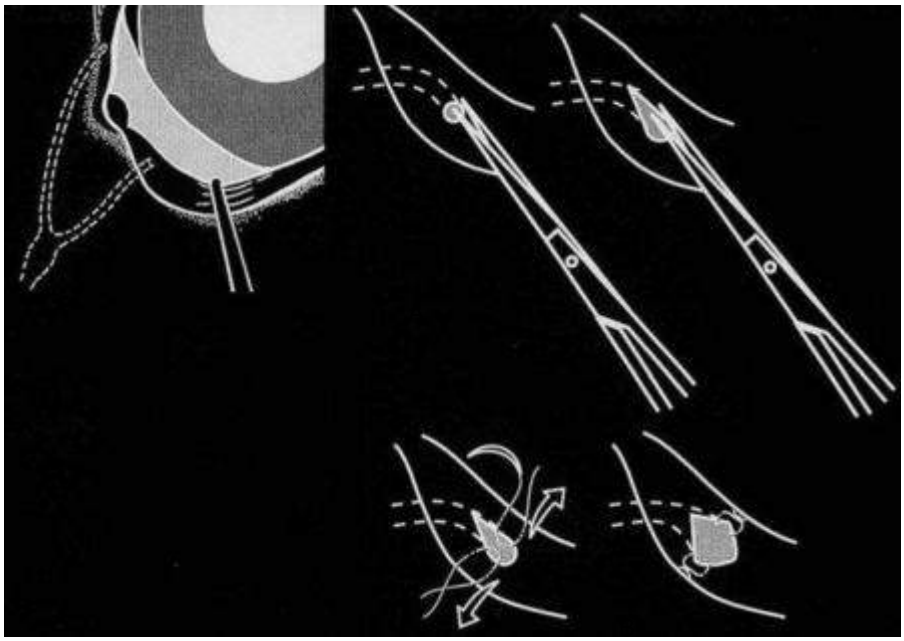


Figure 16.15 An illustration of the punctal pucker technique. The ventral puncta and canaliculus and overlying palpebral conjunctiva are cut with small Vanna's scissors (**A**). A horizontal mattress suture is placed with enough tension to cause the punctum and canaliculus to gape (**B**). The suture is left in place until the punctum and canaliculus are epithelialized and the wound has healed.

place for as long as possible provided that it is secure. To ensure a permanent fistula, the cannula should be left in place for a minimum of 12–20 weeks. The affected eye is treated with topical antibiotic steroid drops to decrease scarring and bacterial growth while the epithelium is growing over the exposed tissues around the tube.

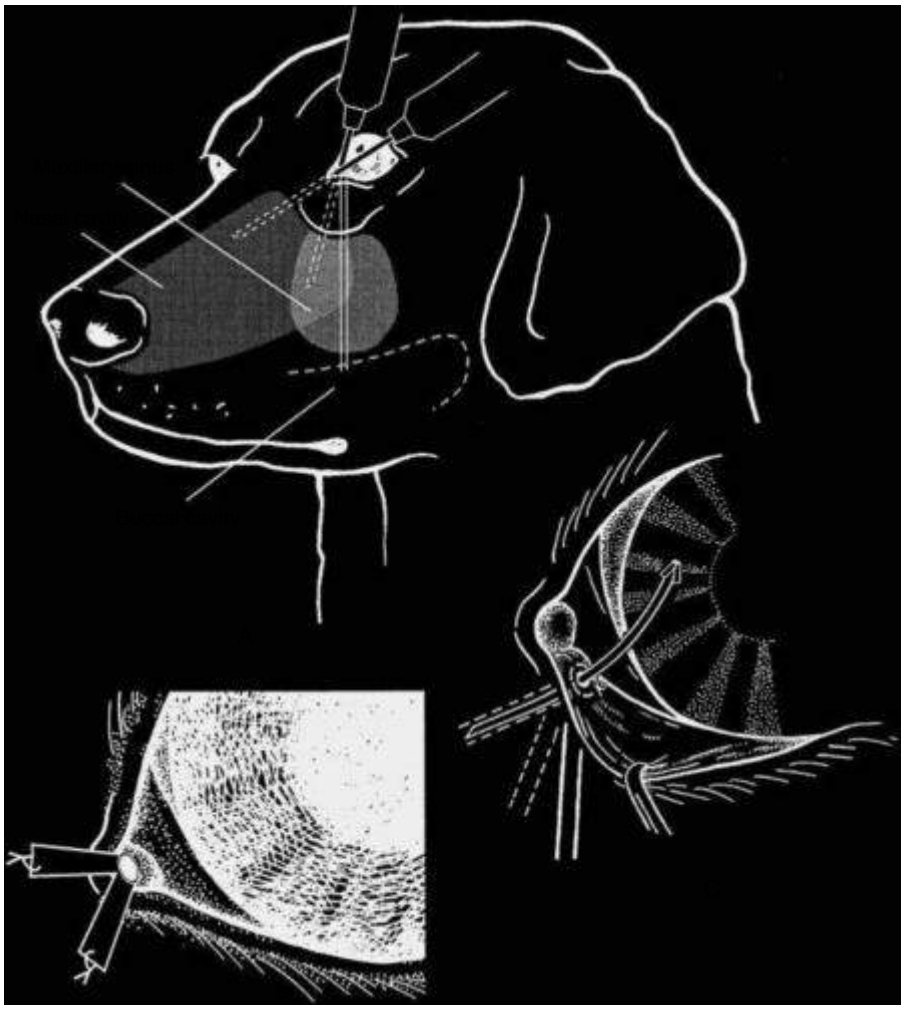
Complications related to these procedures include corneal ulceration secondary to cannula or suture contact, dislodgement of the cannula, and strictures of the fistula after the cannula has been removed. Surgeons must take care to avoid iatrogenic damage to neighboring tissues (e.g., the facial and infraorbital veins, arteries, and nerves). The longer the cannula is left *in situ*, the less likely strictures will develop.

A surgical technique based on the transposition of the parotid duct to the medioventral conjunctival fornix to allow tear drainage into the mouth was successful for treatment of a nonpatent nasolacrimal drainage system in a dog (Scotti et al., 2007). In this procedure, the parotid duct is cannulated with 2/0 nylon from the oral papilla. A 3 cm skin incision centered on the cranial border of the masseter muscle is made over the lateral aspect of the cheek. The parotid duct is identified between the buccal branches of the facial nerve and carefully dissected from surrounding tissues. The proximal duct is ligated and sectioned near the parotid gland and transposed to the medioventral conjunctival fornix, between the lower eyelid and nictitating membrane through a subcutaneous tunnel. The transected end is then spatuled and sutured to the conjunctiva with simple interrupted sutures (Scotti et al., 2007). Parotid gland atrophy was reported following the procedure. This technique may avoid some of the complications of conjunctival rhinostomy, conjunctival buccostomy, and conjunctival maxillary sinusotomy.

Congenital Puncta and Canaliculi Misplacement

Congenital puncta and canaliculi misplacement is often asymptomatic in dogs. When chronic epiphora is present and relates to the position of the ventral punctum, surgical repositioning is indicated. This procedure should be completed with the aid of an operating microscope. After routine presurgical preparation and positioning, the affected punctum and canaliculus are cannulated with a sterile, 24-gauge intravenous catheter or monofilament suture. This allows the ophthalmic surgeon to microdissect the punctum and thin-walled canaliculus accurately and to move them through a conjunctival incision to the eyelid margin approximately 3 mm from the medial canthus. The conjunctival rim around the punctum is sutured to the medial canthal region with 9-0 absorbable sutures (Fig. 16.17), and the catheter is removed. Specific care and attention to detail are required during dissection, translocation, and suturing to prevent strictures or corneal contact. Topical ophthalmic antibiotics are applied until the incisions have healed (in approximately 1 week).

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B

Figure 16.16 Conjunctival rhinostomy. **A.** Conjunctival rhinostomy is completed by drilling a hole into the nasal cavity with a Steinmann pin and Jacob's chuck. **B.** Conjunctival maxillary sinusotomy is completed by drilling a hole into the maxillary sinus from the medial canthus. Conjunctival buccostomy is completed by blunt dissection from the medial canthus to the oral cavity. **C.** A custom-made cannula is then inserted into the tract and sutured to the medial canthus.

Congenital Canaliculi Obstruction

Epiphora secondary to compression of the canaliculi by a congenital cyst of canalicular origin (i.e., canaliculops) has been reported in the dog (Gerding, 1991). In this report, canalicular patency was restored by surgical removal of the cyst.

Congenital Nasolacrimal Duct Obstructions

The nasolacrimal duct in the dog has been reported to be occluded by dacryops (Grahn & Mason, 1995). These cystic obstructions were assumed to be congenital and similar to those reported to affect the canaliculi (Gerding, 1991). They were diagnosed through the use of DCG and rhinoscopy, and they were confirmed with biopsy and light microscopic examination. They were treated by surgical exploration of the nasal cavity, curettage, and cyst drainage (Grahn & Mason, 1995), cyst removal (Lussier & Carrier, 2004; Ota et al., 2009), and by nasal endoscopic cyst perforation (White et al., 1984), which relieved the nasolacrimal duct obstructions.

Laser dacryocystorhinostomy has been reported as a successful therapy for congenital obstructions of the nasolacrimal duct system in humans (Bartley, 1994; Dutton & Holck, 1996; Javate et al., 1995; Schauss et al., 1996; Seppa et al., 1994; Tutton & O'Donnell, 1995). As this technology becomes more readily available, these techniques may be applied to the dog.

Developmental Disorders

Reported inherited nasolacrimal duct anomalies are limited to puncta atresia in Bedlington Terriers; these are congenital

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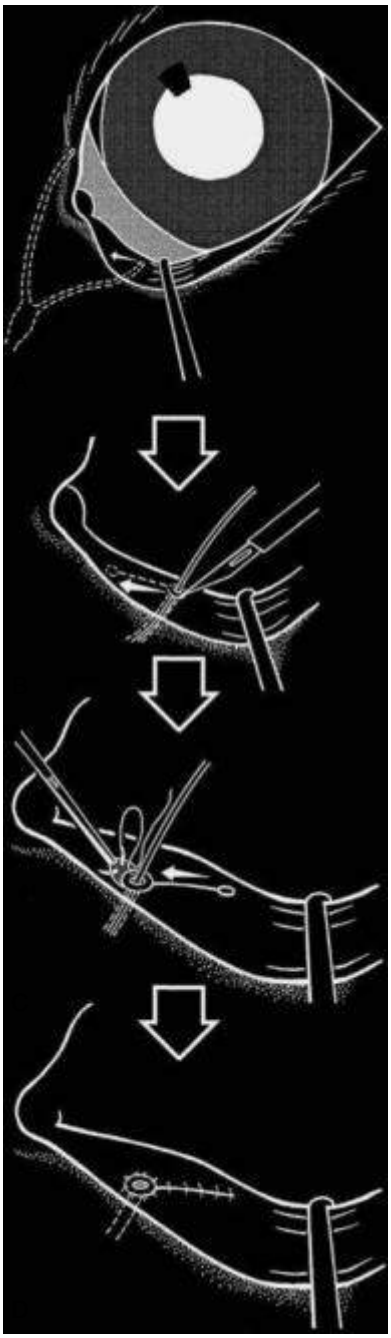


Figure 16.17 Microsurgical repositioning of a misplaced lower puncta and canaliculi. **A.** The lower lacrimal punctum is identified. **B.** The punctum is cannulated by monofilament suture and the punctum microdissected with the canaliculus. **C** and **D.** Both lower punctum and canaliculus are moved through the conjunctival incision to the medial canthal eyelid margin.

disorders, discussed previously in this chapter. However, many brachycephalic and toy dogs have epiphora related to multiple anomalies of the medial canthal region and inferior puncta (Fig. 16.18). These anomalies are inherited as part of the facial development in these breeds of dogs, and epiphora usually manifests in the first year of life. Therefore, it is appropriate to categorize this nasolacrimal dysfunction as developmental. The inferior puncta and canaliculi are commonly displaced inward and ventrally by a subtle, medioventral entropion, which rolls the medial eyelid margin into the cornea and partially obstructs the puncta and narrows the canalicular lumen (see Fig. 16.18). This displacement is integral to the tear-staining syndrome commonly seen in the toy and brachycephalic breeds. This tear-staining syndrome has been examined by comparison of tear production and excretion and of the angle of bend between the vertical and horizontal bony lacrimal duct in tear-stained Poodles and German Shepherds without epiphora (Seo & Nam, 1995). The results of that study revealed that tear staining in the Poodle was related to a prolonged rate of tear drainage. Tear production in these two populations were similar, and the angle of the bony nasolacrimal duct was more obtuse in the German Shepherd. Epiphora and unsightly tear staining in the Poodle and other small breeds (see Fig. 16.3 and Fig. 16.4) develop during the post-weaning period. The puncta are usually normal in these dogs, and the clinical signs relate to multiple factors, including displacement of the ventral puncta and compression of the canaliculi by the medioventral entropion. In addition, tight medial canthal ligaments displace the medial canthus ventrally and, in combination with medial canthal trichiasis and eyelid trichiasis, exacerbate tear spillage in these dogs. Oral tetracycline (Thun et al., 1975) and metronidazole (Filipek & Rubin, 1977; Gale, 1976) have been reported as a therapy for tear staining, but neither has any appreciable effect on tear production or excretion. Their success relates to reduced staining of the medial canthal region rather than to control of the epiphora. Therefore, they are used infrequently as therapy today. Removal of the gland of the third eyelid has also been recommended as a surgical therapy for epiphora (Kerpsack & Kerpsack, 1966), but this is not justifiable when tear production is normal. The treatment of choice for this condition is a Hotz–Celsus repair of the medial ventral entropion in which a triangular piece of skin is excised with the apex of the triangle opposite the lower lacrimal punctum (Peiffer et al., 1978) or, preferably, a bilateral medial canthoplasty to correct the caruncular trichiasis and tight medial canthal ligaments (Fig. 16.19) (Jensen, 1979; Ny et al., 2006). Medial canthoplasty can also be used to reduce the palpebral fissure size in brachycephalic dogs. In this procedure, the superior and inferior lacrimal puncta are identified and perpendicular incisions are made in the eyelid margin medial to these structures. The medial palpebral ligament may be cut, taking care to preserve the canaliculi, and the skin is undermined to free it from its orbital attachments. An arrow-shaped wedge of skin near the medial canthus is removed, as well as the caruncle. The resulting skin wound is closed in two layers using 6-0 to 9-0 absorbable suture to appose the palpebral conjunctiva and

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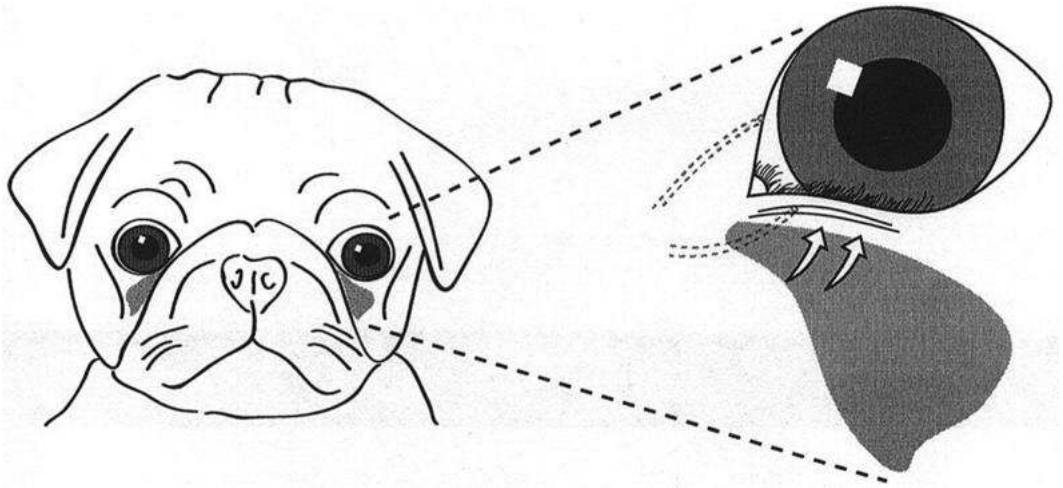


Figure 16.18 The anomalies of the medial canthus of small-breed dogs that predispose to epiphora and pigmentary keratitis. Note the caruncular trichiasis, the tight medial canthal ligaments that create a medial canthal trough, and the medial ventral entropion that compress the ventral punctum and canaliculus.

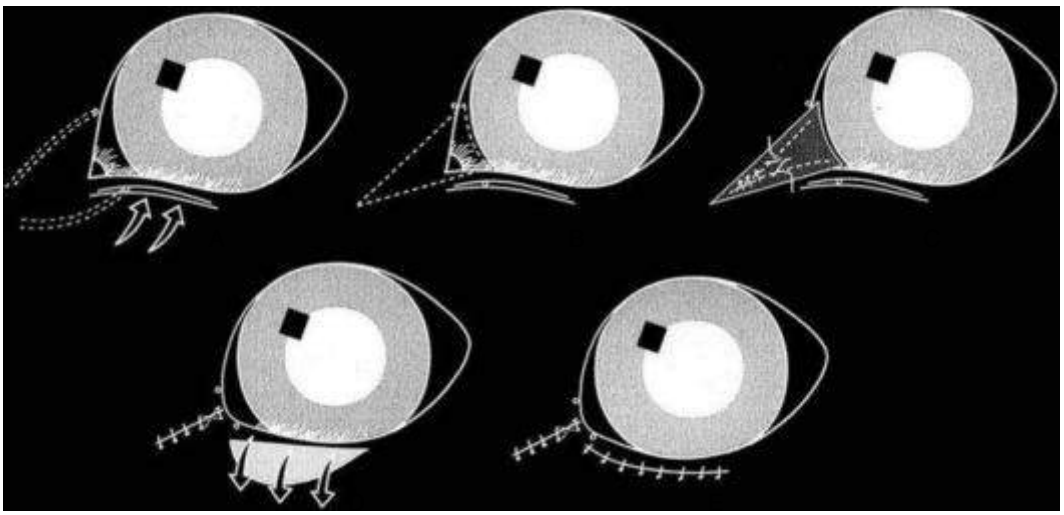


Figure 16.19 A medial canthal plasty to repair the anomalies shown in Figure 16.18. **A.** Note the medial palpebral ligament is cut. **B.** The caruncular trichiasis and medial canthal trough are excised to the level of the dorsal and ventral puncta. **C.** The palpebral conjunctival is apposed with 9-0 absorbable suture. **D** and **E.** The medial canthal skin is apposed with 5-0 nylon sutures. The medial ventral entropion is corrected with a Hotz–Celsus repair.

5-0 nylon sutures to close the skin, employing a figure-of-eight suture at the lid margin (Ny et al., 2006). The medial ventral entropion may then be corrected with a Hotz–Celsus repair if necessary (see Fig. 16.19D, E).

Acquired Diseases

Acquired nasolacrimal disorders of the dog include traumatic lacerations (Gelatt & Gelatt, 2011; Hill et al., 1974a, 1974b; Lavach, 1993; Peiffer et al., 1987), dacryocystitis and obstruction with foreign bodies (Gelatt & Gelatt, 2011; Hill et al., 1974a, 1974b; Laing et al., 1988; Lavach, 1993; Nykamp et al., 2004; Severin, 1995), and invasion or compression by neoplasms (Carter, 1970; Gelatt & Gelatt, 2011; Hill et al., 1974a, 1974b; Lavach, 1993).

Lacerations

Facial trauma may result in lacerations of the puncta, canaliculi, medial canthus, and eyelids. Lacerations of the canaliculi are diagnosed with use of biomicroscopic examination and the bubble test (Loff et al., 1996), which involves cannulation of both puncta and injection of air. The resultant

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bubbling allows the surgeon to detect and cannulate the lacerated canalicular ends with a silastic tube (Fig. 16.20). Deploying viscoelastic superficially in the vicinity of the injured canaliculus and injecting it into the proximal torn end can also improve visualization of the operative field because it promotes retraction of the surrounding tissue and tamponades bleeding. This also dilates and lubricates the torn canaliculus allowing for easier intubation (Örge & Dar, 2015). The lacerated eyelid surfaces are then repaired by microsurgical apposition of the tissues around the cannulated duct (Fig. 16.20). The eye is treated with topical antibiotic solutions four times a day until the cannula is removed (at approximately 3 weeks).

Fractures of the maxillary or lacrimal bones may compress or lacerate the nasolacrimal duct or canaliculi as well. Plain radiography and DCG are required to confirm the diagnosis. Lacerated nasolacrimal ducts often form permanent fistula intranasal at the point of laceration. Extensive trauma that results in epiphora and a nonpatent nasolacrimal duct, however, should be treated with conjunctival rhinostomy, conjunctival–maxillary sinusotomy, or conjunctival buccostomy (Gelatt & Gelatt, 2011; Latimer & Wyman, 1984). Balloon dilatations of recurrent obstructions in the human nasolacrimal duct have been reported (Iigit et al., 1996; Janssen et al., 1994; Liermann et al., 1996; Örge & Dar, 2015).



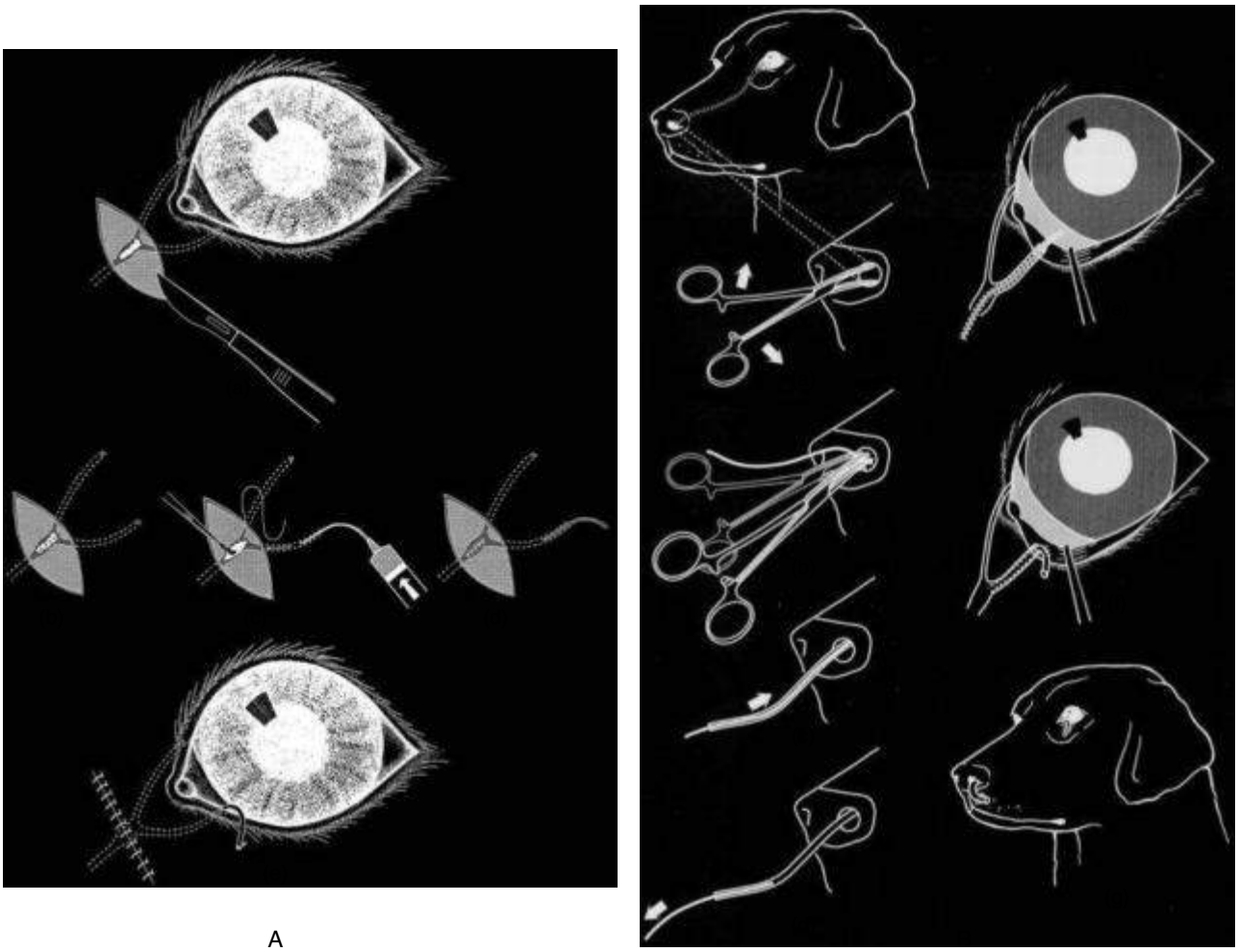
Figure 16.20 Microsurgical repair of a lacerated canaliculus. Note the distal lacerated end of the duct is identified by injection of viscous fluid and air bubbles (**A**), is cannulated (**B**), and is then repaired by meticulous apposition of the tissue around the canaliculus (**C** and **D**). The cannula is sutured to the ventral eyelid (**E**) and left *in situ* for approximately 3 weeks.

Dacryocystitis and Foreign Bodies

Clinical manifestations of dacryocystitis and nasolacrimal duct foreign bodies include epiphora, purulent conjunctival discharge, punctal foreign bodies (see Fig. 16.5), and draining skin fistulas ventral to the medial canthus (Bessler et al., 1994; Gelatt, 1991b; Gelatt & Gwin, 1981; Laing et al., 1988; Severin, 1995). Dacryocystitis in the dog usually develops secondary to nasolacrimal duct obstruction. This is most commonly caused by foreign bodies that lodge in the nasolacrimal sac (Pope et al., 2001). These foreign bodies must be removed for effective therapy. Dacryocystitis has also been reported in a dog secondary to nasolacrimal duct obstruction caused by an ectopic, unerupted, intranasal tooth (Voelter-Ratson et al., 2015), and in humans secondary to obstruction with congenital cysts (Choi et al., 1995), tuberculosis (Arstenstein et al., 1993; Bessler et al., 1994; Cotton et al., 1995), and dacryoliths (Dhillon et al., 2014). Dacryocystitis has been reported in dogs to induce nasal cysts (Lussier & Carrier, 2004; van der Woerdt et al., 1997; Voelter-Ratson et al., 2015).

The diagnosis of dacryocystitis is confirmed through use of imaging modalities and cytological examination of the contents from a nasolacrimal lavage or from biopsies from tissues excised during surgical exploration (i.e., dacryocystotomy). Foreign bodies may be flushed from the nasolacrimal duct system by retrograde or normograde lavages. Depending on the location, foreign bodies may be removed manually using alligator forceps guided by ultrasound, endoscopy, rhinoscopy, or fluoroscopy (Barsotti et al., 2019; Strom et al., 2018). They may also be removed via a dacryocystotomy (Fig. 16.21). The skin incision for a dacryocystotomy is ventral to the medial canthus over the lacrimal fossa. The maxillary and lacrimal bones are commonly burred or removed with rongeurs until the lacrimal sac is exposed and incised (Fig. 16.21). The foreign material is removed and submitted for aerobic and anaerobic cultures and cytological examination. The nasolacrimal duct system is then cannulated with a silastic tube and treated with topical broad-spectrum antibiotics for approximately 3 weeks postoperatively (Dhillon et al., 2014; Gelatt, 1991b; Gelatt & Gwin, 1981; Getty, 1975; Laing et al., 1988; Lavach et al., 1984; Murphy et al., 1977; Severin, 1995). Cannulation of the nasolacrimal duct system may be anterograde or retrograde. For retrograde cannulation, the nasal punctum is located using rhinoscopy or using a nasal speculum inserted into the nostril and directed ventrally (Fig. 16.21B). A pair

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A

Figure 16.21 **A.** Dacryostomy in the dog. (a) An incision is completed ventral to the medial canthus into the lacrimal sac. (b) and (c) The foreign material is removed and submitted for laboratory evaluation. (d) The nasolacrimal duct system is cannulated with a silastic tube, and (e) the incision is closed routinely. **B.** Retrograde cannulation of the nasolacrimal duct. (a) The nasal punctum is identified by gently spreading the external nares with a small curved hemostat. (b) A flame-rounded end of 5-0 nylon suture is introduced into the punctum with the aid of a second small hemostat. The suture is advanced up the duct (c and d) and through the canaliculus and (e) exits the ventral punctum. (f) A small silastic tube is threaded over the indwelling suture and through the nasolacrimal duct system, and (g) both ends are secured with sutures to the ventral eyelid and nares skin after the indwelling suture is removed.

of curved mosquito forceps introduced through the nasal speculum and into the nasal puncta and slight opening of the jaws will facilitate passage of a flamed, rounded 5-0 nylon suture tip held with a second pair of mosquito forceps, which directs the suture up through the nasolacrimal duct and out through the ventral canaliculus and puncta. A small silastic tube is threaded over the suture and up the nasolacrimal duct and out of the puncta. The tube is then secured with a suture to the ventral eyelid and nasal skin, and the indwelling suture is removed. Fluoroscopy-guided stent placement has recently been described (Strom et al., 2018). This technique utilized a hydrophilic guidewire introduced anterograde through the superior or inferior puncta or retrograde through the nasal punctum under fluoroscopic guidance, followed by passage of an appropriately sized stent retrograde over the guidewire into the nasal punctum. The guidewire was then removed and the stent secured to the adjacent skin (Strom et al., 2018). Fluoroscopy was useful in identifying appropriate passage of the guidewire and facilitated stent placement in a minimally invasive manner (Strom et al., 2018).

Dacryolithiasis

Dacryoliths are concretions of debris and protein which form in the nasolacrimal sac. They may calcify and contribute to nasolacrimal duct obstruction. They are reported in humans to form in any part of the lacrimal system (Lew et al., 2004). Dacryolithiasis may be asymptomatic. However, the most common clinical manifestations are

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epiphora, acute or recurrent dacryocystitis, punctal discharge, and medial canthal swelling (Mishra et al., 2017). Dacryoliths have been found in up to 17% of people undergoing dacryocystorhinostomy (Iliadelis et al., 1999; Iliadelis et al., 2006; Lew et al., 2004; Mishra et al 2017; Repp et al., 2009; Wilkins & Pressly, 1980,). There is one report of dacryolithiasis in a Labrador Retriever (Malho et al., 2013). Dacryoliths were located within a canalicular cyst which was presumed to have developed from a canalicular diverticulum. Mineral analysis of the dacryoliths revealed them to be composed of calcium carbonate (Malho et al., 2013). The mechanism of dacryolith formation is poorly understood. However, changes in tear flow are thought to play an important role (Lew et al., 2004). In humans, removal of dacryoliths is the most effective treatment in symptomatic cases (Mishra et al. 2017).

Neoplasia of the Nasolacrimal Duct

Primary neoplasia of the nasolacrimal duct is rare in all species (Lavach, 1993; Pe'er et al., 1996; Rahangdale et al., 1995). Lymphoma is reported to have invaded the lacrimal sac and to have induced dacryocystitis (Karesh et al., 1993). Pseudotumors of the lacrimal canaliculus have been reported in a dog (Williams et al., 1998). Tumors of nasal turbinates and the maxillary sinus, however, may compress or invade the nasolacrimal ducts and spread into the orbit via the nasolacrimal foramen and cause epiphora, mucopurulent or serosanguineous ocular and nasal discharge, masses ventral to the medial canthus (Fig. 16.22), and orbital signs, including prolapse of the third eyelid, enophthalmos, and conjunctival hyperemia (Gelatt et al., 1970). The diagnosis of nasal neoplasia with involvement of the nasolacrimal duct system is established by clinical examination, plain and contrast radiography (see Fig. 16.11), or advanced multisectional imaging (see Fig. 16.12), and it is confirmed through light microscopic evaluation of nasal biopsies. Nasal neoplasia is a therapeutic challenge, and various surgical, medical, and radiation therapies have been reported (Gelatt et al., 1970; Hahn et al., 1992; Laing & Binnington, 1988; Theon et al., 1993).



Figure 16.22 A medial canthal mass in an 8-year-old, neutered male Shetland Sheepdog. Nasal radiographs revealed signs consistent with a nasal tumor, which eroded through the maxillary and lacrimal bones into the medial canthal region. Results of nasal endoscopic biopsies confirmed the diagnosis of a nasal carcinoma.

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17

Diseases and Surgery of the Canine Lacrimal Secretory System

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This chapter focuses on clinical aspects of the canine lacrimal secretory system. The origin of tear components, functions of the preocular tear film, and diagnostic procedures aimed at detecting or confirming tear deficiencies are reviewed. Because tear abnormalities are among the most common causes of canine ocular surface disease, the pathogenesis and resulting surface changes are emphasized. Medical and surgical procedures applicable to treatment of tear-deficient ocular surface diseases are discussed. Clinical findings and treatment of other conditions of the lacrimal secretory system (i.e., neoplasia, cysts) are also presented.

Formation and Dynamics of Tear Components

The precorneal tear film (PTF) is crucial for the maintenance of ocular surface health and clear vision because it is the first refractive surface of the eye. Its functions include: primary oxygen source to the avascular cornea; lubricant between the lids and ocular surface; source of protective antimicrobial proteins; and removal of debris and exfoliated cells through drainage. The PTF is classically described as a superimposition of three structurally and functionally unique layers consisting of lipid, aqueous, and mucin components (Fig. 17.1) and in some references, a fourth innermost layer of glycocalyx extending from the superficial layer of the ocular surface epithelia is described (Leonard et al., 2016; Levin et al., 2011). Over the past two decades, emerging research regarding tear film dynamics support the concept that there is no clear-cut barrier between the three "classic" components of the PTF and that the lipid, aqueous, and mucin layers are intricately mingled (Sack et al., 2000; Tiffany, 2008). Tear film thickness is a key variable in the study of normal tears and dry eye diseases. In humans, currently accepted PTF thickness is estimated to be $3.4 \pm 2.6\,\mu m$ (Levin et al., 2011; Wang et al., 2006). However, measuring a changing fluid layer is challenging. Reports of the static human tear film thickness have varied widely as newer optical techniques utilizing laser interferometry, confocal microscopy, and meniscometry have shown that earlier estimates by mechanical and chemical techniques, which disturb PTF structure during sampling, may substantially underestimate tear film thickness (Prydal & Campbell, 1992; Prydal et al., 1992; Prydal et al., 1993; Tung et al., 2014; Yokoi & Komuro, 2004). Reports of total tear film thickness have ranged from 332 to 40 μm in humans with no consensus (Carrington et al., 1987b; Carrington et al., 1988; King-Smith et al., 1999; King-Smith et al., 2004; Prydal & Campbell, 1992; Prydal et al., 1992; Prydal et al., 1993; Wang et al., 2006; Yokoi & Komuro, 2004). As technology advances and use of newer imaging modalities such as real-time optical coherence tomography (OCT) become more available, differences between central tear film thickness and tear menisci of the upper and lower eyelids are being discovered (Wang et al., 2006). The important role between tear film and vision emphasizes the need for further research in veterinary ophthalmology (Koh & Maeda, 2007; Montés-Micó, 2007; Montés-Micó et al., 2010). Further validation of tear film composition and thickness in various species is still needed. For descriptive purposes in this chapter, the three components of the PTF will be discussed separately.

The lipid layer is secreted by the tarsal (i.e., meibomian) glands, and provides a thin, oily component to the PTF, thus retarding evaporation and promoting a stable, even spread of tears over the cornea (Bron et al., 2004; Butovich, 2011; Butovich et al., 2008; Butovich et al., 2012; Floyd et al., 2012; Mathers, 2004). Meibomian glands are holocrine, modified sebaceous glands arranged linearly within the dense connective tissues (i.e., tarsal plate) of the eyelid margin (Fig. 17.2). Meibomian secretions consist of wax monoesters, sterol esters, hydrocarbons, triglycerides, diglycerides, free sterols (i.e., cholesterol), free fatty acids, and polar lipids (including phospholipids) (Levin et al., 2011). The molecular weight of

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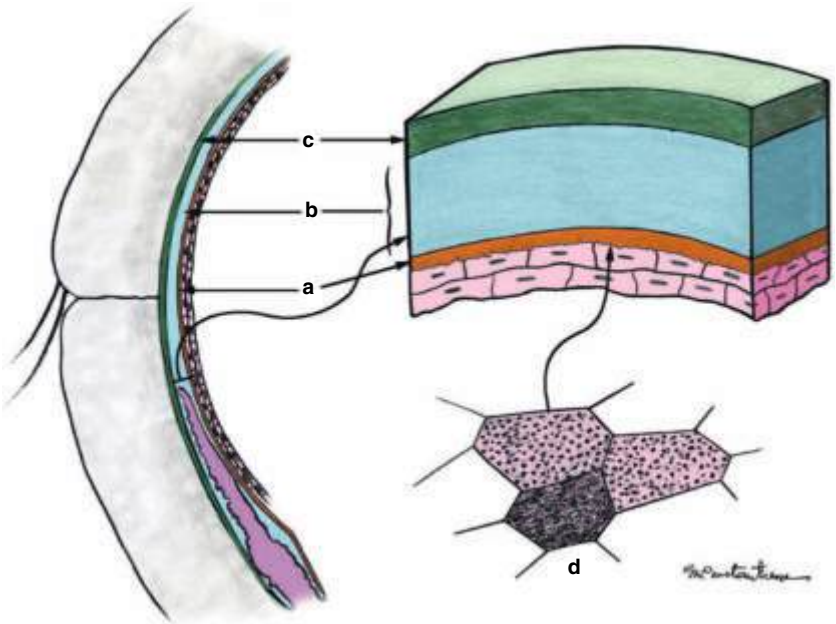


Figure 17.1 The precorneal tear film is classically depicted with three layers, consisting of a deep mucin layer (a), an intermediate aqueous tear layer (b), and a superficial lipid layer (c). These three layers are secreted by conjunctival goblet cells and surface epithelial cells, nictitans and orbital lacrimal glands, and meibomian glands, respectively. Enlargement (d) depicts extensions (microplicae) of corneal surface cells, which are believed to provide an interface between the membrane-bound mucin, a product of the surface epithelial cells, and the conjunctiva-derived mucin. (*Source:* Courtesy of G. Constantinescu.)

meibomian lipids (i.e., meibum) is higher, and the polarity is lower, than that of sebum, thus meibomian lipids are fluid at body temperature (Driver & Lemp, 1996). Some models have proposed that a combination of PTF proteins and lipids could interact and behave similarly to lung surfactant to provide a noncollapsible viscoelastic gel that would allow for proteins to remain in their lowest free energy states while in contact with lipids (Butovich, 2011; Butovich et al., 2008; Rantamaki et al., 2011).

Meibomian glands are highly developed in the dog, with 20–40 glands per eyelid typically being present (Pollock, 1979). Glands are located within the tarsal plate, in which they form linear aggregates of secretory acini that are usually visible through the semitransparent palpebral conjunctiva. These acini open into central ductules arranged at right angles to the eyelid margin, and they deliver lipid to the surface of the eyelid through small openings just external (i.e., anterior) to the mucocutaneous junction (Pollock, 1979). Openings from the meibomian glands form a trough or line on the eyelid margin, which is sometimes referred to as the "gray line." Gentle pressure applied to the eyelid margin may express secretions from the gland openings and help in the identification of the "gray line," an important surgical landmark for most blepharoplastic procedures. Compression of the eyelids during normal blinking contributes to release of meibomian secretions, but the precise neural and hormonal mechanisms regulating the secretion of meibomian lipid are not well understood (Dartt, 2004; Davidson & Kuonen, 2004; McCulley & Shine, 2004; Sullivan et al., 2000). Noninvasive meibometry can be used in conscious dogs and has been described as a means to quantify meibomian gland secretions in this species. However, results have been variable (Benz et al., 2008; Ofri et al., 2007).

The aqueous component of canine tears is secreted by lacrimal glands of the orbit and nictitating membrane (Fig. 17.2 and Fig. 17.3). Gross anatomy and morphometric evaluation of the canine lacrimal and third eyelid glands as well as computed tomographic imaging characteristics of the normal canine lacrimal glands have been reported in recent years (Park et al., 2016; Zwingenberger, 2014). The aqueous tear serves most of the avascular cornea's metabolic needs by supplying glucose, electrolytes, oxygen, and water to the superficial cornea. Aqueous fluid also lubricates the cornea, conjunctiva, and nictitating membrane. In addition, it removes metabolites such as carbon dioxide and lactic acid, and it flushes away particulate debris and bacteria from the ocular surface. The aqueous portion of the PTF is 98.2% water and 1.8% solids (i.e., mostly proteins) and consists of water, electrolytes, glucose, urea, surface-active polymers, glycoproteins, and tear proteins (Davidson & Kuonen, 2004; Winiarczyk et al., 2015). Examples of primary tear proteins include globulins (i.e., secretory IgA, IgG, IgM), albumin, lysozyme, lactoferrin, lipocalin, epidermal growth factor, transforming growth factors, lacritin, and interleukens (Bron, 1997; Dartt, 2004; Klenkler et al., 2007; Levin et al., 2011; McKown et al., 2009; Roberts & Erickson, 1962; Selinger

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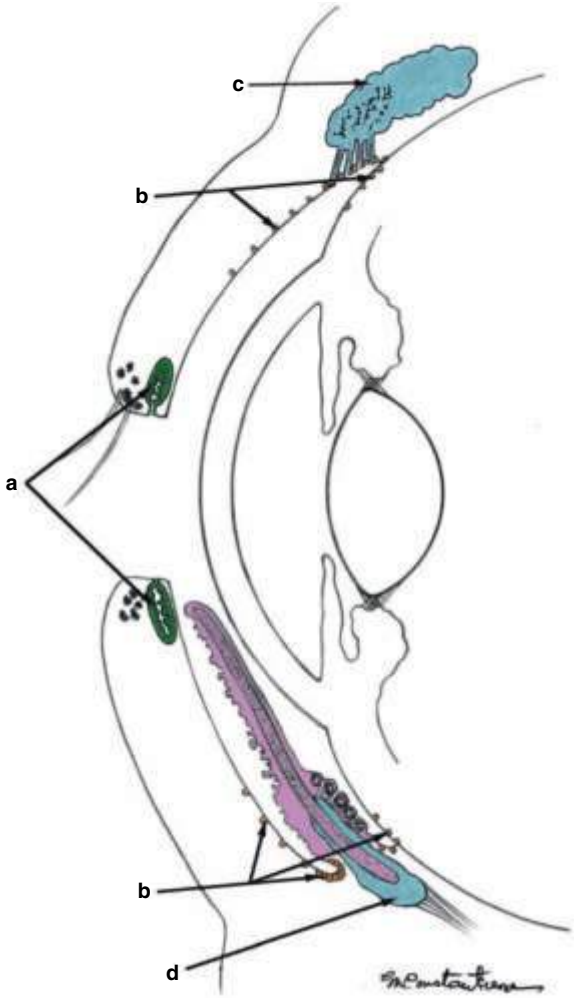


Figure 17.2 Anatomic location of the primary secretory tissues responsible for production of the tear components. a. Meibomian glands located within the tarsal plate. b. Conjunctival goblet cells. c. Orbital lacrimal gland. d. Nictitans lacrimal gland. (*Source:* Courtesy of G. Constantinescu.)

et al., 1979; Winiarczyk et al., 2015). Alterations in tear film composition is commonly investigated in dogs with corneal disease (Sebbag et al., 2017; Williams & Burg, 2017; Wichayacoop et al., 2009). Alterations may also occur in dogs affected with cancer (de Freitas Campos et al., 2008). However, further research is warranted. Antibodies, immunoglobulins, lysozyme, lactoferrin, transferrin, ceruloplasmin, and glycoproteins all contribute to the antibacterial properties of tears (Bron et al., 2004; Fullard & Tucker, 1994). Certain topical medications (e.g., EDTA) may reduce the gelatinase activity present in tears of normal dogs (Couture et al., 2006). The PTF contains proteinase inhibitors as well as proteinases that play an important role in both ocular immunity and in the prevention of excessive degradation of normal healthy ocular tissues (de Souza et al., 2006; Winiarczyk et al., 2015). Two matrix metalloproteinases (MMP-2, synthesized by keratocytes, and MMP-9, synthesized by corneal epithelial cell and/or neutrophils after corneal wounding) are of major importance in corneal stromal remodeling and degradation. Because of the intimate association between the PTF and the cornea, tears have commonly been used to evaluate these proteinases. The total proteolytic activity in tears has been found to be significantly increased after corneal wounding. More specifically, ulcerative keratitis in animals has been associated with initially high levels of tear film proteolytic activity which decrease as ulcers heal and proteinase levels in melting ulcers remain elevated leading to rapid progression of the ulcers (Ollivier et al., 2007).

The lacrimal glands of the orbit and the nictitating membrane are tubuloacinar and histologically similar (Cabral et al., 2005; Martin et al., 1988). Ductules from these glands deliver aqueous tear secretions into the conjunctival fornices. In the dog, three to five ductules from the orbital lacrimal gland open into the dorsolateral conjunctival fornix (see Fig. 17.2), whereas the nictitans gland delivers aqueous tears onto the corneal surface through multiple ducts opening between lymphoid follicles on the posterocentral third eyelid (Fig. 17.4) (Moore et al., 1996; Park et al., 2016).

The relative contributions by each of the main lacrimal glands to reflex tear secretion have been investigated in the dog by surgical removal of either one or both glands and measurement of the resulting tear production (Helper, 1970; Helper, 1976; Helper et al., 1974; Saito et al., 2001). The volume of tear fluid produced by each gland varied considerably among animals. The orbital lacrimal gland was the main source of aqueous tears in some dogs, whereas the nictitating membrane gland was the main source in others (Helper et al., 1974). When either gland was removed singly, a compensatory increase in tear production appeared to occur in the remaining gland. Removal of both glands resulted in near-total absence of secretions, thereby suggesting that accessory conjunctival glands may not be present in the dog, or that they play an inconsequential role in aqueous secretions. The role of each gland (i.e., orbital or nictitans glands) in the production of basal secretions versus reflex tear secretions has not been determined.

The chemical mediators of lacrimal gland secretion are cholinergic agonists, released from parasympathetic nerves, and norepinephrine, released from sympathetic nerves, located in both the cornea and conjunctiva (Dartt, 2004; Dartt, 2009; Tiffany, 2008). These neurotransmitters activate signal transduction pathways affecting the myoepithelial, acinar, and duct cells, and blood vessels of the lacrimal gland leading to secretion. Other stimuli of lacrimal gland secretion include various proteins (i.e., EGF growth factor, neuropeptide Y, substance P, calcitonin gene-related peptide) and hormones (Dartt, 2004; Davidson & Kuonen, 2004; Lemp, 2008). Androgen deficiency results in lacrimal tissue degeneration, decreased total volume of tears, and decreased tear protein content (Baudouin, 2001; Sullivan et al., 2000).

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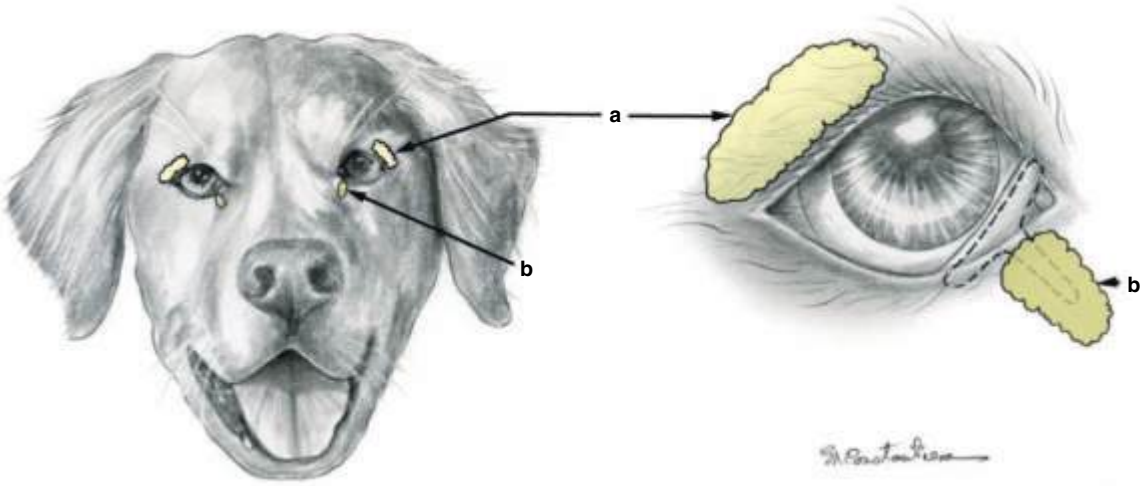


Figure 17.3 Topographic location of the orbital and nictitans lacrimal glands in the dog. a. Orbital gland. b. Nictitans gland. (*Source:* Courtesy of G. Constantinescu.)



Figure 17.4 Scanning electron micrograph of the bulbar surface of a canine third eyelid (nictitating membrane). A nictitans ductule opening onto the posterocentral surface of the third eyelid is well visualized. (Original magnification, 800×.)

Estrogen effects on the lacrimal gland remain controversial. Some studies have linked estrogen deficiency to the development of KCS, whereas others have shown no change in lacrimal gland or tear film (Sullivan et al., 1998).

Mucus, the third component to the PTF, is composed of mucin, immunoglobulins, urea, glycoproteins, salts, glucose, leukocytes, cellular debris, and enzymes (Davidson & Kuonen, 2004; Nichols et al., 1985; Royle et al., 2008). The mucus layer helps to provide a smooth refractive surface over the cornea, lubricates the cornea and conjunctiva, anchors the aqueous tear film to the corneal epithelium thus decreasing shear forces, inhibits bacterial adherence, and prevents desiccation (Davidson & Kuonen, 2004; Leonard et al., 2016). Neurologic regulation of goblet cell mucin production is more thoroughly reviewed elsewhere (Levin et al., 2011). Ocular surface mucins show differences in species-specific glycan expression, which likely has implications for their defensive properties where different microbial and environmental challenges are encountered (Royle et al., 2008). Mucins, classified as either secretory or membrane-bound, are hydrated glycoproteins produced largely by the conjunctival goblet cells but also by corneal and conjunctival epithelial cells, glycocalyx, and the lacrimal gland (Corfield, 1997; Ellingham et al., 1997; Hicks et al., 1997; Leonard et al., 2016; Watanabe, 2002). At present, many mucin (MUC) genes have been identified (Hicks et al., 1997; Hicks et al., 1998; Hirt et al., 2012; Leonard et al., 2016; Watanabe, 2002). Membrane-associated mucins are believed to: (1) promote water retention; (2) provide a barrier function against pathogens and debris; (3) participate in signal transduction (through EGF-like domains); and (4) interact with the actin cytoskeleton (Gipson, 2004; Leonard et al., 2016). Membrane-bound mucins are concentrated on the tips of the microplicae of stratified ocular surface epithelial cells and form a dense glycocalyx at the epithelial tear film interface (Gipson, 2004). Secreted mucins are soluble in the tear film and are distributed over the ocular surface during blinking, eventually shunted to the nasolacrimal duct. In this way, secreted mucins act both as debris-removing multimeric networks and by their hydrophilic nature, hold fluid in place and harbor defense molecules secreted by the lacrimal gland (Gipson, 2004). By contrast, membrane-bound mucins form a dense barrier in the glycocalyx at the epithelial tear film interface. This barrier both prevents pathogen penetrance and lubricates the ocular surface, allowing eyelid epithelia to glide over the corneal epithelia without adherence, thus decreasing shear forces and enhancing the spread, stability, and coherence of aqueous tears. The secreted mucins move easily over the glycocalyx mucins because both have anionic character that creates repulsive forces between them (Gipson, 2004).

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Conjunctival goblet cells are aprocrine secretory cells. In the dog, they are found at highest density in the conjunctival fornices and are the major source of preocular mucins (see Fig. 17.2) (Moore et al., 1987). Mature goblet cells become filled with mucin glycoprotein packaged as small droplets, which coalesce into larger droplets as the secretions move toward the cell's apex. After deposition of secretions onto the conjunctival surface, goblet cells lose their connections to the epithelial basement membrane and are desquamated. Bacteria and foreign particles are trapped by mucoproteins. Mucin also harbors immunoglobulins (i.e., immunoglobulin A) and lysozyme, and it aids in lubrication and hydration of the conjunctiva and cornea. Origin, secretion, and functions of ocular mucins have been thoroughly reviewed elsewhere in the veterinary ophthalmic literature (Davidson & Kuonen, 2004; Leonard et al., 2016).

In addition to the production of normal secretory components, health and function of the PTF depends on eyelid integrity, normal ocular motility, and an intact blink mechanism (King-Smith et al., 2008; Knop et al., 2010). As the eyelids close, the superficial lipid accumulates on the eyelid margins, where it is compressed into a relatively thick layer between the upper and lower eyelid margins. The melting range of PTF lipid ensures fluidity for its delivery from the meibomian glands to the tear film. However, lipid secretions exhibit a higher viscosity at the cooler temperature of the ocular surface, thus slowing tear evaporation from the ocular surface (Bron et al., 2004). Basal levels of aqueous tears are secreted into the conjunctival cul-de-sacs and bathe the globe with most of the tear volume remaining under the eyelids. It is believed that polar lipids, interacting with lipid-binding proteins in aqueous tears (i.e., lipocalin), spread in advance of the nonpolar components, which form the bulk of the tear film. With movement of the eyelids and globe, stretching of the fornix, and contact between the palpebral conjunctiva and cornea, mucin is released and spreads over the glycocalyces of surface cells. The continuous distribution of mucus glycoprotein over the ocular surface provides a hydrophilic interface between aqueous tear and the hydrophobic corneal and conjunctival epithelial cell membranes.

The tear film, lacrimal glands, and eyelids act together with the ocular surface as a functional unit to preserve the quality of the refractive surface of the eye and to protect the globe from injury (Maggio & Pizzirani, 2009a). Important to any discussion of the homeostasis of this functional unit is the mucosal immune system. The conjunctiva forms a continuous mucosal surface from the eyelid margin to the cornea and continuously contacts airborne antigens as well as those on adjacent eyelid skin and in the PTF (Chodosh & Kennedy, 2002; Stern et al., 2010). Conjunctival lymphoid follicles, routinely identified on the bulbar surface of the nictitans in dogs, will undergo hyperplasia upon stimulation by a variety of pathogens (Fig 17.5) (Alexandre-Pires et al., 2008; Cabral et al., 2005; Hong et al., 2011; Schiegel et al., 2003). In addition to innate defense mechanisms, an increasing body of evidence supports the role of conjunctival lymphoid cells to the normal homeostasis of the ocular surface as part of the body's larger mucosa-associated lymphoid tissue (MALT) (Chodosh & Kennedy, 2002; Knop & Knop, 2005; Huanga et al., 2010; Neutra & Kozlowski, 2006; Phillips et al., 2010). More specifically, eye-associated lymphoid tissue (EALT) is composed of conjunctiva-associated lymphoid tissue (CALT) and lacrimal drainage-associated lymphoid tissue (LDALT) (Knop & Knop, 2000, 2001, 2002a, 2002b, 2005; Steven & Gebert, 2009). Specialized antigen-sampling cells, known as M-cells, are found in the follicle-associated epithelium above organized lymphoid tissue in many mucosae (Liu et al., 2005; Meagher et al., 2005; Neutra & Kozlowski, 2006). M-cells play a key role in initiating the mucosal immune response and act as a site of entry for opportunistic pathogens. Canine and feline CALT contains M-cells analogous to those described in other regions of MALT (Fig 17.6) (Giuliano & Finn, 2011; Giuliano et al., 2002). The follicle-associated epithelium

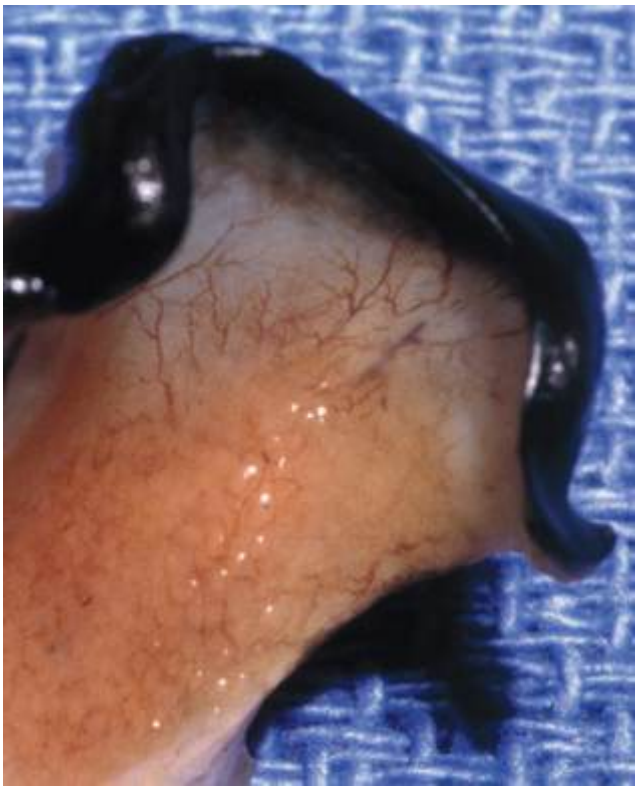


Figure 17.5 A canine third eyelid from a healthy research dog with a normal ocular examination and minimum ophthalmic database was removed and photographed immediately after humane euthanasia. Multiple lymphoid follicles can be visualized as round, raised nodules on the bulbar surface of the third eyelid. This is a common clinical finding in dogs when examining the bulbar (posterior) surface of the third eyelid and, without evidence of conjunctivitis or ocular irritation, is considered normal. The lymphoid follicles are important components of the conjunctiva-associated lymphoid tissue (CALT).

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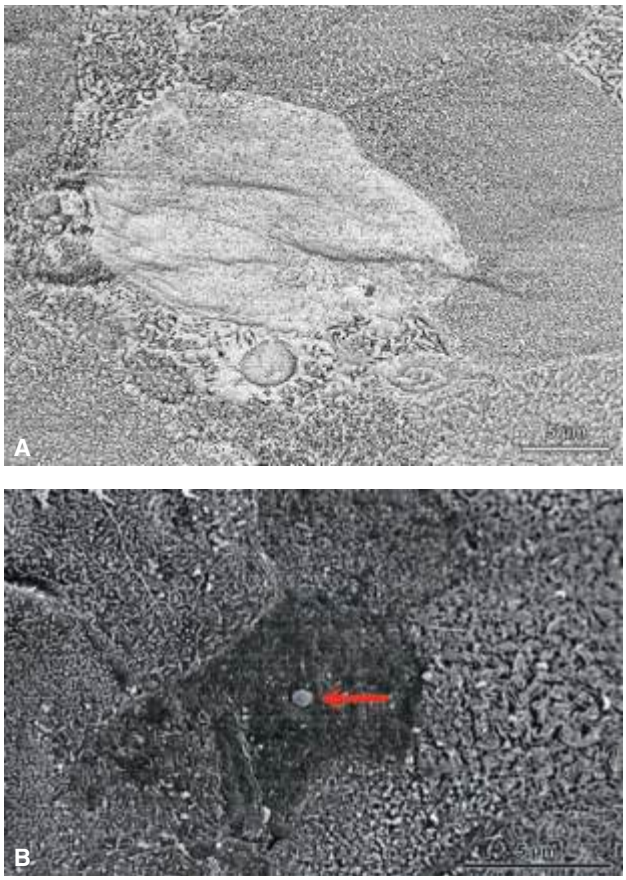


Figure 17.6 **A.** Representative scanning electron microscopy image of a feline conjunctival M cell. The follicle-associated epithelium on feline nictitan follicles show darker staining M cells that possess fewer, shorter, and less organized microvilli compared with the adjacent epithelial cells. **B.** M cells in mucosa-associated lymphoid tissue (MALT) have been shown to be responsible for antigen uptake. Note that the feline conjunctival follicle-associated epithelium M cell in this image appears to have bacteria, probably a *Staphylococcus*, adhered to its apical surface (arrow) and may be preparing to phagocytize this microorganism. (*Source:* Reprinted with permission from Giuliano, E.A. & Finn, K. (2011) Characterization of membranous (M) cells in normal feline conjunctiva-associated lymphoid tissue (CALT). *Veterinary Ophthalmology*, **14**(Suppl. 1), 60–66.)

overlying CALT in dogs and cats shows morphologic characteristic of M cells, including an attenuated apical cell surface with blunted microvilli and microfolds, invaginated basolateral membrane forming a cytoplasmic pocket containing lymphocytes and macrophages, and diminished distance between the apical and pocket membrane.

Pathogenesis of Tear Film Disease

Ocular surface health is ensured by a close relationship between the PTF and normal adnexal conformation and function. Normal tear production in dogs fluctuates slightly during the day (differences of less than 2 mm/min) in a predominantly nocturnal acrophase (Giannetto et al., 2009; Piccione et al., 2009) and decreases with age (Hartley et al., 2006). Tear production in puppies reaches normal levels by 9–10 weeks of age (Broadwater et al., 2010; da Silva et al., 2013; Verboven et al., 2014). Abnormalities in either the quantity or quality of any tear component (lipid, aqueous, mucus) may alter tear fluid dynamics and compromise tear function (Beckwith-Cohen et al., 2014; Bron et al., 2009; Foulks, 2007; Perry, 2008). Hypertonicity and dehydration of conjunctival and corneal epithelia are initial pathophysiologic events associated with tear deficiency (Sebbag et al., 2017). Hypoxia of the corneal epithelium and subepithelial corneal stroma also occurs early in the course of tear film disease (Johnson and Murphy, 2004). Lack of appropriate lubrication results in frictional irritation of the ocular surface by the eyelids and third eyelid. Potentially toxic tissue metabolites (i.e., lactic acid, desquamated cells, denatured mucus, other "micro" debris) may accumulate on the ocular surface as well. In tear-deficient patients, microorganisms more readily colonize affected eyes, thereby resulting in increased incidence of ocular surface infections (Petersen-Jones, 1997). Whatever the underlying cause of tear film disease, ocular surface inflammation results, which in turn becomes the cause and consequence of cell damage, creating a self-perpetuating cycle of deterioration (Maggio & Pizzirani, 2009b; Schaumburg et al., 2011; Stern et al., 2004).

In experimental canine keratoconjunctivitis sicca (KCS), thickening and degeneration of the conjunctival and corneal epithelium has been shown by electron microscopy (Kern et al., 1988). The intimate relationship between ocular surface cells and PTF is appreciated during tear-deficient diseases in which the surface epithelia undergo squamous metaplasia or necrosis (or both) with resultant inflammatory disease (Calonge et al., 2010; Izci et al., 2015; Johnson & Murphy, 2004; Tseng & Tsubota, 1997). Squamous metaplasia results in loss of expression of membrane-bound glycoproteins by the epithelial cells, thus preventing mucin adherence and resulting in further destabilization of the tear film. Because ocular surface epithelia and PTF are so closely related and function as a unit, the phrase "ocular surface and tear disorders" has been proposed as a more explicit description of these ocular surface phenomena (Tseng & Tsubota, 1997).

Disease states may cause decreased secretion of tear components by affecting the secretory tissues either directly or indirectly (e.g., by compromising the nerve supply to lacrimal glands). KCS, or dry eye, is the clinical condition associated with lacrimal gland hyposecretion. Insufficient aqueous fluid production is considered to be synonymous with quantitative tear deficiency. Abnormalities or deficiencies of tear components other than aqueous fluid are considered here to be qualitative disorders (Moore, 1990). Distributional abnormalities resulting from lagophthalmos, buphthalmos, eyelid

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paresis, corneal anesthesia, eyelid or nictitans deformities, or frictional irritants may result in abnormal tear coverage, with rupture of the tear film and concurrent surface drying. These disorders must be distinguished from primary quantitative or qualitative tear deficiencies.

Quantitative Tear Deficiency

KCS is a common ocular disease in the dog (Carter & Colitz, 2002; Williams, 2008). It is characterized by aqueous tear deficiency resulting in desiccation and inflammation of the conjunctiva and cornea, ocular pain, progressive corneal disease, and reduced vision (Fig. 17.7). In one report, the incidence of KCS in canine patients, as presented to the North American Veterinary Medical Colleges, is approximately 1% (i.e., 9–12 cases per 1000 admissions) (Table 17.1) (Helper, 1996).

Causes of Aqueous Tear Deficiency

Absence or reduction of lacrimal secretions may result from a single disease process or a combination of conditions affecting the orbital and nictitans glands (Table 17.2) (Carter & Colitz, 2002; Kaswan et al., 1998; Moore, 2000). Infectious causes of lacrimal adenitis in the dog include canine distemper virus (de Almeida et al., 2009; Martin & Kaswan, 1985), chronic blepharoconjunctivitis (Helper, 1996), and other ocular surface infections (Severin, 1973; Williams, 2008). Congenital causes include acinar hypoplasia (i.e., congenital alacrima), recognized as a breed-related cause in miniature breeds (Aguirre et al., 1971), and ichthyosiform dermatosis in Cavalier King Charles Spaniels (Forman et al., 2012; Hartley et al., 2012a, 2012b). Cases of congenital lacrimal gland hypoplasia are often unilateral, and they are characterized by extreme dryness (i.e., xerosis).

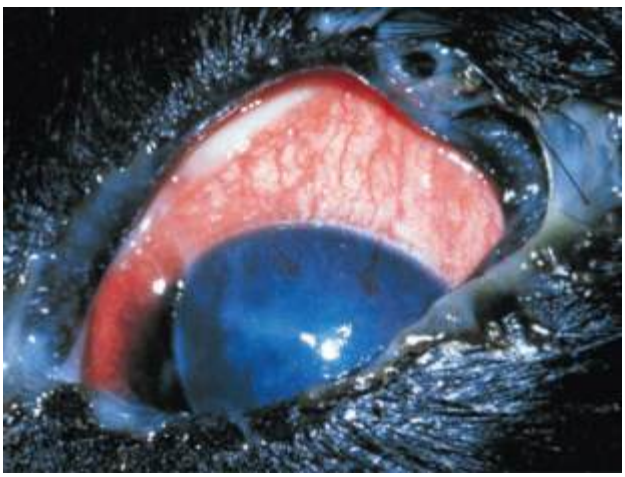


Figure 17.7 Left eye of a dog with keratoconjunctivitis sicca. Note the intense conjunctival hyperemia, thick mucopurulent discharge, and chronic keratitis characteristic of a subacute or chronic aqueous tear deficiency.

Drug-induced KCS may occur in the dog after systemic sulfonamide therapy or administration of topical atropine. Systemically administered sulfonamides causing KCS in dogs include phenazopyridine, sulfadiazine, sulfasalazine, and trimethoprim-sulfonamide combinations (Berger & King, 1998; Berger et al., 1995; Collins et al., 1986: Morgan & Bachrach, 1982: Trepanier, 2004; Trepanier et al., 2003). The mechanism for toxicity is not completely understood but may be caused by a T-cell mediated response to proteins haptenated by oxidative sulfonamide metabolites (Trepanier, 2004). With administration of relatively short duration, adverse effects on lacrimation are usually transient, and lacrimal function returns with discontinuance of the drug. Prolonged, systemic usage of these agents may cause permanent KCS after complete atrophy and fibrosis of the secretory structures. In one study, dogs receiving oral trimethoprim-sulfadiazine weighing less than 12 kg were at significantly greater risk of developing KCS (Berger et al., 1995). Certain nonsteroidal anti-inflammatory drugs have also been associated with KCS in dogs (Stiles, 2004). A retrospective study examined the features of KCS associated with oral administration of etodolac (EtoGesic®, Fort Dodge Animal Health, Fort Dodge, IA, USA) in 211 dogs (Klauss et al., 2007). In this report, dogs administered oral etodolac for less than 6 months prior to the diagnosis of KCS were 4.2 times more likely to experience complete resolution of KCS than dogs that were treated for 6 months or longer. One study examining the oral administration of diphenhydramine to dogs over 21 days showed decreased corneal sensitivity and tear film breakup time, although these effects were not deemed clinically important and a second study found no significant decrease in aqueous tear production in normal dogs after administration for 20 days (Evans et al., 2012; Montgomery et al., 2011).

Atropine administered as a preanesthetic agent transiently decreases tear production (Ludders & Heavner, 1979). Topically applied atropine, often used to treat anterior uveitis associated with ulcerative keratitis, may significantly decrease tear production in the dog (Hollingsworth et al., 1992). When corneal ulceration has occurred in cases of borderline or unrecognized tear deficiency, administration of atropine will exacerbate the dryness and complicate the ulcerative disease. Therefore, it should be used only "to effect" to achieve pupillary dilation. Single dose 1% tropicamide does not significantly lower tear production rates as measured by the STT in normal dogs, but further research is needed to evaluate multiple doses of tropicamide on canine tear production (Margadant et al., 2003). Both preanesthetic and anesthetic agents are also known to reduce tear secretion for at least 24 hours after an anesthetic event (Collins et al., 1995; Costa et al., 2015; Doering et al., 2016; Herring et al., 2000; Komnenou et al., 2013; Mayordomo-Febrer et al., 2017;

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Table 17.1 Cases of canine keratoconjunctivitis sicca (KCS) and parotid duct transposition reported by the American Veterinary Medical Data Program (1975–1996).

Year	Total new canine admissions all schools	Cases of KCS	KCS/100 admissions	Parotid transposition	Percent of KCS cases treated by parotid duct transposition
1975	69,561	261	3.75	36	13%
1976	54,731	277	5.06	40	14%
1977	51,300	278	5.42	50	17%
1978	54,688	271	4.96	39	14%
1979	51,471	325	6.31	53	16%
1980	53,677	373	6.95	58	16%
1981	49,478	366	7.40	27	7%
1982	48,267	375	7.77	46	12%
1983	53,351	451	8.45	53	12%
1984	55,403	630	11.37	39	6%
1985	50,566	641	12.68	45	7%
1986	48,978	605	12.35	46	7%
1987	49,475	646	13.06	57	9%
1988	56,993	746	13.09	32	4%
1989	48,529	675	13.91	15	2%
1990	75,997	725	9.54	29	1.6%
1991	60,068	681	11.34	10	1.7%
1992	49,994	563	11.26	17	3.0%
1993	46,789	562	12.01	7	1.2%
1994	39,258	473	12.05	8	1.7%
1995	33,303	381	11.79	7	1.8%
1996	20,605	188	9.12	5	2.6%

(*Source:* Modified from Helper, L.C. (1996) The tear film in the dog. Causes and treatment of diseases associated with overproduction and underproduction of tears. *Animal Eye Research*, **15**, 5–11.)

Pontes et al., 2010; Sanchez et al., 2006; Vestre et al., 1979). The duration of anesthesia has been shown to affect STT levels significantly, with anesthetic events longer than 2 hours in duration having a prolonged effect compared with those lasting less than 2 hours (Herring et al., 2000). Importantly, clinicians should be careful to regularly monitor all patients for development of KCS after cataract surgery (Gemensky-Metzler et al., 2015).

The nictitans gland is a significant contributor to the aqueous component of the PTF; thus, removal of this gland in dogs is an important iatrogenic cause of KCS (Plummer et al., 2008; Saito et al., 2001; Saito et al., 2004). Third eyelid removal may also increase the already high risk of KCS in breeds predisposed to the disease (Table 17.3) (Dees et al., 2015; Helper, 1996). Other conditions associated causally with canine KCS include uncorrected nictitans gland prolapse, traumatic or inflammatory orbital diseases, loss of parasympathetic innervation to the lacrimal glands (cranial nerve VII), and loss of sensory innervation (i.e., sensation) to the ocular surface (cranial nerve V) (Carter & Colitz, 2002; Kaswan & Salisbury, 1990; Kaswan et al., 1989; Kern & Erb, 1987; Wieser et al., 2013). KCS may also be a complication of local irradiation of head neoplasms (Pinard et al., 2012; Roberts et al., 1987) or seen as a long-term sequela to evisceration/prosthesis (Blocker et al., 2007). Decreased aqueous tear production may also occur secondary to trauma or systemic metabolic diseases such as hypothyroidism, diabetes mellitus, and Cushing's disease (Carter & Colitz, 2002; Kaswan & Salisbury, 1990; Sansom & Barnett, 1985) and congenital diseases such as ichthyosiform dermatosis in Cavalier King Charles Spaniels (Forman et al., 2012; Hartley et al., 2012a, 2012b).

Several breeds are disproportionately affected by acquired KCS, thus suggesting a genetic predisposition (Helper, 1996; Kaswan & Salisbury, 1990). In a review of 754 cases, Helper (Helper, 1996) found the breeds at greatest relative risk (RR)

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Table 17.2 Causes of keratoconjunctivitis sicca in the dog.

Chronic blepharoconjunctivitis
Congenital:
Pug
Yorkshire Terrier
Cavalier King Charles spaniel
Drug-induced:
Topical/general anesthesia
Topical/parenteral atropine
Drug toxicity:
5-Aminosalicylic acid
Phenazopyridine
Sulfadiazine
Sulfasalazine
Trimethoprim/sulfonamide
Immune-mediated:
Local
Systemic
Breed disposed (See Table 17.3)
Irradiation
Neurogenic
Surgically induced:
Excision of lacrimal/nictitans glands
Evisceration/prosthesis
Systemic disease:
Canine distemper
Metabolic disease
Trauma to the eye and orbit

(*Source:* Modified from Gelatt, K.N. (1991) Canine lacrimal and nasolacrimal systems. In: *Veterinary Ophthalmology* (ed. Gelatt, K.N.), p. 283. Philadelphia: Lea & Febiger.)

Table 17.3 Breed disposition to keratoconjunctivitis sicca (KCS).

Breed	Relative risk of KCS
Cavalier King Charles Spaniel	11.5
English Bulldog	10.8
Lhasa Apso	9.8
Shih Tzu	6.2
West Highland White Terrier	5.5
Pug	5.2
Bloodhound	4.5
American Cocker Spaniel	4.1
Pekingese	4.0
Boston Terrier	2.0
Miniature Schnauzer	1.8
Samoyed	1.7
All breeds	1.0

(*Source:* Modified from Kaswan, R.L. & Salisbury, M.A. (1990) A new perspective on canine keratoconjunctivitis sicca: treatment with ophthalmic cyclosporine. *Veterinary Clinics of North America: Small Animal Practice*, **20**, 583.)

of developing KCS were English Bulldogs (RR, 12.5), West Highland White Terriers (RR, 5.5), and Pugs (RR, 4.5). Other breeds found to have a high RR (>2.0) were Yorkshire Terriers, American Cocker Spaniels, Pekingese, Miniature Schnauzers, and English Springer Spaniels. Kaswan and Salisbury (Kaswan & Salisbury, 1990) later confirmed an increased risk in six of the top seven breeds listed by Helper, and they added Boston Terriers, Cavalier King Charles Spaniels, Lhasa Apsos, Bloodhounds, and Samoyeds as additional high-risk breeds (see Table 17.3). Gender has also been identified as a significant factor in West Highland White Terriers, whereby females are predisposed to KCS. More recent studies have supported earlier findings of breed and gender predispositions for this disease (Barnett, 2006; Herrera et al., 2007; Sanchez et al., 2007; Westermeyer et al., 2009).

Although the list of possible causes of KCS is extensive (see Table 17.2), in many cases the definitive cause is not determined. Histopathologic studies of the lacrimal tissue from dogs affected with idiopathic KCS have revealed varying degrees of mononuclear cell (i.e., lymphocytic-plasmacytic) infiltrates associated with acinar atrophy, thereby suggesting an immunologic basis for the disease (Kaswan et al., 1984). Given these histopathologic features, reports of concurrent immunopathies (i.e., hypergammaglobulinemias) (Kaswan et al., 1983), and the response to immunomodulating therapy (discussed later), immune-mediated KCS is believed to constitute a large percentage of clinical cases. KCS may be associated with systemic autoimmune conditions (Kaswan et al., 1985), but canine KCS appears to occur more often as a localized tissue-specific, immune-mediated disorder.

Clinical Findings in Keratoconjunctivitis Sicca

Clinical signs of KCS will vary depending on the period of time since onset and the extent of dryness. A very acute, severe form of KCS is sometimes seen, in which the eye becomes acutely painful in association with corneal ulceration. In such cases, suppurative inflammation may result in progressive corneal disease with stromal malacia, descemetocele formation with resultant staphyloma, and iris prolapse (Fig. 17.8). In most cases, however, onset of KCS is more gradual, with increasing severity over a period of several weeks.

In the early stage of the typical disease, affected eyes initially appear to be red and inflamed, with intermittent mucoid or mucopurulent discharge. Because clinical signs are nonspecific in early disease, KCS may be misdiagnosed as an irritant or primary bacterial conjunctivitis (Fig. 17.9). As the severity of the KCS increases, however, the ocular surface becomes lackluster, the conjunctiva appears to be extremely hyperemic, and persistent tenacious mucopurulent ocular

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Figure 17.8 Acute onset keratoconjunctivitis sicca in a 5-year-old female pug with mucopurulent discharge, hyperemic conjunctiva, and an infected axial corneal ulcer, stromal malacia, diffuse corneal edema, and ciliary flush OD.



Figure 17.9 A 4-year-old female spayed Boston Terrier with keratoconjunctivitis sicca (KCS). This patient presented early in the course of her disease. Note mucoid ocular discharge, moderate conjunctival hyperemia, and mild chemosis OD. The dog had Schirmer tear test values of 8 and 10 mm of wetting/60 seconds OD and OS, respectively. This case illustrates the importance of performing a complete ophthalmic minimum database to avoid the misdiagnosis of KCS as an allergic or primary bacterial conjunctivitis.

discharge is observed. If KCS is not recognized and treated appropriately, progressive keratitis characterized by extensive corneal vascularization and pigmentation with or without ulceration may occur (Fig. 17.10 and Fig. 17.11). Severe pigmentary keratitis may be refractory to medical and surgical therapy (Fig. 17.12) (Stiles et al., 1995). Blepharitis and periocular dermatitis often occur simultaneously with an accumulation of exudates on the eyelid margins and periocular skin. With progressive disease, the level of discomfort intensifies, thus resulting in persistent blepharospasm.

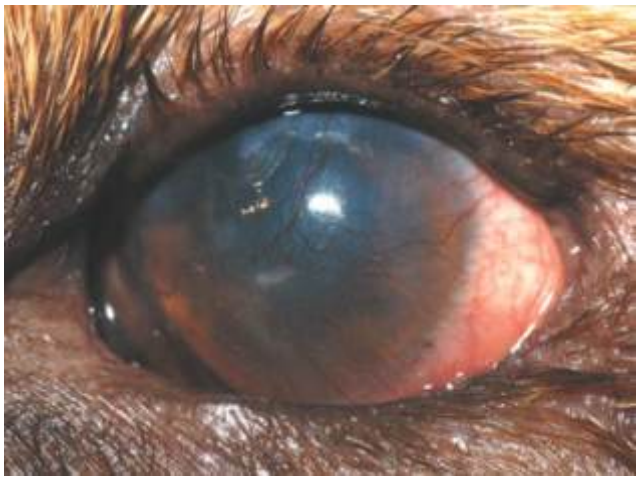


Figure 17.10 A 6-year-old male, castrated mixed-breed dog with chronic keratoconjunctivitis sicca. Note the marked conjunctival hyperemia, lackluster appearance to the corneal surface, and superficial corneal neovascularization OS.



Figure 17.11 A 10-year-old female spayed Chihuahua with keratoconjunctivitis sicca. Conjunctival hyperemia is evident as the upper eyelid is retracted in this extraocular photograph, and extensive pigmentary keratitis precludes the view of the pupil OS.

In acute KCS, the initial histopathologic changes of the cornea include epithelial degeneration with vacuolization and thinning of the epithelium (Fig. 17.13). The cornea is not initially infiltrated with inflammatory cells or blood vessels, but with progressive loss of epithelium, suppurative keratitis and stromal ulceration may occur, thereby inducing a marked fibrovascular response. In chronic KCS,

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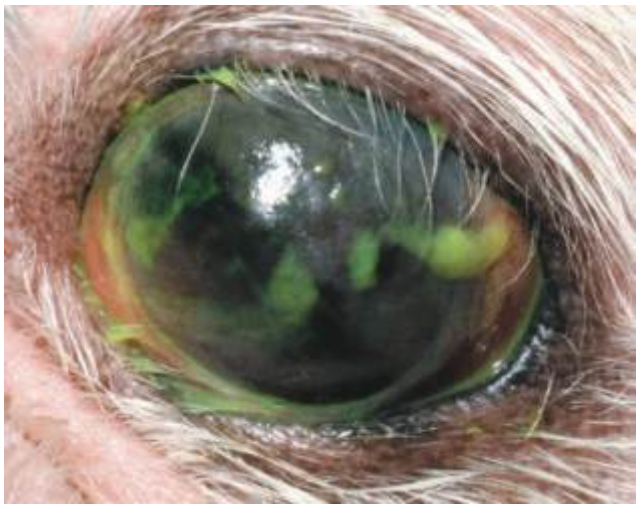


Figure 17.12 An 8-year-old female spayed Shih Tzu with chronic keratoconjunctivitis sicca. Note the mucopurulent discharge highlighted by fluorescein stain and the extensive pigmentary keratitis OS. In addition to tear deficiency, predisposing factors for the pigmentary keratitis include an inherently heavily pigmented eye, conformational exophthalmos, and frictional irritation to the cornea (entropion-trichiasis).

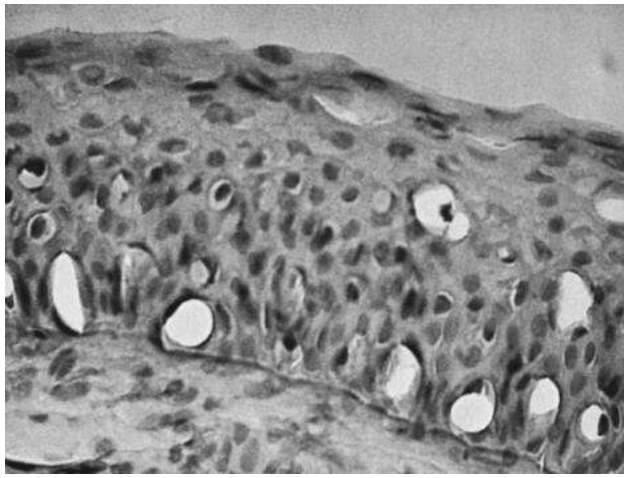


Figure 17.13 Acute keratoconjunctivitis sicca in a dog. Note the evidence of corneal epithelial degeneration and increased thickness of this layer. (Original magnification, 400×. Hematoxylin and eosin.) (*Source:* Reprinted with permission from Gelatt, K.N. (1991) Canine lacrimal and nasolacrimal diseases. In: *Veterinary Ophthalmology* (ed. Gelatt, K.N.), 2nd ed., pp. 276–289. Philadelphia: Lea & Febiger.)

the corneal epithelium becomes hyperplastic and keratinized, and melanin pigment granules are noted throughout the epithelium and anterior stroma (Fig. 17.14). With chronicity, the basal epithelium appears to be undulated, forming epithelial pegs, and the anterior corneal stroma becomes extensively vascularized and diffusely infiltrated with plasma cells and lymphocytes.

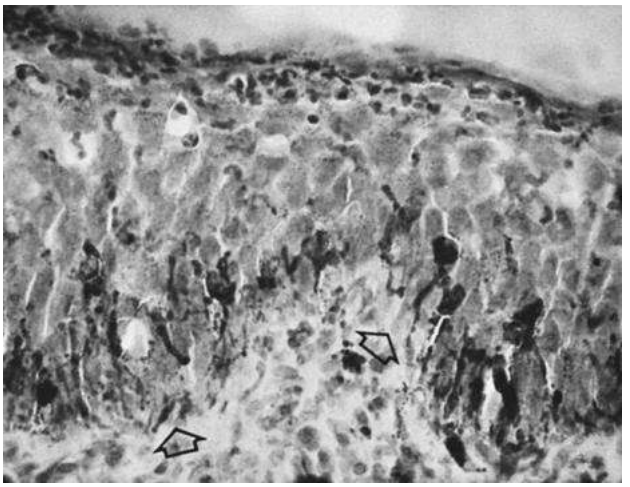


Figure 17.14 Chronic keratoconjunctivitis sicca in a dog. Note the increased thickness and pigmentation of the corneal epithelial layer. Rete formation is also present (arrows). (Original magnification, 400 ×. Hematoxylin and eosin.) (*Source;* Reprinted with permission from Gelatt, K.N. (1991) Canine lacrimal and nasolacrimal diseases. In: *Veterinary Ophthalmology* (ed. Gelatt, K.N.), 2nd ed., pp. 276–289. Philadelphia: Lea & Febiger.)

Diagnosis of Aqueous Tear Deficiency

The diagnosis of KCS is made on the basis of typical clinical signs, positive ocular staining using vital stains, and reduced quantitative tear readings. Rose Bengal stain will detect devitalized cells, subtle epithelial defects on either the conjunctiva or corneal surfaces, and adherent mucus tags (Gelatt, 1972). The phenol-red-thread tear test is a method of tear measurement that employs a small thread placed in the ventral conjunctival fornix for 15 seconds; a normal range of 30–38 mm of wetting per 15 seconds has been determined by one study (Brown et al., 1996) and 29.3 mm ± 3.45 mm of wetting per 15 seconds in another (Saito & Kotani, 2001). Fluorescein stain detects concurrent corneal ulceration and may also be used to evaluate tear breakup (discussed later). Tear ferning and strip meniscometry have been recently reported (Rajaei et al., 2017; Williams & Hewitt, 2017). The Schirmer tear test (STT), however, remains the standard means for quantifying aqueous tear production (Gelatt et al., 1975). Canine patients with a red, irritated eye and ocular discharge, with or without corneal disease, should undergo STTs.

STTs may be done either without (i.e., STT I) or with (i.e., STT II) use of topical anesthetic (Berger & King, 1998; Gelatt et al., 1975; Hamor et al., 2000). STT I measures the ability of the eye to produce reflex tears in addition to basal secretions, and is the most commonly performed test, whereas STT II estimates only basal tear secretion (Hamor et al., 2000). STT I and STT II values are significantly different in the normal dog (Berger & King, 1998; Gelatt et al., 1975;

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Hamor et al., 2000) and vary with age (Broadwater et al., 2010; Hartley, 2008). In the clinical setting, STT I readings in dogs are generally interpreted as follows:

- ≥15 mm/min = normal production
- 11–14 mm/min = early or subclinical KCS
- 6–10 mm/min = moderate or mild KCS
- ≤5 mm/min = severe KCS

Variation in absorbency among tear test strips manufactured by different companies has been documented in a number of different studies, therefore the same brand should be used for repeated measures in a given patient (Hawkins & Johnson, 1985; van der Woerdt & Adamcak, 2000; Wyman et al., 1995). Some tear test strips are impregnated with a dye that marks the test strip at the level of tear fluid migration, thereby allowing easier reading of the results (Wyman et al., 1995). In a comparison of test results from conventional strips versus color-bar strips, no significant differences were found (Hirsh & Kaswan, 1995). For additional information, the reader is referred to the ocular examination Chapter 10, Part 1.

Repeat STT measurement is advised in dogs stressed by examination or receiving medical therapy for ulcerative corneal disease, because either factor (i.e., sympathetic stimulation or current topical treatments such as atropine) may reduce tear secretions. A relatively small percentage of affected dogs will not have clinically apparent disease despite low STT readings. These cases may represent transient or borderline KCS cases and they should be closely monitored with follow-up examinations, including subsequent STTs. Fluctuations in STT values may occur on both a daily and a weekly basis; however, only weekly fluctuations are considered to be biologically significant (Hawkins & Johnson, 1985; Hawkins & Murphy, 1986). Body weight also has a significant effect on STT values, with higher values being measured in larger dogs (Hawkins & Murphy, 1986).

The evaluation of patients with KCS should include examination for possible associated systemic diseases (e.g., hypothyroidism), assessment of eyelid function and blink reflexes, and in selected cases, ocular surface cultures and cytology (Calonge et al., 2004). Secondary bacterial conjunctivitis is common in dogs with KCS, and resistant organisms can develop after prolonged administration of topical antibiotics or long-term immunosuppressive therapy (Beckwith-Cohen et al., 2016; Driver & Lemp, 1996). Therefore, antibiotic susceptibility testing may be an important adjunctive component to the diagnostic assessment of a dog with KCS.

Qualitative Abnormalities

Problematic cases of KCS can occur in which aqueous tear volume appears to be adequate and other recognized causes of surface disease (e.g., infection, frictional irritation, ineffectual blinking) have been excluded. In such instances, qualitative tear deficiency from an abnormality of either the lipid or the mucin tear components may be a primary (or a contributing) cause of the surface disease.

Causes of Qualitative Tear Deficiencies

Disturbances of the tarsal or meibomian glands may result in abnormal secretions and subsequent disruption of the superficial lipid layer of the tear film (Bron & Tiffany, 1998; Bron et al., 2004; Butovich, 2011). With diseased meibomian glands, highly polar lipids are produced that disrupt the nonpolar lipid surface of the tear fluid (Holly, 1987; McCulley & Sciallis, 1977; McCulley & Shine, 2004). The resultant loss of the normal oily covering may allow premature dispersion of the aqueous layer. Abnormal lipids may also be directly toxic to surface cells. Surface disease probably results from a combination of insults, including poor surfacing of the tear film, frictional irritation from disturbed eyelid margins, and toxic effects from abnormal secretion or inflammatory products (Pflugfelder et al., 2007).

Inflammation of the mucocutaneous junction, which is referred to as marginal blepharitis, usually involves the meibomian glands. Marginal blepharitis, blepharoconjunctivitis, and meibomianitis are commonly caused by suppurative bacterial infections (i.e., *Staphylococcus* sp.) and result in swelling of the eyelid margin, accumulation of exudates, and abnormal lipid secretions (Moore, 1990). Yeast organisms, including *Candida* and *Malassezia* sp., may also cause infectious blepharitis. Yeast infections most often occur after chronic administration of topical antibiotic–corticosteroid combinations.

Dogs with generalized seborrhea may produce abnormal meibomian lipids. By affecting the mucocutaneous junctions, autoimmune diseases such as lupus erythematosus and bullous pemphigoid may affect the eyelid margins and meibomian secretions. It should be noted that some dogs have relatively serious meibomian gland disease with little or no apparent corneal changes. These patients usually have abundant aqueous tear production, thus suggesting that reflex tearing may compensate for the lack of tear conservation. It is also possible that toxic inflammatory products and abnormal lipids are simply diluted or flushed away by the aqueous tears.

Deficiency of meibomian secretion resulting from maldevelopment of the meibomian glands, though rare, has been reported in humans (Bron & Mengher, 1987). Eyelid agenesis is a relatively uncommon congenital condition of small companion animals in which affected areas of the eyelid are devoid of normal eyelid tissue, including meibomian glands. Most cases are seen in cats and the predominant clinical signs are epiphora, conjunctivitis, and superficial keratitis. Surface pathology presumably results from the combined insults of absent meibomian secretions, exposure, trichiasis, and in some cases, spastic blepharitis.

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Insufficient production of preocular mucin also results in loss of tear film stability, with subsequent corneal desiccation (Bron, 1997; Moore, 1990). In the dog, pathogenesis of spontaneously occurring, mucin-deficient dry eye disease may vary among cases (Moore & Collier, 1990). Chronic, diffuse conjunctival inflammatory cell infiltrates may reduce or eliminate goblet cells. Although the cause for these infiltrates is often not determined, both infectious and immune-mediated mechanisms have been hypothesized (Moore & Collier, 1990).

Severe cicatrization after diffuse ulcerative conjunctival disease is another cause of abnormal epithelium and goblet cell loss. The relative avascularity of the conjunctiva that occurs with scarring has been proposed to result in decreased blood supply and local deficiency of essential nutrients (e.g., vitamin A) in the conjunctival mucosa (Tseng, 1985; Tseng & Tsubota, 1997; Tseng et al., 1984, Tseng et al., 1985). Experimentally induced vitamin A deficiency results in squamous metaplasia of the conjunctiva, with abnormal keratinization of the secretory epithelium and loss of conjunctival goblet cells (Soong et al., 1988).

Clinical Findings in Qualitative Tear Abnormalities

Dogs with acute meibomianitis typically have swollen eyelid margins, with slight "pointing" of the meibomian openings. Affected openings may be plugged with dried or discolored meibum. Chronic meibomianitis may result in rupture of glandular acini and release of lipid secretions into the periacinar tissues. Formation of lipid granulomas and multiple chalazia may frictionally irritate the eye and complicate any tear film abnormality present (Fig 17.15).



Figure 17.15 Seven-year-old female spayed Maltese with meibomianitis (*Source:* Courtesy of Dr. Claudia Hartley, Animal Health Trust, UK.)

In some cases of chronic meibomianitis, superficial keratitis is also present. Clinical findings in this keratopathy may be somewhat subtle, with faint localized or geographic epithelial edema, small and multifocal punctate areas of roughened epithelium that may or may not retain fluorescein stain, as well as fine and superficial perilimbal vascular infiltrates. The corneal disease present in such cases likely may be attributable to both deficient lipid with unstable tear film and direct frictional effects from roughened eyelid margins.

Loss of conjunctival goblet cells results in an unstable tear film, as manifested by rapid breakup of the PTF, lackluster appearance of the ocular surface, and corneal desiccation (Moore & Collier, 1990). Clinical features of preocular mucin deficiency in the dog may include chronic keratoconjunctivitis, corneal ulceration, and absence of appreciable ocular discharge in the presence of adequate aqueous tear measurements. In some cases, the conjunctiva may appear to be thickened and inelastic.

Diagnosis of Qualitative Tear Deficiencies

Making the diagnosis of lipid tear abnormalities depends on findings from a detailed examination using a focused light and a magnifying source. A slit-lamp biomicroscope is recommended, though binocular magnifying loupes and a separate focal light source (e.g., a Finoff transilluminator) may be used. During examination, particular attention is focused on the appearance of the eyelid margins and meibomian glands. With the eyelid everted, the serial arrangement of multiple meibomian glands is normally noted just beneath the tarsal conjunctiva. Individual glands should appear parallel to adjacent glands and perpendicular to the eyelid margin. Visualization of the glands may be enhanced by transillumination of the eyelid.

Swollen, rounded eyelid margins indicate acute or subacute marginal blepharitis. Hyperemia of the mucocutaneous junction, with dry, crusty, porphyrin-stained exudates on the lid margins, is also indicative of marginal blepharitis. Any elevated, focal, beige subconjunctival masses typical of chalazia should be noted (Fig. 17.16). When present, chalazia indicate chronic meibomianitis with periglandular granulomatous inflammation.

After administration of a topical anesthetic solution, gentle manipulation of the eyelid margin using blunt-tipped forceps with shallow serrations will allow inspection of secretions expressed from the meibomian glands. Normal meibomian lipid is a relatively clear, viscous oil, similar in appearance to vegetable cooking oil. Abnormal meibomian secretions are typically thick, opaque, and may appear to be inspissated, with a cream-cheese consistency. Expression of coiled, semisolid strands of abnormal lipid is not uncommon in chronic meibomian disease.

The technique of polarized light biomicroscopy has been used to characterize ocular surface lipid morphology in

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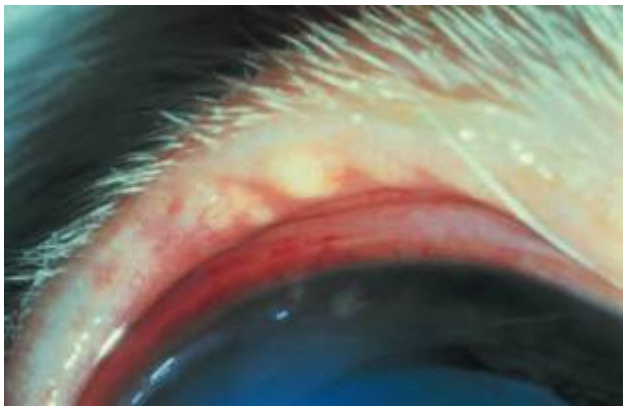


Figure 17.16 Right upper eyelid of a dog with meibomian gland disease and multiple chalazia. Note the beige nodules resulting from inspissated contents of obstructed meibomian glands. Mild superficial keratitis is also present. (*Source:* Reprinted with permission from Moore, C.P. (1990) Qualitative tear film disease. *The Veterinary Clinics of North America. Small Animal Practice*, **20**, 565–581.)

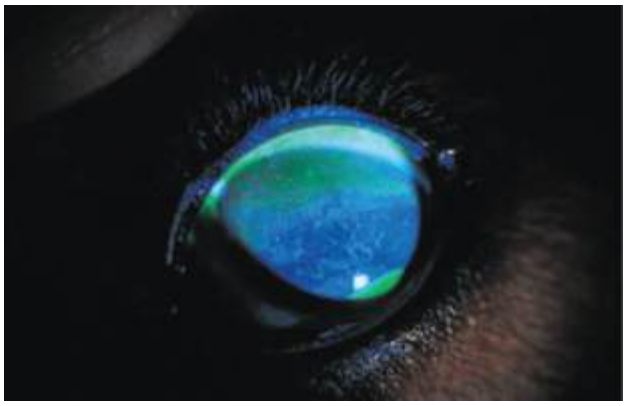


Figure 17.17 Tear film breakup time (TBUT) test can be performed in the dog with some difficulty. Immediately after instillation of one drop of fluorescein stain, the eyelids are digitally held open, and the dispersion of fluorescein is observed with a portable slitlamp microscope using a cobalt filter. The TBUT is the time from instillation of the dye to the first appearance of fluorescein dissipation, as evidenced by the appearance of dark spots on the cornea.

normal dogs and to study surface abnormalities in dogs with confirmed or suspected tear film disease (Carrington et al., 1987a, 1987b). Patterns of lipid distribution were described, and the overall thicknesses of surface lipids using polarized light biomicroscopy were judged to be between 0.013 and 0.581 μm in normal dogs. Further research is needed to confirm normal canine ocular lipid thickness and to validate this technique. Other techniques such meibometry in dogs have been reported with variable results (Benz et al., 2008; Ofri et al., 2007).

The clinical diagnosis of canine ocular mucin deficiency may be supported by the results of a tear film breakup time test (Fig. 17.17). The diagnosis may also be confirmed by the results of conjunctival biopsy and quantification of epithelial goblet cells. The tear breakup time evaluates the ability of the corneal surface to retain a homogeneous tear covering. Tear film breakup time is performed by instilling one drop of fluorescein stain into the eye, then manually holding the eyelids open. The time is recorded from the last blink to the appearance of the first dry spot, which appears as a dark area in the yellow-green fluorescent film. A cobalt-blue filter should be used when viewing the cornea. The normal breakup time in dogs should be 20 seconds or longer (Moore et al., 1987). In animals affected with mucin deficiency, however, tear breakup usually occurs in less than 5 seconds (Moore & Collier, 1990).

Determination of goblet cell numbers from conjunctival biopsy specimens provides an indirect measure of mucin production. Collecting a sample of conjunctiva for histopathology involves instilling a topical anesthetic solution, using Bishop-Harmon forceps to tent an area of conjunctiva from the ventral fornix just anterior to the base of the third eyelid, and removing a 3- × 4-mm specimen with conjunctival scissors. Because a heterogeneous density and distribution of conjunctival goblet cells has been shown in the dog, a conjunctival site with the highest and most predictable density of goblet cells should be selected for sampling; the reader is referred to the original article for complete description of technique and interpretation of results (Moore et al., 1987). In dogs suspected to be mucin-deficient, the most optimal area for conjunctival biopsy is the lower medial fornix, between the third eyelid and the lower eyelid.

Treatment of Tear Film Deficiencies

Medical Treatment

Medical therapy is the primary means of treating tear-deficient ocular surface disease. Specific treatment regimens are tailored to individual patients and are influenced by the underlying pathogenesis, disease severity, and owner's ability to comply with recommended treatment schedules. Treatment generally consists of some combination of the following: tear stimulation, tear replacement, topical and/or oral antimicrobial agents, mucinolysis, and anti-inflammatory therapy.

Lacrimostimulants

Lacrimostimulants, which are drugs administered to promote tear secretion, include two categories of therapeutic agents: cholinergics and immunomodulators.

Cholinergic Agents

The lacrimal gland is innervated by both the parasympathetic and sympathetic branches of the autonomic nervous system (Dartt, 2009; Klauss & Constantinescu, 2004; Matheis

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et al., 2012). The parasympathetic innervation of the lacrimal gland has enabled cholinergic drugs to be used to stimulate tear secretions in select cases. Ophthalmic pilocarpine solution has been administered, either topically or orally, as a tear stimulant (Matheis et al., 2012; Rubin & Aguirre, 1967; Smith et al., 1994). The use of pilocarpine for dry eye is indicated in cases of KCS resulting from parasympathetic denervation of the lacrimal glands (e.g., neurogenic KCS) and will only be effective if some functional lacrimal gland remains (Klauss & Constantinescu, 2004; Tsifetaki et al., 2003; Vivino et al., 1999) (Fig. 17.18). Oral administration has consisted of applying 1%–2% ophthalmic solution to the food; a safe initial oral dosage is one drop of 2% topical pilocarpine per 10 kg of body weight twice daily. The dose may be increased by one-drop increments at each dosing until signs of systemic toxicity develop (i.e., salivation, vomiting, diarrhea, cardiac arrhythmias). The dose should then be lowered to the previously tolerated dose. Alternatively, topical dilute pilocarpine has been applied directly to the eyes. Concentrations of either 0.125% or 0.25% have been formulated by adding 1 mL of 2% pilocarpine to 15 mL of artificial tears (0.125% solution) or 2 mL of 2% pilocarpine to 14 mL of artificial tears (0.25% solution). Topical pilocarpine may cause blepharospasm, conjunctival hyperemia, and miosis. In some cases, sufficient irritation results for topical treatments to be discontinued. The irritative effects of topical pilocarpine may be controlled with use of topical steroidal or nonsteroidal anti-inflammatory agents (Giuliano, 2004; Holmberg & Maggs, 2004). The route of pilocarpine administration is determined by the individual patient's tolerance of one method over the other. One study performed on normal dogs found that topically applied pilocarpine did not significantly increase tear production (Smith et al., 1994).

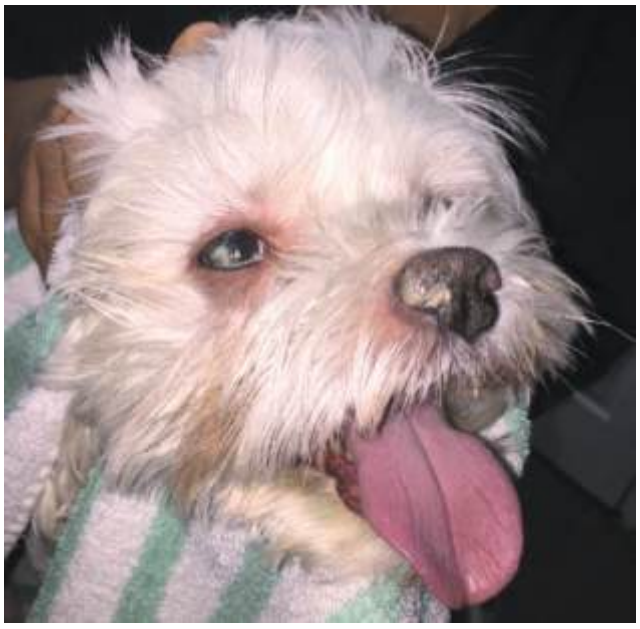


Figure 17.18 Extraocular photograph taken by the author of a 6-year-old male castrated West Highland White Terrier exhibiting classic clinical signs of neurogenic keratoconjunctivitis sicca OD.

Immunomodulating Agents

Cyclosporine A (CsA), a derivative of the fungus *Tolypocladium inflatum*, and tacrolimus (formally FK 506), a macrolide antibiotic produced by *Streptomyces tsukubaensis*, are both T-cell activation inhibitors initially developed for their systemic uses in preventing graft rejection after organ transplantation. Although structurally nonhomologous, the mechanism of action of both CsA and tacrolimus is similar: T-cell proliferation and activation are altered by the inhibition of interleukin (IL)-2 gene expression in $CD4^+$ T helper lymphocytes. IL-2 transcription blockage leads to impaired T-helper and T-cytotoxic proliferation (Moore, 2004). More specifically, CsA binds intracellularly to a specific immunophilin known as cyclophilin (CpN) and tacrolimus binds to immunophilins called FK506-binding proteins (FKBPs). Calcium-dependent calcineurin (CaN), sometimes called phosphatase 2B, is a key rate-limiting enzyme in T-cell signal transduction via its effect on nuclear transcription factors of activated T cells. In brief, when CsA crosses the lymphocyte's cell membrane, it binds to CpN and the resulting complex (CsA-CpN) binds to CaN, thus preventing CaN's normal induction of IL-2 production. More detailed description of the intracellular mechanisms of action have been reviewed elsewhere (Moore, 2004). In addition to reduction of IL-2 release from lymphocytes, these drugs interfere with IL-2 receptors on lymphocyte surfaces. CsA and tacrolimus have been reported to reduce eosinophil production, block mast cell degranulation, and suppress tumor necrosis factor-α by B cells (Moore, 2004; Thomson, 1992; Vaden, 1997). Topical CsA has also been noted to reduce conjunctival epithelial apoptosis in chronic canine and human KCS (Gao et al., 1998; Stonecipher et al., 2005; Strong et al., 2005).

When administered systemically as an immunosuppressive agent to humans with normal tear flow, CsA stimulates lacrimal secretions (Palmer et al., 1995, 1996). The ability of CsA to stimulate tear production in the dog is well documented (Bounous et al., 1995; Fullard et al., 1995; Hadži-Milić et al., 2013; Kaswan & Salisbury, 1990; Kaswan et al., 1989). Both immuno-modulating and tear-stimulating properties appear to account for the dramatic responses observed in many affected dogs after topical application (Fullard et al., 1995). In animal models of immune-mediated lacrimal disease, the balance between T-suppressor and T-helper cells plays an important role in lacrimal gland regulation. T-suppressor cells normally predominate, but in immune-mediated KCS, T-helper cells become the prevalent T lymphocytes (Jabs & Prendergast, 1987). Therefore, it is believed that by inhibiting T-helper cells in KCS, CsA allows the T-suppressor cells to sustain normal lacrimal function.

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Most cases of canine KCS are presumed immune mediated. CsA has been the primary treatment for KCS in the dog for over two decades (Bounous et al., 1995; Izci et al., 2002; Kaswan & Salisbury, 1990; Sansom et al., 1995; Olivero et al., 1991) and has now been approved for topical use in people with dry eye (Perry & Donnenfeld, 2004; Sall et al., 2000; Stevenson et al., 2000; Stonecipher et al., 2005; Tang-Liu & Acheampong, 2005). Before the commercial availability of CsA for ophthalmic use, 1%–2% oil-based solutions were compounded from 10% oral CsA solution using a vegetable oil (i.e., olive or corn oil) solvent. Currently, either the 0.2% commercial ointment (Optimmune®, Merck Animal Health, Madison, NJ, USA) is prescribed or different formulations (e.g., aqueous-based, higher concentrations of CsA) are obtained through compounding pharmacies. The vehicle used for the commercial product is reported to maximize the bioavailability of active drug (Fullard et al., 1994). Use of episcleral cyclosporine implants in canine KCS patients is useful in those cases where daily topical drug therapy has proven difficult because of either patient or client compliance issues (Barachetti et al., 2015). Tacrolimus and pimecrolimus, calcineurin inhibitors, have both been shown to improve tear production in dogs (Berdoulay et al., 2005; Hendrix et al., 2011; Nell et al., 2005; Ofri et al., 2009; Radziejewski & Balicki, 2016). In two studies, the efficacy of topical tacrolimus compared with cyclosporine for treating KCS in dogs, both drugs were found to increase STT values significantly in affected dogs over time and tacrolimus may be effective in dogs nonresponsive to cyclosporine (Hendrix et al., 2011; Radziejewski & Balicki, 2016). Investigation into new agents for the treatment of canine KCS is on-going, including autografts and stem cell therapy (Arnold et al., 2014; Bittencourt et al., 2016; Bunya et al., 2017; Chen & Powell, 2015; Cherry et al., 2018; Gilger et al., 2013; Linares-Alba et al., 2016; Murphy et al., 2011; Park et al., 2013; Spatola et al., 2018; Villatoro et al., 2015; Wood et al., 2012).

To stimulate tear production, these agents are generally recommended for initial application every 12 hours to affected eyes; however, in severe cases, treatments may be initially administered every 8 hours. Several weeks of continuous treatment are usually needed before substantial increases in tear production are observed. Alternatively, in cases where treatments have been administered every 12 hours, if STT values remain at or less than 10 mm/min after 3 weeks of topical therapy, the topical frequency may then be increased to every 8 hours. To provide the most accurate assessment of response to CsA, measuring tear production 3 hours after topical administration is recommended (Kaswan & Salisbury, 1990). If a favorable response to treatment every 12 hours restores tears to physiologic levels (i.e., STT $\geq$20 mm/min), topical immunomodulating therapy can usually then be reduced to once daily, as maintenance therapy. Dogs with STT values of 0–1 mm/min have an approximately 50% chance of responding to topical CsA with increased tear secretion; dogs with pretreatment STT values of 2 mm/min or greater have a more than 80% chance of improved tear production (Kaswan & Salisbury, 1990). In responsive animals, return of functional secretory tissues has been shown histologically after topical CsA treatment (Bounous et al., 1995). Most dogs will show clinical improvement as evidenced by a decrease in mucopurulent discharge, corneal vascularization, and pigmentation even without increased tear production, including those with STT values of 2 mm/min or less. Many dogs benefit from the transition to, or the addition of, topical tacrolimus (Fig. 17.19 and Fig. 17.20).

A number of other presumed immune-mediated keratopathies have been treated successfully with topical immunomodulating therapy including chronic superficial keratitis (pannus), plasmacytic conjunctivitis, eosinophilic keratoconjunctivitis, superficial punctuate keratitis, and nodular granulomatous episclerokeratitis (Jackson et al., 1991; Moore, 2004; Nell et al., 2005; Williams et al., 1995). Although topical CsA therapy has been widely used for over two decades and appears relatively free of undesirable side effects, it does reach the systemic circulation in both dogs and people (Gilger et al., 1995; Small et al., 2002). In dogs, topical 2% cyclosporine has been shown to cause a suppression of lymphocyte proliferation after 1–3 months of use in one study (Gilger et al., 1995). Another study, using radioimmunoassay and enzyme-multiplied immunoassay techniques, found no change in lymphocyte stimulation index and low blood levels of cyclosporine after topical administration of either 0.2% or 2% cyclosporine (Williams, 2010). Although clinically evident altered peripheral cellular immunity has not been documented with long-term use of topical CsA ophthalmic



Figure 17.19 A 10-year-old male castrated Shih Tzu with chronic keratoconjunctivitis sicca. Treated with intermittent topical antibiotic/steroid combination ointment and twice-daily topical CsA therapy for 4 years. Note extensive dried eyelid exudate, marked thickened mucopurulent ocular discharge, moderate conjunctival hyperemia, and corneal neovascularization OD.

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Figure 17.20 Same dog as in Fig. 17.19 1 month after discontinuing topical CsA therapy and instituting twice daily topical 0.02% tacrolimus ointment. The patient exhibited a marked improvement in mucopurulent discharge and ocular comfort. Corneal neovascularization was slightly improved from previous examination 1 month prior.

preparations at doses that are clinically efficacious for treating canine KCS, long-term topical immunomodulating therapy may predispose canine patients to surface disease and infection (Beckwith-Cohen et al., 2016). A report of a Chinese Pug undergoing treatment for chronic KCS with a combination of 0.2% CsA, 0.03% tacrolimus, and neopolydex ointments in both eyes over a 6-year period may have predisposed the dog to corneal and conjunctival infections with *Toxoplasma gondii* (Swinger et al., 2009). Chronic KCS treated with topical immunosuppressive therapy may also be a risk factor for developing primary corneal SCC in dogs (Dreyfus et al., 2011).

Tear Substitutes (Lacrimomimetics)

Tear substitutes contain ingredients, or combinations of ingredients, to replace deficiencies in one or more of the three primary tear components (i.e., aqueous, mucin, lipid). Many ophthalmic solutions and ointments are commercially available for tear replacement therapy (Table 17.4) and new products frequently emerge on the market. Selection of a particular agent is influenced by the nature of the deficiency, availability, cost, clinician preference, patient compatibility, and owner acceptance. Aqueous tear replacement agents may initially be applied four to six times daily to affected eyes and are generally used concurrently with other topical therapeutic agents. Although more frequent applications (i.e., q. 1 or 2 hours) are often desirable, this treatment regimen is rarely possible or practical for the pet owner to accomplish. Despite their limitations, lacrimomimetics are warranted in the treatment of qualitative tear film abnormalities and as an adjunct to lacrimostimulant therapy for quantitative tear film deficiencies. Given the plethora of commercially available lacrimomimetics today, veterinarians are cautioned to carefully review any literature that professes improved corneal "repair" (e.g., wound healing times) by use of one or more such substances (Williams & Mann, 2014, 2013; Williams et al., 2012). Published references rarely compare the test product to a topical control with similar viscosity, thus rhealogical biomechanics between eyelid and PTF are dramatically different (for example, hyaluronic acid or carboxymethylcellulose test agents compared with saline controls). A recent study found that topical addition of a viscoelastic lacrimomimetic did not accelerate corneal wound healing compared with a topical control with similar viscosity in dogs (Gronkiewicz et al., 2017).

Methylcellulose products are virtually inert, water-soluble, viscous, semisynthetic cellulose colloids. Because cellulose derivatives are nonirritating to the eye and compatible with most drugs, they are commonly used as aqueous tear substitutes and aqueous vehicles for other ophthalmic preparations. Polyvinyl alcohol (PVA) is a synthetic hydrophilic resin that is less viscous than methylcellulose but has good corneal adhesive properties. Usually provided as a 1.4% solution, PVA is the primary ingredient in a number of artificial tear products. Because nonviscous polymers are very well tolerated by most human patients, many products containing PVA have been formulated and marketed commercially. Viscous lubricants enhance ocular surface wettability and have extended contact time with the ocular surface. Linear polymers such as dextran and polyvinylpyrrolidone (povidone) have mucinomimetic properties. Polymers have been combined with buffered solutions of substituted cellulose esters to form preparations for treating deficiencies of both the aqueous and mucin components of the preocular tear film. Among tear substitutes advocated for their lubricating and hydrating properties, solutions containing linear polymers remain on the eye for longer periods than solutions without these derivatives.

Viscoelastic substances with mucinomimetic properties include sodium hyaluronate, chondroitin sulfate, and 1%–2% methylcellulose preparations (Nepp et al., 2001). Sodium hyaluronate is a naturally occurring, high-molecular-weight glycosaminoglycan with excellent viscoelastic and lubricating properties. Evaluation of the biologic and physical properties of these substances typically show excellent rheologic properties (i.e., elasticity, viscosity, and pseudoplasticity), thereby indicating these lacrimomimetic formulations should serve as effective viscoelastic and protectants for the ocular surface (Gronkiewicz et al., 2017; Larson & Balazs, 1994). Chondroitin sulfate, which is a glycosaminoglycan polymer made of disaccharide units, is slightly less viscous than sodium hyaluronate.

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Table 17.4 Tear substitutes.[a]

Product	Viscosity agents/concentration(s)	Preservative	Source
Polyvinyl alcohol solutions			
AKWA Tears	PVA 1.4%	BAC	Akorn
Artificial Tears	PVA 1.4%	BAC	Many
LiquiTears	PVA 1.4%	BAC	Major
Cellulose-based solutions			
Refresh Celluvisc	CMC 1%	None	Allergan
GenTeal Mild	HPMC 0.2%	None	Alcon
GenTeal Mild to	HPMC 0.3%	None	Alcon
Moderate	HPMC 0.3%	None	Alcon
GenTeal Moderate to	CMC 0.25%		
Severe			
Gonak	HPMC 2.5%	BAC	Akorn
Goniovisc	HPMC 2.5%	BAC	Contacare
Bion Tears	HPMC 0.3%	None	Alcon
Isopto Tears Plain	HPMC 0.5%	BAC	Alcon
Refresh Tears	CMC 0.5%	None	Allergan
Refresh Plus	CMC 0.5%	None	Allergan
Retaine	CMC 0.5%	None	Ocusoft
Polymer combinations			
GenTeal Mild Lubricant	DEX-70 0.1%, HPMC 0.3%	POLYQUAD or PF	Alcon
Natural Balance Tears	DEX-70 0.1%, HPMC 0.3%	BAC	Major
Nature's Tears	DEX-70 0.1%, HPMC 0.3%	BAC	Rugby
GenTeal Moderate	DEX-70 0.1%, Glycerin 0.2%, HPMC 0.3%	None	Alcon
Tears Naturale Forte	DEX-70 0.1%, Glycerin 0.2%, HPMC 0.3%	POLYQUAD	Alcon
Optixcare	Carbomer, Sorbitol	EDTA, Cetrimide	CLC Medica
Clear Eyes Natural	PVA 0.5%, Povidone 0.6%	BAC	Meditech
Tears	Povidone 2%, PVA 2.7%	POLYQUAD	Focus
FreshKote Lubricant	PEG-400 1%, PVA 1%	BAC	Alcon
Hypo Tears	HPMC 0.3%, DEX-70 0.1%	None	Novartis
Bion Tears	Glycerin 0.3%, Propylene glycol 1%	BAC	Bausch & Lomb
Moisture Eyes	DEX-70 0.1%, HPMC 0.8%	BAC or PF	Bausch & Lomb
Moisture Eyes Liquid Gel	PVA 1.4%, Povidone 0.6%	None	Allergan
Refresh Classic	CMC 0.5%, Glycerin 0.9%	None	Allergan
Refresh Optive	CMC 0.5%, Glycerin 1%, PSB 0.5%	None	Allergan
Refresh Optive Advanced	PEG-400 0.4%, Propylene glycol 0.3%	None	Rugby
Lubricant Eye Drops	PEG-400 0.4%, Propylene glycol 0.3%	POLYQUAD or PF	Alcon
Systane Lubricant	Glycerin 0.2%, HPMC 0.2%, PEG-400 1%	BAC	McNeil
Visine Dry Eye Relief	Glycerin 0.2%, HPMC 0.2%, PEG-400 1%	None	McNeil
Visine Pure Tears Portables			
Viscoelastic Products			
i-drop Vet Gel	Hyaluronate 0.3%, Glycerin	None	I-Med Pharma
i-drop Vet Plus	Hyaluronate 0.25%	None	I-Med Pharma
Remend Drops	0.4% Hyasent-S	None	Bayer
Remend Gel	0.75% Hyasent-S	None	Bayer

(Continued)

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Table 17.4 (Continued)

Product	Viscosity agents/concentration(s)	Preservative	Source>
Glycerin, propylene glycol, and PEG Products			
Clear Eyes Pure Relief	Glycerin 0.25%	None	Meditech
Systane	Propylene glycol 0.6%	POLYQUAD	Alcon
Opti-Free Balance	Propylene glycol 0.6%	POLYQUAD	Alcon
Moisture Eyes	Propylene glycol 0.95%	None	Bausch & Lomb
Blink Tears	PEG-400 0.25%	Sodium Chlorite	Abbott
Ointments			
AKWA Tears Ointment	White petrolatum 83%, MO 15%, lanolin 2%	None	Akorn
Soothe Night Time	White petrolatum 80%, MO 20%	None	Bausch & Lomb
Refresh PM	White petrolatum 57.3%, MO 42.5%	None	Allergan
Stye Sterile Lubricant	White petrolatum 57.7%, MO 31.9%	None	Meditech
Puralube	White petrolatum 85%, MO 15%	None	Paddock
GenTeal Nighttime PM	White petrolatum 85%, MO 15%	None	Novartis
Sterilube Nighttie	White petrolatum 85%, MO 15%	None	FERA
Artificial Tears	White petrolatum 57.3, MO 42.5%	None	Rugby
Systane Nighttime	White petrolatum 94%, MO 3%	None	Alcon
Tears Naturale PM	White petrolatum 94%, MO 3%	None	Alcon
Refresh Lacri-Lube	White petrolatum 56.8%, MO 42.5%	Chlorobutanol	Allergan
Advanced Eye Relief Nighttime	White petrolatum 80%, MO 20%	None	Bausch & Lomb

BAC, benzalkonium chloride; CMC, carboxymethyl cellulose; DEX, dextran; EDTA, ethylenediaminetetraacetic acid; GEL, gelatin; HEC, hydroxyethyl cellulose; HPMC, hydroxypropyl methylcellulose; MC, methylcellulose; MO, mineral oil; PEG, polyethylene glycol; POLYQUAD, polyquaternium-1; PSB, polysorbate 80; PVA, polyvinyl alcohol; PF, preservative free.
[a] Percentage composition given where information available.
(*Source:* Compiled December 1, 2017, courtesy of Brandon Haake, PharmD)

Lanolin, petrolatum, and mineral oil are used as bases for ophthalmic lubricating ointments. These ingredients mimic the function of naturally occurring meibomian lipids by preventing evaporation, thus preserving existing tears. Because ointments may cause blurring of vision in humans, use of these products is primarily limited to bedtime, as an adjunct to artificial tears used throughout the day. Nonmedicated ophthalmic ointments containing one or more of these ingredients are used to lubricate and protect eyes when corneal exposure is a problem, such as during anesthesia and surgery or in cases of eyelid paresis or eyelid swelling.

Ointment vehicles prolong corneal and conjunctival contact for agents such as corticosteroids and antibiotics. Antibiotic ointments may be more economical than and as effective as straight lubricants, with the additional advantage of antibacterial effects. Ointment bases may also provide a sustained-release mechanism for delivering lipophilic agents such as CsA. Although ophthalmic ointments remain on the eye longer, they may be more difficult than drops for some owners to apply. With the ointment cap firmly sealed, warming the tube of ointment under hot water for 10–15 seconds immediately prior to ointment instillation can facilitate application.

Preservatives (e.g., benzalkonium chloride, chlorobutanol, methylparthimerosal) are often used in lacrimomimetic formulations to maintain stable solutions in multiple-dose bottles and to prolong shelf life (Grahn & Storey, 2004). If a tear replacement containing preservative is recommended, topical application should be limited to six or fewer applications per day to avoid epithelial toxicity (Ubels et al., 1995). Preservative-free tear solutions should be used when more frequent application is indicated.

Antibacterials

Antibiotics with broad-spectrum activity, such as triple antibiotic ointment or solution, are commonly administered to control secondary bacterial infections which occur in KCS cases because of inadequate cleansing of the ocular surface (Petersen-Jones, 1997). Initially, frequency of treatment is usually three to four times daily, which may then be reduced to twice daily as mucopurulent discharge decreases and eventually discontinued when signs of infection have abated

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(Kern, 2004). In cases of persistent mucopurulent discharge, bacterial culture and sensitivity testing as well as fungal culture should be performed.

Mucinolytic–Anticollagenase Agents

Good ocular hygiene (i.e., frequent cleansing of discharges) is essential to minimize the accumulation of debris with degradative enzymes that contribute to ocular surface inflammation and ulceration. To facilitate removal of copious exudates and mucoid debris that may accompany KCS, a 5%–10% solution of acetylcysteine may be applied topically two to four times daily. In addition, the anticollagenase properties of acetylcysteine may aid in preventing enzymatic degradation of surface tissues and may be useful in treatment of corneal ulceration. Acetylcysteine solution has been advocated as one component of a combination solution for treating dry eye (i.e., Severin's KCS solution), which also contains artificial tears, pilocarpine, and an antibiotic. At present, Severin's KCS solution is infrequently used because of the sometimes irritating nature of this combination and the newer, more effective lacrimostimulants (e.g., CsA, tacrolimus) currently available.

Anti-Inflammatory Therapy

Anti-inflammatory therapy may be a valuable adjunct to other medical therapy in improving clinical signs of KCS (Giuliano, 2004; Holmberg & Maggs, 2004). Topical corticosteroids are commonly administered to minimize conjunctivitis, to alleviate discomfort, and to reduce corneal opacities associated with chronic keratitis. Triple-antibiotic ointment in combination with dexamethasone is beneficial in many KCS patients. Caution must be exercised, however, when administering topical corticosteroids, because their use may significantly complicate healing of an ulcerated cornea. Therefore, these agents are contraindicated when the cornea retains fluorescein stain. Chronic administration of topical corticosteroids can also cause local immunosuppression and predispose the eye to secondary infections and ulceration (Beckwith-Cohen et al., 2016).

In addition to its marked lacrimostimulant effects, topical CsA also has beneficial anti-inflammatory properties (e.g., reducing corneal inflammatory infiltrates). Although some conflicting reports exist, use of CsA is deemed safe in the presence of noninfected corneal ulceration, and CsA does not appear to substantially alter corneal wound healing or ocular surface flora (Salisbury et al., 1995) (Fig 17.21). CsA and other immunomodulators (e.g., tacrolimus, pimecrolimus) may also be beneficial in reducing corneal vascularization in dogs with chronic keratitis from causes other than KCS (Jackson et al., 1991).

Miscellaneous Considerations

Other Considerations in Aqueous Tear Deficiency

Cases of acute KCS may present with corneal stromal ulceration requiring aggressive medical or surgical therapy (or both). Because opportunistic infections may contribute to rapid degradation of ulcerated cornea, bacterial culture of the ulcer margins with subsequent sensitivity testing is indicated. When corneal ulceration occurs as a sequela to KCS, local atropine administration should be used judiciously and only for as long as is necessary to treat the concurrent uveitis, because surface drying will be exacerbated by its application. In cases of deep stromal ulceration or descemetocele formation, reconstructive corneal surgery (i.e., conjunctival grafting) may be necessary to stabilize the cornea and to stimulate fibrovascular resolution of the ulceration (Fig. 17.22).



Figure 17.21 KCS-affected eye after 3 weeks of treatment with topical CsA. Initial Schirmer tear test (STT) reading was 2 mm/min, and a central stromal ulcer was present before treatment. Note the absence of discharge and minimal conjunctival hyperemia. STT reading increased to 13 mm/min after topical therapy. Granulation tissue seen in the axial cornea is a result of the resolving stromal ulceration.

Special Considerations in Qualitative Tear Deficiencies

Specific treatment of lipid tear abnormalities depends on the particular meibomian disorder. Because opportunistic and pathogenic infections are often present in cases of acute and chronic meibomianitis, aerobic bacterial cultures of expressed secretions may be indicated. Antibiotics should be selected on the basis of antibacterial susceptibility testing results. Bacterial meibomianitis should be treated with both topical and systemic antibiotics. Oral tetracyclines and omega 3 fatty acids are commonly recommended in people (Lemp, 2008) and have been shown to reach the tear film in dogs (Collins et al., 2016). Chronic bacterial meibomianitis is often recurrent and requires intermittent, intensive treatments or continuous, low-level maintenance therapy; topical application of an antibiotic ointment two to three times daily may be indicated as long-term maintenance therapy in some cases. In such cases, periodic expression of meibomian material from the glands with blunt-tipped, mildly serrated thumb forceps after application of topical anesthesia may also be helpful in removing inspissated secretions.

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Figure 17.22 A 5-year-old female spayed Pug with keratoconjunctivitis sicca and corneal ulceration. A conjunctival pedical graft was performed 4 weeks prior. The graft is vascularized and well-adhered to the corneal stromal defect. Tear production has improved on topical CsA therapy; however, pigmentary keratitis persists.

In cases of granulomatous blepharitis secondary to ruptured meibomian glands, concurrent administration of systemic corticosteroids may be necessary to resolve the diffuse eyelid swelling. Surgical curettage of chalazia is indicated to permit resolution of focal granulomas. Warm, moist compresses applied to the eyelids for several minutes two to three times daily may stimulate local vasodilation and result in improved hemodynamics to the affected areas. In addition, exudates may be softened and removed by regular use of moist eyelid compresses, particularly during the initial treatment period.

Another aspect of treating diffuse meibomian diseases is providing lipid substitutes through topical emollients containing petrolatum, mineral oil, liquid lanolin, or some combination of these ingredients (see Table 17.4). In addition to serving as lipid substitutes, emollients lubricate the ocular surface, which is especially beneficial during treatment of conjunctival granulomas (Fig. 17.15 and Fig. 17.16). Antibiotic or antibiotic–corticosteroid ointments contain emollients and may be quite useful in treating surface disease resulting from meibomianitis.

Congenital absence of meibomian glands associated with eyelid agenesis is usually treated both medically and surgically. Grafting of periocular skin into the defective area using either a pedicle or sliding/rotational skin flaps will partially restore eyelid function (Whittaker et al., 2010). In addition to surgical reconstruction of the affected eyelid, topical application of lubricant ointments will generally provide a lipid-like effect to enhance wetting of the ocular surface.

Treatment for mucin-deficient keratoconjunctivitis consists of topical mucin replacements (i.e., mucinomimetics), symptomatic treatment of corneal ulcers if present, and topical anti-inflammatory therapy in selected cases. Topical mucinomimetics (see Table 17.4) applied at 4- to 6-hour intervals are the mainstay of therapy. The more viscous lubricants mimic mucin by enhancing ocular surface wettability and providing extended contact time with the epithelial surfaces.

Conjunctival inflammatory cells appear to inhibit normal goblet cell populations (Moore, 1990), thus topical anti-inflammatory therapy may be indicated when marked mucosal and submucosal mononuclear inflammatory cell infiltrates are noted on histopathology. When ulcerative keratitis is present, corticosteroids should not be administered until the ulcerations have healed, as evidenced by negative fluorescein stain retention. In addition, any concurrent infections must be treated simultaneously with appropriate antimicrobials (Kern, 2004). Results of *in vitro* studies have shown CsA to increase mucus production in a secretory cell line capable of producing goblet cell mucin (Phillips et al., 2000). In addition to its known anti-inflammatory effects, these *in vitro* findings, together with a canine KCS *in vivo* study whereby 2% CsA restored conjunctival mucin stores to control levels over a 4-week period after surgical removal of both lacrimal and nictitans, suggest CsA may also be beneficial in treating mucin deficiencies because of its direct secretagogue activity (Moore et al., 2001).

Use of topical retinoic acid in treatment of mucin-deficient ocular surface disease has been reported. In people with KCS, Stevens–Johnson syndrome, ocular pemphigoid or drug-induced pseudopemphigoid, and surgery or radiation-induced dry eye, all-trans retinoic acid ointment has resulted in some reversal of squamous metaplasia as evidenced by impression cytology, as well as clinical improvements in symptoms, vital stain testing, and STT in some reports (Tseng, 1985; Tseng et al., 1985). Other studies have found no real beneficial effect of topical retinoid therapy for various ocular abnormalities characterized by squamous metaplasia (Soong et al., 1988). Naturally occurring vitamin A deficiency is extremely uncommon in the dog, so the availability of retinoic acid products suitable for topical application has been limited to experimental protocols. Therefore, topical vitamin A has not generally been recommended for treatment of mucin-deficient surface disease in dogs.

Miscellaneous therapies for KCS include the use of topical androgen and topical nerve growth factor, but further research is warranted to fully understand their potential applications in veterinary ophthalmology (Coassin et al., 2005; Worda et al., 2001). Acupuncture has been advocated by some veterinary ophthalmologists and scattered reports exist in the human literature (Gronlund et al., 2004). A preliminary study was performed to evaluate the effectiveness of oral use of interferon-alpha (IFN-alpha) in the treatment of naturally occurring, immune-mediated, canine KCS (Gilger et al., 1999). Study dogs were each given either two

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or three separate escalating doses (20, 40, 80 IU) of the IFN-alpha. A favorable response was observed in 55% (11/20) of all dogs treated. Clinical findings of those dogs that responded included increased wetting of the eyes, decreased mucus discharge, and fewer signs of discomfort. Nutraceutical diets as an adjuvant to pharmacological treatment in dogs affected by KCS has been reported (Destefanis et al., 2016).

Surgical Treatment of Tear Deficiencies

Surgical procedures indicated for treatment of selected KCS cases are parotid duct transposition (PDT), which provides saliva as a substitute for tears, and permanent partial tarsorrhaphy, which reduces exposure and enhances blinking. Nasolacrimal puncta occlusion is commonly used in humans as a tear-conserving procedure by blocking tear drainage and has been reported in the treatment of canine KCS (Gelatt et al., 2006; Williams, 2002). However, in the total absence of tears these puntal occluders are not effective. Replacement of the nictitans gland (versus gland removal) is regarded as a preventative surgical procedure for canine KCS.

Parotid Duct Transposition

Physiologic similarities between saliva and tear fluid, including similar osmolarity and pH, led to the supposition that saliva might serve as a substitute for tears (Table 17.5). PDT surgery was subsequently developed for humans to provide symptomatic relief in cases of refractory KCS. From the mid-1960s to mid-1980s, before CsA was available, this surgery was also being performed successfully in dogs affected with KCS nonresponsive to medical therapy (Baker & Formston, 1968; Gelatt, 1970; Glen & Lawson, 1971; Jensen, 1979; Lavingnette, 1966; Severin, 1973). After the introduction of CsA in 1987, the percentage of KCS cases treated by PDT declined dramatically (see Table 17.1) (Helper, 1996). Nonetheless, the few dogs with persistent absolute sicca (STT, 0 mm/min) after several weeks of medical treatment remain candidates for PDT (Rhodes et al., 2012).

Table 17.5 Composition of parotid and tear secretions in humans.

Characteristic	Parotid secretion	Lacrimal secretion
pH	5.2–8.4	5.3–7.8
Osmolarity	Physiologic	Physiologic
Lysozyme	Present	Present
Translucency	Clear	Clear
Total solids (%)	1.8	1.6
Ash	1.05	0.81

(*Source:* From Gelatt, K.N. (1991) Canine lacrimal and nasolacrimal systems. In: *Veterinary Ophthalmology* (ed. Gelatt, K.N.), p. 283. Philadelphia: Lea & Febiger.

Preoperative Considerations

In the dog, PDT is usually delayed until KCS has proved unresponsive to at least 8 weeks of conventional medical therapy. For cases in which even a minimal response is noted to medical treatment during this period, treatment should be extended for an additional 4 weeks before recommending PDT. Dogs with KCS may occasionally have xerostomia and these animals are not candidates for PDT surgery. Testing flow of salivary fluid from the parotid duct is easily done by administering a bitter substance (e.g., one drop of ophthalmic atropine solution or lemon juice) to the tongue and observing for salivary flow from the papilla.

The parotid gland is located at the junction of the head and neck, near the base of the ear canal. From a lateral perspective, the parotid gland is a "V"-shaped structure, with the apex of the gland directed ventrally (Fig. 17.23). The main duct is formed by the convergence of two or three small branches arising from the ventral anterior border of the gland and uniting over the masseter muscle, several millimeters from the gland. The duct extends subcutaneously over the surface of the masseter muscle, courses forward across the face, and opens into the buccal cavity at a



Figure 17.23 Location of the left parotid gland and the duct coursing rostrally through the facial soft tissues to its point of exit into the oral cavity. Dashed lines illustrate the course of the transposed duct resulting from parotid duct transposition surgery. Insert: placement of the oral papilla after transposition and attachment of papilla to the ventral conjunctival fornix via interrupted 7-0 polyglactin 910 sutures. (*Source:* Courtesy of G. Constantinescu.)

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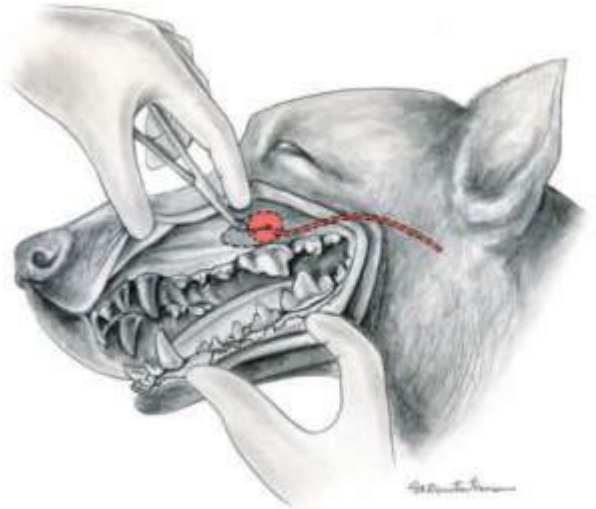


Figure 17.24 Location of the parotid papilla adjacent to the fourth upper premolar and presurgical cannulation with monofilament nylon suture. The incision around the papilla is outlined with dashed lines. The shaded area rostral to the papilla represents the area included in the initial incision around the cannula suture. The circular area around the papilla represents the area of mucosa subsequently retained and sutured to the conjunctiva. (*Source:* Courtesy of G. Constantinescu.)

single papilla slightly posterior and lateral to the fourth upper premolar tooth and rostral to the zygomatic papilla (Fig. 17.24). Duct size and length vary depending on the breed, with mesocephalic breeds having a diameter of approximately 1.5 mm and a length of approximately 6 cm. Small dogs and brachycephalic breeds typically have smaller and shorter ducts, respectively. Because the parotid duct lies in close proximity to the dorsal and ventral buccal nerves (including the interconnecting branches) as well as the facial vein, care must be taken not to damage these structures during PDT surgery.

The teeth should be cleaned before PDT surgery, and when periodontal disease is present, systemic antibiotics should be administered for 7–10 days before the operation. The choice of anesthetic is not particularly critical when performing PDT but use of atropine in the preanesthetic regimen has caused concern because of the possibility of impeding duct cannulation. Although systemic atropine transiently reduces salivary secretions, experienced PDT veterinary ophthalmologists do not report any particular difficulty in cannulating the parotid duct as a result of preanesthetic atropine.

After induction of general anesthesia and insertion of an endotracheal tube, the oral cavity is flushed and swabbed with betadine solution diluted (1:10) with physiologic saline. The parotid duct is cannulated by placing a monofilament nylon suture into the duct opening. Optimal suture size may range from 0-0 to 2-0 depending on the size of the duct. Suture with a swaged-on cutting needle is necessary so that the needle may subsequently be used to anchor the suture to the oral mucosa. Before cannulation, the tip of the nylon suture may be momentarily flamed, forming a small, smooth "bulb" on the end of the suture. Curved mosquito forceps are used to grasp the nylon suture 4 to 5 mm from the end and to direct the suture tip into the duct. The mucosa in grasped just anterior to the papilla with Bishop-Harmon forceps, and the blunted suture end is inserted into the opening as the mucosa is gently pulled forward.

After the suture has been introduced into the duct, it is gently threaded with the curved forceps to the proximal end of the duct until the suture exhibits slight resistance or recoil. The suture should not be forced beyond this point. The attached needle is inserted into the mucosa just rostral to the papilla, is pulled through, and the slack is drawn out, leaving only a small loop of suture between the papilla and mucosal anchor. Using this loop, a knot is tied, and the suture is securely anchored to the mucosa (Fig. 17.25). The mucosal anchor suture allows the suture material with attached mucosa to be manipulated during surgery, thereby minimizing direct manipulation of mucosa and any possible associated trauma to the parotid papilla. As a final step in preparation for the surgery, cotton or gauze soaked with betadine solution is placed against the mucosa and over the papilla, and the lip is returned to its normal position.

Either of two approaches (i.e., closed [oral] or open [lateral]) may be used when performing PDT surgery. Both approaches appear to be equally effective, and the choice of an open versus closed PDT procedure is simply one of surgeon preference.



Figure 17.25 Before performing parotid duct transposition surgery, the parotid duct is cannulated with monofilament nylon suture. To minimize surgical manipulation of the papilla during the procedure, the suture is anchored to the oral mucosa approximately 1 cm rostral to the papilla, and the resulting loupe of suture is grasped and handled during the surgical procedure. The mucosal incision is then made around the papilla and anchor suture.

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Closed Procedure

In the closed PDT procedure, the antiseptic-soaked cotton or gauze packing is removed from the mouth. An oral speculum is placed between the canine teeth of the opposite side, and the lip is raised and stretched, thereby exposing the papilla. Using a No. 15 Bard-Parker blade, an elliptical incision is made in the oral mucosa, around the papilla posteriorly and the fixed nylon suture anteriorly. A minimum of 3 mm of mucosal tissue should be left surrounding the papilla posteriorly. More than this is left anteriorly, however, because the incision is made rostral to the anchor suture (see Fig. 17.24).

The submucosal space is entered with conjunctival scissors, and the papilla and attached mucosa (including the anchor suture) are carefully dissected from the submucosa and adjacent circumpapillary oral mucosa. As the duct initially courses posteriorly, it is closely adherent to the mucosa, which necessitates a slow, careful dissection. Once the papilla and an initial 1 cm of duct are free from the overlying mucosa, the remaining duct is more easily dissected from the relatively loose connective tissues present posteriorly. This additional posterior dissection may be achieved using either conjunctival or small Metzenbaum scissors.

After dissecting as much of the duct as possible through the initial incision, the buccal mucosa is opened further by extending the incision caudally and parallel to the gum line, which maximizes exposure and facilitates additional dissection of the duct. Dissection should free the duct sufficiently to provide an adequate length for reaching the lower conjunctival fornix with little resistance. During dissection, the duct is kept from twisting by grasping the suture with forceps and maintaining a steady grasp and a constant position. Handling only the anchored suture prevents damage to the mucosa around the papilla.

After the duct is free, curved Metzenbaum scissors are used to tunnel, subcutaneously, dorsally from the point near where the duct attaches to the gland and to dissect bluntly toward the ventral lateral canthus of the eye. As the subconjunctival space is subsequently entered, the ventral fornix con junctiva is tented by the tips of the scissors. The tented conjunctiva is then grasped and externalized, and a 6-mm stab incision is made with a No. 15 Bard-Parker blade between the lower eyelid and the lateral insertion of the nictitans. This fornix incision creates a recipient conjunctival site for anchoring the papilla. For cases in which the eyelid conformation is relatively tight, a lateral canthotomy may facilitate this step. After making the conjunctival incision, the tips of the scissors are inserted through this opening, thus establishing communication with the previously dissected tunnel. The subcutaneous tunnel is enlarged by blunt dissection, and the scissors are removed.

Next, small curved forceps are replaced into the conjunctival opening. The forceps are inserted into the tunnel and passed toward the now-free parotid duct. The anchor suture (with attached papilla) is grasped, and the duct is pulled into the subcutaneous tract. Taking care not to twist the duct, it is brought through the lower conjunctival fornix incision. Once the papilla is in the fornix, and before trimming any excess mucosa, the posterior half of the circumpapillary mucosa is sutured to the conjunctiva with four simple interrupted 7-0 polyglactin 910 sutures (Fig 17.26). Magnification is necessary for proper suture placement.

After the four initial sutures have been placed, the mucosa is carefully trimmed so that the retained rostral half of the circumpapillary mucosa is nearly symmetrical with the posterior half. This is accomplished by inserting conjunctival scissors between the papilla and the fixed suture, then trimming and releasing the mucosa with attached suture. The long portion of the suture is left in the duct as a cannula (see Fig 17.26). The external portion with attached knot is trimmed 3–4 mm external to the papilla. After the excess mucosa (with anchor suture) is removed and discarded, four additional simple interrupted sutures are placed in the rostral half of the retained peripapillary mucosa, thus finishing the conjunctival–mucosal repair and completely securing the papilla into the conjunctival fornix.

The buccal mucosa is sutured using 5-0 polyglactin 910 in a continuous submucosal pattern so that the knots are buried. If a lateral canthotomy was necessary, it is closed routinely. Facial swelling and postoperative discomfort are minimal with the closed technique, and healing occurs rapidly. Antibiotics are administered both topically and systemically for 7–10 days postoperatively. After PDT surgery, multiple daily feedings are recommended to stimulate



Figure 17.26 Parotid duct transposition surgery in a dog. The papilla has been surgically transposed into the ventral conjunctival fornix and the posterior half of the circumpapillary mucosa is sutured to the conjunctiva with four simple interrupted 7-0 polyglactin 910 sutures. The originally placed 2-0 black nylon suture can be seen emerging from the duct opening.

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parotid secretions. Soft food is recommended for the first postoperative week. Because there is no skin incision or external sutures, a restraint collar is usually not needed after closed PDT.

Open Procedure

The open PDT procedure was the original technique described by Lavingnette (Lavingnette, 1966). It involves exposing the parotid duct through a facial skin incision. The cannulated duct is palpated, and an incision is made over the duct through the skin and superficial facial muscles. The duct is carefully dissected from the masseter muscle and retracted using umbilical tape or a muscle hook (to minimize surgical trauma). The duct is then dissected from the masseter muscle posteriorly to the angle of the mandible and rostrally to the buccal mucosa. The duct continues submucosally for 0.5–1.0 cm before terminating at the papilla in the buccal mucosa. During dissection, the facial vein and anastomotic branch between the dorsal and ventral buccal nerves must be avoided.

After elevating the lip, the mucosa around the papilla and suture is incised with a scalpel and penetrated just to the level of the submucosa. (Some surgeons prefer to use a 6-mm trephine to make the peripapillary incision; however, this precludes anchoring the nylon suture to the oral mucosa and necessitates leaving the suture end free to extend slightly beyond the papilla.) The papilla and surrounding mucosa are carefully dissected free using conjunctival scissors, and the papilla with retained suture and duct are retracted back into the facial incision. Using small Metzenbaum scissors, a subcutaneous tunnel is established and directed to the ventral lateral conjunctival fornix (as described previously for the closed PDT procedure). Placement and suturing of the papilla as well as removal of excess mucosa are identical to the closed PDT procedure. The oral incision is closed using 5-0 polyglactin 910 in a submucosal pattern. Skin closure involves two layers, with a continuous subcutaneous layer of 4-0 or 5-0 absorbable material and simple interrupted skin sutures using 4-0 or 5-0 nonabsorbable suture. A restraint collar may be needed to prevent self-trauma after the open PDT; otherwise, the same recommendations for postoperative care apply.

Complications, Sequelae, and Postoperative Considerations

Various postoperative complications have been reported after PDT surgery (Guinan et al., 2007; Rhodes et al., 2012). Twisting, laceration, or trauma to the parotid duct may occur with either the closed or the open PDT procedure. Some surgeons indicate a greater chance of twisting and damaging the duct with the closed approach, whereas Jensen (Jensen, 1979) discusses potential difficulties associated with the open PDT procedure, including trauma associated with dissection of the highly vascular and innervated facial tissues, increased postoperative swelling, and potential discomfort from the extensive surgical dissection. Regardless of the approach, exercising great care when dissecting and manipulating the duct cannot be overemphasized, because damage to the duct during surgery can result in temporary malfunction or, in the worst scenario, permanent dysfunction, thus negating any potential benefit from the operation.

Causes for delayed failure in PDT surgery include retraction of the papilla into the subcutaneous space with fibrous closure of the conjunctival opening, occlusion of the duct by sialoliths, and acute or chronic sialoadenitis (Betts & Helper, 1977; Harvey & Koch, 1971; Jensen, 1979; Termote, 2003). The ability to salvage function depends on the cause and, in some cases, the promptness of intervention. The most frequent cause of PDT failure is occlusion of the transposed duct, either at or near the conjunctival attachment (Harvey & Koch, 1971; Schmidt et al., 1970). This usually results from inadequate dissection of the duct, thereby causing increased tension and retraction of the papilla from the recipient site into the adjacent subconjunctival space. Such occlusions may be successfully repaired by making a facial incision, redissecting the duct, and reattaching the papilla to the conjunctiva (Betts & Helper, 1977).

Saliva contains a higher concentration of minerals compared with tears and owners should be advised that mineral deposits are considered a normal sequel on the cornea and eyelid margins after PDT surgery (Fig. 17.27) (Rhodes et al., 2012). Should this occur, a chelating solution containing 1%–2% EDTA (ethylenediaminetetraacetic acid) in artificial tears may be applied topically two to three times daily to aid in control of the mineral precipitates. Some practitioners use oral doxycycline as a chelating agent; however, long-term



Figure 17.27 Right eye of a 7-year-old female spayed Yorkshire Terrier 9 months after parotid duct transposition surgery, showing mineral precipitates on the ocular surface and eyelids.

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use of oral antibiotics is not without possible side-effects. In an attempt to alter the pH and mineral content of saliva, a number of anecdotal improvements have been discussed in various nonpeer reviewed forums including oral supplementation with tomato juice, vitamin C, calcium carbonate, buttermilk, and systemic carbonic anhydrase inhibitors. To the author's knowledge, no evidence-based medicine exists to support or refute the use of such agents after PDT surgery. Continued use of topical CsA or similar agent also appears to be helpful in reducing irritation from mineral deposits, probably by virtue of its lubricant, mucinogenic, and anti-inflammatory properties.

An overabundance of salivary secretions may result in facial wetting and discoloration, which can be objectionable to some owners, especially in light-coated dogs (Fig 17.28). In rare cases, overproduction may prompt consideration of partial duct ligation (Kuhns & Keller, 1979; Schilke & Sapienza, 2012), reversal of the surgery, or enucleation (Rhodes et al., 2012; Young et al., 2018). A recent report found additional complications after PDT surgery to include bullous keratopathy, corneal ulceration with associated stromal mineral deposition, iatrogenic corneal ulceration, lower lid entropion, recurrent epithelial erosion, and stromal abscessation (Rhodes et al., 2012). An orbital sialocele after enucleation of a globe previously treated for KCS by PDT has been reported (Guinan et al., 2007). Despite ligating the duct distally at the time of enucleation, sialocele development 1 month later necessitated further surgical exploration to remove the abnormal tissue and re-routing of the remaining proximal normal portion of the parotid duct back into the oral cavity.

After PDT, the bacterial flora of the eyes changes significantly and will consist of large numbers of mixed bacteria genera, with many uncommon isolates and some potential pathogens (Petersen-Jones, 1997). The heavy bacterial colonization does not appear to be associated with overt ocular disease, but it may contribute to the blepharitis sometimes seen as a sequela to overflow of saliva from the conjunctival sac (Petersen-Jones, 1997).



Figure 17.28 A 6-year-old male castrated Siberian Husky 10 months after parotid duct transposition surgery. Note the chronic keratitis with superficial neovascularization, mineral deposition on the axial cornea, and chronic, moist, mucoid blepharitis extending to include moderate periocular dermatitis.

Partial Tarsorrhaphy

A partial permanent tarsorrhaphy may be beneficial in dogs with KCS, especially among brachycephalic breeds, to afford greater corneal protection and to conserve existing tears. Lateral canthoplasty is easier to perform, but medial canthoplasty provides additional protection from medial canthal trichiasis, especially in brachycephalic breeds. The technique is the same as the one used for treating ocular exposure resulting from conformational exophthalmos. When performing medial canthoplasty, care should be taken not to damage the lacrimal puncta or canuliculi.

Replacement of a Prolapsed Nictitans Gland

Removing a prolapsed nictitans gland or allowing chronic prolapse without treatment may predispose an affected eye to KCS (Kaswan & Martin, 1985; Kaswan et al., 1984). Repair of a prolapsed nictitans gland using an appropriate replacement procedure may prevent the sequela of KCS (Kaswan & Martin, 1985; Kaswan et al., 1984; Plummer et al., 2008; Sapienza et al., 2014). A number of replacement techniques have been described, and the reader is referred to Chapter 18.

Cysts, Foreign Bodies, and Neoplasms of the Lacrimal Secretory System

Cysts involving lacrimal tissue or surrounding conjunctiva, though uncommon, have been reported and may originate from either the orbital or the nictitans glands (Delgado, 2013; Lamagna et al., 2012; Latimer et al., 1983; Martin et al., 1987; Ota et al., 2009; Playter & Adams, 1977). Depending on the site of origin, cysts may distend the conjunctiva and protrude into the palpebral fissure, expand within the orbit and cause displacement of the globe, or both (Fig. 17.29). Possible causes include developmental defects, blunt trauma, foreign-body injury, or inflammation affecting the ducts. Basset Hounds and Labrador Retrievers may be predisposed (Ota et al., 2009). Lacrimal cysts are characterized histopathologically by inflammation of the cyst wall, which is lined by flattened, cuboidal epithelium and affected glands exhibit features of secretory stasis (i.e., dilated acini and ducts, epithelial atrophy). Surgical excision of cysts is curative (Fig. 17.30). Tear secretion may be compromised depending on the amount of lacrimal gland involved initially or excised subsequently.

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Figure 17.29 Dacryops in a 3-year-old female spayed Labrador Retriever.



Figure 17.30 Intraoperative photograph of cyst dissection of a 1-year-old male castrated Labrador Retriever. The cystic mass has been partially dissected from the surrounding tissue and is being gently lifted from underlying associated connective tissue. (*Source:* Reprinted with permission from Ota, J., Pearce, J.W., Finn, M.J., Johnson, G.C. & Giuliano, E.A. (2009) Dacryops (lacrimal cyst) in three young Labrador Retrievers. *Journal of the American Animal Hospital Association*, **45**, 191–196.)

Cysts of the canine nictitating membrane may arise secondary to Morgan pocket surgical repair of a prolapsed gland of the third eyelid (Fig. 17.31). Marsupialization of these cysts is effective at resolving the problem and maintaining important third eyelid contributions to the PTF (Fig. 17.32) (Barbe et al., 2017).



Figure 17.31 One-year-old male English Bulldog with cyst formation of the nictitating membrane occurred approximately 7 weeks after morgan pocket surgery was performed by the primary care veterinarian.



Figure 17.32 Same patient as in Fig. 17.31 in surgery demonstrating successful marsupialization of the cyst wall performed by the author. The author advocates that marsupialization be performed on the palpebral aspect of the nictitating membrane to avoid any iatrogenic damage to the cornea from suture irritation.

Although lacrimal neoplasms are also uncommon in the dog, primary adenomas and adenocarcinomas of the orbital and nictitans glands have been reported (Headrick et al., 2004; Miyazaki et al., 2015; Rebhun & Edwards, 1977; Wilcock & Peiffer, 1988). These tumors tend to be locally invasive and have a guarded prognosis. Adenocarcinoma of the nictitans gland constitutes one of the rare indications for

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complete excision of the nictitans. Mucosal grafting is possible after this procedure (Kuhns, 1981). Orbital exenteration with adjunctive irradiation or chemotherapy may be indicated for cases of adenocarcinoma of the orbital lacrimal gland. In one report, 15 cases of lobular adenomas of the orbit were reviewed. These tumors presented clinically and histologically as a benign neoplasm of lacrimal or salivary gland origin. Recurrence was likely unless the mass was completely excised, at times requiring orbital exenteration (Headrick et al., 2004).

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Diseases and Surgery of the Canine Conjunctiva and Nictitating Membrane

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Conjunctiva

The conjunctiva is associated with many adnexal and bulbar diseases because of its exposure and close proximity to ocular structures. Conjunctival disease may be indicative of systemic or severe disease, and therefore a thorough physical and ophthalmic examination should be undertaken. The cause of localized conjunctival disease can often be determined solely on the basis of history and a complete ocular examination. When the cause is not obvious after a complete examination, the conjunctiva is easily accessible for cytology or biopsy.

Functional Anatomy and Physiology

The conjunctiva is a mucous membrane with roles in tear dynamics, immunologic protection of the eye, ocular movement, and corneal healing. The palpebral conjunctiva lines the inside of the eyelids, beginning at the eyelid margin (and continuous with the epidermis of the eyelid) and extending deep toward the orbit to become a conjunctival fornix (i.e., "cul-de-sac"). From here the conjunctiva reverses direction and extends over the globe to the limbus as the bulbar conjunctiva and is continuous with the corneal epithelium.

Medially, the conjunctiva covers both the palpebral and bulbar surfaces of the nictitating membrane (NM). Redundancy of the conjunctiva at the fornices allows ocular movement. Attachment of the bulbar conjunctiva to the bulbar fascia and insertions of the rectus muscles prevent the bulbar conjunctiva from drooping over the cornea (Srinivasan et al., 1992). The substantia propria of the palpebral conjunctiva is tightly adhered to the tarsus and therefore is not freely movable. The bulbar conjunctiva, however, is freely movable, except near the limbus. As the bulbar conjunctiva approaches the limbus, it fuses to Tenon's capsule (Jakobiec & Iwamoto, 1992). The lack of adhesion between the bulbar conjunctiva and the deeper tissues facilitates use of the conjunctiva in many surgical procedures and as a site for injecting medications.

Microscopic Anatomy

Histologically, the conjunctiva is composed of nonkeratinized, stratified squamous epithelium and an underlying substantia propria. The substantia propria is divided into superficial and deep layers. The superficial layer contains many lymphoid nodules, which are the major components of the conjunctiva-associated lymphoid tissue (CALT; Srinivasan et al., 1992). The purpose of CALT is to receive antigen and to present it to circulating mononuclear cells (Eichenbaum et al., 1987). The lymphatics that drain this area represent the only known lymphatic drainage of the normal canine eye (Eichenbaum et al., 1987), although lymphatic vessels have been immunohistologically demonstrated within the inflamed cornea (Kafarnik, C., personal communication). The deeper layer of the substantia propria is fibrous and contains the conjunctival vessels and nerves (Srinivasan et al., 1992). While the NM of the dog shows evidence of microfold cells (M cells), they have not been observed in the remaining conjunctiva (Chodosh et al., 1998; Giuliano et al., 2002). M cells are unique epithelial cells overlying a lymphoid follicle that function to sample antigen at a mucosal surface and transcytose it to the underlying lymphoid cells (see Chapter 6).

Goblet cells are also present in the epithelial layer of the conjunctiva. These cells produce a gel-like mucin, which forms the deepest of the three layers of the preocular (i.e., precorneal) tear film (Chiapino & Dawson, 1985; Lemp & Wolfley, 1992). This mucin protects the ocular surface by trapping debris and bacteria, and by providing a medium for adherence of immunoglobulins (i.e., immunoglobulin A, IgA) and microbicidal lysozymes (Holly & Lemp, 1971; Lemp et al., 1970; Nichols et al., 1983). The areas of highest canine goblet cell density are the lower nasal fornix, lower

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middle fornix, and lower nasal tarsal region. Goblet cells are essentially absent from the upper and lower bulbar areas (Moore et al., 1987).

Vascular Supply and Innervation

The vascular supply of the conjunctiva is extensive. Branches of the dorsal and ventral palpebral and malar arteries, as well as terminal branches from the anterior ciliary arteries, provide the conjunctiva with its blood supply (Murphy & Pollock, 1993). Innervation is provided by branches of the long ciliary, zygomaticofacial, zygomaticotemporal, infratrochlear, and frontal nerves (Murphy & Pollock, 1993).

Normal Bacterial and Fungal Flora

Bacteria can be cultured from the conjunctival sac in 46%–90% of normal dogs (Bistner et al., 1969; McDonald & Watson, 1976; Teixeira et al., 2002; Thangamuthu & Rathore, 2002; Urban et al., 1972). Gram-positive aerobes are the most commonly cultured, with *Staphylococcus* spp., *Bacillus* spp., *Corynebacterium* spp., and *Streptococcus* spp. predominating (Bistner et al., 1969; McDonald & Watson, 1976; Teixeira et al., 2002; Thangamuthu & Rathore, 2002; Urban et al., 1972; Wang et al., 2008). Canine conjunctival bacterial culture rates in normal dogs varied with season (highest in spring and summer) in Beijing, China (Wang et al., 2008). Gram-negative bacteria have been recovered from the conjunctival sac in 7%–8% of normal dogs (Bistner et al., 1969; McDonald & Watson, 1976; Urban et al., 1972). Anaerobes are rarely isolated (McDonald & Watson, 1976; Thangamuthu & Rathore, 2002). In a recent study, fungal organisms were cultured from 22% of dogs (most frequently *Alternaria*, *Cladosporium*, *Penicillium*, and *Aspergillus* spp.) in Southern France (Verneuil et al., 2014). In this study the presence of conjunctival fungal organisms was correlated to the presence of fungi on the skin. In another study, conjunctival fungi were rare (most commonly cultured *Cladosporium oxysporum, Curvularia lunata,* and *Malassezia pachydermatis;* Samuelson et al., 1984).

Normal Cytology

Cytologic examination of scrapings from normal conjunctiva reveals sheets of epithelial cells with large, round, homogenous nuclei and abundant cytoplasm. Keratinized epithelial cells are uncommon. Bacteria are occasionally seen and leukocytes are rare (Lavach et al., 1977). Cytologic samples are easy to obtain from the conjunctiva. After administration of a topical anesthetic, a cytobrush, the blunt end of a scalpel blade, or even an impression using a membrane filter can be effective for obtaining cells (Bauer et al., 1996; Bolzan et al., 2005; Braus et al., 2017; Willis et al., 1997).

General Response to Disease

The conjunctiva responds to insult with a limited number of mechanisms. Chemosis, hyperemia, blepharospasm, and cellular exudation characterize acute conjunctivitis (Yanoff & Fine, 1989). The loose arrangement of the conjunctival stroma, extensive vascular supply, and presence of lymphoid tissue allow marked edema to develop rapidly after trauma or exposure to allergens or toxins, as well as hyperemia and a cellular response. Chronically, multinucleated giant cells are seen as a nonspecific change (Lavach et al., 1977). The normally nonkeratinized epithelial cells may become keratinized secondary to prolonged exposure associated with ectropion, lagophthalmos, or keratoconjunctivitis sicca (KCS); keratinization may also occur with vitamin A deficiency and irradiation (Murphy, 1988). Goblet cell proliferation occurs with KCS, chronic conjunctivitis, and vitamin A deficiency (Murphy, 1988).

Conjunctival flora is altered in dogs with various diseases. Bacteria are more likely to be isolated from the conjunctiva of dogs with ulcerative keratitis than from dogs with healthy eyes (Prado et al., 2005). *Malassezia pachydermatis,* alipophilic yeast that is most commonly associated with otitis and dermatitis, was found to be present in 23% of eyes with corneal ulceration and only 3% of healthy eyes (Prado et al., 2004). The increased number of bacteria and yeast cultured from dogs with ulcerative keratitis could be caused by decreased ocular defenses, increased phospholipids secondary to inflammation, or decreased concentration of tear lysozyme from increased tear production secondary to ulceration (Murphy et al., 1978; Prado et al., 2005). Another study evaluating cytologic and culture differences between the conjunctiva of dogs with atopic dermatitis and normal dogs found that affected dogs had significantly more bacteria, keratinized and nonkeratinized epithelial cells, eosinophils, and lymphocytes, and had more positive cultures regardless of clinical parameters (Furiani et al., 2011). The incidence of culturing *M. pachydermatis* from the conjunctiva of atopic dogs varies between studies (Nardoni et al., 2007; Prado et al., 2008).

Ocular redness, which can result from conjunctival hyperemia or episcleral congestion, occurs with many diseases, including abnormal eyelid conformation, abnormal cilia, allergic conjunctivitis, corneal disease, KCS, anterior uveitis, glaucoma, orbital disease, and toxic or septic shock. Conjunctival hyperemia should be differentiated from episcleral injection and ciliary flush, which occur with glaucoma and anterior uveitis. Generally, the conjunctival vessels are smaller in diameter, have a branching pattern, blanch quickly with topical application of 1%–2% epinephrine, and are mobile. Episcleral vessels are larger in diameter, do not branch as frequently, do not blanch quickly with topical application of epinephrine, and are not mobile. The

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episcleral vessels associated with ciliary flush form a branching network near the limbus. Because many ocular diseases can cause a "red eye," a complete ophthalmic examination should always be performed when this clinical sign is present. Trauma, allergic or bacterial conjunctivitis, mechanical irritants, conjunctival parasites, orbital inflammation, and other ocular and systemic infectious agents can cause conjunctivitis. Conjunctival ulceration, while uncommon in dogs, can occur secondary to varying kinds of trauma, including alkali burns (Singh et al., 2004).

Infectious Conjunctivitis

Infectious conjunctivitis indicates the association with specific pathogens and is uncommon in the dog.

Bacterial Conjunctivitis

Primary bacterial conjunctivitis is an uncommon disease in the dog. In most cases, bacterial conjunctivitis develops secondary to eyelid abnormalities or KCS. Bacterial conjunctivitis is usually caused by *Staphylococcus* spp. and other gram-positive organisms (Gerding et al., 1988; Murphy et al., 1978). Multiple dogs with conjunctivitis were screened for *Chlamydiaceae* and were found to be negative in one study (Holst et al., 2010). Another study identified *Chlamydophila psittaci* genotype C infection in four dogs in the same location that had recurrent keratoconjunctivitis, respiratory distress, and reduced litter size (Sprague et al., 2009). Cytologic examination of conjunctival scrapings from dogs with bacterial conjunctivitis can help to confirm the diagnosis. Neutrophils with few mononuclear cells, many bacteria, and degenerating epithelial cells are present in acute infections (Fig. 18.1; Lavach et al., 1977; Murphy, 1988). In chronic disease, neutrophils remain the predominant cell type, but there are many more mononuclear cells. Additionally, degenerate or keratinized epithelial cells are seen, with the presence of bacteria being variable (Lavach et al., 1977; Murphy, 1988). Generally, a complete ophthalmic examination, appropriate ancillary tests such as cytology, culture with sensitivities, and appropriate treatment (usually consisting of broad-spectrum ophthalmic antibiotics in solution or ointment) lead to a rapid response. Pending culture results, topical chloramphenicol, erythromycin or bacitracin, neomycin, and polymyxin B can be used for gram-positive bacteria conjunctivitis, and tobramycin, ofloxacin, gentamicin, or topical bacitracin, neomycin, and polymyxin B can be used for bacterial conjunctivitis caused by gram-negative bacteria (Gerding et al., 1988). Antibiotic resistance can develop rapidly to some topical antibiotics and therefore chronic use or prophylactic use should be carefully considered (Sandmeyer et al., 2017).

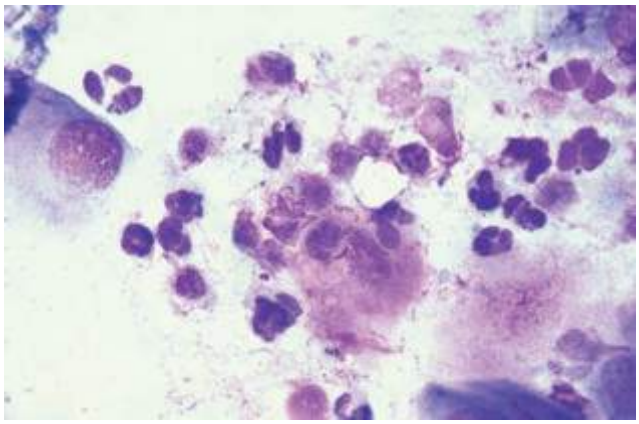


Figure 18.1 Neutrophils, cocci, and conjunctival epithelial cells in a cytologic specimen from a dog with bacterial conjunctivitis. (Diff-Quik; original magnification, 330×.)

Viral Conjunctivitis

In the past, viral conjunctivitis was most commonly associated with canine distemper virus; however, a recent virologic survey and other research have brought attention to canine herpes virus-1 (CHV-1). The survey evaluated for multiple viruses using virus isolation and polymerase chain reaction (PCR) on samples from dogs with conjunctivitis and control dogs. Of 30 dogs with conjunctivitis, 5 were positive for CHV-1 and 2 for canine adenovirus-2. Being sexually intact and having frequent exposure to dogs outside the household were positively associated with viral detection in the conjunctivitis group (Ledbetter et al., 2009b).

An outbreak of CHV-1 in a closed colony of Beagles caused conjunctivitis and keratitis in all dogs, ulcers in 26% of dogs (punctate, dendritic, or geographic), and nonulcerative keratitis in 19% of dogs. All dogs tested were positive for CHV-1 on PCR and virus isolation (Ledbetter et al., 2009c). Experimentally, dogs inoculated topically with CHV-1 in one eye developed signs of mild to moderate conjunctivitis in both eyes that peaked at 7 days in the inoculated eye and 10 days in the noninoculated eye (Fig. 18.2). The conjunctivitis began to decrease in severity over the following 15 days and returned to normal by day 35. In general, ocular disease scores were higher and increased more quickly in the inoculated eye versus the noninoculated eye. No dogs developed keratitis or signs of systemic disease. Ocular viral shedding was detected in all infected dogs between days 3 and 10 postinfection. All infected dogs also developed CHV-1 serum-neutralizing antibody titers, beginning at 7 days postinoculation and peaking on day 21 (Ledbetter et al., 2009a).

Recrudescent CHV-1 disease has been induced in dogs with latent CHV-1 infection by administration of an immunosuppressive dosage of prednisolone for 7 days. Bilateral mild to moderate conjunctivitis, characterized by intermittent blepharospasm, conjunctival hyperemia, chemosis, and

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Figure 18.2 Experimentally induced recurrent canine herpesvirus-1 conjunctivitis in a dog. Courtesy of Eric Ledbetter.

mucoid-to-mucopurulent ocular discharge or keratitis, was detected in 83% of dogs between days 3 and 18 after initiating the prednisolone. *In vivo* confocal microscopic abnormalities included conjunctival leukocyte infiltration and corneal leukocyte infiltration, abnormal epithelial cell morphology, and Langerhans cell infiltration. Ocular viral shedding was detected in half of the dogs, and fourfold elevations in CHV-1 serum neutralization antibody titers were detected in all dogs. Mean duration of ocular disease was 8.6 days (Ledbetter et al., 2009d). As with cats, it appears as if conjunctival herpesvirus infections are self-limiting. Two dogs with CHV-1 keratitis responded to treatment with idoxuridine or trifluridine, both administered 6–8 times daily for 48 hours and then every 6 hours (Ledbetter et al., 2009d). In a further experimental study, 10 CHV-1-inoculated Beagles responded to topical trifluridine (on the same schedule) with reduced ocular disease scores and viral shedding (Spertus et al., 2016). Topical cidofovir twice daily has also been reported to be beneficial, but may be associated with more adverse reactions (Gervais et al., 2012).

A subunit vaccine for CHV-1 was successful in inducing peripheral immunity (as demonstrated by T and B lymphocyte subpopulation percentage distributions, lymphocyte expression of major histocompatibility complex Classes I and II, CHV-1 virus-neutralizing antibody titers, lymphocyte proliferation, and interferon-g levels), but did not prevent ocular disease or viral shedding (although clinical disease scores were reduced in the 2-week postvaccinal period; Ledbetter et al., 2016).

Canine distemper virus is associated with conjunctivitis, chorioretinitis, KCS, and optic neuritis (Fischer, 1971; Gelatt et al., 1985; Jubb et al., 1957; Martin & Kaswan, 1985; Render et al., 1982; Sansom & Barnett, 1985). Conjunctivitis generally occurs with the rhinitis and tracheobronchitis that accompany the initial febrile episode (Peiffer, 1981). A mucopurulent discharge is often present (Gelatt et al., 1985; Peiffer, 1981). Initially, mononuclear cells are seen on cytology, followed by increasing numbers of neutrophils, and plasma cells, goblet cells, and cellular debris are also seen (Lavach et al., 1977). Canine distemper virus can cause similar clinical signs in a range of carnivores, including wolves, raccoon dogs, foxes, bears, lions, tigers, hyaenas, civets, ferrets, and mink (Beineke et al., 2015; Zhao et al., 2015).

Distemper virus reaches the epithelial cells 6–9 days after exposure, and then the virus levels decrease with antibody formation (Appel, 1969). Distemper viral antigens can be detected using direct immunofluorescence and PCR (Decaro et al., 2004; Fairchild et al., 1967). In experimentally infected dogs, the antigens can be detected in conjunctival smears on days 7 through 35 using direct fluorescence antibody testing (Sen et al., 2002). An immunochromatography assay that does not require special instrumentation has shown 100% specificity and sensitivity when run on conjunctival swab samples from naturally infected dogs (An et al., 2008). Scarce cytoplasmic inclusion bodies may be infrequently found in the conjunctival epithelial cells after 6 days of infection and are seen more frequently in cells acquired from the NM (Appel & Gillespie, 1972; Erno, 1964).

Dogs have been reported to be highly sensitive to H5N1 avian influenza virus, resulting in pyrexia, conjunctivitis, and respiratory signs (Chen et al., 2010). Conjunctivitis has also been reported in conjunction with respiratory signs in a dog infected with H5N2 influenza virus in China, and subsequent studies demonstrated that dog-to-dog, dog-to-cat, and dog-to-chicken transmission was possible (Hia-Xia et al., 2014; Qian-Qian et al., 2013).

Fungal Conjunctivitis

Fungal conjunctivitis is very rare in the dog. Infection with *Blastomyces dermatitidis* can cause nodule formation in the inferior conjunctiva. The diagnosis can be made on the basis of cytology or biopsy results. Treatment with systemic itraconazole may resolve the condition (Brooks, 1991). *Aspergillus* spp. infection has been associated with tarantula hair foreign bodies in the conjunctiva and cornea of a Rat terrier (Reed et al., 2016).

Rickettsial Conjunctivitis

Infection with *Rickettsia rickettsii* is frequently associated with ocular lesions of the conjunctiva, uvea, and retina. Evidence of conjunctivitis usually begins with the onset of fever and includes conjunctival hyperemia, chemosis, petechial hemorrhages, and a mucopurulent-to-purulent ocular discharge (Davidson et al., 1989; Keenan et al., 1977). Canine ehrlichiosis can cause conjunctival hyperemia, serous ocular discharge, conjunctival hemorrhages, anterior uveitis, and

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retinal hemorrhages (Davidson et al., 1989; Kuehn & Gaunt, 1985; Swanson & Dubielzig, 1986).

Parasitic Conjunctivitis

Canine ocular thelaziasis occurs in the western United States, Europe, Southeast Asia, and Russian far east (Dorchies et al., 2007; Gardiner et al., 1993; Hermosilla et al., 2004; Khrustelev et al., 2015; Magnis et al., 2010; Yang et al., 2006) and is a zoonotic disease. *Thelazia* is a nematode that can be found under the NM and in the conjunctival sac and lacrimal duct. Both *Thelazia callipaeda* and *Thelazia californiensis* infect the dog (Hermosilla et al., 2004; Nimsuphan & Prihirunkij, 2000; Otranto & Traversa, 2005). The milky white worms are approximately 10–14 mm long (Hermosilla et al., 2004; Nimsuphan & Prihirunkij, 2000). The lateral serrations of the cuticle of the nematodes cause mechanical damage to the conjunctiva and cornea, leading to lacrimal secretions upon which nonbiting diptera feed. The adult nematodes live under the eyelids or behind the nictitans. The first-stage larvae are ingested by flies. Then, after undergoing two molts, the third-stage larvae are transferred back to the eye when the fly feeds (Bianciardi & Otranto, 2005). *Musca autumnalis* in North America and *Phortica variegata* in Asia are known intermediate hosts (Bowman et al., 2011; Otranto et al., 2006). Foxes and wolves may be important in the spread and maintenance of disease (Dorchies et al., 2007; Otranto & Traversa, 2005). The parasitic infection causes a unilateral or bilateral purulent conjunctivitis with blepharospasm, epiphora, conjunctivitis, keratitis, and intense lacrimal secretion. Topical moxidectin (1% aqueous solution) and tetramisole (0.5% solution), spot-on imidacloprid (10%) and moxidectin (2.5%), oral milbemycin/praziquantel, and physical removal of the nematodes are effective treatments (Bianciardi & Otranto, 2005; Lia et al., 2004; Motta et al., 2012; Otranto et al., 2016; Peng & Jiang, 1983).

Toxoplasma gondii was diagnosed in a dog with KCS that had a yellow/tan conjunctival mass located at the limbus. Histopathology revealed protozoa and necrotizing conjunctivitis. On immunohistochemistry, the protozoa were identified as *Toxoplasma gondii*. The lesions recurred in the opposite eye after treatment with clindamycin, but resolved with treatment with ponazuril. Since titers were negative, it was hypothesized that the lesion was secondary to local immunosuppression from tacrolimus used to treat KCS (Swinger et al., 2009).

Noninfectious Conjunctivitis

Allergic Conjunctivitis

Allergic conjunctivitis occurs frequently in the dog and is often a component of atopic dermatitis (Glaze, 1991; Lourenco-Martins et al., 2011). Atopy is a Type 1 hypersensitivity reaction. The common allergens are pollens, molds, and dust mites. Clinical signs include conjunctival hyperemia, chemosis, facial pruritis, periocular alopecia, and ocular discharge. With chronic antigenic stimulation, conjunctival lymphoid follicles develop. History, physical examination, and intradermal skin testing are used to make the diagnosis of atopy in the dog. Results of cytology and histopathology performed on conjunctival scrapings and biopsy specimens, respectively, can suggest the presence of an allergic response. Finding one eosinophil on cytologic examination of a conjunctival scraping is considered to be diagnostic for an allergic process; however, plasma cells and lymphocytes are more commonly seen with allergic responses in the dog (Lavach et al., 1977). The conjunctival provocation test using dust mite allergens showed an etiologic relationship between conjunctivitis and specific mite sensitizations, and may be a new tool for confirming an etiologic diagnosis for allergic conjunctivitis (Lourenco-Martins et al., 2011).

Avoidance of the offending allergen, hyposensitization, and pharmacologic modification of the clinical signs are the primary forms of treatment. Intermittent use of a topical ophthalmic hydrocortisone or dexamethasone may be necessary to relieve clinical signs; alternate-day treatment with systemic corticosteroids initiated for the skin disease may also relieve the ocular signs (Glaze, 1991). Topical antihistamines, such as naphazoline, and mast cell stabilizers may have some benefit, but studies on their efficacy in the dog have not been reported.

Intense chemosis and blepharedema may occur as an immediate-type reaction mediated by histamine and immunoglobulin E after food absorption, drug administration, and envenomation by ant, bee, wasp, or hornet stings as well as spider bites (Fig. 18.3). The chemosis is often bilateral, and the actual area of trauma (if caused by an insect) is rarely identified and may be distant from the eyes. These cases usually respond rapidly to intravenous or intramuscular short-acting corticosteroids and an antihistamine with or without topical corticosteroid ophthalmic ointments administered 3–4 times daily.



Figure 18.3 Chemosis associated with a bee sting.

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Follicular Conjunctivitis

Follicular conjunctivitis develops secondary to chronic antigenic stimulation (Bromberg, 1980). There is no evidence to link follicle formation to a viral or bacterial cause (Jackson & Corstvet, 1980; Nell et al., 2000). Semitransparent follicles form primarily on the bulbar surface of the NM, but they may also form elsewhere on the conjunctiva (Fig. 18.4). The follicles on the bulbar surface of the NM that are present with this disease greatly outnumber those normally seen, and they can be significantly larger. Frequently, hyperemia of the conjunctiva and a mucoid ocular discharge are present concurrently. This condition occurs most frequently in dogs younger than 18 months of age.

The diagnosis is made on the basis of characteristic clinical signs. Cytologic results of conjunctival scrapings will confirm the diagnosis by revealing the lymphoid nature of the follicles (Glaze, 1991). Most cases respond to treatment with saline irrigation and symptomatic use of ophthalmic dexamethasone administered 3–4 times daily (Glaze, 1991). Irrigation appears to play a large role in decreasing follicular formation, especially in dogs with deep fornices exposed to large amounts of vegetative matter, such as Labrador Retrievers in field training. Some authors recommend that nonresponsive cases are treated by mechanically debriding the follicles, although studies demonstrating benefit clinically, histologically, or prognostically are lacking. After instillation of ophthalmic anesthetic, the follicles are debrided with dry gauze placed over the tip of a cotton-tipped applicator. The follicles should not be sharply excised with a blade or cauterized with copper sulfate crystals, because the lymphoid tissue is critical to the ocular defense system (Glaze, 1991).

Environmental Irritants and Contact Hypersensitivity

Over 60% of the dogs deployed to assist in relief efforts at the World Trade Center site following the terrorist attacks in 2001 developed acute conjunctival irritation characterized by severe conjunctival hyperemia, tearing, squinting, and face rubbing. Conjunctival irritation and fatigue were the most common health problems to affect the dogs. The irritation was secondary to exposure to toxic chemicals, smoke, and massive amounts of particulate matter. Affected animals were treated by means of gentle irrigation of the conjunctival fornices with eye solution (Fox et al., 2008).



Figure 18.4 Follicular conjunctivitis involving the bulbar conjunctiva of the nictitating membrane.

Ophthalmic medications can occasionally lead to contact hypersensitivity reactions, which are exhibited by blepharitis and conjunctivitis. Neomycin, gentamicin, dorzolamide and timolol combinations, thimerosal, and benzalkonium chloride are the most likely drugs used in canine ophthalmology that can cause this reaction. Affected dogs usually present with a history of conjunctivitis that is nonresponsive to topical medications. The skin ventral to the medial canthus may become swollen, hyperemic, and eventually ulcerate (Glaze, 1991). Initially, a serous discharge may be present, which becomes purulent if the conjunctiva is secondarily infected with bacteria.

Diagnosis and treatment involve cessation of all medications for 1 week. If negligible improvement occurs, further diagnostic studies, such as a conjunctival scraping or biopsy, should be performed. If improvement is seen but the initial disease process is still present, medications should be changed to different, less irritating drugs (Glaze, 1991).

While any medication can be irritating in certain individuals, some medications such as topical commercial pilocarpine (pH 4–5) are notorious for causing conjunctival hyperemia and chemosis (Carrier & Gum, 1989; Smith et al., 1994).

Conjunctivitis Associated with Tear Deficiencies

KCS is a frequent cause of conjunctivitis in the dog, and it is the most common cause of secondary bacterial conjunctivitis. Thus, the Schirmer tear test (STT) should be performed on all dogs with conjunctivitis. Cytologic examination of conjunctival scrapings from dogs with chronic KCS reveals increased and altered mucins, increased goblet cells, and keratinization; cytology from dogs with acute KCS reveals bacteria, neutrophils, mucus, and debris (Lavach et al., 1977). Impression cytology of the bulbar conjunctiva in dogs with KCS before and after treatment with cyclosporine shows a change from moderate squamous metaplasia with neutrophils to improvement with a more normal cuboidal epithelium (Bounous et al., 1998). Treatment of KCS with cyclosporine has been shown to result in greater intraepithelial mucin quantities *in vivo* and to promote goblet cell differentiation *in vitro* (Moore et al., 2001). Treatment with cyclosporine, tacrolimus, or pimecrolimus decreases the conjunctival inflammation and mucous discharge associ-

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ated with KCS (Berdoulay et al., 2005; Hendrix et al., 2011; Moore et al., 2001; Ofri et al., 2009).

Loss of conjunctival goblet cells can lead to a qualitative tear film deficiency, resulting in keratoconjunctivitis and keratitis with absence of ocular discharge. These dogs have adequate aqueous tear production but shortened tear film breakup times (see Chapter 17; Moore & Collier, 1990).

Ligneous Conjunctivitis

Ligneous conjunctivitis is a rare disorder in dogs that results in thickened, hyperemic palpebral conjunctivae with proliferative, opaque membranes (Fig. 18.5). It has been reported in four Doberman Pinschers, a Golden Retriever, a Yorkshire Terrier, and three related Scottish Terriers (Mason et al., 2016; McLean et al., 2008; Ramsey et al., 1996a; Torres et al., 2009). The age range of those reported is from 2 months to 6 years, and all but three have been female. There are varying degrees of concurrent systemic illness (e.g., mucosal ulceration and fibrinous membranes elsewhere in the body). A plasminogen deficiency was diagnosed in two dogs (McLean et al., 2008; Torres et al., 2009). A genetic cause has been postulated more recently (Mason et al., 2016). Histologically, the affected conjunctiva has a thick, amorphous, eosinophilic, hyaline-like material in the substantia propria, with a moderate mononuclear infiltrate. Topical therapies have included corticosteroids, heparin, and cyclosporine or tacrolimus. Systemic treatment with prednisone, azathioprine, fresh frozen plasma, danazol, and diethylstilbestrol has been attempted, but generally yields poor results (McLean et al., 2008; Ramsey et al., 1996a; Torres et al., 2009).

Conjunctival Neoplasia

Melanomas, squamous cell carcinomas, angioendotheliomatosis, mast cell tumors, hemangiomas, hemangiosarcomas, angiokeratomas, papillomas, lymphosarcomas, histiocytomas, and transmissible venereal tumors all may affect the canine conjunctiva (Bonney et al., 1980; Boscos et al., 1998; Buyukmihci & Stannard, 1981; Collier & Collins, 1994; Collins et al., 1993; George & Summers, 1990; Gwin et al., 1982; Hare & Howard, 1977; Hargis et al., 1978; Johnson et al., 1988; Kilrain et al., 1994; Scherlie et al., 1992; Thomsen et al., 1991). The paucity of large studies and case reports, however, supports the clinical impression that conjunctival neoplasia occurs infrequently in the dog. Melanomas of the conjunctiva most commonly involve the NM, but they have also been reported to originate from the upper palpebral conjunctiva (Collins et al., 1993). These tumors tend to be malignant, and recurrences and metastasis are common. No correlations between mitotic index and likelihood of local recurrence or metastasis have been found. The Weimaraner breed may be predisposed. Combined excision and cryotherapy appear to be the most effective treatment (Collins et al., 1993).

Mast cell tumors can arise from the bulbar or palpebral conjunctiva or the NM (Fig. 18.6; Barsotti et al., 2007; Fife et al., 2011; Johnson et al., 1988). Some dogs may have a history of intermittent swelling and redness of the conjunctiva (Johnson et al., 1988). These tumors are easily diagnosed via fine needle aspirate. Surgical excision is usually curative. Conjunctival mast cell tumors have a low risk of recurrence and are unlikely to metastasize regardless of tumor grade or having incomplete surgical margins (Barsotti et al., 2007; Fife et al., 2011).

Papillomatosis occurs on the palpebral and bulbar conjunctivae as well as the NM. The lesions are well demarcated, rough, and papillary or sessile (Fig. 18.7). Histopathology shows various degrees of epithelial hyperplasia, acanthosis, hyperkeratosis with koilocytosis, and vascular and connective tissue cores (Bonney et al., 1980; Brandes et al., 2009; Hare & Howard, 1977). Some lesions have been tested and



Figure 18.5 Ligneous conjunctivitis in a Doberman Pinscher.



Figure 18.6 Conjunctival mast cell tumor in the temporal conjunctiva.

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Figure 18.7 Multiple papillomas on the skin and bulbar conjunctiva. Courtesy of Nancy McLean.

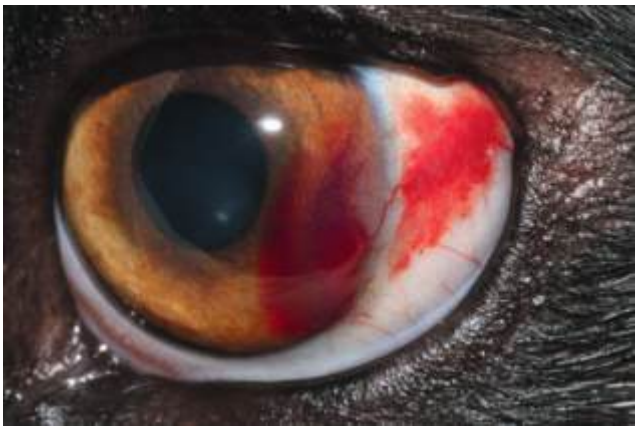


Figure 18.8 A 5-year-old male neutered border collie with conjunctival and corneal hemangiosarcoma.

are positive for gene fragments of canine oral papillomavirus DNA. While most lesions in young dogs regress spontaneously, excision is curative and may be necessary if the lesion is irritating (Bonney et al., 1980; Brandes et al., 2009; Collier & Collins, 1994; Hare & Howard, 1977).

Squamous cell carcinoma of the perilimbal area is seen infrequently. These tumors are white to pink, elevated, and papillomatous (Gwin et al., 1982; Hargis et al., 1978). While p53 immunostaining has been found in squamous cell carcinomas of several mammalian species, including horses, cattle, and cats, p53 immunostaining was not found to be positive in the one case of canine squamous cell carcinoma evaluated (Sironi et al., 1999).

Conjunctival hemangiomas and hemangiosarcomas tend to occur at the nonpigmented, leading edge of the NM and at the temporal bulbar conjunctiva (Fig. 18.8). Hemangiosarcomas of the conjunctiva can encroach on the cornea, thereby causing corneal edema and vascularization (Hargis et al., 1978). These tumors have a propensity to occur in breed groups that tend to have increased outdoor activity, and occur most frequently in middle-aged dogs (Pirie et al., 2006). There is also a linear trend showing an increased risk of tumor development with increased ultraviolet (UV) exposure, and there is a statistically significant risk for conjunctival hemangiosarcoma development, compared to hemangioma, with increased UV levels (Pirie et al., 2006). However, these tumors do not adhere to deeper tissue. Histologically, hemangioma and hemangiosarcoma are differentiated by the degree of cellular differentiation and local tissue invasion. Resection appears to be curative in most cases, but recurrences are possible (Gwin et al., 1982; Hargis et al., 1978; Pirie et al., 2006). Metastasis has not been confirmed (Hargis et al., 1978).

Angiokeratomas are rare, benign vascular tumors or telangiectasias of mucocutaneous tissue or skin. They can involve the bulbar conjunctiva and nictitans. Angiokeratomas are generally single, small, raised red masses, but they may also



Figure 18.9 Infiltration of the bulbar conjunctiva and conjunctiva of the nictitating membrane by lymphosarcoma. The conjunctiva was thickened and firm. Cytology from a conjunctival scraping revealed neoplastic lymphoblasts.

be black. Excision appears to be curative (Buyukmihci & Stannard, 1981; George & Summers, 1990).

Lymphosarcoma can infiltrate the conjunctiva, causing conjunctival thickening (Fig. 18.9; McCowan, 2014; Moore, 1989). In one case series all canine (n=5) conjunctival lymphoma cases were of T-cell origin (McCowan et al., 2014). In another retrospective study of ocular and periocular lymphoma cases, only one canine case had conjunctival involvement and this was of T-cell origin (Ota-Kuroki et al., 2014). Cytology of a conjunctival scraping may be diagnostic for lymphosarcoma, but in one known case of lymphosarcoma a scraping revealed only reactive lymphoid hyperplasia (Vascellari et al., 2005). Histopathologically, the conjunctival substantia propriae is infiltrated by a diffuse arrangement of polygonal neoplastic lymphoid cells with a high nucleus : cytoplasmic ratio, moderate amounts of lightly eosinophilic cytoplasm, multiple nuclei, and frequent mitotic figures.

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While conjunctival lymphosarcoma is usually considered to be associated with systemic lymphosarcoma, apparent ocular extranodal presentation has been reported with T-cell (Vascellari et al., 2005) and B-cell phenotypes (Olbertz et al., 2013). An extranodal B-cell lymphoma has also been reported affecting the mucosal-associated lymphoid tissue of the NM conjunctiva in an American Cocker Spaniel (Hong et al., 2011).

Canine lobular orbital adenomas can appear as a subconjunctival mass, eyelid swelling, or exophthalmos. The masses are either nodular or solid and extend into the orbit. They can be bilateral and commonly recur after excision. Histopathology reveals well-differentiated, lobulated, glandular tissue resembling either lacrimal or zygomatic salivary gland, with a mucoserous secretory pattern and a complete lack of ductular structures. These tumors differ from regular adenomas in that they extend into the loose orbital connective tissue (Headrick et al., 2004).

Nonneoplastic Conjunctival Masses

Nonneoplastic conjunctival masses can be inflammatory nodules, dermoids, displaced orbital fat, or cysts. Specific inflammatory diseases of the sclera, including episcleritis and scleritis, cause conjunctival hyperemia and swelling; they are described in Chapter 19.

Inflammatory Masses

Nodular granulomatous episclerokeratitis, fibrous histiocytoma, and recurrent proliferative keratoconjunctivitis are thought to represent very similar diseases, or even an identical disease syndrome. Collies appear to be predisposed, but the disease occurs in many breeds (Latimer et al., 1983b; Paulsen et al., 1987; Wheeler et al., 1989). This group of nonneoplastic diseases primarily affecting the cornea, limbus, episclera, and nictitans often presents as a subconjunctival mass. Limbal masses infiltrate the corneal stroma, causing vascularization and edema (Fig. 18.10). Histopathologically, the lesions are primarily granulomatous with lymphocytes, plasma cells, histiocytes, fibroblasts, and reticulin formation. The lesions tend to recur when excised, but excision with adjunctive cryotherapy is reported to be a successful mode of therapy (Wheeler et al., 1989). Some lesions will respond to 1% ophthalmic prednisolone acetate with treatment initiated four times a day and very gradually tapered to the lowest effective dose. Unfortunately, many dogs will develop lipid corneal degeneration with chronic topical steroid usage. Additionally, azathioprine, with or without topical corticosteroids, can be used to induce resolution of the lesions. Typically, treatment is initiated with 2.2 mg/kg once daily for approximately 3–10 days, and then slowly tapered based on response to the lowest effective dose, with possible discontinuation after several months (Latimer et al., 1983b; Paulsen et al., 1987). Dogs should be monitored for hepatotoxicity and myelosuppression every 4–6 weeks. Cryotherapy or intralesional triamcinolone at 4–12 mg per eye, with higher dosages for larger dogs, can also be used (Regnier & Toutain, 1991; Wheeler et al., 1989). Ocular nodular fasciitis, which may be a different disease syndrome, usually causes subconjunctival, scleral, corneal, nictitans, limbal, and eyelid masses (Fig. 18.11). Histopathologically, fibroblasts and abundant reticulin formation are the primary changes, with lower numbers of lymphocytes, plasma cells, and histiocytes occurring as well (Bellhorn & Henkind, 1967; Gwin et al., 1977; Lavignette & Carlton, 1974). Excision of the lesions, even when incomplete, is curative (Bellhorn & Henkind, 1967; Gwin et al., 1977).



Figure 18.10 Nodular granulomatous episcleritis with associated corneal edema.

Idiopathic sterile granulomatous disease has been diagnosed in dogs with multiple masses on the conjunctiva, eyelids, nictitans, and skin (Collins et al., 1992). One report described plaque-like lesions in the sclera, a 360° area of perilimbal infiltrate, thickening of the conjunctiva, and concurrent raised white plaques in both nasal passages (Gionfriddo et al., 2003). Histopathologically, granulomatous inflammation with large epithelioid cells, plasma cells, and lymphocytes, primarily T lymphocytes, is seen. Treatment with L-asparaginase, azathioprine, interferon α_{2a}, and topical and systemic prednisone have all been successful (Collins et al., 1992; Gionfriddo et al., 2003; Riis, 2000).

Dermoids

A dermoid is a benign congenital mass of ectodermal and mesodermal origin, usually affecting the lateral limbal region, but it can also involve the cornea, sclera, conjunctiva, eyelid, or NM (Fig. 18.12). Frequently, the presence of a dermoid is not appreciated until long, coarse hair extends from the surface and causes irritation. Histopathologically, the

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Figure 18.11 Nodular fasciitis on the temporal aspect of the globe. An immature cataract is also present.



Figure 18.12 Conjunctival dermoid with hair at the temporal aspect of the globe.

tumor resembles normal haired skin, and excision is curative (Gwin et al., 1982).

Subconjunctival Fat Prolapse

Subconjunctival prolapse of orbital fat is seen as a nonpainful, movable, light pink mass at the limbus (Fig. 18.13). Cytologic examination reveals multiple lipid droplets and few mononuclear cells. It most likely occurs secondary to a weakness in Tenon's capsule. Surgical removal, while curative, should not be overzealous, as enophthalmia can result (Allevi et al., 2003; Grahn & Wolfer, 1993).

Parasitic Granulomas

Onchocerciasis causes bean-sized masses in the conjunctiva, nictitans, and sclera (Fig. 18.14; Gardiner et al., 1993; Orihel et al., 1991; Sreter et al., 2002; Szell et al., 2001). The surface of the masses is generally irregular, with nodular thickenings caused by the coiled adult worms (Sreter et al., 2002).



Figure 18.13 Orbital fat prolapse in the ventral fornix.



Figure 18.14 *Onchocerca* granuloma in the ventral bulbar conjunctiva. Courtesy of Dr. Nancy McLean.

Other common ophthalmic manifestations are periorbital swelling, exophthalmos, excessive lacrimation, discharge, discomfort, photophobia, conjunctival congestion, protrusion of the NM, granuloma formation, localized corneal edema, and anterior and posterior uveitis (Komnenou et al., 2003; Zarfoss et al., 2005). Histopathologically, a pyogranulomatous or granulomatous reaction with eosinophils is associated with the presence of adult worms. Lymphoplasmacytic uveitis, preiridal fibrovascular membranes, and evidence of secondary glaucoma are also seen (Zarfoss et al., 2005). Microfilariae are seen in the uteri of females and in the tissues surrounding them and can be isolated from skin biopsy specimens (Szell et al., 2001).

While there is debate as to whether the organism is *Onchocerca lienalis* or *Onchocerca lupi,* the morphology of parasites found in different parts of the world differs slightly (Gardiner et al., 1993; Komnenou et al., 2003; Szell et al., 2001; Zarfoss et al., 2005). However, a comparison of the *Onchocerca* isolated from dogs in Greece and Hungary, done by testing sequences of the cytochrome oxidase gene of the filarial parasites and the 16S ribosomal RNA gene from the

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Wolbachia endosymbionts, showed that they were the same species (Komnenou et al., 2003). Treatment includes surgical removal of the masses followed by medical therapy (Gardiner et al., 1993; Komnenou et al., 2003; Zarfoss et al., 2005). Medical therapy includes prednisolone 0.5 mg/kg orally (PO) twice a day (BID) for 3–4 weeks and doxycycline 5 mg/kg PO BID for 6–8 weeks. One week after surgery, 2.5 mg/kg of melarsomine is given intramuscularly twice within 24 hours, followed by ivermectin 50 µg/kg subcutaneously (SC) and melarsomine 1 month after surgery. Or where melarsomine is not available, ivermectin at 200 µg/kg PO or SC as a single dose alone 1 week after surgery cases can be effective (Komnenou, A., personal communication).

Subconjunctival *Dirofilaria repens* has been reported in a German Shepherd dog, resulting in a conjunctival mass and follicular conjunctivitis. Treatment with spot-on 10% imidacloprod and 2.5% moxidectin was successful (Agapito et al., 2018).

Granulomatous lesions with intralesional protozoal organisms (*Acanthomoeba*, *Toxoplasma*, *Leishmania* spp.) in the absence of systemic involvement have been reported in five dogs receiving long-term immunosuppression (Beckwith-Cohen et al., 2016). Cases were reported to improve on cessation of immunosuppressive therapy in conjunction with partial or complete surgical excision, with two dogs also receiving systemic antiprotozoal therapy (Beckwith-Cohen et al., 2016).

Cysts

Multiple causes of cyst formation in the conjunctiva have been described, but all occur only rarely in the dog. Conjunctival epithelial inclusion cysts, cystic neoplasms, parasitic cysts, lacrimal cysts (i.e., dacryops), orbital cysts with conjunctival fistula formation, and cysts of the canaliculi can occur (Gerding, 1991; Harvey et al., 1968; Murphy et al., 1989; Playter & Adams, 1977). A lacrimal gland cyst appears as a fluctuant mass dorsolateral to the globe (Harvey et al., 1968; Playter & Adams, 1977). Surgical resection is curative. One dog had a fistula open to the conjunctival fornix. Histopathology revealed cysts with associated ducts and lacrimal glandular tissue (Harvey et al., 1968; Playter & Adams, 1977).

Conjunctival Hemorrhages

Conjunctival and subconjunctival hemorrhages occur commonly in the dog and most frequently result from trauma. When this condition is caused by trauma, no treatment is necessary if the remaining ophthalmic and physical examinations are normal (Fig. 18.15). If there is no history or evidence of trauma, a coagulopathy or vasculitis must be considered as the possible cause. Specifically, conjunctival hemorrhage has been reported with angiostrongylosis and von Willebrand factor deficiency (Whitley et al., 2005). No treatment is needed specifically for the conjunctival hemorrhages.



Figure 18.15 Conjunctival hemorrhage secondary to trauma in a dog. Note the miosis indicating anterior uveitis that is also a result of the trauma.

Subconjunctival hemorrhage, especially in conjunction with subconjunctival pigment migration, extending through 360° has been reported to be associated with open globe injury (e.g., scleral rupture) in humans (Hartley et al., 2007; Moraczewski, 2007). Anecdotally, this has also been witnessed in veterinary patients with open globe injuries due to blunt trauma.

Foreign Bodies

Physical irritation caused by foreign bodies lodged within the conjunctiva or NM can cause a severe reaction, including blepharospasm, mucoid discharge, hyperemia, and corneal ulceration. Grass awns and other plant material are the most common culprits (Brennan & Ihrke, 1983). Results of a retrospective study of grass awn migration showed that in 174 dogs, the grass awn was lodged in the conjunctiva or NM in 26 cases (Fig. 18.16; Brennan & Ihrke, 1983). Most foreign bodies can be removed with forceps after administration of a topical ophthalmic anesthetic (Bromberg, 1980). Chemical exposure can also cause irritation. Conjunctival hyperemia, chemosis, and corneal ulceration occurred in a dog that was sprayed by a walking stick insect *(Anisomorpha buprestoides;* Dziezyc, 1992). Several dogs developed severe conjunctivitis and tongue necrosis associated with ingestion of the pine processionary moth caterpillar, *Thaumetopoea wilkinsoni*. The conjunctivitis was thought to be secondary to irritation from the caterpillar hairs or to histamine-mediated effects (Bruchim et al., 2005). Tarantula hair foreign bodies of the cornea and conjunctiva have also been reported in a Rat terrier (Reed et al., 2016).

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Figure 18.16 Plant foreign body protruding from the temporal conjunctiva.



Figure 18.17 Severe conjunctivitis associated with systemic and retrobulbar blastomycosis.

Orbital Disease

The conjunctiva is frequently affected by orbital disease. The redundancy and elasticity of the conjunctiva allow it to be the path of least resistance; therefore, it may be the first tissue to show swelling or displacement (Fig. 18.17). Conjunctival hyperemia also occurs commonly with orbital disease (Attali-Soussay et al., 2001; Wang et al., 2001).

Zygomatic mucoceles can cause protrusion of the conjunctiva beyond the palpebral fissure, in addition to causing exophthalmos, prolapse of the NM, and periorbital swelling (Schmidt & Betts, 1978). A ranula and mucocele of the zygomatic salivary gland and duct were diagnosed surgically in a dog with fluctuant swelling under the conjunctiva of the lower lid and under the upper lip; marsupialization to the oral mucosa was curative (Martin et al., 1987). A conjunctival swelling that occurred only when a dog was placed in dorsal recumbency, the head was lowered, or pressure was applied to the jugular veins resulted from an orbital varix. In this dog, the pink conjunctival swelling was aspirated and found to be blood-filled (Millichamp & Spencer, 1991).

Orbital cellulitis can be localized or associated with sinus disease. Clinical signs of cellulitis can include prolapsed necrotic NM, severe mucopurulent discharge, fistulous tracts, blepharedema, and exophthalmos (Homma & Schoster, 2000; Willis et al., 1999). Infectious organisms include bacteria, fungi such as *Blastomyces* and *Aspergillus,* and parasites such as *Toxocara canis* (Laus et al., 2003; Willis et al., 1999). Occasionally, periapical abscesses, slab fractures of the fourth maxillary premolar, and extraction or fracture of the first or second maxillary molars can cause the same clinical signs (Ramsey et al., 1996b).

Anatomic Abnormalities

Conjunctival disease can develop secondary to anatomic defects that cause inadequate tear drainage, chronic exposure, and other changes.

Medial Canthal Pocket Syndrome

Medial canthal pocket syndrome refers to the chronic conjunctivitis occurring in dogs with deep orbits, enophthalmia, narrow skulls, slight entropion, and inadequate tear drainage. It has been reported in the Afghan Hound, Doberman Pinscher, Golden Retriever, Gordon Setter, Great Dane, Great Pyrenees, Ibizan Hound, Labrador Retriever, Newfoundland, Standard Poodle, Rottweiler, Samoyed, and Weimaraner (Rubin, 1989). Selective breeding for the specific head shape has made these dogs slightly enophthalmic. This enophthalmia then creates a "pocket" in the ventral conjunctival fornix that collects dust, dirt, and other foreign material. The resultant clinical signs include conjunctival and nictitans hyperemia, as well as a slight mucoid discharge (Rubin, 1989). The conjunctivitis occurs secondary to the irritation and poor tear drainage, and it is poorly responsive to medical therapy. In certain dogs, especially those that are active outdoors, frequent flushing of debris from the ventral fornix with eye wash may help to alleviate the clinical signs. Fortunately, in most cases this syndrome does not result in significant corneal disease.

Medial Aberrant Dermis (Caruncular Trichiasis)

Aberrant dermis derived from the facial skin may continue past the intermarginal space in the medial canthus and onto the conjunctiva and caruncle. When this occurs, irritation from the hair, which can grow very long, can cause keratitis,

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epiphora, or both. The condition has been observed in the Pekingese, Shih Tzu, and Lhasa Apso. Surgical treatment with the medial pocket canthoplasty or removal of the aberrant dermis using conjunctiva and the medial palpebral ligament for closure can be done (Carter, 1973; Rubin, 1989). Cryotherapy can also be used to destroy the hair follicles, but depigmentation of the caruncle can result (Rubin, 1989).

Conjunctival Manifestations of Systemic Disease

Many systemic diseases cause conjunctival manifestations. Some diseases, such as canine distemper, may cause a primary conjunctivitis, while others cause anterior uveitis, which leads to a ciliary flush or episcleral injection that is often misinterpreted as conjunctivitis. Because intraocular disease can lead to blindness, and because the diagnosis of anterior uveitis aids in narrowing the list of differential diagnoses in a dog with systemic disease, any dog with a reddened conjunctiva should have a complete ophthalmic examination. Several diseases that commonly cause conjunctival manifestations are mentioned here; for further discussion, see Chapter 36, Part 1.

Leishmaniasis caused by *Leishmania infantum* can manifest with conjunctivitis, keratitis, blepharitis, retinitis, anterior uveitis, lymphadenomegaly, cutaneous signs, cachexia, abnormal locomotion, and other clinical signs (McConnell et al., 1970; Nicolau & Perard, 1936; Pena et al., 2000; Slappendel & Ferrer, 1990; Swenson et al., 1988). The use of PCR from conjunctival swabs and conjunctival biopsies is helpful in assessing exposure, screening, and diagnosis of leishmaniasis (Ferreira et al., 2008; Gramiccia et al., 2010; Leite et al., 2010; Solano-Gallego et al., 2001; Strauss-Ayali et al., 2004). Experimentally infected dogs are positive by conjunctival PCR at 45 days of infection before seroconversion. Treatment of canine leishmaniasis with allopurinol leads to a significant improvement in clinical signs, but does not eliminate the organisms (Koutinas et al., 2001).

Dogs experimentally inoculated with *Leptospira kirschneri* serovar *grippotyphosa* developed clinical signs including conjunctivitis with a thick ocular discharge, lethargy, diarrhea, dehydration, vomiting, and icterus (Greenlee et al., 2004). Conjunctivitis along with dermatologic signs, anorexia, lethargy, fever, and vomiting has been reported in dogs with *Babesia gibsoni* infection. Rapid improvement was seen with treatment with imidocarb dipropionate (Tarello, 2003). Conjunctivitis, neurologic signs, and pancytopenia have occurred in a dog with generalized *Listeria monocytogenes* infection (Schroeder & van Rensburg, 1993). Several dogs from Nigeria with hepatozoonosis had conjunctivitis, fever, anorexia, and lameness (Ibrahim et al., 1989).

Multisystemic inflammatory disease was reported in a Borzoi that presented with conjunctivitis and signs referable to other organ systems; however, the cause of this inflammation could not be determined (Cheeseman et al., 1995). Weimaraners with low serum immunoglobulin concentrations may develop conjunctivitis as well as other recurrent diseases involving the alimentary tract, joints, skin, lymph nodes, and central nervous system (Day et al., 1997).

Engorged conjunctival blood vessels have been observed in a dog with complications from a thymoma and in four dogs with type C botulism (Cornelissen et al., 1985; Peaston et al., 1990). Bilateral conjunctivitis, mucopurulent discharge, keratitis, and erosions, as well as ulcerations of the nose and foot pads, were present in a dog with tyrosinemia (Kunkle et al., 1984).

Dogs with multiple myeloma can develop congested conjunctival blood vessels in association with anterior uveitis and retinal changes (Kirschner et al., 1988). A thickened and hyperemic conjunctiva infiltrated perivascularly with histiocytes, lymphocytes, and plasma cells occurred in a dog with systemic histiocytosis; other ocular and orbital tissues were also involved (Scherlie et al., 1992). Conjunctival involvement of systemic lymphoma is also reported (see "Conjunctival Neoplasia").

Severe anemia can cause pallor of the conjunctiva and other mucous membranes, as well as lightness of the retinal vessels. Polycythemia can cause "brick red" mucous membranes (Clerc & LaForge, 1995; Curtis et al., 1991). Clotting deficiencies can cause periocular hemorrhages, but more commonly cause intraocular hemorrhages (Fig. 18.18; Martin, 1982). Jaundice is most easily seen in the dog in the mucous membranes, sclera, and skin. Jaundice is an indication of hemolysis, hepatic disease, or biliary tract obstruction (Dimski, 1995). Many systemic



Figure 18.18 Petechial and ecchymotic hemorrhages are present in the conjunctiva of the nictitating membrane in a dog with thrombocytopenia.

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diseases in humans are well documented as causing conjunctival changes; however, they are either infrequently seen or not documented in the dog.

Effects of Radiation

Because of the close proximity of the globe and adnexa to the nasal and paranasal sinuses, the globe is frequently within the field of irradiation used in treatment of sinus neoplasia. Mild to severe conjunctivitis is the most frequently occurring early ocular complication (Fig. 18.19), and this conjunctivitis is usually poorly responsive to medical therapy (Jamieson et al., 1991; Roberts et al., 1987). The conjunctival disease results from a direct effect of radiation on the basal epithelial stem cell layer (Nakissa et al., 1983). KCS can occur as an early or a late complication; therefore, an STT should be performed on all dogs that develop conjunctivitis as a complication of radiation therapy (Jamieson et al., 1991; Roberts et al., 1987).

Pharmacologic Research

Conjunctivitis is a frequently noted sign of toxicity in experimental studies of new drugs administered both systemically and topically (Aguirre et al., 2009; Dominick et al., 1993; Kerry et al., 1993; Lanigan, 2001; Mally & Thiebault, 1990). Pharmacologic studies have investigated the systemic absorption of drugs administered by the topical conjunctival route (Buhring et al., 1990; Nomura et al., 1990, 1994). A soluble, bioadhesive ophthalmic drug insert has been developed that was tolerated by dogs in one study (Baeyens et al., 2002).

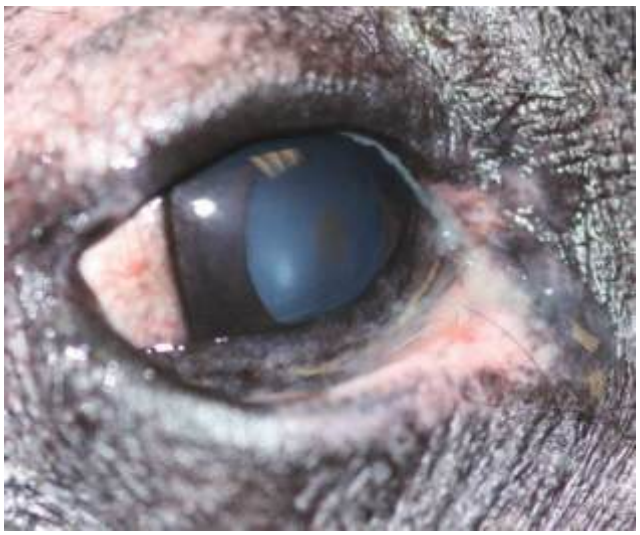


Figure 18.19 Blepharitis, conjunctivitis, and keratoconjunctivitis sicca in a terrier dog following radiotherapy for a nasal adenocarcinoma (eyes included in field of radiotherapy).

A subconjunctival sustained-release cyclosporine delivery device for the treatment of KCS has been studied and appeared to be effective in a wolf (Acton et al., 2006; Beale et al., 2004).

Surgical Procedures

The conjunctiva is an invaluable tissue to ophthalmic surgeons. Because of its redundancy and rather loose bulbar adhesions, the bulbar conjunctiva can be easily resected and relocated. Conjunctival biopsy specimens can be simply and quickly obtained and are an effective diagnostic modality in patients with chronic conjunctivitis or conjunctival masses. Conjunctival grafts created by incising the conjunctiva and relocating a part of it to the cornea are used to deliver a focal blood supply to an otherwise avascular cornea in the face of progressive infection or deep corneal defects. Conjunctival grafts can be used alone for the treatment of deep ulcers, or can be used to cover tectonic corneal grafts and porcine small intestinal submucosa used for the repair of full-thickness corneal defects (Bussieres et al., 2004; see Chapter 19).

Conjunctival Biopsy

Conjunctival biopsy is quite easy to perform and usually can be done in conscious dogs. After several drops of a topical ophthalmic anesthetic have been applied, the conjunctival area in question is gently elevated with fine-toothed forceps, and the conjunctiva is then excised with tenotomy scissors. Extra anesthesia can be achieved by holding a cotton-tipped swab soaked in topical anesthetic onto the intended biopsy site. The conjunctival defect (smaller than 1 cm diameter) is allowed to heal by second intention. In addition, an antibiotic ophthalmic solution is instilled for 5–7 days. Conjunctival biopsies are indicated for chronic conjunctivitis that is nonresponsive to therapy and for suspected neoplasia.

Excision of Small Masses

Conjunctival neoplasia occurs infrequently; however, complete excision of the tumor, with or without ancillary treatment, is usually the treatment of choice. Most conjunctival neoplasms do not invade the sclera and are rather easily dissected from the underlying tissue. Dermoids can also occur in the conjunctiva and often need to be excised. With small masses, excisional biopsies can be done in the awake animal. When excising a neoplasm, the surgeon should try to obtain a 2 mm margin. Small defects can be allowed to heal by second intention, but defects larger than 1 cm in diameter should be closed in a simple, continuous pattern with 5-0 to 7-0 polyglactin 910 suture.

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Laceration Repair

Small lacerations of the conjunctiva (< 1 cm) can be allowed to heal by secondary intention (Fig. 18.20). Large lacerations should be carefully cleansed, but debridement should be kept to a minimum. Any foreign material is removed. Severe conjunctival lacerations are rare and may be associated with intraocular damage, and the sclera underlying the conjunctival defect should be carefully evaluated for damage, especially if hyphema is present. After the area has been cleansed and explored, simple interrupted, 5-0 to 7-0 absorbable sutures are used to appose the edges. Most commonly, conjunctival lacerations are associated with lacerations of the entire eyelid, and repair of these lacerations is described in Chapter 15.

Treatment of Symblepharon

Symblepharon occurs rarely in the dog and is usually secondary to trauma or chemical burns. Repair involves excising fibrous adhesions that have developed between the conjunctiva and the cornea or eyelid. A superficial keratectomy is performed to remove any adhesions between the conjunctiva and the cornea; if the adhesions continue into the conjunctiva beyond the limbus, these too are severed. After the abnormal tissue has been excised, the edge of the remaining normal conjunctiva is sutured to the limbus, and a soft corneal contact lens is placed to allow the cornea to reepithelialize before the conjunctiva readheres. A silicone-sheeting implant may also be placed in the conjunctival fornix to prevent interconjunctival adhesions (Gelatt & Gelatt, 2011). Amnion graft scaffolds are utilized in humans with unilateral symblepharon to provide limbal stem cells and avoid recurrence, a common sequela in veterinary patients (Amescua et al., 2014; Basu et al., 2016).



Figure 18.20 Conjunctival laceration that resulted from a dog bite.

Surgical Repair of Conjunctival Defects

Conjunctival defects smaller than 1 cm in diameter can either be allowed to heal by second intention or can be closed with 5-0 to 7-0 polyglactin 910 suture in a simple interrupted or simple continuous pattern. Burying the knots decreases postoperative irritation. Repair of defects larger than 1 cm in diameter usually involves autografts from the bulbar conjunctiva of the other eye or from the buccal mucosa (Gelatt & Gelatt, 2011).

Conjunctival Autografts to the Cornea

Conjunctival autografts are used to treat deep corneal ulcers for several reasons. They preserve corneal and ocular integrity, replace lost corneal tissue, and supply vascularization (Peiffer et al., 1977). Many types of grafts have been described. Selection of the conjunctival graft in a clinical situation depends on the ulcer size, depth, and position; the presence of infection; the surgeon's abilities; and the available instrumentation.

Necessary Instrumentation and Surgical Fundamentals

Specialized ophthalmic instrumentation is necessary to perform conjunctival grafting procedures. An eyelid speculum, Steven's tenotomy scissors, Colibri forceps or tying forceps with 1 × 2 teeth for fixation, and ophthalmic needle holders are the minimal necessary instruments. Generally, 7-0 to 10-0 polyglactin 910 suture is used, with 8-0 or smaller suture being more satisfactory. Magnification with a head loop or operating microscope is preferable to no magnification for corneal procedures.

Maintenance of the blood supply and prevention of graft retraction are both important in assuring success. Grafts must be wide enough that an adequate blood supply is maintained, and the base should be wider than the tip. To prevent graft retraction, Tenon's capsule should be dissected from the substantia propria (Fig. 18.21). The graft should be thin enough that the tips of the scissor blades can be seen through it. The graft tissue should also be sufficiently loose so that when positioned over the corneal lesion, it does not retract. This is accomplished with adequate undermining and dissection with tenotomy scissors. In addition, it is imperative that the graft created is larger (~1–2 mm) than that necessary to cover the wound to allow for graft contraction. During dissection and removal of Tenon's capsule, the surgeon must use care to avoid creating holes in the graft, because these holes tend to expand and cause failure of the graft. If a small hole is created,

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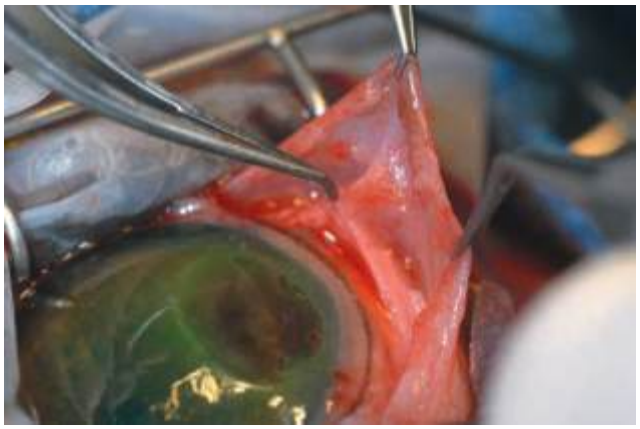


Figure 18.21 During harvest of a conjunctival graft, Tenon's capsule is dissected from the substantia propria of the conjunctiva to prevent graft retraction. Tenon's capsule is pulled away from the overlying conjunctiva so that it can be excised.

placing a suture of 8-0 to 10-0 polyglactin 910 across it may prevent the hole from enlarging.

Preparation of the ulcer site is important for graft retention. Necrotic and collagenolytic corneal stroma should be debrided using a scalpel blade. Frequently, a partial-thickness keratectomy is indicated to remove the necrotic tissue. Sutures must be placed in healthy corneal stroma to prevent dehiscence of the graft. Grafts will not adhere to corneal epithelium; therefore, if corneal epithelium is present at the edge of the wound, it should be excised with a scalpel blade (e.g., Beaver No. 64) if the graft is to cover that specific area.

Island Grafts

Island grafts can be created from the palpebral conjunctiva of the upper eyelid. A chalazion clamp may be placed on the dorsal eyelid before harvesting the graft to decrease hemorrhage. Grafts should be sized 10% greater than the corneal lesion to allow for graft contraction. Grafts are then sutured into the prepared ulcer bed using a simple interrupted pattern. To help ensure the success of this type of conjunctival graft, sutures must be placed very close to each other, and the graft must be in perfect apposition to the edges of the prepared corneal defect. Generally, the grafts will remain a blanched white for approximately 10 days, by which time corneal vascularization has usually invaded the graft tissue (Scagliotti, 1988). Because island grafts are not vascularized, they should not be used in cases of bacterial infection and are ideally used in already vascularized corneas.

Bulbar Pedicle Graft

The pedicle graft created from the bulbar conjunctiva is the graft used most frequently by veterinary ophthalmologists. The advantages of this procedure include the following:

- The graft can be made to cover any part of the cornea.
- Vision can usually be retained while the graft is in place.
- The graft moves in relation to the globe.
- No tension is created with the eyelid movement.

The graft is most easily created from the area lateral and dorsal to the limbus, where exposure is greatest and incorporation of the third eyelid into the graft can be avoided (Fig. 18.22). Three factors have been associated with graft dehiscence: aqueous leakage, keratomalacia, and a graft direction of more than 45° from the vertical (Hakanson & Merideth, 1987; Hakanson et al., 1988). If the pedicle is very wide or corneal perforation has occurred, a suture should be placed through the midline of the pedicle and into firm corneal stroma at the dorsal edge of the ulcer. When placing this suture, care should be taken to avoid the major conjunctival vessels (Hakanson et al., 1988). Alternatively, sutures can be placed on both edges of the pedicle extending to the limbus. Another alternative is to suture a separate layer(s) of graft material as an aqueous-tight layer (e.g., extracellular collagen matrix or amnion), which is then overlaid with a conjunctival graft. Typically, if the cornea has healed well, the pedicle of the graft is excised using tenotomy scissors after administration of a topical anesthetic 6–8 weeks postsurgery (Fig. 18.23). The graft will not be adhered where corneal epithelium was present at the time of surgery. The scissor blades are slid beneath the pedicle and closed. Care should be used so that traction is not placed on the graft, which could pull the pedicle off the corneal lesion.

Tarsoconjunctival Pedicle Graft

The tarsoconjunctival pedicle graft can be used for deep corneal ulcers (Peiffer et al., 1977). To prepare the graft, the



Figure 18.22 Pedicle bulbar conjunctival graft. A viable conjunctival graft 2 weeks postsurgery. Multiple vessels are seen extending to the edges of the graft. The polyglactin 910 sutures are still present. The remaining corneal edema resolved, and the corneal vessels regressed with time. While not visible in this image, the pupil was mydriatic.

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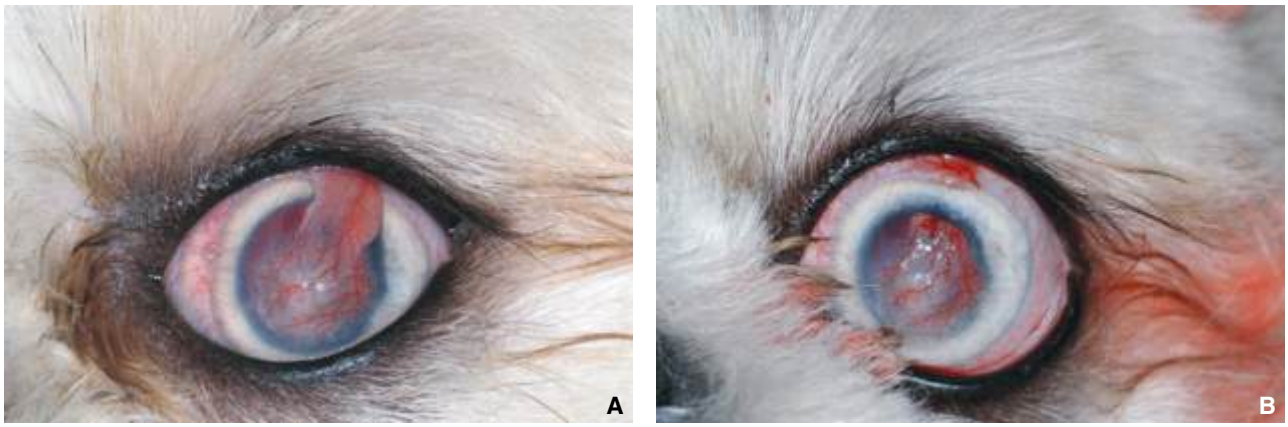


Figure 18.23 **A**. A pedicle graft 8 weeks postsurgery. The graft is viable, and the pupil is pharmacologically dilated. **B**. A pedicle graft immediately posttransection of the pedicle.

upper eyelid is clamped and everted with a chalazion clamp. The graft is created by dissecting a pedicle of palpebral conjunctiva from the underlying orbicularis oculi muscle of the superior eyelid using sharp dissection with a Bard-Parker No. 15 or Beaver No. 64 blade and tenotomy scissors. The pedicle is created with the base toward the eyelid margin. The base of the graft should be wide enough to ensure an adequate blood supply, and the length should be constructed to minimize tension and to allow eyelid mobility. The graft is then sutured to the corneal defect in a simple interrupted pattern (Peiffer et al., 1977). Disadvantages of this type of graft include the potential for eyelid movement causing premature retraction of the graft and the greater difficulty of harvesting the palpebral conjunctiva compared with the bulbar conjunctiva. A temporary tarsorrhaphy should be placed to decrease tension on the graft, minimizing the probability of retraction caused by eyelid movement.

Bridge Grafts

A bridge graft has a blood supply feeding the graft from both ends. The graft is created by using tenotomy scissors to make two concentric conjunctival incisions, one near and parallel to the limbus and one parallel to the limbus but distant enough from the first incision to create a graft of the appropriate width. Tenon's capsule should be dissected from the graft. The graft should be wide enough to ensure adequate perfusion. Both edges of the graft are sutured to the cornea after sliding the graft over the corneal defect (Gelatt & Gelatt, 2011). The leading edge of the remaining bulbar conjunctiva can be sutured to the limbus depending on the size of the defect created.

Advancement Grafts (180-Degree or Hood)

Hood grafts, also known as advancement or 180-degree grafts, are most useful for dorsal and lateral paracentral corneal defects and peripheral corneal defects. The graft is created by incising the bulbar conjunctiva near the limbus and dissecting the conjunctiva from the underlying Tenon's capsule caudally toward the fornix. The conjunctiva is then sutured to the cornea so that the graft extends beyond the defect. Finally, supporting sutures are placed along the remainder of the leading edge of the graft (Gelatt & Gelatt, 2011). These grafts tend to have more tension than pedicle grafts and therefore may be more likely to dehisce. An exceptionally thin hood graft, termed keratoleptynsis, is being used for the treatment of severe corneal edema. After a thin keratectomy is done down to clear cornea, a thin conjunctival graft is sutured over the effected cornea. If a large area is affected, the graft may be made to cover only two-thirds to three-fourths of the corneal surface (Horiakawa et al., 2016; Miller, 2010).

Complete Bulbar Grafts (360-Degree)

A 360-degree bulbar conjunctival graft, also known as a complete bulbar graft, can be used to surgically treat central and paracentral, as well as very large-diameter, corneal defects. To create the graft, limbal traction is created to rotate the globe ventrally. A 180-degree incision is made parallel to, but at sufficient distance from, the limbus so that the graft created will be wide enough to cover the cornea. After the limbal-based graft is created, a 360-degree peritomy is made, and the graft is slid into position and sutured either to the inferior and superior limbal cornea, the episclera, or the inferior and superior conjunctival incisions (Gelatt & Gelatt, 2011; Gundersen, 1960). A modification to this procedure is to make a 360-degree peritomy and undermine the conjunctiva toward the fornix; the edges are then brought together as a horizontal line across the middle of the cornea and apposed with horizontal mattress sutures (Fig. 18.24). The graft can be also directly sutured to the corneal defect if corneal rupture is imminent or aqueous humor is leaking. This type of

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Figure 18.24 A 360-degree bulbar conjunctival graft 2 weeks postsurgery. The stents of the temporary tarsorrhapy are visible.

graft has several disadvantages, however, because the entire cornea is covered by the graft. The patient is blind while the graft is in place, evaluation of the eye is impossible, penetration of topical drugs is probably impaired, and dehiscence is common if there is tension on the graft.

Corneoconjunctival Transposition

Corneoconjunctival transposition is a modification of the conjunctival graft. Partial-thickness cornea adjacent to the defect is mobilized into the defect, with the attached bulbar conjunctiva sliding into the area from which the corneal transplant was harvested. This graft is most frequently used with axial corneal lesions, because there is typically less scar tissue associated with the transplanted corneal tissue than with a conjunctival pedicle graft. However, brachycephalic breeds such as the Pug may develop pigmentation of the transplanted corneal tissue as well as the conjunctival portion. The corneoconjunctival transposition is not recommended for use in infected cornea, and some surgeons find it more time-consuming to create than a bulbar pedicle graft. An alternate, even more time-consuming technique, known as corneoscleral transposition, transplants cornea with attached sclera into the defect (Gelatt & Gelatt, 2011). This procedure is described more fully in Chapter 19.

General Postoperative Care and Success Rates

Treatment for a corneal ulcer after conjunctival graft placement includes topical ophthalmic antibiotics and parasympatholytic drugs. Because a blood supply is created, systemic antibiotics will be able to reach the corneal ulcer and therefore are often initiated. Serum, which is frequently used for its anticollagenase and antiproteinase properties, is not necessary; the graft will supply this therapy. Generally, the base of a conjunctival pedicle graft is severed from the limbus 6–8 weeks postoperatively (Hakanson & Merideth, 1987). Leaving the pedicle intact has been recommended in some instances (e.g., following corneal sequestrum removal) to maintain a patent blood supply to the cornea involved.

Conjunctival grafts are a highly successful treatment modality for deep and perforated corneal ulcers in the dog (Hakanson & Merideth, 1987; Hakanson et al., 1988; Wagner et al., 1992). In one study, corneal clarity compatible with useful vision was achieved in 25 of 35 cases, and graft dehiscence occurred in only 3 of 35 eyes (Hakanson & Merideth, 1987). In another study, structural integrity of the cornea was reestablished in 91% of eyes with bacterial ulcerative keratitis that underwent conjunctival graft placement, and partial or total graft dehiscence occurred in 32% of eyes (Wagner et al., 1992). Graft failure has been associated with incorrect corneal graft-bed preparation or suturing, incomplete covering of keratomalacia, aqueous leakage, a graft direction of more than 45% from the vertical, and excessive stretching of the graft between opposite sutures (Hakanson & Merideth, 1987; Hakanson et al., 1988).

Nictitating Membrane

The NM, which is also called the membrana nictitans, third eyelid, or haw, is a thin sheet of tissue found in the medial canthus of most domestic animal species. The primary purpose of the NM is physical protection of the cornea. Its gland also contributes significantly to normal tear production and distribution. The NM is affected by a number of inflammatory and neoplastic conditions as well as anatomic malformations that require surgical correction.

Anatomy, Histology, and Function

The basic shape of the canine NM is defined by a T-shaped piece of hyaline cartilage (Fig. 18.25). The "arm" of the T parallels the free margin of the NM, and the "shaft" is perpendicular to the free edge. The shaft of the NM cartilage is cone shaped at the basal end and terminates to form a triangular plate. The arm or "crossbar" at the leading edge of the NM is crescent shaped with a prominent bulge. The cartilage is of hyaline material, with some elastic fibers detectable only in the neighboring connective tissue (Schlegel et al., 2001). The ventral extent of the shaft originates from the periorbital connective tissue associated with the inferonasal aspect of the globe.

The base of the NM is intimately associated with the fasciae of the ocular musculature (Constantinescu & McClure, 1990). Conjunctiva covers the anterior and posterior surfaces of the NM. The conjunctival mucosa on the posterior surface is contiguous with the bulbar conjunctiva mucosa; the conjunctival mucosa on the anterior surface is contiguous with the palpebral conjunctival mucosa. In addition to

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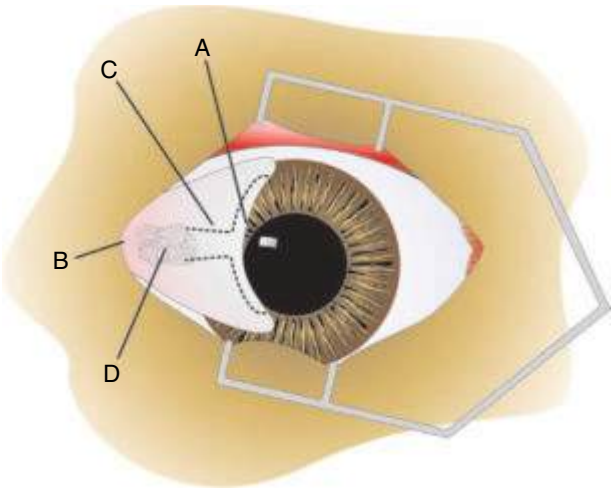


Figure 18.25 Normal canine NM. Note the leading edge (**A**), its base (**B**), the T-shaped hyaline cartilage (**C**), and the superficial gland of the nictitans (**D**). (Reproduced with permission from Gelatt, K.N. & Gelatt, J.P. (2011) Surgical procedures for the conjunctiva and the nictitating membrane. In: *Veterinary Ophthalmic Surgery* (eds. Gelatt, K.N. & Gelatt, J.P.), pp. 157–190. Edinburgh: Elsevier-Saunders.)

the cartilage, a fibrous connective tissue stroma is present between the anterior and posterior conjunctival surfaces (Mane et al., 1990). Numerous lymphoid aggregates populate the posterior subconjunctiva of the NM, and goblet cells are found between the lymphatic nodules and the epithelium (Prince et al., 1960). The NM of dogs lacks inherent musculature (Bromberg, 1980; Samuelson, 2007). The movement of the NM is accomplished passively when the globe is retracted, which displaces orbital fat and thereby pushes the NM across the cornea. The NM sweeps over the cornea from inferonasal to superotemporal.

In most dogs, 4–5 mm of the free edge of the NM is visible at the medial canthus and is usually pigmented. Some individual animals have an encircling NM in which the free margin continues circumferentially around the eye posterior to the limbus (Fig. 18.26; Bromberg, 1980), but does not result in ocular pathology.

A tubuloacinar gland surrounds the ventral portion of the cartilage shaft. When the NM is in its normal position, the gland is deeply seated posterior to the orbital rim and is not visible. Histochemical studies have shown that in the canine NM gland, the tubular cells are primarily serous, the acinar cells are primarily mucus, and the principal mucus secretory product is sialomucin (Alexandre-Pires et al., 2008; Martin et al., 1988). Lipid-secreting acini similar to those in the Harderian gland, which is present in many animals but not the dog, have been identified in the canine NM gland. The function of the Harderian gland is hypothesized to have been incorporated into the NM gland in dogs (Martin et al., 1988; Munnell & Martin, 1988; Samuelson, 2007). The NM gland contributes a significant proportion of the aqueous



Figure 18.26 Completely encircling nictitating membrane in an American Cocker Spaniel.

tear film as measured by the STT (STT-1 without topical anesthesia; STT-2 with topical anesthesia followed by drying of the lower conjunctival sac; Chang & Lin, 1980; Helper et al., 1974). Studies have shown that third eyelid removal causes a temporary decrease in results of the phenol-red-thread test and STT-1 and a continued decrease of 60% of the STT-2. Furthermore, the pH of the tears is increased, tear breakup time is reduced, and vital staining is seen (Saito et al., 2001, 2004).

The NM also provides immunologic support to the ocular surface. IgA-positive plasma cells are located near the surface of the conjunctival epithelium of both sides of the NM and within the connective tissue stroma of the nictitating gland (Schlegel et al., 2003). Additionally, the follicle-associated epithelium overlying the CALT located on the bulbar surface of the NM in dogs has cells with an appearance characteristic of M cells, which includes attenuated apical cell surfaces with blunted microvilli and microfolds, invaginated basolateral membranes forming cytoplasmic pockets, and a diminished distance between apical and pocket membrane. These M cells are believed to act as antigen-presenting cells within the conjunctiva. The presence of B-cell germinal centers and T-cell apical caps in the lymphoid follicles are further support that this tissue is analogous to mucosal-associated lymphoid tissue (MALT) in other tissues (Giuliano et al., 2002).

The blood supply of the NM is supplied by the malar artery. As the artery enters the base of the NM, it divides into smaller branches that cross almost the entire length superficially to the free border, before ramifying deeply toward an inner segmental level. Thus, the first ramifications of the primary artery run to the free edge of the NM, postulated to improve vascularization efficiency. The larger veins are also located superficially. It is thought that this spatial microvascular arrangement probably results from an adaptation of the NM normally being compressed into a small area (Alexandre-Pires et al., 2008).

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Anomalous, Congenital, and Developmental Disorders

Bent Cartilage

Eversion of the shaft of the NM cartilage is a commonly occurring anomaly in large breeds (Bromberg, 1980; Gelatt, 1970, 1972; Martin, 1970) and may be hereditary in German Shorthaired Pointers (Fig. 18.27A; Martin, 1970). It is thought to result from more rapid growth of the posterior portion of the cartilage compared with that of the anterior portion (Martin, 1970). The everted cartilage appears as an anterior folding of the leading edge of the NM with exposure of the posterior aspect. The result is chronic conjunctivitis and ocular discharge.

Many therapies, including placement of an NM flap for 10–14 days, resection of the NM margin and cartilage, radical resection of the NM cartilage and gland, shortening of the NM, and NM cartilage transplant, have been reported to be successful (Kuhns, 1975, 1977a, 1977b, 1981a, 1981b; Mane et al., 1990; Martin, 1970; Peruccio, 1981). The most popular surgical correction is simple excision of the folded portion of the NM cartilage (Barnett, 1978; Bromberg, 1980; Crispin, 1991; Gelatt, 1972; Peiffer et al., 1987; Stades, 1976; Fig. 17.27B).

A rare anomaly of the NM is inversion of the medial and lateral tips of the NM cartilage arm. Irritation from this cartilage can result in keratitis and corneal ulceration. The bent tips can be surgically excised, however, without conjunctival dissection or suturing (Ward, 1999).

Prolapse of the Gland

Prolapse of the NM gland (or "cherry eye") is the most common primary disorder of the NM (Fig. 18.28). The pathogenesis of this disorder has not been determined; however, it is thought to result from weakness in the connective tissue attachment between the NM ventrum and the periorbital tissues (Severin, 1996). This weakness allows the gland, which normally is located ventrally, to flip up dorsally to protrude above the leading edge of the

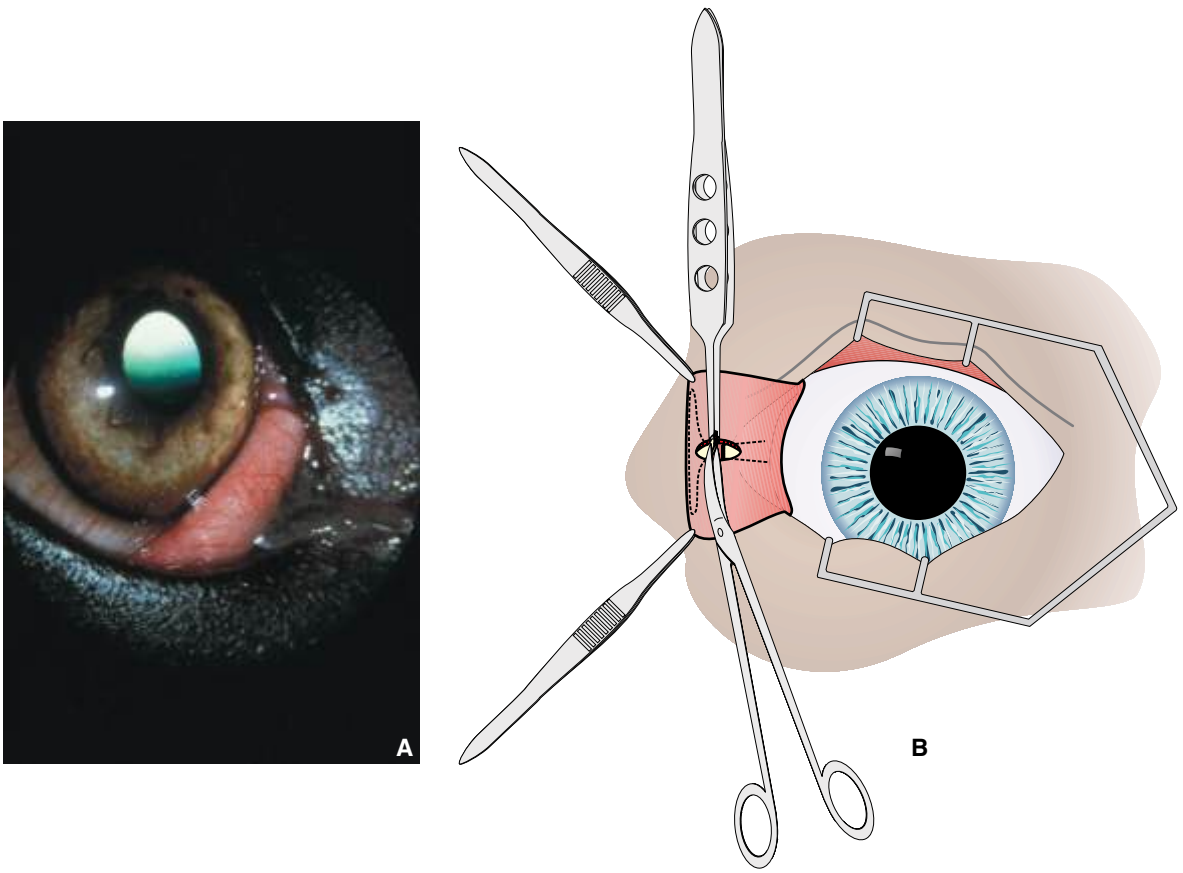


Figure 18.27 **A**. Eversion of the cartilage of the nictitating membrane (NM) in a Great Dane. **B**. To repair, a linear incision is made over the folded portion of the cartilage (posterior surface of the NM). The section of the everted cartilage is excised, and the wound does not need to be apposed. (Reproduced with permission from Gelatt, K.N. & Gelatt, J.P. (2011) Surgical procedures for the conjunctiva and the nictitating membrane. In: *Veterinary Ophthalmic Surgery* (eds. Gelatt, K.N. & Gelatt, J.P.), pp. 157–190. Edinburgh: Elsevier-Saunders.)

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Figure 18.28 Prolapse of the gland of the nictitating membrane ("cherry eye") in an English Bulldog.

NM, where it then becomes enlarged and inflamed from chronic exposure. Prolapse of the NM gland can be either unilateral or bilateral, and it generally occurs before 2 years of age (Dugan et al., 1992; Morgan et al., 1993). Prolapse of the NM gland is common in the American Cocker Spaniel, Lhasa Apso, Pekingese, Beagle, and English Bulldog (Morgan et al., 1993; Severin, 1996). Pedigree analysis and test breeding of two closed canine breed lines supported the hypothesis that prolapse of the NM gland has an inherited basis. The mode of inheritance was not determined (although simple Mendelian inheritance was excluded) and was suggested to be complex and possibly multigenic (Edelmann et al., 2015). The prolapsed gland appears as a smooth, red mass protruding from behind the leading edge of the NM. If uncorrected, chronic conjunctivitis and ocular discharge occur (Dugan et al., 1992). The reduction in tear production seen with excised glands or glands surgically repositioned was not clinically important in a 6-month study (Dugan et al., 1992). However, a long-term study showed that dogs treated with surgical replacement of the gland had a lower incidence of KCS later in life than dogs that were not treated or had the prolapsed gland excised (Morgan et al., 1993).

Surgical Repositioning

When the importance of the NM gland in tear production became apparent, surgical repositioning of the gland, rather than excision, became widely recommended (Chang & Lin, 1980; Helper et al., 1974). While many modifications of repositioning techniques have been published, the surgical techniques can be divided into methods that anchor the gland and methods that create a pocket for the gland. In the original anchoring technique described by Blogg (1980), the prolapsed gland is sutured to the inferior episcleral tissue. Following a posterior conjunctival incision, a suture of 3-0 polyglycolic acid is placed into the deep episcleral tissues on the inferonasal aspect of the globe. The suture is then passed through the ventral aspect of the gland and pulled tight, thus retracting the gland. Gross (1983) modified this technique by anchoring the gland to the inferior sclera with 5-0 chromic gut rather than to the episcleral tissues. Albert et al. (1982) anchored the proximal end of the cartilaginous NM shaft to the origin of the ventral oblique muscle in two cats with eversion of the NM cartilage. Presumably, this technique could also be used to reposition prolapsed NM glands in dogs. A perilimbal incision is made in the bulbar conjunctiva 4 mm from the inferonasal limbus, and the episcleral tissues are dissected away, thus exposing the inferior oblique muscle. A second conjunctival incision is made perpendicular to the first, so exposing the gland. A 5-0 silk suture is passed through the ventrum of the gland and then through the tendinous origin of the muscle, tucking the gland into its natural position. Sapienza et al. (2014) described a technique of anchoring the NM gland to the ventral rectus muscle insertion in 100 dogs with a 0% recurrence rate.

Theorizing that the approaches from the posterior aspect of the NM used in these anchoring techniques could damage the excretory ductules of the gland, Kaswan and Martin (1985) sutured the gland to the periosteum of the ventral orbital rim using an anterior approach (Fig. 18.29). A modification of this technique, which facilitates the approach to the orbital periosteum, has been described by Stanley and Kaswan (1994). Plummer et al. (2008) described a technique that anchors the gland to the cartilage of the NM, allowing mobility. For this procedure, a 4-0 nylon suture is passed from the anterior surface of the third eyelid through the base of the cartilage to the posterior aspect, and tunneled circumferentially beneath the conjunctiva over and around the prolapsed gland. The suture is then passed through the cartilage again to the anterior face of the third eyelid. The gland returns to its normal position as the suture is slowly tightened and then tied on the anterior aspect of the NM (Plummer et al., 2008).

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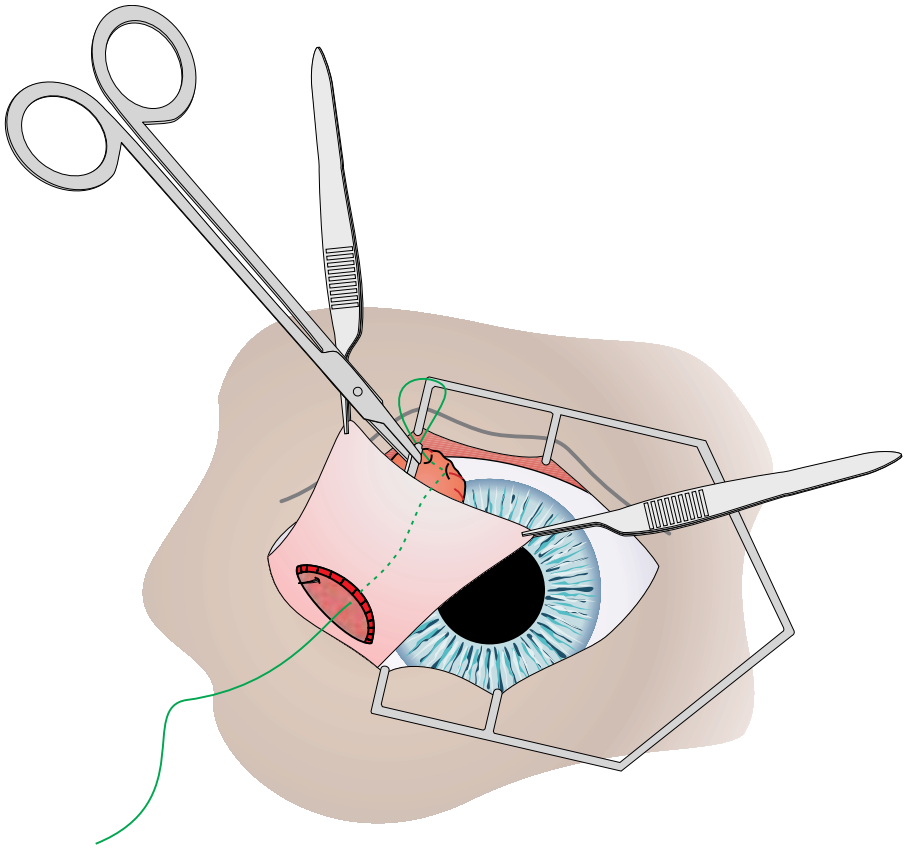


Figure 18.29 In the orbital rim–anchoring technique of Kaswan and Martin (1985) to treat "cherry eye" in the dog, an incision parallel to the orbital rim is made in the anterior conjunctiva near the ventrum of the nictitating membrane, and 4-0 nonabsorbable monofilament suture material is inserted into the medial extent of the resulting conjunctival pocket and directed toward the orbital rim. A blind bite is taken into the periosteal tissues and directed out of the pocket at its lateral extent; this bite can also be taken from lateral to medial. Adequate purchase into the periosteal tissues should be confirmed by firmly tugging at the suture before proceeding. A T-shaped continuous suture is then placed to encompass the gland by reinserting the suture at each exit point, and the suture is pulled tight, thus anchoring the gland to the orbital rim. The conjunctiva can either be left open or closed with 6-0 polyglactin 910 suture material in a simple continuous pattern. (Reproduced with permission from Gelatt, K.N. & Gelatt, J.P. (2011) Surgical procedures for the conjunctiva and the nictitating membrane. In: *Veterinary Ophthalmic Surgery* (eds. Gelatt, K.N. & Gelatt, J.P.), pp. 157–190. Edinburgh: Elsevier-Saunders.)

Rather than anchoring the gland, some advocate burying it in a pocket created by conjunctiva on the anterior or posterior surface of the NM (Moore, 1983, 1990; Morgan et al., 1993; Twitchell, 1984). In the Twitchell technique, an incision is made in the conjunctiva on the palpebral surface of the NM, and a pocket is created by dissection of subconjunctival tissues (Twitchell, 1984). The gland is then reduced into the pocket and sutured anteriorly with 5-0 absorbable suture material. Moore described resection of the posterior conjunctiva from over the prolapsed gland and then imbrication of it with two simple interrupted sutures of 7-0 absorbable suture material (Moore, 1983). A later modification did not involve conjunctival resection (but suggested light scarification) and used a single purse-string suture (Moore, 1990). The Morgan technique may be the most commonly used pocket technique (Fig. 18.30; Morgan et al., 1993).

The choice of repositioning technique is a matter of personal preference. The pocket techniques of Moore and Morgan may be the easiest to learn, but the anchoring techniques, once mastered, are simple and quick to perform. No systematic studies have compared effects on tear production among all the described techniques. Success rates with the pocket techniques have been reported as 87.5% to 97% (Dehghan et al., 2012; Mazzucchelli et al., 2012; Morgan et al., 1993; Premont et al., 2012). Reprolapse rates were compared in one large retrospective study comparing a pocket technique with the same pocket technique combined with an orbital rim tacking procedure (described by Stanley and Kaswan, 1994) and demonstrated a slightly lower recurrence rate using the combined technique (Multari et al., 2016).

Tear production following both anchoring and pocket techniques, however, is superior to that following gland excision, and Moore et al. (1994) demonstrated that neither posterior pocket technique alters tear production or the morphology of the NM gland excretory ductules (Dugan et al., 1992; Morgan et al., 1993). Results of one

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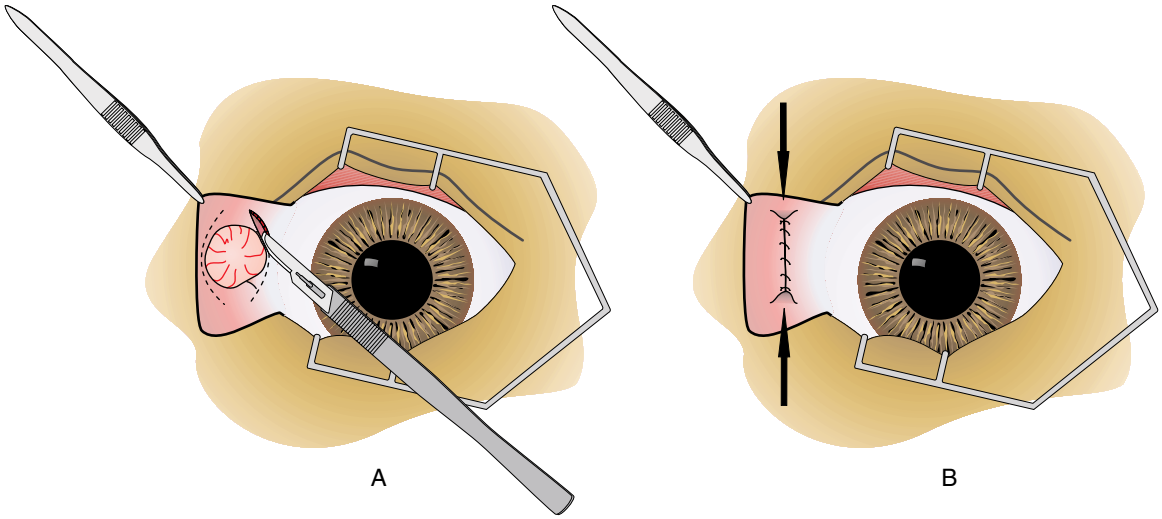


Figure 18.30 Morgan pocket technique to treat "cherry eye" in the dog. **A**. Two parallel incisions are made into the posterior conjunctiva dorsal and ventral to the prolapsed gland. **B**. The gland is reduced into the pocket, and the pocket is closed with a simple continuous suture of 5-0 or 6-0 polyglycolic acid or polyglactin 910, securing the knot on the anterior surface. Suturing should begin and end 1–2 mm from the ends of the incision to prevent cyst formation because of the entrapment of tears within the pocket. At the end of the suture run, another run using a Cushing pattern may be placed in the opposite direction to conceal the sutures, but this is not necessary and may result in an increased suture reaction. (Reproduced with permission from Gelatt, K.N. & Gelatt, J.P. (2011) Surgical procedures for the conjunctiva and the nictitating membrane. In: *Veterinary Ophthalmic Surgery* (eds. Gelatt, K.N. & Gelatt, J.P.), pp. 157–190. Edinburgh: Elsevier-Saunders.)

study demonstrated a significantly lower reprolapse rate with a pocket technique compared to an anchoring technique, but others have reported reprolapse rates of 0%–4% following anchoring techniques (Gross, 1983; Kaswan & Martin, 1985; Morgan et al., 1993; Stadsvold, 1992). After the pocket technique is done, cysts can form if the elliptical incisions are connected, which then prevents tears from escaping (Fig. 18.31). Creation of a stoma allows the tears to escape. When properly performed, all techniques result in a cosmetically acceptable outcome. Reprolapse of the gland is a possible complication of any of the procedures and is more common in large-breed dogs such American Bulldogs and Mastiff breeds. The same or another procedure can be repeated and is often successful. While surgical repositioning is recommended, it should not be assumed that retention of the gland guarantees that dry eye will not develop, since many breeds that commonly develop prolapsed NM glands are also predisposed to KCS.



Figure 18.31 A cyst developed in the nictitating membrane of this Bassett Hound after the pocket technique was done and the ends of the incisions were sutured together.

Protrusion

Primary protrusion of the NM without prolapse of the gland can occur in several large breeds (Peruccio, 1981). Though principally a cosmetic problem, the protrusion sometimes causes conjunctivitis and epiphora. The NM can be shortened surgically to return it to a more normal position (Peruccio, 1981).

Protrusion can also occur secondary to enophthalmos, microphthalmos, and space-occupying retrobulbar lesions (Barnett, 1978). If the primary problem can be resolved, the NM often returns to its normal position. Protrusion may also occur in Horner's syndrome, dysautonomia, cannabis intoxication, tetanus, and rabies (Bagley et al., 1994; Harkin et al., 2002; Johnson & Miller, 1990; Martin, 1990; Schrauwen et al., 1991; Valentine, 1992; Wise & Lappin, 1989).

In animals with one pigmented and one nonpigmented NM margin, an optical illusion makes the nonpigmented NM appear to protrude abnormally (Barnett, 1978). In most

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instances, no problems result from lack of pigmentation, and no treatment is necessary. Occasionally, however, solar conjunctivitis occurs, which can be treated with topical anti-inflammatory drugs (Bromberg, 1980).

Neoplasia

Neoplasia of the NM, like neoplasia in the rest of the conjunctiva, is uncommon in the dog. Melanomas, adenocarcinomas, squamous cell carcinomas, mastocytomas, papillomas, hemangiomas, hemangiosarcomas, angiokeratomas, lymphosarcoma, and basal cell carcinoma have all been reported (Buyukmihci & Stannard, 1981; Collier & Collins, 1994; Collins et al., 1993; Hallstrom, 1970; Johnson et al., 1988; Lavach & Snyder, 1984; Liapis & Genovese, 2004; Peiffer et al., 1978; Rodriguez Galarza et al., 2016; Saunders & Rubin, 1975; Wilcock & Peiffer, 1988). Additionally, tumors described above for the conjunctiva can also affect the NM.

Results of one study revealed adenocarcinomas (several varieties), papillomas, and malignant melanomas to be the most common primary tumors of the third eyelid (Schäffer et al., 1994). Papillomas have papillary, cauliflower-like surfaces. Excision of the masses with a margin of normal tissue appears to be curative (Collier & Collins, 1994). When melanomas of the conjunctiva develop, they most commonly occur on the NM (Collins et al., 1993). Conjunctival melanomas tend to be malignant, and recurrences and metastasis are common. There is no correlation between the mitotic index and the likelihood of local recurrence or metastasis (Collins et al., 1993; Schäffer et al., 1994). A breed predilection for the Weimaraner may exist. Combined excision and cryotherapy appear to be the most effective treatment for melanomas of the conjunctiva and NM (Collins et al., 1993).

Adenocarcinoma

The most common neoplasm of the canine NM gland is adenocarcinoma (Dees et al., 2016). Adenocarcinomas of the NM gland generally are localized, firm, smooth, pink swellings that appear to involve the gland (Wilcock & Peiffer, 1988). These are typically tumors of older dogs. Examination of histopathologic sections may reveal clean margins, but recurrence is common (Schäffer et al., 1994). Removal of the entire third eyelid is currently the recommended treatment (Wilcock & Peiffer, 1988). With recurrence, surgery in conjunction with external beam radiation therapy can be successful. Adenomas of the NM gland also occur (Fig. 18.32).

Other Neoplasms

Squamous cell carcinoma has been reported to arise from both the palpebral and bulbar surfaces of the NM, and it may



Figure 18.32 Adenoma of the gland of the nictitating membrane.

appear dark in color. Excision of the third eyelid is curative (Lavach & Snyder, 1984). When extensive, squamous cell carcinoma of the NM may invade the orbit (Miller & Dubielzig, 2001). In one case of a mastocytoma, the mass was very firm, and local excision appeared to be curative (Hallstrom, 1970). Hemangiomas (Fig. 18.33), hemangiosarcomas, and angiokeratomas of the NM appear as red, proliferative, protruding masses (George & Summers, 1990; Liapis & Genovese, 2004; Peiffer et al., 1978; Pirie et al., 2006; Saunders & Rubin, 1975). Local surgical excision tends to be curative (George & Summers, 1990; Liapis & Genovese, 2004). Bilateral lymphosarcoma of the NMs was reported in a German Shepherd (Guaguere et al., 1993). These NMs were thickened, hyperemic, and multifocally depigmented, and the animal was euthanized shortly after diagnosis because of progression of systemic disease. Bilateral MALT lymphoma of the NM was diagnosed in a 4-year-old American Cocker Spaniel, and lobulated masses were present on the bulbar surface of both NMs. Histologically, there were proliferations of lymphoid follicles surrounded by lymphoid cells forming a marginal zone, with some occasionally infiltrating into the conjunctival epithelium. Excision appeared curative for one NM; there was no growth in the opposite NM over the following year. There was no apparent associated ocular or systemic involvement (Hong et al., 2011). Myoepithelioma of the NM gland has been reported in a dog (Bondoc et al., 2014).

Inflammatory Conditions

Nodular Granulomatous Episclerokeratitis

Nodular granulomatous episclerokeratitis is an inflammatory disease that most commonly arises from the temporal limbus, but it may involve the NM as well. Collies are predisposed (Dugan et al., 1993; Paulsen et al., 1987). Clinically, the affected NM is hyperemic, depigmented, and edematous,

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Figure 18.33 Hemangioma of the nictitating membrane in a Bassett Hound.

with multiple, smooth, tubular-shaped thickenings involving the palpebral surfaces. On histopathology, these lesions show a chronic granulomatous inflammatory response. The disease process is generally controllable with use of systemic prednisone and azathioprine, but oral doxycycline and niacinamide have also been used successfully (Dugan et al., 1993; Hurn et al., 2005; Latimer et al., 1983b; Paulsen et al., 1987).

Plasma Cell Infiltration (Plasmoma)

Plasma cell infiltration of the NM, or "plasmoma," can cause thickening, depigmentation, and follicle formation (Fig. 18.34; Barnett, 1978; Bromberg, 1980; Helper, 1981; Read, 1995; Rubin, 1989; Teichert, 1966). Pannus (i.e., chronic superficial keratitis) is often associated with this condition. German Shepherds appear to be predisposed, and plasmoma has bilateral potential in the Belgian Sheepdog, Borzoi, Doberman Pinscher, English Springer Spaniel, and German Shepherd breeds (Barnett, 1978; Bromberg, 1980; Read, 1995; Rubin, 1989; Teichert, 1966). Histopathology reveals a subepithelial inflammatory infiltrate consisting primarily of plasma cells, with fewer lymphocytes and stromal pigmentary incontinence (Alonso-Alegre et al., 1999; Barnett, 1978; Helper, 1981; Rubin, 1989; Teichert, 1966). Treatment generally consists of topical ophthalmic dexamethasone 4 times daily initially, or subconjunctival or systemic corticosteroids (Barnett, 1978; Helper, 1981; Rubin, 1989; Teichert, 1966). Topical ophthalmic cyclosporine ointment, tacrolimus drops, or 1% pimecrolimus administered 2–3 times daily are also effective (Bigelbach, 1994; Nell et al., 2005; Read, 1995). Comparison of 2% cyclosporine solution and 0.1% dexamethasone showed that dexamethasone gave more rapid results, but the disease returned more slowly in the cyclosporine-treated dogs (Alonso-Alegre et al., 1999). Once there is resolution, medication administration is slowly decreased to the lowest effective frequency.

Idiopathic Granulomatous Disease

Idiopathic sterile granulomatous disease manifests as multiple masses on the conjunctiva, eyelids, NM, and skin. On histopathologic examination, granulomatous inflammation with large epithelioid cells, plasma cells, and lymphocytes is seen. Treatment with L-asparaginase, prednisone, or azathioprine has shown some efficacy (Collins et al., 1992; Gionfriddo et al., 2003; Latimer et al, 1983b; Riis, 2000). Treatment with tetracycline and niacinamide was successful for resolution of the granulomas in one report; however, optic neuritis developed, presumably secondary to treatment with the niacinamide (Rothstein et al., 1997). Anecdotally, treatment with tetracycline or doxycycline alone may be successful in some cases.

Follicular Conjunctivitis

Follicular conjunctivitis most frequently involves the bulbar aspect of the NM, but the follicles can be present anywhere on the conjunctiva (see Fig. 18.4). A small area of lymphoid follicles is normally present on the bulbar side of the NM, closely associated with the NM gland. With follicular conjunctivitis, the follicles are more numerous and larger than normal in size, and conjunctival hyperemia as well as a mucoid discharge commonly are present. (See the conjunctival section of this chapter for more information and treatment.)

Ocular Nodular Fasciitis

Ocular nodular fasciitis most commonly affects the sclera, episclera, and corneal stroma, but it has also been reported to involve the NM. In the one case described, an irregular nodular thickening involved the anterior aspect of the NM (Lavignette & Carlton, 1974). The mass was excised and there was no recurrence. On histopathologic examination,

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Figure 18.34 Plasma cell infiltration of the nictitating membrane (plasmoma) in a German Shepherd.

histiocytes, fibroblasts, capillaries, fibrous connective tissue, and a few inflammatory cells were seen (Lavignette & Carlton, 1974).

Trauma, Reconstruction, and Foreign Bodies

Trauma to the medial canthal area may result in lacerations of the NM. Small lesions heal spontaneously, but larger lesions should be sutured with 6-0 braided, absorbable suture material, taking care not to leave sutures or knots where they could abrade the cornea. If the NM has been removed because of neoplasia or extensive areas were lost because of trauma, it may be reconstructed from oral and labial mucosa (Kuhns, 1977b, 1981a, 1981b).

Foreign bodies lodged either within or behind the NM can cause persistent corneal ulceration as well as inflammation of the NM. Other frequently observed clinical signs are epiphora, blepharospasm, protrusion of the NM, and severe discomfort. The foreign bodies, which are commonly grass awns, seeds, or other plant material, usually are loosely embedded and can be removed using thumb forceps following instillation of a topical anesthetic. Generally, topical ophthalmic antibiotic should be used after removal of the foreign body, especially if the cornea is ulcerated (Brennan & Ihrke, 1983; Bromberg, 1980).

Miscellaneous Diseases

A cyst of the NM gland has been treated successfully by excision of the well-demarcated mass (Latimer et al., 1983a). Clinically, the mass was pigmented and could be visualized from both sides of the NM. Cysts of the NM gland may also be treated by marsupialization of the cyst to the conjunctival surface (Barbe et al., 2017). One dog with visceral leishmaniasis developed a grayish white, fibrous appearance to its NM, along with keratoconjunctivitis, thickened eyelids, and anterior uveitis (McConnell et al., 1970).

Nictitating Membrane Surgery

The NM can be used as a corneal shield in select cases of corneal ulceration. These NM "flaps" have been purported to aid in the healing of midstromal ulcers, iatrogenic ulcers created by lamellar keratectomy in brachycephalic animals, and, in particular, refractory indolent ulcers. They have also been used in conjunction with frozen lamellar corneal grafts to protect the graft from blinking movements and to help maintain pressure on the graft's surface (Hansen & Guandalini, 1999).

Nictitating Membrane Flaps

Several types of flaps have been described. In the most widely advocated technique, the free margin of the NM is sutured to the temporal aspect of the superior eyelid (Bistner et al., 1977; Gelatt & Gelatt, 2011; Peiffer et al., 1987; Quinn, 1990). Two to three horizontal mattress sutures of 3-0 monofilament nonabsorbable material are placed between the free edge of the NM and the lateral aspect of the superior lid. The lid sutures should be placed well within the superior cul-de-sac, and the NM sutures should be approximately 2 mm from the free edge, incorporating cartilage into the center suture (Fig. 18.35A). Alternatively, a single mattress suture can be placed between the superior lid and the midpoint of the cartilage shaft (Helper & Blogg, 1983). The surgeon must be careful to seat the NM margin as deeply as possible in the superior conjunctival fornix. If the NM margin is too far from the cul-de-sac, corneal injury from sutures is likely. Alternatively, the NM margin can be sutured to the superotemporal episcleral tissue (Slatter, 1990; Fig. 18.35B). Care must be taken to place the sutures deeply enough to ensure that the NM is held securely, but not placed so deeply as to perforate the globe. The advantage of this technique is that the flap moves in concert with the globe, minimizing corneal trauma and stimulation of any exposed corneal nerve endings (i.e., pain). When an NM flap is sutured to the superior lid, movements of the globe cause the cornea to rub against the posterior aspect of the NM, theoretically exacerbating corneal disease; however, serious consequences of the superior lid technique are rare. Complete corneal coverage by the NM may not be possible in individuals with physiologic exophthalmia. For these animals, the NM may be sutured to the superotemporal conjunctiva several millimeters away from the limbus, thus avoiding the deeper episcleral tissue. The mobile conjunctiva will pull down over that part of the cornea not adequately covered by the NM. A fourth technique is to dissect

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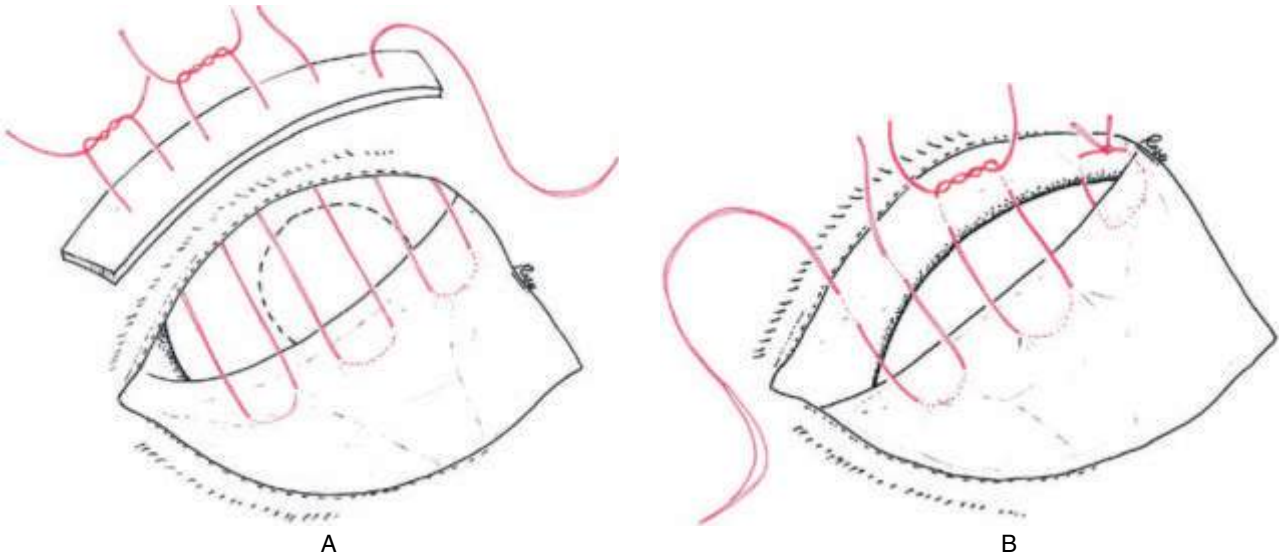


Figure 18.35 **A**. Nictitating membrane (NM)-to-superior-lid flap. Two to three horizontal mattress sutures of 3-0 monofilament nonabsorbable material are placed between the free edge of the NM and the superior lid. The lid sutures should be placed well within the superior cul-de-sac, and the NM sutures should be approximately 2 mm from the free edge, incorporating cartilage into the central suture. **B**. NM-to-episclera flap. Suturing the free edge of the NM to the superotemporal episclera allows the cornea and flap to move in concert, thus minimizing corneal trauma. Illustration courtesy of Roser Tetas Pont.

the superior 180 degrees of bulbar conjunctiva free from the underlying episclera, pull it down over the uncovered portion of the cornea, and suture it to the free edge of the NM (Kuhns, 1975). A combined local anesthetic technique including auriculopalpebral nerve block, topical anesthesia of the eye, and infiltration anesthesia of the superotemporal bulbar conjunctiva and palpebral surface of the NM has been described for use when placing an NM to superotemporal bulbar conjunctiva flap. The technique facilitated placement of the flap without general anesthesia or sedation (Park et al., 2009).

Complications of NM flaps include necrosis of the upper lid if sutures are placed too tightly in the NM-to-superior-lid technique, and inadvertent penetration of the globe in the NM- to-episclera technique (Quinn, 1990). Corneal trauma from inadvertent suture contact as a result of poorly placed NM flap sutures may also result in corneal ulceration or delayed healing of an established corneal ulcer. The sutures are generally left in place for 2–3 weeks, but with the NM-to-episclera technique sutures may pull free prematurely (Slatter, 1990). It should be remembered that these flaps obscure visualization of the cornea and intraocular structures. They also do not deliver a blood supply or give as much support as a conjunctival pedicle graft, and they may inhibit topical medications from reaching the cornea. To allow visualization of the cornea, the suture ends can be left long so that the flap can be released and retied (Gelatt & Gelatt, 2011; Helper & Blogg, 1983; Quinn, 1990). Generally, NM flaps should be avoided in cases of infected ulcers, collagenolytic ulcers, and descemetoceles. Instead, a conjunctival graft should be placed.

Other Surgeries

Both the strength and pliability of the NM can be an advantage in cases of eyewall defects. Blogg et al. (1989) used island and pedicle grafts of NM to repair full- and partial-thickness corneoscleral resections in dogs with epibulbar melanomas. These grafts remained healthy in all cases, and the authors theorized that these same techniques could be used to repair traumatic avulsions of the fibrous tunics.

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Diseases and Surgery of the Canine Cornea and Sclera

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The cornea is a unique portion of the outer fibrous tunic of the eye. It is transparent and serves a major refractive function while maintaining an impermeable physical barrier between the eye and the environment. The transparency of the cornea enables it to perform two main functions: to refract light and to allow sufficient quantity and quality of light into the eye to form an image on the retina. Despite exposure to environmental hazards, the cornea must maintain the smooth outer surface necessary for retinal image formation. This is partially achieved by the continuous replacement of the surface epithelium and maintenance of a healthy preocular tear film. The relatively simple structure of the cornea limits its pathologic responses to insults. Since most pathologic corneal responses are associated with a loss of transparency, many different corneal disorders can lead to opacification and loss of vision.

Fortunately, most corneal pathology is amenable to medical or surgical therapy. The most important goals of corneal treatment are to preserve or improve the quantity and quality of light entering the eye in the presence of corneal opacities (e.g., eyes with scarring or dystrophy) and to promote corneal healing (e.g., eyes with ulceration or neoplasms). To achieve these goals, damage to normal corneal tissues should be avoided and therapies selected to induce as little trauma as possible. Minimizing corneal trauma reduces the likelihood and severity of scarring and maintains maximal corneal transparency.

This chapter provides an overview of corneal and scleral disorders in the canine eye and should serve as a stimulus to further elucidate the clinical, histopathologic, ultrastructual, biochemical, and genetic aspects of corneal disease.

Corneal Anatomy and Pathophysiology

Review of Corneal Anatomy

The fibrous tunic of the canine eye consists of the sclera and the cornea. The limbus is the transition zone between the cornea anteriorly and the sclera posteriorly. The canine cornea consists of the corneal epithelium externally, the corneal stroma, Descemet's membrane, and corneal endothelial cells (Fig. 19.1) (Shively & Epling, 1970; Spreull, 1966). Descemet's membrane, the basement membrane underlying endothelial cells (Abrams et al., 2002), becomes thicker with age as it is continuously produced. Canine endothelial cells are hexagonally shaped with a normal density of approximately 2500–3175 cells/mm^2 (Gwin, et al., 1982b; Kafarnik, et al., 2007; Nasisse, et al., 1986). Endothelial cells decrease in number with age, with the number of cells in older dogs being frequently below 2100 cells/mm^2 (Gwin et al., 1982b), resulting in an increased diameter per endothelial cell to compensate for the reduced number. The peripheral cornea is thicker on average than the central cornea (Gilger et al., 1991). In neonatal puppies, there is a decrease in corneal thickness until approximately 6 weeks of age; then it increases with age until approximately 30 weeks (Montiani-Ferreira et al., 2003). In adult dogs, corneal thickness increases gradually with age (Gilger et al., 1991).

Mean corneal thickness, as measured by ultrasonic pachymetry (USP) and *in vivo* confocal microscopy (IVCM), is $562 \pm 6.2\,\mu m$ and $585 \pm 79\,\mu m$, respectively (Gilger et al., 1991; Kafarnik et al., 2007). Spectral-domain optical coherence tomography (SD-OCT) in normal dogs showed that the epithelial thickness (ET) was $72.3 \pm 4.6\,\mu m$, non-epithelial thickness (NET) was $538.9 \pm 42.5\,\mu m$ and central corneal thickness (CCT) was $611.2 \pm 40.3\,\mu m$ (Alario & Pirie, 2014a). There were no significant differences for all measurements based on eye, age or gender. The same authors compared USP and SD-OCT in normal dogs (Alario & Pirie, 2014b). The mean CCT by SD-OCT was $587.72 \pm 32.44\,\mu m$ and by USP was $598.54 \pm 32.28\,\mu m$. There was no significant difference in CCT based on age or sex and USP consistently overestimated CCT by a mean value of $10.82\,\mu m$. The mean CCT and ET by SD-OCT in normal dogs were similar at $535\,\mu m$ and $55\,\mu m$, respectively (Famose, 2014). The same study

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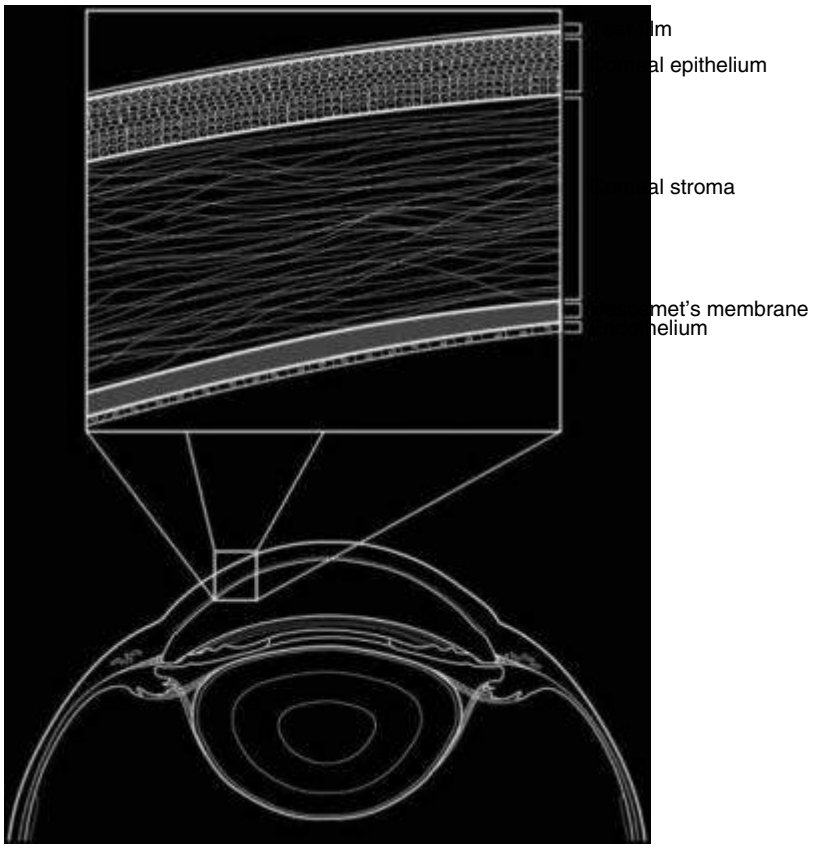


Figure 19.1 The canine cornea consists of the corneal epithelium externally, the corneal stroma, Descemet's membrane, and corneal endothelial cells.

showed the efficacy of SD-OCT in the evaluation of pathologic disease states of the cornea in both dogs and cats. A diurnal variation in CCT measured by USP was found in normal dog corneas with CCT values significanltly lower in the evening (Martin-Suarez et al., 2014). In normal dogs, increased intraocular pressures (IOPs) over time had CCTs that were significantly increased when measured by USP (Park et al., 2013). The increases in CCT were particulary evident when the IOP was >45 mmHg for over 40 minutes, greater than 60 mmHg for over 20 minutes and greater than 75 mmHg for over 10 minutes. When CCT was evaluated by USP in normal dogs in relation to IOP, every 100 µm increase in CCT was associated with an elevation of 1 mmHg (Tono-Pen® XL, Reichert Inc., Buffalo, NY, USA) and an elevation of 2 mmHg (TONOVET®, Vantaa, Finland) (Park et al., 2011). When evaluated in both normal and diseased canine eyes, mean CCT (measured by USP), had no significant effect on IOP measured by (Tono-Pen® XL) or by (AccuPen®, Keeler Instruments Inc., Malvern, PA, USA) (Kato, 2014). In the same study, the mean CCT tended to decrease with age. In normal female dogs, high-resolution IVCM allowed detailed noninvasive evaluation of corneal epithelial cells, nerve fiber diameter, keratocyte density, and endothelial cell density **(**Table 19.1**)** (Strom et al., 2016b). In another study of normal dogs, high-resolution time-domain and fourier-domain optical coherence tomography (TD-OCT and FD-OCT) and USP were used to evaluate cornea and conjunctival data (Strom et al., 2016a). The mean CCT was 497.54 ± 29.76 µm, 555.49 ± 17.19 µm and 594.81 ± 33.02 µm when measured by FD-OCT, USP, and TD-OCT, respectively. The central, superior paraxial and superior perilimbal ET were 52.38 ± 7.27 µm, 56.96 ± 6.47 µm and 69.06 ± 8.84 µm when measured by FD-OCT. When comparing measurement techniques, USP and TD-OCT generated significantly greater values compared with FD-OCT and CCT significantly increased with both age and body weight in both male and female dogs.

The corneal stroma consists primarily of collagen fibrils, keratocytes, nerves, and glycosaminoglycans (GAG). Corneal collagen fibrils exist in broad belts called lamellae that run approximately parallel to the corneal surface. Keratan sulfate, chondroitin sulfate, and dermatan sulfate are the predominant GAG in the cornea (Scott & Bosworth, 1990a, 1990b). Keratan sulfate is present at high levels in the human corneal stroma and Descemet's membrane. High levels of chondroitin sulfate are found in human epithelium, endothelium, and keratocytes (Bairaktaris et al., 1998). In the equine cornea, chondroitin 4-sulfate is more concentrated in the

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Table 19.1 Normal corneal measurements in dogs by *in vivo* confocal microscopy.

Superficial epithelial cell diameter	43.25 ± 6.64 µm
Basal cell diameter	4.43 ± 0.67 µm
Subepithelial nerve fiber diameter	2.38 ± 0.69 µm
Anterior stromal nerve fiber diameter	16.93 ± 4.55 µm
Anterior stroma keratocyte density	993.38 ± 134.24 cells/mm^2
Posterior stroma keratocyte density	789.38 ± 87.13 cells/mm^2
Endothelial cell density	2815.18 ± 212.59 cells/mm^2

deep central, peripheral, and middle central layers of the cornea compared with chondroitin 6-sulfate (Biros et al., 2002). This may be important because chondroitin 6-sulfate tends to hold more water than does chondroitin 4-sulfate. Aquaporins are transmembrane proteins that transport water across the cell membranes of many cell types. Aquaporins 1, 3, and 5 have been identified in various cell types comprising the cornea of dogs and other species, suggesting their involvement in water homeostasis in the canine cornea (Karasawa et al., 2011; Nautscher et al., 2016).

The canine cornea is innervated by an average of 11.5 large "trunks" of the trigeminal nerve (cranial nerve V) that enter the midstromal region circumferentially at the limbus (Barrett et al., 1991). These trunks course radially to the central cornea forming anterior and posterior nerve plexuses in the anterior stroma (Barrett et al., 1991; Marfurt et al., 2001). Subepithelial plexus formation and extensions into the basal epithelium with free nerve endings extending to the epithelial wing layers also occurs. Axons from the subepithelial plexus give rise to the sub-basal nerve plexus after penetrating the epithelial basal lamina (Fig. 19.2). The nerve fiber density of the central subepithelial nerve plexus, as determined by *IVCM*, was 12.39 ± 5.25 mm/mm^2 in mesocephalic dogs and 10.34 ± 4.71 mm/mm^2 in brachycephalic dogs (Kafarnik et al., 2008). The nerve fiber density of the central sub-basal nerve plexus was 14.87 ± 3.08 mm/mm^2 in mesocephalic dogs and 11.80 ± 3.73 mm/mm^2 in brachycephalic dogs. In one study, 99% of canine corneal nerves contained both calcitonin gene-related peptide and substance P, approximately 30% contained tyrosine hydroxylase, and none contained vasoactive intestinal polypeptide (Marfurt et al., 2001).

Corneal sensitivity, or corneal touch threshold (the minimum stimulation of the corneal surface by a Cochet-Bonnet esthesiometer to elicit a blink reflex), was higher in dogs with dolichocephalic skull types compared with dogs with mesaticephalic or brachycephalic (which had the least sensitive cornea) skull types (Barrett et al., 1991). In general, the central corneal region was most sensitive, followed by the nasal, temporal, dorsal, and then ventral corneal regions (Barrett et al., 1991). Dogs with diabetes mellitus have reduced corneal

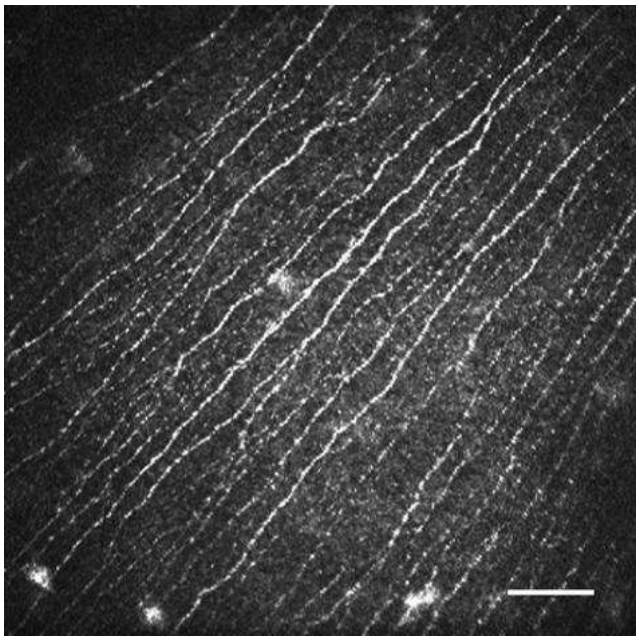


Figure 19.2 *In vivo* confocal photomicrograph of the canine sub-basal nerve plexus. (Bar = 50 µm.)

sensitivity in all corneal regions (Good et al., 2003). Topically applied 0.5% proparacaine significantly lowered corneal sensitivity as expected but had little effect on IOP measurements in dogs and rats (Kim et al., 2013). No correlation between corneal sensitivity and the quantity of reflex tearing was noted in dogs, cows, horses, sheep, goats, cats, rabbits, and guinea pigs (Wieser et al., 2013). Ambient humidity has an effect on corneal sensitivity measurements, because decreasing ambient humidity was significantly associated with an increase in corneal sensitivity measurements (Dorbandt et al., 2017). In the same study, administration of topical 0.1% diclofenac or 0.03% flurbiprofen did not have any significant effect on corneal sensitivity. A similar study showed that topical 0.1% diclofenac significantly decreased corneal sensitivity at 75 and 90 minutes after instillation, topical 0.5% ketorolac had no significant effect at any time point, topical 0.03% flurbiprofen significantly increased corneal sensitivity at 15 minutes and topical 0.01% benzalkonium chloride significantly increased corneal sensitivity at 15 minutes (Cantarella et al., 2017). These results suggest that, aside from a potential irritative effect of topical 0.03% flurbiprofen, topical NSAIDs do not have any significant effect on corneal sensitivity. Compared with a placebo, topically applied 0.3% naltrexone had no effect on corneal sensitivity in normal brachycephalic dogs (Arnold et al., 2014). Similar findings were noted in dogs with uncontrolled keratoconjunctivitis sicca (KCS) (Chen & Powell, 2015).

Opioid growth factor and its receptor are present in the corneal epithelium of normal dogs (Robertson & Andrew, 2003). Opioid growth factor has been shown to delay wound

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healing in ulcerated corneas (Zagon et al., 2000), and inhibitors of opioid growth factor (such as naltrexone) may improve corneal epithelialization, especially in diabetics (Zagon et al., 2002). In another study, opioid receptors (primarily Δ-receptors and only a small number of μ-receptors) were identified in normal corneas of dogs, and use of topical 1% morphine sulfate provided analgesia to dogs with corneal ulcers and did not delay corneal epithelialization (Stiles et al., 2003).

A noncontact infrared thermometer (NCIT) was compared with a standard rectal digital thermometer (RDT) in 300 dogs (Kreissl & Neiger, 2015). Median body temperature measured by the RDT and NCIT were 38.3 °C (35.5–41.1 °C) and 37.7 °C (35.9– 40.1 °C), respectively. Overall, there was poor agreement between body temperatures taken over low, normal, and high values as well as between experienced and inexperienced investigators. The NCIT tended to overrecognize hypothermic and hyperthermic conditions.

Corneal Clarity

Factors supporting transparency of the normal canine cornea include the absence of blood vessels and pigment, the absence of keratinization of the anterior surface epithelium, a well-organized stromal collagen lattice, and the small diameter of the collagen fibrils (Goldman & Benedek, 1967; Goldman et al., 1968; Maurice, 1957). The collagen fibrils that comprise the corneal stroma are themselves composed of parallel arrays of long collagen molecules held together by intermolecular bonds. The collagen fibrils in the cornea have a uniform diameter of approximately 25 nm (Komai & Ushiki, 1991). Some nonfibrillar collagens are also found in the corneal stroma, types VI and XII being the most notable. They are believed to interact with fibrillar collagen and are likely to be important physiologically (Komai & Ushiki, 1991; Meek & Fullwood, 2001a; Meek & Quantock, 2001b). Studies suggest that corneal clarity may not be dependent only on the absolute size of the stromal collagen or spacing of the fibrils. Rather, the fibril volume fraction (i.e., the proportion of the stroma that is occupied by hydrated collagen fibrils) may also be a major factor in clarity (Connon et al., 2000; Meek & Fullwood, 2001a; Meek & Quantock, 2001b; Meek et al., 2003a, 2003b).

The sclera is composed of collagen fibrils with various diameters ranging from 25 to 230 nm (Komai & Ushiki, 1991). Scleral collagen fibrils are arranged in irregular, nonparallel bundles that vary in width and thickness, intertwine with each other, and branch extensively (Komai & Ushiki, 1991).

The corneal endothelium uses physiologic pumps (i.e., water and ion transport systems) to remove and transport fluid from the corneal stroma into the anterior chamber. In this way, the corneal endothelium regulates hydration of the corneal stromal collagen matrix, which provides mechanical strength (Arndt et al., 2001; Befanis et al., 1981; Gwin et al., 1983b).

A variety of corneal diseases, accidental injury, and surgery can lead to changes that affect corneal transparency. There are very few objective corneal clarity grading scales in human and veterinary medicine; a novel corneal clarity score has recently been tested in dogs (Sanchez et al., 2016b).

The following scoring system was used to describe corneal clarity: note G4 is clear cornea, G0 is the most opacity of the cornea.

- G0: no fundus reflection is visible on retroillumination (RI) using a head-mounted indirect ophthalmoscope.
- G1: a fundus reflection is visible with RI.
- G2: a 0.1 mm diameter light beam is visible on the anterior surface of the iris and/or lens.
- G3: gross fundic features are visible when viewed with indirect ophthalmoscopy (IO) using a head-mounted indirect ophthalmoscope and a hand-held 30D lens, although fine details are not clear
- G4: fine details of the fundic features are clearly visible with IO.

Intra- and interuser reliability was excellent with the scoring system (Sanchez et al. 2016b).

Corneal Wound Healing

Epithelial Healing

The corneal epithelium is maintained by a constant cycle of proliferation of cells in the basal layer and shedding of cells at the surface. Renewal of basal cells also occurs by centripetal migration of stem cells from the limbus (Cenedella & Fleschner, 1990).

An epithelial defect of the cornea heals by epithelial sliding and mitosis. After a short lag period of approximately 1 hour, the normal epithelium at the edge of the defect flattens, retracts, thickens, and loses its hemidesmosomal attachments to the basement membrane (Pepose & Ubels, 1992). The cells enlarge and the epithelial sheet begins to migrate by amoeboid movement to cover the defect. During this process, the corneal epithelium develops a migratory phenotype.

Molecular mechanisms underpinning corneal healing are being elucidated. Heat shock proteins, specifically Hsp70, appear to play an important role in corneal wound healing because they are potent inducers of cellular migration and proliferation. Suppressed expression of Hsp70 may contribute to the pathophysiology of nonhealing corneal defects (Peterson et al., 2016). Slug, a member of the Snail family of transcription factors, plays a role in modulating the transition to a migratory phenotype, and increased expression of the mesenchymal markers smooth-muscle-specific α-actin and tropomyosin facilitate cellular migration (Chandler et al., 2007). The cytokine, interleukin-11 (IL-11), which modulates immune and inflammatory processes, has been

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detected in corneal epithelium, keratocytes, and endothelium of normal canine eyes and can be strongly induced in cultured corneal cells by treatment with TGF-β1, a regulator of cell proliferation and differentiation. The presence of IL-11 in the normal canine cornea suggests its involvement in corneal inflammation and immunity (Richards et al., 2014). Striatin protein has been localized to the basement membrane in the area containing hemidesmosomes suggesting that striatin protein plays a likely role in cell adhesion (Stern et al., 2015). Small leucine rich proteoglycans (SLRPs) are constituents of the extracellular matrix (ECM) and are involved in the production, organization, and remodeling of collagen and elastin. The presence of SLRPs was noted in the corneal epithelium of dogs, with little to no stromal staining and no staining of the corneal endothelium (Yang et al., 2012). Initially, the healing epithelial layer is thinner than the normal corneal epithelium, but mitotic cell division of the epithelium restores normal thickness. If the entire corneal epithelium is removed, the cornea will be covered by sliding conjunctival epithelium in most species within 48–72 hours (Gilger et al., 2007). Larger corneas, such as in horses, may take longer because the epithelial growth rate has been estimated at 0.6 mm/day in horses (Neaderland et al., 1987). After 4–5 weeks, in rabbits, the conjunctival epithelium assumes the morphologic characteristics of normal corneal epithelium (Shapiro et al., 1981). Corneal epithelium is completely replaced in approximately 2 weeks (Cenedella & Fleschner, 1990).

Limbal stem cells appear to play an important role in the maintenance of corneal epithelial health and corneal clarity (Sanchez et al., 2016a). The limbal epithelium in multiple animal species has been examined for the stem cell crypts found in humans (Patruno et al., 2017). While the limbal epithelium showed invagination similar to humans, no crypt-like structures were found in dogs. Canine corneal epithelial stem cells appear to reside in the limbus and give rise to proliferative cells in response to stimulation (Morita et al., 2015). Canine limbal epithelial cells have been collected and cultivated on denuded canine amniotic membrane, temperature-responsive culture dish, and atelocollagen gel (Nam et al., 2015). Corneal epithelial cell sheets have also been cultivated from limbal stem cells on amniotic membrane (Nam et al., 2013). Each culture technique may allow for the potential of the use of corneal epithelial sheets in the treatment of corneal surface disease in the future. When seeded on a canine xenogeneic acellular matrix *in vitro*, rat mesenchymal stem cells expressed multiple growth factors (VEGF, EGF, and TGF-β1) at a higher level than rat limbal stem cells (Zhang et al., 2012). Neurotropic keratitis in a dog has occurred secondary to a partial limbal stem cell deficiency after metaherpetic corneal disease (Ledbetter et al., 2013). Canine corneal models, both *in vivo* and *ex vivo*, have been developed to allow documentation of corneal healing with and without therapies that may improve corneal healing and clarity (Berkowski et al., 2018; Gronkiewicz et al., 2016; Proietto et al., 2017).

Stromal Healing

Epithelial sliding and stromal replacement mainly accomplish healing of corneal defects that involve the epithelium and anterior stroma. Stromal replacement requires synthesis and crosslinking of collagen, proteoglycan synthesis, and gradual wound remodeling. Epithelium from the edge of the injured area flattens and slides over the wound to fill the defect. Mitosis of the epithelium then results in a normal, or slightly greater than normal, epithelial thickness, but it may not restore the normal corneal curvature. The stroma adjacent to the defect exhibits edema early, followed by an influx of neutrophils from the tear film (via the lacrimal gland and conjunctival blood vessels) within 1–2 hours of injury. Regional keratocytes transform into fibroblasts that proliferate and rapidly synthesize collagen and other components of the ECM. Stromal fibroblasts produce fibronectin, an ECM glycoprotein that stimulates cell adhesion, cell migration, and protein synthesis (Schultz et al., 1992a). Shortly thereafter, fibroblastic proliferation begins in the stroma. Fibroblasts also arise from the stromal histiocytes, and as the fibrous reaction continues, the epithelium is displaced anteriorly to its normal surface level. New collagen fibers and lamellae are produced, but disorganized arrangement may result in opacity or corneal scarring. The main cell type involved in the corneal fibrosis and scarring is the myofibroblast. Fibrotic diseases are characterized by the presence of increased numbers of myofibroblasts, disorganized ECM, and subsequent tissue contraction (Bosiack et al., 2012). Gene therapies have the potential for modulating corneal fibroplasia (Bosiak et al., 2012).

Endothelial Healing

The endothelial cell layer is the inner limiting layer of the cornea. Endothelial cells normally form a hexagonal, mosaic pattern on Descemet's membrane (Aguirre et al., 1975; Arndt et al., 2001; Befanis et al., 1981; Gwin et al., 1983b; Stapleton & Peiffer, 1979; Yee et al., 1987). The hexagonally shaped canine endothelial cells tend to enlarge in size and decrease in number with age (Gwin et al., 1982b). In the young dog, the number of endothelial cells averages 2500–3175 per mm^2 (Chandler et al., 2003; Kafarnik et al., 2007). Injury to endothelial cells results in decreased cell density in dogs, suggesting a limited capacity for mitosis (Gwin et al., 1983b). Phacoemulsification, radiofrequency hyperthermia, and CO_2 photokeratotomy resulted in damage to corneal endothelial cells in dogs (Glaze & Turk, 1986; Gwin et al., 1983b; Hoffman et al., 2009). Intraocular irrigation with various saline solutions (Nasisse et al., 1986), low doses of tissue plasminogen activator (25 μg/100 μL) (Gerding et al., 1992), and transcorneal diode laser iridal photocoagulation (Chandler et al., 2003) did not appear to damage the corneal

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endothelium or increase corneal thickness. Diabetic dogs, which were experimentally induced by feeding galactose, had endothelial changes characterized by marked polymegathism (i.e., increased size) and pleomorphism (i.e., cell shape variations) (Neuenschwander et al., 1995; Yee et al., 1985). Endothelial cell alterations in diabetic dogs may explain their increased corneal complications after cataract surgery and may contribute to delay of corneal wound healing (Good et al., 2003).

Repair of Full-Thickness Corneal Laceration or Perforation

Healing of a full-thickness corneal laceration may be divided into approximately six phases. The first, or immediate, phase is initiated by mechanical factors, the fibrin plug, and corneal stromal edema. The normal elasticity of stromal fibers causes retraction. Descemet's membrane is also elastic and recoils when severed. This combination of retraction by the outer stromal fibers and recoiling by Descemet's membrane leads to anterior and posterior gaping of the corneal wound. When the fibrinogen of the inflamed aqueous humor contacts the cut edges of the wound, it precipitates as fibrin and forms a plug that seals the wound and acts as a scaffold for the fibroblastic reparative processes.

After a short delay (from 30 minutes to 5 hours), the second, or leukocytic, phase of healing begins, in which polymorphonuclear leukocytes migrate into the corneal wound. Similar to more superficial corneal wounds, most of the neutrophils arrive from conjunctival blood vessels and lacrimal gland via the tear film. In perforations, neutrophils may arrive via the aqueous humor, and with chronicity, from the perilimbal blood vessels. Mononuclear cells arrive after a delay of 12–24 hours, then act as scavengers or, in the case of monocytes, may transform into fibroblasts.

The third, or epithelial, phase appears to begin after 1 hour of injury. By the process of sliding and mitosis, the epithelium grows into the anterior part of the wound during this phase. The initial epithelium in the wound appears to be an important moderator for healing of the underlying stroma. It plays a key role in the transformation of keratocytes and mononuclear cells into fibroblasts; if the epithelium does not cover the wound, healing is significantly delayed. Epithelium can synthesize collagen and may mediate stromal collagen elaboration by fibroblasts and keratocytes. Epithelium also secretes enzymes, such as collagenase, when the cells are damaged. Proteolytic enzymes, such as collagenase and protease that are released by epithelial cells, neutrophils, and keratocytes may be major factors in the continued progression of corneal ulcerations. Other regulators of corneal wound healing include peptide growth factors, such as epidermal growth factor (EGF), transforming growth factor beta (TGFβ), and platelet-derived growth factor (PDGF) (Swank & Hosgood, 1996). EGF increases protein synthesis and mitosis in corneal epithelium and stromal fibroblasts (Schultz et al., 1992a, 1994). PDGF stimulates the synthesis of fibronectin, hyaluronic acid, and collagenase (Schultz et al., 1992a, 1994). TGFβ can stimulate synthesis of ECM and chemotaxis of inflammatory cells (Imanishi et al., 2000; Li et al., 1999; Schultz et al., 1992a). Studies are ongoing on the manipulation (i.e., inhibition, expression, supplemention) of these growth factors to enhance corneal healing.

The fourth, or fibroblastic, phase begins after 12 hours. Fibroblasts are formed mainly from keratocytes, initially from the keratocytes closest to the wound margin. Fibroblasts may also form from mononuclear cells that have migrated to the cornea from the tears or perhaps from perilimbal vessels. The fibroblasts enlarge, multiply, and form an active fibroblastic tissue that elaborates collagen and ground substance composed of GAG. The epithelium is slowly pushed anteriorly as the new stroma increases the volume beneath the defect.

The fifth, or endothelial, phase of corneal healing begins 24 hours after the injury. The endothelium appears to heal mainly by endothelial sliding or amitotic multiplication. In adult dogs, there appears to be minimal mitotic activity in the endothelial cells (Befanis et al., 1981). To cover posterior defects in the cornea, the endothelial cells initially enlarge and slide. The overall result, once healing is complete, is a reduction in endothelial cell density. The endothelial cells produce a new Descemet's membrane after a few weeks. Duplication of Descemet's membrane may occur in dogs after full-thickness corneal wounds (Kafarnik et al., 2009).

The sixth and final phase of corneal healing begins 7 days after injury. Cellularity in the cornea slowly diminishes, and nuclei in the fibers reorient themselves parallel to the corneal surface. At first, the fibroblastic tissue is highly cellular and unorganized, but with time, the cellularity decreases and the cells and fibrils reorient in a manner similar to that of the normal cornea. The fibroblastic tissue decreases in size and becomes less cellular, and a thin scar is formed. Corneal incisions heal to sufficient tensile strength for suture removal in 19 days (Gilger et al., 2007).

Role of Proteases in Corneal Wound Healing

Healing of corneal wounds is a complex process involving the integrated actions of proteinases, growth factors, and cytokines produced by epithelial cells, stromal keratocytes, inflammatory cells, and the lacrimal glands. Multiple autocrine and paracrine interactions occur between epithelial cells, activated stromal fibroblasts, and the exocrine actions of factors secreted by lacrimal gland cells into the precorneal tear film (PTF). Various proteinases, proteinase inhibitors, growth factors, and cytokines in the tear film and aqueous humor play a role in the natural turnover of the corneal cells and corneal wound healing (Sivak & Fini, 2002).

Proteinases and Proteinase Inhibitors

Maintenance and repair of the corneal stromal ECM require a tightly coordinated balance of ECM synthesis, degrada-

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tion, and remodeling (Ollivier et al., 2007). Proteolytic enzymes (proteinases) perform physiological functions in the slow turnover and remodeling of the corneal stroma. Excessive degradation of normal healthy tissue is prevented by natural proteinase inhibitors in the PTF and cornea, such as α1-proteinase inhibitor, α2-macroglobulin, and tissue inhibitors of metalloproteinases (TIMPs) (Hibbets et al., 1999; Twining et al., 1994a, 1994b). Pathological degradation of corneal stromal collagen and proteoglycans occurs when the balance between proteinases and proteinase inhibitors favors the proteinases (Geerling et al., 1999; Matsubara et al., 1991). The rapid degradation of the corneal stroma associated with some severe corneal ulcers is caused by proteolytic enzymes acting on the collagen, proteoglycans, and other components of the stromal ECM and is referred to as keratomalacia or "corneal melting" (Fig. 19.3). Imbalance with high levels of proteinases (matrix metalloproteinase [MMPs] or plasmin) might also contribute to the pathogenesis of certain types of superficial nonhealing ulcers in dogs (Bentley, 2005).

Major Proteinases in the Cornea and Their Origin

Microorganisms, inflammatory cells (e.g., polymorphonuclear leukocytes and macrophages), corneal epithelial cells, and fibroblasts produce and release proteolytic enzymes (Fini & Girard, 1990; Twining et al., 1994a). Endogenous proteinases are produced by host cells. Exogenous proteinases are secreted by infectious organisms (Gopinathan et al., 2001; Hibbets et al., 1999; Zhu et al., 1990). Examples of exogenous proteinases include the variety of proteases produced by *Pseudomonas aeruginosa* (e.g., alkaline protease, elastase A and B, protease IV, modified elastase, *P. aeruginosa* small protease), and serine proteinases production by *Aspergillus* and *Fusarium* spp. (Gopinathan et al., 2001; Matsubara et al., 1991; Matsumoto, 2004; Zhu et al., 1990). Extracellular enzymes of bacterial or fungal origin also contribute indirectly to corneal proteolytic activity by activating endogenous proteinases (Gopinathan et al., 2001; Twining et al., 1994a).



Figure 19.3 Keratomalacia in a dog with bacterial keratitis.

Two important families of enzymes that affect the cornea are the MMPs and serine proteases. Neutrophil elastase, an abundant serine proteinase in tears, is synthesized by polymorphonuclear leukocytes and macrophages (Sathe et al., 1998). It degrades native III and IV collagen as well as corneal ECM compounds such as laminin and fibronectin (Barletta et al., 1996). Two MMPs (MMP-2 and MMP-9) are of major importance in the remodeling and degradation of corneal stromal collagen (Fini et al., 1992). MMP-2 and MMP-9 were identified by immunohistochemistry in both healthy and ulcerated corneas of humans, dogs, and a variety of other animal species (Carter et al., 2007; Kenney et al., 1998; Reviglio et al., 2003; Yang et al., 2003). In most species, MMP-2 is constitutively present in the unwounded corneal epithelium and stroma and is upregulated after wounding, whereas MMP-9 is found only in the wounded cornea (Kenney et al., 1998; Reviglio et al., 2003; Yang et al., 2003). In a study of nonhealing corneal ulcers in dogs, MMP-9 was found predominantly at the level of the epithelium (Carter et al., 2007). In dogs with chronic superficial keratitis (CSK), MMP-9 was present in both the corneal epithelium and anterior stroma (Chandler et al., 2008). Studies support a different origin and purpose for corneal MMP-2 and MMP-9. MMP-2 is synthesized by corneal keratocytes and performs a surveillance function in the normal cornea, becoming locally activated to degrade collagen molecules that become damaged as a result of normal wear and tear (Matsubara et al., 1991; Twining et al., 1994b). Alternatively, MMP-9 is produced by epithelial cells and leukocytes after corneal wounding (Fini & Girard, 1990; Matsubara et al., 1991).

Proteolytic Activity in Healthy and Diseased Corneas

In damaged corneas, proteinase activity increases in the tear film and is considered a fundamental response of the mammalian eye to corneal injury (Matsubara et al., 1991; Wang et al., 2008a). If infection is present, proteinases secreted by infectious organisms further contribute to corneal damage (Kernacki et al., 1997). In dogs with traumatic keratoconjunctivitis, PTF levels of MMP-9 were significantly increased compared with clinically normal dogs (Arican & Ceylan, 1999). In dogs with *P. aeruginosa* ulcerative keratitis, PTF concentrations of MMP-2 and MMP-9 were significantly higher than contralateral unaffected eyes and clinically normal dogs (Wang et al., 2008a). Protease levels subsequently decreased as corneal healing progressed after medical or surgical therapy. Markedly increased levels of MMP-2 and MMP-9 were detected in the corneal epithelium and stroma of dogs with CSK (Chandler et al., 2008). Corneal levels of MMP-9 were significantly elevated relative to unwounded

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corneas in dogs with acute experimental superficial corneal wounds, chronic experimental superficial corneal wounds, and naturally acquired spontaneous chronic corneal epithelial defects (Carter et al., 2007). Treatment of superficial canine corneal ulcers with topical 0.2% hyaluronic acid had no significant effect on corneal epithelialization or MMP2 or MMP9 protein expression as compared with a similar viscosity topical vehicle control (carboxymethylcellulose) (Gronkiewicz et al., 2017).

Corneal Pigmentation

Corneal pigmentation is most commonly associated with chronic inflammation. Corneal pigmentation is found in disorders such as CSK (i.e., pannus) in the German Shepherd; the pigmentary keratitis syndrome in brachycephalic breeds (Fig. 19.4), which may be a pigmentary or epithelial dystrophy; KCS; and scarring with ulcerative keratitis. Congenital corneal melanosis or pigmentation occurs infrequently in the dog. Corneal pigmentation results from migration of melanocytes from the limbal and perilimbal tissues (Bellhorn & Henkind, 1966). Melanin pigment may accumulate within corneal epithelial cells, macrophages, and fibroblasts in the dog. Other signs of active keratitis, such as corneal vascularization, stromal inflammatory cell infiltration, and granulation tissue formation, usually accompany pigment cell migration. Melanin is transferred to the basilar or suprabasilar cells of the cornea and the anterior stromal tissue (Bellhorn & Henkind, 1966).

Superficial corneal pigment (SCP) in the dog has historically been defined in the veterinary literature broadly as 'pigmentary keratitis', a degenerative or inflammatory condition of the cornea, characterized by a brownish or black deposit.



Figure 19.4 Superficial corneal pigment in a Pug with chronic pigmentary keratitis.

Despite many descriptions of SCP and associated ocular surface inflammation (Azoulay, 2014; Bernays et al., 1999; Kaswan et al., 1989; Ledbetter & Gilger, 2013; Slatter et al., 1977; Yi et al., 2006) few investigations have been performed to determine its underlying etiology or breed susceptibility (Labelle et al., 2013a).

Only two previous studies investigating the histopathology of canine corneal pigment are available (Bellhorn & Henkind, 1966). Corneal epithelial melanin deposition is usually concurrent with blood vessels and inflammatory cells. Ocular surface disease and signalment certainly plays a role in the condition. Recent studies investigating corneal pigment in Pugs specifically, identified a high prevalence in this breed, with approximately 70%–82% of examined dogs affected (Krecny et al., 2015; Labelle et al., 2013a). Both studies also identified a high prevalence of ocular comorbidities, including disorders of the lacrimal system and eyelids. A statistical association between KCS and SCP was reported in one study, but it was also noted that SCP developed in the absence of KCS in other dogs (Krecny et al., 2015). In the other study, no significant associations between eyelid conformation or tear film characteristics and the detection of corneal pigment were identified (Labelle et al., 2013a). The absence of consistently identifiable inflammatory risk factors (ocular adnexal or tear film abnormalities) and the detection of SCP were considered suggestive of a hereditary epithelial or pigmentary dystrophy in the Pug, or pigmentary keratopathy (Labelle et al., 2013a). Like the Pug, several other brachycephalic dog breeds develop SCP commonly and without an identifiable underlying etiology. These breeds include the Boston Terrier, Lhasa Apso, Pekingese, and Shih Tzu (Christmas, 1992; Dreyfus et al., 2011; Ledbetter & Gilger, 2013)

Using IVCM, pigmentary keratitis was morphologically characterized by six specific pathological lesions that were common to Pugs and non-Pug brachycephalic dogs (Vallone et al., 2017). Abnormalities were mostly confined to the corneal epithelium and included several cellular changes consistent with chronic inflammation. The significant presence of these inflammatory cellular markers supports the use of the term pigmentary keratitis to denote accurately the underlying chronic inflammatory pathology of this syndrome (Vallone et al., 2017). Pigmentary keratitis appears morphologically as a centripetal corneal migration of microanatomic features normally confined to the perilimbal region of the cornea. Additonal studies with biomicroscopy, IVCM, immunohistochemical staining, and electron microscopy are needed to characterize pigmentary keratitis better. Since a genetic basis has been postulated, additional pedigree analyses might elucidate an etiology.

Another less common source of corneal pigmentation is anterior synechiae and the adherence of anterior uveal cysts to the cornea (Fig. 19.5) (Corcoran & Koch, 1993; Gelatt, 1972). Cysts of the anterior uvea may be either congenital or

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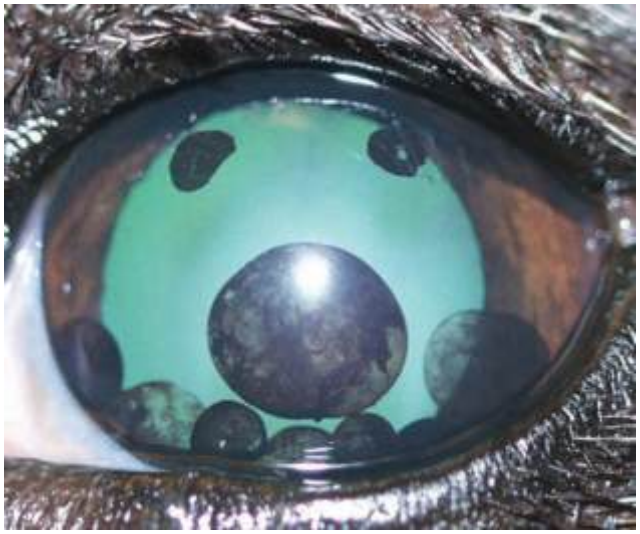


Figure 19.5 Pigment deposits on the endothelial surface of the cornea resulting from the rupture of uveal cysts. Several intact uveal cysts remain in the anterior chamber and adjacent to the corneal endothelium.

acquired (as the result of uveal inflammation or degeneration). The pigmented cells may arise from the pigment epithelium of the ciliary body, iridal stroma, and posterior iridal epithelium. These cysts can be large and attach to the corneal endothelium, or they can rupture and liberate pigment that adheres to the posterior aspect of the cornea.

Corneal Edema

Corneal edema or swelling (i.e., corneal overhydration) may result from imbibition of fluid by the epithelium or stroma (Fig. 19.6). Corneal transparency depends both on its physical structure and on mechanisms that prevent overhydration. The major barriers to edema are the endothelium and the epithelium. In rabbits, removal of the epithelium produced an average increase in corneal thickness of 200% in 24 hours, whereas removal of the endothelium produced an increase of 500% (Maurice & Giardin, 1951). Alterations in endothelial cells result in the cornea absorbing aqueous humor and becoming edematous. The endothelium maintains corneal deturgescence by an energy-dependent sodium potassium transport pump as well as by a physical barrier. The barrier function of the endothelium results from tight cellular junctions known as '*zonula occludens*.' Traditionally, corneal edema was regarded simply as increased corneal water content that results in increased thickness, increased scattering of light, and decreased transparency; however, corneal edema also involves loss of stromal GAG and water uptake (Kangas et al., 1990). When the cornea swells, fluid is not uniformly distributed within the corneal stroma. Instead, posterior corneal lamellae are hydrated to a greater extent, possibly because of differences in the glycosaminoglycan



Figure 19.6 Afghan Hound with diffuse corneal edema after canine adenovirus type 1 vaccination.

content between the anterior and posterior stroma or presence of lamellar interweave in the anterior stroma that limits the extent to which these lamellae can swell (Meek et al., 2003a, 2003b).

Corneal edema in the dog may be associated with a variety of causes, including endothelial dystrophy, age-related degeneration, endothelial damage associated with persistent pupillary membranes (PPMs), mechanical trauma, toxic reactions, anterior uveitis, endotheliitis, glaucoma, neovascularization, and ulceration. Endothelial dystrophy occurs in several breeds, including Boston Terriers, Chihuahuas, Dachshunds, and German Shepherds (Brooks et al., 1990; Dice, 1980; Gwin et al., 1982a; Martin & Dice, 1982). Light microscopic findings have included stroma edema, fibrous tissue proliferation on a thickened Descemet's membrane, and endothelial cell hypocellularity. This condition is similar to Fuchs' dystrophy in humans and is commonly bilateral (see more information later in this chapter) (Bergmanson et al., 1999). Boston Terriers with endothelial dystrophy were evaluated by IVCM and FD-OCT (Thomasy et al., 2016). Affected dogs had significantly decreased corneal endothelial density and increased central corneal thickness compared with age-matched controls, consistent with disrupted fluid homeostasis associated with reduced endothelial cell function.

Corneal edema associated with endothelial changes is commonly seen with anterior uveitis in the dog. Intraocular inflammation results in corneal edema via an increase in endothelial permeability and a decrease in Na^+/K^+-ATPase pump activity (MacDonald et al., 1987). The immune-mediated Arthus-type reaction of infectious canine hepatitis, which is an immune-mediated, Arthus-type reaction, develops in the anterior uveal tract and progresses to destruction of the corneal endothelium with resultant corneal edema, thus causing the "blue eye" appearance (Aguirre et al., 1975; Carmichael et al., 1975; Curtis & Barnett, 1973a, 1973b, 1983). Corneal endothelial cell damage and secondary

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corneal edema is a manifestation of type III hypersensitivity in which immune complex formation results from the release of virus from infected corneal endothelial cells (Curtis & Barnett, 1973a, 1973b). Natural infections or vaccination with modified live canine adenovirus type 1 may result in the development of corneal edema. Afghan Hounds are particularly susceptible (Fig. 19.6). Vaccination with canine adenovirus type 2 decreases the incidence to below 1%. Approximately 30% of dogs that develop corneal edema from adenovirus infection or vaccine do not completely resolve (Curtis & Barnett, 1973a, 1973b, 1983).

Traumatic endothelial damage may occur with anterior lens luxation. Trauma to the endothelium may also result from intraocular surgery, such as phacoemulsification, intracapsular lens extraction, and intraocular lens replacement. Irrigation solutions used in phacoemulsification also damage the corneal endothelium (Gwin et al., 1983b). Results of one study on the response of canine corneal endothelium to intraocular irrigation solutions indicated that irrigating fluid composition has a less deleterious effect on the corneal endothelium than the volume of fluid and time of irrigation (less than 100 mL of fluid for less than 20 minutes had the least damaging effect) (Nasisse et al., 1986). In other canine studies, diode laser iridal photocoagulation showed no adverse effects on the corneal endothelium, but CO_2 photokeratotomy resulted in multiple punctate and linear regions of endothelial cell destruction associated with a significant increase in corneal thickness (Chandler et al., 2003; Hoffman et al., 2009).

There are a number of known compounds that result primarily in corneal edema in dogs. Chlorpromazine accumulates in the canine posterior corneal stroma, lens, and uveal tract. In addition to causing cataracts, it produces posterior corneal precipitates and pigmentation. Chlorpromazine is a phototoxic compound, and the cellular damage to endothelial cells occurs after light exposure (Barron et al., 1972a, 1972b; Rubin et al., 1970; Tousimis & Barron, 1970). Lortalamine, a nontricyclic antidepressant compound, produced high levels of the compound and its metabolite in the cornea after oral administration and resulted in bilateral mydriasis, conjunctivitis, epiphora, corneal edema, and ulcerations for the first week after therapy (Mally & Thiebault, 1990). Bilateral corneal edema occurred in three of 12 dogs after long-term treatment (>3 months) with tocainide, an antiarrhythmic agent. Because of the lack of inflammation, this was presumed to be a direct endothelial toxic effect of the drug (Gratzek et al., 1996).

Corneal Vascularization

Corneal stromal vascularization is a nonspecific response to corneal injury or inflammation (Lee et al., 1998). The healthy canine cornea is avascular and the presence of blood vessels within the cornea represents pathologic change. Vascularization is a normal component of the reparative response after injury in a variety of tissues; however, in the cornea, this process can result in disrupted corneal architecture, opacification, and reduced vision.

The avascular state of the cornea is actively maintained by a balance of antiangiogenic and angiogenic factors (Pearce et al., 2007; Qazi et al., 2009). Corneal vascularization occurs when this balance is lost and the local corneal microenvironment favors angiogenic factors. The presence of VEGF receptor 1 and VEGF receptor 2 has been shown in normal canine eyes (Binder et al., 2012). In the normal canine cornea, superficial and basal corneal epithelium, corneal endothelium, and limbal vascular endothelium contained VEGF receptor 1 whereas VEGF receptor 2 was found in the scleral vascular endothelium. Both VEGF receptor 1 and 2 were detected in pathologic vascular endothelium and corneal neovascularization. Any corneal insult that induces inflammation or hypoxia may result in corneal angiogenesis (Maddula et al., 2011; Safvati et al., 2009). Corneal vessels may arise from conjunctival, scleral, or iridal vessels. Once blood vessels penetrate the cornea, they grow along collagen lamellar planes (unless these planes are disrupted).

The depth and appearance of corneal blood vessels is often indicative of the anatomic location of the underlying pathologic process inciting the vascular invasion (Cogan, 1962). Superficial corneal vessels are located in the subepithelial and anterior stromal regions and are typically a response to ocular surface or superficial corneal disease. Superficial vessels arise from conjunctival vessels and are bright red, fine, branch repeatedly, and can be observed to cross the limbus (Fig. 19.7). Deep corneal vessels are located in the posterior stroma and suggest deep corneal or intraocular disease. Deep corneal vessels arise from anterior ciliary vessels and appear dark red, straight with few or no branches, and do not cross the limbus (Fig. 19.8). Less commonly, deep corneal vessels may originate from iridal vessels when anterior synechiae are present.

Developmental Abnormalities and Congenital Diseases

Microcornea

Microcornea is a small cornea in an otherwise normal globe. The appearance in dogs is a cornea with a horizontal diameter of less than 12 mm. A small cornea may also occur with ocular or systemic conditions associated with multiple ocular anomalies. Microcornea is reported as a feature of merle ocular dysgenesis in a variety of breeds, including Australian Shepherds and Dachshunds (Dausch et al., 1978; Gelatt & McGill, 1973; Gelatt & Veith, 1970). The Collie, Miniature and Toy Poodle, Miniature Schnauzer, Old English Sheepdog, St. Bernard, and possibly other breeds may be predisposed to

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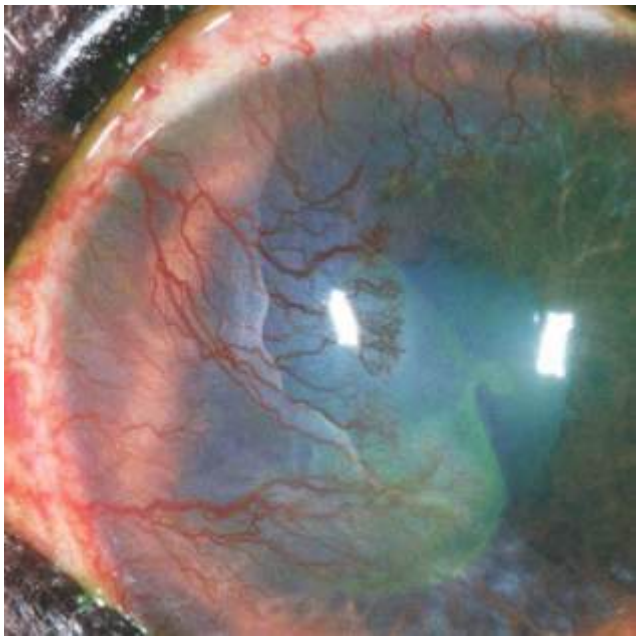


Figure 19.7 Superficial corneal vascularization in a dog with chronic keratoconjunctivitis sicca.

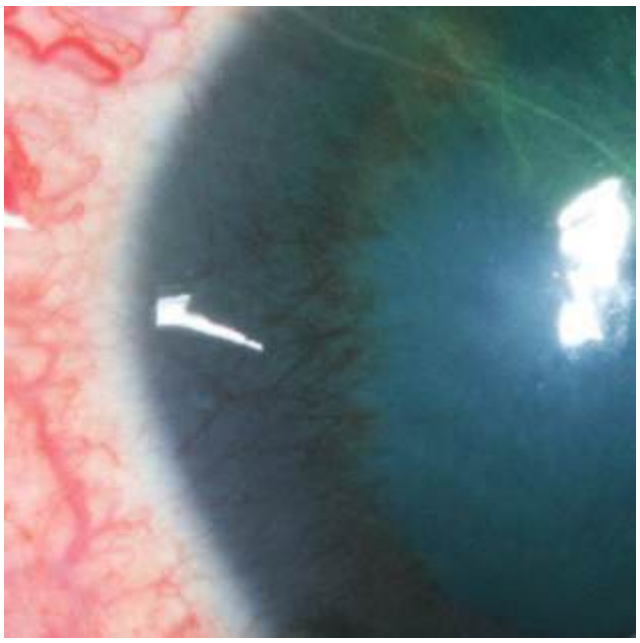


Figure 19.8 Deep corneal vascularization in a dog with chronic anterior uveitis.

microcornea and multiple ocular anomalies as well (Gilger et al., 2007). In these dogs, microcornea may be associated with microphthalmia, goniodysgenesis, and PPMs. Microcornea may also occur in dogs with the systemic connective tissue disorder Ehlers–Danlos syndrome (Barnett & Cottrell, 1987). Microphthalmia, including microcornea, has been described in Alaskan Huskies affected by a polyneuropathy with ocular abnormalities and neuronal vacuolation similar to Warburg microsyndrome in humans (Wiedmer et al., 2016). Similar phenotypes have also been reported in Boxers, Rottweilers and Black Russian Terriers.

Megalocornea

Megalocornea is a cornea of greater than normal size, normal being approximately 16–18 mm in horizontal diameter. This is a rare, congenital anomaly in the dog and is usually concurrent with congenital glaucoma and buphthalmus (or megalophthalmos).

Dermoids

A dermoid is a choristoma, or normal tissue in an abnormal position. Dermoids occur most commonly at the temporal limbus and can involve the eyelids, conjunctiva, cornea, or a combination of these structures (Fig. 19.9). Rarely, dermoids may involve the central cornea in dogs (Brudenall et al., 2007). Dermoids may contain keratinized epithelium, hair, blood vessels, fibrous tissue, fat, nerves, glands, smooth muscle, and cartilage (Horikiri et al., 1994; Lawson, 1975; Minamide & Suzuki, 1997). Dermoids are present at birth, but they may not be recognized clinically until the dog is several weeks old. If they are irritating or obstructing vision, dermoids can be treated by surgical removal. The procedure of choice for corneal dermoids is superficial lamellar keratectomy (see next section). In the uncommon situation where a dermoid requires deep keratectomy, a conjunctival graft may be warranted (Lee et al., 2005). Surgical placement of canine amniotic membrane after excision of large dermoids is reported to enhance healing and reduce corneal scarring (Kalpravidh et al., 2009). Small dermoids with few hair follicles may not be clinically problematic and can be left alone.

Superficial Keratectomy

As mentioned, one of the most common surgical procedures for removal of a corneal dermoid is superficial keratectomy. Other corneal lesions amenable to superficial keratectomy include indolent ulcers, corneal neoplasms, sequestrums, foreign bodies, corneal abscesses, inclusion cysts, bacterial and fungal keratitis (usually in conjunction with a conjunctival graft or flap), and corneal degeneration (Bentley et al., 2001; Bouhanna et al., 2008; Brudenall et al., 2007; Choi et al., 2010; Dreyfus et al., 2011; Karasawa et al., 2008; Morgan & Abrams, 1994; Peiffer et al., 1976a; Sansom & Blunden, 2010; Simonazzi et al., 2009; Takiyama et al., 2010). The specific procedure or method for the superficial keratectomy is determined by the type of lesion. Before performing a superficial keratectomy, determining the depth of the lesion using biomicroscopy, high-frequency ultrasound,

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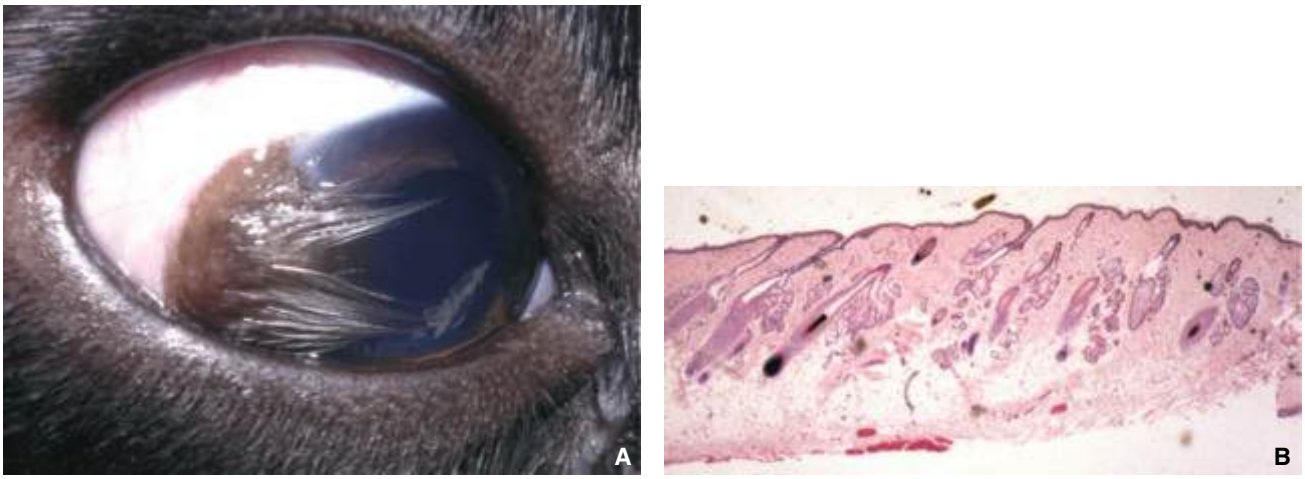


Figure 19.9 **A.** A dermoid, or choristoma, at the temporal limbus in a young dog. **B.** A histologic section of a dermoid after keratectomy. Note the hair follicles and glands that are typical of haired skin. (Hematoxylin and eosin. 110×)

confocal microscopy, or optical coherence tomography will help in planning the surgery. If the resulting corneal wound extends deeper than one-half corneal thickness, use of a conjunctival pedicle flap or amniotic membrane graft (Barros et al., 2005; Kalpravidh et al., 2009) is warranted to protect the cornea, to help prevent perforation, and to promote healing. Because corneal stromal tissue may not completely regenerate, the number of superficial keratectomies that can be performed at the same site is limited to two or three, depending on the depth of the tissue removed with each procedure.

Superficial keratectomy is most commonly performed in veterinary medicine using traditional microsurgical instruments (see Chapter 12); however, it can also be performed using carbon dioxide or excimer laser ablation (Shieh et al., 1992). Use of magnification (e.g., an operating microscope) is essential to perform the surgery, and specialized surgical equipment (e.g., corneal dissector, dermatology punch, corneal trephine, micrometer diamond knife) greatly facilitates the removal of corneal tissue and may improve the clinical outcome.

There are two common methods to perform a superficial keratectomy: the complete and the partial incision keratectomy. In the first method, the *complete incision keratectomy*, an initial corneal incision is made that surrounds completely the lesion to be removed. The incision needs to be at appropriate depth to allow complete removal of the lesion. It is made using a corneal trephine, diamond knife, or microsurgical blade (Fig. 19.10). The initial incision can be round, square, or triangular. After the initial incision is made, the edge of the tissue to be removed is grasped with forceps, and a corneal dissector (e.g., Martinez corneal dissector, microsurgical blade #6400 or #6900, iris spatula) is introduced and held parallel to the cornea. The dissector is used to separate the corneal lamella without penetrating deeper than the original incision. The cornea is then separated until the opposite incision line is reached.

In the second type of superficial keratectomy, the *partial incision keratectomy*, a small corneal incision is made adjacent to the lesion that is to be removed. This initial incision is made at the appropriate depth but only wide enough to allow insertion of the lamellar-separating device (e.g., Martinez corneal dissector, microsurgical blade #6400 or #6900, iris spatula) to be inserted. Using this separator instrument through the initial incision, the entire lamellar plane under the lesion to be removed is separated, thus undermining the lesion. Corneal section scissors are then introduced into the initial incision and used to complete the keratectomy (Fig. 19.11).

The carbon dioxide laser generates heat and coagulates tissue. It can effectively ablate superficial corneal lesions; however, the surrounding area of the cornea can be significantly damaged because of the heat generated, thus resulting in scarring and opacity (Gilmour, 2003). Surgical margins may be difficult to interpret if the laser is used exclusively for mass removal (Rizzo et al., 2004). Therefore, use of the carbon dioxide laser is not recommended for corneal surgery. However, the carbon dioxide laser can be used for adjunctive therapy after surgical removal of superficial corneal, limbal, or scleral neoplasms (English et al., 1990; Gilmour, 2003).

In contrast to the carbon dioxide laser, the argon-fluoride excimer laser removes precise (i.e., submicron) amounts of tissue with virtually no damage to adjacent tissue. The laser beam is controlled by a computer, and both the pattern and depth of the keratectomy can be precisely achieved. In the dog, treatment of crystalline corneal degeneration, corneal scarring, corneal calcification, and pigmentary keratitis with the excimer laser has achieved some success (Shieh et al., 1992).

Following keratectomy, the cornea is treated much like a corneal ulcer with topical broad-spectrum antibiotics to

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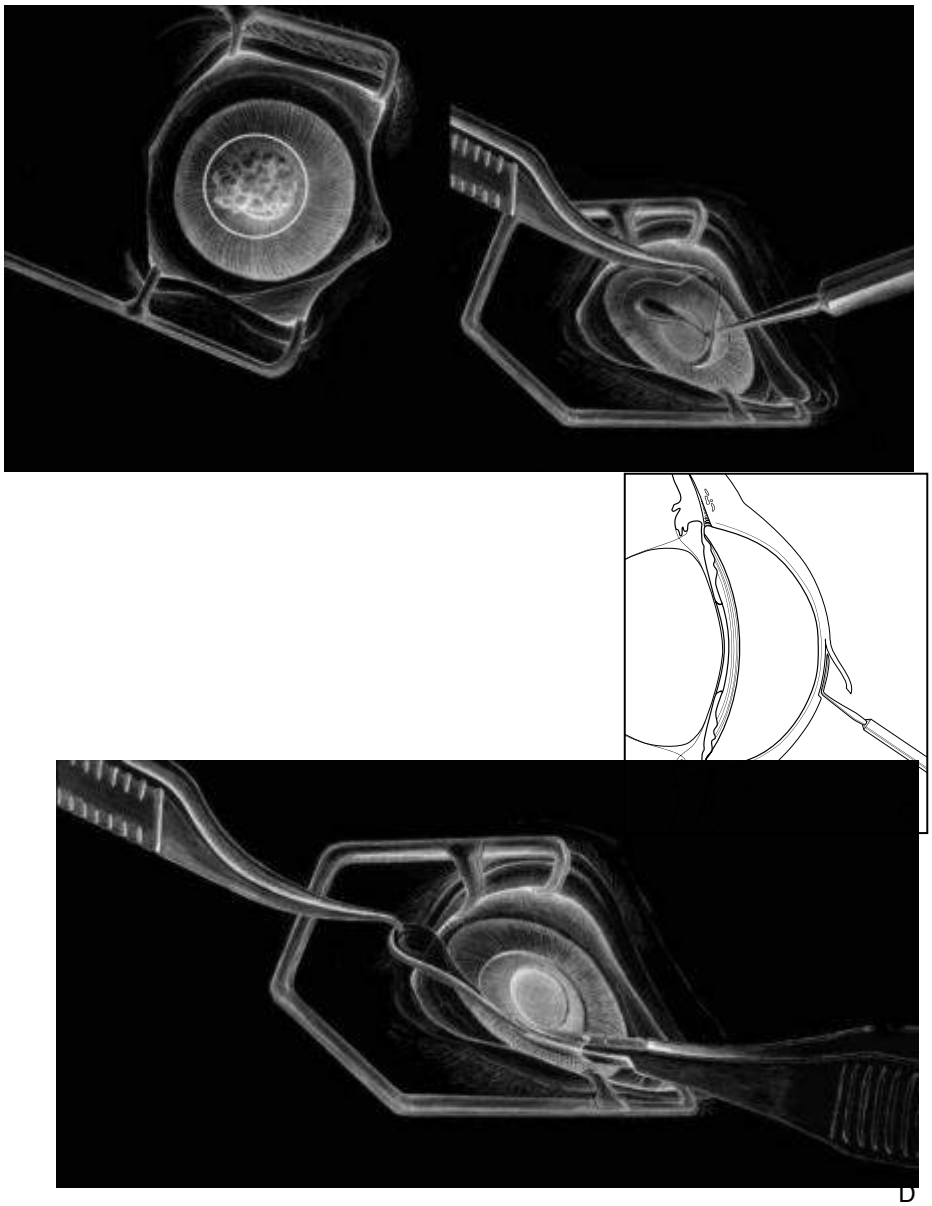


Figure 19.10 Complete incision superficial keratectomy. **A.** The initial corneal incision, which may be round, square, or triangular, should completely surround the lesion to be removed and can be made using a corneal trephine, diamond knife, or microsurgical blade. **B** and **C.** After the initial incision is made, the edge of the tissue to be removed is grasped by forceps and a corneal dissector (e.g., Martinez corneal dissector, Beaver No. 64 microsurgical blade, iris spatula) is introduced and held parallel to the cornea. The dissector is used to separate the corneal lamella without penetrating deeper than the original incision. The cornea is then separated until the opposite incision line, or limbus, is reached. **D.** Scissors may be needed to connect the dissection to the opposite incision or to remove the corneal tissue from the limbus.

prevent infection and with topical atropine to decrease ciliary spasm and discomfort. A potentially devastating complication after keratectomy is corneal perforation, which generally results from infection at the surgical site. The potential for infection is exacerbated by deep, extensive keratectomies but is largely preventable by use of conjunctival flaps or other supportive surgeries. Frequent reevaluations after surgery (with monitoring of healing by use of fluorescein dye application) and use of topical antibiotics should prevent most postsurgical complications.

Congenital Corneal Opacities

Corneal opacities are commonly classified by the degree of opacity and are described as a nebula, macula, or leukoma. A nebula is a minor, diffuse, hazy opacity with indistinct

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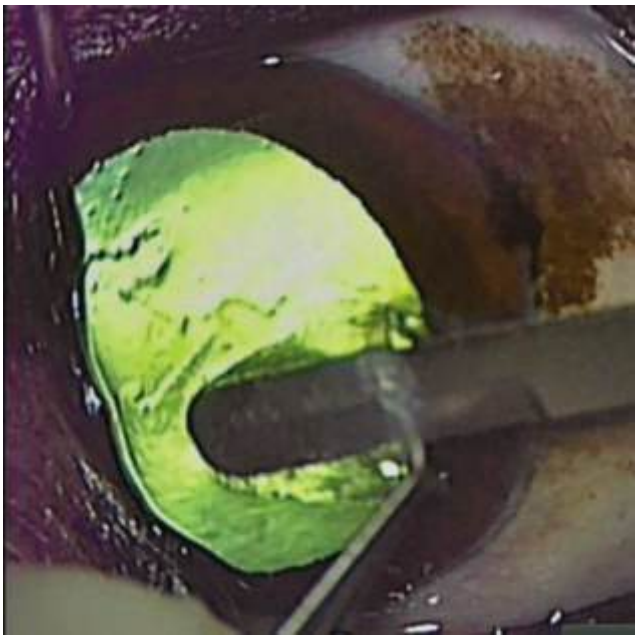


Figure 19.11 Partial incision superficial keratectomy in a dog with a chronic indolent corneal ulcer. A small corneal incision is made adjacent to the lesion that is to be removed and a lamellar-separating device is inserted, in this case a #64 microsurgical blade. The entire lamellar plane under the lesion to be removed is separated, thus undermining the lesion. Corneal section scissors are then introduced into the initial incision and used to complete the keratectomy.

borders. A macula is a moderately dense opacity with a circumscribed border. A leukoma is a dense, white opacity. When iris tissue adheres to the posterior surface of the cornea beneath an area of corneal opacity, the condition is described as an adherent leukoma.

Infantile Corneal Dystrophy

Infantile corneal dystrophy, or puppy keratopathy, is a congenital, subepithelial, geographic corneal opacity that is nonhereditary, transient, and observed in puppies younger than 10 weeks (Fig. 19.12). This type of noninflammatory corneal opacity occurs in many breeds of dogs, but is most common in Bichon Frise, Collie, English Springer Spaniel, Miniature Poodle, Shetland Sheepdog, and Yorkshire Terrier puppies (Gilger et al., 2007; Ledbetter & Gilger, 2013; Whitley & Gilger, 1999) The condition slowly resolves, and in most cases is absent by 12–16 weeks of age. There is no interference with functional vision and treatment is unnecessary.

Corneal Opacities with Persistent Pupillary Membranes

PPMs are congenital lesions that occur in many canine breeds and are known to be hereditable in some. Persistent pupillary tissue strands arise from the iris collarette and represent failure of normal embryonic vasculature structures to

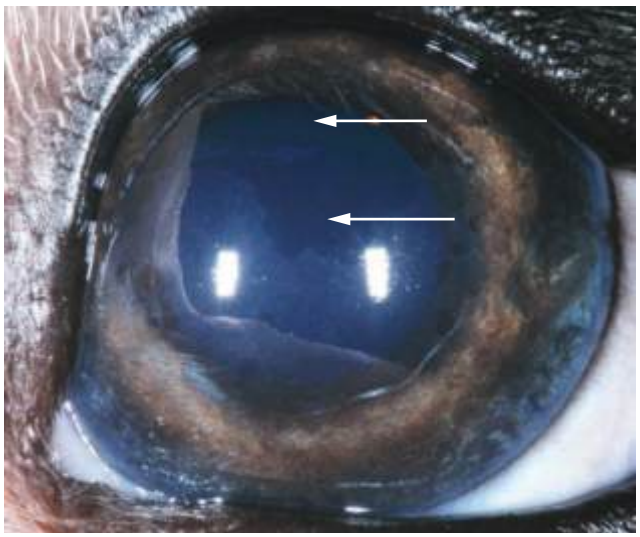


Figure 19.12 Infantile corneal dystrophy, a congenital, nonhereditary, transient, subepithelial, geographic corneal opacity, in an 8-week-old puppy.

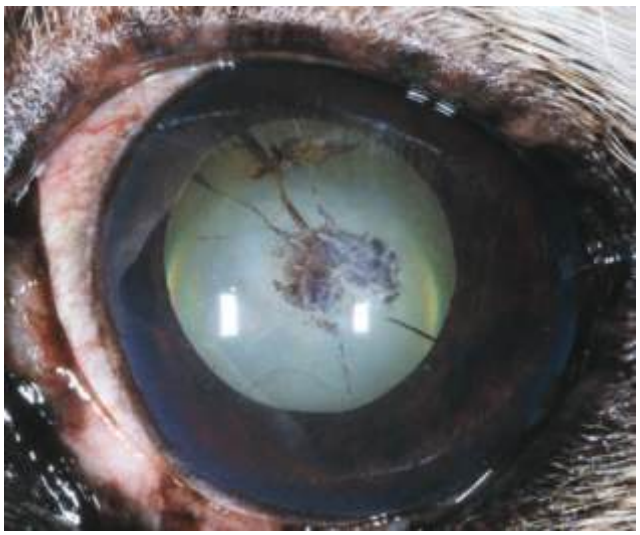


Figure 19.13 Dog with persistent pupillary membranes adherent to the posterior surface of the cornea and resulting in a focal corneal opacity.

completely regress. Corneal lesions (i.e., adherent leukomas) can be associated with adherence of PPMs (Fig. 19.13). Both focal and diffuse corneal opacities occur, but the former is more frequent (Mason, 1976; Peiffer & Gwin, 1977; Roberts & Bistner, 1968). Focal lesions appear as punctate, linear, or round deep corneal opacities that may be pigmented or unpigmented. Small focal opacities of the cornea are characterized by thickening and distortion of Descemet's membrane in the area of the opacity. Larger, more diffuse corneal opacities also affect Descemet's membrane and may result from generalized stromal edema (Peiffer & Gwin, 1977).

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PPM-associated leukomas may be isolated anomalies or a component of a more extensive anterior segment dysgenesis. These conditions are, in general, poorly described in dogs (Peiffer & Fischer, 1983; Williams, 1993). Peter's anomaly is a form of anterior segment dysgenesis in which abnormal cleavage of the anterior chamber occurs. There is paracentral corneal opacity, because of damaged corneal endothelium and Descemet's membrane, and clear surrounding peripheral cornea. Iris strands extend from the collarette to the posterior surface of the cornea (Swanson et al., 2001). The lens may be clear or cataractous.

Limbal Colobomas and Staphylomas

Colobomas or staphylomas of the limbus or sclera are rare in the dog. The lesions are thin regions of the globe's fibrous tunic lined by uveal tissue and appear as a tan, gray, or blue raised mass covered with conjunctiva. Strabismus may be present. Etiologies include congenital malformation and secondary to inflammation, glaucoma, neoplasia, trauma, or surgery (Barros & Safatle, 2000; Mitterer et al., 1987). Congenital, noninflammatory colobomas and staphylomas of the limbus or sclera occur most commonly in Miniature Dachshunds and with Collie eye anomaly and, in other breeds, with multiple ocular anomalies. Equatorial scleral staphylomas occur in the Australian Shepherd associated with multiple ocular anomalies (Gelatt & McGill, 1973; Gelatt & Veith, 1970). A case of congenital scleral staphyloma in a young Poodle was successfully repaired using a preserved homologous peritoneum graft (Barros & Safatle, 2000).

Metabolic and Connective Tissue Disorders

Lysosomal storage diseases are a heterogeneous group of rare inherited disorders caused by deficient activity of one or more enzymes within the lysosomes. Lysosomal enzyme deficiency results in the accumulation of storage material within cells and a diverse array of clinical signs. Many canine lysosomal storage diseases may be associated with corneal pathology, including gangliosidosis and mucopolysaccharidosis (Skelly & Franklin, 2002). The circular or irregular-shaped anterior stromal corneal opacities in Shiba Inus with GM1 gangliosidosis are the result of keratocyte accumulation of neutral carbohydrates, swelling, and dysfunction with subsequent irregular arrangement of stromal collagen fibers (Nagayasu et al., 2008). Multifocal or diffuse corneal opacities are reported in dogs with various types of mucopolysaccharide storage disorders and result from stromal keratocyte accumulation of GAG (Neer et al., 1995; Shull et al., 1994; Silverstein et al., 2004; Wilkerson et al., 1998). Mucopolysaccharidosis I is an inherited disorder that results from a deficiency of α-L-iduronidase and lysosomal accumulation of GAG in corneal stromal cells (Newkirk et al., 2011). Accumulated GAG was found in corneal stromal cells and scleral fibroblasts and increases with age. Enzyme replacement therapy, particularly at a very early age, resulted in significantly less GAG accumulation in the corneal stroma (Dierenfeld et al., 2010). A Miniature Poodle cross with mucopolysaccharide VI, caused by a deletion in the arylsulphatase B gene, had bilateral corneal stromal opacities along with multiple skeletal abnormalities (Jolly et al., 2012). Corneal endothelial cell hypertrophy and vacuolization are also prominent histopathologic features in dogs with mucopolysaccharide VII, but this is not reported to result in clinical endothelial dysfunction or corneal edema (Mollard et al., 1996). Mucopolysaccharidosis VII is caused by a deficiency in β-glucuronidase enzymatic activity and may result in GAG accumulation within the corneal stroma. Corrective β-glucuronidase transfer with a helper-dependent canine adenovirus vector has been shown to reduce pathology in affected canine corneas (Serratrice et al., 2014). Lysosomal acid lipase deficiency is reported in Fox Terriers and was associated with circular corneal lipid deposition (von Sandersleben et al., 1986).

Tyrosinemia results from deficient enzymatic activity to catabolize tyrosine with subsequent accumulation of the amino acid in tissues. Naturally acquired and experimentally induced tyrosinemia in dogs is associated with formation of refractile stellate-shaped corneal epithelial opacities (Kunke et al., 1984; Lock et al., 2006). Ehlers–Danlos syndrome is an inherited connective tissue disorder characterized by skin fragility, skin hyperextensibility, joint hypermobility, and vascular fragility. Corneal lesions reported in dogs with Ehlers–Danlos syndrome include microcornea, sclerocornea, and corneal granular opacities, edema, and pigmentation (Anderson & Brown, 1978; Barnett & Cottrell, 1987; Matthews & Lewis, 1990).

Inflammatory Keratopathies

Corneal diseases may be categorized into inflammatory and noninflammatory causes. Inflammatory corneal disorders can be further classified into ulcerative and nonulcerative keratitis.

Ulcerative Keratitis

Corneal ulceration, or ulcerative keratitis, is one of the most common ocular diseases in the dog. A corneal ulcer is present when there is a break in the corneal epithelium that exposes the underlying corneal stroma. Clinically, this results in lacrimation, blepharospasm, photophobia, conjunctival hyperemia, corneal edema, and possibly miosis and aqueous flare. The diagnosis of a corneal ulcer is made on the basis of these clinical signs and the retention of topically applied fluorescein dye by the corneal stroma (Fig. 19.14).

Uncomplicated superficial ulcers usually heal rapidly, with minimal scar formation. Complicated deep ulcers, such as those with microbial infection, however, may lead to

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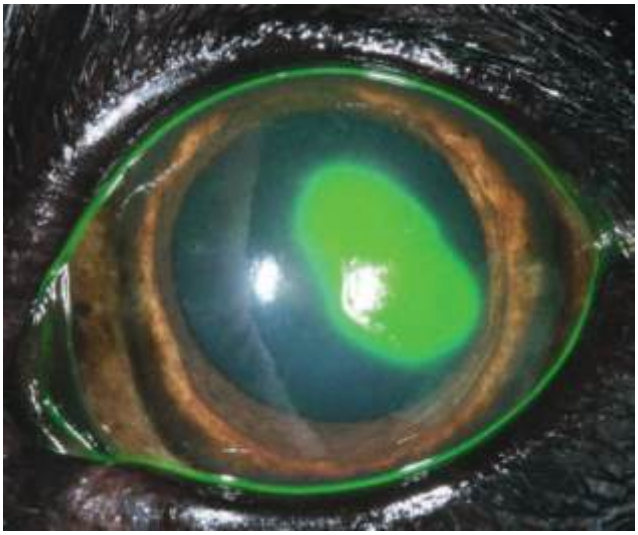


Figure 19.14 The diagnosis of a corneal ulcer is made on the basis of retention of topically applied fluorescein dye by the corneal stroma as observed in this superficial corneal ulcer.

impaired vision because of corneal scarring or, when corneal perforation occurs, to anterior synechia formation. Severe ulcerative keratitis may lead to loss of the eye because of endophthalmitis, glaucoma, phthisis bulbi, or a combination of these. Corneal ulcers are classified by depth of corneal involvement and by their underlying cause.

The first step in treating all corneal ulcers involves identifying and removing the inciting cause, which may be eyelid abnormalities (e.g., masses, lagophthalmos, distichiasis, ectopic cilia), foreign bodies, trauma, and KCS. Chronic, infected, or progressive corneal ulcers should undergo microbiologic culture and antibiotic susceptibility tests and cytologic examination of corneal samples. These diagnostic procedures help guide specific antimicrobial therapy.

Epithelial and superficial stromal foreign bodies may be successfully removed with saline hydropulsion, a cytobrush, an ophthalmic spear sponge, or a Kimura spatula (Labelle et al., 2014; Pont et al., 2016). This can generally be performed under topical anesthesia alone with excellent success rates. Stromal or penetrating foreign bodies, without lens involvement and without significant anterior uveitis, usually require general anesthesia for removal but have a good prognosis for vision retention after surgery (Pont et al., 2016). There is a report of a penetrating gunshot injury with lead shot entrapped within the choroid where the dog retained vision for 4.5 years after penetrating corneal and lenticular injury (Sansom & Labruyere, 2012).

Ulcerative Keratitis: Depth of Corneal Involvement

Corneal ulcers are classified by the depth of corneal involvement and by their underlying cause. Depth of corneal involvement is reviewed first and includes superficial corneal ulcers, stromal corneal ulcers, descemetoceles, and perforations.

Superficial Corneal Ulcers

Superficial corneal ulcers (see Fig. 19.14) are further classified as uncomplicated, progressive, or refractory. For successful management of ulcerative keratitis, the inciting cause of the ulcer is identified and removed, the stage and severity of the ulcer is determined, and an appropriate therapeutic modality is selected. Identifying the cause or contributing factors requires a thorough ocular examination. Eyes should always be evaluated for eyelash abnormalities, eyelid structure and function, and preocular tear film disorders (e.g., Schirmer tear test, tear breakup time, rose Bengal retention). Uncomplicated superficial ulcers can resolve with topical antibiotic therapy applied three to four times daily to prevent secondary bacterial infection. Combination ophthalmic preparations (e.g., neomycin, bacitracin, and polymixin B), erythromycin, or oxytetracycline are frequently good antimicrobial selections which provide broad-spectrum coverage. Stimulation of the abundant sensory receptors in the cornea by ulceration results in a localized neurogenic reflex anterior uveitis associated with miosis of the pupil, iris hyperemia, and increased protein levels in the aqueous humor (i.e., aqueous flare). Therefore, a mydriatic agent (1% atropine or tropicamide) is applied topically once or twice daily to control ciliary muscle spasm, a dilated pupil, and the ocular discomfort associated with the secondary uveitis. The ulcer should resolve in 2–6 days; if not, it should be reevaluated for an undetected, underlying cause or contributing factor.

Corneal erosions and superficial corneal ulceration have been documented as a complication of general anesthesia for non-ophthalmic procedures in dogs, even those whose eyes were lubricated with topical lubricating gel (Dawson & Sanchez, 2016). Evaluation of 199 canine eyes lubricated before general anesthesia showed corneal ulceration in one eye and corneal erosion in 25 eyes. Neither the length of general anesthesia nor the service admitted were associated with corneal erosion or ulceration. The results of this study supports incorporating ocular examination with fluorescein staining in postanesthetic physical examinations.

Spontaneous Chronic Corneal Epithelial Defects

Spontaneous chronic corneal epithelial defects (SCCEDs) in dogs are chronic superficial ulcers that fail to resolve through normal wound-healing processes. A variety of terms are used to describe this entity, including indolent erosions or ulcers, canine recurrent erosions, refractory corneal ulcers, Boxer ulcers, nonhealing erosions, persistent corneal erosions, recurrent epithelial erosions, and idiopathic persistent corneal erosions (Champagne & Munger, 1992; English, 1989; Gelatt & Samuelson, 1982; Kirschner, 1990; Kirschner et al., 1989; Morgan & Abrams, 1994; Stanley et al., 1998). Although originally referred to as Boxer ulcers because of a predilection for Boxer dogs, subsequent larger studies document occurrence in almost every breed (Murphy et al., 2001;

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Whitley & Gilger, 1999). Dogs affected with SCCEDs are typically middle-aged, overrepresented by the Boxer breed, and exhibit varying degrees of blepharospasm. The initiating event in dogs with SCCEDs is likely superficial corneal trauma. These epithelial defects result in variable amounts of ocular discomfort along with the potential for corneal neovascularization, fibrosis, and edema (Aldave et al., 2009; Bentley 2005; Bentley & Murphy, 2004; Dawson et al., 2017; Dees et al., 2017; Lassaline-Utter et al., 2014; Spertus et al., 2017; Stanley et al., 1998; Woof & Norman, 2015). Hallmark clinical and histologic features of SCCED include a superficial axial or paraxial corneal ulcer that does not extend into the stroma, associated with redundant, nonadherent corneal epithelial borders that may be associated with an acellular hyaline zone in the anterior stroma, neovascularization, and, when not treated adequately, may persist for weeks to months (Bentley 2005; Bentley & Murphy, 2004; Dawson et al., 2017; Dees et al., 2017; Spertus et al., 2017; Stanley et al., 1998; Woof & Norman, 2015). Therapeutic interventions for SCCEDs are aimed at removing non-attached epithelium and the acellular hyaline zone from the superficial cornea to allow new healthy epithelium to form and adhere to the basement membrane.

A condition similar to canine SCCEDs has been described in horses, with epithelium demonstrating dysmaturity and non-adherence, and variable anterior stromal hyalinization, stromal inflammation, fibrosis, and neovascularization (Hempstead et al., 2014). The anterior stromal acellular hyaline zone commonly described in the canine counterpart is not a consistent finding in affected equine corneas (Hempstead et al., 2014).

The pathophysiology of SCCEDs has not been completely elucidated; however, several morphologic and functional abnormalities are described in dogs with this condition. The epithelium adjacent to the defects exhibits dysmaturation and is poorly attached to the underlying stroma (Fig. 19.15) (Bentley et al., 2001). The basement membrane and adhesion complexes are typically absent or present in small discontinuous segments on the surface of the exposed stroma, and fibronectin is present on the stromal surface (Bentley et al., 2001; Bentley, 2005; Dees et al., 2017; Kirschner, 1990; Ledbetter & Gilger, 2013; Murphy et al., 2001).

A thin, superficial, acellular hyalinized zone in the anterior stroma is common and composed of collagen fibrils admixed with an ill-defined amorphous or fine fibrillar material (Bentley et al., 2001). Stromal fibroplasia, vascularization, and leukocyte infiltrate are variably present. No abnormalities consistent with the basement membrane and anterior stromal dystrophies associated with recurrent erosions in humans have been identified (Bentley et al., 2001). Normal dogs subjected to repeated epithelial debridement for 8 weeks to mimic SCCEDs developed epithelial dysmaturation and nonadherence that was similar, but less extensive, to dogs with SCCEDs (Bentley et al., 2002). The experimentally wounded corneas did not develop the superficial stromal hyalinized zone found in SCCED samples, suggesting the stromal changes in SCCED have a role in the underlying pathophysiology of the disease.

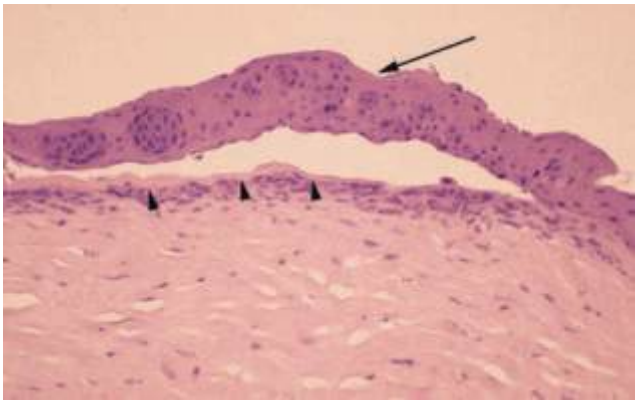


Figure 19.15 Photomicrograph of keratectomy sample from a canine patient with a spontaneous chronic corneal epithelial defect. Note the sheet of poorly attached epithelium that exhibits epithelial dysmaturation, or loss of the normal ordered epithelial architecture (arrow). Also note the superficial stromal hyalinized zone (arrowheads) with underlying stromal fibroplasia. (Hematoxylin and eosin, 200×.) (*Source:* Courtesy of Ophthalmology Optics and Anatomy Laboratories, University of Wisconsin-Madison.)

A dense, abnormal plexus of substance P and calcitonin gene-related peptide immunoreactive nerve fibers is present surrounding the erosion in the corneal stroma of dogs with SCCEDs (Murphy et al., 2001). This altered innervation was not present in the corneas of normal dogs undergoing weekly epithelial debridement for 4 weeks, suggesting these stromal changes were not secondary to the chronic epithelial defect. Substance P levels are elevated in the epithelial cells, but not the tears, of dogs with SCCEDs (Murphy et al., 2001).

Upregulation of MMPs is postulated to cause the basement membrane loss in SCCEDs. Levels of MMP-2 and MMP-9 in keratectomy samples from dogs with SCCEDs and normal dogs that underwent repeated debridement to mimic SCCED were compared (Carter et al., 2007). MMP-2 was not altered from normal in SCCED samples, chronically wounded samples, or acutely wounded samples. MMP-9 levels were similar in keratectomy samples from dogs with SCCEDs and dogs that underwent multiple epithelial debridement procedures (Carter et al., 2007). MMP-9 levels were lower in the SCCED and chronically wounded samples compared with acutely wounded corneas. These results suggest MMP-2 does not play a role in SCCEDs, and alterations in MMP-9 result from the presence of a chronic corneal epithelial defect and are not part of the underlying pathophysiology of SCCEDs.

After corneal wounding in normal dogs, the corneal epithelium develops a migratory phenotype similar to that observed during the process of epithelial-mesenchymal

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transition (Chandler et al., 2007). Epithelial cells at the edge of the defect flatten, with partial dissolution of intracellular junctions, and cells migrate over the wound. Slug, a member of the Snail family of transcription factors, modulates epithelial–mesenchymal transition, and its expression is associated with markers of cell migration including internalization of E-cadherin and β-catenin from cell membranes and enhanced expression of smoothmuscle-specific α-actin, tropomyosin, and MMPs. Slug expression is enhanced and markers of cell migrations are evident at sites of epithelial cell migration in normal dogs with corneal wounds, but not in dogs with SCCEDs (Chandler et al., 2007). TGFβ increases expression of the Snail family of transcription factors and decreased levels of TGFβ is reported in the tears of dogs with SCCEDs (Jurk et al., 2000).

In summary, these studies suggest the stromal alterations (i.e., superficial hyalinized acellular zone, abnormal nerve plexus) are distinct to SCCEDs and play a pathophysiologic role in the disease. The high success rates of treatments (e.g., keratotomy and keratectomy) that breech or remove the abnormal stroma further support this theory. No evidence currently exists that SCCEDs in dogs are associated with basement membrane dystrophies as found in humans, and the older age distribution of dogs with this condition is inconsistent with a dystrophy.

Diagnosis SCCED should be considered in any middle-aged dog with an erosion that has not healed in 1–2 weeks. Studies of SCCED report an average age of 8–9 years (Bentley et al., 2001; Morgan & Abrams, 1994; Murphy et al., 2001; Stanley et al., 1998); therefore, young dogs with nonhealing erosions should be very carefully examined prior to a diagnosis of SCCED. Possible underlying causes for delayed wound healing must be ruled out by thorough examination. Causes for delayed wound healing can include mechanical trauma (e.g., eyelid abnormalities such as masses, entropion, and lagophthalmia), foreign bodies, infection, tear film abnormalities, exposure from poor conformation, facial nerve paralysis, neurotrophic keratitis, exophthalmia or buphthalmia, or corneal edema leading to bullous keratopathy. Addressing these underlying problems should result in resolution of the erosion; if not, or if no underlying causes are present, then a diagnosis of SCCED can be reached if the lesion has a compatible appearance.

SCCEDs have a typical clinical appearance (Fig. 19.16 and Fig. 19.17). A ring of loose epithelium surrounds a SCCED, resulting in a diffuse ring or halo of less-intense fluorescein staining around the defect as fluorescein diffuses underneath the poorly attached epithelium. A SCCED is always superficial, with no stromal loss. Defects are often in the axial or paraxial cornea, although any portion of the cornea may be affected. If corneal edema is present, it is mild and confined to the area of the defect. Severe, diffuse corneal edema suggests that the underlying cause is corneal edema

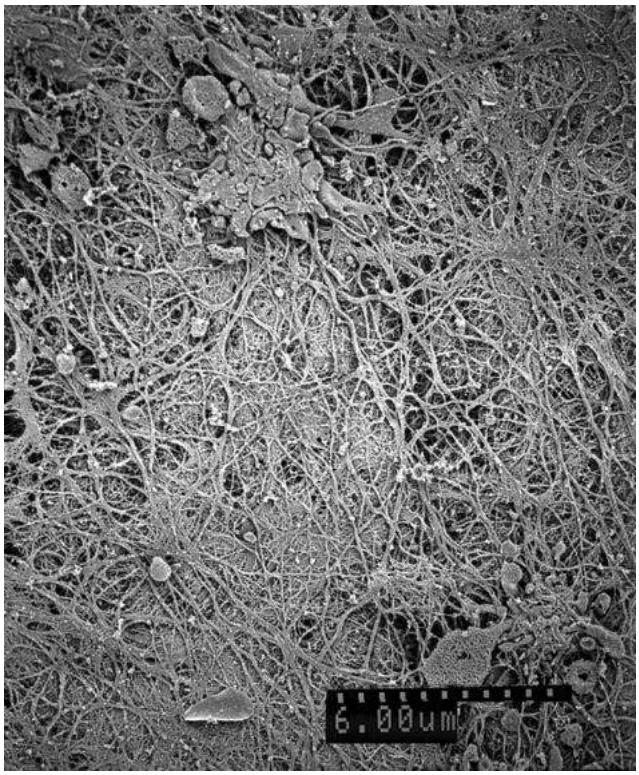


Figure 19.16 Scanning electron micrograph of a keratectomy sample from a canine patient with a spontaneous chronic corneal epithelial defect. Note the bare stromal fibrils, demonstrating loss of basement membrane in the area of the defect. (*Source:* Courtesy of Ophthalmology Optics and Anatomy laboratories, University of Wisconsin-Madison.)

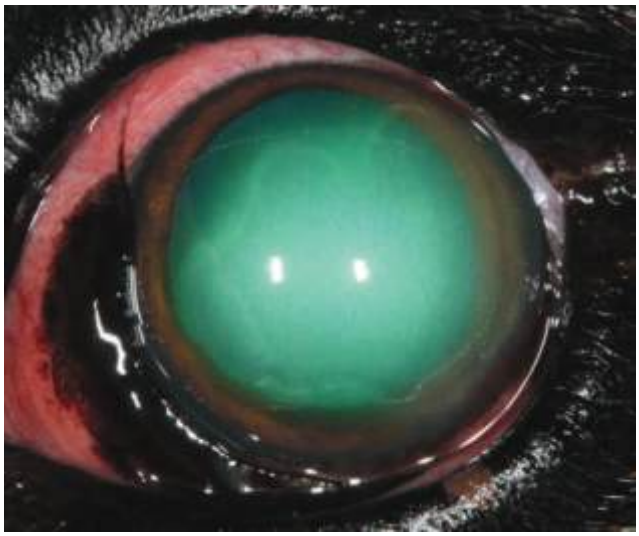


Figure 19.17 A large nonvascularized spontaneous chronic corneal epithelial defect in a 9-year-old Boxer dog. Note the axial location, ring of loose epithelium, and the decrease in intensity of the fluorescein staining as it migrates under the loose epithelium surrounding the defect.

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with secondary bullous keratopathy rather than an SCCED. Varying degrees of vascularization occur in SCCED, with studies reporting 58%–64% of lesions exhibiting neovascularization (Bentley et al., 2001; Murphy et al., 2001). Peripheral lesions are more likely to vascularize whereas central lesions may persist for months with no vascular response. The degree of pain shown by blepharospasm varies between dogs but tends to decrease with chronicity.

Treatment After diagnosis, clients should be educated that multiple treatments are sometimes required to resolve these lesions and recurrence in the same or contralateral eye is possible. Communication of the issues will increase owner compliance and satisfaction. A number of treatment options exist for the treatment of SCCEDs. With all treatments, prophylactic antibiotics should be administered q6h to q8h to prevent secondary infection of the compromised cornea. A cycloplegic (e.g., atropine) to improve comfort and Elizabethan collar to prevent self-trauma are usually indicated. The exact treatments chosen are dependent on clinician preference because few controlled clinical trials for the treatment of SCCEDs have been performed to assist in evidence-based decisions.

A wide variety of medical therapies have been utilized in the therapy of SCCEDs. Treatment with topical polysulfated GAGs resulted in healing of 82% of the treated dogs (Miller, 1996). A separate study evaluated aprotinin, with a resulting healing rate of 33% (Morgan & Abrams, 1994). Both polysulfated GAGs and aprotinin are postulated to work by decreasing proteolytic activity. Only a portion of dogs with SCCEDs, however, demonstrate increased proteolytic activity in their tears; therefore, proteolytic inhibition may be beneficial in only a subset of dogs with SCCEDs (Willeford et al., 1998). Application of EGF led to healing in 80% of dogs in one study (Kirschner et al., 1991). Treatment with topical substance P alone or combined with insulin-like growth factor resulted in healing of erosions in 70% and 75% of dogs, respectively (Murphy et al., 2001). A chondroitin sulfate–antibiotic combination brought about healing in 81% of treated dogs, but treatment had to be continued for 4 weeks, which is longer than many other reported therapies (Ledbetter et al., 2006a). A non-randomized clinical trial evaluating topical treatment with aminocaproic acid, an antiproteolytic agent, resulted in SCCED healing in 94% of eyes after 3 weeks compared with 41% of control eyes treated with gentamicin (Regnier et al., 2005).

Inhibition of MMPs has received attention as a novel therapy for the treatment of dogs with SCCEDs. Doxycycline and tetracycline inhibit MMPs in epithelial cell culture and tears (Ollivier et al., 2007). Recent work, however, showed no difference in MMPs in keratectomy samples from dogs with SCCEDs and dogs that underwent multiple epithelial debridement procedures as a model for SCCEDs (Carter et al., 2007). Specific treatment with MMP inhibitors, therefore, seems unlikely to directly resolve SCCEDs by this mechanism of action.

A randomized, controlled clinical trial evaluated adjunct tetracycline treatment in dogs with SCCED (Chandler et al., 2010). All dogs were treated with manual debridement and grid keratotomy followed by oral doxycycline (5 mg/kg q12h) and topical triple antibiotic (q8h), topical oxytetracycline ophthalmic ointment (q8h) and oral cephalexin (22 mg/kg q12h), or a control group of topical triple antibiotic ointment and oral cephalexin. Dogs treated with topical oxytetracycline ophthalmic ointment healed significantly faster (74% healed within 2 weeks) than dogs in the control group (10% healed within 2 weeks). Dogs treated with oral doxycycline healed more rapidly than dogs in the control group, but the difference was not statistically significant. It was postulated that tetracyclines may be useful for the treatment of SCCEDs by mechanisms unrelated to MMP inhibition. Specifically, upregulation of specific growth factors (e.g., TGFβ and transcription factors) was hypothesized to promote corneal reepithelialization.

The effects of topically applied heterologous serum versus isotonic saline was evaluated in 41 dogs with SCCEDs (Eaton et al., 2017). In this study, all dogs received epithelial debridement (at all visits) and grid keratotomy (at visits 2, 3, and 4) along with topical 0.3% tobramycin q8h and topical 1% atropine daily along with topical serum or saline q8h. Median time to epithelialization was not significantly different between serum or saline treated eyes and was not significantly different between Boxer versus non-Boxer breeds. Regardless of treatment group, dogs with increased vascularization had slower time to reepithelialization.

Topical corticosteroids generally should be avoided in SCCEDs because they decrease the rate of corneal wound healing and inhibit host defense mechanisms. Some clinicians believe that SCCEDs with excessive granulation tissue, however, may benefit from judicious use of topical corticosteroids, with the aim of reducing the formation of vision-obscuring scar tissue. While corticosteroids may accelerate the retreat of granulation tissue and vascular perfusion in the cornea, they do not decrease scar tissue formation in the cornea unless they are used prior to the infiltration of vessels into the cornea in humans and laboratory animals. Alternatively, topical nonsteroidal anti-inflammatory drugs may be used to reduce corneal granulation tissue. Dog with epithelial defects should be monitored very carefully during treatment with topical corticosteroids or nonsteroidal medications.

Most studies of topical medications for the treatment of SCCEDs consist of small, non-randomized, non-masked, and/or uncontrolled clinical trials. The lack of controls and small sample sizes makes interpretation of these results difficult, particularly because statistical power is often too low to detect a meaningful difference between treatment groups. Additionally, most studies of a medical treatment for

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SCCEDs include epithelial debridement, and it is difficult to ascertain whether the debridement or the medical treatment led to healing. Furthermore, many of these treatments are cost prohibitive, unavailable, or require a frequency of application that is difficult for most owners, often making their use impractical in the usual clinical setting.

The most common therapy for the treatment of SCCEDs is epithelial debridement, used alone or in combination with other medical or surgical therapies. After application of topical anesthetic, epithelial debridement is performed using multiple dry cotton-tipped applicators, beginning in the center of the erosion and working out to the periphery with radial strokes (Fig. 19.18). Normal corneal epithelium cannot be removed with a cotton-tipped applicator, so debridement should be continued until only firmly adhered epithelium remains. Debridement can also be performed with corneal burrs, excimer laser spatulas, scalpel blades, spatulas (Kimura and iris), or forceps. Some of these instruments can remove normal epithelium and damage the corneal stroma, so care must be taken to debride appropriately. Typically, debridement can be repeated at 7- to 14-day intervals. Success rates and time to healing vary between studies from 20% in 14 days to 84% in an average of 23 days (Kirschner et al., 1991; Morgan & Abrams, 1994; Stanley et al., 1998). The number of debridement surgeries, the time between procedures and examinations, and the number of dogs differed between studies, which may contribute to the wide range of success rates. All of these were small, uncontrolled trials, but combining the success rates results in an overall success rate of approximately 50%. It was noted that adding a soft contact lens or third eyelid flap increased healing rates after debridement to 58% and 64%, respectively (Morgan & Abrams, 1994). Third eyelid flaps and soft contact lenses may provide mechanical protection to the healing cornea from trauma and eyelid rubbing.

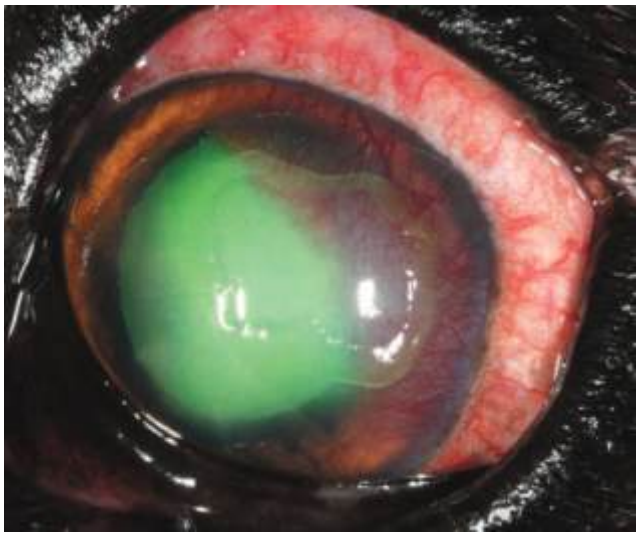


Figure 19.18 A vascularized spontaneous chronic corneal epithelial defect in a 10-year-old Boxer dog. Note the peripheral location of the erosion, superficial corneal vascularization, ring of loose epithelium surrounding the defect, and fluorescein leakage under surrounding loose epithelium.

Superficial corneal debridement performed with a diamond burr was described in dogs with SCCEDs and compared favorably with treatment by grid keratotomy (Davis & Gionfriddo, 2011; Gosling et al., 2013; Sila et al., 2009). Although uncommon (three of 100 dogs), keratomalacia was a complication in dogs treated with the diamond burr (Sila et al., 2009). Histologic evaluation of a specific protocol for diamond burr corneal debridement in normal dogs with experimental corneal wounds determined the instrument does not create defects beyond the epithelial basement membrane (da Silva et al., 2011).

Making small punctures or linear scratches in the affected cornea is another common therapy for SCCEDs. Many different variations and names exist for these procedures, including punctate keratotomy, anterior stromal puncture (ASP), multiple punctate keratotomy, multifocal superficial punctate keratotomy, and grid keratotomy. All of these procedures use the same principle to improve healing by producing anterior stromal adhesions and can be grouped together. Immunohistochemical studies after ASP demonstrate increased ECM components, including collagen IV and laminin, which are important in epithelial adhesion and often absent in SCCED cases (Bentley et al., 2001; Hsu et al., 1993).

To perform ASP or any variant thereof, a 25-gauge needle is grasped with a hemostat so that the tip of the needle is barely exposed. This improves control of penetration depth. A commercially available needle with a small bend in the tip to control depth is also available. After administration of topical anesthetic, the epithelium is debrided prior to performing the procedure to determine the extent of corneal involvement and the area requiring treatment. In an ASP or punctate keratotomy, multiple small punctures are placed 0.5–1.0 mm apart over the entire affected cornea and extending 0.5–1.0 mm into the normal surrounding cornea (Fig. 19.19). In a grid keratotomy, small lines are placed in a crosshatched pattern across the surface of the cornea and extending approximately 1.0 mm into unaffected surrounding cornea. ASP or grid keratotomy can be repeated at 7- to 14-day intervals. Multiple uncontrolled clinical studies of these procedures found success rates ranging from 68% using ASP to 87% using a grid keratotomy (Champagne & Munger, 1992; Morgan & Abrams, 1994; Stanley et al., 1998). Combining success rates from these various studies leads to a success rate of approximately 80%. A contact lens or third eyelid flap may be used after these procedures.

One study found that 12 of 12 eyes healed after treatment with grid keratotomy followed by a third eyelid flap (Stanley et al., 1998). In a study evaluating SCCEDs in Boxers, treatment by linear grid keratotomy combined with therapeutic

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Figure 19.19 Epithelial debridement of a spontaneous chronic corneal epithelial defect in a 9-year-old Golden Retriever. One cotton-tipped applicator is used to remove loose epithelium, while a second cotton-tipped applicator is used to prevent prolapse of the third eyelid.

soft contact lens showed that the use of bandage contact lenses (BCL, Acrivet™) had a statistically significant decrease in median healing time (7 days) compared with those without contact lenses (10 days). There was no difference in subjective comfort score between the two groups (Wooff et al., 2015). In a European study, polyxylon BCL (AcriVet Pat D™, S&V Technologies AG, Acrivet Veterinary Division, Berlin, Germany) showed healing times of 14 days or fewer compared with a mean of 36 days in animals not receiving a BCL (Grinninger et al., 2015). Blepharospasm resolved in 4 days after debridement with BCL use, compared with 30 days in the group without a BCL.

A larger study of 237 dogs designed to evaluate the effect of BCL wear and type of postoperative medical treatment on corneal healing rates in dogs after debridement showed the effectiveness of BCL use and ofloxacin (Dees et al., 2017). In this study, overall BCL retention rate varied between contact lens brands.

Superficial keratectomy can also be used for the treatment of SCCEDs. Superficial keratectomy works by completely removing the abnormal superficial layer of stroma and allowing reformation of normal epithelial adhesion complexes. Unlike the other procedures, the success rate is consistently 100% across studies, with healing resulting in a relatively short time period (Peiffer et al., 1976a; Stanley et al., 1998). This high success rate implies that the stromal alterations are a critical part of the pathophysiology of this disease. Although superficial keratectomy results in rapid resolution, it is not always recommended as the first line of therapy because of the need for general anesthesia, increased cost, and increased likelihood of corneal scarring (Whitley & Gilger, 1999).

Other small case series report alternative therapies for the treatment of SCCEDs. Thermal cautery resulted in healing in nine of nine eyes in 2.1 weeks (Bentley et al., 2004). Similar to the other procedures described, thermal cautery alters the abnormal superficial stroma, allowing normal epithelial wound healing to occur. This procedure has the potential to result in increased corneal scarring if not performed carefully, so it is generally reserved for cases that do not respond to other therapies. Thermal cautery is a reasonable option for dogs that are refractory to other treatments and cannot be anesthetized, because it can be performed under sedation.

Cyanoacrylate tissue adhesive has been used as a treatment for nonhealing erosions and SCCEDs. In one study, non-healing erosions were present for a variety of reasons, but 20 eyes healed in a mean time of 3.4 weeks (range 2–8 weeks) after cyanoacrylate therapy (Bromberg, 2002). Cyanoacrylate can be applied using a 1-mL syringe in conscious dogs, or it can be applied in anesthetized animals using a small-gauge needle. A contact lens after application improves comfort and aids in cyanoacrylate retention. This procedure aids healing but appears to have a longer healing time than ASP, grid keratotomy, or superficial keratectomy.

Stromal Corneal Ulcers

Ulcerative keratitis that extends into the corneal stroma usually involves a secondary microbial infection that initiates or participates in the stromal destruction. Less commonly, traumatic injuries can result in a wound that extends into the deeper stroma. Generally, any visible defect in the corneal surface suggests possible stromal involvement (Fig. 19.20) because most ulcers involving only the epithelium are not readily visible (except possibly for indolent corneal ulcers) and require fluorescein staining for definitive diagnosis. Any ulcer with a suspected stromal defect should be cultured and corneal scrapings for cytologic examination performed, prior to instillation of fluorescein or other topical substances, to determine the underlying etiology, because of the high likelihood of microbial infection. These diagnostic tests are performed first to maximize growth of the organisms on culture and to avoid altering surface organisms or cell types.

Stromal ulcers may be divided into progressive and non-progressive types. Non-progressive deep ulcers can be managed medically, similar to superficial ulcers, with treatment directed by the results of culture and susceptibility testing. Surgical intervention is indicated in deep corneal ulceration (i.e., when depth of the corneal lesion is 50% of the corneal thickness or deeper). Surgical procedures most commonly employed in these cases include grafts from conjunctiva, amniotic membrane, bovine pericardium, or porcine urinary bladder, cornea, or synthetic or bioengineered grafts (Barros & Safatle, 2000; Barros et al., 1998, 2005; Blogg et al., 1989; Brightman et al., 1989; Dice et al., 1973; Hacker, 1991; Hakanson & Merideth, 1987; Hakanson et al., 1987; Hansen & Guandalini, 1999; Keller et al., 1973; Kuhns, 1979; Lewin,

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Figure 19.20 Anterior stromal puncture performed for treatment of a spontaneous chronic corneal epithelial defect in a dog. A commercially available hypodermic needle with a small bend at the tip to control depth of penetration is used for the procedure shown here. A cotton-tipped applicator is used to prevent prolapse of the third eyelid.



Figure 19.21 Central, deep stromal corneal ulcer in a brachycephalic dog.

1999; Mueller, 1968; Mueller & Formston, 1969; Parshall, 1973; Scagliotti, 1988).

Progressive deep stromal ulcers in the dog are potentially vision- and globe-threatening, and therapy must be aggressive. Antibiotic selection is frequently made on the basis of cytology, culture, and susceptibility test results. Topical 1% atropine is administered to minimize the discomfort from ciliary muscle spasm and to prevent synechiae formation. If rapid stromal loss or melting are present, intensive topical antibiotic therapy (every 1–2 hours) is indicated, and bactericidal antibiotics with a spectrum that includes Gram-negative rods, such as *Pseudomonas aeruginosa*, and Gram-positive cocci, such as *Staphylococcus* and *Strepotococcus* spp. should be empirically selected while culture results are pending. Monotherapy with a broad-spectrum antimicrobial such as a late-generation fluoroquinolone (e.g., moxifloxacin, gatifloxacin) or combination therapy with an early-generation fluoroquinolone (e.g., ciprofloxacin, ofloxacin) or aminoglycoside (e.g., tobramycin), in addition to a first-generation cephalosporin (e.g., cefazolin) or triple antibiotic, are good empiric choices (Ledbetter et al., 2007a; Tolar et al., 2006; Varges et al., 2009). After culture and susceptibility testing results are received, the antibiotic regimen can be altered to more specifically target the infectious agent. Topical anticollagenase–antiproteinase preparations are also strongly recommended in cases of progressive ulcerative keratitis.

Corneal Tissue Adhesives

Corneal tissue adhesives may also be used as a non-surgical therapy for nonhealing corneal ulcers. Isobutyl cyanoacrylate tissue adhesive has been used in treatment of deep stromal ulcers, descemetoceles, small perforations, lacerations, and refractory corneal ulcers in the dog (Fig. 19.21) (Bromberg, 2002; Kern, 1990; Watté et al., 2004). The procedure for proper application of the tissue adhesive can be difficult and involves use of topical anesthesia (if general anesthesia is not used); debridement of the defect (as necessary and judiciously); drying of the site with a cotton-tipped swab, cellulose sponge, or a warm-air (i.e., hair) dryer; application of a thin layer of tissue adhesive through a 25- to 30-gauge needle; and prevention of blinking for 15–60 seconds while the cyanoacrylate solidifies. Care must be taken to apply a minimal amount of adhesive.

Tissue adhesives are recommended only as an alternative treatment for use in small corneal lesions (diameter <2 mm) (Erdey et al., 1991; Leahey et al., 1993). Tissue adhesives may have antibacterial effects and help to decrease stromal necrosis. A transient increase in discomfort may occur after adhesive application. Topical medications are still required after placement of the adhesive and should be chosen on the basis of cytologic and culture results. Once the lesion reepithelializes, the adhesive is usually spontaneously extruded from the cornea. Thick or uneven application of adhesive will result in premature loss and re-ulceration. Adhesive application is usually recommended in those animals not sufficiently healthy to undergo general anesthesia for placement of conjunctival grafts or keratoplasty. Cornea adhesive is generally not recommended for corneal perforations or descemetoceles because of possible ocular toxicity (Markowitz et al., 1995).

Conjunctival Flaps and Grafts

The surgical procedure most commonly used for chronic, infected, or progressive corneal ulcers is a conjunctival flap or graft. Conjunctival flaps provide corneal support, provide fibrovascular tissue to fill the corneal defects, and bring a blood supply (as well as blood-associated immune components, systemic antibiotics, and natural anticollagenases

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[e.g., α_2-macroglobulin]) to the lesion (Hakanson & Merideth, 1987; Hakanson et al., 1987). Because partial conjunctival flaps cover only a small area of the normal cornea, the clinician can visualize much of the cornea and anterior chamber, which in turn allows continuous examination of these structures to monitor ulcer progression and possible anterior uveitis. Having only a small portion of the cornea covered may also allow the animal to continue to be visual. This technique has distinct advantages over other types of surgical procedures once used for corneal ulcers, which are now considered to be archaic, such as third eyelid flaps. Third eyelid flaps are especially contraindicated for most corneal ulcers because they do not provide a blood supply or fibrovascular tissues to the ulcer, they make it essentially impossible to monitor disease progression, and they cover normal cornea. Furthermore, third eyelid flaps impede the penetration of topical medications and retain inflammatory exudate adjacent to the lesion.

Available types of conjunctival grafts include the total or 360-degree conjunctival graft (Gunderson flap), the bridge or bipedicle, the hood, and the pedicle conjunctival graft. Conjunctival grafts consist of thin conjunctival tissue transposed onto the cornea to cover the lesion. Conjunctival grafts are generally harvested from adjacent bulbar conjunctiva; however, the tarsal conjunctiva can be used. The disadvantage of a tarsoconjunctival graft is that the eyelid is mobile, and some tension can be applied to the flap by movement of the eyelids, thereby leading to a possible higher rate of dehiscence. The bulbar conjunctival flap moves with the eye; thus, no tension is applied to the flap itself.

With all types of conjunctival flaps, it is important that the corneal graft bed and ulcer be properly prepared. The recipient bed for the conjunctival graft is prepared by debriding the lesion, thereby removing loose epithelium and devitalized corneal tissue (Hakanson & Merideth, 1987). Great care should be taken to prevent corneal perforation during this debridement. In general, conjunctival grafts should not cover intact corneal epithelium (which will impair adhesion of the graft), except under the pedicle portion of the graft. Covered corneal epithelium may migrate under the conjunctival graft, possibly leading to dehiscence. Therefore, to prevent epithelial down-growth, the corneal epithelium should be gently debrided for approximately 0.5–1 mm surrounding the corneal lesion.

Total (360-Degree) Conjunctival Flap The total or 360-degree conjunctival flap (Gunderson flap) covers the entire cornea and is rarely indicated. It has been described in cases when the ulcerative keratitis or other lesion involves the entire cornea (Pumphrey et al., 2011). There are two types of 360-degree conjunctival grafts described. The first type requires a 360-degree conjunctival incision 8–10 mm behind the limbus and reflection of the graft over the cornea (i.e., limbus-based). The conjunctiva is then sutured to itself in the center of the cornea in a linear or purse-string-like fashion. This type of graft is not recommended because it causes epithelial-to-epithelial contact and does not readily allow vascularization of the lesion.

The second type of 360-degree conjunctival graft is begun by making a 360-degree conjunctival incision immediately adjacent to the limbus, which undermines the conjunctiva and advances it to the center of the cornea. As with the first type of graft, the second is closed by suturing it to itself, not to the cornea (Fig. 19.22). The 360-degree conjunctival graft is easy to perform, and it is effective for large corneal lesions. It does, however, cover the entire cornea, which decreases vision and prevents monitoring of the corneal lesion or inflammation within the eye and results in a very large, probably blinding scar. If the goal is to only salvage the globe (and not vision), then this graft should be considered. The flap can be trimmed around the original ulcer and adherent area, to provide peripheral vision after healing.

Bridge or Bipedicle Graft The bridge or bipedicle graft is a linear graft attached to the conjunctiva at two sites. This graft is generally indicated in long, linear corneal lesions, such as corneal lacerations that require conjunctival graft covering after direct suturing or in ulcers that may require additional vascularization, such as some central corneal lesions. These grafts are begun by incising the conjunctiva from the limbus for approximately 180 degrees both adjacent and parallel to the linear corneal lesion (Fig. 19.23). This area is extensively undermined, and the underlying fibrous tissue is removed. A second conjunctival incision is made 5–8 mm peripheral and parallel to the original conjunctival incision, thus creating a "bridge" of conjunctiva. This bridge is then advanced over the lesion and sutured using simple, interrupted sutures in the cornea around the lesion (see

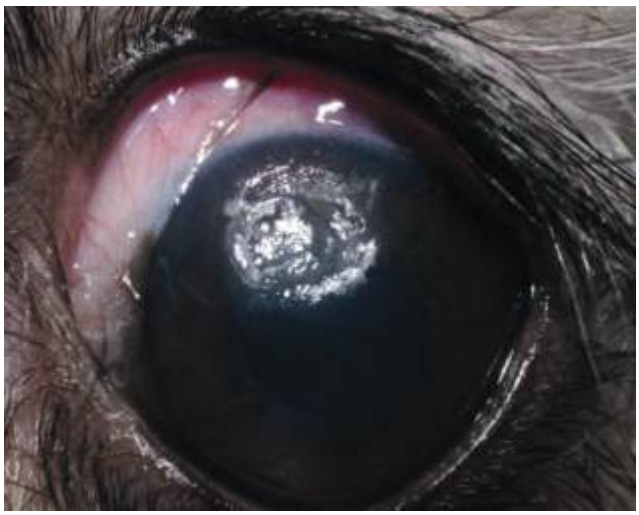


Figure 19.22 Corneal ulcer after topical application of cyanoacrylate tissue adhesive.

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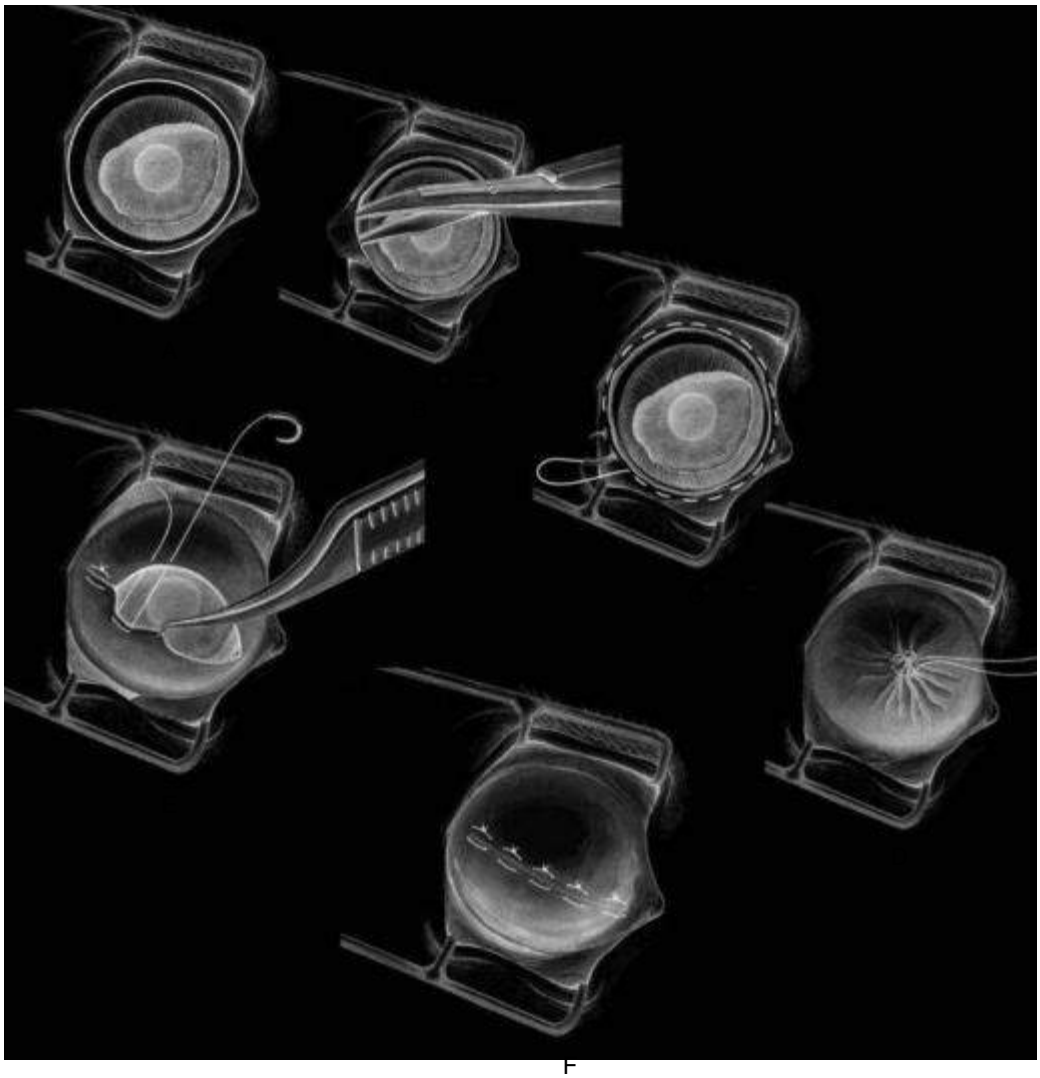


Figure 19.23 Total or 360-degree conjunctival graft/flap. This flap is started by making a 360-degree conjunctival incision immediately adjacent to the limbus, which undermines the conjunctiva and advances it to the center of the cornea (**A** and **B**). The conjunctival graft is then closed by suturing it to itself, and not to the cornea, either in a purse-string fashion (**C** and **D**) or in a horizontal mattress pattern (**E** and **F**).

Fig. 19.23). The original graft-harvesting site is closed by apposing the remaining conjunctiva with a simple continuous suture. The advantage of this procedure is that it provides exquisite blood supply to long, linear lesions of the cornea. Whether bridge grafts are more successful than pedicle grafts in these types of lesions is not definitively known, but pedicle grafts are easier to perform and rarely fail when used in large or long, linear lesions (Hakanson & Merideth, 1987; Hakanson et al., 1987).

Hood (180-Degree) Conjunctival Flap The hood or 180-degree flap is indicated for peripheral corneal lesions. The conjunctiva adjacent to the lesion is cut from the limbus and undermined (Fig. 19.24), and the graft is then advanced to cover the lesion and sutured in place, generally with simple, interrupted sutures. The combination of superficial keratectomy and a conjunctival advancement hood flap has been used successfully in the treatment and management of dogs with bullous keratopathy (Horikawa et al., 2016). Mean CCT measured by FD-OCT was $1163 \pm 290\,\mu m$ preoperatively and significantly decreased to $795 \pm 197\,\mu m$, $869 \pm 190\,\mu m$ and $969 \pm 162\,\mu m$ at 2.2, 6.8, and 12.3 months, respectively. Keratocyte and endothelial cell densities, measured by IVCM did not significantly change over time. Larger conjunctival flaps covering a greater percentage of the cornea, such as hood flaps, may result in stabilization of the corneal thickness over a longer time period. Owners also reported a significant improvement in vision and corneal cloudiness at 6.8 and 12.3 months.

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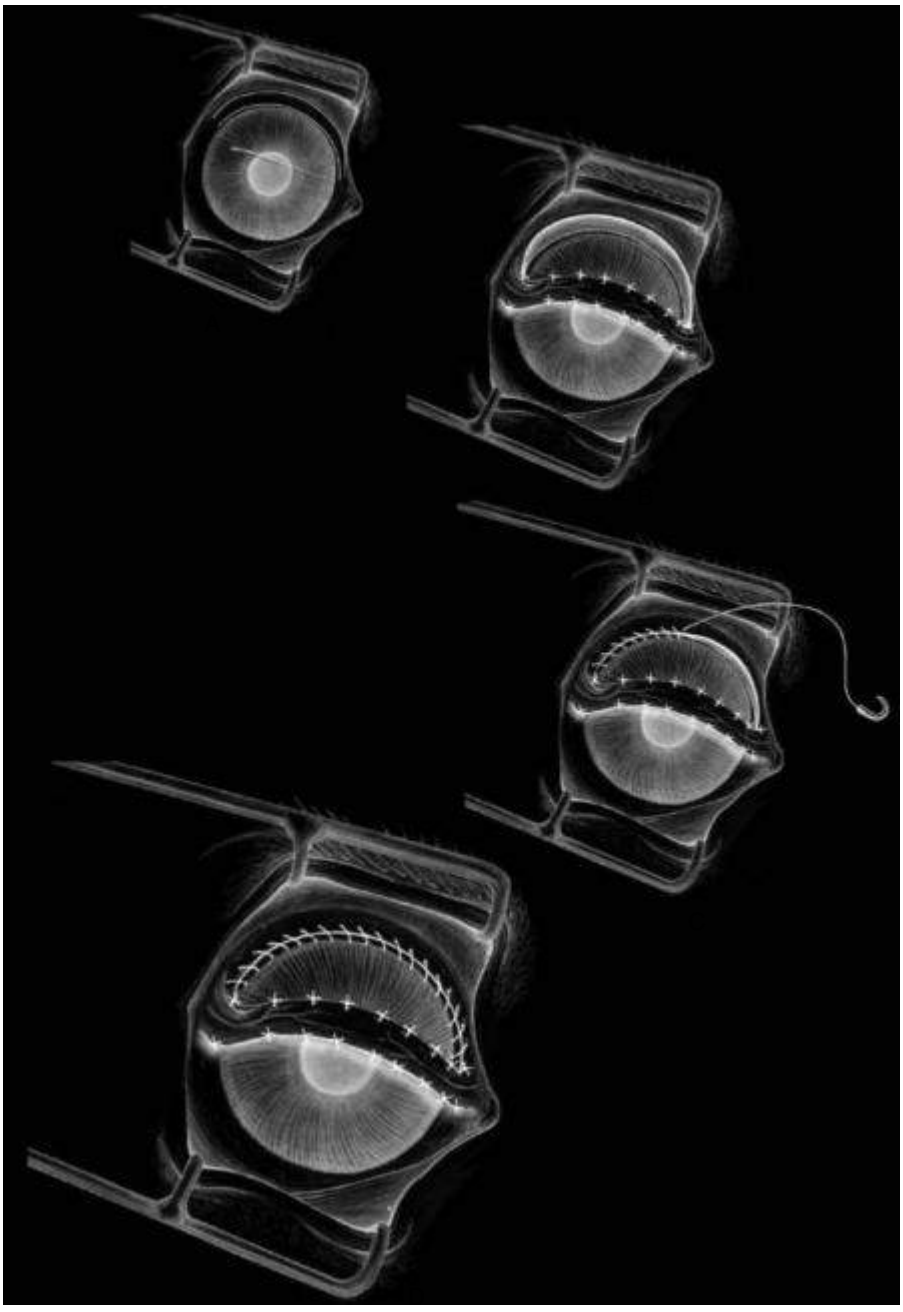


Figure 19.24 Bridge or bipedicle conjunctival graft. **A.** The conjunctiva is excised from the limbus for approximately 180 degrees both adjacent and parallel to the linear corneal lesion. This area is extensively undermined, and the underlying fibrous tissue is removed. A second conjunctival incision is made 5–8 mm peripheral and parallel to the original conjunctival incision, thus creating a "bridge" of conjunctiva. **B** and **C.** The bridge is advanced over the lesion and then sutured, using simple, interrupted sutures into the cornea around the lesion. **D.** The original graft-harvesting site is closed by opposing the remaining conjunctiva with a simple, continuous suture.

Pedicle Conjunctival Graft The pedicle or rotational graft (Hakanson & Merideth, 1987; Hakanson et al., 1987; Holmberg, 1981) is probably the most useful and versatile conjunctival graft. The base of the pedicle graft should be directed toward the area of the limbus nearest to the lesion. It is also suggested that the graft be within 45 degrees of the vertical to minimize the vascular and traction effects of the eyelids on the graft (Hakanson & Merideth, 1987; Hakanson et al., 1987). Once the location of the base is determined, a site 1.0–1.5 cm temporal to the base is located, which will be sited where the graft is initiated (Fig. 19.25). A small slit is cut in the conjunctiva perpendicular to the limbus, and through this slit the entire conjunctival

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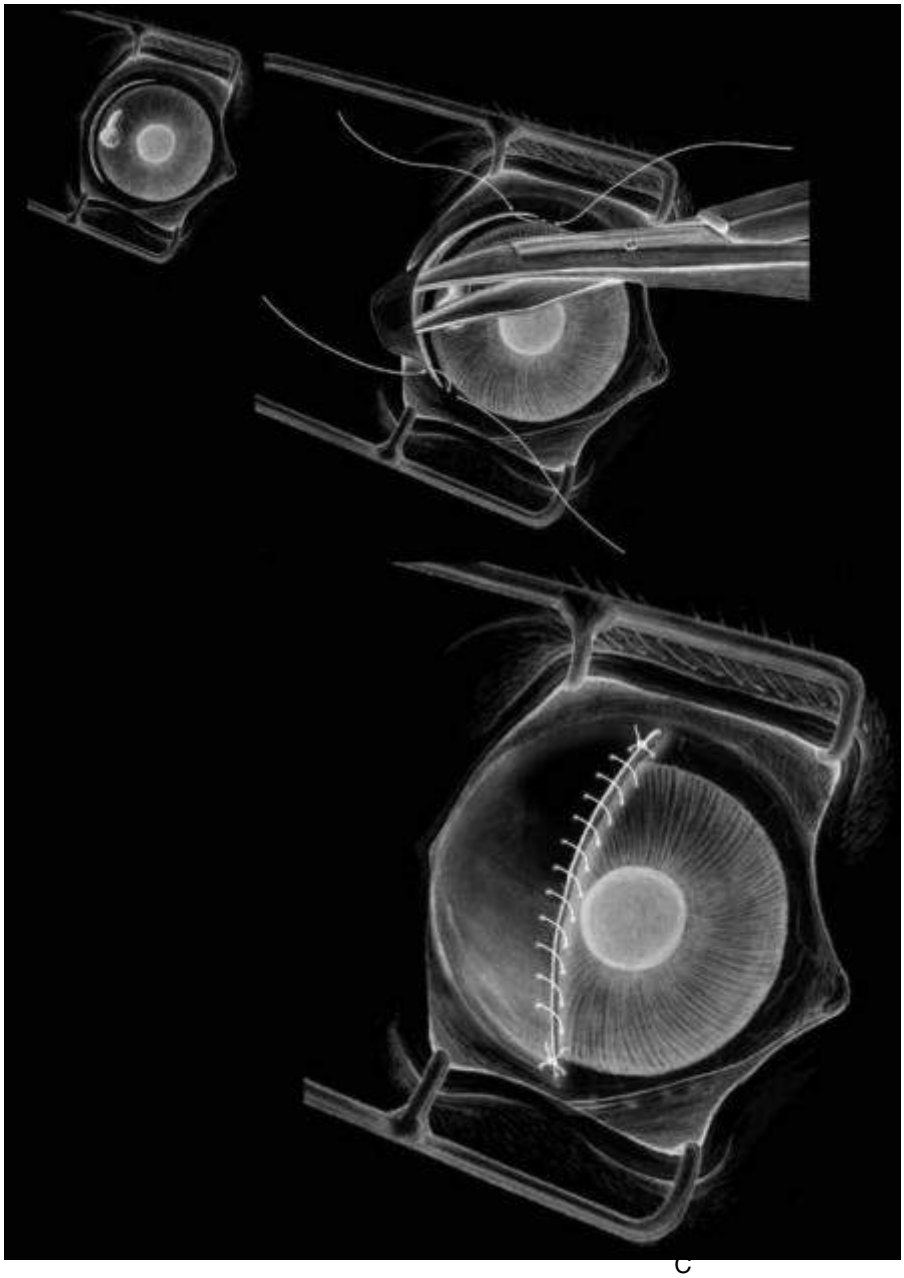


Figure 19.25 Hood or 180-degree conjunctival graft. **A** and **B.** The conjunctiva immediately adjacent to the lesion is cut from the limbus and undermined. **C.** The graft is advanced to cover the lesion and is sutured in place, generally with two or four simple, interrupted sutures or a continuous suture pattern.

graft site is undermined using blunt dissection (see Fig. 19.25). The underlying fibrous tissue (i.e., Tenon's capsule) should be freed from the overlying conjunctiva so that the conjunctiva appears transparent. Next, two parallel cuts are made to create a strip of conjunctiva, which is rotated to cover the corneal lesion. The flap is then sutured to the cornea with simple, interrupted sutures of 7-0 to 9-0 polyglactin 910™ or nylon. The sutures are placed first at the distal end of the graft and then 1.0–1.5 mm apart (see Fig. 19.25**).** To prevent disruption of the blood supply, sutures are not placed within the pedicle portion of the graft or at the proximal portion of the lesion (Hakanson & Merideth, 1987; Hakanson et al., 1987). The graft-harvest site on the bulbar conjunctiva may be closed using a continuous suture of 7-0 to 9-0 polyglactin 910™.

Conjunctival tissue will adhere to the corneal lesion and epithelialization surrounding the graft, but they will not adhere underneath the conjunctiva where there is normal corneal epithelium. Four to 12 weeks after placement of the

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grafts, the blood supply may be interrupted by cutting the base of the pedicle flap at the limbus. This can usually be performed with use of topical anesthesia and Westcott or Stevens tenotomy scissors (Fig. 19.26). Eliminating the blood supply will allow the conjunctival graft to recede and lessen the resulting corneal scar.

Island Conjunctival Graft A conjunctival free island graft is a modified conjunctival graft in which the blood supply is severed from the outset. These grafts are essentially a transplant of conjunctival tissue to the cornea, and their use has been described in deep corneal lesions or corneal perforations (Kuhns, 1979; Scagliotti, 1988). The donor site can be either the tarsal (Scagliotti, 1988) or bulbar conjunctiva (Kuhns, 1979). The conjunctiva is undermined and excised from the donor site and then transposed to cover the corneal lesion. It is important that the epithelial site remains external (upright) to allow proper attachment of the graft to the lesion. Simple interrupted or a combination of simple interrupted and continuous sutures are used to secure the graft to the cornea (Fig. 19.27). The graft usually becomes revascularized within 3–5 days depending on the amount of corneal vasculature present near the lesion before surgery (Scagliotti, 1988). The success of this surgical procedure may depend on the regained vascularity of the lesion; therefore, lesions without corneal vascularization may heal better with a conjunctival pedicle flap. The advantages of the free island grafting procedure are that: tissue is readily available; a watertight, 360-degree closure can be made; and the graft does not require trimming after surgery, as do conjunctival flaps that require excision of their blood supply after surgery, such as conjunctival pedicle or bridge flaps.

Complications The most common complication from any type of conjunctival grafting procedure is dehiscence of the graft from the corneal lesion. This may occur because the corneal lesion is progressing, worsening, and damaging the cornea at the points where sutures secure the graft. Excessive tension on the graft or allowing a significant portion of the fibrous Tenon's capsule to remain attached to the graft may result in premature dehiscence of the graft. Proper suture placement in healthy cornea (after adequate debridement of diseased cornea and surrounding corneal epithelium) using a thin, conjunctival graft and concurrent, appropriate medical therapy, will greatly decrease complications after conjunctival graft surgery.

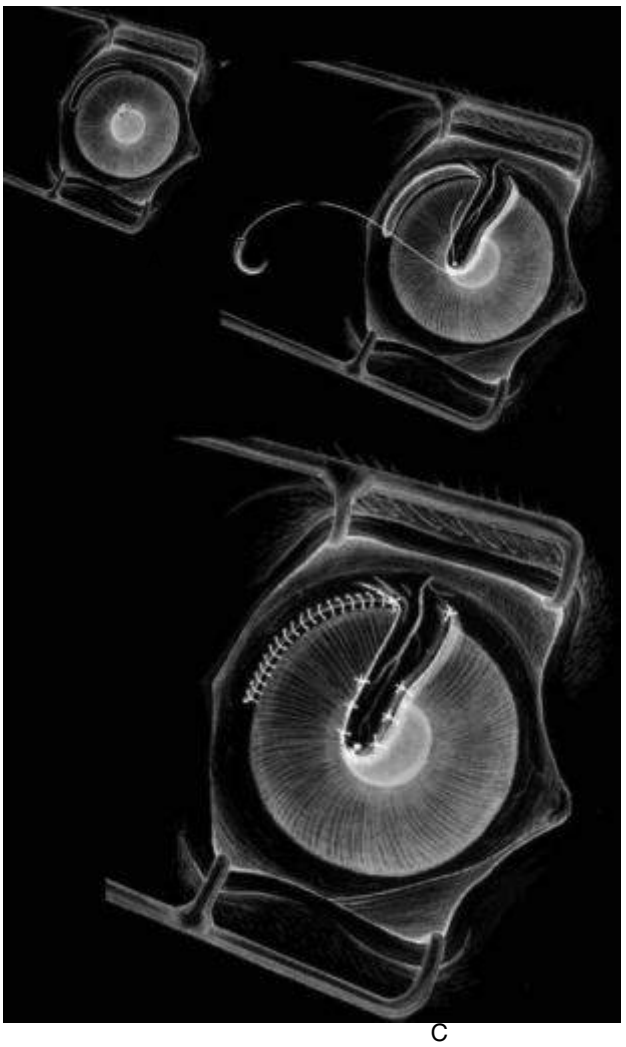


Figure 19.26 Pedicle conjunctival graft. **A.** The base of the pedicle flap should be directed toward the area of the limbus nearest to the lesion. Once the location of the base is determined, a site 1.0–1.5 cm temporal to the base is located, at which the flap will be initiated. Through a small slit in the conjunctiva, the entire conjunctival flap site is undermined using blunt dissection. Two parallel cuts are then made to create a strip of conjunctiva. **B.** The strip of conjunctiva is rotated to cover the corneal lesion. The flap is sutured to the cornea with simple, interrupted sutures of 7-0 to 9-0 polyglactin 910 or nylon. **C.** The sutures are placed first at the distal end of the flap and then 1.0–1.5 mm apart.

Amniotic Membranes

Amniotic membranes have been described for treatment of corneas after superficial keratectomy and bullous keratopathy (Barros et al., 2005), and for corneal reconstruction after removal of an inclusion cyst (Choi et al., 2010) and dermoids (Kalpravidh et al., 2009) in dogs (Fig. 19.28). Amniotic membranes have also been used as grafting material after full-thickness keratotomy, both experimentally (Barros et al., 1998) and clinically (Barros et al., 2005). Benefits of amnion include its antifibrotic, antiangiogenic, antiprotease, and anti-inflammatory properties (Lassaline et al., 2005).

Indications for the use of amniotic membrane transplants are steadily growing and include grafting to replace diseased, missing or excised tissue, patching to support diseased tissue during the healing process, and as a substrate for the expansion of epithelial cells for transplantation to the cornea. Sections of amnion are collected aseptically and prepared by

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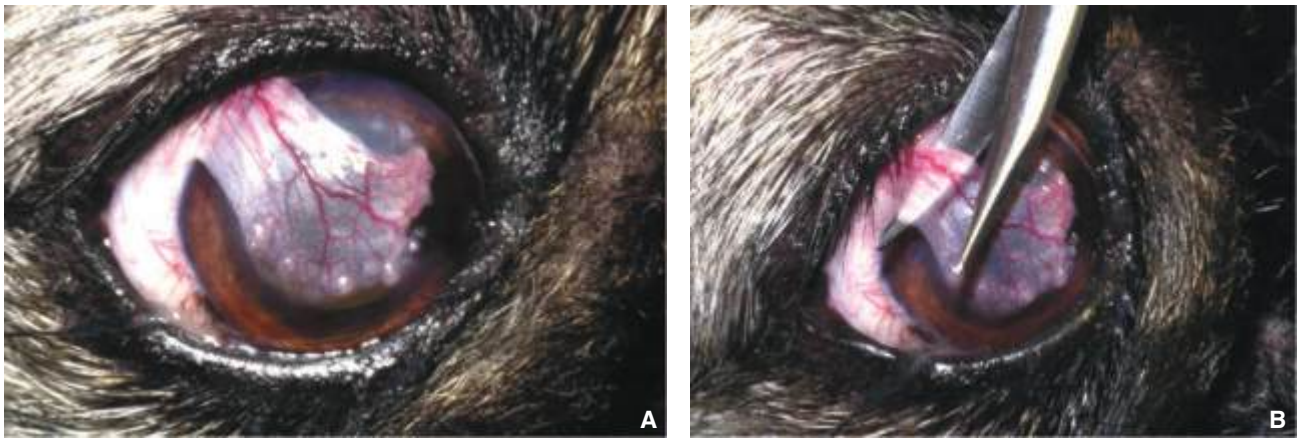


Figure 19.27 After the corneal ulcer is healed, the blood supply to the conjunctival graft can be trimmed (**A**). After applying topical anesthetic, scissors can be placed under the pedicle portion of the graft, which is not adhered to the underlying normal corneal epithelium (**B**).

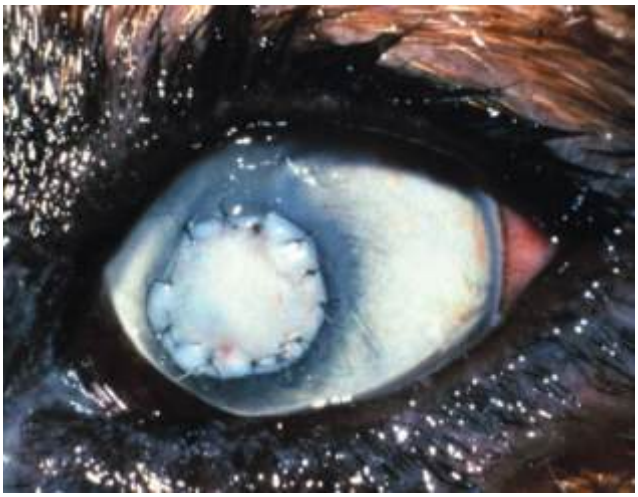


Figure 19.28 Conjunctival island graft.

separating the allantoamnion from the allantochorion and rinsing with sterile saline containing antibiotics (Lassaline et al., 2005; Plummer et al., 2009). The amnion is then separated from the allantois by blunt dissection, sectioned, and placed on a nitrocellulose membrane in Delbecco's modified Eagle medium with glycerol, penicillin, streptomycin, neomycin, and amphotericin B. It is stored at minus 80 °C and thawed as needed (Lassaline et al., 2005). In a series of three horses, one or multiple layers of amnion were sutured to the surface of the cornea in eyes with severe infectious keratomalacia (Lassaline et al., 2005). The amnion sloughed over a 4- to 6-week period and successfully preserved the eyes in these three cases (Lassaline et al., 2005). In another series of 58 equine cases that received amniotic membrane transplants for melting ulcers, bullous keratopathy, after keratectomy or in conjunction with a corneal transplant, 53 eyes retained functional vision and had subjectively less scar than they might have had without surgical intervention or with conjunctival or corneal grafting (Plummer, et al., 2009). Amnion has also been secured to the cornea using fibrin glue, thus possibly decreasing scarring associated with sutures (Pirouzian et al., 2011; Tsujita et al., 2012).

Few controlled studies comparing amnionic membrane therapy to other standard therapies have been performed. In one study, a prospective, randomized, controlled clinical trial of 100 human patients with acute ocular burns, patients with moderate ocular burns treated with amniotic membrane transplantation had significantly better epithelial wound healing than those treated with standard medical therapy alone. However, there was no overall difference in the final visual outcome, symblepharon formation, corneal clarity, and vascularization with or without amniotic membrane transplantation (Tandon et al., 2011). In another study, bovine freeze-dried amnionic membrane therapy was compared with controls, third eyelid flaps, and use of contact lenses in an experimentally induced central superficial corneal ulcer in Shih Tzu dogs (Kim et al., 2009). The epithelial healing rate and epithelial cell proliferation was higher in eyes treated with amnion compared with the other treatments (Kim et al., 2009). Further study is warranted to determine the clinical effect and overall success of amnion membrane and amnion homogenate therapy for corneal disease in dogs.

Descemetoceles and Corneal Perforations

A descemetocele is a deep corneal lesion in which the corneal epithelium and stroma are completely destroyed, leaving a lesion lined only by Descemet's membrane and corneal endothelium (Fig. 19.29). Descemet's membrane is a tough, elastic membrane, but it is only 3–12 µm thick and thus easily ruptured. Once this final barrier is breached, a full-thickness lesion occurs, aqueous humor is lost, and iris prolapse may occur. Contamination of the anterior chamber also

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Figure 19.29 **A.** Melting corneal ulcer in a dog. **B.** One week after placement of equine amnion with mild sloughing of the amnion. **C.** Two weeks after placement of equine amnion with characteristic sloughing of the membrane. **D.** Five months after placement of the amnionic graft. (*Source:* Courtesy of Dennis Brooks and Stacy Andrew.)

occurs after rupture of Descemet's membrane, which may lead to endophthalmitis and a much poorer prognosis for saving the eye as well as for vision. Descemetoceles and full-thickness corneal perforations can develop from the progression of deep corneal ulcers or from trauma. However, all deep corneal lesions should be considered infected, and preoperative bacterial and fungal culture and sensitivity tests should always be performed, along with conjunctival cytology, to help direct medical therapy after surgery.

Because of the fragile nature of descemetoceles as well as the potential for infection and intraocular inflammatory damage with perforations, repair of the lesions should be considered a surgical emergency. Before surgery, the posterior segment of the affected eye should be assessed (or attempted) to help determine the prognosis for vision. Posterior segment examination may be possible in descemetoceles, but it is usually difficult with perforations and iridal prolapses. In cases when ophthalmoscopy is not possible, evaluation of consensual pupillary light reflex and the dazzle reflex may provide some information regarding the integrity of the posterior segment. Presence of consensual pupillary light and dazzle reflexes is a positive clinical sign but does not ensure a normal posterior segment. For example, eyes with retinal detachments may have both consensual pupillary light and dazzle reflexes early in the disease process. Absence of consensual pupillary light and dazzle reflexes, however, indicates a poor prognosis, and alternatives to surgical repair (i.e., enucleation) should be

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considered in these cases. Ocular ultrasonography can also be used to assess posterior segment damage with corneal perforations, but it is important that the ultrasound coupling gel does not get into the wound or anterior chamber, which may cause additional inflammation. It is recommended that sterile methoylcellulose-based coupling gel be used instead of standard ultrasonography gel to minimize contamination and irritation. If ultrasonography of the injured eye is attempted, the animal should be sedated or anesthetized so that movement of the animal does not further damage the eye, and a standoff pad (e.g., solid-gel standoff pad or a water-filled balloon) should be used to separate the globe, gel, and eye. Use of 7.5, 10.0, 12.0, or 20 MHz ultrasound transducers should give excellent views of the eye (Bentley et al., 2003; Dziezyc & Hager, 1988).

Most small descemetoceles (i.e., less than 5 mm in diameter) can be repaired successfully using conjunctival grafts (described earlier). If a conjunctival flap is used, however, the corneal lesion will remain fragile, and in many instances, a large stromal scar will develop. Corneal perforations have also been treated successfully with conjunctival flaps and grafts (Holmberg, 1981), but in many instances conjunctival tissue may not have adequate structural integrity to maintain a watertight seal and a formed anterior chamber after surgery. This results in continuing leakage of aqueous humor, which in turn results in increased inflammation and anterior synechia formation. Use of cornea or another tissue having more structural integrity than conjunctival tissue may help to overcome some of these problems. The difficulty is finding a source of these tissues. The tissues may be harvested from: an adjacent normal cornea (e.g., as in autogenous corneal grafting or corneoscleral transposition) (Brightman et al., 1989; Dice et al., 1973; Lavignette, 1962; Parshall, 1973); from donor animals, with corneal tissue used either fresh or frozen (Hacker, 1991; Hansen & Guandalini, 1999); or from tissues, such as oral or vaginal mucosa, peritoneum, pericardium, renal membrane, amnion, or cartilage (Andrade et al., 1999; Barros & Safatle, 2000; Blogg et al., 1989; Tanner et al., 1968).

There is an increasing number of reports describing the use of synthetic grafting material that temporarily stabilizes an eye and acts as a scaffolding for growth of fibrous tissue. Bioengineered porcine small intestinal submucosa (Bussieres et al., 2004; Featherstone & Sansom, 2000; Featherstone et al., 2001; Lewin, 1999; Vanore et al., 2007) and ECM derived from porcine urinary bladder have been used for corneal surgery. However, lack of sufficient support and extensive tissue reaction (i.e., vascularization and fibrosis) may make these substances less desirable than fresh or frozen corneal tissue for repair of corneal perforations.

More recent reports have shown increased success and fewer complications with these synthetic materials utilized with or without a conjunctival graft. The use of a conjunctival pedicle flap, both with and without acellular submucosa, was evaluated in canine eyes (Dorbandt et al., 2015). There was no significant difference in success rate of either group with 97% of eyes treated with a conjunctival flap alone and 89% in eyes that also had acellular submucosa remaining visual and comfortable. Increasing patient age was significantly associated with an unsuccessful outcome but lesion size, corneal perforation or concurrent KCS were not associated with a negative outcome. Porcine small intestinal submucosa, when used for deep corneal wounds in 106 dogs and cats, resulted in little to no scar in 74 cases (69.8%) whereas 32 cases (30.2%) had a mild or marked scar. Nine cases (8.5%) had minor complications and there was faint or mild corneal pigmentation in 24 cases (22.6%). All globes were intact but five cases had some visual impairment secondary to corneal pigmentation (Goulle, 2012). Porcine urinary bladder submucosa has been used as the sole grafing agent in dogs and cats with severe ulcerative keratitis or a superficial keratectomy (Chow & Westermeyer, 2016). Patients in this study did also receive a BCL and a temporary tarsorrhaphy. Scarring was minimal in 47/68 eyes (69%), moderate in 12/68 eyes (17%) and severe in 9/68 eyes (13%). Graft dehiscence occurred in 19 eyes; however, 12 healed without surgical intervention, three required a second graft, two became phthisical and two were enucleated. Bovine pericardium has been utilized as the sole grafting material in the treatment of deep melting corneal ulcers in three dogs (Dulaurent et al., 2014). Two months after surgery, five of six canine corneas had minimal scarring and the eyes were visual, but one cornea required a second surgery and became blind. Porcine urinary bladder acellular matrix was evaluated as the sole grafting agent after lamellar keratectomy for deep, melting corneal ulcers in dogs and cats (Balland et al., 2016). The biomaterial was completely integrated in over 93% of the eyes with deep, melting corneal ulcers and, at 90 days after surgery, all eyes were sighted. Tissue-engineered human anterior hemi-corneas (TE-aHC) were created with nontransfected human corneal stroma and corneal epithelial cells with acellular porcine corneal stromata as a carrier scaffold (Xu et al., 2017). These grafts were placed onto canine corneas after lamellar keratoplasty and followed for 360 days after surgery. The constructed TE-aHC was highly transparent, composed of corneal epithelium and stroma, and maintained positive expression of their marker and functional proteins. Omental transposition for the treatment of severe alkaline corneal burns was followed for 6 months (Shadmani et al., 2014). Corneal opacity and vascularization were significantly reduced in surgically treated dogs compared to medical therapy alone.

Direct suturing of the perforation or descemetocele is rarely possible but may be attempted in small lesions (<1 mm) with firm, healthy corneal margins. Direct suturing of larger lesions may cause significant corneal astigmatism and poor visual outcome after surgery. Tissue adhesives are

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not recommended for use in descemetoceles because heat is generated during polymerization of the glue after application, which may cause perforation of Descemet's membrane (Markowitz et al., 1995). Because of aqueous humor leakage, it is nearly impossible to sufficiently dry the corneal lesion in corneal perforations to allow the glue to adhere to the lesion. Furthermore, intraocular leakage of the glue may cause severe damage as well (Markowitz et al., 1995).

Corneoscleral and Corneoconjunctival Transposition

Corneoscleral or corneoconjunctival transposition is a type of autologous corneoscleral graft that uses a sliding pedicle of cornea and attached sclera (or conjunctiva) to repair corneal defects (Parshall, 1973). It is indicated in central, deep, or perforated corneal lesions with sufficient peripheral healthy cornea that can be used for the grafting procedure (Fig. 19.30). In general, the distance from the peripheral edge of the lesion to the corneal limbus must be at least 1 mm longer than the diameter of the corneal lesion itself (Gelatt & Brooks, 2011; Gilger & Whitley, 1999; Wilkie & Whittaker 1997). Because autologous ("self") tissue is used, corneoscleral transposition eliminates the need for corneal tissue donors and minimizes immune-mediated inflammation. This may decrease corneal scarring and allow a clearer postoperative cornea than that seen after conjunctival and some other corneal grafts. A disadvantage, however, is that corneoconjunctival transposition damages normal, healthy corneal tissue and may leave a larger scar than other corneal grafts. In a study evaluating corneoconjunctival transposition as a treatment for deep corneal ulcers, descemetoceles, and full thickness defects, vision was preserved in 96% of patients (Gorgova et al., 2020).

After the animal is anesthetized, necrotic cornea is debrided using sharp dissection. If the cornea is not perforated, great care should be taken during this debridement not to rupture Descemet's membrane. Following debridement, a microsurgical blade (i.e., Beaver No. 64) is used to create two diverging, linear, one-half to three-quarter corneal thickness incisions that extend from the periphery of the lesion to the limbus (Fig. 19.31). If the eye is perforated, filling the anterior chamber with a viscoelastic substance (e.g., sodium hyaluronate) will greatly enhance the ability to create corneal incisions and facilitate suture placement. The incisions are then extended over the limbus and into the conjunctiva and sclera. This is the area from which the graft will be harvested. The width of the graft should be slightly more than that of the corneal defect. The edge of the lesion at the leading edge of the graft is grasped with forceps and elevated, and the cornea is split and undermined toward the limbus. A corneal dissector greatly facilitates this stromal lamellar dissection; however, microsurgical blades or a flat iris spatula can also be used. The undermining should cross over the limbus into the sclera. Sufficient dissection should be performed so that the graft can be advanced to cover the lesion without tension.



Figure 19.30 Central corneal descemetocele in a dog with chronic corneal disease.

A modification of the original description of this procedure involves undermining only the conjunctiva (and leaving the sclera intact) and converting to a corneoconjunctival transposition. This modification significantly decreases hemorrhage during the procedure as well as the damage done to normal tissues of the eye. With both procedures, however, the corneal graft tissue is advanced to cover the lesion and is trimmed to fill the corneal defect – either square in shape or curved. The leading edge of the corneal graft should be trimmed, especially if it was traumatized by forceps during the dissection phase of the procedure. The graft is sutured to the cornea using simple, interrupted sutures of 8-0 to 10-0 polyglactin 910™ or nylon. The sclera or conjunctiva (or both) is then sutured to the cornea at the diverging linear incision with a continuous suture pattern using the same type of suture material used in the corneal graft (see Fig. 19.30). As with any corneal surgery, sutures should not penetrate the entire thickness of the cornea but instead be placed at a depth of two-thirds to three-quarters the depth of the cornea.

In cases of corneal perforation, the eye must be re-inflated after surgery. A 27- or 30-gauge needle attached to a tuberculin syringe filled with balanced salt solution (BSS™) or lactated Ringer's solution is introduced into the eye at a site opposite to the corneal graft by undermining the needle for several millimeters adjacent to the limbus, then passing it through the limbus and into the anterior chamber (parallel to the iris). Generally, 0.5–0.8 mL of fluid is sufficient to reinflate the eye. The corneal graft should be evaluated carefully for leakage; if leakage is present, additional sutures should be placed to create a watertight seal.

Postoperative management of corneoscleral transposition is similar to that of conjunctival flaps. Topical antibiotics, which are chosen on the basis of culture, sensitivity,

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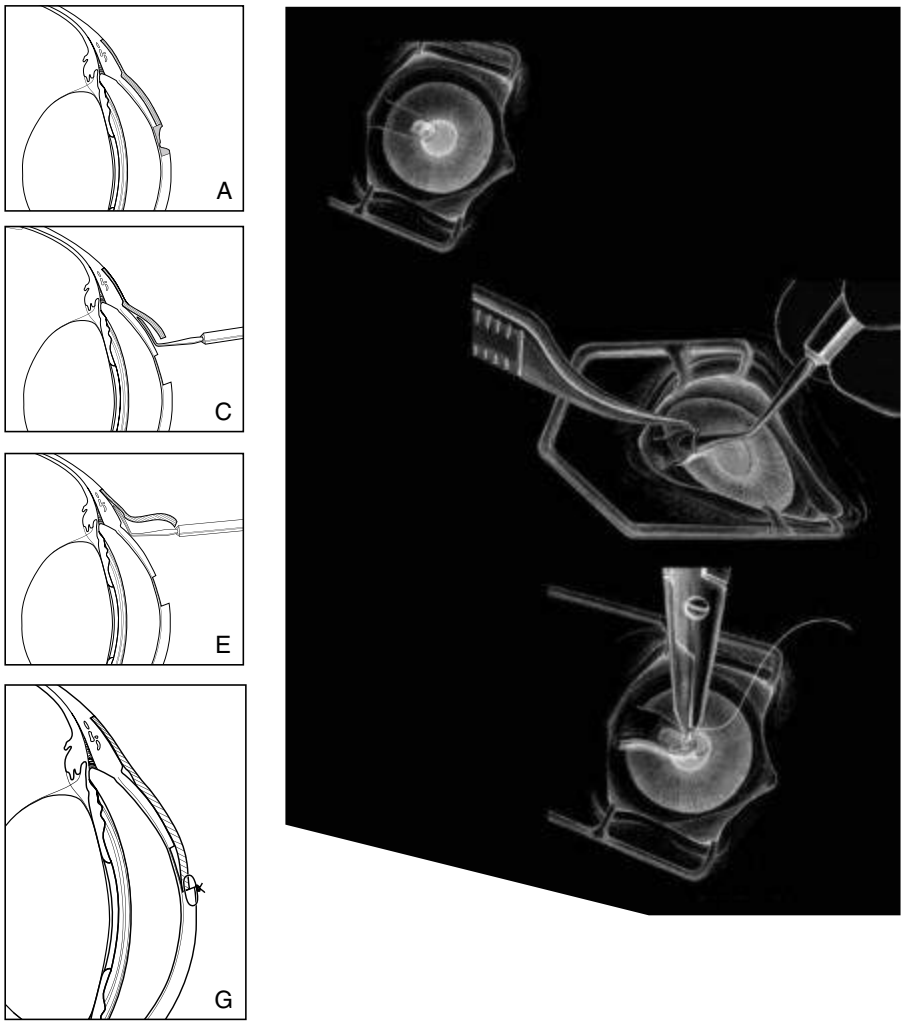


Figure 19.31 Corneoscleral or corneoconjunctival transposition. **A** and **B.** Following debridement of the corneal lesion, a microsurgical blade (Beaver No. 64) is used to create two diverging, linear, one-half to three-quarter corneal thickness incisions extending from the periphery of the lesion to the limbus. The incisions are then extended over the limbus and into the conjunctival and sclera. The width of the graft should be slightly more than that of the corneal defect. **C** and **D.** The edge of the lesion at the leading edge of the graft is grasped with forceps and elevated. **E.** The cornea is split and undermined toward and over the limbus and into the sclera or conjunctiva. **F.** The corneal graft tissue is advanced to cover the lesion and is trimmed to fill the corneal defect. **G.** The graft is sutured to the cornea using simple, interrupted sutures of 8-0 to 10-0 polyglactin 910 or nylon. The cornea can be oversewn with a continuous suture. The sclera or conjunctiva (or both) is then sutured to the cornea at the diverging linear incision with a continuous suture pattern using the same type of suture material as used in the corneal graft.

and cytologic results, and medications to control postoperative uveitis and pain (e.g., topical atropine, systemic nonsteroidal anti-inflammatory medications, or both) should be used. Generally, the conjunctival and scleral sliding graft is well adhered to the cornea and cannot be trimmed, as is typically done with conjunctival flaps. In some animals, however, after the cornea has completely healed (usually in 4–6 weeks), the conjunctiva can be cut, undermined, and excised. This usually requires general anesthesia but, in most cases, it is not required because the conjunctiva is on the peripheral cornea and does not significantly obstruct vision.

Autogenous Lamellar Corneal Grafts

Autogenous lamellar corneal grafts are indicated in corneas with descemetoceles, stromal abscesses, and perforated ulcers (Brightman et al., 1989). These grafts use adjacent corneal tissue slid to cover the corneal defect (Fig. 19.32). Advantages of this procedure are: that autografts are used, thus minimizing graft rejection; that tissue is usually readily

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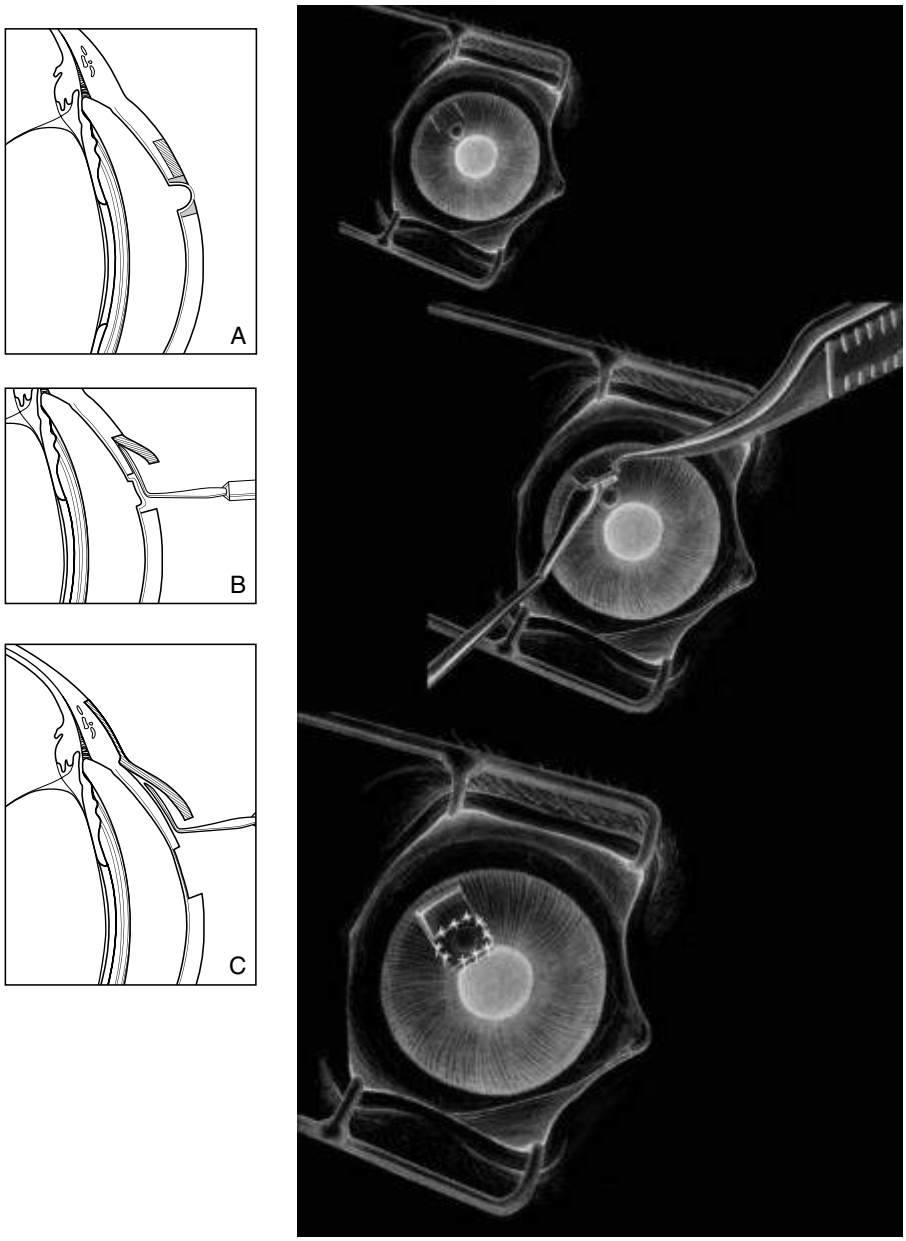


Figure 19.32 Autogenous lamellar corneal graft. **A.** Two parallel incisions are made that extend past the lesion toward the limbus. The distance between the incisions is 2–3 mm wider than the diameter of the lesion. **B.** The incisions are joined by making a perpendicular incision, and a one-half-thickness keratectomy is performed. The graft should be 0.5–1.0 mm wider and deeper than the lesion. **C.** The graft is positioned in the graft bed of the lesion and is then sutured into place with a continuous or interrupted suture pattern. (*Source:* Modified from Brightman, A.H., McLaughlin, S.A. & Brogdon, J.D. (1989) Autogenous lamellar corneal grafting in dogs. *Journal of the American Veterinary Medical Association*, **195**, 469–475.)

available; and that a clear cornea may result after surgery (Brightman et al., 1989; Lavignette, 1962). The main disadvantage of this procedure is that an area of normal cornea is weakened. In seven dogs with corneal disease, Brightman et al. (1989) found that six of the seven grafts remained translucent and that only one had pigmentation.

The surgical procedure is initially similar to corneoscleral transposition. Two parallel incisions are made that extend past the lesion toward the limbus. The distance between the incisions is 2–3 mm wider than the diameter of the lesion. The incisions are then joined by making a perpendicular incision (see Fig. 19.32), and a half-thickness keratectomy is

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performed. The graft should be 0.5–1.0 mm wider and deeper than the lesion. The graft is positioned in the graft bed of the lesion and then sutured into place with a continuous or interrupted suture pattern (Brightman et al., 1989). A conjunctival pedicle flap can be placed over both the graft and the lesion to help promote healing, to bring in blood supply, and to add strength to the corneal lesions and graft site. Use of the conjunctival flap may be especially important with infected or rapidly progressing ulcers; however, increased scarring may subsequently occur.

Fresh or Cryopreserved Corneal Grafts

Other techniques for treatment of descemetoceles and full-thickness corneal perforations include grafts from using cryopreserved tissue and corneal transplantation (i.e., penetrating keratoplasty). Fresh corneal transplantation is described later in this chapter. Corneal grafting using homologous (i.e., from the same species) frozen corneal tissue has also been described for treatment of corneal descemetoceles and perforations (Hacker, 1991; Hansen & Guandalini, 1999). In both studies, fresh corneal tissue was collected at euthanasia of donor animals, placed in antibiotic solution containing neomycin and bacitracin, and stored at a temperature of −30 °C for up to 12 months. A recent study evaluated bacterial contamination and structural integrity of cryopreserved canine cornea that was stored up to 6 years at -20 °C (Costa et al., 2018). Long-term cryopreservation reduced bacterial contamination and preserved the architecture of stromal collagen, suggesting that these samples could be useful for tectonic keratoplasty. When needed, the tissue is thawed in sterile, warm water or at room temperature. The grafts are cut and placed over descemetoceles or perforations, and they are sutured into place with simple, interrupted sutures (Fig. 19.33). In the studies reported, no attempt was made to limit vascularization until the graft was completely vascularized and the cornea stains fluorescein-negative. In a series of 19 cases, 84% resulted in vision despite vascularization and scarring of the graft (Hacker, 1991). In a series of 30 cases, 100% were visual at 60 days despite various complications such as focal dehiscence of the wound (30%), partial graft necrosis (23%), and graft pigmentation (13%) (Hansen & Guandalini, 1999).

Full-Thickness Corneal Lacerations

Surgical repair of most corneal lacerations generally is not overly challenging provided proper instrumentation, magnification, and suture materials are used. A successful visual outcome after traumatic corneal laceration (Fig. 19.34), however, requires a careful, thorough preoperative evaluation and selection of appropriate surgical procedures. The extent of ocular trauma must be determined before repairing the cornea, and in many cases, this can be difficult. Deflation of the anterior chamber, iris prolapse, hyphema, hypopyon, and significant corneal edema may prevent a complete ophthalmic examination. A consensual pupillary light reflex and dazzle reflex are positive clinical signs, but they do not ensure a normal posterior segment. Ocular ultrasonography, as described previously, can also be used to assess posterior segment damage with corneal lacerations; however, it is important that the ultrasound coupling gel does not enter into the wound or anterior chamber. If ultrasonography of the injured eye is attempted, the animal should be sedated or anesthetized so that movement of the animal does not further damage the eye. A standoff pad (e.g., solid-gel standoff pad or water-filled balloon) should also be used to separate the globe, gel, and probe. If possible, the integrity of the

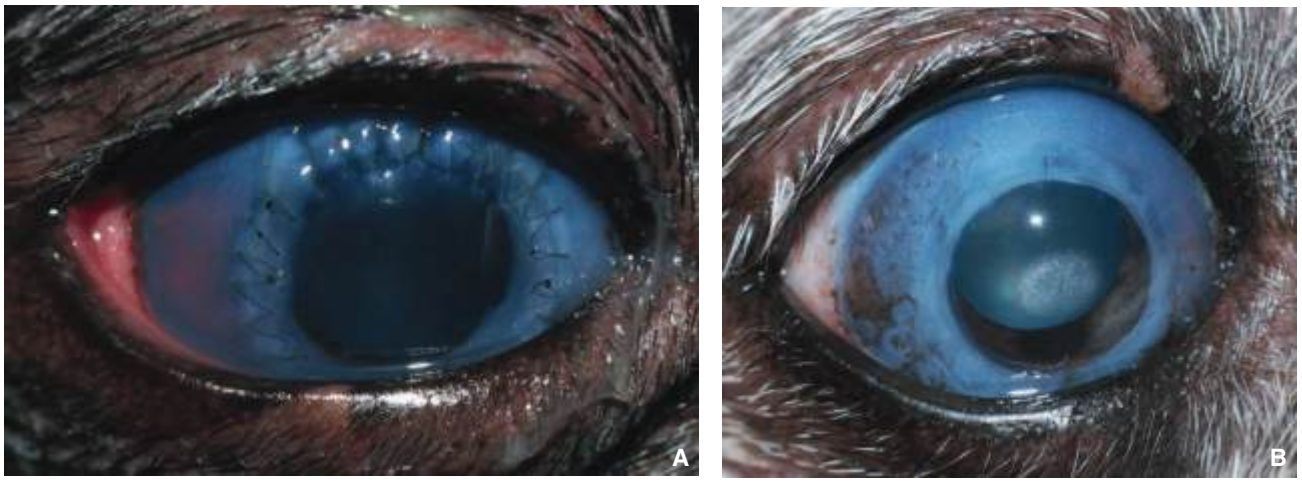


Figure 19.33 Penetrating keratoplasty using fresh tissue in a dog with diffuse corneal edema, immediately after surgery (**A**) and 3 years later (**B**). Frozen cornea can also be used for perforations, but a clear cornea, as observed here, should not be expected. (*Source:* Courtesy of Bob English.)

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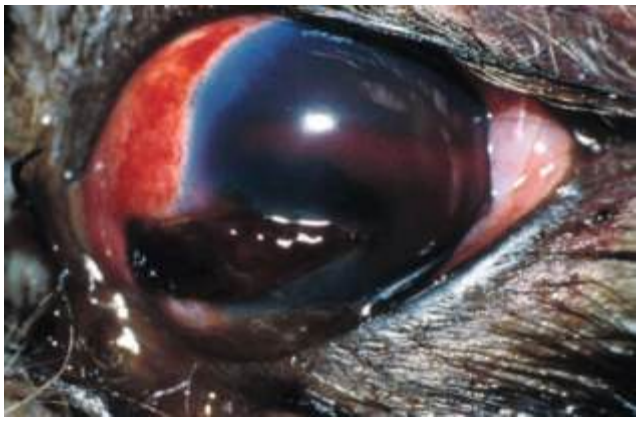


Figure 19.34 Horizontal full-thickness corneal laceration with uveal prolapse and hyphema in a dog.

anterior lens capsule should be examined; if a careful examination is not possible before surgery, it should be conducted during the surgical procedure. If the lens capsule is ruptured, significant lens-induced uveitis and cataractogenesis may occur. Phacoemulsification of the lens and implantation of a synthetic intraocular lens simultaneous with the corneal repair will decrease the postoperative inflammatory response and help to maintain vision (Davidson et al., 1991; Denis, 2002).

Full-thickness corneal lacerations may or may not have incarcerated uveal tissue. Incarcerated yet viable iris tissue should be repositioned in the anterior chamber when possible; iris tissue that has been prolapsed for longer than 6–8 hours should be amputated with electrocautery. When removing a prolapsed iris, gentle traction is placed on the prolapsed portion, and the fresh uveal tissue is cauterized near the cornea. Care must be taken not to cauterize the cornea. The anterior chamber is irrigated with BSS or lactated Ringer's solution, and the lens is carefully inspected (as described earlier). Viscoelastic substances, such as 2.0% hyaluronic acid, can be used to re-inflate the anterior chamber and to keep it formed while suturing the cornea. Removal of the viscoelastic substances by irrigation is recommended before placement of the final suture, however, to help prevent ocular hypertension after surgery.

Appropriate suture material for corneal lacerations includes 7-0 to 10-0 absorbable or nonabsorbable suture. Choice of suture type depends largely on surgeon preference. Nylon is easiest to handle and least reactive in the cornea initially, but in most cases, it needs to be removed after 4–6 weeks. Several suture patterns have been described for corneal wounds, and each has advantages and disadvantages. Simple interrupted, simple continuous or running, shoelace, and others have been described (Eisner, 1990). Sutures should be tied in a manner that

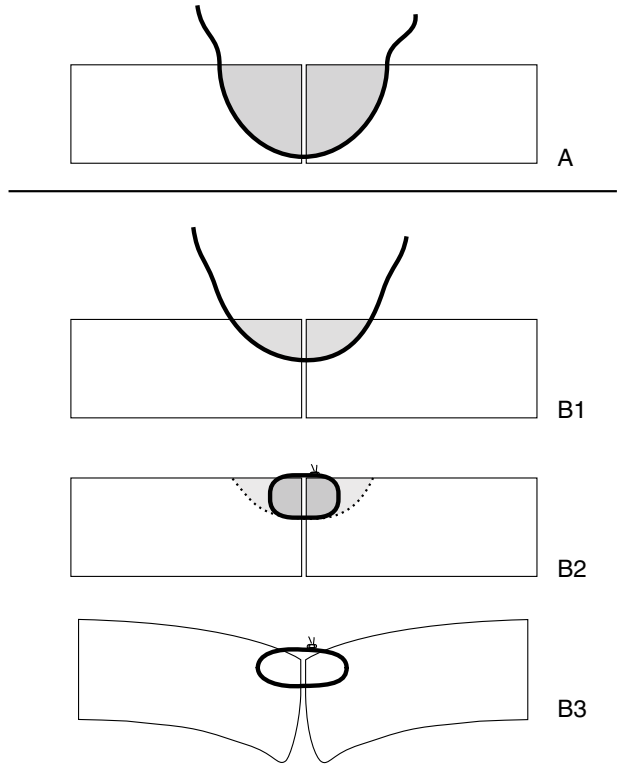


Figure 19.35 Placement of corneal sutures. **A.** Proper placement of corneal sutures. **B.** Too shallow of placement (B1) or excessive tension on the shallow sutures (B2) results in gaping of the deep wound edges (B3). Sutures should be tied in a manner that achieves apposition of the tissue without compression of the tissue. (*Source:* Adapted with permission from Eisner G. (1990) Suturing the cornea and sclera. In: *Eye Surgery: An Introduction to Operative Technique* (ed. Eisner, G.), 2nd ed., pp. 182–190. Berlin: Springer-Verlag.)

achieves apposition of the tissue. No compression of the tissue is required, however, because compression causes gaping of the deep wound edges (Fig. 19.35) (Eisner, 1990). Also, a tight suture placed slightly oblique to the incision will cause the wound edges to shift along the entire wound line (Fig. 19.36) (Eisner, 1990). When corneal sutures are placed properly, minimal shift of the wound edges occurs. Proper placement involves placing the suture plane perpendicular to the corneal surface, having the needle inserted perpendicular to the tissue surface, and having the needle tip exiting the cornea perpendicular to the wound surface (Fig. 19.37) (Eisner, 1990). Following closure of the cornea, the anterior chamber is reformed with BSS™ or BSS Plus™ via a limbal injection using a 27- to 30-gauge needle. After wound closure, sterile fluorescein dye may be applied to the wound to ensure proper wound closure and to detect leaks (i.e., Seidel test) (May et al., 2010).

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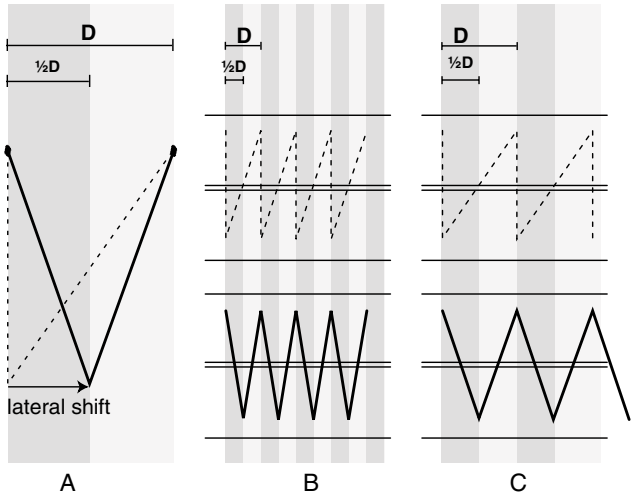


Figure 19.36 Placement of continuous corneal sutures. Properly placed corneal sutures will cause only minimal shifting of the wound edges. If sutures are inadvertently placed too tightly or in an oblique fashion to the incision, wound edges will shift along the entire wound. (*Source:* Adapted with permission from Eisner, G. (1990) Uniting of tissues. In: *Eye Surgery: An Introduction to Operative Technique* (ed. Eisner, G.), 2nd ed., pp. 89–109. Berlin: Springer-Verlag.)

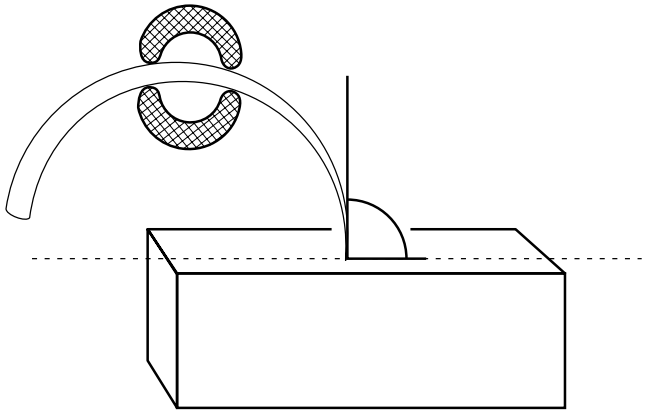


Figure 19.37 Placement of corneal sutures. Proper placement of corneal sutures involves placing the suture perpendicular to the corneal surface, inserting the needle perpendicular to the corneal surface. (*Source:* Adapted with permission from Eisner, G. (1990) Suturing the cornea and sclera. In: *Eye Surgery: An Introduction to Operative Technique* (ed. Eisner, G.), 2nd ed., pp. 182–190. Berlin: Springer-Verlag.)

Corneal Foreign Bodies

Corneal foreign bodies occur as two different types: those that adhere to the corneal surface or become embedded on the surface of the cornea, and the type that penetrates into the cornea or actually penetrates into the globe. Corneal foreign bodies should be removed to reduce the potential for infection, limit pain, and to prevent vascularization and scar formation. Most small, adherent foreign bodies are removed by propulsion with a fine stream of saline or eye wash directed forcefully at the corneal surface after application of a topical anesthetic (Labelle et al., 2014). Prior to using a forceful stream of fluid, the integrity of the cornea must be assessed. This procedure is safe only if the cornea is not weakened, because a stream of fluid can rupture a descemetocele or other deep ulcer (Maggs, 2013). Penetrating foreign bodies have the potential for greater ocular damage and commonly require the expertise of an ophthalmic specialist for removal and management. Foreign bodies may be removed using a sterile hypodermic needle or small ophthalmic forceps. Some penetrating foreign bodies may require removal by an incision (6500 microsurgical blade) made in the cornea over the long axis of the foreign body utilizing an operating microscope. After removal of a corneal foreign body, a broad-spectrum topical antibiotic and atropine are administered to limit infection and secondary uveitis. If perforation of the globe has occurred, a systemic antibiotic is needed.

Recently, a case series of cactus spine-induced keratoconjunctivitis described penetrating corneal and/or conjunctival foreign bodies associated with geographic superficial corneal ulceration and keratomalacia with *Proprionicimonas* spp. bacteria (Fig. 19.38**)** **(**Dowler et al., 2020). Light microscopy of extracted foreign bodies and/or IVCM were used to confirm the presence of cactus spines in all cases. Botanical identification of the spines was consistent with prickly pear cactus species. Surgical intervention with medical therapy or medical therapy alone was used. Cactus spines were visible biomicroscopically within the cornea at the last follow-up in three cases despite resolution of clinical signs. Follow-up IVCM exams showed persistent corneal cactus spines associated with extensive linear tracks of epithelial downgrowth in two cases **(**Fig 19.39). Positive clinical outcomes were achieved despite persistence of organic foreign material in the cornea (Dowler et al., 2020).

Ulcerative Keratitis: Cause of Corneal Disease

Corneal ulcers are classified by the depth of corneal involvement (as described in the preceding section) and by their underlying etiology. Common causes of ulcerative keratitis include bacterial, viral, and fungal infections and chemical burns. Primary or secondary corneal ulceration has been associated with snakebite envenomation in dogs (Martins et al., 2016).

Bacterial Corneal Ulcers

The intact and healthy canine cornea is highly resistant to bacterial infection. If the anatomic and physiologic defenses of the cornea are compromised, such as by external trauma or KCS, bacteria invasion may occur. Bacterial keratitis is the most common type of corneal infection encountered in the dog. *Staphylococcus* spp., *Streptococcus* spp., and *P. aeruginosa*

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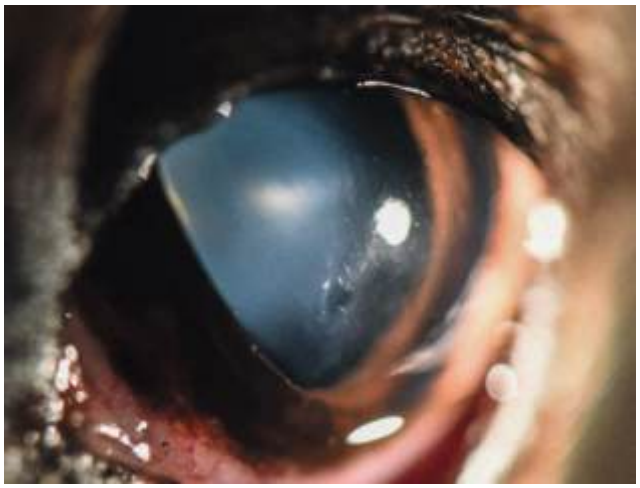


Figure 19.38 Cacti foreign body. Trans-illuminated photograph of a 10-year-old Dachshund with linear intrastromal corneal opacities located within the central cornea, 2 months after brushing against a prickly pear cactus. (*Source:* Courtesy of Lucien Vallone, Texas A & M University.)

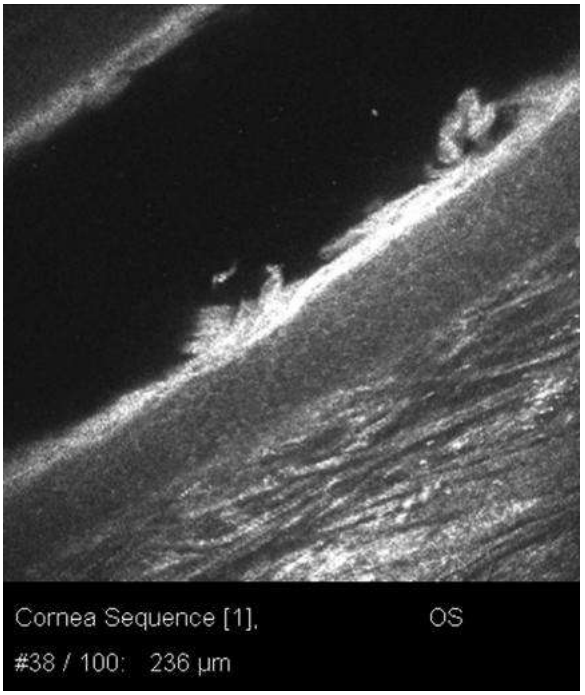


Figure 19.39 Epithelial downgrowth, stromal disorganization (fibrosis), and an apparent stromal cleft are apparent via *in vivo* confocal microscopy within the mid stroma of this patient. The width of this field is 400 µm (*Source:* Courtesy of Lucien Vallone, Texas A & M University.).

are the most frequent etiologic agents of canine bacterial ulcerative keratitis; however, numerous other Gram-positive and Gram-negative aerobic bacteria are isolated from dogs with corneal ulcers including: *Acinetobacter*, *Bacillus*, *Corynebacterium*, *Enterobacter*, *Enterococcus*, *Escherichia*, *Klebsiella*, *Micrococcus*, *Pantoea*, *Pasteurella*, and *Proteus* spp. (Gerding & Kakoma, 1990; Gerding et al., 1988; Lin et al., 2007; Prado et al., 2005; Tolar et al., 2006; Wang et al., 2008b). Obligate anaerobic bacteria, including *Actinomyces, Bacteroides, Capnocytophaga, Clostridium*, *Fusobacterium*, *Peptococcus*, and *Peptostreptococcus* spp., are isolated less frequently from dogs with ulcerative keratitis (14% of dogs with ulcerative keratitis in one study; Ledbetter & Scarlett, 2008) (Fig. 19.40).

Methicillin-resistant *Staphylococcus aureus* (MRSA) has been recognized as a cause of infectious canine keratitis (Fig. 19.41) (Tajima et al., 2013; Varges et al., 2009). MRSA may be acquired from multiple potential sources, both veterinary and non-veterinary. Transmission of MRSA from the home environment was ranked as the most influential predictor of MRSA acquisition (Varges et al., 2009). Exposure to and transmission from MRSA-positive family members were also found to influence acquisition of MRSA by pet dogs. In one case, MRSA was sensitive only to chloramphenicol, vancomycin, lincomycin, and clindamycin; the ulcer resolved by topical and systemic treatment with chloramphenicol followed by vancomycin (Tajima et al., 2013).

The basic pathophysiologic steps of bacterial keratitis are: (1) bacterial adherence to the damaged corneal surface; (2) bacterial invasion of the corneal epithelium and underlying stroma; (3) bacterial multiplication; (4) elaboration of bacterial exotoxins, endotoxins, and proteases; and (5) influx of leukocytes and soluble inflammatory mediators with further tissue damage. Progression (i.e., stromal loss and ulcer deepening) with bacterial keratitis is often rapid and attributable to both bacterial and host-derived toxins and proteases (Hobden, 2002; Wang et al., 2008a). Corneal leukocyte infiltrates and concurrent anterior uveitis (i.e., miosis, aqueous flare, and hypopyon) are frequent clinical findings. Some bacteria, such as *P. aeruginosa*, possess additional virulence mechanisms that contribute to tissue invasion, immune system evasion, and tissue destruction. Some strains of *P. aeruginosa* isolated from dogs with ulcerative keratitis are capable of invading, residing, and multiplying within corneal epithelial cells and other canine *P. aeruginosa* strains induce toxin-mediated killing of corneal epithelial cells (Ledbetter et al., 2007b, 2008).

Diagnosis of bacterial infection of corneal ulcers is made on the basis of cytologic examination and microbiologic culture of corneal samples. Use of both microbial culture and cytologic evaluation of corneal specimens is recommended because the combination maximizes identification of infectious keratitis (Massa et al., 1999). Ideally, cultures should be obtained before the application of topical anesthetics and the eyelid margins and facial hair should be avoided to minimize contamination of the sample.

Viral Keratitis

Canine herpesvirus-1 (CHV-1) infection may result in ulcerative or nonulcerative keratitis in dogs of all ages. Despite

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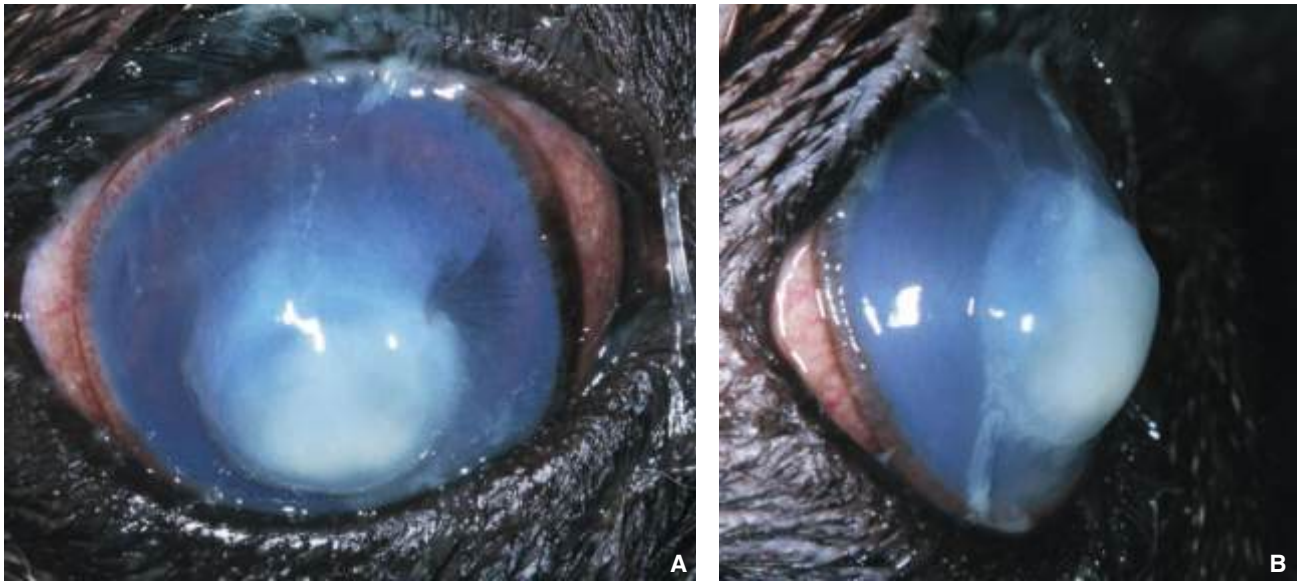


Figure 19.40 Front (**A**) and side (**B**) views of bacterial keratitis in a dog associated with extensive keratomalacia.



Figure 19.41 A deep corneal ulcer with active vascularization, caused by an MRSA corneal infection. The edge of the excised third eyelid is visible. (*Source:* From Tajima, K., Sinjyo, A., Ito T., et al. (2013) Methicillin-resistant Staphylococcus aureus keratitis in a dog. *Veterinary Ophthalmology*, **16**, 240–243.)

the ubiquitous presence of latent infection in domestic dogs worldwide, corneal disease associated with naturally acquired CHV-1 infection is infrequently reported (Gervais et al., 2012; Ledbetter et al., 2006b, 2009b). Corneal lesions may develop during primary or recurrent ocular CHV-1 infection. CHV-1 keratitis appears to occur most commonly, and is most severe, in immunocompromised dogs.

A variety of clinical manifestations are observed in the cornea associated with CHV-1 infection (Gervais et al., 2012; Ledbetter et al., 2006b, 2009b). CHV-1 infection may produce punctate, dendritic, or geographic corneal ulcers (Fig. 19.42). Unless complicated by secondary bacterial infection, CHV-1 corneal ulcers remain superficial and are not associated with stromal loss. Nonulcerative keratitis is a less frequent corneal lesion reported with CHV-1 infection and appears as a circumferential ring of superficial corneal vascularization with epithelial and subepithelial leukocyte infiltrates in the peripheral cornea (Ledbetter et al., 2009b). Diagnosis of CHV-1 keratitis is achieved by virus isolation or polymerase chain reaction (PCR) assay of corneal or conjunctival samples. In contrast to some other alphaherpesviruses associated with keratitis in domestic animals, subclinical ocular shedding of CHV-1 occurs uncommonly in mature dogs, and viral detection in dogs with compatible clinical signs is strongly suggestive of an etiologic role (Ledbetter et al., 2012). A robust serologic response is detected in dogs with primary or recurrent CHV-1 ocular infection; however, this diagnostic approach requires acute and convalescent serum samples to be collected and is less useful for the initial management of an acute infection (Ledbetter et al., 2009a, 2009c).

In addition to treatment to prevent secondary bacterial infection of the compromised cornea (topical ocular antibiotic) and improve comfort (topical ocular atropine), antiviral therapy with 0.1% idoxuridine, 1% trifluridine, and 0.5% cidofovir is used for CHV-1 keratitis (Gervais et al., 2012; Ledbetter et al., 2006b). Idoxuridine and trifluridine are administered six to eight times daily for the first 48 hours and then four times daily until resolution of active clinical signs of infection. Cidofovir is administered twice daily. This dosage reduced the duration of viral shedding in dogs with experimentally induced recurrent CHV-1

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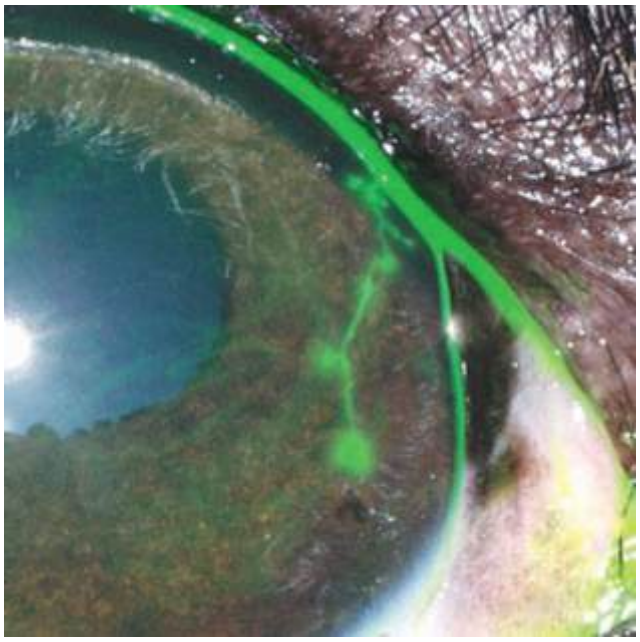


Figure 19.42 Canine herpesvirus-1 dendritic ulcerative keratitis in a dog receiving systemic immunosuppressive therapy (cornea stained with fluorescein).

but did cause exacerbation of conjunctivitis, marked conjunctival pigmentation and ulcerative blepharitis as well as increased corneo-conjunctival leukocyte infiltrates (Ledbetter et al., 2015). When possible, ophthalmic and systemic immunosuppressive medication administration should be discontinued. After resolution of the keratitis, dogs remain at risk for recurrent episodes of infection associated with reactivation of latent CHV-1 (Ledbetter et al., 2009c).

Mycotic Keratitis

Fungal keratitis in the canine has been increasingly reported in the literature (Ben-Shlomo et al., 2010; Gerding et al., 1988; Grundon et al., 2010; Marlar et al., 1994; Newton, 2012; Qualls et al., 1985; Rampazzo et al., 2009; Scott & Carter, 2014; Smedes et al., 1992) and can present as either ulcerative or nonulcerative lesions. *Aspergillus* spp. are the most common isolates. Other fungi recovered include *Acremonium*, *Alternaria*, *Aspergillata*, *Candida*, *Cephalosporium*, *Chrysosporium*, *Cladosporium*, *Curvularia*, *Fusarium*, *Hormographiella*, *Penicillium*, *Phialemonium*, *Pseudoallescheria,* and *Scedosporium* spp. (Ben-Shlomo et al., 2010; Gerding et al., 1988; Grundon et al., 2010; Marlar et al., 1994; Nevile et al., 2016a; Newton, 2012; Qualls et al., 1985; Scott & Carter, 2014; Whitley & Gilger, 1999). Clinical histories may include long-term antibiotic or corticosteroird therapy or previous corneal trauma. Infections with *Aspergillus* spp. are usually ulcerative in nature with extensive stromal inflammation and melting (Fig. 19.43). Lesions associated with *Candida* spp. are often raised yellow-white or gray-white plaques or ulcerated lesions. In 14 dogs in south Florida with keratomycosis, oral terbinafine, or a combination of oral terbinafine and topical voricoazole, was more successful than topical voriconazole alone or in combination with oral fluconazole (Colitz & Ternullo, 2017).

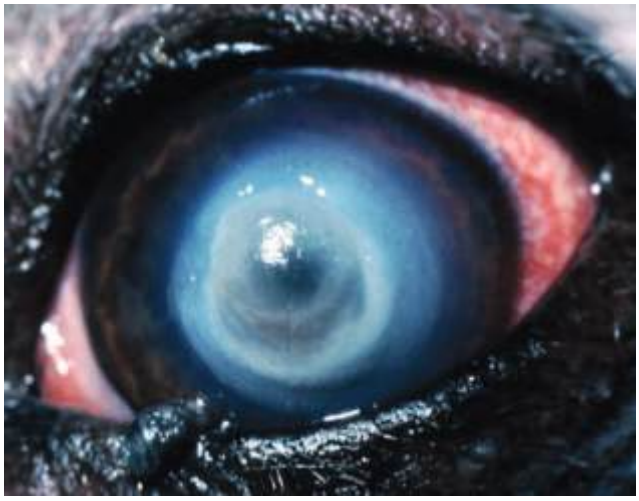


Figure 19.43 Mycotic keratitis in a dog.

Results of exfoliative cytologic examination (Fig. 19.44), fungal cultures, and histologic examination of keratectomy specimens are diagnostic. PCR-based diagnostic fungal tests are being developed to identify fungal DNA in corneal specimens quickly (Lindsley et al., 2001; Rampazzo et al., 2009) and are available at some state medical and/or veterinary diagnostic laboratories. Most cases show evidence of fungal hyphae and/or yeasts on corneal cytology, validating the importance of this diagnostic modality in evaluating canine ulcerative keratitis. *In vivo* confocal microscopy has been used for detection of fungi and monitoring response to therapy (Ledbetter et al., 2016).

Classes of antifungal medications include the polyenes (natamycin, nystatin, amphotericin B), imidazoles (micona-

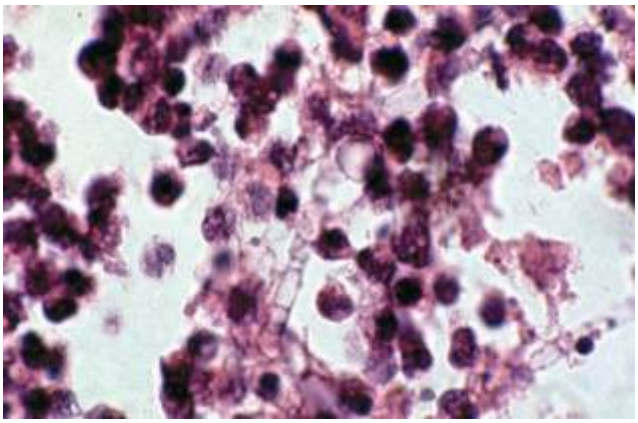


Figure 19.44 Cytologic examination of corneal scraping revealing fungal hyphae. (Diff-Quik Stain, 400×.)

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zole, ketoconazole), triazoles (fluconazole, itraconazole, voriconazole), and fluorinated pyrimidines (5-fluorocytosine). Antifungal medications have been studied extensively in the horse because fungal keratitis is common in this species and the treatment of dogs with mycotic keratitis is often extrapolated from equine information (Brooks et al., 2017; Clode, 2011). Natamycin is the only topical ophthalmic antifungal medication commercially available in the United States and is effective against *Fusarium* and *Aspergillus* (Johns & O'Day, 1988). However, natamycin does not have good penetration through intact corneal epithelium and can be irritating (O'Day et al., 1984). Itraconazole compounded with dimethyl sulfoxide (DMSO) reaches adequate corneal concentrations but does not enter aqueous humor and can be irritating (Ball et al., 1997). Fluconazole penetrates well in both inflamed and normal corneas when applied topically but may have poor activity against some *Aspergillus* spp. (Ledbetter et al., 2007b). Miconazole has broad activity against filamentous fungi, yeast, and Gram-positive bacteria, excellent corneal penetration, and does not retard corneal healing or cause pathologic changes during corneal epithelial regeneration (Johns & O'Day, 1988; O'Day et al., 1984). Voriconizole (1%) penetrates the cornea well, has low toxicity, and has good activity against *Aspergillus* and *Fusarium* (Clode et al., 2006; Ghannoum & Kuhn, 2002; Grundon et al., 2010; Hariprasad et al., 2008; Hoffman et al., 2002).

Appropriate topical broad-spectrum antibiotic therapy is used concurrently with antifungal therapy because bacterial coinfection is common and it helps prevent bacterial infection with chronic corneal compromise. Antifungal drugs are instilled in the conjunctival sac at 1- to 2-hour intervals for the first 2–3 days. The frequency can then be reduced to between six and eight times daily for 5–10 days, and then to four times daily. Therapy should generally be continued for 14–21 days, or until resolution of the keratitis. Superficial keratectomy with or without a conjunctival graft is required in many cases to resolve the infection, preserve the cornea, and promote healing. Lamellar keratectomy along with topical administration of voriconazole can be used successfully to treat dematiaceous fungal keratitis in dogs (Pucket et al., 2012).

Chemical-Induced Corneal Ulceration

Chemical burns to the cornea are rarely reported in the dog (Christmas, 1991; Singh et al., 2004). A chemical burn should be considered in any dog with unexplained acute blepharospasm and severe corneal opacity (Fig. 19.45). There are two general types of chemical burns to the cornea: acidic and alkali. Clinical signs for either type may include edema, opacity, loss of corneal epithelium, pain, rapid dissolution of the corneal stroma, and anterior uveitis. Alkali burns tend to be more severe, as the chemical damage is deeper.

Acidic chemicals that may cause burns to the cornea include sulfuric acid, sulfurous acid, hydrochloric acid, nitric acid, acetic acid, chromic acid, and hydrofluoric acid. Automobile batteries, which contain sulfuric acid, are the most common source of acidic burn of the eye in humans (Siebert, 1982). Hydrofluoric acid may be found commonly at home in rust removers, aluminum brighteners, and heavy-duty cleaners. Alkali chemicals include ammonium hydroxide, potassium hydroxide, sodium hydroxide, calcium hydroxide, and magnesium hydroxide. Substances in a home that contain these compounds include lye, cement, lime, ammonia, sparklers, and flares (which contain magnesium hydroxide and phosphorus).

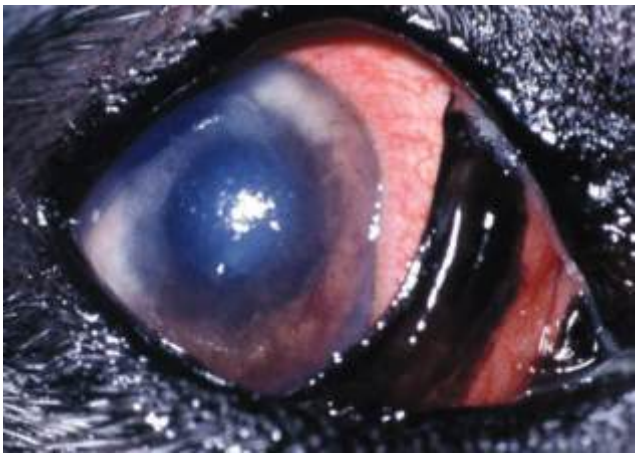


Figure 19.45 Chemical burn or keratitis after mace exposure in a dog.

Chemical mace has the active ingredient chloroacetophenone, a severe lacrimation and irritating substance. In dogs, rabbits, and humans, high levels of exposure may produce intense necrotizing keratitis, blepharitis, conjunctivitis, and anterior uveitis (Ballantyne et al., 1975; Gaskins et al., 1972). Treatment for mace exposure is the same as for other chemical irritants.

Acid burns cause protein coagulation in the corneal epithelium, which limits further penetration and thus further damage to the eye. Thus, these burns usually are nonprogressive and superficial. Alkali substances are lipophilic. Saponification of cell membrane fatty acids causes cell disruption and death. In addition, the hydroxyl ion hydrolyzes intracellular GAG and denatures collagen. The damaged tissues stimulate an inflammatory response, which damages the tissue further by the release of proteolytic enzymes. A case series of four dogs with alkaline ocular injury has been reported (Busse et al., 2015). In all but one case, outcomes were poor and affected dogs had decreased to no vision. In acute cases, treatment should focus on removing the alkaline agent and neutralizing the ocular surface pH. The use of purpose-made ocular flushes is limited in veterinary medicine because of cost but tap water is preferred to isotonic saline. It can take several months for the cornea to heal and a fully vascularized cornea may not result in a visual outcome.

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Treatment for chemical burns of the cornea starts with copious irrigation. Sterile physiologic saline, BSS™, or eyewash reduces further damage to the eye. The goal of irrigation is to dilute the chemical, remove particulate matter, and normalize ocular surface pH. Irrigation should continue for 15–30 minutes, or until the ocular surface pH returns to a normal level. Ocular pH can be determined with the pH section of a urinalysis strip. General anesthesia or sedation, with an eyelid speculum, may be needed to facilitate thorough irrigation, and the third eyelid should be elevated if possible to ensure irrigation beneath it. A swab can be used to remove any particulate matter that may be retained under the third eyelid or conjunctival fornices.

Once irrigation is completed, assessment of the cornea and globe can be performed. Treatment with anticollagenase medications, topical antibiotics, mydriatics, systemic tetracycline, and systemic steroidal or nonsteroidal medication are recommended (Pfister et al., 1991; Schultz et al., 1994; Seedor et al., 1987). In cases of deep ulceration or perforation, emergency conjunctival or amniotic membrane grafts may be needed to preserve the eye. Prognosis for vision is guarded in these dogs.

Corneal ulceration in the dog may also result from ocular exposure to the defensive spray of walking stick insects in the genus *Anisomorpha* (Brutlag et al., 2011; Dziezyc, 1992). These insects are indigenous to the southeastern United States, Central America, and South America. When threatened, the walking stick insects release a chemical spray containing the toxin terpene dialdehyde. Canine ocular exposure to the spray may result in intense blepharospasm, epiphora, conjunctivitis, and superficial corneal ulceration. Ocular irrigation, topical antibiotics, topical atropine, and ocular lubricants resulted in clinical resolution without permanent corneal sequelae in the reported canine cases (Brutlag et al., 2011; Dziezyc, 1992).

Melting Ulcers (Collagenase-and Protease-Associated Ulcers)

Melting ulcers with progressive stromal dissolution (i.e., keratomalacia) are not a specific group; rather, they are a complicating component of corneal ulcers. During normal corneal healing, proteases and collagenases are produced that aid in removal of devitalized cells and debris from the cornea. Corneal epithelial cells, fibroblasts, polymorphonuclear leukocytes, and some microorganisms produce proteases and collagenase (Matsumoto, 2004). In some corneal ulcers, these enzymes contribute to the progressive breakdown and rapid "melting" of the corneal stroma. With keratomalacia, the corneal stroma assumes a gelatinous appearance and may be anteriorly displaced from its normal anatomic boundaries (see Fig. 19.40).

Acute ulcerative keratitis with progressive melting requires vigorous topical therapy. Appropriate broad-spectrum antibiotics and atropine are applied (see earlier discussion). Successful management of melting ulcers lies in eliminating infection and reducing the impact of collagenase and other proteases on the cornea.

Control of Proteolytic Activity in the Treatment of Ulcerative Keratitis

There is increased proteinase activity in animal eyes with corneal ulcers and particularly melting ulcers (Ollivier et al., 2007; Wang et al., 2008a). Success of medical and surgical treatment of corneal ulcers is reflected by the proteolytic activity in tears. Effective treatment leads to a rapid reduction in tear film proteolytic activity that corresponds with the improvement in the clinical signs of corneal ulceration (Wang et al., 2008a). Normalizing proteolytic activity in the tear film is an objective of the treatment of corneal ulcers.

Protease inhibitors are recommended for treatment of ulcerative keratitis to reduce progression of stromal ulcers, speed epithelial healing, and minimize corneal scarring (Berman, 1975; Berman et al., 1975). Protease inhibitors that can be used include autologous serum (Berman, 1975; Berman et al., 1975; Conway et al., 2015; Conway et al., 2016), *N*-acetyl-cysteine (NAC) (Kanao et al., 1993; Petroutsos et al., 1982), disodium ethylenediaminetetraacetic acid (EDTA), tetracyclines (e.g., oxytetracycline, doxycycline) (Perry et al., 1993; Seedor et al., 1987), and newer compounds such as thiol agents, including ilomostat (Table 19.2) (Barletta et al., 1996; Schultz et al., 1992b). The inhibitory effect of these compounds on tear proteolytic activity was shown *in vitro* (Ollivier et al., 2007). As these compounds function by different mechanisms to inhibit various proteases, a combination of protease inhibitors may be beneficial (Woessner, 1991, 1999). In general, proteinase inhibitors should be instilled in the eye every 1–2 hours until healing begins, indicated by a reduction in pain, a static or contracting ulcer, and smoothing of the epithelial margin. Thereafter, the application can be reduced to four to six times a day (Ollivier et al., 2007). Serum from a variety of species (canine, feline or equine) appears to be similarly effective and remains effective when stored at either -20 °C or -80 °C for up to 180 days (Conway et al., 2015). Plasma has also been shown to be an effective substitute for serum for the treatment of keratomalacia (Conway et al., 2016).

Corneal Cross-Linking

Corneal collagen cross-linking (CXL) is based on the principles of exposure of the photosensitizer riboflavin (Vitamin B_2) to UV-A light with a wavelength at the riboflavin absorption peak of 370 nm. The photopolymerization process is driven by oxygen free radicals resulting in the introduction of additional covalent cross-links within collagen fibers and in the proteoglycan–glycosaminoglycan ground substance of the corneal stroma up to a depth of 300 μm (Famose, 2013; McKay et al., 2017; Spoerl et al., 2007; Williams et al., 2017).

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Table 19.2 Antiproteolytic agents for topical treatment of melting corneal ulcers.

Compound	Concentration used	Inhibitory activity	Inhibitory mechanism
Tetracyclines (doxycycline, oxytetracycline)	0.1%[a]	MMPs inhibitor	Chelating agent (Ca and Zn)
N-acetyl-cysteine (NAC)	5%–10%	MMPs inhibitor	Chelating agent (Ca and Zn)
Disodium ethylene-diaminetetra-acetic acid (EDTA)	0.2%[b]	MMPs inhibitor	Chelating agent (Ca and Zn)
Ilomostast (Galardin)	0.1%	MMPs inhibitor	Chelating agent (Ca and Zn)
Serum	Undiluted[c]	MMPs and serine proteinases inhibitor	Various
(_2-macroglobulin and _1-proteinase inhibitor)			Entrapment of the protease
_1-proteinase inhibitor	0.1%	Serine proteinase inhibitor	Entrapment of the protease

Matrix metalloproteinases (MMPs) require Ca and Zn as cofactor and stabilizing ion, respectively.
[a] Note that doxycycline can also be administered orally (10 mg/kg, SID).
[b] Easily made by the addition of 5 mL of sterile water to a commercial blood collection tube.
[c] Serum stored in the refrigerator can be used for up to 8 days. It should then be discarded because of the risk of bacterial contamination.

The benefit to the cornea is an increase in the biomechanical and biochemical stability, an increase in collagen packing density and a reduction in the swelling tendency of the glycosaminoglycan-rich ground substance. Reactive oxygen species (ROS)-induced damage to cells and reduction in microorganisms in the irradiated area has also occurred (Speiss et al., 2014; Pot et al., 2014).

Following the introduction of CXL for the treatment of progressive keratoconus in humans (Wollensak et al., 2003), other uses for CXL emerged rapidly, including the treatment of melting keratitis, Fuchs' dystrophy and bullous keratopathy. Melting keratitis and bullous keratopathy are two interesting indications for the use of CXL in veterinary medicine because these diseases are potentially blinding and can be difficult to control both medically and surgically. CXL is effective in the treatment of corneal melting in dogs, cats, and horses (Speiss et al., 2014)

Therapy options are limited for bullous keratopathy in dogs. The frequent necessary application and local irritation can limit the usefulness of topical hypertonic saline treatment (Gilger et al., 2007). More invasive treatments including thermokeratoplasty and 360° conjunctival flap (Gunderson flap) placement can be used successfully to treat the epithelial defects, but these treatments further decrease corneal transparency. Partial coverage of the corneal surface with a thin conjunctival flap can function as a drainage sink for the edematous fluid in the stroma. This has been reported to increase corneal transparency. CXL with riboflavin and UV-A (CXL) decreases corneal edema and increases visual acuity in human patients with bullous keratopathy (Pot et al., 2014). Presumed mechanisms are an increase in collagen packing density and a reduction in the swelling tendency of the glycosaminoglycan-rich hydrophilic ground substance of the cornea (Pot et al., 2015). CXL has been successful in treating bullous keratopathy in dogs (Pot et al., 2015).

Corneal Sequestrum

Corneal sequestrum is rarely reported in dogs (Bouhanna et al., 2008; Deutsch et al., 2011; Dubin et al., 2013). Brown- or black-discolored corneal stroma associated with nonhealing corneal ulceration was observed clinically (Fig. 19.46). The corneal lesions corresponded microscopically with an acellular layer of corneal stroma surrounded by vascularization and leukocytes without the presence of melanin. Canine corneal sequestrum appears to be clinically and histologically similar to feline corneal sequestrum (see Chapter 28). Keratectomy is reported to be curative.

Nonulcerative Keratitis

Pigmentary Keratitis (Superficial Pigmentary Keratitis)

Pigmentary keratitis develops secondary to chronic corneal irritation in the dog (Fig. 19.47). Corneal pigmentation can be a nonspecific response to chronic keratitis in any canine breed; however, some brachycephalic breeds (e.g., Pug, Boston Terrier, Shih Tzu, Lhasa Apso, Pekingese) appear prone to marked and rapid corneal pigmentation. The term 'pigmentary keratitis' is often used to specifically describe this clinical syndrome in brachycephalic dogs. Focal corneal pigmentation often begins in these dogs in the nasal cornea and then progresses at a highly variable rate over

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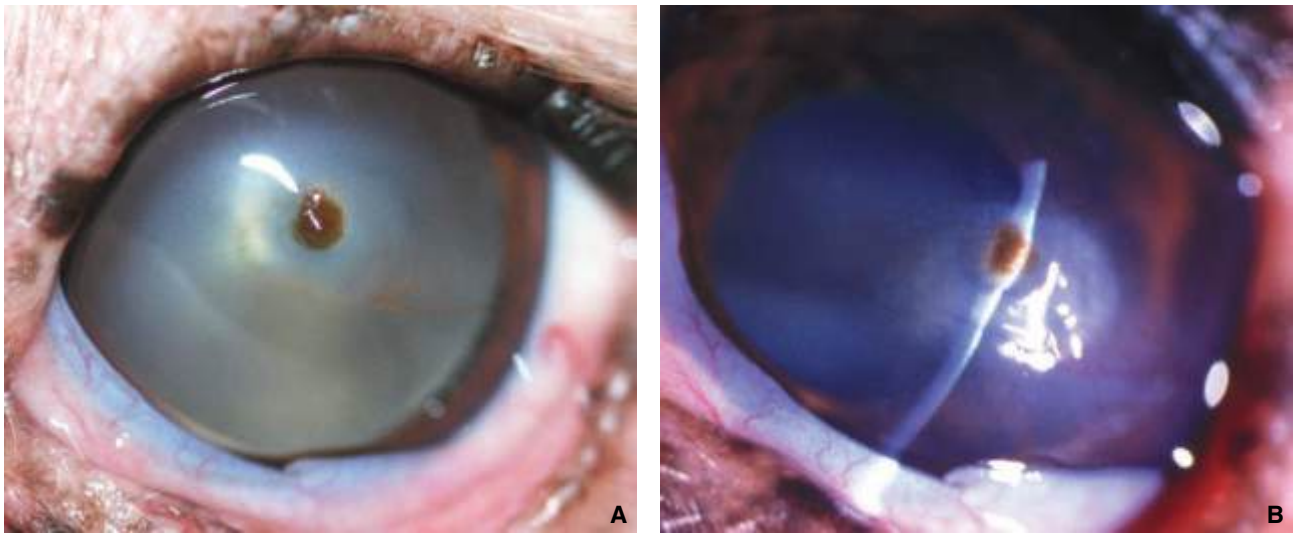


Figure 19.46 Clinical (**A**) and slit lamp (**B**) photographs of a corneal sequestrum in a Havanese dog developing secondary to external corneal trauma in a Havanese dog. (*Source:* Courtesy of the Animal Health Trust.)



Figure 19.47 Pigmentary keratitis in a dog with chronic keratitis.

the ocular surface. Corneal pigmentation results from migration of perilimbal melanocytes into the cornea and deposition of melanin granules within corneal epithelial cells (Bellhorn & Henkind, 1966; McCracken & Klintworth, 1976). Pigmentation is frequently associated with chronic keratitis and vascularization of the cornea. Pigmentary keratitis is often a multifactorial condition. The most common causes of pigmentary keratitis include chronic irritation from distichiasis, nasal fold trichiasis, entropion, ectropion, KCS, and chronic exposure resulting from macropalpebral fissure which occurs in many brachycephalic breeds (Krecny et al., 2015).

In a recent study, IVCM was used to demonstrate features of SCP in two groups of untreated brachycephalic dogs: Pugs and non-Pug brachycephalic dog breeds. When superficial corneal pigmentation was present, both groups of dogs showed microscopic evidence of presumed corneal melanin with associated inflammatory pathology, supporting the continued use of the term 'pigmentary keratitis' to describe this condition (Vallone et al., 2017). Pigmentary keratitis was morphologically characterized by specific pathological lesions that were common to Pugs and non-Pug brachycephalic dogs observed using IVCM. Abnormalities were seen consistently in the corneal epithelium and included several cellular changes consistent with chronic corneal inflammation. In addition to epithelial pigment granules within the superficial and basal corneal epithelium, SCP-affected dogs from both groups consistently showed epithelial disorganization, anterior stromal dendritic cells, Langerhans cells, and vascularization. The presence of these cell types, which are cellular markers of inflammation, supports the nomenclature of pigmentary keratitis to denote accurately the underlying chronic inflammatory pathology of this syndrome (Vallone et al., 2017). In the brachycephalic breeds represented in this study, pigmentary keratitis appears morphologically as a centripetal corneal migration of microanatomic features normally confined to the perilimbal region of the cornea. Future studies are needed to characterize better the pathogenesis of this syndrome in order to develop targeted treatment strategies.

Treatment, currently, is directed at halting the progression of pigmentation and correcting the inciting cause. Correction of entropion or ectropion, removal of abnormal lashes and aberrant dermis, and possible partial removal of nasal folds usually prevents additional pigmentation. In brachycephalic breeds, a combination of surgical procedures, which usually include removal of aberrant dermis in the medial canthus, correction of lower medial eyelid entropion, and lateral or

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medial canthoplasty, will often prevent disease progression (Yi et al., 2006). Tear production should be evaluated frequently in these dogs because KCS is a common contributory cause of diffuse pigmentary keratitis (Kaswan et al., 1989). Low temperature cryotherapy has also been reported to be successful (Azoulay et al., 2014).

Surgical removal of pigmentary keratitis has been suggested if the inciting causes have been corrected (Gilger et al., 2007). However, frequent recurrence of the pigment and corneal scarring, despite appropriate therapy, generally limits the success of superficial keratectomy alone. Application of beta radiation by strontium-90β plesiotherapy or cryotherapy has also been used, but the overall success rate is unknown. Topical cyclosporine, corticosteroids, and tacrolimus have been administered topically in the treatment of pigmentary keratitis. The clinical efficacy of these treatments is unknown, although studies have shown effectiveness in treatment of inflammatory disease of the canine cornea (i.e., CSK) and its associated corneal pigmentation (Nell et al., 2005; Williams et al., 1995). Cyclosporine is also shown to inhibit cell proliferation and melanogenesis in cultured human melanocytes (Lee & Kang, 2003).

Chronic Superficial Keratitis (Pannus)

CSK is a progressive, bilateral, inflammatory, and potentially blinding disease of the canine cornea (Bedford & Longstaffe, 1979; Campbell & Synder, 1973; Campbell et al., 1975; Eichenbaum et al., 1986; Nell et al., 2005; Rapp & Kolbl, 1995; Slatter et al., 1977; Williams, 1999; Williams et al., 1995). It is also known as German Shepherd pannus, Uberreiter's syndrome, and degenerative pannus. Clinically, CSK is manifested initially at the temporal or inferior temporal limbus as a red, vascularized, conjunctival lesion. Early in the disease, vascularization and pigmentation occur at the temporal cornea and progress centrally (Fig. 19.48). As the disease progresses, it spreads as a fleshy, well-vascularized lesion that migrates toward the central cornea. A white, crystalline line or small white foci often can be found clinically in the clear corneal stroma, located 1–2 mm in front of the leading edge of the lesion and advancing blood vessels. With time, corneal neovascularization also begins at the nasal limbus and extends centrally. As with many corneal diseases involving superficial vascularization, limbal melanocytic pigment invasion occurs. The superior portion of the cornea usually remains unaffected until late in the disease. Eventually, the entire cornea may become vascularized, pigmented, and opaque. Some dogs with CSK also develop concurrent thickening and pigmentation of the palpebral surface of the nictitating membrane.

German Shepherds, Shepherd crosses, and Greyhounds are most commonly affected dogs with CSK, but it can occur in any canine breed. A sex-bias toward females is frequently reported (Bedford & Longstaffe, 1979; Jokinen et al., 2011) but a male bias has also been reported (Drahovska et al., 2014). Both the incidence and severity increase at higher altitudes (>4000 feet) (Bedford & Longstaffe, 1979; Slatter et al., 1977). In one study, dogs living at altitudes >7000 ft above sea level were 7.75 times more likely to develop CSK than dogs living at elevations between 3000 and 5000 ft (Chavkin et al., 1994). Dogs from lower elevations with CSK tend to respond more favorably and with less intensive topical therapy than animals with the disease living at higher elevations.

The age of onset and breed of the affected animal are of prognostic value in this condition. In German Shepherds affected at a fairly young age (i.e., 1–5 years), the condition is usually rapidly progressive and severe. In those animals first affected later in life (i.e., 4–6 years), however, the lesions appear be less severe and to progress more slowly.



Figure 19.48 Mild (**A**) and severe (**B**) chronic superficial keratitis in the German Shepherd breed.

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Greyhounds, however, tend to be affected at younger ages, usually less than 2 or 3 years, but exhibit relatively mild lesions (Lynch, 2007).

Histopathologic Features of Chronic Superficial Keratitis

CSK appears initially as superficial corneal vascularization, with progressive infiltration of granulation tissue into the superficial corneal stroma. The invading fibrovascular tissue is accompanied by lymphocytes and plasma cells. Generally, the corneal epithelium remains intact, but may be variably hyperplastic or atrophied. Migration of pigment-laden cells (i.e., corneal melanosis) commonly accompanies the fibrovascular inflammatory infiltrate invading the anterior stroma. Infiltrating $CD4^+$ lymphocytes are the predominant cell types found in CSK, suggesting an immune-mediated pathogenesis. The CD4/CD8 ratio of infiltrating lymphocytes was consistently above two and rose to above four at the advancing border of the lesion in one study (Williams, 1999). In another study, immunohistochemical staining for canine immunoglobulin was noted in the superficial conjunctival stroma near the limbus and, in some specimens, in the superficial corneal stroma, but immunoglobulin was not present in the overlying epithelium, differentiating this condition from several other autoimmune diseases such as the pemphigus group and systemic lupus erythematosus (Eichenbaum et al., 1986). Increased stromal and epithelial cell MHC class II antigen expression was detected in the central cornea of dogs with CSK (Williams, 2005). Since upregulation of MHC class II expression occurs on peripheral antigen presenting cells during an inflammatory response and is associated with increased presentation of extracellular antigens and activation of an immune response, this finding suggests that these cells play a role in perpetuating corneal inflammation and permitting the development of autoimmune reactions to normal canine corneal antigens. Elevated expression of MMPs in the cornea of dogs with CSK is reported, and it was suggested that induction of MMPs activity by ultraviolent radiation may be linked to the development of CSK (Chandler et al., 2008). Combining the results of these two studies suggests that MMP-mediated enzymatic generation of altered ECM components, may be subsequently presented by MHC Class II by corneal keratinocytes and/or stromal keratocytes, resulting in the generation of an immune response to the damaged matrix.

Cause

The cause of CSK in the dog has not been established, but current evidence suggests the condition is an immune-mediated disease with a genetic basis. The cornea possesses tissue-specific antigens that may be modified by external factors such as ultraviolet light. Ultraviolet radiation may alter the antigenicity of susceptible corneas, thereby resulting in cell-mediated inflammation in susceptible dogs (Campbell et al., 1975; Eichenbaum et al., 1986; Stanley, 1988). An MHC class II risk haplotype was identified in German Shepherds with CSK, strongly suggesting the autoimmune nature of the condition. Dogs with the risk haplotype were 2.7 times more likely to develop CSK than dogs with other haplotypes, and homozygosity of the risk haplotype increased this risk to more than 8 times (Jokinen et al., 2011). CSK is characterized by increased numbers of mast cells and increased degranulation of mast cells compared with those of normal dogs and dogs with other forms of keratitis. This increase in mast cell activity, as well as the hypersensitivity response to corneal proteins displayed by dogs with CSK, further suggests involvement of an immune-mediated mechanism (Campbell et al., 1975). An additional indication that CSK is an immune-mediated condition is the clinical observation that CSK can be controlled by topical administration of corticosteroids and cyclosporine (Williams et al., 1995).

Evaluations for underlying infectious agents did not demonstrate the presence of organisms in CSK. Evaluation of CSK samples for *Chlamydia* was negative (Campbell & Synder, 1973). The finding of cylindrical cytoplasmic inclusions in corneal fibroblasts, vascular endothelial cells, macrophages, and trabecular cells of the eyes of dogs with CSK, but not normal dogs, suggested a viral infection, but none was detected (Rapp & Kolbl, 1995).

Diagnosis and Differential Diagnosis

Signalment and clinical appearance of the lesions are usually sufficient to allow a diagnosis of CSK to be made (see Fig. 19.48). CSK must be distinguished from pigmentary keratitis resulting from other causes (e.g., chronic irritation), KCS, and corneal granulation tissue resulting from vascular healing of corneal wounds.

Treatment

CSK can usually be controlled by a variety of medical and surgical methods, but it cannot be cured. Owners should be advised of the need for lifelong therapy to control this disease and that both severity and prognosis depend on many factors, including age of onset, altitude, and geographic location. Vision can usually be preserved with medical therapy alone in areas of low to medium elevation (i.e., <1220 meters) and in cases of mild lesions occurring in middle-aged and older dogs (Austad & Oen, 1978a, 1978b). At higher elevations, additional therapies may be required. Initial therapy usually consists of topical corticosteroid ointments or solutions (i.e., 0.1% dexamethasone or 1.0% prednisolone) three to four times daily for 3–4 weeks, followed by a reduced maintenance schedule. Dogs on long-term corticosteroids should be monitored for ocular infection or corneal ulceration.

Topical cyclosporine (0.2%–2.0%), with or without concomitant corticosteroids, is often effective in controlling CSK. Cyclosporine ophthalmic ointment (0.2%) applied to affected

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corneas twice daily was shown to be as effective as treatment with topical dexamethasone at ameliorating clinical signs (Williams et al., 1995). In one study, 1% pimecrolimus given topically three times a day resulted in total or moderate regression of the CSK in four of six dogs (Nell et al., 2005). Topical treatment with 0.02% tacrolimus and 50% DMSO has also been reported to be effective (Balicki, 2012). In some cases, subconjunctival injection of corticosteroids in addition to topical therapy may also be necessary to control the disease. If topical and subconjunctival corticosteroids are ineffective or only minimally effective, application of beta radiation (i.e., strontium-90β plesiotherapy) may be used alongside medical therapy (Höcht et al., 2002). Two 15 Gy surface doses administered twice within 2 days was reported to markedly improve clinical signs with minimal adverse effects (Höcht et al., 2002). An alternate single dose protocol was described: 4500–7500 rads per circle, up to a maximum of six slightly overlapping circles per cornea, with complete corneal coverage and overlapping the limbus by 1–2 mm (Whitley & Gilger, 1999; Gilger et al., 2007; Ledbetter & Gilger, 2013). Radiotherapy with soft X-rays (low energy and longer wavelengths) is described for the dogs with CSK that respond poorly to medical therapy alone (Allgoewer & Hoecht, 2010). A total corneal dose of 30 Gy, administered in two 15 Gy fractions over a 48- to 96-hour period, resulted in improvement in corneal pigmentation and vascularization with only minor and transient adverse effects.

Superficial keratectomy may be required for severe cases in which blindness has resulted from pigmentation of the central cornea, but recurrence should be expected and repeat keratectomies may need to be performed. Intensive medical therapy, beta irradiation, or soft X-ray irradiation should be used after keratectomy to prevent or delay recurrence. Ultraviolet light-blocking soft contact lenses were evaluated for the treatment of dogs with CSK (Denk et al., 2011). No positive effects were detected with the contact lenses, but complications associated with lens wear, owner compliance issues, and possible changes in ultraviolet light transmittance by the lens cleaning process may have impacted study results.

Neurogenic Keratitis

Two forms of neurogenic keratitis occur: *neurotrophic keratitis*, which is associated with lack of sensory innervation (trigeminal nerve); and *neuroparalytic keratitis*, which results from lack of motor innervation (facial nerve) to the orbicularis oculi muscle of the eyelids, with facial paralysis.

Neurotrophic keratitis is a form of chronic keratopathy and poor corneal healing resulting from damage to the trigeminal nerve, which provides sensory innervation to the cornea (Scott & Bistner, 1973). It has a variety of etiologies in the dog, including after orbital trauma or with cavernous sinus syndrome (Rossmeisl et al., 2005; Theisen et al., 1996). This disease leaves the cornea susceptible to injury and decreases reflex tearing. The lack of sensory innervation to the cornea results in decreased cell metabolism, increased permeability, and decreased cell mitosis. Lack of sensory neuromediators (e.g., acetylcholine, substance P, and calcitonin gene-related peptide) may decrease epithelial cell proliferation and lead to an epithelial defect even in the absence of injury.

Clinical features early in the disease process may include a roughened corneal surface, rose Bengal-positive staining, decreased tear breakup time, and punctate fluorescein dye retention (Mackie classification stage 1). A Cochet-Bonnet esthesiometer can be used to assess corneal sensitivity (Barrett et al., 1991) and assist with early diagnosis. With increased severity, with or without chronicity, there may develop a superficial corneal ulcer surrounded by a rim of loose epithelium, corneal edema, and a secondary anterior uveitis (Mackie classification stage 2). In some cases, the disease progresses to corneal melting and perforation (Mackie classification stage 3) (Mackie, 2000).

A complete neurologic workup including cranial nerve examination should be performed to locate the underlying abnormality for neurotrophic keratitis. Treatment is directed at the underlying cause for neurotrophic keratitis. Additionally, for stage 1 disease, topical artificial tears and antibiotics are used until sensitivity recovers. For stage 2, topical oxytetracycline, atropine, and management of the corneal ulcer are indicated. In some cases, a conjunctival or amniotic membrane graft may be required, especially for those that have progressed to stage 3. Topical nerve growth factor or other neuropeptides may also be considered (Lambiase et al., 2003; Woo et al., 2005).

Neuroparalytic keratitis from loss of eyelid movement often results in severe exposure ulcerative keratitis and possible vision loss (Kern & Erb, 1987). During the early stages of these diseases, epithelial degeneration and stromal edema occur. As the condition advances, there is corneal drying, vascularization, and opacification. The ulcerative keratitis may progress to corneal perforation. Treatment is often symptomatic. Temporary tarsorrhaphies may prevent corneal trauma and drying. If there is no response in 2–3 weeks, a temporary tarsorrhaphy with suturing of the eyelids for up to 6 months to 1 year may be used. Animals should also be treated with topical lubricants and antibiotics to prevent secondary bacterial infection. If response to therapy is not satisfactory, a permanent tarsorrhaphy or enucleation may be necessary.

Corneal Abscessation

A corneal abscess is an accumulation of inflammatory cell debris in the superficial or deep stroma. Affected eyes are intensely painful and have a distinct, raised, yellow-white corneal stromal opacity. Abscesses must be differentiated from a corneal epithelial inclusion cyst, which is generally not painful (see later discussion). The abscess may be sterile or contain an infectious agent (Ledbetter et al., 2006a). Corneal stromal abscessation appears to be less common in

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the dog than in the horse. Corneal scrapings are obtained for bacterial and fungal culture, susceptibility tests, and for cytologic examination. Therapy consists of topical antimicrobials and atropine. Curettage or keratectomy followed by placement of a conjunctival graft is highly effective.

Parasitic Keratitis

Leishmania is a genus of protozoal parasites transmitted by sandflies. Canine leishmaniasis is endemic in the Mediterranean basin but is reported in many other regions of the world including Asia and North, Central, and South America (Alvar et al., 2004). Keratitis occurs frequently in dogs with leishmaniasis and is usually present concurrent with systemic disease and other ocular lesions. Corneal lesions associated with leishmaniasis are commonly distributed adjacent to the limbus and include regional corneal edema, leukocyte infiltrates, vascularization, and raised corneal nodules (Fig. 19.49) (Ciaramella et al., 1997; Peña et al., 2000). Granulomatous or lymphoplasmacytic inflammation with *Leishmania* organisms are detected microscopically in the cornea of infected dogs (Brito et al., 2010; Peña et al., 2008).

Onchocerca spp. are filarial nematodes that most frequently produce periorbital inflammation or subconjunctival nodules in dogs (Sreter et al., 2002). Canine ocular onchocercosis is reported in Europe and the western United States. Canine ocular onchocercosis may be associated with concurrent keratitis, and peripheral corneal vascularization, stromal granulation tissue, corneal edema, epithelial ulceration, and limbal granulomas are described (Komnenou et al., 2003; Zarfoss et al., 2005). Viable mature *Onchocerca* have been surgically extracted from the canine cornea (Eberhard et al., 2000). Canine ocular onchocercosis in the United States has been documented to be caused by *Onchocerca lupi* (Labelle et al., 2013b).

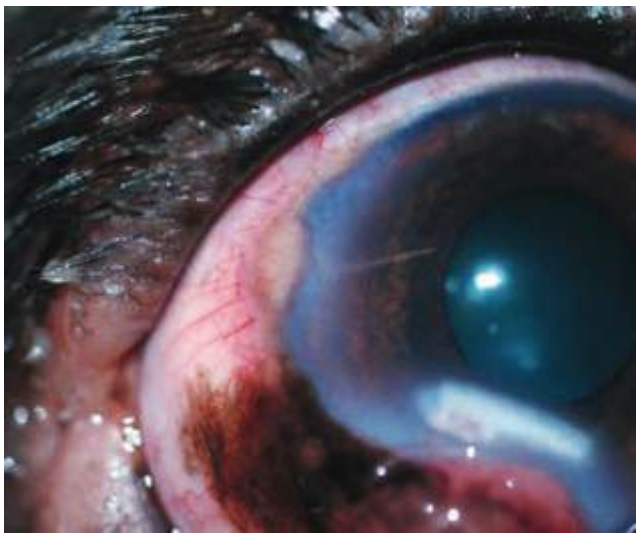


Figure 19.49 Peripheral keratitis in a Boxer with leishmaniasis. Corneal edema, leukocyte infiltrates, vascularization, and a discrete white limbal nodule are present. (*Source:* Courtesy of Dr. M.T. Peña.)

Toxoplasma gondii keratitis was described in a dog with KCS and pigmentary keratitis that presented with a raised, pink, vascular corneal mass (Swinger et al., 2009). The mass was removed by superficial keratectomy and consisted of suppurative inflammation with protozoal organisms. It was speculated that development of localized ocular toxoplasmosis in the dog was associated with administration of topical immunomodulating therapeutics.

Protozoal keratitis and conjunctivitis were noted in five dogs with fleshy corneal or conjunctival masses (Beckwith-Cohen et al., 2016). Histologic examination revealed granulomatous inflammation with intralesional protozoal organisms: amoeba (2), *Toxoplasma gondii* (2), or *Leishmania mexicana* (1). All dogs had been treated with topical tacrolimus or cyclosporine for at least 1.2 years. These lesions clinically appeared similar to nodular episcleritis or squamous cell carcinoma emphasizing the importance of biopsy prior to aggressive therapy or enucleation.

Seven dogs in Brazil with varying degrees of superficial corneal opacities affecting the perilimbal and central regions of the cornea were found to have free microfilaria within the cornea (Morales et al., 2018). Affected dogs were not in pain and did not have corneal ulceration. Microfilaria were also found in skin lesions, but no adult worms were found in any tissue of any dog. The species of microfilaria was not able to be identified. Monthly doses of oral ivermectin improved both the ocular and dermal lesions.

Severe symblepharon secondary to suspected ophthalmomyiasis externa has been reported in a dog (Delgado, 2012). At presentation, dipterous fly larvae were removed from both eyes. Both eyes were treated with resection of the symblepharon and superficial keratectomy. The patient regained vision and remained visual 36 months after surgery.

Superficial Punctate Keratitis

Superficial punctate keratitis can be found most commonly, but not exclusively, in the Shetland Sheepdog and Longhaired Dachshund (Clerc & Jegou, 1996; Dice, 1984). Clinically it appears as multiple, punctate or circular, grey, superficial corneal opacities that may or may not be ulcerated (Fig. 19.50). The condition is bilateral and lesions are frequently symmetric. When ulcerated, dogs demonstrate signs of discomfort (e.g., epiphora and blepharospasm). The corneal ulcers are typically recurrent, and lesions can progress to crystalline corneal deposits and diffuse corneal edema, pigmentation, and vision loss. The pathogenesis of this condition is unknown, but superficial punctate keratitis has been suggested to be an

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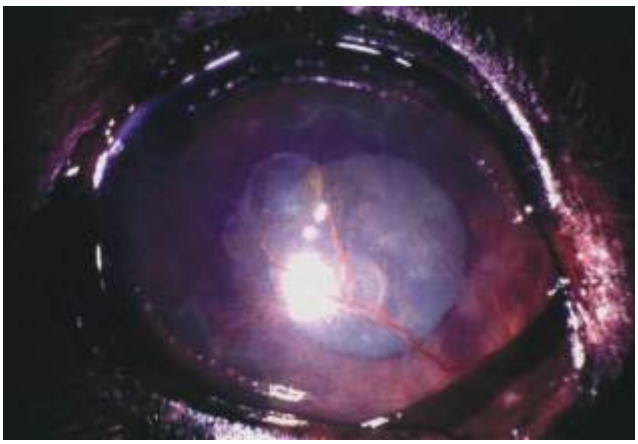


Figure 19.50 Dachshund with superficial punctate keratitis.

immune-mediated or dystrophic corneal disease. Lymphoplasmacytic inflammation is reported in corneal biopsies from Dachshunds with acute disease (Clerc & Jegou, 1996). The relationship of this condition in the Shetland Sheepdog to what has also been described as Shetland Sheepdog corneal dystrophy (see later section) is undetermined, but they may be analogous (Dice, 1984). Treatment consists of topical cyclosporine or corticosteroids combined with a topical antibiotic when ulcerations are present (Clerc & Jegou, 1996). The clinical response to therapy is typically rapid. Long-term maintenance therapy with cyclosporine may prevent recurrence of corneal ulcers.

Infectious Crystalline Keratopathy

Infectious crystalline keratopathy (ICK) has recently been described in dogs and cats (Ledbetter et al., 2017). ICK is a distinct corneal infection first described in human patients in the 1980s (Gorovoy et al., 1983; Meisler et al., 1984). Dogs and cats presented with fine, needle-like, and branching white crystalline anterior stromal opacities emanating from corneal facets or corneal epithelial defects (Ledbetter et al., 2017) (Fig. 19.51). Concurrent ocular and systemic diseases were common, including KCS, diabetes mellitus, hyperadrenocorticism, and malignant neoplasia. Bacteria, with minimal or absent leukocytes, were present in histopathology and cytology. Histologically, the crystalline corneal opacities corresponded with dense accumulations of bacteria present in the interlamellar corneal stromal spaces and forming projections in the stroma (Fig. 19.52). *In vivo* confocal microscopy showed deposits of reflective crystalline or amorphous structures within the stroma with a paucity of associated inflammatory changes (Fig. 19.53) (Ledbetter et al., 2017). The most commonly cultured bacteria were alpha-hemolytic *Streptococcus* and *Staphylococcus*

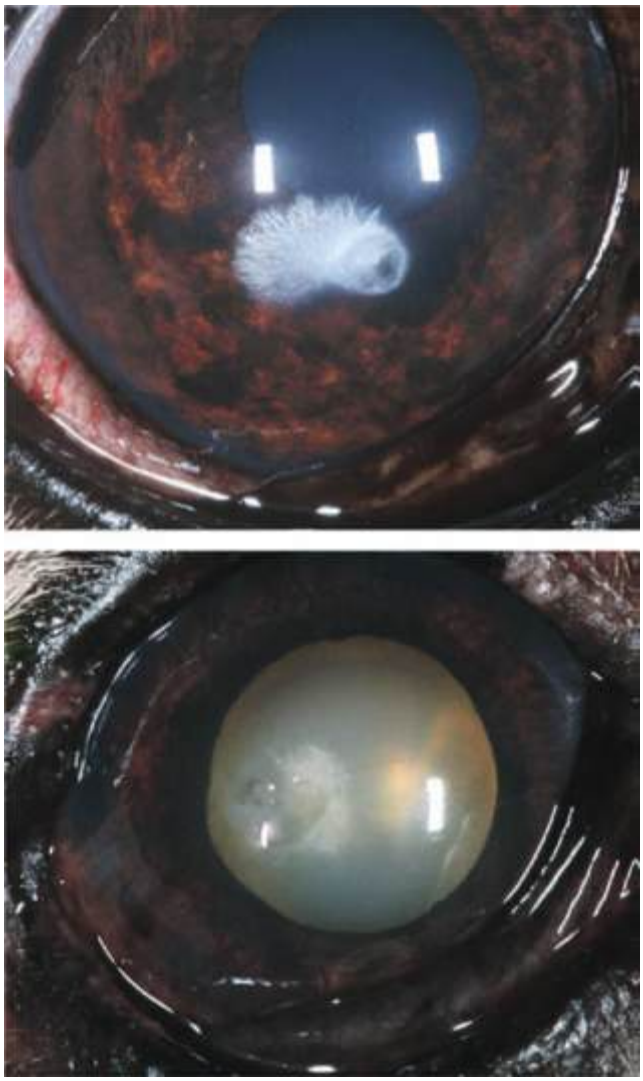


Figure 19.51 Clinical photographs of infectious crystalline keratopathy in a dog; fine, needle-like, branching, white crystalline anterior stromal opacities emanate from the peripheral borders of a corneal facet. (*Source:* From Ledbetter, E.C., McDonough, P.L. & Kim, K. (2017) Infectious crystalline keratopathy in dogs and cats: clinical, in vivo confocal microscopic, histopathologic, and microbiologic features of eight cases. *Veterinary Ophthalmology*, **26**, 250–258.)

species (McDonnell et al., 1991). *In vivo* confocal microscopy of the cornea was performed in most of the dogs and cats of this report and all had multiple, reflective, crystalline, or amorphous material in the corneal stroma corresponding to the region of the keratopathy. An abstract in 2014 described a single dog with a bacterial corneal infection clinically resembling ICK, but additional details were not provided (Beckwith-Cohen et al., 2014).

The proposed pathophysiology of ICK begins with an epithelial defect (surgical or associated with other ocular

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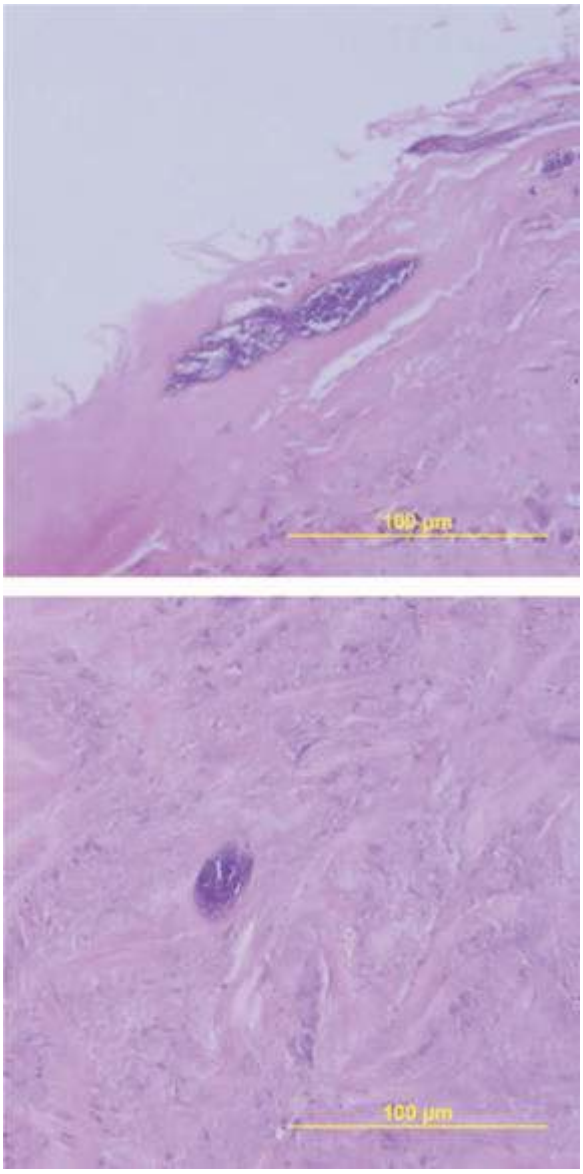


Figure 19.52 Histopathologic photomicrographs of anterior lamellar keratectomy specimens stained with hematoxylin and eosin from a dog with infectious crystalline keratopathy: interlamellar spaces are distended by pockets of bacterial cocci with a paucity of inflammatory cells in the stromal regions immediately surrounding the bacteria. (*Source:* From Ledbetter, E.C., McDonough, P.L. & Kim, K. (2017) Infectious crystalline keratopathy in dogs and cats: clinical, in vivo confocal microscopic, histopathologic, and microbiologic features of eight cases. *Veterinary Ophthalmology*, **26**, 250–258.)

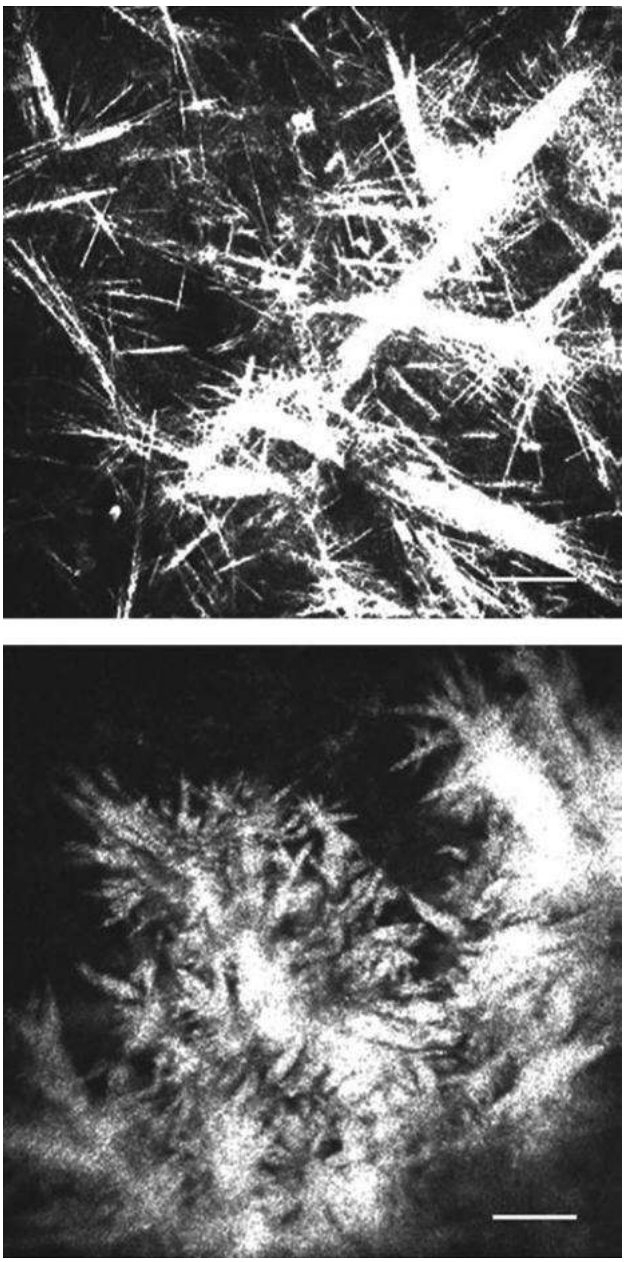


Figure 19.53 (**A, B**) In vivo corneal confocal photomicrographs of infectious crystalline keratopathy in two dogs: numerous, moderately to highly reflective stromal deposits that appear as needle-like branching structures, random geometrical shapes, or amorphous structures are present in the regions of the clinical keratopathy. Leukocytes and normal corneal anatomic structures are not present in the immediate vicinity of the keratopathy lesions. (Bars: 50 µm.) (*Source:* From Ledbetter, E.C., McDonough, P.L. & Kim, K. (2017) Infectious crystalline keratopathy in dogs and cats: clinical, in vivo confocal microscopic, histopathologic, and microbiologic features of eight cases. *Veterinary Ophthalmology*, **26**, 250–258.)

surface diseases) that allows invasion of the corneal stroma by relatively low virulence microorganisms (Matoba et al., 1994). Under these suboptimal growth conditions, the microorganisms slowly replicate along lamellar planes, with glycocalyx deposition, unhindered by host immunity or inflammation (Fulcher et al., 2001).

Biofilm production, low virulence organisms with slow growth rates, and local immunosuppression are all theorized to contribute to the absence of corneal inflammation. Local

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ocular immunosuppression appears especially critical to the development of ICK in humans as the majority of reported cases were receiving topical ophthalmic corticosteroid therapy (Chua et al., 2000; Huerva et al., 2012). Some of the dogs were also affected by immunosuppressive systemic diseases or receiving immunosuppressive systemic medications (Ledbetter et al., 2017). ICK is reported in systemically immunosuppressed humans, including individuals not receiving topical ophthalmic corticosteroids, and these conditions and medications may be additional risk factors for development of ICK in dogs (Ledbetter et al., 2017).

Long-term medical or surgical therapy was necessary for the resolution of clinical signs. Starting antimicrobial therapy was met with a pronounced and acute keratitis and anterior uveitis in some animals (Ledbetter et al., 2017).

Non-Inflammatory Keratopathies

Crystalline Corneal Opacities

There are three main clinical groups of corneal lesions that are associated with crystalline corneal opacities. Many of the clinical features are similar in these diseases, although the underlying causes of the opacity differ (Table 19.3). These groups include the corneal dystrophies, lipid keratopathy, and corneal degeneration. In general, corneal dystrophies are bilateral and inherited (i.e., observed in specific breeds), lipid keratopathy is associated with systemic lipid abnormalities (e.g., hypothyroidism, Cushing's disease), and degeneration is secondary to a localized ocular inflammatory process. These groups are not mutually exclusive and may have components of others, especially the development of degenerative components with chronicity (Laus et al., 2002).

Corneal Dystrophies

A corneal dystrophy is any primary, bilateral, inherited disorder of the cornea not accompanied by corneal inflammation or systemic disease (Cooley & Dice, 1990; Crispin, 1988; Crispin & Barnett, 1983). Most corneal dystrophies in the dog appear clinically as gray-white or silver, crystalline or metallic opacities in the central or paracentral cornea. The condition is bilateral and often appears as nearly symmetric lesions. Corneal dystrophy may affect the corneal epithelium, stroma, or endothelium. Variations in both size and density may represent different stages of progression for the dystrophy (Cooley & Dice, 1990; Crispin, 1988). Typically, the opacity is oval or circular, with the edge of the lesion well demarcated. The opacity is often in the anterior stroma with intact epithelium. On slit lamp biomicroscopy, a myriad of fine, small particles are often seen. These particles may be present throughout the cornea but are most commonly subepithelial. Frequently, cholesterol crystals and clefts are observed as well. In many cases, there are discrete, oval, or round areas of uniform opacity, though in some animals, the lesions are oval, ring-like (i.e., doughnut-shaped) opacities with a clear central zone (Cooley & Dice, 1990; Crispin, 1988). Corneal dystrophy is not primarily associated with corneal vascularization; however, with chronicity, the lipid accumulation may cause cell death and induce inflammation with subsequent development of corneal vascularization (Crispin, 1987b). This process is called corneal degeneration.

To rule out corneal infiltration from systemic disease (i.e., corneal lipidosis) in cases that are not typical of hereditary dystrophy, serum chemistry panels may be useful. In addition to cholesterol, high-density lipoprotein, low-density lipoprotein, fasting blood glucose, triglycerides, calcium, and phosphorus levels, it is often useful to evaluate thyroid and adrenal function. In a recent study, altered lipid metabolism (i.e., hypercholesterolemia, hypertriglyceridemia, and abnormal results of serum lipoprotein electrophoresis) was identified in some dogs with corneal dystrophy, but the pathophysiologic significance of these abnormalities has not been determined (Barsotti et al., 2008).

In general, corneal dystrophies do not respond to medical treatment and topical anti-inflammatory medications may exacerbate the lesion. Low-fat diets, such as Hill's w/d™ (Hill's Pet Nutrition Inc., Topeka, KS, USA), are anecdotally suggested to prevent progression of the disease (Barsotti et al., 2008; Gilger et al., 2007). The corneal lesions can be removed by keratectomy if the opacity is obstructing vision significantly. However, it is possible that the opacities will recur after keratectomy; therefore, surgery is recommended for corneal dystrophy only as a last-resort measure in dogs with significant visual deficit.

Breed-Predisposed Corneal Dystrophy

Several forms of corneal dystrophy occur in specific breeds, but detailed descriptions are available for relatively few of these (see Table 19.3). These include corneal dystrophy in the Beagle, Siberian Husky, Shetland Sheepdog, Cavalier King Charles Spaniel, Airedale Terrier, and Rough Collie. Posterior polymorphous dystrophy is described in the American Cocker Spaniel. Endothelial corneal dystrophy is observed in several breeds, including the Basset Hound, Boston Terrier, Boxer, Chihuahua, Dachshund, Miniature Schnauzer, and Poodle.

Oval Lipid Corneal Dystrophy in the Beagle Corneal stromal dystrophy containing lipid deposits occurs in the Beagle. Among 497 Beagles from 8 to 15 years of age, oval corneal opacities occurred in approximately 17%, and most of these animals were bilaterally affected (Waring et al., 1977, 1979). The corneal opacities are located at the junction of the middle and ventral one-third of the cornea. The lesions are horizontally oval and average 3 by 5 mm in size. Three morphologic types have been described: nebular,

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Table 19.3 Crystalline corneal opacities in the dog.

Clinical features	Associated conditions	Composition of opacity	Breed predisposition	Treatment
Corneal dystrophy				
Crystalline	Hereditary	Cholesterol	Beagles	Low-fat diet
Bilateral		Phospholipids	Siberian Husky	Do not breed
Symmetrical or asymmetrical		Fatty acids	Cavalier keratoconjunctivitis sicca	
Superficial or deep stroma			Rough Collie	
± ring-like			Shetland Sheepdog	
			Airedale	
Lipid keratopathy				
Unilateral or bilateral	Cushing's disease	Cholesterol	Rottweiler	Treat underlying cause
Asymmetrical	Hypothyroidism	Phospholipids	Miniature Schnauzer	Low-fat diet
Superficial stroma	Primary hyperlipoproteinemia	Fatty acids		
± perilimbal	Diabetes mellitus			
	High-fat diet			Low-fat diet
Corneal degeneration				
Unilateral	Keratitis	Cholesterol	Afghan Hound	Treat underlying cause
	Uveitis		Cocker Spaniel	
			German Shepherd	
Corneal vascularization	Episcleritis	Phospholipids	Golden Retriever	Low-fat diet
Superficial stroma	Scleritis	Fatty acids	Great Dane	Superficial keratectomy
Plaque-like or lacy (Ca^{++})	Chronic lipid keratopathy	Calcium	Labrador Retriever	1% disodium EDTA (Ca^{++})
± blepharospasm	Chronic corneal dystrophy		Old English Sheepdog	
Gritty (Ca^{++})			Rough Collie	
Epithelial loss (Ca^{++})			Springer Spaniel	
			Boxer	

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racetrack, and white arc. The nebular form has a uniform, ground-glass appearance, and occurs in the anterior one-third of the stroma (Fig. 19.54 and Fig. 19.55). The racetrack type consists of a more sharply demarcated, denser, gray oval ring and extends through the full thickness of the corneal stroma (Fig. 19.56). The white arc type has subepithelial, dense, white plaques of granular or spicule-shaped material overlying the nebular or racetrack pattern (Fig. 19.57). The epithelium is generally intact. Progression appears to be from the nebular to the racetrack to the white arc type (Ekins et al., 1980; Waring et al., 1977, 1979). Tear production and tear breakup times are normal, and no eyelid abnormalities are present.

Serum cholesterol values and triglyceride levels are within normal limits. Histochemically, the corneal deposits consist of neutral fats, cholesterol, and phospholipids (Ekins et al., 1983; Roth et al., 1981). Neutral fats appear both within keratocytes and diffusely in the stroma; the cholesterol and phospholipids primarily appear intracellular. Approximately 50% of the corneas in one study showed intracellular fatty acids, and glycosaminoglycan levels were within normal limits (Ekins et al., 1983; Morrin et al., 1982).

Crystalline Corneal Dystrophy in the Siberian Husky Crystalline corneal dystrophy is inherited as a recessive trait with variable expressivity in the Siberian Husky (MacMillan et al., 1979; Waring et al., 1979, 1986). This form of dystrophy appears round or horizontally oval, with a diffuse, gray, homogeneous haze in the anterior stroma or an array of fine, polychromatic crystals in the posterior stroma (or both) (Fig. 19.58). The corneas are not inflamed. This form of dystrophy is apparent in dogs between 5 and 27 months of age (Waring et al., 1986).



Figure 19.54 Clinical appearance of a nebular form of corneal dystrophy in a Beagle.

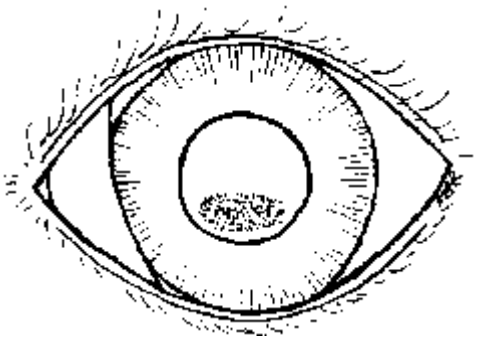


Figure 19.55 Nebular-type oval corneal opacity in a Beagle. The edges are indiscrete and variation in density is present.

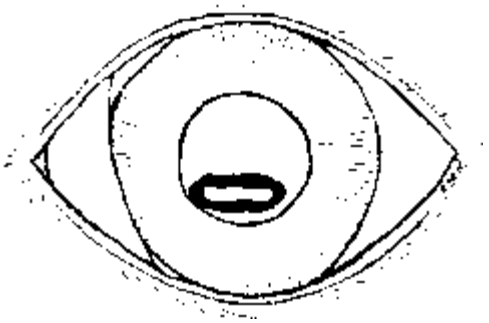


Figure 19.56 Racetrack-type oval corneal opacity in a Beagle. Note the outer, dense, irregular gray opacity and the clearer inner zone.

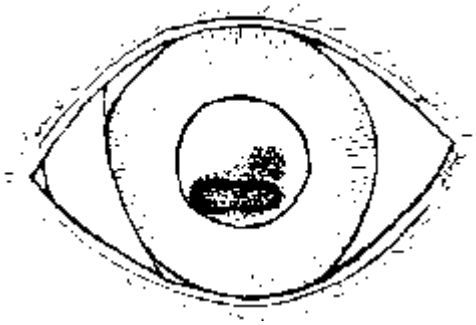


Figure 19.57 White arc-type oval corneal opacity in a Beagle. Note the white peripheral arc forming a complete circle around a homogeneous, gray-brown zone.

Five clinical patterns of crystalline corneal opacities can occur. The first and earliest pattern consists of refractile polychromatic crystals in the posterior stroma adjacent to Descemet's membrane. The second has gray-brown, homogenous, smudgy deposits within the anterior stroma and the posterior stromal crystalline opacities, with clear stroma between. The third has gray-brown, homogeneous deposits in the anterior stroma, with the remainder of the stroma

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Figure 19.58 Crystalline corneal dystrophy in the Siberian Husky.

clear. In the fourth, gray-brown, homogeneous deposits involve the posterior two-thirds of the stroma, and in the fifth, gray-brown, homogeneous deposits involve the entire thickness of the corneal stroma.

Results of histochemical staining reveal lipids in the subepithelial stroma and in some keratocytes. The dystrophic areas contain neutral fats, phospholipids, and cholesterol (MacMillan et al., 1979; Waring et al., 1979, 1986).

Corneal Dystrophy in Shetland Sheepdogs A potentially unique form of bilateral corneal dystrophy occurs in the Shetland Sheepdog. It develops as superficial, multifocal, gray-white, circular or irregular rings 1–3 mm in diameter (Dice, 1984). This type of dystrophy begins in the central or paracentral cornea, but it becomes scattered throughout the cornea as the dog ages. The rings may contain facets or corneal erosions, and in some cases, recurrent corneal erosions occur. The dystrophic areas may contain crystalline material resembling corneal lipid deposits. A viral cause has been suggested, but this has not been confirmed.

Both males and females are affected equally. The age of onset is 6 months to 6 years, with most animals being affected at 3–4 years of age. In some cases, the condition is accompanied by blepharospasm and photophobia. Distichiasis may accompany the problem as well. Affected corneas do not tend to vascularize. Tear film breakup time is decreased to less than 10 seconds in affected dogs, and low T_4 (free serum thyroxine) levels as well as positive rheumatoid factors have been observed (Dice, 1984).

Microscopically, there is scarring in the epithelial area, with necrotic and dyskeratotic cells scattered within the epithelium (Dice, 1984). Epithelial cells have pyknotic nuclei, and the basement membrane may be focally absent. The anterior corneal stroma has increased numbers of cells.

Therapy for corneal erosions, when present, includes topical antibiotics, atropine, cyclosporine, and hyperosmotic preparations. Recurrent erosions may respond to debridement or superficial keratectomies. The condition can be controlled in some dogs with topical corticosteroids or cyclosporine used chronically or intermittently. Spontaneous remission of clinical signs may also occur. Although described and named as separate entities in published literature, this condition may be synonymous with superficial punctate keratitis (described in a preceding section) (Clerc & Jegou, 1996).

Corneal Dystrophy in the Cavalier King Charles Spaniel A subepithelial paracentral corneal lipid deposit occurs in some dogs between 2 and 4 years old. A characteristic bull's eye-shaped dystrophic lesion is found (Crispin, 1987a). Lesions were first noted after estrus in some dogs. No alterations in serum cholesterol, triglycerides, or lipoproteins were found. Corneal deposits contain fine striate crystals, usually packed closely in the subepithelial stroma. The underlying defect may be a local abnormality of corneal fibroblasts, and a polygenic mode of inheritance, possibly modified by environmental influences, has been proposed as well (Crispin, 1987a).

Corneal Dystrophy in the Airedale Terrier A form of lipid corneal dystrophy has been described in the male Airedale Terrier. In one study, animals were 9–11 months of age at presentation (Dice, 1974). Clinical signs include a milky opacity of both corneas with a 4–6 mm, clear peripheral zone. Marked subepithelial stromal opacity was seen extending to a depth of one-half to three-quarters of the corneal stroma. Pedigrees suggest a possible sex-linked, recessive pattern (Dice, 1974).

Microscopically, there is no evidence of inflammation, but subepithelial clumps of eosinophilic refractile bodies are observed. Results of histochemical studies are indicative of positive reactions for various lipids. No systemic dysfunctions of lipid metabolism have been noted (Dice, 1974).

Corneal Dystrophy in the Rough Collie The Rough Collie has been reported to have corneal dystrophy, which may or may not be associated with Collie eye anomaly (Crispin, 1988). The crystalline opacities were central or paracentral and were bilateral. The opacities were subepithelial in location, and there was no associated inflammation or vascularization of the cornea. Lesions were first noted after estrus in some dogs. Histologically, the lesions were primarily composed of cholesterol, with phospholipids and free fatty acids present, but to a lesser degree. Triglycerides were not detected in the cornea. No alterations in serum cholesterol, triglycerides, or lipoproteins were found (Crispin, 1988).

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Lipid Keratopathy

Lipid keratopathy in the dog has been associated with systemic lipid abnormalities, such as hypothyroidism, pancreatitis, diabetes mellitus, spontaneous hyperlipoproteinemia, and postprandial (overindulgence) plasma lipid elevations (Crispin, 1987b, 1989; Harrington & Kelly, 1980). Lipid keratopathy is characterized by peripheral and central corneal crystalline opacities (Fig. 19.59) (Crispin, 1987b). Clinically, lipid keratopathy can be unilateral or bilateral, and the corneas are nonvascularized, especially early in the disease process; however, corneal degeneration commonly occurs with chronicity, and this is associated with vascularization (see more information on corneal degeneration later in the chapter). There is usually a clear peripheral perilimbal zone (Crispin, 1987b). All dogs with lipid keratopathy should undergo a lipid serum profile and be screened for thyroid function, pancreatitis, and diabetes mellitus (i.e., fasting blood glucose). Most serum lipid profiles include measurements of serum cholesterol, serum triglycerides, serum total lipids, and lipoprotein electrophoresis. In some cases, serum cholesterol esters and phospholipids are also useful.

Deposition of lipid into the cornea is thought to occur by perilimbal blood vessels or by *in situ* lipid deposition. Tears are not likely a source because in one study, the lipid levels of tears in a dog with lipid keratopathy were normal (Linton et al., 1996). Corneal cholesterol was much higher than in normal cornea ($12.2 \pm 3.58\,\mu g/mg$ tissue vs. $85.26\,\mu g/mg$, respectively) (Linton et al., 1996). Hyperlipoproteinemia, especially high HDL, promotes lipid keratopathy and possibly worsens after steroidal and estrogen therapy (Crispin, 1987b, 1993).

Corneal lipidosis (arcus lipoides corneae) has been reported in the German Shepherd breed. Lipidosis has been associated with hyperlipoproteinemia resulting from hypothyroidism (i.e., thyroid atrophy and lymphocytic thyroiditis), and corneal lipidosis has been reported in a dog with bilateral thyroid carcinoma (Crispin, 1993; Crispin & Barnett, 1978; Harrington & Kelly, 1980).

Treatment of these underlying systemic disorders and feeding of a low-fat diet (e.g., Hill's w/d™) may prevent the corneal opacities from progressing and, in some cases, allow them to fade. Topical anti-inflammatory medications may exacerbate the lesion (Crispin, 1987b). The lesions can be removed by keratectomy if the opacity is obstructing vision significantly. However, it is likely that the opacities will recur; therefore, surgery is recommended only as a last resort in dogs with significant visual deficit.

Corneal Degeneration

Corneal degenerations are crystalline corneal opacities secondary to pathologic changes within the cornea. Degenerations can consist of lipid, cholesterol, or calcium, and are preceded by keratitis, vascularization, and possibly melanosis (Crispin & Barnett, 1983). Corneal degeneration can occur in chronic corneal dystrophy or lipid keratopathy. Vascularization is the hallmark clinical feature of corneal degeneration, not typically seen in primary corneal dystrophy or lipid keratopathy. Clinically, corneal degeneration has a highly variable appearance. Lesions may be dense white, grayish-white, and crystalline, with well-demarcated borders (Fig. 19.60). They can occur in any area of the cornea, but generally, they are axial or paraxial. Epithelial disruption with vascularization is common, and cholesterol and calcium deposits occur as the degeneration progresses. In some dogs, the presence of calcium may contribute to the delay of corneal healing (Fig. 19.61). Corneal scraping for cytology may reveal a gritty or sandpaper-like feel. Histologically, the epithelium is of variable thickness, rang-

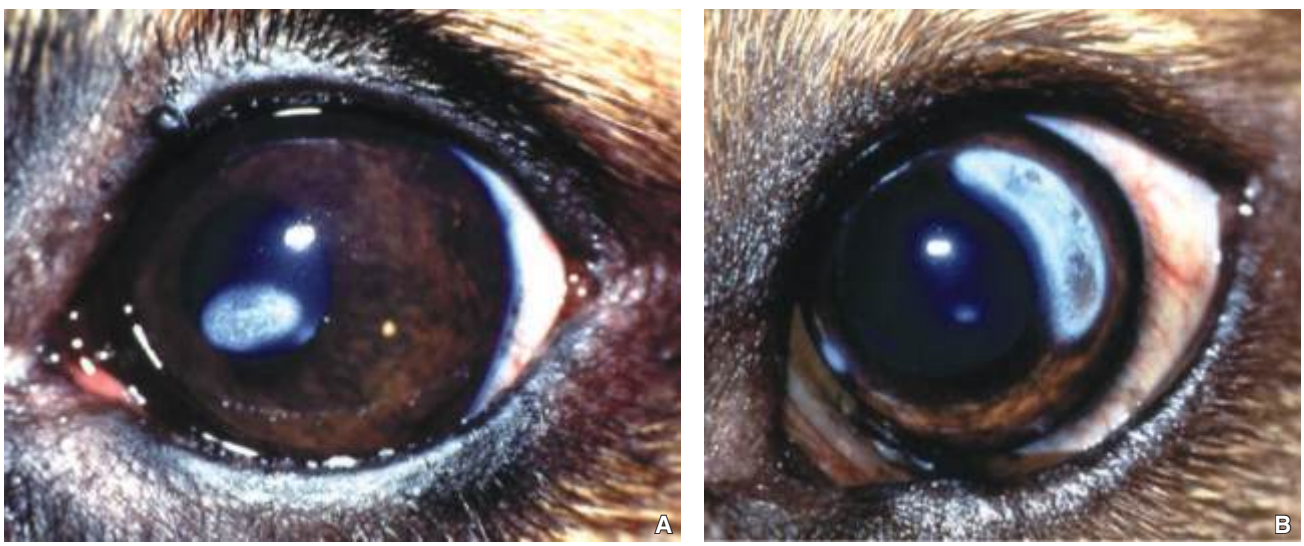


Figure 19.59 **A.** Dog with Cushing's disease with focal lipid keratopathy. **B.** Dog with perilimbal lipid keratopathy.

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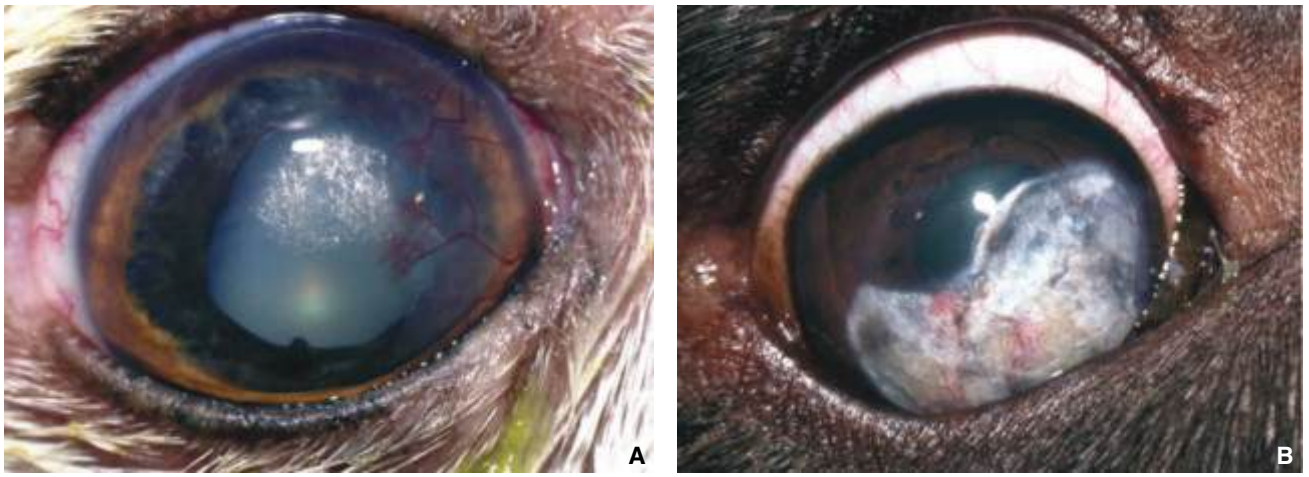


Figure 19.60 **A.** Dog with focal corneal degeneration with lipid infiltration and vascularization. **B.** Diffuse corneal degeneration with a dense white plaque and vascularization.

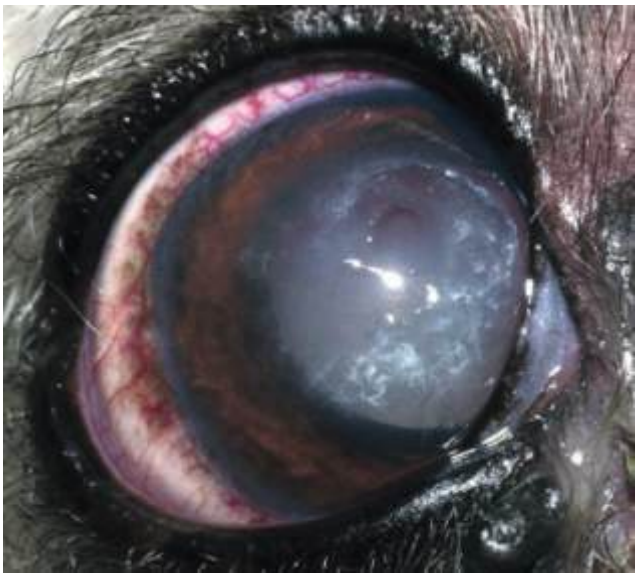


Figure 19.61 Lacy corneal opacity typical of calcium corneal degeneration. There is a chronic central corneal ulcer.

ing from an increased number of cell layers in some areas to a total absence in others. In the stroma, there is frequently a distinctive subepithelial band of fine, granular calcium deposits, which stains black with Von Kossa's stain. Needle-shaped clefts in the anterior stroma represent cholesterol. Small vacuoles in frozen and fixed cryostat sections are sudanophilic.

Calcium degeneration may occur secondary to systemic disease or may be spontaneous (i.e., associated with local inflammation). Hypercalcemia, hyperphosphatemia, hyperadrenocorticism, uremia, and hypervitaminosis D may potentially be accompanied by secondary corneal calcification. Calcium degeneration appears punctate, bright white, irregular, and is usually superficial, whereas lipids may be present throughout the cornea (Laus et al., 2002). Other ocular diseases may produce secondary spontaneous calcareous degeneration such as corneal injury, KCS, uveitis, glaucoma, and phthisis bulbi. Fatty degeneration and hyaline degeneration may precede or accompany corneal calcification.

Localized inflammation or injury may precipitate *in situ* lipid formation by fibroblasts and keratinocytes. Alternatively, vascularization of the cornea or anterior segment inflammation may allow hematogenous lipid to be deposited in the cornea. With inflammation, cells die, become necrotic, and liberate crystalline and noncrystalline lipids (Crispin, 1987b). Presence of lipid, especially noncrystalline and esterified cholesterol, causes additional inflammation, and subsequently, further degeneration of the cornea. These lesions are cleared by vascularization, attraction of macrophages, and phagocytosis of the lesion (Crispin, 1987b). Therefore, corticosteroid therapy should be avoided in corneal degeneration because this therapy will decrease vascularization, macrophage function, and subsequently, resolution of the lesion. However, keratectomy may be considered if the lesion is progressive and vision is compromised (Linton et al., 1996). Keratectomy may decrease or stop this cycle of cell death and lipid deposition by removing the necrotic tissue. Calcium, which in itself is irritating to the cornea, is also effectively removed by keratectomy. Calcium is deposited commonly in inflamed corneas, likely because in the cornea, calcium is close to saturation, and small changes in pH, temperature, or crystallization inhibitors result in precipitation, as suggested in the rat cornea (Bellhorn et al., 1988). Use of corticosteroids is also not indicated with calcium degeneration because it promotes attraction and binding of calcium by inducing rearrangement of the molecular structure of collagen and elastin (Laus et al., 2002; Ward et al., 1989).

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Band Keratopathy

Band keratopathy is a specific type of corneal degeneration characterized by a gray-white, superficial crystalline corneal opacity oriented in the horizontal interpalpebral fissure (Fig. 19.62). In dogs, the term "band" may be confusing because the corneal opacity within the interpalpebral fissure often does not assume the classic band appearance described in humans. The opacification usually results from subepithelial calcium deposition. Calcific band keratopathy can usually be attributed to localized corneal inflammation (i.e., dystrophic calcification) or systemic hypercalcemia (i.e., metastatic calcification) (Ward et al., 1989). In the dog, calcific band keratopathy is frequently associated with hyperadrenocorticism (Ward et al., 1989; Sansom & Blunden, 2010). In a series of dogs with axial or paraxial corneal calcification restricted to the interpalpebral fissure, the keratopathy was frequently bilateral, in elderly dogs (mean age 13.6 years), and associated with other ocular (e.g., corneal ulcers, KCS) and systemic (e.g., hyperadrenocorticism, diabetes mellitus, hepatopathy) conditions (Sansom & Blunden, 2010).

Therapy of Corneal Degeneration or Band Keratopathy

When degeneration is progressive, interferes with functional vision, causes discomfort, or prevents epithelialization of a corneal ulcer, removal of the calcium may be required, either by superficial keratectomy or by use of topical chelating agents (e.g., 1% sodium EDTA). In cases of corneal calcification, topical disodium EDTA (0.40%–1.38%) in artificial tears may be effective (Crispin & Barnett, 1983). Many ophthalmologists now use 1% disodium EDTA topically, but the clinical efficacy is unknown. In cases of corneal cholesterolosis, dietary restriction of cholesterol, dietary additives to reduce cholesterol (e.g., flax seed oil, oat bran, niacin), and cholesterol-lowering drugs may be effective.

Surgical removal of corneal degeneration via keratectomy may be considered if the lesion is progressive and vision is compromised. Because corneal degeneration may progress from corneal dystrophy or lipid keratopathy, underlying causes of these conditions must be identified and treated, otherwise the opacity may recur after surgery. Dogs with calcium corneal degeneration may require surgical removal of the calcium, and sometimes conjunctival grafting, for healing of chronic corneal ulcers. Diamond burr keratotomy is a safe and effective treatment for the rapid resolution of superficial corneal ulceration and ocular pain secondary to presumed corneal calcareous degeneration in dogs (Nevile et al., 2016b).

Non-Crystalline Cornea Opacities

Corneal Endothelial Dystrophy

Endothelial cell dystrophy is a disease of spontaneous, progressive corneal edema resulting from abnormal dystrophic endothelial cells. In the dog, this condition is most prevalent in the Boston Terrier, Chihuahua, and Dachshund (Martin & Dice, 1982). It occurs more frequently in females. The age of onset in the Boston Terrier breed ranges from 5 to 9 years (mean age, 7.5 years) (Fig. 19.63); the age of onset in the Chihuahua ranges from 6 to 13 years (mean age, 9.5 years). Gwin et al. (1982a) reported four cases of primary canine corneal endothelial dystrophy: a 12-year-old male Boxer, a 2-year-old male Miniature Schnauzer, a 3-year-old male Miniature Poodle, and a 12-year-old male Boston Terrier. A similar condition also occurs in the aged Wire-Haired Fox Terrier and the Basset Hound.

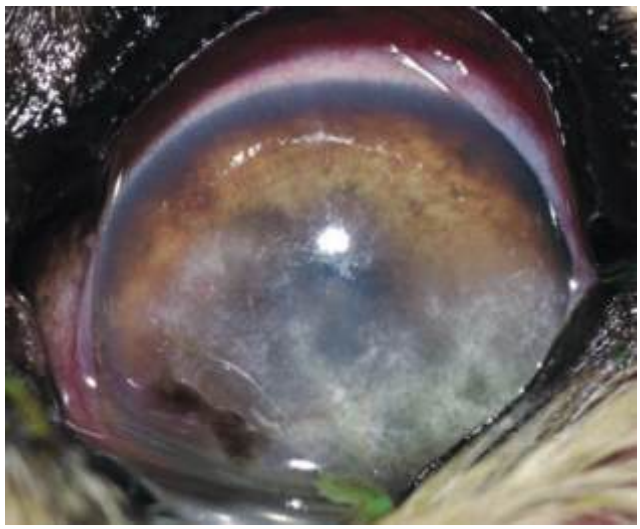


Figure 19.62 Band keratopathy in a dog. This is corneal degeneration primarily located in a horizontal band corresponding to the opening of the palpebral fissure.



Figure 19.63 Diffuse corneal edema in a dog with advanced corneal endothelial dystrophy.

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Canine endothelial cell dystrophy, in at least the Boston Terrier breed, may represent a disease process similar to, and possibly an animal model of, Fuchs' dystrophy in humans (Thomasy et al., 2016). Fuchs' dystrophy is a progressive, bilateral degeneration of corneal endothelial cells that results in an edematous, avascular cornea (Adamis et al., 1993; Bergmanson et al., 1999). It is characterized by a slow, continuous loss of morphologically and physiologically altered endothelial cells, leading to corneal edema. Fuchs' dystrophy is inherited as an autosomal-dominant inherited disease with incomplete penetrance trait in humans and is three times more common in females. Treatment options are palliative medical therapy or corneal transplantation (penetrating keratoplasty or Descemet's stripping endothelial keratoplasty) (Adamis et al., 1993; Bergmanson et al., 1999; Boo et al, 2019). The corneal endothelium and Descemet's membrane have abnormalities on specular, confocal, light, scanning-electron, and transmission-electron microscopy. The endothelium has a decreased number of cells and exhibits fibrous metaplasia. Descemet's membrane is thickened because of fibrillar deposits and exhibits some guttata (Adamis et al., 1993; Bergmanson et al., 1999). Boston Terriers with endothelial dystrophy evaluated by IVCM and FD-OCT had significantly decreased corneal endothelial density, significantly increased central corneal thickness, and significantly increased endothelium-Descemet's complex thickness compared with age-matched controls (Thomasy et al., 2016).

In dogs with endothelial dystrophy, the corneal opacity clinically has a blue-white appearance, with a lack of corneal vascularization or conjunctival hyperemia. The initial lesion, corneal edema, is located temporally and progresses slowly, over several months to a few years, to involve the entire cornea (Fig. 19.64). Involvement between fellow eyes is often initially asymmetric but progresses to bilateral, complete corneal opacity. On biomicroscopy, the main observations are increased corneal thickness, corneal opacity, epithelial bullae, and subepithelial scarring. In some dogs, the posterior corneal surface has fine, bright, compacted striae and occasionally, with specular reflection, black spots or holes in the endothelial mosaic pattern (Fig. 19.65) (Martin & Dice, 1982). Specular microscopy may assist in early diagnosis and therapy (Gwin et al., 1982a).

Palliative therapy is most commonly used for canine endothelial dystrophy. Most dogs maintain limited vision with this disease and only develop morbidity when corneal ulcers develop after rupture of epithelial bullae (Fig. 19.66). These ulcers are managed using topical broad-spectrum antibiotics and topical hyperosmotic medications (e.g., 5% sodium chloride). Hyperosmotic agents may decrease the extent of epithelial bullae formation, but significant corneal clearing does not occur. Ocular irritation and lacrimation

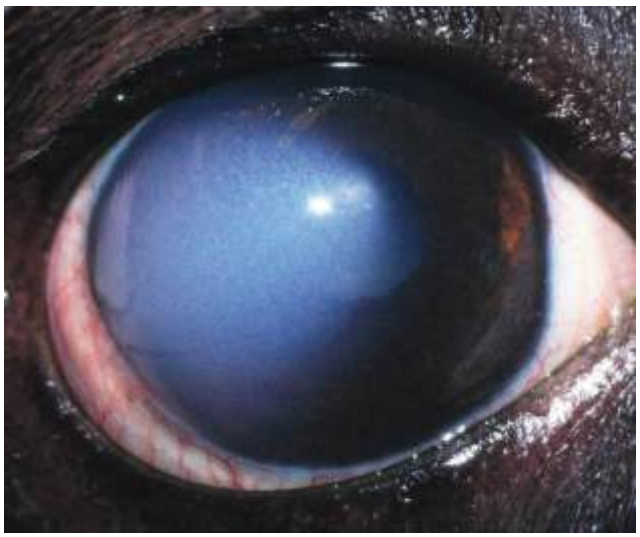


Figure 19.64 Boston Terrier dog with early endothelial dystrophy. The initial lesion, corneal edema, is located temporally and progresses slowly, over several months to a few years, to involve the entire cornea

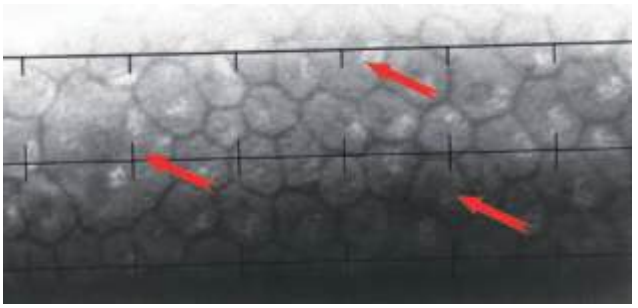


Figure 19.65 Abnormal endothelial cell mosaic in a 12-year-old Boxer. There are occasional very large cells (arrows) and generalized pleomorphism. Cell density is 1320 cells/mm^2. (*Source:* Courtesy of Robert M. Gwin.)

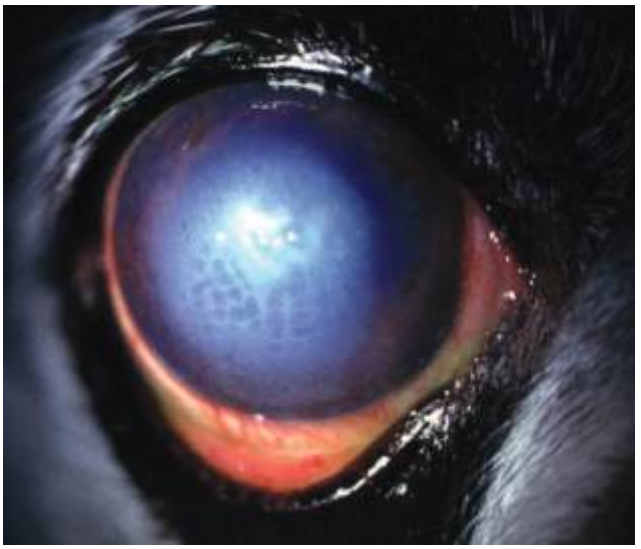


Figure 19.66 Bullous keratopathy in a dog with endothelial dystrophy.

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from use of hyperosmotic preparations, which may cause drug dilution and reduce corneal contact time, also limits their usefulness. Topical corticosteroids have been advocated on an empiric basis for stromal edema in humans with Fuchs' dystrophy and in affected dogs; however, topical corticosteroids (e.g., dexamethasone) or nonsteroidal medications appear to have no beneficial effect in dogs (Gwin et al., 1982a; Martin & Dice, 1982; Wilson & Bourne, 1988).

Dogs with persistent bullous keratopathy and nonhealing corneal ulcers as a result of endothelial dystrophy (or degeneration, discussed earlier in this chapter) may benefit from thermokeratoplasty (TKP) (Michau et al., 2003). In TKP, the use of multifocal points of superficial thermal cautery (Fig. 19.67a) applied in a circular fashion to the exposed corneal stroma results in contraction of the anterior stromal collagen fibers. The goal is to develop mild superficial stromal contracture and opacity, and not a focal burn, with the use of minimal probe temperatures. The resulting subepithelial scar tissue acts as a partial barrier to the flow of fluid through the cornea and helps to reduce the build-up of fluid that results in epithelial bullae (Fig. 19.67b) (Michau et al., 2003). The procedure is performed in sedated or anesthetized dogs. A lid speculum is placed, and the cornea and conjunctiva flushed with 1% povidine-iodine and rinsed with sterile eyewash. Loose corneal epithelium is debrided with sterile cellulose sponges or cotton-tipped applicators. TKP is performed only in the areas of exposed stroma, after debridement of nonadherent epithelium (Fig. 19.67c).

Post-TKP medications include the topical administration of antibiotics, a topical mydriatic/cycloplegic, and oral nonsteroidal anti-inflammatory medications for pain management. In a study reviewing the results of TKP in 13 dogs with corneal ulcers from endothelial disease (for a mean duration of 16.1 weeks), the mean time to corneal ulcer healing after



Figure 19.67 **A.** Thermokeratoplasty (thermal cautery) uses multifocal points of superficial thermal cautery. The goal is to develop mild superficial stromal contracture and opacity, and not a focal burn, with the use of minimal probe temperatures. **B.** Cornea immediately after thermokeratoplasty. **C.** Cornea 4 weeks after thermokeratoplasty. The resulting subepithelial scar tissue acts as a partial barrier to the flow of fluid through the cornea and helps to reduce the build-up of fluid that results in epithelial bullae.

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TKP was 2.2 ± SD 1.1 weeks (Michau et al., 2003). Thermal cautery of the cornea is also described for treatment of SCCEDs in dogs (discussed earlier in this chapter) (Bentley & Murphy, 2004). Superficial keratectomy with conjunctival advancement hood flap has been used with considerable success to slow the progression of edema and help with ulcerations (Horikawa et al, 2016). The only definitive treatment for endothelial dystrophy is replacement of the endothelial cells via a homologous corneal transplant (see subsequent text); however, nonpenetrating and penetrating keratoprosthesis implantation is also described in a limited number of dogs with vision loss attributed to endothelial dystrophy (Allgoewer et al., 2010; Isard et al., 2010).

Posterior Polymorphous Dystrophy

A syndrome of corneal endothelial cell dysfunction and degeneration resulting in multifocal posterior corneal opacities in the dog resembles posterior polymorphous dystrophy in humans (Presberg et al., 1985). In one study, the posterior corneal opacities were multifocal, nonpigmented, and vesicular to linear in appearance (Fig. 19.68) (Gwin et al., 1983a). Slit lamp examination revealed opacities limited to the endothelial cell–Descemet's membrane region (Fig. 19.68). Contact specular microscopy revealed intracellular opacities and local cellular enlargement (Fig. 19.69). In affected American Cocker Spaniels, an autosomal-dominant or incomplete dominant inheritance has been suggested (Gwin et al., 1983a).

Scanning-electron microscopy showed a background of normal-appearing cells, with multifocal areas of degeneration. Zones of advanced cellular degeneration were manifested by exposed Descemet's membrane. Transmission-electron microscopy revealed a monolayer of normal cells, with an underlying membrane immediately anterior. The affected endothelium displays sparse mitochondria and ribosomes, and the cytoplasm has a "moth-eaten" appearance (Gwin et al., 1983a).

Florida Keratopathy

Corneal opacities, apparently unique to tropical and subtropical climates, are described in the dog and cat. These opacities have been referred to as Florida keratopathy, Florida spots, Florida fungus, and tropical keratopathy. Clinically, this condition is characterized by multifocal, round, gray to gray-white, fluffy, cotton-like opacities of varying size in the corneal stroma (Fig. 19.70) (Barros & Safatle, 1997; Peiffer & Jackson, 1979). The corneal lesions frequently have a dense center and a less dense periphery. These opacities occur at varying levels throughout the corneal stroma; however, most appear in the anterior stroma. Opacities may

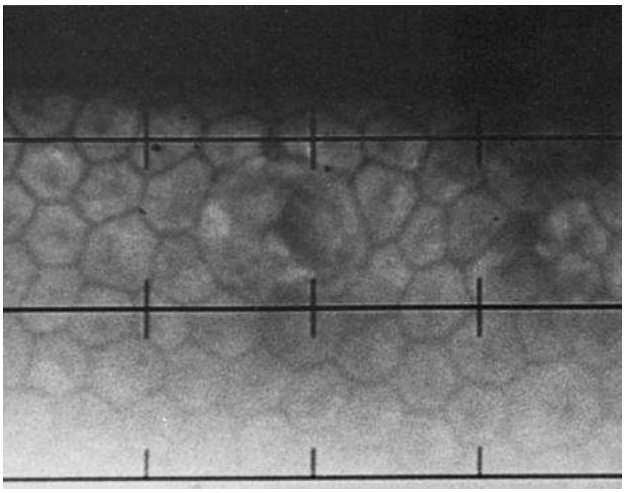


Figure 19.69 Specular micrograph of canine posterior polymorphous dystrophy. Note the cellular enlargement and intracellular opacities. (*Source:* Courtesy of Robert M. Gwin.)

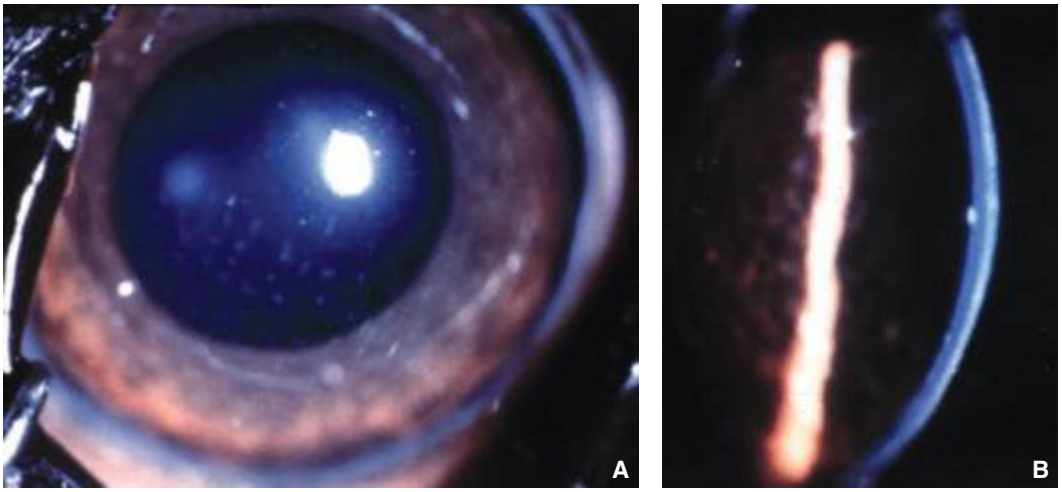


Figure 19.68 Clinical (**A**) and slit lamp (**B**) photographs of posterior polymorphous dystrophy in an American Cocker Spaniel. The posterior corneal opacities are multifocal and vesicular to linear in appearance. (*Source:* Courtesy of Robert M. Gwin.)

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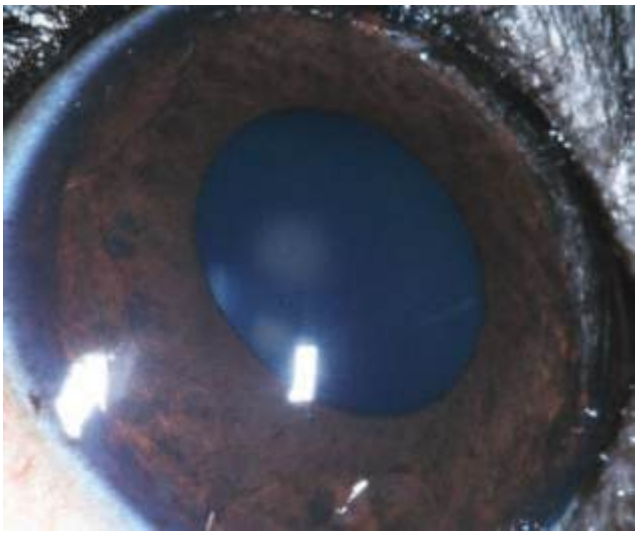


Figure 19.70 Dog with Florida keratopathy.

be unilateral or bilateral. The corneal epithelium is intact and Schirmer tear test values are within normal limits. The condition appears to be self-limiting and does not respond to topical corticosteroids and/or antifungal drugs. Superficial lamellar keratectomy is reported to be curative, but the need for this procedure is questionable because the corneas are devoid of evidence of inflammation, the eyes exhibit no discomfort, and visual compromise is generally not appreciable (Peiffer & Jackson, 1979).

The etiology and composition of the corneal opacities in dogs with Florida keratopathy is unknown, but several theories have been proposed. In one study, keratectomy specimens from diseased corneas were cultured and processed for light microscopy (Peiffer & Jackson, 1979). Cultures failed to reveal pathogenic microorganisms consistently, including fungi. With light microscopy, numerous round-to-oval vacuoles ranging in size from 30 to 200 µm were present in an otherwise normal corneal stroma. It was suggested the vacuoles could represent *Rhinosporidium* organisms. Staining of corneal tissues from a dog with Florida keratopathy showed acid-fast structures within the stromal collagen lamellae (Fig. 19.71) (Fischer & Peiffer, 1987). The staining characteristics of the bodies in the anterior stroma were considered consistent with those of acid-fast organisms. Transmission electron microscopy showed a homogeneous, light-staining material that could be a lipoidal substance. Round to oval vacuoles measuring 0.5–1 µm in diameter were seen scattered throughout the corneal stroma. These vacuoles variably contained an amorphous material and granular, nonmembrane-bound, rod-like structure that suggested mycobacterial organisms (Fig. 19.72). Other researchers have failed to identify histopathologic abnormalities or infectious agents in the corneas of dogs and cats with Florida keratopathy (Sarfaty, 2009). Corneal envenomation by a fire ant (*Wasmannia auropunctata*) was recently suggested as the etiology of Florida keratopathy based largely upon correlation between the geographic range of the ants and the geographic distribution of the keratopathy (Sarfaty, 2009).

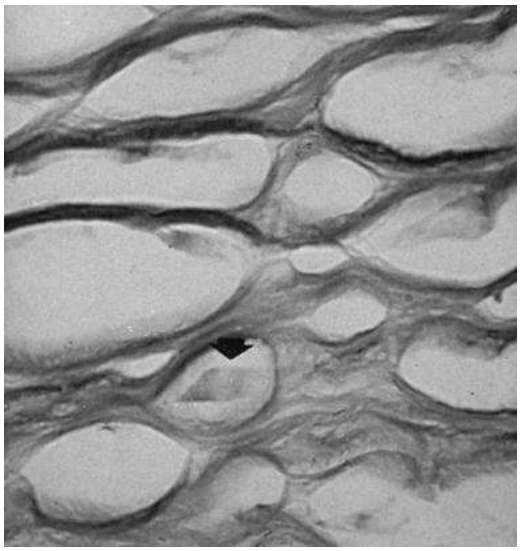


Figure 19.71 Ziehl–Neelsen-stained canine corneal tissue demonstrating acid-fast material (arrow). (Original magnification, 800×.) (*Source:* Courtesy of Craig Fischer.)

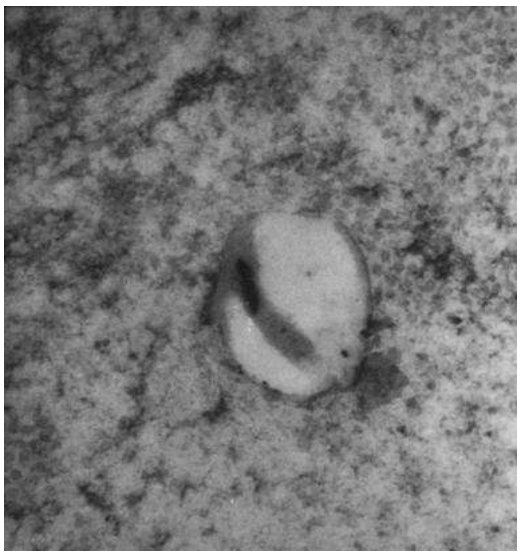


Figure 19.72 Transmission-electron micrograph of a vacuole containing a granular, nonmembrane-bound, rod-like structure suggestive of a mycobacterial organism. (Original magnification, 3200×.) (*Source:* Courtesy of Craig Fischer.)

Intracorneal Stromal Hemorrhage

Intracorneal stromal hemorrhage (ICH) in dogs has been reported in two retrospective studies with differing results and recommendations (Fig. 19.73**)** (Matas et al., 2012;

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Figure 19.73 Intrastromal hemorrhage associated with corneal neovascularization. Appearance of the intracorneal hemorrhage at the initial presentation (upper), after 3 weeks (middle), and at 7 months (lower). (*Source:* From Matas, M., Donaldson, D. & Newton, R.J. (2012) Intracorneal hemorrhage in 19 dogs (22 eyes) from 2000 to 2010: a retrospective study, *Veterinary Ophthalmology* **15**, 86–91.)

Violette & Ledbetter, 2017). In the original study by Matas and co-workers, ICH occurred more frequently in dogs over 10 years of age, could not be linked to a specific ocular or systemic disease, and resorbed with time with or without medical treatment. In the more recent study by Violette and Ledbetter, concurrent ocular disease was present in 40 (59%) of eyes and included KCS, cataracts, and corneal ulcers. Twenty-three (59%) were affected with concurrent systemic disease such as diabetes mellitus, hyperadrenocorticism, hypothyroidism, and systemic hypertension. Although uncommon, ICH may be associated with severe immune-mediated, infectious or neoplastic systemic disease. Based on this study, affected patients should, at the very least, have a complete physical examination and systemic bloodwork particularly if other systemic clinical signs are present.

Pharmaceutical Deposits and Corneal Opacities

Pharmaceutical corneal opacities may occur from direct deposition of drugs or secondarily as the result of metabolic or toxic effects of the drug. Topically applied or systemically administered pharmaceuticals may access the cornea through the tear film, limbal vasculature, or aqueous humor. Corneal opacities associated with drug administration are infrequently reported in dogs. White, refractile, punctate corneal opacities are anecdotally described in dogs during long-term administration of topical corticosteroids including prednisolone acetate and dexamethasone sodium phosphate (Holmberg & Maggs, 2004). Clinically similar punctate crystalline corneal opacities were detected in dogs under experimental conditions during topical ophthalmic prednisolone acetate administration (Ledbetter et al., 2010). The opacities developed after 24 days of prednisolone administration and were biomicroscopically located in the subepithelial and anterior stromal regions. The composition of the opacities was not determined, but with *in vivo* corneal confocal microscopy, the opacities appeared as linear, reflective, branching crystalline structures that were located throughout the full thickness of the axial corneal stroma with the highest concentration in anterior stroma. The corneas were otherwise unremarkable by ophthalmic examination and IVCM. The crystalline opacities resolved clinically in some of the dogs after discontinuation of topical prednisolone.

The antibiotic, levofloxacin, was identified in a corneal plaque in an older dog receiving the drug as part of a therapeutic regime for a corneal ulcer (Fig. 19.74) (Park et al., 2015). Following surgical removal of the plaque, levofloxacin was identified from the plaque by mass spectrometry (Park et al., 2015).

Amiodarone is an antiarrhythmic drug that is used in dogs for both atrial and ventricular arrhythmias. Corneal microdeposits in the basal epithelium occur infrequently in dogs treated with amiodarone and are clinically and histologically similar to the intracytoplasmic lamellar inclusion bodies detected more commonly in the corneas of humans after chronic amiodarone therapy (Bicer et al., 2002; Mantyjarvi et al., 1998). Tocainide is a narrow spectrum antiarrhythmic drug used for ventricular arrhythmias. When administered

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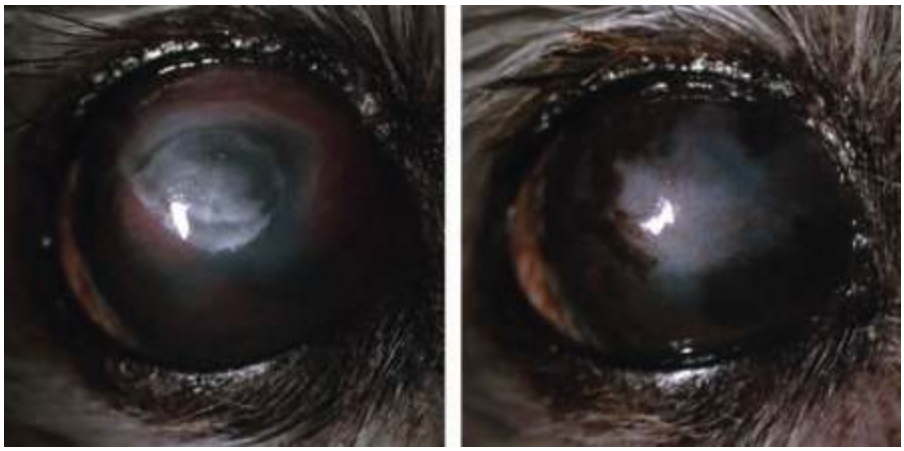


Figure 19.74 Representative images of the right eye of a 13-year-old castrated male Yorkshire Terrier. **A.** A white corneal plaque developed in the central cornea 2 weeks after the development of a corneal ulcer. In addition, corneal pigmentation and neovascularization were observed around the corneal plaque. **B.** Four weeks after surgical removal of the levofloxacin corneal plaque. The corneal pigmentation progressed slightly, and corneal opacity was observed in the central cornea. (*Source:* From Park, Y.W., Kang, B-J, Lim, H.J., et al. (2015) Corneal plaque containing levofloxacin in a dog. *Veterinary Ophthalmology*, **18**, 521–526.)

to Doberman Pinschers with cardiomyopathy, tocainide produced bilateral, progressive, and often severe corneal edema in 25% of dogs after several months of therapy (Calvert et al., 1996; Gratzek et al., 1996).

Capecitabine is an oral antineoplastic and immunosuppressive medication that is used in dogs to prevent renal allograft rejection and for the chemotherapy of various cancers. A portion of dogs administered capecitabine in an experimental model of renal transplant rejection developed superficial crystalline corneal deposits, geographic erosions, pigmentation, and vascularization (Zarfoss et al., 2007). Oral administration of the fluoropyrimidine-based antineoplastic agent designated S-1 in dogs resulted in partially reversible corneal pigmentation, vascularization, and inflammation similar to alterations that may occur in humans receiving this agent (Hayashi et al., 1996; Kitajima et al., 1996; Kobashi et al., 2011).

Induction of tyrosinemia in dogs by administration of the 4-hydroxyphenylpyruvate dioxygenase inhibitor 2-(2-nitro-4-trifluoromethylbenzoyl)-cyclohexane-1,3-dione resulted in refractile stellate-shaped corneal epithelial opacities similar to those observed in humans with tyrosinemia II and reported in a dog with congenital tyrosinemia (Kunke et al., 1984; Lock et al., 2006). Oral administration of an ansamycin hypolipidemic agent to dogs produced irreversible changes in some of the dogs, including posterior stromal edema, deep stromal vascularization, and polymorphic infiltrates in the region of Descemet's membrane (Schiavo & Bentley, 2000). Histopathologic alterations in the cornea induced by the hypolipidemic agent consisted of vascularization, vacuolar degeneration of keratocytes, and Descemet's thickening. Lortalamine, a nontricyclic antidepressant and selective norepinephrine reuptake inhibitor, resulted in corneal opacities, progressive ulcerative keratitis, and diffuse corneal edema in as few as 2 days after administration to dogs (Mally & Thiebault, 1990). High doses of the experimental sympathomimetic agent fluoromethane-sulfonanilide were associated with the formation of corneal opacities, keratitis, and corneal ulcerations in dogs during a preclinical safety evaluation study (Steffen et al., 1980).

Surgery for Corneal Opacities

Several nonulcerative corneal opacities lead to vision decrease or loss. These include lipid corneal degenerations, pigmentary keratitis, stromal abscesses, corneal edema, corneal scarring, corneal neoplasms, limbal melanomas, and calcific keratopathy. Lesions involving the superficial stroma or epithelium may be managed with superficial keratectomy, using either a traditional surgical method or an excimer laser (discussed earlier). Deep or full-thickness lesions, such as corneal or limbal neoplasms (i.e., squamous cell carcinoma, limbal or epibulbar melanoma), usually require a full-thickness excision and grafting procedure. There are several procedures to repair full-thickness corneal or scleral defects, and these include lamellar keratoplasties (i.e., corneoscleral transposition and autogenous lamellar grafts), tectonic frozen corneal or scleral grafts, use of synthetic or bioengineered materials, amniotic membranes and other mucus membranes, and penetrating keratoplasty using fresh, viable corneal tissue (Barros & Safatle, 2000; Barros et al., 1998, 2005; Blogg et al., 1989; Brightman et al., 1989; Bussieres et al., 2004; Dice et al., 1973; Donaldson et al., 2006a; Hacker, 1991; Hansen &

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Guandalini, 1999; Holmberg, 1981; Lewin, 1999; Parshall, 1973). These surgical techniques are discussed earlier in the chapter; however, the choice of technique depends basically on three considerations: (1) whether the site requires the cornea to be clear; (2) surgeon experience; (3) the availability of appropriate instrumentation; and (4) the availability of fresh donor corneas. Homologous grafts, using frozen and fresh tissue, have been evaluated for repair of corneal perforations in dogs. Corneal structural integrity was achieved in 86% of cases with 82% retaining vision (Lacerda et al., 2017).

Homologous Keratoplasty Procedures

There are essentially two types of keratoplasty procedures – lamellar keratoplasty and penetrating keratoplasty – with both types using homologous corneal grafts (i.e., corneal tissue from animals of the same species) (Fig. 19.75). Autologous corneal grafts (i.e., graft material from the same animal) were described earlier. Lamellar keratoplasty is the excision of corneal epithelium and stroma with replacement by graft tissue of equal thickness (Fig. 19.76). With this procedure, the Descemet's membrane remains intact, and complications of intraocular surgery (e.g., intraocular inflammation) are largely avoided. Indications for lamellar keratoplasty include corneal degeneration, corneal sequestrations, and corneal neoplasia (Andrade et al., 1999; Donaldson et al., 2006a, 2006b; Featherstone et al., 2009; Hansen & Guandalini, 1999).

In penetrating keratoplasty, all corneal layers are excised and replaced by a homologous, full-thickness corneal graft (Fig. 19.77). Penetrating keratoplasty is indicated when a central corneal opacity obstructs vision. Generally, the goal of this procedure is acceptance of this graft and maintenance of a clear cornea. This is achieved by replacing all corneal layers with a graft containing viable endothelial cells. In an eye with glaucoma, KCS, lid or cilia abnormalities, active infections, or any other inflammatory condition of the anterior segment, however, the likelihood of graft failure is greatly increased. In fact, corneal vascularization of more than two quadrants of the eye has been associated with a graft failure rate of 50% in humans (Koay et al., 2005). Use of penetrating keratoplasty in veterinary medicine has been rare; however, there are several clinical and experimental reports (Dice et al., 1973; Jenson, 1963; McEntyre, 1968; Mueller & Formston, 1969). Corneal endothelial cell decompensation and subsequent corneal edema are the most common indications for this procedure in the dog (Dice et al., 1973; McEntyre, 1968; Mueller & Formston, 1969).

Preparation of Donor Tissue for Penetrating Keratoplasty

Readily available sources of corneal donor material for animals are a major problem when considering penetrating kera-

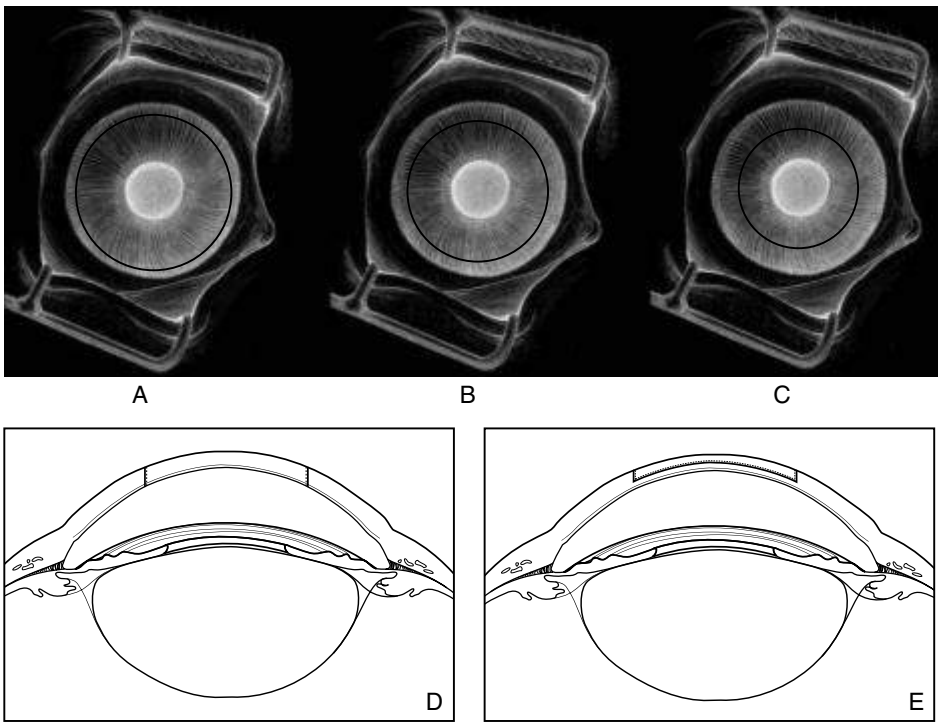


Figure 19.75 Classification of keratoplasty procedures. **A.** Total keratoplasty. **B.** Paracentral or subtotal keratoplasty **C.** Central keratoplasty. **D.** Penetrating keratoplasty. **E.** Lamellar keratoplasty.

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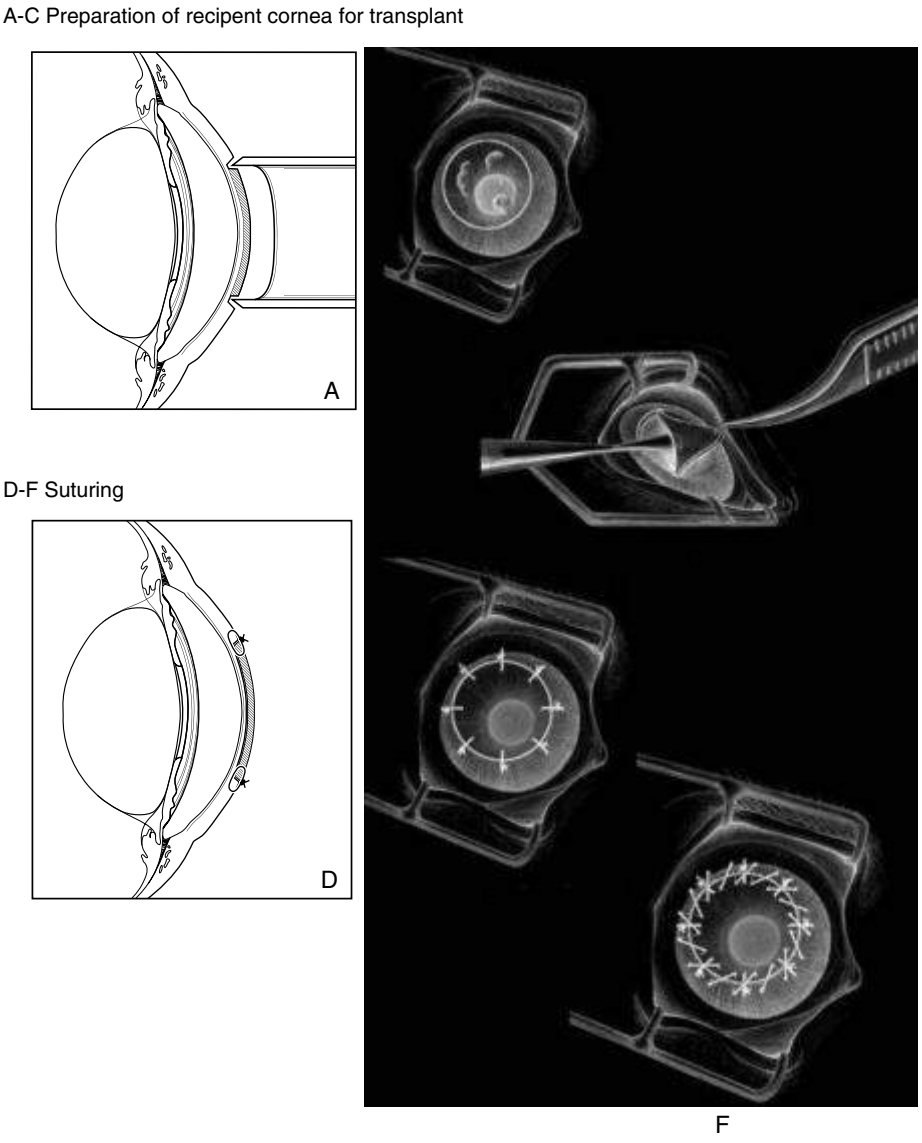


Figure 19.76 Lamellar keratoplasty. Lamellar keratoplasty is the excision of corneal epithelium and stroma with replacement by graft tissue of equal thickness. **A**–**C.** A superficial keratectomy is performed using a trephine to initiate the one-half thickness corneal incision. **D**–**F.** A corneal graft of equal thickness but 0.5–1.0 mm larger in diameter is placed into the graft bed and sutured into place.

toplasty. Long-term storage of corneal tissues is not practical or economically feasible in most veterinary practices. Generally, ocular tissues are harvested when an animal is being euthanized for a non-ocular or a systemic infectious disease. The best donor tissue is that from young animals because of the likelihood of obtaining healthier corneal endothelial cells. Specular or confocal microscopy of the corneas before use as donors would be ideal to ensure that healthy-appearing corneal endothelial cells are obtained. The time between death, enucleation, and use of tissues should be as short as possible to minimize any damage to the donor tissue. Owner permission for collection of donor tissues should be obtained, and immediately after the death of the animal (or within 6 hours), a subconjunctival enucleation is performed. Before enucleation, however, a topical triple-antibiotic solution or 1% povidone-iodine irrigation should be applied to the surface of the cornea, and the surgery should be performed as aseptically and atraumatically as possible.

There are several methods for preservation of donor material:

1) The enucleated whole globe can be stored at 4 °C for up to 2 days and still maintain its endothelial cell integrity. It is rinsed in sterile saline both before and after enucleation, and it is placed in a sealed container for storage.
2) The cornea can be stored in the short term by preserving it in artificial media. After enucleation and rinsing of the globe, the cornea and a 2 mm rim of sclera can be removed

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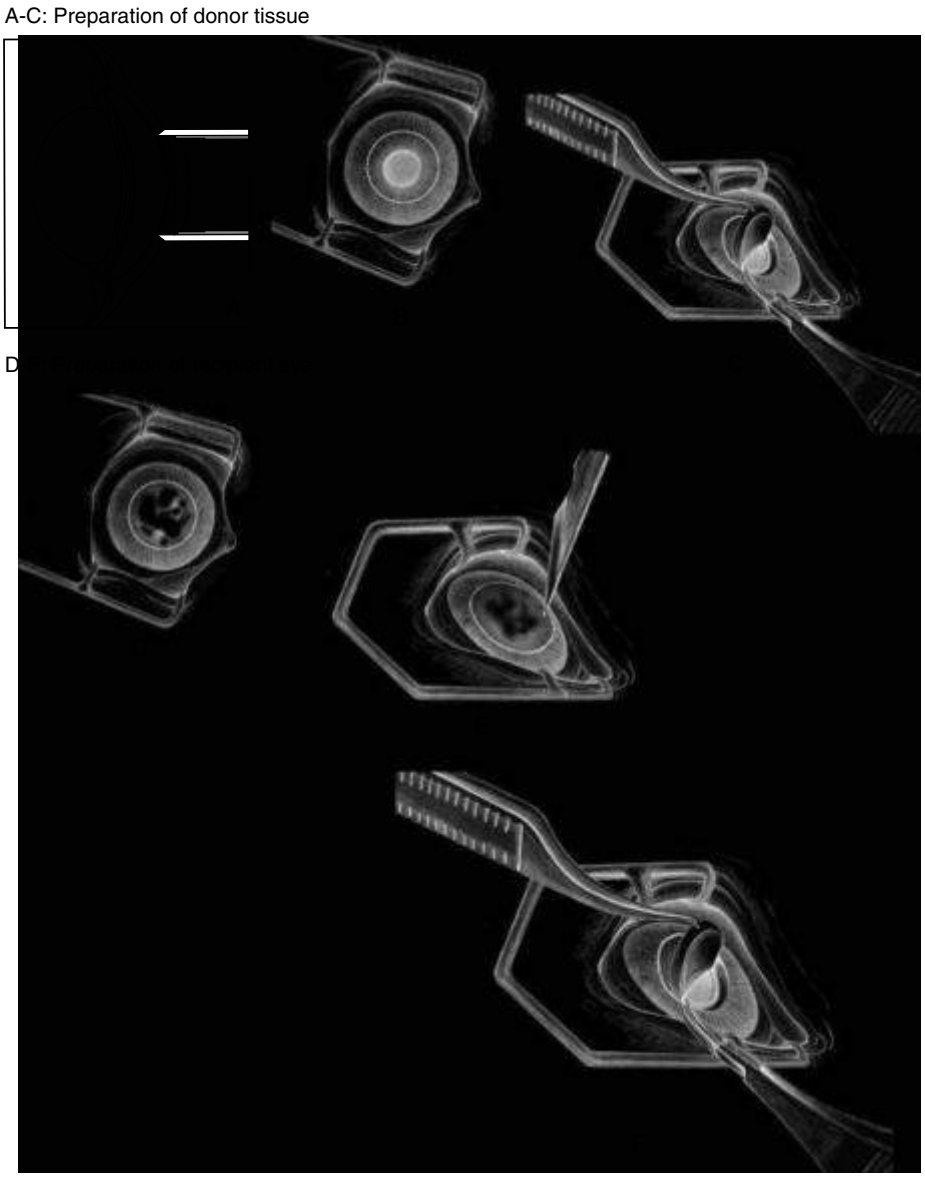


Figure 19.77 Penetrating keratoplasty. The preparation of the donor tissue (**A** through **C**) and the recipient's eye (**D** through **F**) are nearly identical. The trephine is positioned vertically to prevent beveling of the incisions (**A**). The cornea should be trephined to approximately one-half corneal thickness. A sharp knife should be used to make the corneal perforation, and the remainder of the button is removed with fine corneal scissors (**C** and **F**).

from the eye. This tissue is then stored in a tissue-culture media. Using Optisol GS™ (OGS, Bausch & Lomb Surgical, Irvine, CA, USA) as a preservative, corneoscleral tissue of dogs can be preserved with viable endothelium for up to 10 days (and cats up to 18 days) when stored at 4 °C (Arndt et al., 2001).

3) Corneal tissue or whole globes can also be preserved by freezing at −80 °C. Careful freezing and thawing is required to preserve endothelial cell viability, which may or may not be possible, but the tissue may be stored indefinitely with this technique.

Even in human penetrating keratoplasty, tissue typing (human leukocyte antigen [HLA]-A and HLA-B matching) (Bartels et al., 2003) and matching are not routinely performed before surgery unless the patients are considered to be high risk (i.e., those patients with vascularized corneas or who have rejected a corneal graft previously). However, the closest possible donor-recipient match of HLA antigens reduces the rate of allograft rejection and thus improves the prognosis for long-term transparency of corneal grafts in both high- and low-risk patients (Khaireddin et al., 2003). Homologous corneal tissue must be used for transplantation because xeno-

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graphs are associated with a high failure rate. When preparing the corneal tissue at surgery, remember that the tissue is not sterile and that the instruments used to handle and cut the graft tissue should not be used on the recipient's eye.

With a fresh tissue transplant, the cornea should not be dissected from the graft eye until it is ready to be taken into the operating room. The donor eye should be wrapped in gauze and kept at 4°C in the surgery area. Loose donor epithelium should be removed with a moistened sponge, and the eye should be cleansed with normal saline. To facilitate trephination of the cornea, the eye can be injected through the optic nerve into the vitreous. Before trephination, the cornea should be sponged dry. A sharp corneal trephine or sharp dermatology biopsy punch should be used to make the cut. Vertical positioning of the trephine is critical to prevent beveling of the donor graft button. Once the anterior chamber is entered (i.e., aqueous leaks out), the trephination should be discontinued and the incision completed with fine corneal scissors or Vannus-type scissors (see Fig. 19.77). If the corneal graft tissue is a corneoscleral segment, the trephination should be performed in a Teflon-coated or plastic block with the epithelial side down. The endothelial surface is cut first by the trephine, again ensuring that the instrument is positioned vertically.

If the donor button is punched from the endothelial surface (as in corneoscleral segments), a button 0.5 mm larger than the button punched from the recipient's cornea should be used because of the disparity in posterior corneal dimensions.

Preparation of the Recipient's Eye and Surgical Technique

Generally, the center portion of the cornea should be trephined; grafts closest to the limbus have a higher rejection rate (Koay & Figueiredo, 2005). To minimize irregular incisions, the trephine should be rotated in one direction, not in an oscillating motion (Langston, 1996). The cornea should be trephined to approximately one-half the corneal thickness. A sharp knife (#6500 microsurgical blade) should be used to make the corneal perforation, and the remainder of the button is removed with Vannus scissors or fine corneal scissors (see Fig. 19.77) (Langston, 1996). Viscoelastic materials can be used after the corneal button has been removed to help reform the anterior chamber. A running (i.e., continuous) or interrupted suture pattern of 9-0 to 11-0 nylon can be used to close the wound. Four to eight simple, interrupted (i.e., cardinal) sutures can be placed before performing the running suture to help hold the graft in place. To minimize postoperative astigmatism, the second suture should be placed exactly opposite the first. These cardinal sutures may or may not be removed at the end of surgery. Twenty-five to thirty bites of the running suture are usually needed to secure the graft (Fig. 19.78). Before tying the final suture, the viscoelastic material should be aspirated from the anterior chamber to decrease the possibility of postoperative hypertension, and the anterior chamber should be re-inflated with BSS™ or BSS-Plus™ solution.

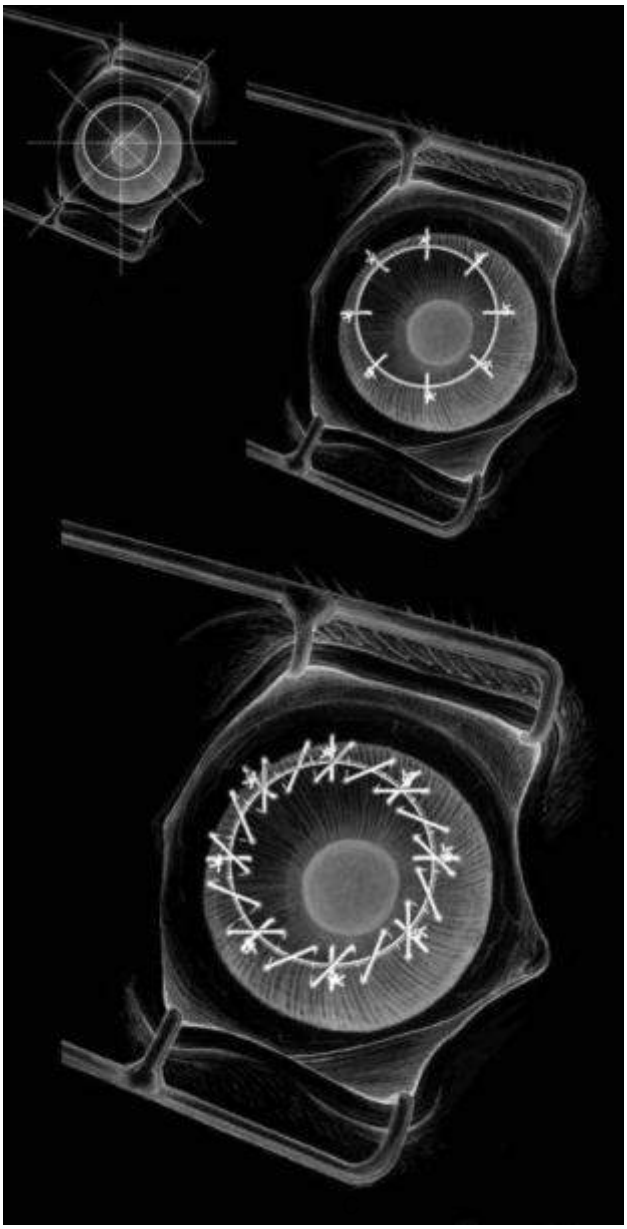


Figure 19.78 Suturing of penetrating keratoplasty. **A.** The graft should be split into sections, as illustrated by the dotted lines. **B.** The sections act as guides for placement of simple, interrupted cardinal sutures. **C.** A simple, continuous suture pattern can be used to cover the cardinal sutures. These cardinal sutures may be then removed.

Postoperative Care and Complications of Penetrating Keratoplasty

After penetrating keratoplasty is performed in humans, topical antibiotics and corticosteroids are commonly used for varying periods, and corticosteroids may be used indefinitely in patients for whom penetrating keratoplasty was used in eyes with corneal edema (Langston, 1996). Topical cyclosporine generally is only used in high-risk patients (Belin et al., 1989). Because of the high graft rejection rate in the dog

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and the inflammatory response of the canine eye to intraocular surgery, frequent use of topical antibiotics, corticosteroids, systemic nonsteroidal anti-inflammatory medications, and topical cyclosporine is recommended after surgery.

Postoperative complications usually occur immediately after surgery (usually within the first week) or at a long-term interval. Complications in the immediate postoperative period usually involve problems directly associated with the surgical procedure and include leaking of the corneal wound, pupillary block glaucoma, endophthalmitis, and choroidal hemorrhages and detachment. The most significant late postoperative complication is graft rejection; corneal epithelial or endothelial cell graft rejection can occur. Epithelial rejection manifests by the appearance of linear (i.e., mild) or round, patchy (i.e., moderate) infiltrates in the subepithelial zone (Boruchoff, 1994). This rejection can cause some discomfort and decreased vision, but it is generally controlled with topical corticosteroids (Boruchoff, 1994). Endothelial rejection is much more serious, however, and may result in permanent corneal edema. Early signs of endothelial graft rejection include localized edema, keratic precipitates, and increased vascularization of the limbus adjacent to a portion of the graft. Later, the endothelial precipitates develop into a linear arrangement (i.e., Khodadoust's line) that progresses across the endothelium (Boruchoff, 1994). The type of graft rejection with the poorest prognosis is generalized corneal edema associated with aqueous flare and keratic precipitates. Treatment with topical corticosteroids is the most common therapy for graft rejection (Boruchoff, 1994). However, the addition of topical, oral, or intraocular cyclosporine may or may not improve graft survival. On the other hand, tacrolimus or rapamycin therapy has been shown to more effectively prevent corneal graft rejection (Chatel & Larkin, 2010; Hill, 1994; Inoue et al., 2001; Rehany & Waisman, 1994; Reinhard et al., 1996; Reis et al., 1998; Shi et al., 2005, 2006; Sloper et al., 2001; Unal & Yucel, 2008; Wang et al., 2002; Yalcindag et al., 2008). Recently, there has been clinical evidence to suggest that antivascular endothelial growth factor (anti-VEGF) antibody therapy (subconjunctival bevacizumab [Avastin™]) may improve graft survival in high-risk (vascularized) corneal transplantation (Symes & Poole, 2010; Vassileva & Hergeldzhieva, 2009). Reports of use for these treatments are not available for canine corneal transplantation and much work needs to be done to make this penetrating keratoplasty a routine and viable option for canine patients

Corneoscleral Masses and Neoplasms

Corneal, limbal, and corneoscleral masses, in general, are rare in dogs. Masses may include non-neoplastic cysts, abscesses, inflammatory disorders (e.g., nodular granulomatous episcleritis [NGE]), and neoplasms such as squamous cell carcinoma, melanoma, papilloma, lymphoma, and hemangioma/hemangiosarcoma. The immunohistochemical characteristics of normal and neoplastic canine eyes has been documented and reviewed allowing for more accurate diagnosis of corneal and other ocular masses (Labelle et al., 2012).

Corneal Epithelial Inclusion Cysts

Cyst formation in the canine cornea may involve any of the four layers. Epithelial inclusion cysts occur as raised, white to pink, corneal masses (Fig. 19.79) (Bedford, 1997; Bedford et al., 1990; Cullen & Grahn, 2001; Koch et al., 1974; Schmidt & Prasse, 1976). They are typically chronic and nonpainful but may impair vision. Inclusion cysts are usually unilateral and solitary, although dogs with multiple inclusions cysts are reported (Simonazzi et al., 2009). A traumatic origin is often suspected, and inclusion cysts may also be congenital or develop after corneal surgery. It is postulated that epithelium is deposited traumatically into deeper cornea, epithelial cells replicate, and a cyst, with central proteinaceous material and desquamated cells, is formed. Inclusion cysts must be differentiated from stromal abscesses (which are usually associated with discomfort) or other infectious keratitis. A minimally uncomfortable mass with no organisms or leukocytes on culture and cytology would suggest a diagnosis of inclusion cyst. Treatment consists of a complete superficial keratectomy, with or without conjunctival or other grafting (depending on the depth of the resulting lesion after excision) (Campos et al., 2002; Choi et al., 2010). Definitive diagnosis is made by histopathology, where a cyst is observed that is lined by nonkeratinizing squamous epithelium (Bedford, 1997; Bedford et al., 1990; Cullen & Grahn, 2001; Koch et al., 1974; Schmidt & Prasse, 1976). *In vivo* confocal

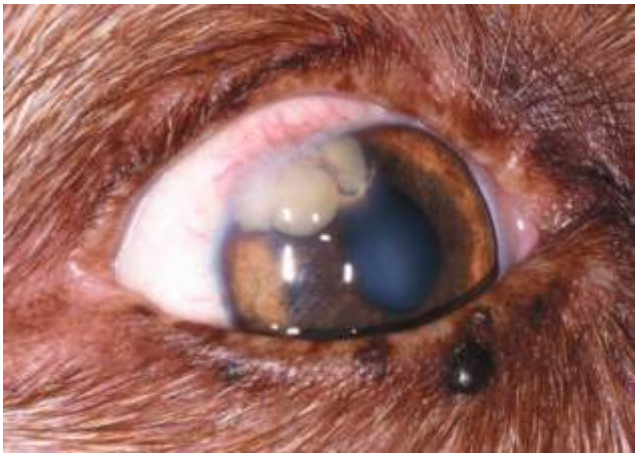


Figure 19.79 Twelve-year-old Brittany Spaniel with multilobulated epithelial inclusion cysts located in the dorsal peripheral cornea.

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microscopy has been used to study the epithelial inclusion cysts in dogs (Vallone, unpublished data 2018) (Fig. 19.80).

Squamous Cell Carcinoma

Primary corneal squamous cell carcinoma (SCC) is uncommon but does occur in the dog when the neoplastic mass arises directly from the cornea. This neoplasm is classified as a corneal intraepithelial neoplasia (carcinoma *in situ*) because the basement membrane is intact (Dubielzig 2010; Latimer et al., 1987; Ward et al., 1992). Primary corneal SCC appears as a raised, multilobulated, pink to white mass (Fig. 19.81). The corneoscleral limbus may be involved, and superficial vascularization as well as diffuse opalescence of the remainder of the cornea is common (Latimer et al., 1987; Ward et al., 1992). The mean age of dogs at the time of diagnosis was 9.6 years (range 6–14.5 years) in one large study (Dreyfus et al., 2011).

Chronic corneal irritation is frequently postulated to contribute to the formation of primary corneal SCC, as this neoplasm is most commonly reported in brachycephalic dogs with a history of chronic keratitis (e.g., pigmentary keratitis, KCS, entropion, distichiasis) (Bernays et al., 1999; Dreyfuss et al., 2011; Ward et al., 1992). Topical immunosuppressive agents used for the therapy of chronic keratitis, such as cyclosporine or tacrolimus, are also theorized to play a role in tumor development (Dreyfuss et al., 2011). Ultraviolet radiation exposure may be an additional canine risk factor for developing primary corneal SCC by inducing mutation of the p53 tumor suppressor gene; however, results of immunohistochemical analysis of canine tumors for p53 are mixed (Montiani-Ferreira et al., 2008; Takiyama et al., 2010).

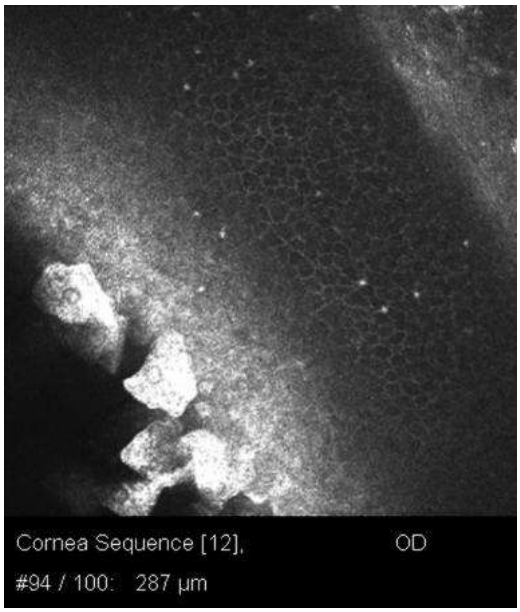


Figure 19.80 At a corneal depth of 287 µm, the boundary of an epithelial inclusion cyst is imaged via *in vivo* confocal microscopy. Basal epithelium is present and contains small hypereflective intraepithelial leukocytes. Large highly reflective superficial epithelial cells can be seen sloughing into the hyporeflective (black) cystic space. The width of this field is 400 µm. (*Source:* Courtesy of Lucien Vallone, Texas A & M University.)

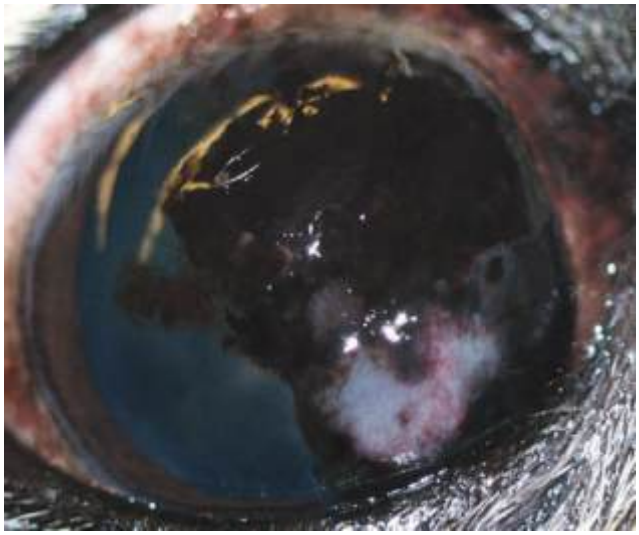


Figure 19.81 Squamous cell carcinoma in the cornea of a Pug dog with chronic keratoconjunctivitis sicca and pigmentary keratitis.

A definitive diagnosis of corneal SCC should be verified by histopathologic evaluation of the biopsy analyzed by an experienced veterinary pathologist versed in ocular pathology. Corneal biopsy samples are placed on slices of cucumber preserved in alcohol to maintain orientation, and are fixed in Davidson's solution or 10% neutral buffered formalin and processed for routine paraffin embedding (Overton et al., 2015). Sections are cut at 5 µm, stained with hematoxylin and eosin or periodic acid–Schiff. Microscopically, corneal SCC consists of an acanthotic squamous epithelium with deep rete pegs, early keratin pearl formation, prominent intercellular bridges, and anisocytosis, anisokaryosis, occasional dyskeratosis, or some combination thereof in the epithelial cells (Latimer et al., 1987). Nuclei are commonly vesicular, with one or more prominent nucleoli. Most of the cells are epithelioid, with a few spindle cells. Therapy is usually excision by lamellar keratectomy, but local recurrence rates are high with incomplete excisions (Dreyfuss et al., 2011). Combining keratectomy with an ancillary therapy such as cryosurgery, beta irradiation (strontium 90, Sr90, carbon dioxide laser photocoagulation, or topical mitomycin-C therapy may decrease recurrence of the tumor versus surgery alone (Busse et al., 2008; Karasawa et al., 2008; Nevile et al., 2015).

Topical monotherapy with 5-flurouracil (5-FU) has been reported as successful in dogs (Dorbandt et al., 2016; Overton et al., 2015). Pulse-dose topical 1% 5-FU treatment has been

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reported (Overton et al., 2015). A compounded topical 5-FU ointment (Prescription Center, Fayetteville, NC, USA) was used q6h for four consecutive days once a month for six treatment cycles over 6 months (Overton et al., 2015). Twenty-three months after diagnosis of corneal SCC and 16 months after completing the topical 5-FU pulse chemotherapy, the eye remained visual and comfortable with no evidence of SCC recurrence. An older Pug with a proliferative mass confirmed as SCC was treated with topical 1% 5-FU ointment four times daily for 2 weeks followed by no treatment for 2 weeks, then treatment again twice daily for 2 weeks (Dorbandt et al., 2016). The cornea remained free of recurrence at last follow-up 10 months after cessation of treatment.

Papillomas

Papillomas are primary corneal tumors that occur most commonly in young dogs and resemble the exophytic, arborizing papillomatous growths in the mouth and eyelids (Fig. 19.82) (Bernays et al., 1999; Bonney et al., 1980; Dubielzig et al., 2010; Kim et al., 2005). Corneal papillomas may result from papillomavirus infection or chronic keratitis. Most papillomas respond well to excision by superficial keratectomy. Recurrence may be decreased by cryosurgery using a double freeze–thaw cycle after the mass has been removed by superficial keratectomy. Beta irradiation combined with superficial keratectomy may also decrease recurrence.

Corneal Lymphosarcoma

Lymphosarcoma may invade the cornea and resemble a pink to white cellular infiltrate (Fig. 19.83). These lesions may be intrastromal, scleral, or episcleral in location and usually are not painful unless the cornea becomes ulcerated. Corneal lymphosarcoma is associated with advanced systemic lymphosarcoma, and the presence of ocular involvement suggests a grade 5 stage of disease. The prognosis for these dogs is poor, and treatment is directed at chemotherapy for the systemic lymphosarcoma. Ocular lymphoma has been reported in the dog and may represent a separate manifestation of lymphoma or may simply represent patients with undiagnosed systemic manifestations of lymphoma (Ota-Kuroki et al., 2014).



Figure 19.82 Corneal papilloma in a dog.

Other Corneal Neoplasms

Several other tumors have been reported in the canine cornea, including hemangiomas, hemangiosarcomas, melanocytoma, and adenocarcinoma (Bauer et al., 2015; Donaldson et al., 2006b; Haeussler et al., 2011; Saha et al., 1989). Corneal hemangiomas and hemangiosarcomas are uncommon in the dog and can be primary corneal neoplasms or originate in the limbus (Donaldson et al., 2006b; Haeussler et al., 2011). They appear as raised, red, irregular masses, and are commonly accompanied by extensive corneal vascularization and perilesional edema (Fig. 19.84). When feasible, therapy is by surgical excision and can be combined with cryotherapy or beta irradiation. With extensive hemangiosarcomas, corneoscleral grafts or enucleation may be required (Donaldson et al., 2006b).

Limbal Melanomas

Limbal or epibulbar melanomas are typically benign neoplasms, but they may invade the cornea or intraocular structures (Fig. 19.85). These tumors are usually smooth and pigmented lesions, but occasionally they may be nonpigmented (i.e., amelanotic). Limbal melanomas occur in two age groups among dogs. In the younger group (i.e., 2–4 years), the tumors tend to be invasive, with a history of rapid growth. In the older group (i.e., 8–11 years), the tumors are more likely to be stationary or found incidentally on physical examination (Wang & Kern, 2015); however, exceptions do occur (Donaldson et al., 2006c). The dorsal arc between the dorsomedial and ventrolateral limbus is usually the site of origination, and the German Shepherd, Golden Retriever, and Labrador Retriever appear predisposed (Donaldson et al., 2006c; Martin, 1981; Sullivan et al., 1996). An association has also been made between occurrence of melanoma and heavily pigmented dogs (Cotchin, 1955; Sullivan et al., 1996). Pedigree analysis suggests limbal melanomas have at least a partial heritable basis in the Golden and Labrador Retrievers (Donaldson et al., 2006c).

Primary limbal melanomas must be differentiated from external extension of intraocular uveal melanomas. Complete intraocular examination, gonioscopy, and high-resolution ultrasonography (Fig. 19.86) can be performed to differentiate between primary intraocular tumors and those

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Figure 19.83 **A.** Bilateral corneal lymphosarcoma in a dog. **B.** Closer image of the right cornea.



Figure 19.84 Limbal and corneal hemangioma in a dog.

originating from the sclera (Bentley et al., 2003). In older dogs with nonprogressive limbal masses, periodic surveillance appears to be adequate.

Treatment of Limbal Melanoma

Treatment of limbal (i.e., epibulbar) melanomas should be considered for dogs in which the mass is enlarging and the surgeon is certain the mass is not a scleral extension of an intraocular neoplasm. Treatments of limbal melanomas include lamellar or full-thickness excision and replacement with grafting procedures (e.g., fresh or frozen homologous corneoscleral graft, third-eyelid graft, synthetic implants, porcine small intestinal submucosa, autologous pinnal cartilage) (Lewin, 1999; Maggio et al., 2013; Martin, 1981; Norman et al., 2008; Wilkie & Wolf, 1991), cryotherapy (Featherstone et al., 2009), strontium-90β plesiotherapy (Donaldson et al., 2006a), and laser photocoagulation (Gilmour, 2003; Sullivan et al., 1996).

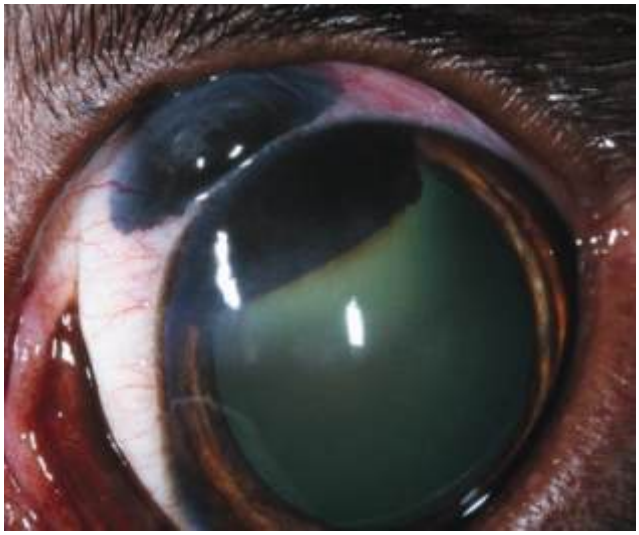


Figure 19.85 Limbal or epibulbar melanoma in a Labrador Retriever with corneal invasion.

Full-thickness, corneoscleral grafts have been used to maintain a functional eye in younger dogs with progressive limbal melanomas (Fig. 19.87) (Martin, 1981; Norman et al., 2008). Grafts of nictitating membrane cartilage with overlying conjunctiva (Blogg et al., 1989), synthetic grafts (Wilkie & Wolf, 1991), porcine small intestinal submucosa (Lewin, 1999), and autologous pinnal cartilage (Mathes et al., 2015) have been used successfully to replace corneal and scleral defects after the removal of limbal melanomas.

A single application of a double or triple free–thaw cycle of cryotherapy can be used as an adjunct to lamellar surgical excision. This approach resulted in no recurrences in 14 dogs in one study with a median follow-up duration of 2.1 years (Featherstone et al., 2009). Complications reported in the dogs included lipid keratopathy, anterior uveitis, and corneal ulcers, granulation, and edema. Similarly, lamellar excision may be

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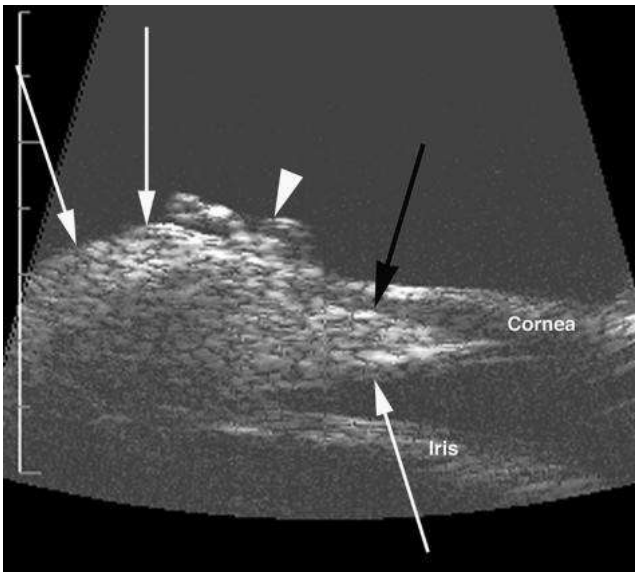


Figure 19.86 High resolution ultrasound of an epibulbar melanoma in a dog. Edges of the mass are highlighted with white arrows. The hyperechoic irregular area on the surface of the tumor is artefact created by conjunctiva and wrinkling of the standoff used with the ultrasound probe (arrowhead). Note tumour growth into the cornea, resulting in alteration of the normal limbal architecture (black arrow). (*Source:* Courtesy of Dr. Ellison Bentley.)

combined with single or multiple applications of ancillary strontium-90β plesiotherapy. A neoplasm recurrence rate of 3% was reported with this therapeutic combination in a study of 30 dogs with a mean follow-up duration of 3.4 years (Donaldson et al., 2006a). Dogs received strontium-90β plesiotherapy immediately after surgery and two additional applications at weekly intervals. Complications observed in the dogs after surgery included corneal scarring, vascularization, conjunctivitis, lipid keratopathy, bullous keratopathy, scleral thinning, scleromalacia, globe perforation, and cortical cataract.

A Nd:YAG or diode laser can be used to treat limbal melanoma. With the dog anesthetized, a surgical Nd:YAG laser 600 µm quartz fiber tip is positioned 1–3 mm from the surface of the mass. The mass is then lasered, with the beam directed away from the interior of the eye. Total energy applied is empiric. In one study, total energy ranged from 7.5 to 572.0 J (Sullivan et al., 1996). Charring and contraction of the mass was seen when adequate laser energy was delivered. The diode laser, which is absorbed by pigment, may also be used to shrink the mass; however, definitive efficacy studies are not available (Gilmour, 2003). With the diode laser, the laser is set at 200 mW, and the repeat interval is set as low as possible (200 mW). With the helium-neon aiming beam focused on the tumor bed, the laser is applied in a "painting" fashion. The desired effect is contraction or shrinkage of the mass. After the shrinkage ceases, the power should be set at 400 mW and the energy applied to obtain charring of the surface of the mass.

In a study evaluating the Nd:YAG laser, all masses initially regressed; however, three of 15 recurred, one at 3 months and two at 1 year after treatment (Sullivan et al., 1996). The advantages of laser treatment of limbal melanomas are that it is noninvasive, it avoids the complications that can occur with full-thickness excisions, it does not require donor tissue or synthetic grafts, and it does not require prolonged general anesthesia. The main disadvantage is the higher recurrence rate (Sullivan et al., 1996). A combination of surgical debulking and diode laser treatment was used to treat limbal melanoma in 21 dogs (Andreani et al., 2017). Only two dogs lost

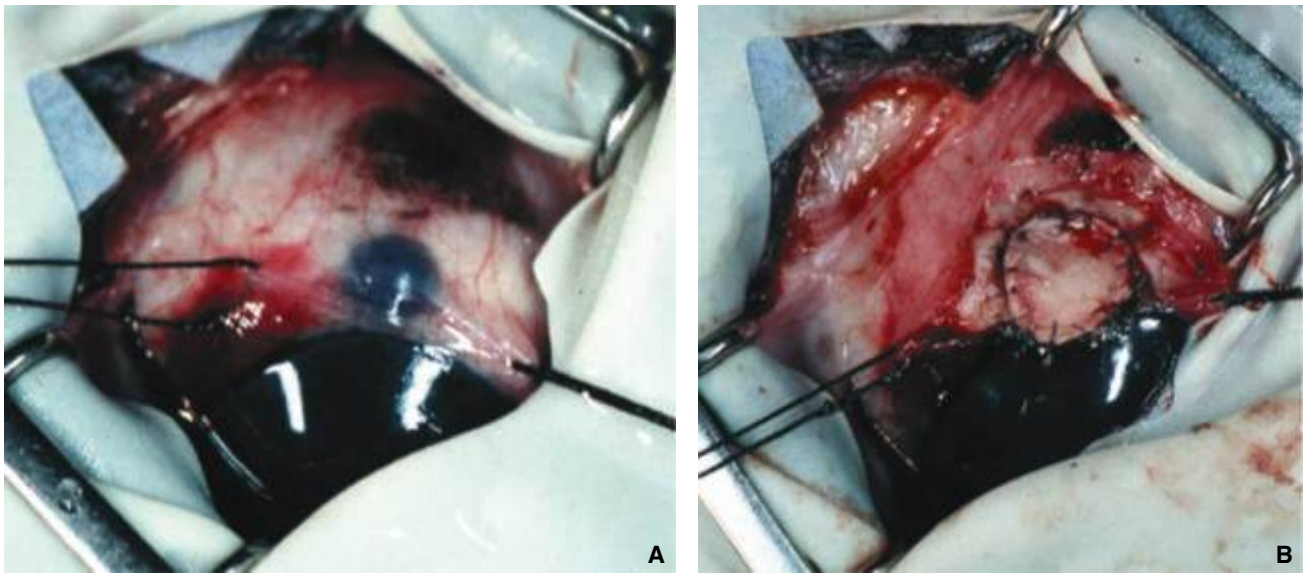


Figure 19.87 Corneoscleral graft, using cryopreserved tissue, for repair of a full-thickness excision of a limbal melanoma. **A.** Limbal melanoma, prior to surgery. **B.** Corneoscleral graft sutured in place prior to covering with conjunctiva.

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vision after surgery because of cataract development 5 years after surgery and severe bullous keratopathy within 1 year of surgery. The authors recommend greater than 400 J of laser energy to avoid recurrence.

Scleral Diseases

Inflammatory diseases that affect the episclera and sclera of the dog are the most common diseases of the canine sclera. Many of these are presumed to be immune-mediated, and most are relatively uncommon compared with corneal diseases.

Episcleritis

Episcleritis in the dog may be divided into primary and secondary types. The primary form can be further subdivided into simple episcleritis and NGE. Simple episcleritis is found infrequently, and it is not associated with systemic disease. It is usually responsive to topical or corticosteroid therapy and, in most cases, is self-limiting. Secondary episcleritis may result from diffuse, severe ocular disorders such as panophthalmitis, chronic glaucoma, or ocular trauma (Grahn & Sandmeyer, 2008).

Nodular Granulomatous Episcleritis

The veterinary literature includes several accounts of episcleral disorders at the limbus resembling corneoscleral fibrous histiocytoma in humans. Several different names have been ascribed to this disorder, including nodular fasciitis, fibrous histiocytoma, proliferative keratoconjunctivitis, limbal granuloma, pseudotumor, and Collie granuloma (Barnes et al., 2010; Bellhorn et al., 1967; Breaux et al., 2007; Grahn et al., 2008; Gwin et al., 1977; Latimer et al., 1983; Lavignette et al., 1974; Paulsen et al., 1987; Peiffer et al., 1976b; Smith et al., 1976; Wheeler et al., 1989). When these cases are reviewed, however, it appears that most have a similar basic inflammatory process, and a morphologic description of NGE seems to be most appropriate (Barnes et al., 2010; Bellhorn & Henkind, 1967; Breaux et al., 2007; Grahn & Sandmeyer, 2008; Gwin et al., 1977; Latimer et al., 1983; Lavignette & Carlton, 1974; Paulsen et al., 1987; Peiffer et al., 1976b; Smith et al., 1976; Wheeler et al., 1989).

Ocular findings in NGE include multiple, elevated, fleshy masses or a single mass arising at the limbus and infiltrating the adjacent corneal stroma (Fig. 19.88). Nictitating membrane involvement is common, and there is a breed predisposition in the Collie, Cocker Spaniel, and Shetland Sheepdog. The lesions tend to be bilateral in the Collie and to recur after therapy (Fig. 19.89). One report describes a retrobulbar nodular episcleritis that appeared as 2-cm-sized mass that appeared connected to the nictitating membrane that resulted in exophthalmos in a 6-year-old German Shorthaired Pointer dog (Barnes et al., 2010). The mass was resected via orbitotomy (Barnes et al., 2010).

Histopathologic features of NGE are consistent with those of chronic granulomatous inflammation. The predominant cell types are histiocytes, lymphocytes, and plasma cells (Paulsen et al., 1987). Epithelioid cell accumulations, fibroblastic cells, abundant reticulin fiber formation, and neovascularization with perivascular polymorphonuclear inflammatory cell infiltration also occur (Paulsen et al., 1987).

In one case of NGE, a population of metabolically active histiocytes, characterized by a prominent nucleolus and numerous lysosomes, were revealed in the cytoplasm at elec-



Figure 19.88 Front (**A**) and side (**B**) views of a dog with focal nodular granulomatous episclerokeratitis. Note the subconjunctival swelling, the conjunctival injection, and the peripheral corneal edema adjacent to the lesion.

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Figure 19.89 **A.** Diffuse, severe nodular granulomatous episclerokeratitis involving both eyes. **B.** In the right eye, the masses were large and obscured the view of the cornea.

tron microscopy (Paulsen et al., 1987). Lymphocytes observed in that case were considered to be T cells because of their content of scattered polyribosomes and lack of rough endoplasmic reticulum. Production of lymphokines by the T lymphocytes and the resulting chemotaxis of histiocytes is a proposed pathogenesis of NGE (Paulsen et al., 1987). Because azathioprine and cyclosporine are T-cell suppressors, it is logical they would be effective therapy for NGE. This was supported by a study of granulomatous scleritis in dogs where inflammatory aggregates contained T lymphocytes, IgG plasma cells, macrophages, and immune-complex deposition, suggesting types III and IV immunopathogenesis (Day et al., 2008). In another study, lesions with a significantly higher percentage of B lymphocytes required ongoing medical therapy to maintain lesion remission compared with those that resolved (Breaux et al., 2007).

Generally, NGE tends to be benign, with good response to topical administration of corticosteroids with or without the use of oral azathioprine treatment or topical or systemic cyclosporine (Breaux et al., 2007; Latimer et al., 1983). Local surgical excision by lamellar keratectomy, intralesional corticosteroid injections, and beta irradiation (7500 rads per surgical site) and cryotherapy have been used (Paulsen et al., 1987; Peiffer et al., 1976b; Wheeler et al., 1989).

Azathioprine for NGE is usually administered orally at 1.5–2.0 mg/kg once daily for 3–10 days, and then at 0.75–1.00 mg/kg once daily for 10–18 days (Latimer et al., 1983). Baseline complete blood count (CBC) and serum biochemical panels are obtained before starting azathioprine treatment. Toxic effects of azathioprine include gastrointestinal toxicosis (i.e., vomiting and bloody diarrhea), hepatotoxicosis, and myelosuppression. Elevated serum alkaline phosphatase and alanine transaminase activities are present in acute hepatic necrosis. Many dogs can be kept in remission with 1–2 mg/kg once every 3–7 days for 1–8 months (then discontinued). Cyclosporine A (CsA) can be used topically in conjunction with steroids initially, but then a sole treatment is necessary to help prevent recurrence once the mass has resolved. CsA can be given orally according to this protocol if the NGE is resistant to therapy. Pretreatment CBC and serum chemistry profile should be performed, and CsA therapy should be avoided if renal or hepatic insufficiency is present in the dog. The starting dose is 5 mg/kg/day for approximately 30 days (once the dog clinically responds well to treatment), then reduce to either 5 mg/kg po every other day or 2.5 mg/kg every 24 hours. Typical total treatment time is approximately 75–90 days (or longer if needed). Monitor CBC and serum chemistry profile at 2, 6, and 10 weeks into treatment.

Other therapies described include intralesional or subconjunctival injections of corticosteroids, or cryotherapy (Wheeler et al., 1989). A more recent treatment protocol for dogs heavier than 10 kg involves oral administration of niacinamide (500 mg) and tetracycline (500 mg), three times daily. Once improvement occurs, administration is continued at once or twice daily. Efficacy of these treatments has not been reported; therefore, more traditional therapies are recommended.

Scleritis

Inflammatory diseases of the sclera (i.e., scleritis) can be divided into non-necrotizing granulomatous scleritis and necrotizing granulomatous scleritis. Dogs with scleritis usually present with pink-tan-colored sector lesions arising near, but posterior to, the limbus. There may also be some adjacent corneal edema (Fig. 19.90). Clinical signs include ocular pain, photophobia, and excessive lacrimation. In some cases, keratitis, anterior uveitis, or both may be present because the scleral inflammation extends into these adjacent tissues. Anterior uveitis, when present, is nongranulomatous. Gonioscopic evaluation of the iridocorneal angle may reveal congestion of the peripheral iris in the area of affected sclera. In advanced scleritis, there may be diffuse corneal stromal infiltration as well as posterior scleral and choroidal

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Figure 19.90 Severe scleritis, peripheral corneal edema, and focal area of corneal degeneration.

progression, with secondary retinal involvement. The scleral lesions may or may not be associated with systemic collagen diseases.

Ophthalmoscopically, fundus lesions may be seen if there is posterior scleral involvement. Fundus observations are facilitated when the cornea, lens, and ocular media are clear. Active posterior segment involvement is characterized by focal or regional areas of retinochoroidal degeneration, with preretinal and vitreal exudates.

In the dog, clinical laboratory parameters used to define systemic collagen diseases (e.g., canine rheumatoid factor, anti-DNA-antibody, lupus erythematosus cells) are negative in most cases of scleritis. Biopsy specimens of focal skin lesions from the face (i.e., muzzle) of some dogs appear to be similar microscopically to the scleral lesions and are characterized by dense infiltrations of lymphocytes and plasma cells. The significance of these observations is unknown. Scleritis seems to be most common in the spaniel breeds, especially the American Cocker Spaniel. In anterior scleritis, partial thickness biopsies are recommended to confirm the clinical diagnosis and to define both the depth and intensity of the inflammatory response.

Non-Necrotizing Granulomatous Scleritis

The histopathologic characteristics of canine scleritis and nodular episcleritis most resemble those of the non-necrotizing form of the disease in humans (Grahn & Sandmeyer, 2008). There is little or no tendency for nodule formation. The typical lesion of canine scleritis consists of granulomatous inflammation and is characterized by the infiltration of lymphocytes, plasma cells, and epithelioid macrophages. Multinucleated giant cells are uncommon. The granulomatous response can be found in the corneal stroma when there is anterior extension. When uveitis is present, the uveal infiltrate is nongranulomatous.

Necrosis of scleral collagen is not characteristic of canine scleritis. In chronic or recurring cases, fibrous replacement of damaged sclera may be evident, or there may be formation of multifocal cystic spaces within the affected sclera. After several episodes of scleritis, regions of scleral thinning develop.

When present, the posterior segment lesions consist of granulomatous scleritis and adjacent nongranulomatous choroiditis. Adjacent to the affected choroid is retinal degeneration, which is characterized by loss of the outer retinal layers and hypertrophy and migration of the retinal pigment epithelium. The vitreous exudate is nongranulomatous. Intralesional corticosteroids usually promote regression of the lesions. Systemic corticosteroids, however, are needed in some cases to provide maximal regression (Grahn & Sandmeyer, 2008).

Necrotizing Granulomatous Scleritis

Necrotizing granulomatous scleritis is rare in the dog (Denk et al., 2012; Grahn & Sandmeyer, 2008). It is a bilateral, progressive, granulomatous, inflammatory disease of the sclera and cornea that induces significant anterior uveitis (Denk et al., 2012). These cases have a limited response to immunosuppressive therapy, involve both the anterior and posterior segment, and involve the uveal tract as well. In this study, there was a dominance of B-cells within the granulomatous inflammation as well as collagen alteration. Dogs with necrotizing granulomatous scleritis have areas of perivascular necrosis and granulomatous inflammation and also have giant cells. In some areas, the inflammation is characterized by palisading epithelioid cells and multinucleated giant cells (Grahn & Sandmeyer, 2008).

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The Canine Glaucomas

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Definition of Glaucoma

The definition of glaucoma in the dog has evolved during the past nearly seven decades, reflecting our better understanding of this group of diseases and its correlations and parallels with human disease. Magrane, who first investigated the canine glaucomas in some detail during the 1950s, wrote: "Glaucoma, whether it be in man or beast, is not in itself a disease entity. It, rather, consists of a 'wastebasket' group of diseases which have as their common feature an abnormal elevation of intraocular pressure (IOP). This group may be referred to as the glaucomas" (Magrane, 1956). Gelatt (1991) defined glaucoma in the canine as "a group of ocular diseases that exhibit increased levels of IOP that are detrimental to the maintenance of vision and health of the eye." The current definition of glaucoma in human beings is based mainly on primary open-angle glaucoma (POAG), which is the most frequent type of glaucoma in North America and most of the world. It underscores that the primary target of tissue degeneration is the retinal ganglion cells (RGCs) and that there is variable sensitivity of the optic nerve head (ONH) to fluctuations in IOP. A common feature of all glaucomas – and, indeed, of all optic neuropathies – is the progressive death of RGCs and their axons, but not all cases of human glaucoma follow the expected sequence of IOP elevation followed by tissue damage. In humans, normotensive glaucoma occurs with progressive damage to the ONH without detected elevations in IOP. This phenomenon has not been documented in animals; however, that may be the result of delayed recognition. Hence, while IOP is a major risk factor for glaucoma in humans, in the nonhuman animal species elevated IOP is the principal and constant risk factor.

Evidence in dogs does indicate that functional abnormalities of the RGCs are present at normal IOP (Ofri et al., 1993a, 1994), as well as abnormalities in the ONH and orbital microcirculatory blood parameters measured by color Doppler imaging before elevations in the IOP (Gelatt-Nicholson et al., 1999) among Beagles with hereditary POAG, thereby suggesting that normotensive phases with no overt signs are present and precede the classical clinical signs caused by elevated IOP (> 21 mmHg) in the canine glaucomas. In the Basset Hound glaucoma pattern, electroretinographic (ERG) changes occur before significant elevations in IOP can be detected (Grozdanic et al., 2010).

The difference in the presentation and detection of glaucoma between humans and animals has much to do with the differences between POAG and primary narrow-angle/angle-closure glaucomas (PACG). POAG is the most common form of glaucoma in humans worldwide. In contrast, PACG in human in North America and Europe is less common, but it is the most frequently diagnosed form of primary glaucoma in Asian countries. In PACG, IOP may be within normal limits and then suddenly experience a series of very high levels, sufficient to result in abrupt clinical signs and significant adverse changes in all retinal layers (RGCs, nerve fiber layers, and the photoreceptors) and even the choroid (Whiteman et al., 2002). While POAG has been recognized in dogs, most notably in a colony of Beagles with inherited glaucoma (Gelatt, 1972; Gelatt et al., 1977b**)**, PACG is considerably more common in veterinary species. However, despite variances of presentation and classification, in-depth study may reveal similarities in pathogenesis despite distinctive etiologies. Recent studies of chronic PACG in the Basset Hound suggest early and gradual elevations in IOP in this breed, and later acute bouts of very high elevations in IOP, which can profoundly affect vision, develop superimposed on these already damaged outflow pathways (Grozdanic et al., 2010).

The glaucomas in animals are all thought to result from the decrease in aqueous humor (AH) outflow through the pressure-affected trabecular meshwork and/or the pressure-independent uveoscleral outflow (the intrascleral pathway between the sclera and ciliary body and/or choroid that extends to the ONH).

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Epidemiology of Primary and Secondary Glaucomas in the Dog

Meaningful epidemiology studies in the dog followed the development of applanation tonometers for animals, implementation of tonometry in the complete ophthalmic examination in veterinary medicine, and development of veterinary ophthalmology as a worldwide clinical specialty in the 1960s. Comparisons of many different animal species indicate that only the dog and the human share closely the frequency of primary and secondary glaucomas. Comparisons of human populations across the board indicate that the frequency of the glaucomas is about 1%–2% of the population. Studies in domestic dog populations also reveal a prevalence of glaucoma of 1%–2%. These studies also document breed dispositions to POAG and PACG. The popularity of breeds of dogs varies by region and country, and new breeds are constantly being introduced. The popularity of each breed as well as the percentage of dogs diagnosed with glaucoma can represent large numbers of potential patients if both factors are high!

Martin (1977) reported the prevalence of the canine glaucomas as 0.5% using the Veterinary Medical Data Base (VMDB). In a larger study covering nearly four decades, it was noted that the frequency or prevalence of the primary or breed-related glaucomas and secondary glaucomas in dogs presented to all veterinary teaching hospitals in North America is gradually increasing (Table 20.1A, Table 20.1B; Gelatt & MacKay, 2004a, 2004b). Prevalence for the breed-related or primary types has increased from 0.29% (1964–1973), 0.46% (1974–1983), 0.76% (1984–1993), to 0.89% (1994–2002). Predisposed breeds varied by decade, but the American Cocker Spaniel (ACS), Basset Hound, Wire Fox Terrier, and Boston Terrier were constantly high from 1964 through 2002. Glaucoma above the baseline of mixed-breed dogs (0.71%) presented in 27 breeds. Gender effect varied among breeds by decade, and in some breeds females were more often affected (i.e., ACS, Basset Hound, Cairn Terrier, English Cocker Spaniel, Jack Russell Terrier, Norwegian Elkhound, Samoyed, and Siberian Husky). A similar effect occurs in humans with narrow- or closed-angle glaucoma, in which females are affected much more often. Age of presentation with these glaucomas varied by breed, but was generally between 4 and 10 years of age. Of the top 27 breeds identified, few have been investigated in detail and reported in the literature.

There have also been reports of glaucoma populations in the dog based on censuses from university veterinary medical hospitals and their academic referral ophthalmology clinics. These reports, like those in medicine, described patient populations in small cities or islands, and provide important information on the prevalence of the specific types of the glaucomas, breeds of dogs predisposed, possible geographic differences, and other factors. Interestingly, these reports of small patient populations provided similar results. Walde published several reports on the frequency of the glaucomas in the dog based at the Vienna Small Animal Hospital from 1975 to 1980 (Walde, 1982a, 1982b). Of the total of 167 glaucomatous dogs, primary glaucoma affected 51 dogs (30.5% of the glaucoma dogs; 84 eyes). Affected dogs included the Miniature Poodle (99), Fox Terrier (9), Welsh Terrier (8), Japanese Terrier (7), English Cocker Spaniel (6), mongrel (6), Dachshund (5), ACS (2), St. Bernard (2), German Shepherd (2), Airedale Terrier (2), Standard Schnauzer (2), and other breeds (17). One publication of this series included 116 dogs with secondary glaucomas. Causes for the secondary glaucomas included cataract, trauma, uveitis, zonular defects and lens displacement, chorioretinitis, intraocular tumor, uveokeratitis, corneal perforation, progressive retinal atrophy, aphakia, Collie eye anomaly, and retrobulbar tumors.

Boevé and Stades (1985) reported on the canine and feline glaucoma patients during a 4-year period at the University of Utrecht, based on 421 patients that accounted for 8.6% of all of the Small Animal Clinic patients. In the canine population, 155 and 224 dogs presented with the primary and secondary glaucomas, respectively. Primary glaucoma occurred most frequently in the ACS, Bouvier des Flandres, Basset Hound and Basset Artésien Normand,

Table 20.1A Breeds of dogs with the primary glaucomas.

Akita	Italian Greyhound
Alaskan Malamute	Lakeland Terrier
Basset Hound	Maltese
Beagle	Miniature Pinscher
Border Collie	Miniature Schnauzer
Boston Terrier	Norfolk Terrier
Bouvier des Flandres	Norwegian Elkhound
Brittany Spaniel	Norwich Terrier
Cairn Terrier	Poodle – Toy/Miniature
Cardigan Welsh Corgi	Samoyed
Chihuahua	Scottish Terrier
American Cocker Spaniel	Sealyham Terrier
Dachshund	Shih Tzu
Dalmatian	Siberian Husky
Dandie Dinmont Terrier	Skye Terrier
English Cocker Spaniel	Smooth Fox Terrier
English Springer Spaniel	Tibetan Terrier
German Shepherd	Welsh Springer Spaniel
Giant Schnauzer	Welsh Terrier
Greyhound	West Highland White Terrier
Irish Setter	Wirehaired Fox Terrier

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Table 20.1B Breeds of dogs with the highest prevalence of the primary glaucomas in North America from 1994 to 2002.

Breed	No. of Individuals	No. with Glaucoma	% Affected
Overall	**267201**	**2381**	**0.89**
American Cocker Spaniel	**10591**	**585**	**5.52**
Basset Hound	**2370**	**129**	**5.44**
Chow Chow	**2083**	**98**	**4.70**
Shar-Pei	**1841**	**81**	**4.40**
Boston Terrier	**2151**	**62**	**2.88**
Fox Terrier, Wire	**832**	**19**	**2.28**
Norwegian Elkhound	**405**	**8**	**1.98**
Siberian Husky	**2867**	**54**	**1.88**
Cairn Terrier	**823**	**15**	**1.82**
Poodle, Miniature	**3684**	**62**	**1.68**
Samoyed	**1383**	**22**	**1.59**
Bichon Frise	**1766**	**28**	**1.59**
Shih Tzu	**4376**	**69**	**1.58**
Australian Cattle Dog	**1461**	**22**	**1.51**
Akita	**1291**	**18**	**1.39**
Jack Russell Terrier	**1679**	**23**	**1.37**
English Cocker Spaniel	**591**	**8**	**1.35**
Lhasa Apso	**2262**	**30**	**1.33**
Bouvier Des Flandres	**609**	**8**	**1.31**
Pekingese	**1562**	**19**	**1.22**
Poodle, Toy	**3003**	**36**	**1.20**

(Continued)

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Table 20.1B (Continued)

Breed	No. of Individuals	No. with Glaucoma	% Affected
Beagle	**3457**	**38**	**1.10**
Brittany Spaniel	**1582**	**15**	**0.95**
Saint Bernard	**859**	**8**	**0.93**
English Springer Spaniel	**3111**	**23**	**0.74**
Poodle, Standard	**2205**	**16**	**0.73**
Dalmatian	**3061**	**22**	**0.72**
Mixed Breed	**55947**	**395**	**0.71**

Beagle, Great Dane and German Shepherd, English Cocker Spaniel, and Toy and Miniature Poodle breeds. The secondary glaucomas were grouped into those with lens dislocations, iritis or uveitis, trauma, tumors, or postlens extraction. Of the secondary glaucomas, 182 (80%) had lens dislocations and were concentrated in the small terrier breeds, which indicated that glaucoma and possible zonulary defects were related.

The most recent study from the University of Zurich in 2011 (Strom et al., 2011a, 2011b) reported 4 congenital, 123 primary, and 217 secondary cases of canine glaucoma documented from a period of 1995 through 2009. Primary glaucoma occurred with an overall male-to-female ratio (M : F) of 1 : 1.41 and an age of onset that ranged from 0.12 to 18.3 years (mean 7.3 ± 3.6 years). Breed predisposition occurred in the Siberian Husky, Magyar Vizsla, and Newfoundland. Secondary glaucomas affected dogs ranging in age from 88 days to 19 years (mean 7.7 ± 3.6 years), and accounted for 3.6% of all ophthalmology patients seen at the University of Zurich. Breed predisposition for the secondary glaucomas included the Cairn Terrier (ocular melanosis), Jack Russell Terrier (lens displacement), and English Cocker Spaniel breeds. For most cases with bilateral disease, both eyes shared the same risk factor (anterior uveitis or lens luxation). Causes identified with the secondary glaucomas included anterior uveitis (23.0%), lens luxation (22.6%), intraocular surgery (13.4%), intraocular neoplasia (10.6%), unspecified trauma to the globe (8.3%), ocular melanosis (6.9%), hypermature cataract (6.9%), and hyphema (3.23%).

The prevalence of five different types of the secondary glaucomas in the dog in North America from 1964 to 2002 varied by decade: 0.25% (1964–1973), 0.46% (1974–1983), 0.79% (1984–1993), and 0.80% (1994–2002) (Gelatt & MacKay, 2004b). The increasing prevalence may be real or may reflect better recognition of the condition, but in general, secondary glaucoma tends to be more prevalent than the primary forms. From the total population of 1,592,831 dogs, secondary glaucoma was diagnosed in 9,695 dogs (Gelatt & MacKay, 2004b). The secondary glaucomas investigated were limited to those associated with cataract formation, lens luxation, cataract surgery, uveitis of unknown cause (7.1%), hyphema of unknown cause (7.3%), and intraocular neoplasia (3.5%). It is likely that the real prevalence was underestimated. In this study, the preexisting condition (e.g., cataract, lens luxation) had to have been diagnosed prior to the onset of the ocular hypertension in order to confirm the secondary nature of the glaucoma. The secondary glaucomas associated with cataract formation and lens-induced uveitis represented 80+% of the total secondary glaucomas.

A 5-year study from the University of California Davis reported secondary glaucoma occurring in 156 of 2,257 (6.9%) dogs examined because of ophthalmic disease. Both eyes were affected in 33 (21.2%) of these dogs (Johnsen et al., 2006). The most common causes of secondary glaucoma were nonsurgical anterior uveitis (44.9%), anterior uveitis associated with prior phacoemulsification (15.8%) and lens dislocation (15.2%). Certain breeds were predisposed to secondary glaucoma and included Parson Russell Terriers, Poodles, Boston Terriers, ACS, Rhodesian Ridgebacks, and Australian Cattle Dogs. No significant effects of gender and neuter status, age, or laterality on the cause of secondary glaucoma were detected.

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Classification of the Glaucomas

In comparative ophthalmology, a glaucoma classification that crosses all species including humans would be ideal. Because no single multispecies classification scheme is totally satisfactory, combinations of a variety of schemes are typically used in the dog. Canine glaucomas may be classified on the basis of the probable cause (primary, secondary, or congenital), the gonioscopic appearance of the filtration angle (i.e., open, narrow, or closed iridocorneal angle (ICA) and open, narrow, or collapsed ciliary cleft), and the duration or stage of the disease (Table 20.2).

The first criterion of classification involves the likely etiology and makes a distinction between primary (open angle or narrow/closed angle), secondary, and congenital forms. In the primary glaucomas, the IOP elevation develops without concurrent ocular diseases, is hereditary in many canine breeds, and has the likelihood of bilateral development. Primary glaucomas may result from abnormal biochemical metabolism of the trabecular meshwork cells of the outflow system (in the POAG) or the physical effects of pupillary blockage and changes in the ICA and ciliary cleft (in the PACG). The canine ICA is the opening of the most anterior portion of the ciliary cleft ICA as viewed by gonioscopy (excluding the ciliary cleft and its contents). Only the pectinate ligaments, part of the uveal trabeculae, and the anterior opening of the ciliary cleft can be visualized via gonioscopy. The entire length of the ciliary cleft can be viewed only with advanced imaging techniques such as ultrasonography (usually 20 MHz or higher). The AH pathway remains constant among most domesticated species with formation by the nonpigmented ciliary body epitheliae, transport through the posterior chamber, pupil and into the anterior chamber, and exit from the eye through the conventional (trabecular meshwork) and unconventional (uveoscleral) pathways. In instances of glaucoma, elevation of IOP results from compromise of AH outflow. In the dog, the majority of the filtration angle (e.g., the deeper corneoscleral meshwork and all of the uveal trabecular meshwork) is located in the ciliary cleft. This anatomic arrangement seems to be based on the needs of the canine lens and accommodation, rather than on AH outflow; in fact, at the microscopic and ultrastructural levels, the AH outflow pathways are nearly identical among most reported species. It is probably more accurate to refer to the ICA as the filtration angle, corneoiridociliary angle, or anterior chamber angle.

Table 20.2 Types of glaucomas in dogs.

A. Primary (Breed-Related) Glaucomas
Open/normal-angle/cleft: Acute/chronic
Narrow/closed-angle/cleft: Acute/chronic
Narrow/closed-angle cleft and pectinate ligament abnormalities: Acute/chronic
B. Secondary Glaucomas
Uveitis
Lens luxations
Intumescent cataract
Phakolytic/phacoclastic uveitis
Hyphema
Intraocular neoplasia
Aphakic
Malignant/ciliary block
Melanocytic/pigment cell proliferation
Pigment cell exfoliation/anterior uveal cysts
Giant retinal tears (Schwartz–Matsuno syndrome)
Anterior chamber silicone oil
Postoperative ocular hypertension
C. Congenital Glaucoma
Pectinate ligament dysplasia
Goniodysgenesis

In the dog, the primary and breed-related glaucomas as well as the secondary glaucomas constitute the largest clinical groups. Open-angle glaucoma is characterized in this way when clinical signs and tissue degeneration develop in the face of an initially open filtration angle and ciliary cleft, as viewed with gonioscopy, high-resolution ultrasonography (HRUS), ultrasound biomicroscopy (UBM), or optical coherence tomography (OCT; see Chapter 10, Parts 2 and 3). However, as the disease progresses, there is gradual observable closure of the filtration apparatus. Narrow or angle-closure glaucoma typically presents with acute IOP elevations and obviously narrowed filtration angle as viewed with gonioscopy. Pectinate ligament dysplasia (PLD) or the consolidation of adjacent pectinate ligaments into broad sheets (initially termed mesodermal dysgenesis) with flow holes is common in the dog, and often described in PACG. Persistent mesodermal bands and PLD-associated glaucomas in selected breeds have been classified with the primary glaucomas because the clinical signs of these glaucomas occur later in life, even though the structural appearance of the filtration angle is abnormal from birth. As the basic pathogenesis for all breed-related glaucomas becomes documented, these glaucomas may be classified into more specific types. The term goniodysgenesis is frequently used in the veterinary literature, and in the dog it usually signals the failure of rarefaction to form pectinate ligaments at gonioscopy, though the status of deeper AH outflow tissues, especially the trabecular meshwork and trabecular extracellular matrix (ECM), is not known. A more accurate phrase than the inclusive goniodysgenesis is PLD. Tonometry of nearly all eyes with extensive PLD indicates a normal range of IOP. Tonographic evidence of outflow problems has not been demonstrated in eyes with PLD, but the persistence of broad sheets of tissue spanning the region of the pectinate ligaments has been frequently associated as a risk factor (but not direct causation), both goni-

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oscopically and histopathologically, for primary narrow or angle-closure glaucomas in the dog. Breed-specific glaucomas in dogs with PLD generally do not occur in early life but in middle-aged to older dogs (i.e., 6–10 years). HRUS supplements routine gonioscopy by providing essential information on the anatomy of the entire ciliary cleft anterior opening and its length.

PLD may also signal an underlying disease (or diseases) of the trabecular meshwork and ECM, as suggested by the results of histologic examination of the Bouvier des Flandres glaucoma, in which deposits of periodic acid-Schiff (PAS)–positive material within the AH outflow pathways occurred concurrently with the PLD (van der Linde-Sipman, 1987). Some percentage of undifferentiated pectinate ligaments may also be normal for the dog eye. The appearance of PLD has been reported to increase in severity with aging in the Basset Hound, Flat-Coated Retriever, and English Springer Spaniel. A recent study in the Basset Hound colony has suggested the disease be classified "chronic angle-closure glaucoma," as tonometry of early-affected dogs has documented that a slow and gradual increase in IOP occurs before the high-pressure acute clinical appearance of the disease (which often prompts the first presentation of clinical patients; Grozdanic et al., 2010).

In the secondary glaucomas, the increase in IOP is associated with some known antecedent or concurrent ocular disease that physically obstructs the aqueous outflow pathways. These tend to be unilateral conditions and are not inherited, except for those glaucomas related to the lens. Some of the conditions that may initiate these forms of glaucoma, however, may be genetically determined in certain breeds, such as those with cataracts and lens subluxation or luxation. Possible mechanisms for the development of the secondary glaucomas include ICA obstructed by preiridal fibrovascular membranes, endothelialization and descemetization or inflammatory cells and proteins or red blood cells, lens luxation, obstruction of the pupil or pupillary block, anterior synechiae, or obliteration of the AH outflow structures secondary to neoplasia or necrotizing inflammation (Smith et al., 1993).

It is useful to assess the condition of the anterior chamber angle and ciliary cleft (open, narrow, closed) with gonioscopy. Unless there is concurrent inherited disease, compromise of the filtration angle in secondary glaucomas is the consequence of the underlying condition rather than being due to a programmed anatomic abnormality. As many glaucomas advance or progress, the anterior chamber angle may be observed to progressively narrow and eventually close with persistent damage. In some breeds in which PLD appears to increase in severity with age, inflammation may play a very important role in elevating IOP. Hence, gonioscopic findings of a glaucomatous eye can change as the disease progresses, which affects the classification of the type of glaucoma and the choice of medical and/or surgical therapies. Therefore, in the classification of the POAG and PACG types, the results of early gonioscopy of the fellow "normotensive" eye is often critical, as secondary changes may have already developed in the hypertensive (presenting) eye. Prophylactic therapy of the fellow normotensive eyes in PACG patients has merit and can prolong vision (Miller et al., 2000).

Congenital glaucomas, which typically present in the first few months of an animal's life with overt and severe developmental anomalies of the anterior segment, are rare (Smith et al., 1993; Strom et al., 2011b). They usually present in puppies or dogs less than 6 months of age. The extent of the angle anomaly may affect the time of onset for the elevation of IOP: the more severe the defect, the sooner the elevation in IOP, and clinical signs, occurs.

Classification of the canine glaucomas by duration (i.e., acute, subacute, chronic) is useful clinically, but may be misleading. The appearance of clinical signs (prompting presentation) may not correlate with the amount of damage already sustained. Corneal edema, episcleral injection, globe enlargement, and a dilated pupil may be the first clinical signs of glaucoma noticed by a pet owner or veterinarian. IOP in excess of 40 mmHg appears necessary for corneal endothelial dysfunction to develop, but these eyes may not truly be at an early or acute stage of the actual disease at presentation. Glaucoma in one eye, with mild or moderate elevation in IOP, is often not noticed by the owner; hence, most dogs are not presented to a veterinarian until extensive damage or even blindness is present in the first eye with primary glaucomas. The longer an eye suffers from elevated IOP, either periodic or persistent, the more damage that eye will sustain. Important also is the degree of elevation. An IOP of 35 mmHg in the short term is not nearly as damaging as an IOP of 70 mmHg. The acute-onset high IOP with PACG tends to be more destructive of the entire retina, choroid, and ONH, whereas POAG dogs often preserve central vision (the peripheral retina is more sensitive to high IOP) for long periods of time.

Clinical Signs

Clinical signs of the glaucomas depend on the stage of disease and, to some extent, on the type of glaucoma. Clinical signs are also directly related to the level and duration of the elevation in IOP. As the glaucomas are usually progressive diseases, the clinical signs of the disease also change and are used to ascertain the relative stage of the glaucoma. The stage of glaucoma may be asymmetric in the fellow eyes of the same dog, with one eye at advanced stages of disease and the other apparently normal or at very early stages.

In the earliest phases of PACG and POAG in the dog, the disease is usually insidious, and the eyes are generally asymptomatic (Fig. 20.1). Early signs may be subtle and range from none to slight mydriasis, mild but transient corneal edema, variable episcleral congestion, to normal ONH appearance,

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Figure 20.1 Early open-angle glaucoma in a dog. Slight mydriasis in a darkened room is the only clinical sign; intraocular pressure is 32 mmHg.



Figure 20.2 Chronic angle-closure glaucoma and pigmentary keratitis in a Shih Tzu. Note the profound buphthalmos of the left globe.

and IOPs are generally just slightly above reference ranges (approximately 25–30 mmHg). In the authors' experience, dogs with early POAG may present only with mild, progressive vision loss, such as agility dogs who miss obstacles. Unless periodic and even diurnal tonometry and careful ophthalmoscopy are performed, these early glaucomatous eyes are not usually presented to the veterinarian for ophthalmic examinations until the disease advances to more overt clinical signs. Cases of POAG (but not PACG) can, however, be detected when tonometry is part of the complete eye examination that occurs with annual eye exams in purebred dogs checked for inherited eye diseases. Dogs with PACG are subject to sudden and marked elevations in IOP. Exactly what triggers this sudden increase in IOP is unknown, but the narrow ICA and ciliary cleft appear to collapse. Periodic tonometry has a low chance of encountering the precise timepoint of IOP elevation in PACG, but diurnal tonometry has not been evaluated as a substitute. In humans with PACG, larger diurnal IOP fluctuations are twice as great as in normal eyes (Baskaran et al., 2009). Not infrequently, the first presentation of a dog with PACG has the initial affected eye already enlarged (buphthalmos) and blind, but the fellow eye may be normotensive (Fig. 20.2). Improvements in diagnostic technologies, such as high-resolution imaging, allow detection of glaucoma at an earlier stage, for example thinning of retinal nerve fiber layer (RNFL) by OCT (Graham et al., 2020), or narrowing of ciliary cleft by UBM (Hasegawa et al., 2016).

The clinical signs of moderate glaucoma include more pronounced degrees of mydriasis (especially in a darkened room), episcleral congestion, variable degrees of corneal edema and striae, slight buphthalmia, early lens subluxation, variable retinal and ONH changes, and untreated IOPs of 30–40 mmHg. When primary glaucoma is advanced, clinical signs may include intermittent visual impairment to total blindness, persistent mydriasis, peripheral anterior synechiae and angle closure with peripheral corneal edema, diffuse corneal edema with corneal striae, buphthalmia, lens displacement from the patella fossa, cortical cataract formation, vitreous degeneration and syneresis, extensive retinal and ONH degeneration, and untreated IOPs of greater than 40–50 mmHg.

Occasionally, with IOPs in excess of 50 or 60 mmHg, mild papilledema may be detected through a less than transparent ocular media. Presumably, the optic nerve fibers within the prelaminar ONH and peripapillary retina are enlarged because of impaired axoplasmic transport at the prelamina cribrosa. With very high elevations in IOP or chronicity, wedge-shaped areas of chorioretinal degeneration based at the edge of the ONH may result, apparently from ischemia secondary decreased blood flow within individual short ciliary arteries (Burn et al., 2017). ONH cupping is usually slight and most obvious with advanced atrophy. Loss of myelin within the ONH in glaucoma results in round and smaller than normal optic discs.

The signs of the secondary glaucomas are like those of the primary glaucomas, but the cause for the rise in IOP, such as an anterior uveitis, an intraocular mass, or a lens luxation, is evident. By gonioscopy the ICA and cleft may be open, narrow, or closed dependent on the inciting cause.

The congenital glaucomas affect young puppies, usually within the first 1–6 months of life, and compared to the primary and secondary glaucomas are quite rare. Often, the first clinical sign in these animals is rapid onset of profound buphthalmia, inability to completely close the palpebral fissure, and the development of exposure corneal disease.

Diagnostics

The three basic clinical procedures for the diagnosis and clinical management of glaucomatous patients are tonometry, gonioscopy, and ophthalmoscopy. However, high-resolution

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imaging procedures, such as 20, 35, 50, 60, or 70 MHz ultrasonography and anterior segment OCT, are supplementing these clinical diagnostics to noninvasively and serially observe the trabecular meshwork and entire ciliary cleft.

Tonometry

Reliable tonometry is essential for optimal clinical management of canine glaucomas. Of the three types of tonometry – that is, indentation (Schiøtz), applanation, and rebound – only the latter two types are recommended in veterinary ophthalmology. Current tonometers for animals are based on either the Mackay–Marg applanation principle, the rebound magnetic effect, or the exchange of gas (now air) with the pneumatonograph. Applanation tonometers are fitted with a force plate in their tips that measures the amount of force necessary to indent or flatten a defined surface area of cornea. That force is then correlated to the IOP, an internal force that generates turgidity. In rebound tonometers, a magnetic field is induced that propels a small magnetized probe (plastic tip 1.4 mm in diameter) against the cornea. The probe "rebounds" from the cornea at different velocities (dependent upon the level of IOP), causing voltage changes within the tonometer's collar, which are converted into electrical signals calibrated to different levels of IOP. For additional information, consult Chapter 10, Part 1. Clinical and experimental impressions suggest that the TonoVet® (rebound tonometer) measurements are slightly lower than those from the Tono-Pen® XL (applanation tonometer) when IOPs are within the normal range (10–25 mmHg), but perhaps more accurate when IOP exceeds 40 mmHg.

The pneumatonograph is an accurate tonometer for the dog that can provide paper verification, but requires 1 or 2 seconds of corneal contact for measurements. Repeated measurements can cause direct superficial corneal damage (the eye often moves during tonometry in the conscious dog). Other tonometers that also require a few seconds of corneal contact for IOP measurements, such as Perkins or Draeger, are not very useful in the dog (Andrade et al., 2009), but in species with limited eye movements (rabbit, sheep, cattle, horse, etc.) the pneumatonograph, available commercially, is quite useful.

Normal variations of IOP have been documented in the dog and are dependent upon a variety of factors, including anatomic conformation, level of excitement, time of day, age, and the instrument used for estimating IOP. Several publications have given ranges for normal IOP with different instruments: 16.7 ± 4.0 mmHg (Tono-Pen XL) and 15.7 ± 4.2 mmHg (Mackay–Marg), and in a larger group, 18.7 ± 5.5 mmHg (Tono-Pen XL) and 18.4 ± 4.7 mmHg (Mackay–Marg; Gelatt & MacKay, 1998a) and 12.9 ± 2.7 mmHg (Tono-Pen XL) and 10.8 ± 3.1 mmHg (TonoVet; Leiva et al., 2006). Tonometry in the outpatient clinic provides only an "instant snapshot" or a single point in time, while multiple measurements of IOP over a 24-hour period can be more informative, because IOP is a biologic variable. The mental state of the dog must also be considered as animals that are highly nervous, or not used to being handled, or closely restrained may yield IOPs that are falsely elevated. Acclimation to the clinical environment and diurnal IOP measurements in these dogs can provide a more accurate estimation of the actual IOP and its trends.

Diurnal variations in IOP has been documented in the dog, with higher levels in the early morning and the lowest readings in the early evening (Gelatt et al., 1981a). In the normal dog, these diurnal variations span approximately 2–4 mmHg, but in the dog with untreated POAG, the diurnal variations may increase to 6–10 mmHg or more. This difference can be informative and may prompt further investigation into the presence of or predisposition to glaucoma. Also, normotensive fellow eyes in a POAG dog will often have IOP differences that can exceed 4–6 mmHg (normal eyes have less than 2–3 mmHg difference). These same differences have been reported in Basset Hound PACG (Grozdanic et al., 2010). The peak levels of IOP are potentially the most damaging; in humans, both normal and with POAG, the diurnal IOP curves represent an inverted "U," while the diurnal curves in human PACG patients form an inverted, steep-troughed "V." In PACG human patients, the highest IOP was at 06:00 and midnight, and there was a comparatively low IOP at 15:00. Following peripheral iridotomies, the diurnal curves of human patients usually convert to the shape associated with normotensive groups. This suggests that pupillary dilatation in these patients may account for the "V"-shape diurnal curve (Baskaran et al., 2009).

IOP screening in "spot checks" for PACG breeds of dog appears to be not very informative and predictive, and may have limited value to detect affected dogs (Sandberg & Miller 2005). Diurnal IOP variations have not been reported in eyes with early to advanced PACG in the dog. The same may not be true for breeds with POAG.

Tonometry is an essential diagnostic for the clinical management of glaucomas in the dog. As discussed later in this chapter, monitoring for response to therapy and determination of whether or not "safe" and "target" IOP levels have been achieved is only possible when tonometry is routinely performed on the glaucomatous patient at every visit. Technologies that allow more frequent IOP measurements will allow more accurate early diagnosis and assessment of response to therapy in the future. Such methods may include user-friendly home tonometry and continuous IOP monitoring with telemetric technologies (Komáromy et al. 2019). In the dog with POAG, the elevations in IOP become progressively higher, and IOPs of 35–40 mmHg may not initially produce dramatic clinical signs. Once overt clinical signs of glaucoma develop, it may be difficult to slow or prevent the progressive damage that results from IOP elevations. And in many forms of POAG, by the time

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overt clinical signs have developed, the drainage angle may have already narrowed or closed.

Gonioscopy

Gonioscopy is the noninvasive visual examination of the ICA and opening of the ciliary cleft (i.e., the filtration angle). The uveal trabeculae are located immediately posterior to the pectinate ligaments and are visualized directly during gonioscopy. Gonioscopy has been documented and performed in the dog since the 1930s (Troncoso, 1948), and it was an important diagnostic in the early reports of PACG in the ACS. Gonioscopy was widely embraced in clinical veterinary ophthalmology in the clinical management of canine glaucomas in the late 1970s (Bedford, 1973, 1977a, 1977b; Martin 1969).

Gonioscopy permits classification of glaucoma on the basis of the ICA and anterior ciliary cleft morphology (i.e., open, narrow, and closed filtration angles and ciliary clefts; see Chapter 10, Part 1). Both direct and indirect gonioscopic lenses are used, with the former type of lenses most popular and less expensive. Gonioscopic findings in both POAG and PACG are dynamic, changing as the glaucoma and globe enlargement progress. Early diagnosis may be the only accurate method of separating POAG from PACG, because in the dog with enlargement of the globe caused by the IOP elevation, the ICA eventually narrows and the ciliary cleft collapses. Also with globe enlargement, zonular breakage can occur, resulting in lens subluxation to total luxation. The loss of zonular tension may also contribute to the ICA closure and ciliary cleft collapse. Accurate distinction between POAG and PACG often depends upon examination of the normotensive fellow eye, due to the confounding changes that may be present in the hypertensive eye.

The gonioscopic lens may be tilted at the apex and periphery of the cornea, thus indenting the cornea in an attempt to differentiate appositional angle closure (i.e., temporary, reversible) from angle closure with peripheral anterior synechiae (i.e., permanent, irreversible; Ekesten & Narfström, 1991). With only apposition of the basal iris across the outflow pathways, a progressive widening of the angle occurs. With peripheral synechial closure, this direct compression of the cornea does not result in a change in the gonioscopic appearance of anterior outflow pathway. If the pressure by the goniolens is applied on the peripheral cornea, the opposite ICA is most affected by the displacement of AH. HRUS (20 MHz), UBM (50–60 MHz), and OCT are useful methods of differentiating the temporary, appositional angle closure (only contact) from more permanent synechial closure (Sakuma et al., 1997) and of evaluating the entire ICA and sclerociliary cleft (see Chapter 10, Part 2; Bentley et al., 2003; Gibson et al., 1998; Mandell et al., 2003; Miller et al., 2004). The combination of gonioscopy with these new imaging modalities can markedly expand the diagnostic and monitoring approach to the canine glaucomas. Gonioscopy can also be used to detect PLD (or the consolidation or fusion of many pectinate ligaments) and the extent of involvement of the entire ICA circumference.

Gonioscopy observations should evaluate the width of the ICA, depth of the sclerociliary opening and cleft, length and diameter of pectinate ligaments, as well as any other anatomic abnormalities such as PLD, extent of dysplastic areas, and number of flow holes by quadrant or degrees. Broader pectinate ligaments are referred to as *fibrae latae*. Ekesten in his investigation of the Samoyed PACG proposed a grading scheme to classify the width of the ICA and ciliary cleft (Ekesten & Narfström, 1991; Fig. 20.3).

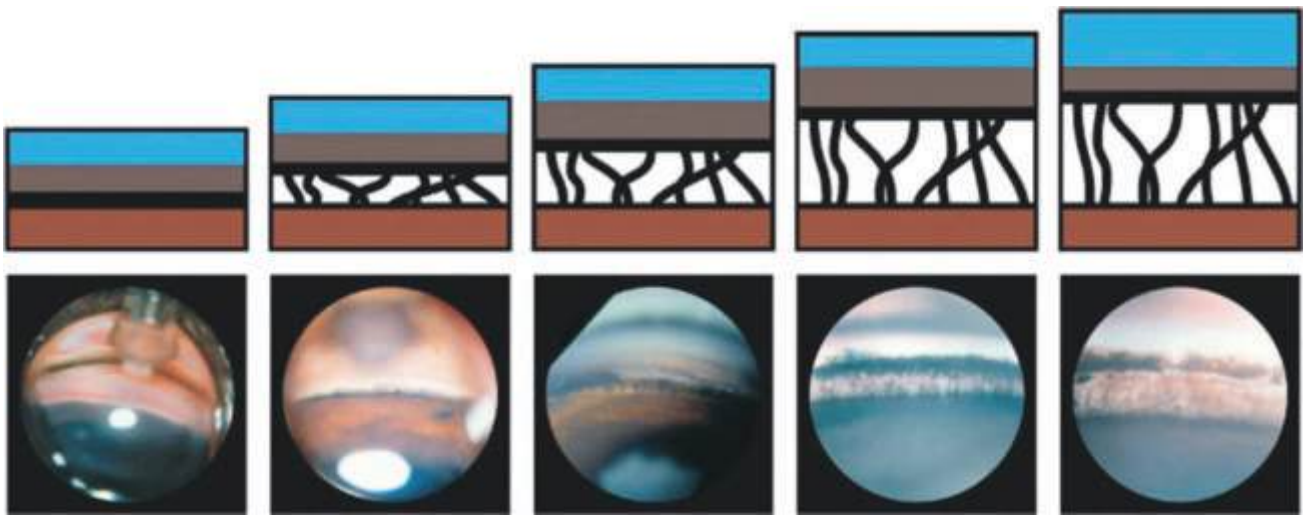


Figure 20.3 Grading by gonioscopy and a schematic of the iridocorneal angle and opening of the sclerociliary cleft (left to right): closed, very narrow, narrow, open (or normal), and more open than normal.

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The information gleaned from gonioscopic examination may be useful for giving breeding advice for breeds predisposed to PLD and glaucoma. Recommendations to examine the ICA by gonioscopy as part of genetic eye screening and in giving breeding advice for dogs with PLD differ between the American College of Veterinary Ophthalmologists (ACVO) and the European College of Veterinary Ophthalmologists (ECVO). The ECVO has stricter guidelines regarding the need for gonioscopy and the exclusion of PLD-affected animals from breeding. Gonioscopy is advised by the ECVO in the following breeds: ACS, all types of Bassets, Bouvier des Flandres, Chow Chow, Border Collie, Dandy Dinmont Terrier, Rough-Haired Dutch Shepherd, English Springer Spaniel, Entlebucher Mountain Dog, Flat-Coated Retriever, Siberian Husky, Leonberger, Magyar Vizsla, Samoyed, and Tatra. PLD is classified by the ECVO, based on severity, as free, fibrae latae (abnormally broad and thickened pectinate ligament fibers), laminae (solid plates or sheets of pectinate ligament tissue), and occlusio (persistence of an embryonic sheet of ICA tissue and the absence of intraligamentary spaces, except for flow holes). Fibrae latae, laminae, and occlusio are associated with a narrow ICA. With fibrae latae affecting 50% or less of the pectinate ligament circumference, the animal can still be considered unaffected; however, a diagnosis of laminae in more than 50% of circumference is considered severely affected. In addition to PLD, the ECVO recommendations also include ICA width: open, narrow, or closed. Performing gonioscopy as part of genetic eye screening remains optional according to the ACVO, despite the recent issue of a special form by the ACVO Genetics Committee and the Orthopedic Foundation for Animals for information gathering and tracking information related to PLD. There are currently no ACVO guidelines against the breeding of PLD-affected dogs. The less restrictive ACVO recommendations were justified by the poor predictive value of gonioscopy findings for PACG development in individual dogs and their offspring. Furthermore, without the additional assessment of the ciliary cleft width by HRUS or UBM, examination of the ICA by gonioscopy alone may not provide a complete picture of the status of the AH outflow pathways.

Ophthalmoscopy

The third diagnostic procedure recommended in clinical management of the glaucomatous canine patient is a combination of direct and indirect ophthalmoscopy. The direct method permits higher magnification (magnification 17.2× lateral and 405× axial with direct; magnification 1.7× lateral and 4× axial with indirect when using a 20 D lens, respectively) to examine the ONH, while the indirect method facilitates examination of the peripheral fundus and its vasculature. The ONH neuroretinal rim and cup should be evaluated for evidence of thinning and enlargement, respectively. The red-free filter of the direct ophthalmoscope, which results in a green light source, permits examination of the RNFL for nerve fiber bundle defects, as well as examination of the neuroretinal rim. The myelinated axons of the canine ONH limit early detection of neuroretinal rim narrowing and cup enlargement in early POAG. The degree of optic nerve recession or cupping can be grossly evaluated by determining the variable diopter settings of the direct ophthalmoscope required to focus on the rim and the center of the optic cup.

PACG glaucomas with abrupt bouts of marked elevations in IOP tend to produce progressive ONH degeneration along with generalized retinal degeneration, while slower and gradual elevations of IOP in POAG tend to produce optic disc cupping, gradual loss of myelin (the ONH becomes round), smaller pigmented optic discs with loss of the peripheral retinal vasculature and retinal degeneration, but preservation of the central retina and vasculature (and central vision). Generalized atrophy of the optic nerve, including loss of myelination, shrinking and darkening of the optic nerve, is common in all instances of glaucoma in the dog.

Ultrasonography and High-Resolution Imaging

Advanced noninvasive imaging techniques that permit examination of the anterior chamber and outflow pathways can nearly approximate the resolution of routine histology and can be performed in the early stages of the disease (and before enucleation is usually justified). Routine 10–12 MHz ultrasonography has 300–400 µm resolution; HRUS 20 MHz and UBM 60 MHz resolutions approach 80 (HRUS) to 20 (UBM) µm, respectively (Bentley et al., 2003; Gibson et al., 1998; Miller et al., 2004). OCT may be useful; its resolutions approach 10 µm (Leung et al., 2005). Both HRUS (20 MHz) and UBM (50–60 MHz) have been reported on in dogs, with both methods using sedation or general anesthesia.

Amplitude scan (A-scan) clinical ultrasonography (10–12 MHz) has been used to measure noninvasively the anteroposterior globe length, anterior chamber depth, lens thickness, and anteroposterior dimension of the vitreous body. Several reports of these ultrasonic measurements on the different parts of the canine eye have been published, although specific breed and age measurements are limited (Cottrill et al., 1989; Ekesten & Narfström, 1991; Gelatt et al., 1983; Schiffer et al., 1982). Results of ultrasonic studies of PACG glaucoma in Samoyeds suggest a narrow- or closed-angle glaucoma pathogenesis with a narrowed anterior chamber, but increased thickness of the axial lens and vitreous body (Ekesten, 1993). These same findings also occur in PACG in people (Marchini et al., 1998). In early POAG of the Beagle, results of A-scan ultrasonography indicate an enlarged anterior chamber and vitreous space, but a normal axial lens length and position (Gelatt et al., 1977b). The lens

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thickness can increase as subluxation and tearing of the zonules occur (the lens less influenced by ciliary body contraction becomes somewhat more round in shape). Color Doppler imaging can noninvasively estimate blood flow parameters in the orbital and ocular tissues. These blood flow parameters have been reported in normal dogs, and reduced levels occur in POAG in the Beagle (Gelatt et al., 2003; Gelatt-Nicholson et al., 1999).

The 20 MHz and 50 MHz models are the most versatile in a clinical setting and permit precise measurements of the anterior segment. They can image the ICA, pectinate ligaments, and sclerociliary cleft, and provide measurements of the entire depth and width of the ciliary cleft, anterior chamber depth, and relationships of the iris and pupil. These numeric measurements also permit statistical analysis of these observations and intraocular relationships.

These imaging procedures are becoming commonplace in the clinical management of the canine glaucomas, and will refine our diagnostics, facilitate accurate determination of the type of glaucoma early in the disease process (open versus closed ICA, open versus closed ciliary cleft, other abnormalities), and increase our success rates in the preservation of vision and normal levels of IOP by permitting intervention in the earliest stages of the disease. UBM studies in Japan indicate that PACG eyes have reduced size in the opening and area of the ciliary clefts and scleral venous plexus. In those globes that responded to medical therapy, the size of the ciliary cleft and scleral venous plexus were increased (Hasegawa et al., 2016). See Chapter 10, Parts 2 and 3, for further discussion of these imaging modalities.

Tonography

Tonography is tonometry expanded over 2–4 minutes that permits quantification of the IOP-sensitive component of the AH trabecular meshwork outflow. Tonography in humans has confirmed that nearly all the different types of human glaucoma (the sole exception being the very rare hypersecretion glaucoma) result from impairment of the AH outflow. In the dog, the prevailing assumption is that the different primary, secondary, and congenital glaucomas also result from impairment of the AH outflow, though tonographic documentation of the progressive obstruction of AH outflow has been obtained only for inherited POAG in the Beagle (Gelatt et al., 1977, 1996; Spiess, 1995). Combined with fluorophotometry, tonography can differentiate, in relative terms, between the conventional (i.e., pressure-sensitive corneoscleral– trabecular outflow) and unconventional (i.e., pressure-insensitive uveoscleral outflow) pathways.

In separate pneumatonographic studies, the mean ± standard deviation (SD) for the normal dog was 0.30 ± 0.15 µL/min/mmHg (Spiess, 1995), 0.28 ± 0.09 µL/min/mmHg (Glover et al., 1995b), and 0.35 ± 0.129 µL/min/mmHg (Gelatt et al., 1996; Fig. 20.4). In the POAGs, the Schiøtz and pneumatonograph tonographic measurements gradually decline as the trabecular disease progresses (Gelatt et al., 1977, 1996). Drugs such as parasympathomimetics that improve conventional AH outflow increase tonographic measurements in both normal dogs and dogs with POAG (Gum et al., 1993c; Spiess, 1995). Drugs that lower IOP by decreasing the rate of AH production or increasing the rate of uveoscleral (i.e., nonconventional) AH outflow do not cause significant changes in tonographic measurements.

In genetic carriers of Beagle POAG mutation (heterozygous for G661R missense mutation in *ADAMTS10*), pneumatonographic measured AH outflow facilities (C) are slightly higher than in Beagles affected with early POAG (homozygous for G661R missense mutation in *ADAMTS10*), but below the normal wild-type (control) Beagles (Gelatt et al., 1996). Hence, in the carriers of Beagle POAG *ADAMTS 10* mutation, the facility of outflow values (C) were between the normal and glaucoma groups. Similarly, tonography in myocilin *Thr377Met* mutation carriers in humans demonstrated facilities of aqueous outflow that were intermediate to lower when compared to the noncarriers, but higher compared to the glaucoma groups (Wilkinson et al., 2003).

Pattern and Flash Electroretinography and Vision-Evoked Potentials

The gold standard to assess vision in humans and to test for visual field loss in glaucoma is standard automated perimetry, which requires patient response and is impractical in veterinary medicine. Thus, the noninvasive electrophysiologic tests are most useful in research settings with animals and clinical veterinary medicine. The noninvasive electrophysiologic tests in humans with glaucoma that have been proven to be most useful are pattern electroretinography (PERG), multifocal, and flash electroretinography (fERG) with different colors of light stimuli, particularly blue (Graham & Fortune, 2009; Kanadani et al., 2014; Korth et al., 1994; Porciatti, 2015). PERG appears to originate from the RGCs of the inner retina, in contrast to fERG, in which the signals are primarily associated with the rod and cone photoreceptors and bipolar cells. Because POAG initially injures preferentially the peripheral RGCs, PERG has evolved as an important diagnostic tool to evaluate the inner retinal layers and assess the level of RGC damage (Ofri et al., 1993c). In contrast, fERG is most useful in PACG patients, where the marked elevations in IOP damage both the inner and outer retinal layers. Significant deterioration of short-wavelength sensitivity (blue sensitive) in eyes with POAG occurs in humans (Graham & Fortune, 2009). The visual evoked potential (VEP) has been evaluated in normal, ocular hypertensive, and glaucomatous human patients. Blue-on-yellow VEP was recommended as a useful test in human glaucoma (Korth, 1997).

Electrophysiology studies in the canine glaucomas are limited. PERGs are more difficult to obtain than fERGs.

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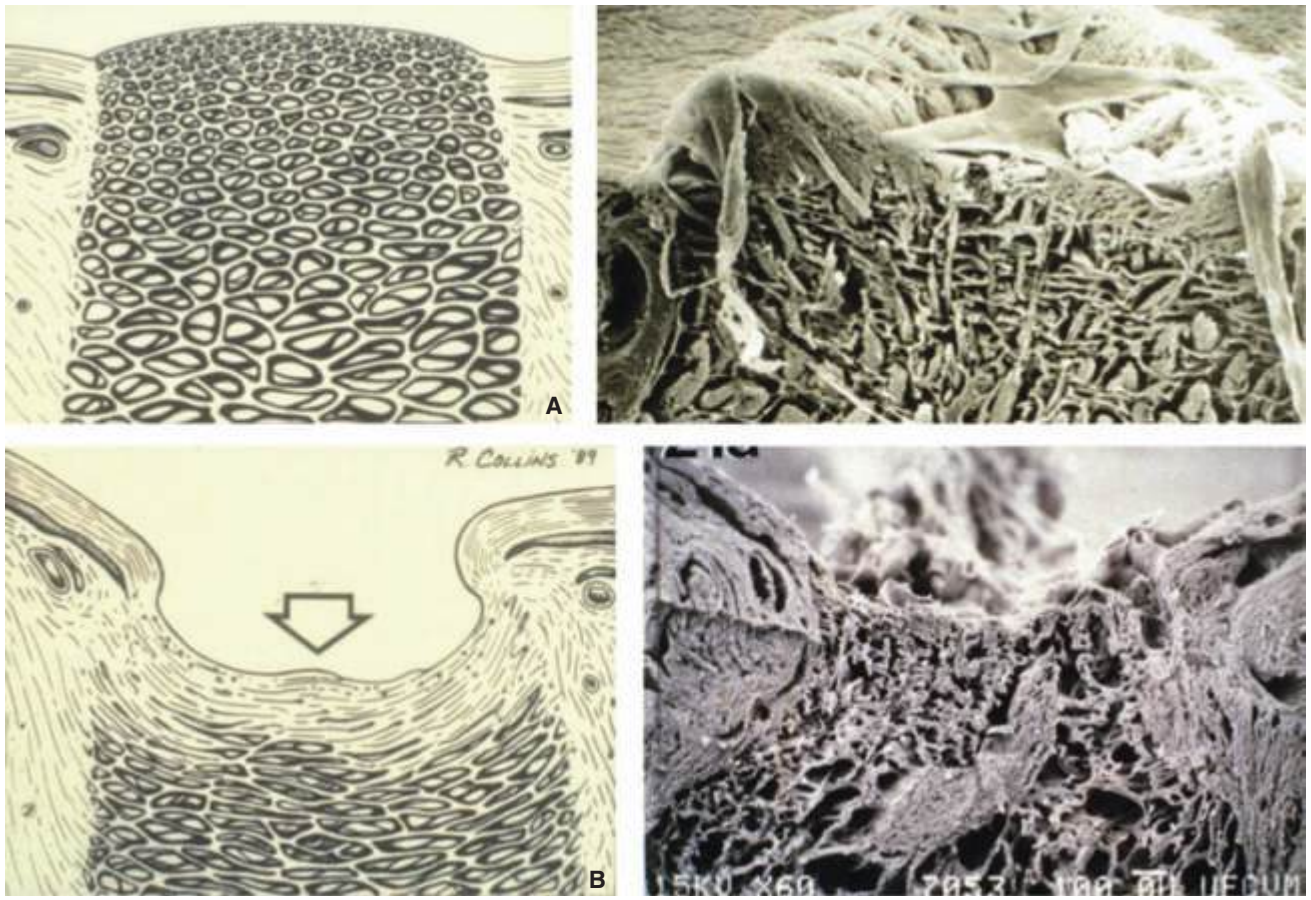


Figure 20.4 Drawings and scanning electron micrographs (SEM) of the scleral lamina cribrosa in normal and glaucomatous eyes. **A**. From the normal pores in the normal eye, glaucoma causes pore misalignment and posterior movement or cupping of the lamina cribrosa (SEM, original magnification, X60). **B**. In the primary open-angle glaucomatous eye, optic nerve head demonstrates posterior displacement and loss of pore arrangement, which may impair axoplasmic and local capillary blood flow (SEM, original magnification, X60).

The major technical difficulties with PERGs are the light/grating stimulator; the low amplitudes of the retinal response, which may require use of skeletal-muscle-paralysis anesthesia to reduce the interference from electromyographic activity; and the need for computer-based recording instrumentation. There are reports of fERGs and PERGs from normal eyes with abruptly induced increased IOP (Brooks et al., 1992; Hamor et al., 2000; Korth, 1997) and POAG and normal control Beagles (Ofri et al., 1993c, 1994). PERGs in Beagles with POAG revealed differences between the central and peripheral retina, suggesting greater peripheral RGC damage, which is similar to events in humans that result in loss of the peripheral visual fields initially (Ofri et al., 1993a). In PERGs in normal and POAG Beagles, administration of sodium thiamylal induced significant amplitude increases in the PERGs of the peripheral retina using larger-pattern gratings compared with those recorded from the central retina (Ofri et al., 1993b, 1994). These findings suggest that in Beagles with POAG, the peripheral (i.e., toroidal) retina and larger RGCs may be more sensitive to this drug and to elevations of IOP. The drug effects may result from ischemic events or decreases in perfusion of the peripheral retina.

The PERG is reduced in the Basset Hound with chronic angle-closure glaucoma (Grozdanic et al., 2010). In normal dogs with acutely very high levels of IOP, the PERG waveforms were most sensitive to increases in IOP (Brooks et al., 1992; Grozdanic et al., 2007). Outer retinal photoreceptor apoptosis was found in dogs with acute PACG, which could indicate that some refinement of fERG, to identify functional changes in the outer retina, might provide some predictive benefit for glaucoma therapy (Miller et al., 1997). Increasing levels of experimentally induced IOP result in increased latency and reduced amplitude of the a- and b-waves and of the oscillatory potentials of the fERG (Hamor et al., 2000). In eyes with prolonged elevations of IOP, however, both the inner and outer retinal layers degenerate and fERG amplitudes decrease and often become nonrecordable (Plummer et al., 2013).

Flash and pattern VEPs are measures of cortical visual activity and may have some benefit in evaluating glaucomatous eyes. Studies of VEPs in clinically normal dogs have

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been reported, but in glaucomatous canines studies are lacking (Strain et al., 1990). See Chapter 10, Part 4 for further discussion of electrophysiologic diagnostics.

Provocative Tests

Provocative tests have been used to determine predisposition to both POAG and PACG. They may provide insight into the possible mechanism(s) for the increase in IOP. Tests for POAGs may include water provocative and steroid provocative tests. The provocative tests for narrow- and closed-angle glaucomas include mydriatic drug and darkroom tests. These provocative tests have been used for several decades in humans to detect suspicious and borderline glaucomatous patients as well as to investigate the heredity of POAG.

Water Provocative Test

The water provocative test has been reported on in normal dogs as well as in the POAG in Beagles, but is not routinely used by veterinary ophthalmologists (Gelatt et al., 1976; Lovekin, 1971). The most useful water dosage for the water provocative test is 50–60 mL/kg, which is administered slowly and at body temperature by a stomach tube in an animal that has been fasted for 12 hours (Gelatt et al., 1976; Lovekin & Bellhorn, 1968). Cold water often results in vomiting. An IOP elevation in excess of 7–8 mmHg is abnormal, and may indicate trabecular dysfunction. In the POAG Beagle, the response to water loading becomes more exaggerated as the disease progresses in older dogs. The same effects have been observed in the glaucomatous Basset Hound.

Corticosteroid Provocative Test

IOP elevations in humans with POAG have been associated with topical and systemic corticosteroids, and the same effects have been documented in the POAG Beagle. Topical 0.1% dexamethasone administered 4 times a day in normal dogs for 6 months increased IOP by approximately 3 mmHg (Gelatt & MacKay, 1998b). With inherited POAG in the Beagle, topical 0.1% dexamethasone instilled 4 times a day increased IOP by 4–5 mmHg within 2 weeks. Once topical dexamethasone therapy is discontinued in Beagles with POAG, the IOP returns to predrug levels within 7–10 days.

Mydriatic or Darkroom Provocative Test

The mydriatic drug and darkroom tests are the classic procedures for PACG in humans. With parasympatholytic-induced mydriasis or physiologically induced darkroom mydriasis, the dilated iris impairs further the outflow of AH, and the IOP becomes elevated acutely. If abrupt elevations in IOP (> 5 mmHg) occur within the first hour after onset of mydriasis, early PACG is suggested. The mydriatic test in early stages of POAG in Beagles is negative; however, more advanced cases may exhibit IOP elevations. In the PACG Basset Hound, both topical 1% tropicamide and 1% atropine cause significant increases in IOP (35% and 50%, respectively; Grozdanic et al., 2010).

Structural and Functional Effects of Elevated Intraocular Pressure

The canine glaucomas are diseases of constant and progressive change and consist of one or more of five features: (1) an abnormality of anatomy or function involving the AH outflow pathways; (2) physical changes causing AH outflow obstruction; (3) elevated IOP that is inconsistent with the health of the eye and impairs normal optic nerve axoplasmic flow and blood flow; (4) RGC dysfunction with resulting optic nerve degeneration and atrophy; and (5) visual field loss and blindness (Shields et al., 1996). The elevation of IOP in glaucoma patients, both human and canine, is responsible for considerable damage to the retina and optic nerve; however, IOP elevation is not the sole cause of ocular tissue damage. A variety of factors may accompany or be exacerbated by IOP elevations. Excitotoxic amino acids, defects in the ONH, changes in microcirculation, and ECM abnormalities may also contribute to damage in both canine and human glaucoma (Fechtner & Weinreb, 1994; Kondrámory et al., 2019; Van Buskirk & Cioffi, 1992; Wilson, 1994). It is known that the changes experienced by the glaucomatous eye are dependent on the level of the IOP elevation, the duration of the elevation change, the onset of secondary effects (i.e., position of the lens, changes in the vitreous, secondary inflammation, etc.), changes in the circulation (some tissues have autoregulation and other ocular tissues do not), and other factors.

Extracellular Matrix–Aqueous Outflow Pathways and the Scleral Laminal Cribrosa

Cellular and ECM abnormalities involving the AH outflow pathways, the peripapillary sclera, and the scleral laminal cribrosa coexist in human and dog eyes with POAG (Boote et al., 2016; Gottanka et al., 1997; Palko et al., 2013, 2016). The number of trabecular cells gradually declines as aging occurs; this loss of trabecular cells appears at a faster rate in human and Beagle POAG. The *ADAMTS10* mutation in Beagles with POAG has been associated with a microfibril abnormality (Kuchtey et al., 2011). A primary collagen defect has been proposed as a possible mechanism for the optic neuropathy of glaucoma. Abnormalities in the composition of collagen in the sclera, the lamina cribrosa, and the trabecular meshwork might be associated with altered pressure resistance in these regions (Boote et al., 2016; Gelatt & Samuelson, 1986; Palko et al., 2013, 2016; Rehnberg et al., 1987). This would suggest a more generalized ophthalmic disease in the primary glaucomas than just a local effect on the aqueous outflow pathways, and it

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might explain the different individual sensitivities of the ONH to different levels of IOP. ONH compliance in response to IOP elevations in eyes predisposed to primary glaucoma may be reduced, and the laminar tissue may be more rigid or stiff, and thus unable to protect the optic nerve axons from damage during IOP fluctuations (Zeimer & Ogura, 1989).

Changes in Globe Size

In contrast to adult humans, enlargement of the globe, which is also termed hydrophthalmos, buphthalmia, megaloglobus, or macrophthalmia, occurs in all animal species, including the dog, cat, horse, cow, rabbit, nonhuman primates, and also in the infant and young human. Globe enlargement in humans is rare today, but early in the 1900s it was not unusual, as IOP control was unusual. Somewhat correlated to the magnitude of the IOP elevation, globe enlargement may develop within several days, or it may develop very slowly over several months. Young puppies with acute glaucoma secondary to anterior uveitis often show marked and rapid increase in globe size. Assuming rapid reduction in the IOP, these globes may reduce to near-normal size. Buphthalmic globes of adult animals usually do not return to their normal, prehypertensive size; however, they may shrink in chronic stages when ocular hypotony (IOP < 5 mmHg) develops, resulting from reduced production of AH because of ciliary body atrophy. Most of the enlargement of the globe results from the expansive effects of IOP elevations on the elastic sclera rather than those on the more rigid cornea.

Corneal Changes

The cornea in the canine glaucomas becomes thicker because of edema within the stroma. This edema is generalized throughout the stroma, and clinically may be concentrated immediately beneath the corneal epithelium initially. The extent of the corneal edema may somewhat parallel the elevation in IOP. When IOP approaches 40 mmHg in the absence of intraocular inflammation, the corneal endothelial "pump" mechanism begins to decompensate, stromal edema develops, and the cornea thickens. With sustained or marked elevations in IOP, corneal endothelial cell death occurs, and gaps in the posterior endothelial cell lining become evident with specular microscopy. The endothelial cell response is hypertrophy and sliding of existing cells to cover the area previously occupied by the lost cells. At specular microscopy, the endothelial cells become larger, lose their hexagonal appearance, and reduce in number. Because fewer cells are present to maintain corneal deturgescence, metabolic demands on each remaining cell are increased. When a critical endothelial cell density is lost, a gradual increase in the central corneal thickness occurs, followed eventually by permanent corneal edema. The corneal thickness increases slightly in early glaucoma and considerably in advanced glaucoma, and this variable thickness with the presence of edema may render tonometry measurements less accurate. Peripheral corneal edema can also develop and is usually associated with the development of peripheral anterior synechiae.

Corneal enlargement also occurs with elevations in IOP, and this enlargement can be appreciated by measuring the vertical and horizontal corneal diameter. Focal, linear breaks, or stretching of Descemet's membrane (i.e., Haab's striae) occur in enlarged corneas, thereby allowing minute amounts of AH direct access to the corneal posterior stroma. Striae may also be associated with acute IOP spikes. As the globe enlargement increases, exposure keratitis and corneal ulceration caused by lagophthalmia, impaired blink reflexes, corneal edema, and increased evaporation of the precorneal tear film may result. Pigmentary keratitis and corneal vascularization may occur with chronicity.

Changes to the Sclera

With both abrupt and sustained elevations in IOP, the sclera is stretched and becomes thinner. The sclera is quite similar to the cornea but with dense, interlacing collagen lamellae and a larger concentration of elastic fibers. The predominant increase in globe size appears to relate mostly to scleral rather than corneal changes. Areas of sclera through which the nerves and blood vessels penetrate are particularly susceptible to thinning, with large staphylomas developing at the equator in some eyes. The scleral lamina cribrosa, where the optic nerve fibers exit the eye, is presented in "Retina and Optic Nerve Head."

Changes of the Anterior Chamber Angle and Aqueous Humor Outflow Pathways

The initial pathogenesis in the elevation in IOP in PACG and POAG appear quite different, but once IOP is elevated, the effects of this elevation eventually converge. The lamina cribrosa of the ONH and aqueous outflow pathways (AH) share many morphologic and physiologic similarities. However, the trabecular meshwork is unique to the regulation of aqueous outflow and IOP. As discussed in Chapters 2 and 3, the conventional outflow of AH in the canine eye through the ciliary cleft passes through the pectinate ligaments into the uveal trabecular meshwork, to the corneoscleral trabecular meshwork, the juxtacanalicular meshwork (probably the site of greatest resistance), and the angular aqueous plexus, to exit mostly into the intrascleral plexus. With normal IOP of about 15–20 mmHg, the total AH outflow resistance is produced by the combination of the corneoscleral trabecular meshwork (about 4–6 mmHg) and the angular aqueous plexus (about 10–12 mmHg). The pectinate ligaments seem

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to have limited, if any, effect on AH outflow, except when extensive undifferentiated pectinate ligaments occur (PLD) and limit or decrease the opening of the ciliary cleft.

Changes in the trabecular meshwork occur with aging, and in POAG and PACG. These changes involve the trabecular cells and the ECM of the trabecular meshwork, and affect both the conventional outflow pathways (pressure sensitive) and uveoscleral outflow pathways (pressure independent), involving the ICA as well as the ciliary or sclerociliary cleft. As the globe enlarges with persistent elevations in IOP in nonhuman species and young children, changes in these outflow pathways may represent a combination of early primary changes compounded by later secondary IOP-related effects on both the morphology and the function of the ICA and ciliary cleft.

Primary Open-Angle Glaucoma

POAG in dogs results from ECM changes in the AH outflow pathways and trabecular cells. These cells produce glycosaminoglycans (GAGs), extracellular glycoproteins, and fibrillar material (Acott, 1993; Lütjen-Drecoll, 1993; Toris et al., 2008). Trabecular cells are highly phagocytic, resulting in a self-cleaning filter for AH to traverse, removing particles, cellular debris, protein molecules, and the occasional pigment granules of different sizes, and even RBCs and experimentally introduced microspheres. Macrophages also wander throughout the trabecular meshwork assisting in the continuous "clean-up" process.

The ECM is the main site for AH resistance and a major contributor of IOP; it is also the pathologic site for increased AH resistance in POAG. The ECM comprises many different proteins, most of which are glycoproteins or proteoglycans. The GAGs isolated in both normal human and dog trabecular meshwork include hyaluronic acid, dermatan sulfate, chondroitin-4-sulfate, keratin sulfate, chondroitin-6-sulfate, and heparan sulfate (Gum et al., 1986). In studies investigating the different glycosaminoglycans within the trabecular meshwork of POAG in humans and the *ADAMTS10*-mutant Beagle (Gum et al., 1993b; Knepper et al., 1996), hyaluronic acid declined, chrondroitin sulfate increased (humans) or decreased (dogs), and an undegradable, hyaluronidase-resistant GAG-like material was identified in both species (Gum et al., 1986, 1987, 1993b). A study using human AH has indicated that the undegraded GAG-like material was a small hyaluronic acid (McCarty et al., 2011). Hyaluronidase-2 and hyaluronidase inhibitors are present in normal humans and those with POAG (McCarty et al., 2011). In the POAG eyes, hyaluronidase-2 levels are increased and hyaluronidase inhibitors are decreased.

Other important glycoproteins include laminin (a large basement membrane "glue"), fibronectin (another ECM "glue"), collagen (interstitial collagen; Type IV basement membrane collagen and Type V collagen), elastin (composed of fibrous protein elastin and formed around microfibrillar protein fibrillin), myocilin (MacKay et al., 2008a, 2008b; Samuelson et al., 2005) and CD44 proteins (Källberg et al., 2006). In POAG Beagles with the *ADAMTS10* mutation, fibrillin, a 350 kDa protein containing glucosamine but not sulfated (10 nm diameter fibrils around amorphous cores of the elastic cores), is likely important to the pathogenesis of POAG and abnormalities are probably responsible for the increasing resistance for AH as it traverses the TM. The TM changes in human and dog POAG are quite similar. Observations from human glaucoma specimens generally include reduced numbers of trabecular cells (greater than by aging alone) with thicker basement membranes, and plaque formation in the corneoscleral beams and juxtacanalicular meshwork (thought to be derived from elastic-like fibers that makeup the subendothelial tendon sheath). These thicker sheaths of the elastic fibers and connecting fibrils decrease the intertrabecular spaces and narrow AH flow pathways to the inner wall endothelium. Alterations of the ECM include collagen abnormalities (fragmentation, altered orientation, and abnormal spacing), fibronectin deposition in the subendothelium of Schlemm's canal, and increased myocilin and αß-crystalline levels (stress proteins). Clearly, the interactions of these proteins create complex changes within the trabecular meshwork and decrease AH flow through this entire area. Although different genes have been associated with POAG in humans, the ultrastructure of the trabecular meshwork has not been differentiated based on these specific genes and possible unique effects on the ECM.

Among the different breeds of dogs with POAG, the Beagle glaucoma has the most documentation. The trabecular meshwork cells, like in humans, decline with aging, and more so in POAG. The ultrastructural changes of the AH outflow pathways of Beagle POAG have been reported at different phases of the disease (pre-, early, moderate, and late; Samuelson et al., 1989). In the preglaucomatous dogs (1–11 months old), no abnormalities were present in the trabecular meshwork. In 12-month-old dogs, clustered basement membrane–like material was scattered throughout the corneoscleral trabecular meshwork. In the same region, elastin-like fibers appeared more numerous and were arranged less regularly. Occasional trabecular cells within the corneoscleral trabecular meshwork possessed small clusters of serrated opaque rods within their cytoplasm. In moderate to advanced POAG, these changes were more generalized and affected the entire corneoscleral trabecular meshwork. Narrowing developed with compression and less organization, with a concomitant build-up of extracellular materials. Intertrabecular spaces were markedly reduced in size in the uveal meshwork and to a lesser extent in the corneoscleral trabecular meshwork. A uniform layer of fibrils, 10–12 nm in diameter, and amorphous material coated most of the endothelial walls along the angular aqueous plexus. Elastin-like fibers frequently pressed against the endothelium of the angular aqueous plexus.

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Microfibrils are macromolecular aggregates located in the ECM of both elastic and nonelastic tissues that have essential functions in the formation of elastic fibers and control of signaling through the transforming growth factor beta (TGF-β) family of cytokines. Microfibril defects could contribute to glaucoma through alterations in the biomechanical properties of tissue and/or through effects on signaling through TGF-β, which is well established to be elevated in the AH of human and feline POAG patients. A role for microfibrils in glaucoma is suggested by the identification of risk alleles and mutations in the microfibril-associated genes *LOXL1* (for exfoliation glaucoma) and *LTBP2* (for primary congenital glaucoma) in humans. Recent identification of a G661R missense mutation in the *ADAMTS10* gene in the dog model of POAG naturally leads to a microfibril hypothesis of glaucoma, which in general states that defective microfibrils may be an underlying cause of glaucoma (Kuchtey & Kuchtey, 2014). Recent work has shown that diseases caused by microfibril defects are associated with increased concentrations of TGFβ protein and chronic activation of TGFβ-mediated signal transduction in humans. Defective microfibrils could provide a mechanism for the elevation of TGF-β2 in glaucomatous AH. However, a recent study in POAG dogs found that AH concentrations of active, latent, and total TGF-β2 were not significantly increased in *ADAMTS10*-mutant dogs compared to age-matched controls. In contrast to reported findings in glaucomatous cats and humans, elevated levels of TGF-β2 may not contribute to the development of open-angle glaucoma in Beagles (Scott et al., 2013c). Alternatively, TGF-β2 may be bound within the ECM rather than free within AH in the anterior chamber. Preliminary immunohistochemical studies to evaluate the expression of TGF-β2 in ocular tissues have characterized patterns of tissue distribution of TGF-β2 in the eyes of dogs with open-angle glaucoma and indicate that there is increased TGF-β2 in the ciliary body epithelium, corneal epithelium, and optic nerve of affected dogs.

Primary Narrow-Angle or Angle-Closure Glaucoma

While the primary mechanism for elevating IOP in POAG lies within the AH outflow pathways, the exact mechanism(s) involved in the genesis of PACG in the dog is poorly understood. Information on PACG in humans may provide some helpful clues. Pupillary block PACG is the most common cause of angle closure. Measurement of PACG in humans indicates smaller corneal diameter, smaller radius of anterior and posterior corneal curvatures, shallower anterior chamber, thicker lens, smaller radius of anterior lens curvature, more anterior lens position, and shorter axial length of the globe (Ritch & Lowe, 1996). Similar finding are reported in PACG in dogs.

Hence, to help our understanding of canine PACG, UBM measurements of the anterior chamber angle and ciliary cleft, as well as the standard ultrasound measurements of the entire axial globe length, anterior chapter depth, width of the lens, and size of the vitreous space, are invaluable. For those globes with PACG in which the AH outflow pathways are normal initially, narrowing of the anterior chamber and a forward displacement of the iris and lens may result in an unusually "tight" contact against the mid to central anterior lens surface. With the pupillary flow of AH somewhat impaired, the increase of only a few mmHg within the posterior chamber results in the forward displacement or "ballooning" of the basal iris, restricting AH access to the AH pathways and the opening of the ciliary cleft. With angle closure and collapse of the ciliary cleft in excess of 180°, formation of peripheral anterior synechiae begins to permanently impair AH outflow and IOP elevations commence. The more of the outflow pathways are apposed by synechiae, the higher the IOP elevates.

In other PACG globes in which the trabecular meshwork or AH outflow pathways are abnormal (as with PLD/goniodysgenesis) and IOP gradually elevates, narrowing of the anterior chamber depth and forward displacement of the lens may occur as IOP insidiously increases. In the Basset Hound these changes appear continuous.

Secondary changes in the ICA and ciliary cleft of the dog invariably involve progressive narrowing, and eventual closure, of the ICA and collapse of the ciliary cleft in moderate and advanced glaucoma. Mechanisms for these phenomena are still unclear, but some theories exist. Enlargement of the globe associated with the stretching of the sclera possibly distorts the ICA both anteroposteriorly and meridionally. The result is compaction of the corneoscleral trabecular meshwork and partial to complete collapse of the aqueous veins and intrascleral venous plexus. Also, the different components of the meshwork ECM, such as collagen, elastin, glycosaminoglycans, and glycoproteins, may become altered. Corneal endothelial cell proliferation and changes in Descemet's membrane across the face of the ICA may develop and further compromise aqueous outflow. Peripheral anterior synechia can develop when the basal iris comes into direct contact with the compacted trabecular meshwork. The trabecular meshwork within the ciliary cleft may be subjected to abnormal stresses as the cleft collapses. Lens zonule disruption associated with lens subluxation and luxation may affect the mechanisms involved with trabecular opening and the overall size of the ciliary cleft space because of reduced tension from the zonules normally attached at the lens equator. Hence, with any form of glaucoma involving globe enlargement, secondary changes to the AH pathways may aggravate further clinical management of IOP control and prevention of additional optic nerve damage.

Matrix Metalloproteinases

The matrix metalloproteinases (MMPs) also play a very important role in determining resistance to the AH outflow on AH within the ECM (Weinstein et al., 2007). The trabecu-

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lar meshwork cells can detect changes in IOP and respond by increasing levels of MMP. The metalloproteinases increase the ECM turnover rate, reduce the resistance to AH outflow though the trabecular meshwork, and lower the IOP. The latent form of MMP-2 seems the most relevant MMP in the canine eye. The AH in glaucomatous dogs had elevated latent MMP-2 compared to normal eyes (Weinstein et al., 2007). In the ICA tissues, the active form of MMP-2 was significantly higher in glaucomatous eyes. Also, in dogs with primary and secondary glaucoma, there was a significant increase in latent MMP-9 forms. *ADAMTS10* and *ADAMTS17* are members of the family of secreted metalloproteinases; mutations in these genes cause POAG (and primary lens luxation, PLL) in dogs (Kuchtey et al., 2010).

Changes of the Iris

Mydriasis is a consistent clinical finding in most types of glaucoma, except for those occurring secondary to anterior uveitis. Pupillary dilation in response to elevated IOP is a complex event. It may result from iris or optic nerve changes (or both). As the elevations in IOP increase, mydriasis is absolute, and pupillary changes after the instillation of diagnostic miotics are either limited or absent. This lack of response by the iridal sphincter muscle and, presumably, the longitudinal ciliary body musculature may be caused by impaired neural or vascular supply (or both) to the central iris. With time, the iridal stroma becomes thin, and the sphincter muscle atrophies. Hence, as the glaucoma progresses, pupillary dilation caused by limited response of the iridal sphincter musculature occurs. A lack of sensory input resulting from RGC dysfunction may also contribute to the mydriasis. The elevation in IOP may mechanically open the pupil to some extent. Pigment granules from the degenerating iridal melanocytes and the posterior pigmented iridal epithelia may be released into the AH and eventually lodge within the corneoscleral and uveal trabecular meshworks, or be phagocytized by the trabecular cells and macrophages.

Changes of the Ciliary Body

The response of the ciliary body to elevated IOP is gradual degeneration with atrophy of the pars plicata and individual ciliary processes. The assumption, which has not yet been confirmed by results of fluorophotometry, is that the rate of AH formation is unchanged as the IOP is elevated until the perfusion pressure (i.e., mean arterial blood pressure minus IOP) approaches zero. With progressive deterioration of the ciliary body processes and nonpigmented ciliary body epithelia, the rate of AH formation probably decreases. With advanced ciliary body atrophy, profound ocular hypotony (< 5 mmHg) results. Corneal edema, cataract formation, retinal detachment, and intraocular hemorrhage often follow.

Changes of the Choroid and Tapetum Cellulosum

The choroid is the primary vascular supply to the eye and particularly to the outer retinal layers. Short posterior ciliary arteries feed choroidal arteries, which form poorly anastomotic, choroidal circulatory lobules. The effect of elevated IOP on the choroid depends on rapidity of onset, duration, and level of the IOP elevation, as well as on the species involved (Yu et al., 1988). In the dog the tapetal retina seems less affected than the nontapetal zone. Once the ocular perfusion pressure (OPP) is reduced by increased IOP, the choroidal blood flow declines, because canine choroidal blood vessels poorly autoregulate in response to this diminished blood flow. It appears the choroidal blood flow is most adversely reduced when IOP is markedly elevated (> 60 mmHg). Thus, both inner (RGCs) and outer (rod and cone photoreceptors and outer nuclear layer) retinal layers are affected at these high levels of IOP. Rabbit choroidal vessels, in contrast, vigorously autoregulate (Kiel & van Heuven, 1995; Whiteman et al., 2002). Reduced blood flow results in a hypoxic-ischemic state, with various cytotoxic and vasoactive substances released that may accelerate local damage within the choroid and adjacent outer retina. After marked elevations of IOP in humans, poorly perfused "watershed zones" between adjacent choroidal lobules are markedly affected by the reduced perfusion. Watershed zones are the border areas between the territories of distribution from any two end- arteries. During a decrease in perfusion pressure in the vascular bed of one or more end artery, the watershed zone, being an area of comparatively poor vascularity, is the most vulnerable to ischemia. Accordingly, watershed zones have been shown to exist in the primate choroid between the distributions of the posterior ciliary arteries, the short posterior ciliary arteries, the short and long posterior ciliary arteries, the posterior and anterior ciliary arteries, the choriocapillaris lobules, and the vortex veins (Hayreh, 1990). This perfusion deficit results in focal areas of chorioretinal ischemia and degeneration in the ischemic zones. Ischemia associated with the nonperfusion of individual short posterior ciliary arteries also occurs in dogs with primary glaucomas, appearing as focal, fan-shaped areas of chorioretinal degeneration radiating from the ONH. As in humans, these apparent watershed zone degenerations in the dog more often seem to follow abrupt and severe elevations in IOP (> 60 mmHg). In the POAG Beagle, both fluorescein and indocyanine green angiography demonstrated wedge-shaped areas of delayed choroidal filling, delayed superior retinal venule filling, and peripapillary and ONH hyperfluorescence. The abnormalities were more distinct with the fluorescein method (Burn et al., 2017).

Changes in the tapetum cellulosum after sustained elevations of IOP include degeneration and thinning, though compared with the nontapetal fundus, the tapetal fundus

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appears somewhat spared initially. Histopathologic examinations of moderately advanced glaucomatous globes may reveal near-complete loss of the RGCs in the nontapetal fundus, but a surprising, though reduced, number of normal-appearing RGCs remain in the tapetal fundus.

Changes of the Lens

Abrupt or sustained elevations in IOP may result in cataract formation and changes in the lens position within the patella fossa. The basis for cataract development is not understood, but it may occur secondary to changes in the composition and rate of AH formation, and perhaps changes in the nutrition and waste removal functions it serves, or due to toxic metabolites present as a result of the glaucoma pathogenesis. These cataractous changes initially affect the active areas of new lens-fiber formation. Focal vacuoles can progress to complete cataract formation.

Transposition of the canine lens from the patella fossa may result from primary zonular disease or be secondary to globe enlargement. In terrier breeds and Border Collies, the zonular defects appear to be primary and inherited (Curtis et al., 1983; Formston, 1945; Foster et al., 1986; Willis et al., 1979). In several breeds, including the Jack Russell Terrier, Parson Russell Terrier, Miniature Bull Terrier, Tibetan Terrier, Lancashire Heeler, Chinese Crested, Australian Cattle Dog, Jagd Terrier, Patterdale Terrier, Rat Terrier, Sealyham Terrier, Tenterfield Terrier, Toy Fox Terrier, Volpino Italiano, Welsh Terrier, Wirehaired Fox Terrier, and Yorkshire Terrier, PLL has been associated with the *ADAMTS17* splice donor site mutation (Farias et al., 2010; Gould et al., 2011; Sargan et al., 2007). The anomalous zonules break down, thereby resulting in subluxation that can progress to total luxation of the lens to the anterior or vitreal chamber. Luxations of the lens may cause pupillary block, which in turn results in acute elevations of IOP. Typically, the terrier breeds with PLL are between 1 and 4 years of age, and are usually distinct from older dogs (7–10 years old) with advanced cataractous formation, zonular degeneration, and lens luxations. Similar to human patients with Weill–Marchesani syndrome (WMS), dogs with *ADAMTS10* and *ADAMTS17* mutations exhibit zonular abnormalities concurrent to elevations in IOP, which follow the ECM abnormalities within both the lens zonules and the trabecular meshwork that accompany these defects (Dagoneau et al., 2004; Gould et al., 2011; Kutchey et al., 2011). In these individuals, lens subluxations and luxations likely occur due to these zonular changes rather than buphthalmic globe stretching.

In secondary lens luxation, globe enlargement appears to be important to its pathogenesis (Gwin, 1982). With globe enlargement, zonular tension appears to be significantly increased. If the zonules are intact, marked traction and elongation of the individual ciliary body processes may be observed through a widely dilated pupil. Tearing of the zonules occurs most frequently near their insertions at the lens equatorial capsule; infrequently, the zonular transection may occur at the level of the ciliary body process, with a small section of the process remaining adherent to the zonule. Often with cataract hypermaturity zonular loss is present; these dogs are typically middle-aged to older (5–8 years old).

Lens luxations can markedly hamper clinical management of the canine glaucomas. A subluxated to totally luxated lens may result in abrupt elevations in IOP, and lens luxations can block the pupil and impair aqueous passage, especially if the pupil is miotic. Attachment of the vitreous to the posterior lens capsule and tearing of the anterior hyaloid face may also cause the cortical or formed vitreous to enter the pupil or anterior chamber (or both) and to impede AH outflow. A secondary iridocyclitis may develop from iridolenticular contact. The lack of zonular tension on the ciliary cleft may hasten its reduction and eventual collapse.

Changes of the Vitreous

Abrupt and sustained elevations in IOP result in vitreal liquefaction and formation of vitreal cortical strands. Tearing of the anterior hyaloid membrane associated with lens subluxation, anterior lens luxation, and posterior (i.e., intravitreal) luxations may allow this liquefied vitreous direct access to the anterior chamber and the AH outflow pathways. The liquefied vitreous can permit a subluxated lens to eventually luxate posteriorly, then contact and even adhere to the ventral retinal surface. The liquefied vitreous may also alter physical support to the retina and predispose to retinal detachment. When high elevations in IOP occur, the posterior vitreous may be displaced into the anterior ONH (Schnabel's cavernous atrophy).

Changes of the Retina, Scleral Lamina Cribrosa, and Optic Nerve

Changes in IOP have profound effects on the retina and the ONH. Normally the scleral lamina cribrosa represents the exit of the RGC axons (with glia and blood vessels) at a pressure of about 10–18 mmHg, to become the intraorbital division of the optic nerve surrounded by cerebrospinal pressures of about 10 mmHg. When the IOP exceeds 30 or even 50 mmHg, the scleral lamina cribrosa faces a considerable pressure difference.

Scleral Lamina Cribrosa

The scleral lamina cribrosa becomes distorted and compressed posteriorly by increases in IOP, thus affecting axoplasmic flow within the RGC axons and probably impairing blood supply to the ONH by compromising the blood vessels in the laminar trabeculae (Brooks et al., 1989b; 1995a;

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Fig. 20.5). Both ischemic and mechanical effects to the lamina cribrosa interfere with optic nerve axoplasmic flow and lead to axonal and RGC death. These changes have been studied in normal dogs with experimentally, acutely elevated IOP, as well as in *ADAMTS10*-mutant Beagles with inherited POAG in which IOP elevations were sustained for 6–36 months (Samuelson et al., 1983). The elevated IOP obstructs both orthograde and retrograde axoplasmic flow of the RGC axons at the scleral lamina cribrosa. Structural and biochemical abnormalities in the ECM of the lamina cribrosa may affect the progressive compression and remodeling of this connective tissue in primate (Zeimer & Ogura, 1989) and possibly in canine glaucoma. The lamina cribrosa from normal, young human eyes has the ECM of a compliant tissue, which may be able to respond and protect the optic nerve axons from acute, mechanical displacement of the ONH during increases in IOP, and changes occurring with age in human laminar ECM result in a reduced ability to respond to episodic IOP spikes (Hernandez, 1992). The cupping of the ONH associated with glaucoma results from optic nerve axonal death as well as from compression, stretching, and rearrangement of the connective tissues of the lamina cribrosa in response to altered IOP. ONH compliance in response to minor alterations in IOP diminishes as glaucomatous optic nerve damage progresses (Hernandez, 1992; Hernandez & Pena, 1997).

A complex relationship exists between the astrocytic, neural, vascular, and fibrous elements of the scleral lamina cribrosa (Elkington et al., 1990; Hernandez & Ye, 1993). Glial cells, blood vessels, and collagen beams form a multilayered

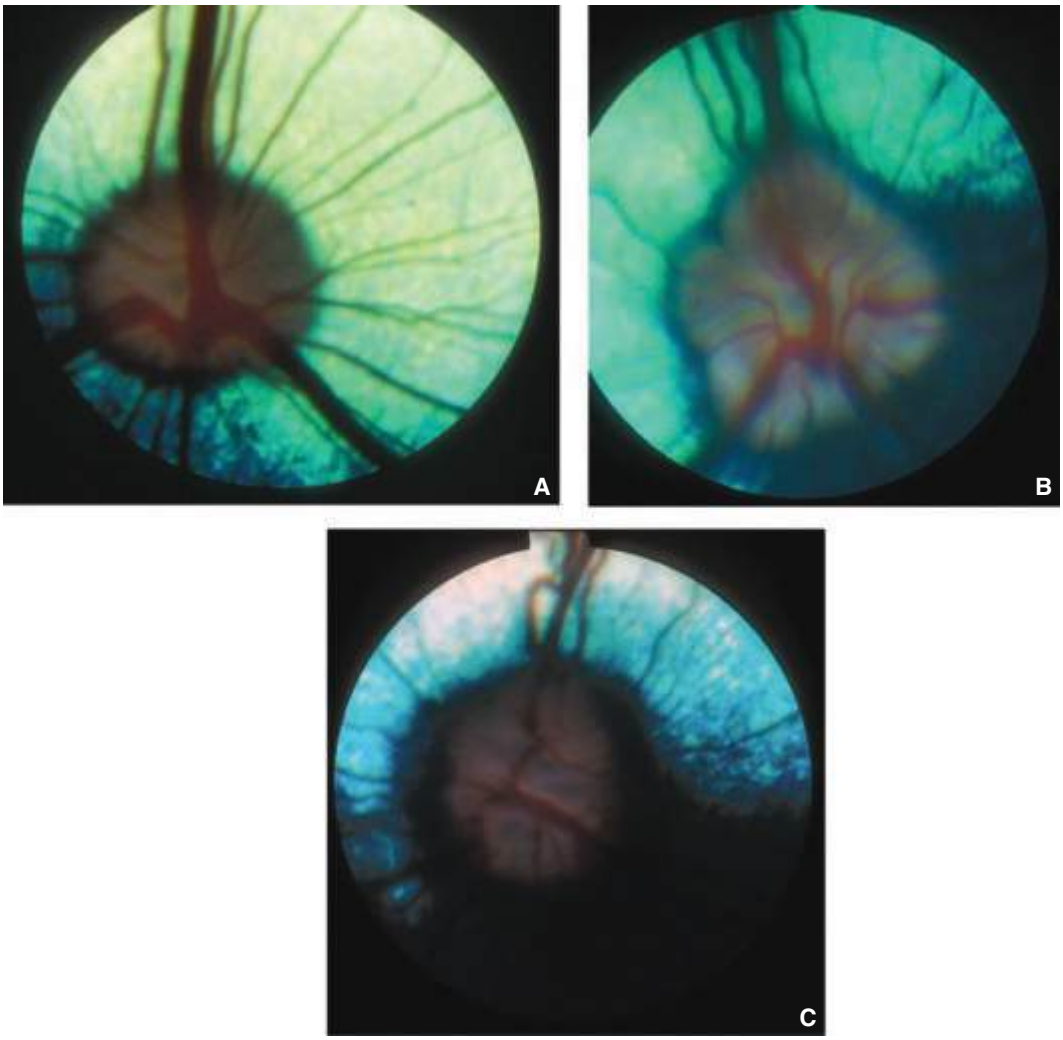


Figure 20.5 Optic nerve heads in three primary open-angle glaucomatous Beagles. **A**. Normal optic disc. **B**. Optic disc in early hypertension with electrophysiologic evidence of glaucoma. **C**. Optic disc in a moderate stage of primary open-angle glaucoma with enlargement of the optic cup.

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meshwork through which the optic nerve fibers are interwoven. Connective tissue in the lamina cribrosa provides biomechanical support to these axons, and the tensile strength and elasticity of this connective tissue mainly result from the presence of collagen and elastic fibers. Cross-bridging between collagen fibers is most dense near the ECM of the collagenous laminar beams, and it is less dense toward the axons (Furuta et al., 1993). This organization may play a role in the smooth transfer from the axon to the laminar beam of tissue-shear stresses associated with IOP.

Elastin, which consists of a central core of α-elastin and a microfibrillar sheath, is a major component of the ECM elastic fibers of the lamina cribrosa, and it is responsible for its elastic properties (Hernandez & Pena, 1997). Elastic fibers undergo marked changes, such as loss and fragmentation, in the lamina cribrosa of humans (Hernandez, 1992) and *ADAMTS10*-mutant Beagles with POAG (Samuelson et al., 1989). Changes occurring with age also affect the elastin of the lamina (Hernandez, 1992). No elastin is found in the ECM of fetal lamina cribrosa. Laminar tissues are undergoing elastogenesis in infant humans, and elastin is present in microfibrillar aggregates in the core of the laminar plates. Thin, elastic fibers run longitudinally in the core of the laminar plates in young adults. With age, elastic fibers become thicker, tubular, and surrounded by densely packed collagen fibers. In POAG Beagles with the *ADAMTS10* mutation, collagen density was significantly reduced and collagen anisotropy was reduced in the mid-posterior sclera (Boote et al., 2016).

In humans with early POAG, tubular elastic fibers are absent, and fragments of elastic fibers and microfibrillar aggregates are found, thereby suggesting that new elastin synthesis is disorganized (Hernandez, 1992). In advanced POAG, masses of nonfibrillar, elastin-positive material with a spotted appearance, proliferation of basement membranes, and bundles of elastin-negative microfibrils are present. Glial hyperplasia, loss of collagen fibers, more severe disorganization and fragmentation of elastin fibers, and accumulation of nonfibrillar, elastic-like material also occur (Hernandez, 1992). It appears that elastin continues to be synthesized. This biosynthesis may be abnormal, however, or there may be abnormal degradation. These changes may be induced by alterations in the ONH microenvironment caused by ischemia or mechanical changes to the lamina cribrosa. The progression of changes in elastic fibers and ECM disorganization is associated with progressive loss of optic nerve function.

Abnormalities of collagen composition in both the lamina cribrosa and the trabecular meshwork may be associated in part with altered pressure resistance in these regions (Gelatt & Samuelson, 1986; Rehnberg et al., 1987). The precise distribution of collagen types and the amino acids associated with collagen, proline, hydroxyproline, and hydroxylysine have been studied immunohistochemically in the eyes of humans with healthy eyes and in humans with glaucoma, to characterize the lamina cribrosa and trabecular meshwork and to determine if those areas are different from the surrounding sclera. Concentrations of the collagen-specific amino acids proline, hydroxyproline, and hydroxylysine were increased in the lamina cribrosa of glaucomatous human eyes, but remained at normal levels in the sclera and trabecular meshwork. Collagen Types I, III, and IV were found in the lamina cribrosa, the trabecular meshwork (weak for Type I), and the retrolaminar optic nerve. Only Type I collagen was found in the sclera. Type IV collagen and laminin were found in the blood vessels and laminar beam margins (i.e., basement membrane components) of both infant and adult humans (Rehnberg et al., 1987), and in another study (Morrison et al., 1989), heavy concentrations of Type I and III fibrillar collagen were found in the interstitium of the laminar beams of adults.

Fibrillin, which is the microfibrillar portion of elastin, was also found in longitudinal bands in the laminar beams; neonatal laminas contained less interstitial collagen, with a predominance of Type III (Morrison et al., 1989). Type III collagen is more distensible, but has less tensile strength, than Type I (Elkington et al., 1990). This may be why optic discs found in congenital glaucoma among humans can display rather remarkable and reversible optic nerve cupping. Mutations recently reported in *ADAMTS10* (POAG in Beagle, Norwegian Elkhound) and *ADAMTS17* (POAG and PLL in over 20 canine breeds) have been associated with microfibrin abnormalities (Kuchtey et al., 2014).

Functionally, elastic fibers and collagen act as parallel mechanical elements to applied stress or strain (Hernandez, 1992; Hernandez & Ye, 1993). Collagen fibers are extended easily at low stress levels, with most of the stress being borne by the elastic fibers. At high levels of strain, collagen fibers limit further laminar tissue distention, thereby providing strength and support to the tissue. The decrease in collagen density and the degenerative changes in elastic fibers of the lamina cribrosa observed in humans with POAG must alter the mechanical properties of the laminar tissue early in the disease process (Hernandez, 1992). It has been demonstrated that dogs with the G661R missense mutation in *ADAMTS10* have an inherently weaker and biochemically distinct posterior sclera, with a reduction in fibrous collagen density even before clinical indications of optic nerve damage. However, it remains to be shown whether and how the altered scleral biomechanics may affect the rate of glaucoma progression following IOP elevation (Boote et al., 2016; Palko et al., 2013, 2016).

Retina and Optic Nerve Head

In spontaneous (noninduced) glaucoma in the dog, elevations in IOP result in damage to RGCs initially, especially in the peripheral and inferior retina, followed by atrophy of the ONH (loss of myelin and RGC axons, changes in neuroretinal rim size and the cup-to-disc ratio) and then degeneration of the outer retinal layers and the retina as a whole. Clinically

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affected animals will have loss of vision, which may be transient or permanent depending upon the degree and duration of IOP elevation, functional mydriasis, and impaired pupillary light reflexes, due to pressure-induced damage. Other clinical signs that may result from IOP elevations include corneal edema, episcleral injection, and further structural and functional injury to the drainage apparatus. Regardless of the role elevations of IOP play in the glaucomas, these diseases are considered neurodegenerative diseases because they result initially in the death of a neural cell, the RGC. Decreased function of large-diameter RGCs in the peripheral retina and decreased blood velocity of the ONH vasculature are present at normal IOP before increases of significant IOP in canine POAG (Gelatt et al., 2003; Gelatt-Nicholson et al., 1999; Ofri et al., 1993a, 1994), suggesting that the disease process has been set in motion prior to the elevation of IOP. There is partial to complete obstruction of axoplasmic flow at the scleral lamina cribrosa and elevated intravitreal glutamate in canine POAG (Brooks et al., 1997; Samuelson et al., 1983). RGC and photoreceptor apoptosis, in addition to intravitreal glutamate elevation, are present in canine PACG glaucoma (Brooks et al., 1997; Miller et al., 1997). All of these abnormalities suggest that for the canine glaucomas, the most accurate definition may be that they are the final common pathway of a group of diseases with increased IOP, decreased RGC sensitivity and function, RGC death, optic nerve axonal loss with concurrent ONH cup enlargement, incremental reduction in visual fields, and blindness.

It remains unclear why elevated IOP tends to damage the RGCs and ONH and why, under certain conditions, similar damage occurs even at normal IOP. A recent study in normotensive dogs predisposed to glaucoma, those in which the fellow eye had already been diagnosed with primary glaucoma, revealed thinner retinas and RNFL as observed with OCT compared to normotensive eyes in controls (Graham et al., 2020). Is axoplasmic flow blocked by some mechanical effect on the axons associated with biomechanical dysfunction of the ONH, or is the blockage secondary to ischemia caused by ONH microcirculatory abnormalities? Both undoubtedly occur to some degree and may be influenced by the magnitude of the elevated IOP. These effects on the different tissues of the eye depend heavily on the IOP variables, which include, but are not restricted to, the magnitude and duration of the pressure elevation, the rate of the elevation (i.e., chronic versus abrupt), and the interrelationship of IOP with the perfusion pressure of the eye (i.e., the mean arterial blood pressure minus the IOP). High IOP, compromised vascular supply to the ONH and inner retinal vasculature, and weakened lamina cribrosa structural support all play a role in glaucomatous optic nerve damage in the dog.

Although the endpoint is usually the same, there may be significant differences in the retina and ONH between POAG and PACG eyes in the early and middle stages. The retina and ONH in POAG are affected more slowly, with gradual reduction in ONH size, loss of myelin and cupping (difficult to detect without serial photographs or high-resolution imaging), and peripheral retinal vasculature (vessel size). POAG is characterized by maintenance of central vision until late in the disease process and relatively slower IOP elevation. The clinical picture is one of slow, peripheral retinal degeneration (initially the RGCs), vascular attenuation, and ONH degeneration. In PACG, the IOP elevations are acute and often very high (> 50 mmHg). ONH degeneration occurs much more quickly and all retinal layers are affected (hence the reduced fERG; Scott et al., 2013a; Whiteman et al., 2002). In POAG eyes, the fERG is usually normal, but the PERG is changed, especially in the peripheral retina (Ofri et al., 1994). Early microscopic examinations (within 24 hours) of PACG globes reveal marked RGC necrosis and mild neutrophil infiltration (Scott et al., 2013a; Whiteman et al., 2002). The entire retina is affected in PACG eyes. Necrosis of the RGCs with segmental nerve fiber layer rapidly progressed to involve all of the retinal layers within 1 day of onset of acute congestive PACG. Apoptosis of the RGCs and photoreceptor death was present within 1 day and prominent by 3 days (Scott et al., 2013a; Whiteman et al., 2002).

The inner retinal layers, especially the RGC and RNFL as well as the ONH, appear to be most sensitive to changes in IOP, and elevations in IOP can produce a cascade of tissue and vascular events that eventually lead to cell death (Quigley, 1996). High IOP, compromised vascular supply to the ONH, and weakened ECM of the lamina cribrosa all play a role in glaucomatous optic nerve damage (Fick & Dubielzig, 2016; Hernandez & Pena, 1997; Spaeth, 1993). Local retinal amino acid excitotoxic injury, neurotropin deprivation to RGCs, and axoplasmic flow impairment at the prelaminar scleral cribrosa may contribute as well, both individually and collectively, to the optic nerve damage in the primary glaucomas, and perhaps in part to that in the secondary glaucomas (Brooks et al., 1997; Fechtner & Weinreb, 1994; Nickells, 1996; Samuelson et al., 1993). Large-diameter optic nerve axons appear to be particularly sensitive to the elevated IOP that occurs during human, monkey, canine, and equine glaucoma (Brooks et al., 1995a, 1995b; Quigley et al., 1987). Axons of all diameters are subject to severe tissue-shearing forces at the lamina cribrosa resulting from the abrupt reduction in hydrostatic pressure (Holländer et al., 1995; Morgan et al., 1995). The large-diameter axons were initially thought to be most susceptible to this sudden pressure transition because the critical collapsing pressure of axons is inversely proportional to the cube of the axon's radius, but this hypothesis has recently become the subject of debate. Even small elevations in IOP may cause a reduction of axoplasmic flow and subsequent axon collapse, with axonal degeneration and atrophy. Sensitivity of the optic nerve to a particular level of IOP may change over time, based on biomechanical tissue properties, with progressive

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damage occurring at an IOP that was previously believed to be safe (Brubaker, 1996; Haefisa & Anderson, 1996). At every level of IOP there is a risk of glaucomatous damage, though the risk increases with increasing IOP. Damage can occur with extreme rapidity, as in angle-closure glaucoma, or it may progress slowly, as in chronic POAG (Haefisa & Anderson 1996). IOP cannot be used by itself to determine whether glaucoma is present or whether optic nerve damage will occur or progress (Spaeth, 1993; Fig. 20.6 and Fig. 20.7).

Deformation of the pores of the canine scleral lamina cribrosa occurs quite early in canine glaucomatous optic neuropathy during the POAGs (Brooks et al., 1989a). This progressive, early deformation of the lamina cribrosa may not be detected ophthalmoscopically. OCT examination of the glaucomatous canine ONH reveals little change to the canine ONH at early to moderate stages of POAG, with sudden and dramatically increased optic disc cup depth and loss of neuroretinal rim at advanced stages of glaucoma (Dawson et al., 1995; Oh et al., 2013). Both elastin and collagen in the lamina cribrosa and trabecular meshwork are progressively disrupted as the disease progresses.

The continued progression of ONH degeneration and deterioration of the animal's vision despite lowering of IOP is classic evidence for the role of non-IOP-related factors in glaucomatous optic neuropathy. Acute and sustained elevated IOP in the rabbit with experimental chymotrypsin glaucoma, in the rabbit with congenital buphthalmia, in the nonhuman primate with laser-induced experimental glaucoma, in humans with spontaneous glaucomas, and in primary glaucoma among several breeds of dog are associated with elevated intravitreal glutamate levels induced by retinal and ONH ischemia (Brooks et al., 1997; Dreyer et al., 1996). Among animals tested, intravitreal glutamate levels are much higher in the ACS with glaucoma than in Samoyed, Shar-Pei, and Akita (Brooks et al., 1997). In all probability, the initial primary optic nerve injury from the elevated IOP induces RGC degeneration and apoptosis caused by glutamate excitotoxicity, neurotropin deprivation, accumulation of intraneuronal calcium, and formation of nitric oxide, proteases, and oxygen free radicals. The more severe the IOP-induced primary injury, the more dramatic the secondary effects; likewise, the less severe the primary IOP-induced injury, the less severe the secondary degenerative effects to the RGCs. Failure of successful treatment of glaucoma relates not only to elevated IOP, but to the creation of a hostile retinal and ONH microenvironment that continues after the IOP has been normalized.

There are several possible sources for the excess vitreal glutamate found in the glaucomas of different animal species. The loss of neurotrophic factor communication between axonal synaptic terminals and neuronal cell bodies when both orthograde and retrograde axoplasmic transport are obstructed at the lamina cribrosa in glaucoma may cause RGC death (Nickells, 1996). Dying RGCs could then release their intracellular stores of glutamate, which in turn results in further retinal cellular injury (Bito, 1977). A second source of increased vitreal glutamate levels could be the increased membrane permeability of diseased RGCs, which allows the release of intracellular glutaminase and conversion of extracellular glutamine to glutamate. Intracellular glutaminase is normally present in RGCs to convert glutamine to glutamate, and glutamine is normally found at high levels in the



Figure 20.7 Chronic bilateral primary open-angle glaucoma in a Beagle dog. Note the buphthalmos, corneal edema, striae, and pigment, and mydriasis.

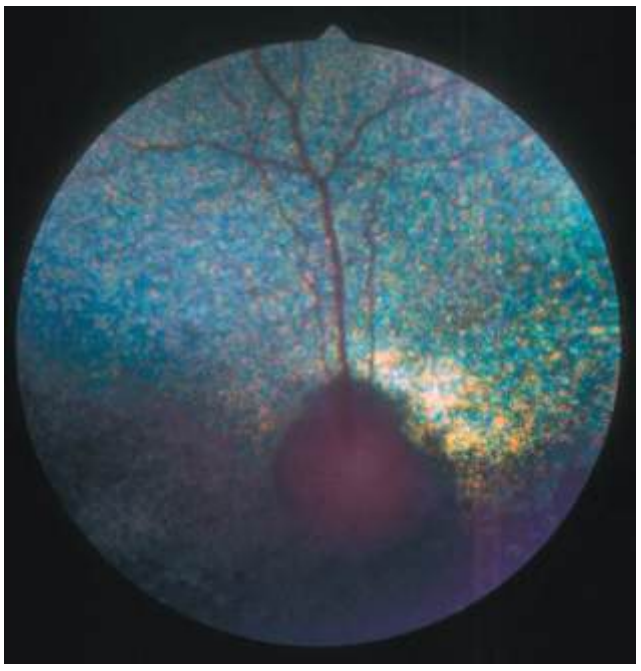


Figure 20.6 Advanced optic disc atrophy in primary closed-angle glaucoma in an American Cocker Spaniel.

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vitreous (Ankarcona, 1995). A third source of glutamate may be disrupted removal of glutamate by the Müller cells (Silveira et al., 1994). Müller cells normally clear the synaptically released glutamate, but this ability may be impaired or overloaded under the ischemic conditions of high IOP (Huang et al., 1996). Under conditions of retinal ischemia, Müller cell transport systems that normally move glutamate into the cells may even actually work in reverse and deposit glutamate into the extracellular spaces (Otori et al., 1995). The Müller cells of dogs with glaucoma are glial fibrillary acidic protein–positive, thus indicating an alteration in cellular physiology (Komáromy et al., 1997). A redistribution of glutamate was seen in the retinas of dogs with primary glaucoma (McIlnay et al., 2004). Glutamate was lost from cell bodies in damaged areas of the inner and outer nuclear layer, whereas other cells, presumably Müller cells, contained an increased level of glutamate. Glutamine synthetase decreases in immunoreactivity with glutamate redistribution (Chen et al., 2008). These decreases occurred in mildly damaged areas of the retina before overt retinal thinning. Reactive Müller cells occurred primarily in chronic primary glaucoma in severely damaged areas of the retina. The decreases in glutamine synthetase may potentiate ischemia-induced early glutamine redistribution and neuron damage. Glutamate levels that are potentially toxic to RGCs are likely associated with the pathogenesis of primary glaucoma in the dog. Mean (± SD) vitreal glutamate concentrations were 31.7 ± 12.4 and 6.9 ± 6.3 mM in glaucomatous and normal eyes, respectively (Brooks et al., 1997).

Other studies have found no increases in vitreal glutamate levels in animal models of glaucoma or in human patients with glaucoma (Levkovitch-Verbin et al., 2002; Wamsley et al., 2005). The reason for the discrepancies in the interlaboratory results may be differences in experimental design, sample collection, or detection methods. However, local concentration of glutamate at the membrane receptors of RGCs is probably a more important issue than vitreal levels of glutamate. If retinal damage differs in intensity in focal areas, as shown in dogs, overall glutamate levels may be normal while there is a focal excess of glutamate in ischemic areas with affected glutamate reuptake (McIlnay et al., 2004).

Retrograde axonal transport obstruction of brain-derived neurotrophic factor (BDNF) and its TrkB receptors in the retina and optic nerve have been demonstrated in the glaucomatous ACS (Iwabe et al., 2007). Both BDNF and TrkB immunostaining was detected in a more intense pattern in glaucomatous eyes when compared to normal eyes. As demonstrated in the Beagle with POAG and acutely elevated IOP in normal dogs, in which there is obstruction of both orthograde and retrograde axoplasmic flow of the RGC axons at the scleral lamina cribrosa (Samuelson et al., 1983; Williams et al., 1983), BDNF retrograde axonal transport is also substantially inhibited by IOP elevation in the ACS. Differences in the degree of IOP elevation and the retina–optic nerve perfusion pressures appear to directly influence the degree of impairment of these orthograde and retrograde axoplasmic flow markers.

Alterations in the retinal levels of the stress-inducible proteins glial fibrillary acidic protein (GFAP), heat shock protein 60, and hypoxia-inducible factor-1α (HIF-1α) in rapidly progressive disease suggests a shift in cell regulation between acute (< 2 days) and chronic (> 7 days) glaucoma groups, and supports previous studies reporting that ischemia is a very important mechanism in this disease (Savagian et al., 2008). This study also correlates with most clinical observations that acute primary glaucoma is a rapidly progressive degeneration involving all layers of the retina (both retinal and choroidal circulation are markedly affected) and a catastrophic event on vision. This study further correlates to clinical observations that differentiate PACG (which is also catastrophic) from the more common POAG in humans.

Weibel-Palade bodies are endothelial storage organelles of von Willebrand factor, which is a high-molecular-weight glycoprotein with a role in hemostasis and has been recently associated with the ADAMTS family of secreted metalloproteinases (Kuchtey et al., 2011). These organelles are often associated with microcirculatory disorders such as diabetes and atherosclerosis in humans, but they are uncommonly found in the circulatory system of normal dogs. Weibel-Palade bodies are, however, found in the laminar capillaries of Beagles with hereditary glaucoma (Brooks, 1989b). The presence of Weibel-Palade bodies in Beagles with hereditary glaucoma is highly suggestive of a primary or secondary ONH microcirculatory disorder.

Changes of Ocular Perfusion Pressure

The concept of OPP is very important in understanding blood pressure and flow in the "pressurized" eye. OPP is equal to the external ophthalmic artery mean blood pressure minus the IOP. OPP is the driving force for blood entering the ocular circulation, and it exists as a range of values. In humans, the OPP is approximately 50 mmHg (Alm, 1983). Increasing the IOP decreases the OPP, as does lowering the blood pressure. In most vascular circulatory beds, blood flow is autoregulated, which means that moderate reductions in OPP induce a dilatation of the vessels and increase the blood flow. In equation form:

$$Q = \left(r^4 \right) \infty \text{blood velocity},$$

where Q is blood flow and r is the radius of the vessel. Blood flow may also be compared with the resistance of the vessels of the microcirculation. In equation form:

$$Q = P \div R,$$

where

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$$R = 8l \div n\ r^4,$$

or

$$Q = pnpr^4 \div 8l,$$

and Q is the blood flow, ΔP is the OPP, n is the number of vessels, r is the radius of the vessel, l is the length of the vessel, and η is the blood viscosity. Blood flow is directly proportional to the radius of the vessel to the fourth power. Thus, small alterations in arterial radius result in dramatic changes in vascular resistance and blood flow (Little & Little, 1989).

Because of the autoregulation of retinal vascular resistance, blood flow remains largely unchanged within a wide range of OPPs (Orgül et al., 1995). When there is no autoregulation, each reduction in perfusion pressure is followed by a corresponding reduction in blood flow (Little & Little, 1989). Influencing stimuli include transmural pressures (i.e., the difference between intravascular and ocular tissue pressures), local accumulations of metabolites, and local anoxia. The retinal and ONH microcirculations are vigorously autoregulated in most species, but some evidence suggests the choroidal circulation has limited or no autoregulatory capability (Orgül et al., 1995).

Both the retinal and ONH circulations can autoregulate their blood flow during reduced OPP caused by elevated IOP (Sossi & Anderson, 1983). Blood flow in the inner retina is practically unaffected by moderate changes in OPP. Blood flow and metabolism of the retina and prelaminar optic nerve are disturbed only at very high IOPs in the dog (Brooks, unpublished data, 1998). The short posterior ciliary arteries in dogs with acute (< 7 days) glaucoma demonstrated pathology with reduced luminal areas and fewer numbers of arteries, suggesting vascular pathology (Fick & Dubielzig, 2016). Changes in the different blood flow parameters, as measured by color Doppler imaging of both intraocular and orbital arteries and veins, have been reported in inherited POAG in Beagles (Gelatt et al., 2003; Gelatt-Nicholson et al., 1999).

Alterations in OPP may result in vascular insufficiency of the ONH if inherent compensatory autoregulatory mechanisms of the ONH are defective. Disease of the optic nerve vascular endothelial cells can result in decreased ability to produce nitric oxide, overproduction of endothelin (i.e., a potent vasoconstrictor), or both (Orgül et al., 1995). Elevations of AH endothelin-1 are found in POAG and normal tension glaucoma in humans and dogs with primary glaucoma (Källberg et al., 2002; Noske et al., 1997; Sugiyama et al., 1995; Tezel et al., 1997). In addition, endothelin-1 levels were increased in the vitreous of glaucomatous dogs (Källberg, unpublished data, 2004). The apparent alterations in the circulation of the glaucomatous optic nerve implicate dysfunction of vascular regulatory mechanisms. Chronic ischemia of the anterior optic nerve has been induced in animal models, either by perineural infusion or intravitreal injections of endothelin-1 (Cioffi et al., 2004). These studies have resulted in glaucomatous-like damage to the optic nerve. However, the elevated endothelin levels may not by themselves be responsible for the optic neuropathy seen in glaucomatous patients. Endothelin-1 is even more highly elevated in a number of systemic diseases, but in these instances optic neuropathy seems not to occur more frequently than in the normal population. Glaucoma patients may have a primary vascular dysregulation, manifesting as an inappropriate arterial constriction or inadequate dilation.

Inflammatory Effects

The role of inflammation before, during the elevation of IOP, and with prolonged periods of elevated IOP (< 50 mmHg) in primary and secondary glaucomas is poorly understood. Clinical observations suggest that anterior and posterior segment inflammations occur with many primary forms of canine primary glaucoma, especially when IOP is markedly elevated (> 50 mmHg). The classic example of concurrent inflammation and primary glaucoma (rather than primary uveitis and secondary glaucoma) is PACG in the Basset Hound, which may be accompanied by anterior uveitis when IOP elevations exceed 50 or 60 mmHg. Anterior segment inflammation concurrent with or following elevated IOP can worsen trabecular AH outflow directly with inflammatory cells and fibrin deposition, quickly followed by peripheral anterior synechia formation. When uveitis precedes and causes secondary glaucoma, the degree of inflammation is often more severe or is at least more long-standing than the uveitis that is concurrent to primary glaucoma.

In the study of goniodysgenesis-related glaucoma, nearly all globes contained inflammation and pigment dispersion from either (1) segmental loss from the posterior iris epithelium epithelium; (2) clumping of the posterior iris pigment epithelium; (3) pigmented cells within the trabecular meshwork or anterior chamber; or (4) preferential settling of pigmented cells in the ventral ICA (Reilly et al., 2005). Both neutrophils (early) as well as lymphoplasmacytic (later) inflammation were often present. These observations support the importance of inflammation in glaucomatous eyes, especially those with high IOP elevations. Although pupillary block associated with iris–lens touching and posterior iris pigment epithelium loss may be important in the genesis of this form of glaucoma, the presence of pigment cells (normally phagocytized by the trabecular cells) in the outflow pathways may further impair AH outflow. The origin of pigment cells may also suggest cell death and loss secondary to the high levels of IOP and local ischemia and the associated inflammation.

Another report documented retinal pigment damage, breakdown of the blood–retinal barrier, and retinal inflammation in dogs with advanced primary glaucoma (Mangan

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et al., 2007). The globes were divided into 11 with acute glaucoma (within 5 days after the onset of acute glaucoma) and 13 with chronic glaucoma (beyond 5 days following onset). The affected dogs included 19 ACS, 3 Basset Hounds, and 1 Dachshund. All dogs had both primary glaucoma as well as goniodysgenesis. Various medical and laser treatments had been attempted in all dogs. Abnormal pigmented cells, including displaced retinal pigment epithelium (RPE) cells and macrophages (identified by lectin binding), were distributed throughout the neuroretinas and vitreous bodies. Both hypertrophy of the RPE cells and loss of RPE cell continuity occurred. The regions of the greater loss of neurons had greater displaced pigment. Signs of retinal inflammation included infiltration of leukocytes, retinal swelling, and albumin leakage from the retinal vessels. Perivascular CD3-positive T lymphocytes occurred in the glaucomatous retinas.

In contrast to the acute glaucomatous globes, the globes with chronic glaucoma contained increased pigmentary changes, fewer neutrophils, and less retinal swelling. These posterior segment changes correlate with pigment dispersion and inflammatory changes reported in the anterior segment (Reilly et al., 2005). It would appear that following elevated IOP there are considerable changes in the anterior and posterior segments related to local tissue ischemia and cell damage. Over time these changes in the posterior segment lead to exposure of the retinal auto-antigens to the immune system, and contribute further to the intensity and duration of the retinal inflammation. The changes in the anterior segment could increase further the elevated IOP and directly damage the outflow pathways.

In another study in the dog, retinas were obtained from advanced glaucoma globes and retinal RNA obtained (Jiang et al., 2010). Global gene expression patterns were determined using oligonucleotide microarrays and confirmed by real-time polymerase chain reaction. The presence of tumor necrosis factor and its receptors was identified by immunolabeling. At least 500 genes were detected with significant changes in expression level in the glaucomatous retinas. Decreased expression levels were detected for a large number of functional groups, including synapse and synaptic transmission, cell adhesion, and calcium metabolism. Genes with increased expression levels were mainly associated with inflammation, including antigen presentation, protein degradation, and innate immunity. Anti-inflammatory mechanisms that protect the retina in early glaucoma may eventually fail and lead to the development of autoantibodies in many glaucomatous eyes. It is conceivable in advanced canine glaucoma that once the immune response develops, it may further accelerate vision loss by IOP-independent mechanisms.

Significant differences in serum autoantibodies against optic nerve antigens have been found in dogs with goniogenesis-related glaucoma (GDRG) compared to normal dogs (Pumphrey et al., 2013a). Although it remains unclear whether these differences are part of the pathogenesis of disease or are sequelae to glaucomatous changes, these findings provide support for the hypothesis that immune-mediated mechanisms play a role in the development or progression of GDRG.

Primary and Breed-Predisposed Canine Glaucomas

The primary glaucomas in the dog are divided clinically into POAG and PACG. In the veterinary medical literature, the association of abnormalities of the pectinate ligaments (often termed goniodysgenesis or more precisely PLD) and angle-closure glaucomas appears to be more than coincidence, and an important risk factor.

Pectinate Ligament Dysplasia

Dysplasia of the pectinate ligaments (i.e., solid sheets of pectinate ligaments; initially termed mesodermal remnants) appears to be common in some breeds, but has not been directly related to an increased resistance to the outflow of AH (Rühli & Spiess, 1996). It would appear that glaucoma may develop in only the most severely affected forms of PLD (those with well in excess of 180° of the ICA involved). The pectinate ligaments appear to provide the basal support (i.e., anchor or pillar) for the iris to the posterior cornea and may affect the opening of the sclerociliary cleft. PLD in the dog is often localized to a few limited areas of the ICA, and it does not appear to increase resistance to AH outflow as measured by applanation tonometry or tonography (Rühli & Spiess, 1996). If PLD alone impairs AH access to the uveal and corneoscleral meshwork in some of these breed-specific, narrow- or closed-angle glaucomas, then goniotomy or transection of a significant circumference the pectinate ligaments of the filtration angle could offer both preventive and therapeutic benefits. It is important to differentiate the iridocorneal anomalies (e.g., persistent mesodermal bands, PLD) from any inflammatory-associated changes (peripheral anterior synechiae). In some breeds, such as the Basset Hound and Flat-Coated Retriever, the extent of the PLD can progress over time and predispose these dogs to glaucoma at later ages (Oliver et al., 2016; Pearl et al., 2015). This suggests that chronic or low-grade anterior uveal inflammation may also be important in the genesis of glaucoma in these breeds and serial gonioscopy may be informative. Other breeds reported to have PLD include the Leonberger (Fricker et al., 2016), Golden Retriever, Border Collie, and Hungarian Vizsla (Oliver et al., 2017).

The diagnosis of PLD is best achieved by a combination of both gonioscopy and biomicroscopy. Unfortunately, differentiation between dysplastic pectinate ligaments and peripheral

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anterior synechiae in chronic glaucoma can be very difficult or even impossible (Bauer et al., 2016). In one report the histologic diagnosis of PLD in the presence of chronic secondary glaucoma was not possible (Bauer et al., 2016). In some breeds, the extent of PLD increases with age, suggesting concurrent inflammation may assume a very important role.

Effect of Gender

The effect of gender appears important in humans with PACG, with the female affected much more frequently, especially in Asian populations (Foster, 2002). In contrast, POAGs are equally divided among men and women. Does the effect of gender also occur in the dog? Differences in the ratios of males to females for PACG by gender appear in the ACS, Basset Hound, Cairn Terrier, Chow Chow, English Cocker Spaniel, Samoyed, and perhaps the Siberian Husky. Magrane (1956) first reported more affected females than males in the ACS in his group of 25 affected animals that were presented with narrow-angle glaucoma, and this also appears to be true in several other breeds. Whether this female predisposition is constant for the different breeds with PACG remains to be documented. From 1964 to 1973, the percentage ratios of male to females for most breeds were approximately equal. However, in the ACS, the females were affected more often than the males (percentage male : female 1 : 1.93). In the 1974–1983 interval, the percentage ratios of females to males were higher in the ACS (male : female 1 : 1.49), Basset Hound (1 : 1.65), English Cocker Spaniel (1 : 7.44), and Welsh Terrier (1 : 2.51). For 1984–1993, the percentage ratios of glaucomatous females to males were higher in the following breeds: ACS (male : female 1 : 1.76), American Eskimo (1 : 2.23), Basset Hound (1 : 1.48), and Samoyed (1 : 1.68). From 1994 to 2002, the ratios of females to males with glaucoma were higher in the ACS (1 : 1.31), Basset Hound (1 : 2.4), Cairn Terrier (1 : 2.42), Chow Chow (1 : 1.78), English Cocker Spaniel (1 : 7.14), Samoyed (1 : 2.23), and Siberian Husky (1 : 1.88). Recently, HRUS has suggested that the predisposition of the female PACG may be related to a reduced ICA opening (Tsai et al., 2012). One possible explanation is a smaller outflow pathway in females. Comparisons of normal Beagles by 20 MHz ultrasonography suggest that female Beagles have smaller angle opening distances and angle recess areas (Tsai et al., 2012). The same study is yet to be performed in most of the PACG breeds.

Effect of Age

Age appears to be an important risk factor and affects the time for presentation of the most of the glaucomas in the purebred dog. This finding may be misleading, as the onset of the disease and time of clinical presentation may be months to years different. In the Beagle with POAG, ocular hypertension starts in dogs between 12 and 18 months of age, but overt clinical signs of glaucoma (i.e., early globe enlargement, mydriasis) and other signs are usually not detected and the dog not presented to the veterinarian until 4–6 years of age or even later. In those breeds with PACG, the time course appears abbreviated, but may span several months. In the majority of breeds, the primary glaucomas are presented most often in dogs at an average age of about 6+ years, except in the Siberian Husky, Samoyed, and Welsh Springer Spaniel, which are younger. A number of breeds, including the Basset Hound, Flat-Coated Retriever, and Dandie Dinmont Terrier, have been identified as having a significant association between appearance and degree of PLD and age (Oliver et al., 2016).

Primary Glaucomas

The discussions of breed-related glaucomas in this section detail what is known or has been published to date. The reader will note that despite the length of this chapter, there is not very much known about the disease process, its etiology, pathogenesis, and treatment strategies. There is much yet to be elucidated. For some breeds, there is a clear understanding and characterization of the condition of the drainage angle (open versus narrow or closed); in others, that distinction has yet to be made. It is possible, or likely, that within each breed there are different forms and manifestation of this frustrating disease.

Inherited/primary open- and narrow- or angle-closure glaucomas occur bilaterally in purebred, and likely also in some mixed-breed, dogs (see Fig. 20.2 and Fig. 20.7). Although the primary glaucomas have been reported in at least 45 breeds in the United States (see Table 20.1A), very few breeds have been thoroughly investigated to date. While much progress has been made in understanding the genetics of canine POAG, there is very limited information on the mode(s) of inheritance for most of the canine PACGs.

Genetics

Based on the specific breed predilection of primary glaucomas, a genetic etiology is suspected to be responsible, and affected dogs should be excluded from breeding. Despite the high prevalence of primary glaucomas in dogs, genetic etiologies have been studied in only a relatively small number of breeds.

Genetics of Canine Primary Angle-Closure Glaucoma

PACG is the most common form of primary, breed-related canine glaucomas, suggesting a genetic etiology. Many breeds have been studied, with the highest prevalences documented in the ACS, Basset Hound, Chow Chow, Siberian Husky, Shiba Inu, Shih Tzu, Magyar Vizsla, and Newfoundland (Gelatt & MacKay, 2004a; Graham et al., 2017b; Kato et al.,

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2006b; Komáromy & Petersen-Jones, 2015; Slater & Erb, 1986; Strom et al., 2011a). Because a simple mode of Mendelian inheritance could not be identified in most canine breeds studied, PACG appears to be a complex trait with multiple suspected genetic and environmental risk factors contributing to the disease (Graham et al., 2017b; Komáromy & Petersen-Jones, 2015). The possible exceptions are the Welsh Springer Spaniel (Cottrell & Barnett, 1988) with a proposed autosomal dominant trait, as well as the Siberian Husky (Nell et al., 1993), Basset Hound (Ahram et al., 2015), and Border Collie (Oliver et al., 2020; Pugh et al., 2019) with suggested autosomal recessive inheritance.

PACG genetics has been investigated most extensively in the Basset Hound, thanks to the availability of a closed colony with informative pedigree (Ahram et al., 2014, 2015; Grozdanic et al., 2010). Genome-wide association study (GWAS) has revealed three genetic loci as possible contributors to the PACG phenotype in this breed with three positional candidate genes: *COL1A2*, *RAB22A*, and *NEB* (Ahram et al., 2014, 2015). All three have been shown to be expressed in the anterior segment of the eye, where they may play a role in AH outflow (Ahram et al., 2014, 2015). While *COL1A2* (encoding the pro-alpha 2 chain of Type I collagen) is a promising PACG candidate gene due to the suspected involvement of collagen and other ECM components in the PACG pathogenesis (Vithana et al., 2011, 2012), subsequent studies have focused on *NEB*, which encodes for nebulin, a protein that that is expressed in the ciliary muscle where it may regulate muscle contractility (Ahram et al., 2015; McElhinny et al., 2003). It is possible that changes in nebulin and its function may alter muscle function and thereby contribute to PACG development (Ahram et al., 2015). The disease-associated *NEB* allele is commonly found in the Basset Hound population: 88% of PACG-affected Basset Hounds in the United States are homozygous for the *NEB* risk allele; the remaining 12% are heterozygous (Ahram et al., 2015). Among PACG-unaffected Basset Hounds, 33% and 44% are homozygous and heterozygous for the *NEB* risk allele, respectively, while 22% are homozygous for the nonrisk allele (Ahram et al., 2015). The identification of the *NEB* risk allele in the Basset Hound represents significant progress toward a better understanding of canine PACG; however, it remains a complex disease, since not all of the homo- and heterozygous animals develop glaucoma – additional genetic and environmental factors likely contribute. In fact, genome-wide association sequencing in a cohort of European Bassett Hounds identified two novel loci associated with pectinate ligament abnormality and PACG. The results were confirmed in American Bassett Hounds, thereby failing to corroborate the associations previously identified in genetic testing of these dogs (*COLIA2, RAB22A*, and *NEB*; Oliver et al, 2019). This supports the likely complex etiology of the condition in this breed.

Progress in the understanding of canine PACG genetics has been made in other breeds as well, and investigations are ongoing. In Shiba Inus and Shih Tzus, *SRBD1* was identified as a PACG risk gene (Kanemaki et al., 2013). It encodes for S1 RNA-binding domain and has been associated with human forms of primary glaucoma; however, its function remains unknown (Liu et al., 2014; Mabuchi et al., 2015; Writing Committee for the Normal Tension Glaucoma Genetic Study Group of Japan Glaucoma et al., 2010). In the Dandie Dinmont Terrier, a 9.5-megabase region on canine chromosome 8 has been identified as a susceptibility locus for canine PACG; no specific disease gene has been identified yet (Ahonen et al., 2014). Most progress in the understanding of canine PACG genetics has been made in Border Collies, where PLD and PACG have been identified as a monogenic, autosomal recessive traits, caused by a missense mutation in the *OLFML3* gene (Oliver et al., 2020; Pugh et al., 2019).

Genetics of Pectinate Ligament Dysplasia and Ciliary Cleft Opening in the Dog

Goniodysgenesis or PLD, combined with the narrowing of the ICA and ciliary cleft, is a well-recognized risk factor of PACG (Bjerkås et al., 2002; Ekesten & Narfström, 1991; Kato et al., 2006a; Martin & Wyman, 1968; van der Linde-Sipman, 1987; Wood et al., 1998, 2001). The inheritance of PLD and the width of the ciliary cleft have been studied in a number of dog breeds, such as the English Springer Spaniel (Bjerkås et al., 2002), Flat-Coated Retriever (Read et al., 1998; Wood et al., 1998), Great Dane (Wood et al., 2001), Samoyed (Ekesten & Torrang, 1995), and Border Collie (Oliver et al., 2020; Pugh et al., 2019). Quantitative polygenic traits are most likely, based on the observation that both the severity of PLD and the narrowing of the ciliary cleft worsen with the degree of kinship in PACG-affected animals (Bjerkås et al., 2002; Ekesten & Torrang, 1995). Breeding of only animals with normal ICAs led to a reduction in the presence and degree of ICA abnormalities in the English Springer Spaniel (Bjerkås et al., 2002). An autosomal recessive inheritance has been proposed for PLD in the Bouvier des Flandres (Rühli & Spiess, 1996) and confirmed in the Border Collie (Oliver et al., 2020; Pugh et al., 2019).

Because much remains unknown about the link between the presence of PLD and glaucoma development and the genetics of PLD, there is no consensus between veterinary ophthalmology organizations regarding the inclusion of gonioscopy as part of routine genetic eye screening in order to provide breeding advice. Furthermore, without the additional assessment of the ciliary cleft width by HRUS or UBM, gonioscopy alone may not provide a full picture of the status of the AH outflow pathways (Grozdanic et al., 2010; Tsai et al., 2012). While the ACVO has not issued recommendations against breeding of PLD-affected dogs, the ECVO has adopted stricter rules with recommended gonioscopy for a number of breeds, including the ACS, all types of Bassets, Bouvier des Flandres, English Springer Spaniel, Flat-Coated

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Retriever, Siberian Husky, and Samoyed (European College of Veterinary Ophthalmologists' Hereditary Eye Disease Committee, 2013). While dogs with a mild degree of PLD (fibrae latae affecting less than 25% of the pectinate ligament circumference) are considered unaffected, a diagnosis of laminae and occlusio will result in a recommendation against breeding (European College of Veterinary Ophthalmologists' Hereditary Eye Disease Committee, 2013; Spiess et al., 2014).

Genetics of Canine Primary Open-Angle Glaucoma and Primary Lens Luxation

Thanks to the monogenic, autosomal recessive inheritance of all currently known forms of canine POAG and the availability of well-established POAG Beagle colonies, great advances were made in recent years toward the better understanding of canine POAG genetics (Ahonen et al., 2014; Forman et al., 2015; Gelatt & Gum, 1981; Kuchtey et al., 2013; Lazarus et al., 1998; Oliver et al., 2018). All currently known canine POAG-causing mutations have been identified in two genes encoding for secreted matrix metalloproteinases: *ADAMTS10* and *ADAMTS17*. The first mutations were identified in the *ADAMTS10* gene of affected Beagles (p.G661R missense mutation with glycine to arginine change at position 661; Kuchtey et al., 2013) and Norwegian Elkhounds (p.A387T missense mutation with alanine to threonine amino acid change at position 387; Ahonen et al., 2014), a gene that is strongly expressed in the trabecular meshwork. These findings were followed by the discovery of *ADAMTS17* mutations in POAG-affected Petit Basset Griffon Vendéen dogs (inversion in intron 12; Forman et al., 2015), Basset Hounds (19 base pair or bp deletion in exon 2; Oliver et al., 2015), Basset Fauve de Bretagne dogs (p.G519S missense mutation with glycine to serine change at position 519; Oliver et al., 2015), and Chinese Shar-Peis (6 bp deletion in exon 22; Oliver et al., 2018). Routine genetic testing for some of these mutations is available. The p.G661R *ADAMTS10* missense mutation responsible for Beagle POAG was excluded as a cause of primary glaucoma in the ACS, Australian Cattle Dog, Chihuahua, Jack Russell Terrier, Jindo, Siberian Husky, Shiba Inu, Shih Tzu, and Yorkshire Terrier (Kuchtey et al., 2013).

Despite the recent discovery of genetic defects responsible for canine POAG, the detailed molecular and cellular mechanisms resulting in the accumulation of extracellular trabecular meshwork plaques and increased trabecular outflow resistance remain unknown (Samuelson et al., 1989). *ADAMTS10* and *ADAMTS17* are matrix metalloproteinases that play a role in fibrillin-1 (FBN1) microfibril structure and function (Hubmacher & Apte, 2011). Canine POAGs are homologous to a group of human connective tissue disorders caused by abnormal microfibril formation: These microfibrillopathies include WMS and Marfan syndrome (MS), which are also caused by mutations in *ADAMTS10* (WMS), *ADAMTS17* (WMS), and FBN1 (MS and WMS; Dagoneau et al., 2004; Hubmacher & Apte, 2011; Kuchtey & Kuchtey, 2014; Kutz et al., 2008, 2011; Le Goff et al., 2011; Morales et al., 2009). The ocular phenotype in affected human patients consists mainly of ectopia lentis/PLL combined with various degrees of open-angle or angle-closure glaucoma, the latter caused by shallow anterior chamber and pupillary block associated with the anterior dislocation of the lens (Chu, 2006; Dagoneau et al., 2004; Faivre et al., 2007; Hubmacher & Apte, 2011; Izquierdo et al., 1992; Kuchtey & Kuchtey, 2014; Kutz et al., 2008; Morales et al., 2009; Wright & Chrousos, 1985). Like human WMS patients, zonular dysplasia and/or various degrees of PLL was reported in most POAG-affected dog breeds, including the Beagle (Teixeira et al., 2013), Petit Basset Griffon Vendéen (Bedford, 2016), and Chinese Shar-Peis (Lazarus et al., 1998; Oliver et al., 2018), thereby closely linking canine POAG and PLL. In these dogs, zonular dysplasia and open-angle glaucoma occur independently from each other, since IOP increases even without the dislocation or presence of a lens, as shown in the *ADAMTS10*-mutant Beagles (Gelatt & Samuelson, 1988). It is likely that modifier genes are involved in determining if an *ADAMTS10*- or *ADAMTS17*-mutant dog presents to the veterinary ophthalmologist because of PLL or primary glaucoma. In our clinical experience, even *ADAMTS10*-mutant Beagles can present with limited PLL (Teixera et al., 2013).

Based on these recent genetic discoveries, we think it is important for the clinician to consider a POAG component in "classic" PLL breeds, such as terriers (Alario et al., 2015; Curtis & Barnett, 1980; Gould et al., 2011; Lazarus et al., 1998; Morris & Dubielzig, 2005; Strom et al., 2011a; Willis et al., 1979), because of their genetic defect in *ADAMTS17* (splice donor site mutation: ADAMTS17c.1473+1 G>A; Farias et al., 2010; Gould et al. 2011). These canine patients may present with elevated IOP without lens displacement into the anterior chamber or pupillary block, but instead with lens subluxation or posterior lens luxation (Curtis et al., 1983; Glover et al., 1995a). Furthermore, glaucoma often persists following surgical lens removal. In other words, glaucoma associated with PLL may not be entirely secondary to anterior lens dislocation and vitreous prolapse, as generally perceived (Gelatt & MacKay, 2004a); instead, there may be a POAG component. Like canine POAG, PLL also appears to be an autosomal recessive trait in most affect breeds (Curtis, 1990; Curtis et al., 1983; Ketteritzsch et al., 2004; Lazarus et al. 1998; Willis et al., 1979); hence, most heterozygous dogs that carry an *ADAMTS17* mutation remain clinically unaffected (Farias et al., 2010; Gould et al., 2011). Interestingly, an estimated nearly 5% of heterozygous Miniature Bull Terriers, and a few heterozygous dogs of other breeds, such as the Parson Russell Terrier, Chinese Crested Dog, and Tenterfield Terrier, may develop PLL (Farias et al., 2010; Gould et al., 2011). This phenomenon

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could be attributed to haploinsufficiency, a dominant negative effect of the mutant ADAMTS17 protein, or additional, still unknown mutations in *ADAMTS17* or elsewhere in the genome (Farias et al., 2010; Gould et al., 2011). The Animal Health Trust recommends that carriers of *ADAMTS17* mutations be regularly screened for signs of PLL. Diurnal IOP and/or tonography studies in dogs with DNA mutations may help separate those dogs with PLL (and secondary glaucoma) from those with a combination of PLL and primary glaucoma that may exhibit at different times.

Because of their important function in microfibril formation, mutations in *ADAMTS10* and *ADAMTS17* not only result in an ocular phenotype with ectopia lentis/PLL and glaucoma in affected human WMS patients, but also short body stature, fingers, and toes (Faivre et al., 2007; Hubmacher & Apte, 2011; Khan et al., 2012; Morales et al., 2009; Robinson, 2006). Until recently, the canine disease phenotype appears to be limited to ocular symptoms. However, there have been speculations that PLL-affected, *ADAMTS17*-mutant dogs may be slightly smaller than unaffected littermates, and that selection toward smaller body size may have contributed to the higher frequencies of the disease allele in affected breeds (Farias et al., 2010; Gould et al., 2011; Jeanes et al., 2019). Significant shorter body height has been confirmed in *ADAMTS17*-mutant Petit Basset Griffon Vendéen and Shar-Pei dogs (Jeanes et al., 2019).

Primary Open-Angle Glaucoma

In the breeds with POAG, the increase in IOP is gradual and progressive, and the clinical signs develop from barely noticeable to advanced over a matter of years (usually 2–4; Miller, 2005). In the early and moderate stages of the disease, IOP is generally between 25 and 40 mmHg, and there is mydriasis, variable corneal edema, and episcleral congestion. Vision is present in these early stages. The dog's eye is not appreciated as abnormal to the casual observer, and the dog is not usually presented to the veterinarian until the eyes are well advanced and enlarged. The descriptions below discuss breeds that have been confirmed to have POAG. Other breeds, even breeds that also have documented forms of PACG, likely have forms of POAG, possibly due to different genetic mutations, including the ACS, Basset Hound, Boston Terrier, Chow Chow, English Springer Spaniel, Miniature Schnauzer, Siberian Husky, and Poodle (Standard and Toy-Miniature breeds).

Glaucoma in the Beagle

The Beagle breed is thought to be a very old breed (previously referred to as Begles), with its genesis in both England and France. Inherited glaucoma in Beagles was first reported in 1972 (Gelatt, 1972), and a colony of affected dogs was established shortly thereafter to permit long-term investigation of this spontaneous disease (Gelatt et al., 1977b, 1981b). POAG in the Beagle is the most well characterized of all spontaneous forms of canine glaucoma. The initial nine Beagles that presented with bilateral primary glaucoma had open ICAs initially in the early glaucoma eyes, and ICA closure and ciliary cleft collapse with enlargement of the globe in eyes with advanced glaucoma. During the past five decades, POAG in the Beagle has been investigated in considerable detail in the research setting and compared to the disease in Beagles and other breeds from the general population that present to the veterinary clinic. In the North American survey from 2004, glaucomatous Beagles were 6.24 ± 1.31 years of age when presented for first diagnosis (Gelatt & MacKay, 2004a). In the closed colony of glaucomatous Beagles, the ocular hypertension begins between 1 and 2 years of age, but becomes first noticeable by owners when secondary globe enlargement, mydriasis, and lens subluxation develop much later, usually at 4–6 years of age.

The elevation in IOP becomes apparent with tonometry in Beagles between 8 and 16 months of age, but the clinical signs of glaucoma are delayed until 2–5 years old (Fig. 20.8). The increase in IOP and decline in outflow facility, as measured by Schiøtz tonography, pneumatonography, and constant-pressure perfusion of the anterior chamber, develop slowly (Gelatt et al., 1977a, 1996; Peiffer & Gelatt, 1980). In affected dogs, the pneumatonographic outflow declines from 0.19 ± 0.07 µL/min/mmHg (3–6 months of age) to 0.07 ± 0.05 µL/min/mmHg (43–48 months of age). The pneumatonographic outflow measurements of genetic carrier (heterozygous) dogs are between those of affected and normal dogs. The mean episcleral venous pressure of both normal and glaucomatous dogs is 10–12 mmHg (Gelatt et al., 1982).

The ICA and sclerociliary cleft are initially open and devoid of any abnormalities (Fig. 20.9). The IOP in early glaucomatous dogs slowly increases from the mean normal IOP of 16–18 mmHg. Animals 2–5 years of age have IOPs in the range of 25–40 mmHg. Diurnal IOP variations (8–12 mmHg) as well as IOP differences between fellow eyes of individual dogs are greater in affected dogs, with the highest IOP in the morning (Gelatt et al., 1981a). Results of serial A-scan ultrasonography indicate that the increased IOP produces slight enlargement (1–2 mm) of the axial length of the globe, with concurrent lens subluxation and narrowing of the ICA and collapse of the sclerociliary cleft in dogs between 1 and 4 years. Lens removal at 6 months and prior to the onset of ocular hypertension in Beagles bred for POAG did not delay the onset of glaucoma (Fig. 20.10; Gelatt & Samuelson, 1988).

Eventual ICA and sclerociliary cleft closure begins in animals 4–6 years of age and progresses. A few individuals maintain a gonioscopically open angle until as late as 8–10 years of age. POAG is inherited in Beagles as an autosomal recessive trait (Gelatt & Gum, 1981) and is associated with a G661R missense mutation in the *ADAMTS10* gene, which is highly expressed in the trabecular meshwork (Kuchtey et al.,

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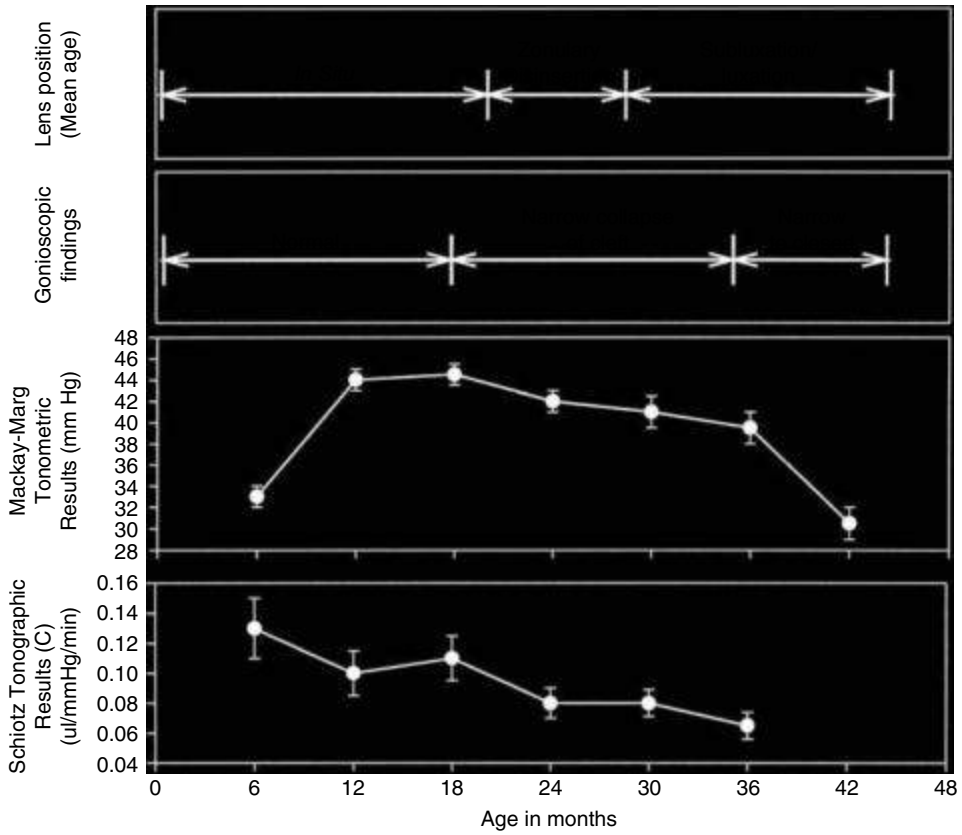


Figure 20.8 Progression of primary open-angle glaucoma in a Beagle with monitoring of intraocular pressure (applanation tonometry), aqueous humor resistance to outflow (*C;* tonography), position of the lens, appearance of the iridocorneal angle and ciliary cleft (gonioscopy), and amplitude scan ultrasonography (axial globe length). With globe enlargement, secondary iridocorneal angle and ciliary cleft closure as well as lens luxation with zonulary disinsertion occur.

2011). The *ADAMTS10* mutation has not only been identified in this colony of glaucomatous Beagles, but also in clinical patients, and a second colony at Michigan State University. POAG in the Beagle, while generally following a slow, gradual, smoldering development (IOPs in mid-30s persistently and maintenance of vision until 8–10 years of age or beyond), may in some individuals present more acutely (high IOP and vision loss by 4 years of age). The male : female ratio for POAG in the Beagle is 1 : 1. Interbreeding of the two different types of Beagles (13 and 15 inches) indicated onset of glaucoma was unaffected by body size.

Before DNA testing was available, provocative tests were useful in differentiating early POAG Beagles or suspect clinical patients from normal animals. Oral administration of water and topical administration of corticosteroids produce abnormal increases in the IOP of glaucomatous Beagles. In normal dogs, oral administration of water (50 mL/kg) increased the IOP by 3.1–8.6 mmHg, whereas in glaucomatous Beagles the rise in IOP ranged from 7.3 to 19.9 mmHg (Gelatt et al., 1976). After 10–14 days of either unilateral or bilateral 0.1% dexamethasone administered 4 times a day in glaucomatous Beagles, the IOP increases by approximately 5 mmHg (Gelatt & MacKay, 1998b). Elevated serum cortisone levels occur in glaucomatous Beagles, suggesting a chronic stress response to the disease and ocular hypertension, and appear to be cyclical with the diurnal IOP changes (Chen et al., 1980).

Visual resolution as measured by PERG in both normal and glaucomatous Beagles has been compared (Ofri et al., 1993a, 1993b, 1993c, 1994). The visual resolution limit of normal dogs was determined to be 6.9 ± 2.6 minutes of arc per phase in the central 15 degrees of the retina and 11.8 ± 2.3 minutes of arc per phase in the toroidal 15 degrees of the retina. In dogs with early glaucoma, the respective results were 7.8 ± 2.1 and 13.0 ± 3.1 minutes of arc per phase. For both groups, the resolution limit of the central 15 degrees was significantly higher ($P < 0.0005$) than that of the more peripheral, toroidal 15 degrees of the retina. There was no significant difference ($P > 0.29$) between the resolution limit of normal and that of early glaucomatous dogs for either the central or toroidal fields. Analyses of PERG results obtained 30 minutes and 2 hours after the injection of thiamylal sodium revealed that the second stimulation of the toroidal

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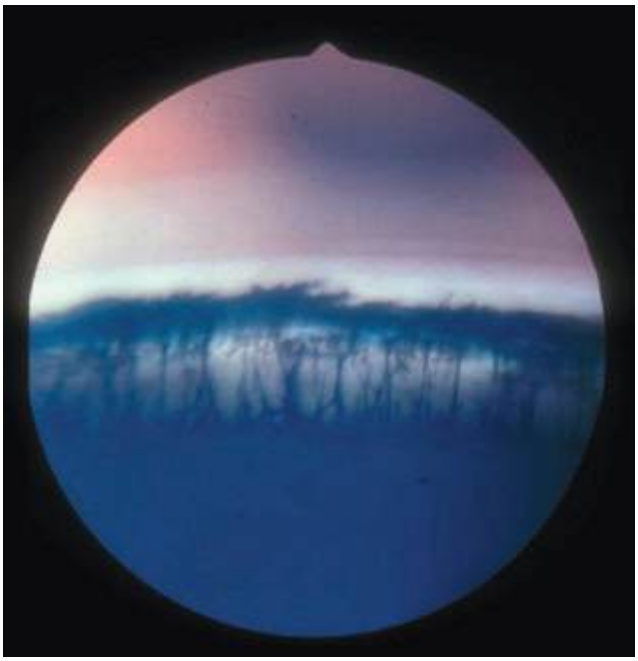


Figure 20.9 Gonioscopic view of the iridocorneal angle and opening of the ciliary cleft in a Beagle with early primary open-angle glaucoma.

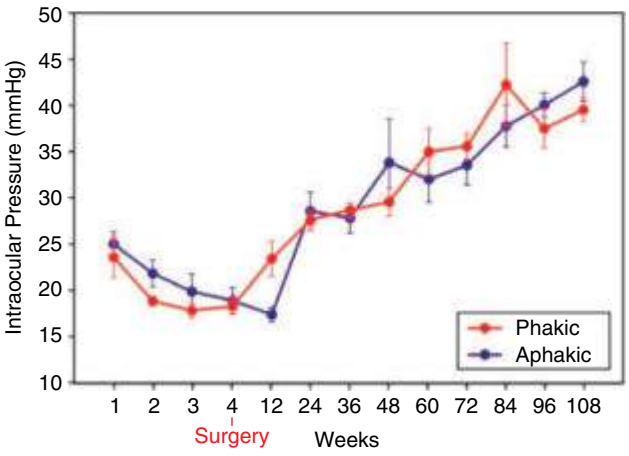


Figure 20.10 Effect of unilateral lens removal in 6-month-old *ADAMTS10* Beagles on the onset of ocular hypertension. Comparison of the intraocular pressure (IOP) results between the phakic and aphakic eyes did not prevent elevations in IOP bilaterally during the 2-year study.

15 degrees of the retina was remarkably larger than the first stimulation only in the glaucomatous dogs, and that it occurred with only the larger (> 48 minutes of arc per phase) gratings. Thiamylal sodium in a glaucomatous dog produced an initial 66% decline in signals from the central 30 degrees of the retina and an 88% decline in those from the more peripheral toroidal 15 degrees of the retina 30 minutes after the injection. Two hours after the injection, signals from the peripheral 15 degrees of the retina again were increased above the first signal, with the central 15 degrees being unaffected. One possible explanation for this may be local effects from this barbiturate anesthetic on the larger RGCs within the less vascular toroidal retina. Barbiturates are known to increase retinal excitability, and perfusion deficits found in glaucoma might delay the drug reaching the retinal cells or prolong the presence of drug metabolites. This discovery supports the finding of initial peripheral retinal loss (similar to humans with POAG who first sustain peripheral field loss). A gradual decrease in amplitudes of the full-field ERG photopic b-wave and photopic negative response with POAG disease progression has been reported (Plummer et al. 2013).

Results of preliminary studies using OCT of the superior and inferior neural rims of the ONHs in dogs indicated that the mean thickness of the RNFL ranged from 278 µm in one normal dog, to 361 µm in one dog with early glaucoma, and 161 ± 35 µm in six eyes with advanced glaucoma (Dawson et al., 1995, 1996). Mean histopathologic RNFL measurements in similar dogs produced values of 242 ± 58 µm in eight normal eyes and 90.5 ± 59.0 µm in the glaucomatous dogs. One possible explanation for this increased peripapillary retinal thickness in dogs with the early glaucoma may be the presence of enlarged RGC axons from impaired axoplasmic flow. ONH cupping and neuroretinal rim loss have recently also been documented by OCT imaging in the POAG Beagles at Michigan State University (Oh et al., 2013).

Results of color Doppler imaging of normal Beagles and those with inherited glaucoma in which the IOP was not medically controlled indicate significant differences in several specific blood flow parameters of many ophthalmic and orbital blood vessels (Gelatt et al., 2003; Gelatt-Nicholson et al., 1999). Differences in blood flow parameters on color Doppler imaging affected the exterior and internal ophthalmic arteries, anterior ciliary arteries, and short posterior ciliary arteries, all of which exhibited significant differences, but the parameters of the primary retinal arteries were not affected. Results of color Doppler imaging also demonstrate characteristic spectral waveforms for several of these blood vessels, as well as further differences when dogs with early, moderate, and advanced glaucoma are compared. Of interest is that initial changes in the color Doppler measurements of most of the orbital blood vessels in the glaucomatous dogs developed prior to the onset of ocular hypertension.

Results of light microscopic examinations of the aqueous outflow indicate no abnormalities in early-affected animals (Peiffer & Gelatt, 1980). By transmission-electron microscopy (TEM), however, abnormalities were first detected in 12-month-old dogs (Samuelson et al., 1989). Clustered basement membrane–like material was scattered throughout the outer corneoscleral trabecular meshwork (Fig. 20.11). Elastin-like fibers appeared to be more numerous and to be arranged less regularly than those in normal dogs, and small clusters of serrated, opaque rods were present within the

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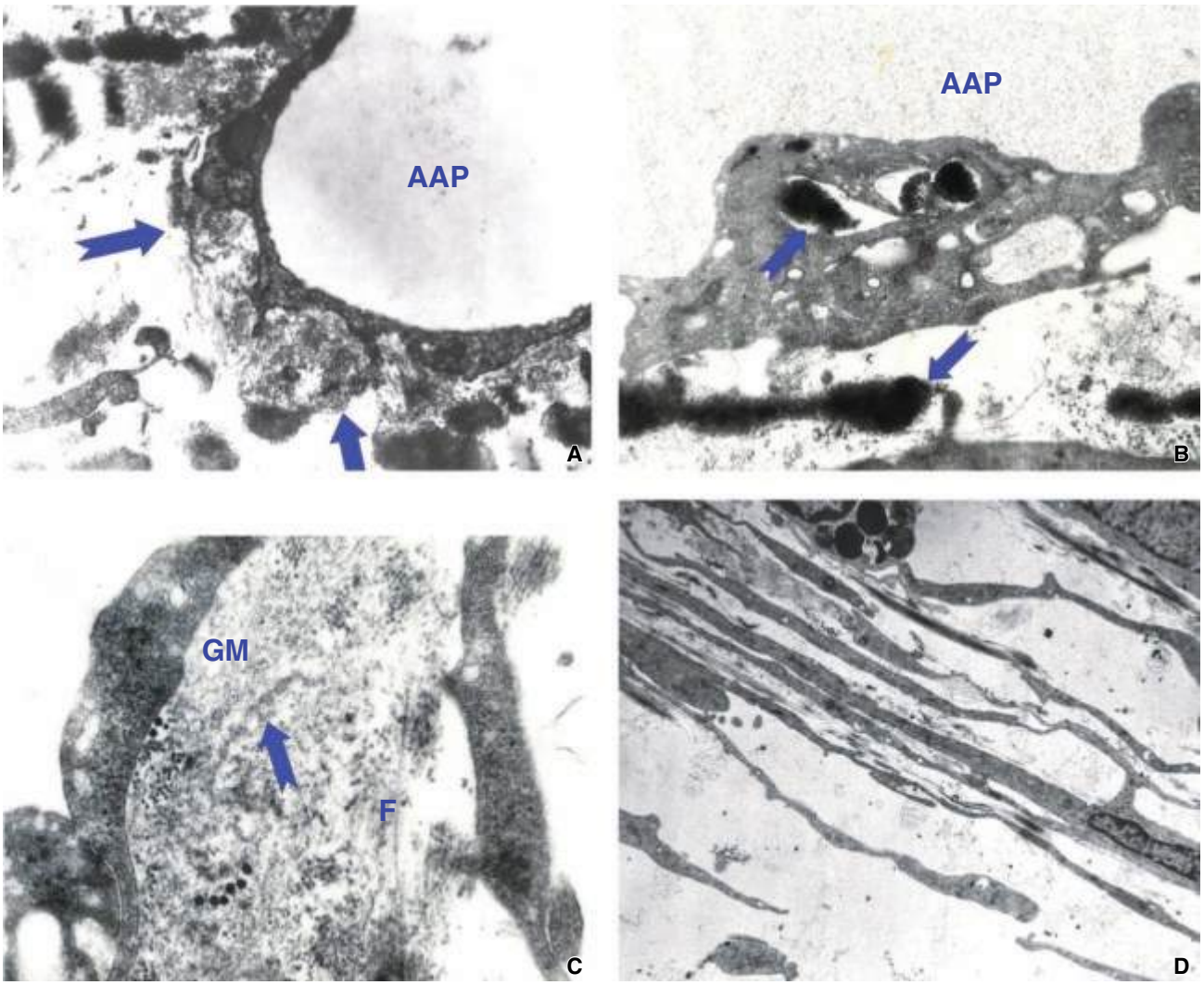


Figure 20.11 Trabecular meshwork of glaucomatous Beagles at 12 months, 2 years, 3.5 years, and 5 years of age. **A**. In the 12-month-old glaucomatous Beagle, note the clustering of fibrils (arrows) along the inner face of the endothelium of the angular aqueous plexus (AAP; 12,000×). **B**. In the 2-year-old glaucomatous Beagle, note the fibrils, including those from elastic fibers (arrows), pressing against and within the vacuoles of the endothelium of the AAP (12,000×). **C**. In the 3.5-year-old moderately advanced glaucomatous Beagle, note the thickened band of granular material (GM) interspersed with fibrils (F) and basement membrane–like material (arrow; 40,000×). **D**. In the 5-year-old glaucomatous Beagle, note the closely packed trabeculae within the corneoscleral meshwork (4,000×). (Courtesy of Don Samuelson.)

cytoplasm of the trabecular cells within the corneoscleral meshwork. In the more advanced stages of the disease, these changes were more extensive and generalized within the corneoscleral meshwork. The trabeculae became more compressed and disorganized, with the concomitant accumulation of extracellular materials.

Perfusion of the anterior chamber in normal dogs with bovine testicular hyaluronidase increases the constant-pressure perfusion rate beyond that of control dogs (Gum et al., 1992; Samuelson et al., 1987). Perfusion of glaucomatous dogs with hyaluronidase, however, did not increase the constant-pressure perfusion rates. Histochemical localization of the glycosaminoglycans within the corneoscleral beams and juxtacanalicular zone in normal dogs reveals that chondroitin sulfate is the major component, with lower amounts of hyaluronic acid, dermatan sulfate, and heparin sulfate (Gum et al., 1986, 1993b). In glaucomatous dogs, the amount of chondroitin sulfate decreases as the disease advances, and a glycosaminoglycan hyaluronidase–resistant material develops. Even though the disease-causing mutation has been identified in the *ADAMTS10* gene (Kuchtey et al., 2011), which is highly expressed within the trabecular meshwork, the molecular disease mechanisms that result in the excessive accumulation of ECM material are still unknown.

Retinal and optic nerve changes in affected dogs have also been studied. Anterior movement of the scleral lamina cri-

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brosa can initially be detected by scanning laser ophthalmoscopy, which is followed by posterior displacement of the multilayered lamina cribrosa (Brooks, 1996). Cupping of the canine ONH develops as the disease progresses. Such cupping is difficult to use as a clinical guide to glaucoma progression, however, because the rate of cup progression is variable. The retinal blood vessels, especially the small, peripapillary retinal arterioles and veins, gradually disappear. The optic discs become round with the loss of myelin, depressed, and atrophied. Results of short-term studies measuring orthograde rapid axoplasmic flow with tritiated leucine in normal dogs at perfusion pressures of 12–100 mmHg (IOP 6–100 mmHg) revealed a pressure-related label accumulation at the scleral lamina cribrosa (Williams et al., 1983). The same effect also occurs in glaucomatous dogs (Samuelson et al., 1983).

Trypsin and detergent digests reveal a well-developed scleral lamina cribrosa in the dog (Brooks et al., 1998b). Slight posterior distortion or bowing of the scleral lamina cribrosa occurs before ophthalmoscopic changes to the optic disc can be observed. Posterior displacement and compression of the scleral lamina occur regularly in moderate stages of the disease. In advanced glaucomatous eyes, extreme posterior displacement of the scleral lamina, marked distortion of the lamina pore space, compression of the lamina, and disturbances of the congruent laminar pores are observed. Vascular casts of the optic nerve microcirculation did not reveal any differences between normal and glaucomatous Beagles (Brooks et al., 1989a). Results of ultrastructural examination of the optic nerve capillaries revealed many spherical, membrane-bound, electron-dense inclusions that closely resemble Weibel-Palade bodies in the pericytes and endothelial cells of affected Beagles at all stages of the disease; the Weibel-Palade bodies have been associated with microcirculatory abnormalities in both humans and diabetic dogs (Brooks et al., 1989a).

The ultrastructural changes of the optic nerve axons at the ONH in glaucomatous dogs are prominent (Samuelson et al., 1983). In dogs with early glaucoma, the optic nerve axons vary in diameter, are irregularly swollen, have various stages of demyelination, and contain occasional swollen mitochondria, dense bodies, and vesicles. Within most of the prelaminar, choroidal, and scleral lamina cribrosa, the axonal mitochondria frequently possess irregular, electron-dense bodies. In globes with moderate and advanced glaucoma, the optic nerve has more extensive pathologic changes. The myelinated axons are widely separated by demyelinated axons, hypertrophied or hyperplastic glial cells (i.e., astrocytes, oligodendrocytes, microglia), and edema. Dense, multilaminar myelin structures with shrunken, degenerated axons occur frequently within the prelaminar regions. Axons in the scleral lamina are extremely swollen with mitochondria and other cytoplasmic organelles, including various types of opaque inclusions and smooth-surfaced vesicles. Frequently, axoplasmic debris fills the spaces between the axons and the glial cells.

Histomorphometry of the optic nerves in age-matched normal and glaucomatous dogs indicate significant differences (Brooks et al., 1995). The mean total optic nerve axon count in normal dogs is nearly 150,000. The mean optic nerve axon diameters in normal, early glaucomatous, and advanced glaucomatous eyes are 1.53, 1.25, and 1.13 µm, respectively. The counts of optic nerve axons 2.0 µm or greater in diameter were reduced by up to 60% in the central regions of the optic nerves of affected dogs. These findings suggest that, as with POAG in humans and laser-induced experimental glaucoma in nonhuman primates, the large-diameter optic nerve axons are more susceptible than the smaller-diameter fibers to damage and disappear first in glaucomatous Beagles. Smaller-diameter axons are extensively damaged later, such that only "resistant" ganglion cell axons are present late in the disease. The dog RGCs have been assigned to the morphologic classes α, β, and γ, which are equivalent to the neurophysiologically classified RGC types Y, X, and W reported in other species. The large RGCs have fast conduction velocities, large retinal receptive field surface areas, large-diameter axons, and preferentially project to layers A and C (i.e., magnocellular layers) of the carnivore lateral geniculate body.

An early focus of study involved the gene and protein myocilin, the first gene associated with several types of early- and late-onset POAGs in humans. The protein myocilin, a secreted 55–57 kDa glycoprotein that forms dimers and multimers, was first reported in 1997 by Polansky and colleagues and termed trabecular meshwork-induced glucocorticoid protein (TIGR; Polansky et al., 1997). In the eye, myocilin is expressed in high amounts in the trabecular meshwork, sclera, ciliary body, and iris; low amounts have been detected in the retina and optic nerve in humans. One of the major characteristics of cultured trabecular meshwork cells is an increased secretion of myocilin following treatment with glucocorticoids (Clark et al., 2001). After myocilin was reported as a novel cytoskeletal protein in the retina and ONH, the term TIGR was replaced with myocilin (*MYOC*) for both the gene and the protein (Kubota et al., 1997). All of the functions and effects of myocilin have not been determined, but *MYOC* mRNA is induced by stress, hydrogen peroxide, mechanical stretch, and steroid treatment. The gene myocilin was reported in the normal dog genome in the summer of 2003. In the same year, the protein myocilin was identified in the AH of normal laboratory-quality Beagles, and in POAG in the Beagles, myocilin AH levels were increased (MacKay et al., 2008b). As POAG progressed in these Beagles, the AH myocilin levels increased further. Myocilin was also localized in the normal and glaucomatous Beagle trabecular meshwork and nonpigmented ciliary body epithelium (Samuelson et al., 2005). As with the aqueous myocilin levels, the glaucoma

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animals had increased amounts of myocilin in these tissues and it increased further in the older glaucomatous dogs. AH levels of myocilin of most primary glaucomas in purebred dogs and secondary glaucomas are also increased when compared to the AH from primary cataractous and diabetic cataracts of different breeds of a large number of dogs (MacKay et al., 2008b). CD-44 is a cell-surface glycoprotein that is involved with cell–cell interactions, cell adhesion, and cell migration, and is expressed in a large number of mammalian cell types. CD44 is also a receptor for hyaluronic acid, found in the AH outflow pathways. CD44 is increased in the AH as well as in several of the ocular tissues in POAG Beagles (Källberg et al., 2006). These preliminary myocilin and CD44 studies suggest these changes are probably "downstream" and represent a common pathway in many primary glaucomas (rather than related to the causative genetic defect).

Even though both the myocilin and CD44 proteins were elevated in AH, the trabecular meshwork, and nonpigmented ciliary body epithelium (Källberg et al., 2006), no mutation was identified in the *MYOC* gene of Beagles with POAG (Gelatt & Wallace, unpublished data, 2004; Kato et al., 2009b; Storey et al., 2008). Similarly, although elevated AH and trabecular meshwork myocilin levels have been documented in a large number of breeds of dogs with the primary glaucomas, *MYOC* gene mutations could not be detected as a cause for primary narrow/angle-closure glaucoma in the Shiba Inu (Gelatt & Wallace, unpublished data, 2004; Kato et al., 2006a, 2007, 2009; Storey et al., 2008). Another candidate gene, *CYP1B1*, was also excluded as the cause for Beagle POAG (Kato et al., 2009a).

A mutation in the *ADAMTS10* gene, caused by the substitution by glycine for arginine (gly661/arg) within a single 4Mb locus on the canine chromosome 20, was documented that is associated with POAG in the Beagle (Kuchtey et al., 2011). The ADAMTS family of proteins are matrix metalloproteinases that have important roles in microfibril formation and connective tissue organization. Despite the recent discovery of genetic defects responsible for Beagle POAG, the detailed molecular and cellular mechanisms resulting in the accumulation of extracellular trabecular meshwork plaques and increased trabecular outflow resistance remain unknown (Samuelson et al., 1989). Investigations of the posterior globe revealed that compared to *wild-type* canine sclera, the *ADAMTS10*-mutant tissue is biomechanically weaker and biochemically distinct, with decreased density and increased anisotropy of the collagen fibers, especially around the ONH (Boote et al., 2016; Palko et al., 2013). Age-associated scleral stiffening and loss of mechanical damping is comparable between *wild-type* and *ADAMTS10*-mutant dogs, regardless of chronic IOP elevation in affected animals (Palko et al., 2016). Because ADAMTS10 plays an important role in microfibril formation, which is a major component of the lens zonules, the G661R missense mutation in the Beagle *ADAMTS10* gene results in zonular dysplasia (Teixeira et al., 2013), which appears to be independent from the changes within the trabecular meshwork; IOP increases months to years before the dislocation or presence of a lens luxation (Gelatt & Samuelson, 1988). Nevertheless, in our clinical experience, *ADAMTS10*-mutant Beagles can present with limited PLL, even though this has not been reported in the literature nor is a significant risk factor.

Although Beagles are usually affected by POAG, there is a recent report of a purebred Beagle with PACG associated with goniodysgenesis (Park et al., 2019). This underscores the importance of a thorough examination and history in order to make the distinction and facilitate prognostication.

Glaucoma in the Norwegian Elkhound

The prevalence of glaucoma in the Norwegian Elkhound has been decreasing in North America (1974–1983: 2.96%; 1984–1993: 2.34%; 1994–2002: 1.98%). POAG was originally described in 29 Norwegian Elkhounds from Norway (Bjerkås et al., 1994; Ekesten et al., 1997). Glaucomatous dogs described in the original reports ranged in age from 3.9 to 13.0 years (median age 6.6 years). The male : female ratio of affected dogs is 1 : 1.3. Dogs in the North American survey were a mean of 6.9 ± 0.8 years at initial presentation (Gelatt & MacKay, 2004a).

Applanation tonometric measurements ranged from 26 to 44 mmHg (median 35.5 mmHg) in the early cases and from 35 to 67 mmHg (median 52 mmHg) in dogs with advanced glaucoma. The ICA and ciliary cleft appeared normal in early-affected dogs, with IOPs ranging from the upper 20s to the 30s. PLD was not observed, though occasional "stout" pectinate fibers were noted, with some narrowing of the ciliary cleft opening. The ciliary cleft gradually closes as the glaucoma advances and the IOP progressively increases. Synechial closure of the ciliary cleft occurred in the advanced cases. Lens subluxation and total lens luxation, buphthalmos and Haab's striae, and ONH atrophy and retinal degeneration occurred late in the disease, with subsequent loss of vision. This breed is an excellent example of one in which individuals with IOPs in the mid-30s mmHg and significant ONH pathology (cupping that involves the entire nerve head) maintain vision longer than expected. These dogs seem to tolerate fairly high IOP for months and can be quite buphthalmic, but can retain some functional vision. An additional retrospective histopathologic study of 9 clinically normal and 22 glaucoma eyes showed open-angle and closed-cleft glaucoma with PLD (2 normal and 18 glaucoma eyes), ciliary cleft abnormalities (hypoplasia or collapse), and linear deposition of PAS-positive basement material within the uveal trabecular meshwork (in 19 glaucoma eyes). TEM demonstrated thickening of uveal trabecular beams by poorly staining large collagen fibrils and irregular deposition of excess basement material. Affected dogs presented between 5.5 and 8 years of age (Oshima et al., 2004).

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A missense mutation in the exon 9 of the *ADAMTS 10* gene appears to be the cause in the Norwegian Elkhound (Ahonen et al., 2014). The alanine to threonine substitution (different than the POAG Beagle) seems to affect the function of this protein on the ECM and microfibril composition (also possible defective structure of the lens zonules). This change occurs within the highly conserved functional metalloprotease domain of the protein. Presence of the zonulary defect (and possible weakness) could predispose to lens displacement, but its effect on the genesis of elevated IOP remained to be established.

Glaucoma in the Petit Basset Griffon Vendéen

POAG was recently reported in the Petit Basset Griffon Vendéen in the United Kingdom based on the examination of 366 dogs over a 6-year period (Bedford, 2016), with 38 dogs affected with POAG (prevalence 10.4%). Clinical signs developed after 3 years of age, with elevated IOP ranging between 34 and 48 mmHg at presentation. Initially the drainage angle appears open gonioscopically and the pectinate ligaments appear normal. In advanced POAG, globe enlargement, lens subluxation, ONH cupping, and impaired to complete loss of vision occurred. Lens subluxation was prominent in 10 dogs with phacodonesis and/or iridodonesis and aphakic crescents before subsequent elevation of IOP. An inversion mutation in intron 12 of *ADAMTS17* was discovered as the cause for POAG (and PLL) in the affected Petit Basset Griffon Vendéen dogs (Forman et al., 2015).

Primary Open-Angle Glaucoma and Primary Lens Luxation in other Canine Breeds

The division of canine primary glaucoma into POAG and PLL-PACG types is still unresolved. Some breeds may share both types of glaucoma (see "Genetics"). Unfortunately there are no detailed clinical descriptions for most of them, only reports of the genetic defect in ADAMTS17. In other words, glaucoma associated with PLL may not be entirely secondary to anterior lens dislocation and vitreous prolapse, as currently perceived (Gelatt et al., 2004); instead, there may be a POAG component. Tonography in some Wirehaired Fox Terriers presented with anterior lens luxations and glaucoma in one eye and the fellow eye with normal IOP and no evidence of lens luxations has suggested decreased aqueous outflow in the normotensive eye. The relationship between lens luxations and glaucoma is at best unsettled, and requires investigations.

The discovery of *ADAMTS17* mutations in POAG-affected Basset Hounds (19 bp deletion in exon 2; Oliver et al., 2015), Basset Fauve de Bretagne dogs (p.G519S missense mutation with glycine to serine change at position 519; Oliver et al., 2015), and Chinese Shar-Peis (6 bp deletion in exon 22; Oliver et al., 2018) means that

It is important for the clinician to consider a POAG component in "classic" PLL breeds, such as terriers, (Alario et al., 2015; Curtis & Barnett, 1980; Gould et al., 2011; Lazarus et al., 1998; Morris & Dubielzig, 2005; Strom et al., 2011a; Willis et al., 1979), because of their genetic defect in *ADAMTS17* (splice donor site mutation: ADAMTS17c.1473+1 G>A; Farias et al. 2010; Gould et al., 2011). These canine patients may present with elevated IOP without lens displacement into the anterior chamber or pupillary block, but instead with lens subluxation or posterior lens luxation (Curtis et al., 1983; Glover et al., 1995a). Furthermore, glaucoma often persists following surgical lens removal. In other words, glaucoma associated with PLL may not be entirely secondary to anterior lens dislocation and vitreous prolapse, as generally perceived (Gelatt & MacKay, 2004b); instead, there may be a POAG component.

Primary Angle-Closure Glaucoma

The clinical stages of PACG dogs are different from those in POAG and are characterized by abrupt increases in IOP, which are initially transient and self-controlled (and unrecognized), but eventually the elevation in IOP persists and prompts presentation to the veterinarian. These abrupt IOP changes are apparently the result of pupillary blockage to AH from posterior chamber to anterior chamber, and the forward displacement of the basal iris with narrowing to closure of the ICA and cleft. These abrupt increases in IOP initially are in the 30+ mmHg range, but as the angle narrowing and closure advance, the increase can reach 50 mmHg or even higher and produce clinical signs that merit presentation to the veterinarian. Eventually (sometimes within days), this appositional narrowing and closure of the ICA and sclerociliary cleft develop peripheral anterior synechiae, "zipping" the outflow pathways closed, and rending the glaucoma refractory to pressure-lowering drugs. During the next decade or so, the PACG breeds will hopefully be characterized further and the genesis of their glaucomas documented. Some breeds may also have both PACG and POAG forms (likely due to different genetic mutations), which further complicates accurate diagnosis. The increased occurrence of the PACG in females of many of these breeds will complicate the search for the mode of inheritance as well as the causative gene.

The stages of canine PACG can be divided clinically into latent or prodromal, intermittent glaucoma, acute congestive or high-pressure glaucoma, or postcongestive and chronic glaucoma, as proposed by Miller (2005; Table 20.3). The clinical types of PACG in humans are quite similar and have been divided into intermittent angle-closure glaucoma, subacute angle-closure glaucoma, acute angle-closure glaucoma, and chronic angle-closure glaucoma (Ritch & Lowe, 1996). Each stage of PACG has certain clinical characteristics that can aid in diagnosis and characterization and serve as a guide for therapy. Because the acute congestive stage of PACG is usually the first stage presented to the veterinarian, it is not surprising that nearly 50% of these eyes are blind

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Table 20.3 The different stages of primary angle-closure glaucoma in the dog.

Stage	History	Intraocular Pressure (IOP) at Exam	Angle-Closure Depth	Gonioscopy	High-Resolution Ultrasonography	Clinical Signs
Latent	Breed-predisposed	Normal	Shallow	Narrow	Sigmoidal iridal occludable	None; watch for configuration; progression; consider prophylactic therapy
Intermittent (subacute)	Transient corneal edema	Normal	Shallow	Narrow to closed/ appositional	Ciliary cleft narrow to closed	Bouts of partial mydriasis and corneal edema; other glaucoma signs variable Prophylactic therapy
Congestive (acute)	Possible previous attacks	Elevated; marked	Shallow	Closed Appositional to periodic acid-Schiff (PAS)	Cleft closed	High IOP with mydriasis; corneal edema; episcleral congestion; other signs
Postcongestive	Glaucoma history	Normal	Shallow	Closed with PAS	Cleft closed	Normal to low IOP due to decrease aqueous humor production Signs of glaucoma
Chronic glaucoma	Glaucoma history	Increased	Shallow	Closed with PAS	Cleft closed	Buphthalmia; other signs of glaucoma; optic disc and retinal degeneration; blindness

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and medical therapy at this stage has limited success that typically is only short-lived.

Glaucoma in the American Cocker Spaniel

In the United States, primary glaucoma in the ACS appears as a narrow-angle or angle-closure type, without significant amounts of PLD (Lovekin, 1964; Magrane, 1956, 1957). The prevalence of glaucoma in the ACS in North America has been increasing (1964–1973: 1.39%; 1974–1983: 2.07%; 1984–1993: 3.95%; 1994–2002: 5.52%, the highest for any breed; Gelatt & MacKay, 2004a). In the first ACS report of 25 animals with glaucoma, 7 were males and 18 were females (1:2.6; Magrane, 1956, 1957). The mean age of affected animals at first presentation was 6.33 ± 1.46 years. Subsequent reports described glaucoma in the ACS in additional dogs in America and the Netherlands (Boevé & Stades, 1985; Lovekin, 1964; Lovekin & Bellhorn, 1968). In the North American survey of 1,982 glaucomatous cockers, 665 were males and 1,331 were females (1:2). The mean ± SD for affected animals was 6.72 ± 1.13 years. The presentation of primary glaucoma in the ACS is highest in middle-aged to older dogs (1–2 years of age: 0.63%; 2–4 years of age: 1.07%; 4–7 years of age: 4.3%; 7–10 years of age: 7.03%; 10–15 years of age: 8.39%; 15+ years of age: 5.32%). Narrow-angle glaucoma in the ACS continues to be the most frequent primary glaucoma presented to US veterinary ophthalmologists (Gelatt & MacKay, 2004a). This breed also continues to be one of the most popular in the United States.

The usual history of PACG or narrow-angle glaucoma in the ACS is unremarkable, with clinical signs unrecognized until an acute congestive crisis occurs; however, occasionally there will be reports of conjunctival hyperemia and even transient corneal edema, both self-limiting. Most affected dogs present with either classic clinical signs of unilateral, acute congestive glaucoma of a few days' duration or with chronic, advanced glaucoma with buphthalmia, lens changes, retinal and ONH degeneration, and blindness (Fig. 20.12). Often, the condition becomes bilateral within several months. In Magrane's series, the second eye was usually affected within 12 months. Both the history and clinical course suggest this glaucoma may be a series of acute IOP attacks, with the subsequent magnitude of the IOP elevation gradually increasing. Tonographic measurements are usually within normal limits in dogs with mild to moderately narrow ICAs, but they are lower than normal (≤ 0.10–0.15 µL/min/mmHg) in dogs with very narrow and closed (due to synechiae formation) ICAs and clefts. Tonometry of the acute congestive glaucomas often yields IOPs as great as 50–70 mmHg. The corneal edema that parallels the elevation in IOP after approximately 40 mmHg usually prevents gonioscopy. Gonioscopy of the ACS with ocular hypertension generally reveals a narrow to closed ICA and reduced ciliary clefts; as the glaucoma progresses, angle closure and ciliary cleft collapse with peripheral anterior synechia formation are common. More recently, PLD in the ACS has also been reported, but it does not appear to occur commonly (Smith et al., 1993).

Changes of the ocular fundus in the ACS may not correlate well with the duration and magnitude of the elevated IOP because of the wide range of IOP elevation. It is not unusual for an ACS to present with a very high IOP (70–80 mmHg) and a history of signs of glaucoma being present for less than 1

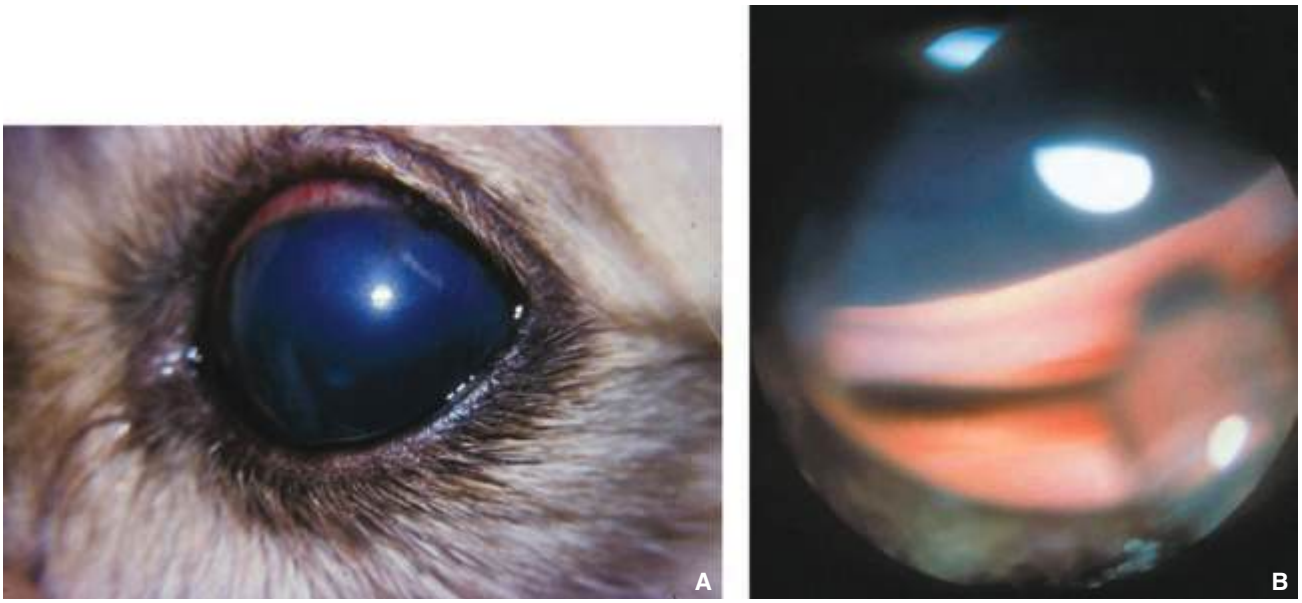


Figure 20.12 Narrow-angle and cleft glaucoma in an American Cocker Spaniel. **A**. Both corneal edema and striae are present, and the intraocular pressure is 52 mmHg. **B**. Gonioscopy reveals a closed iridocorneal angle and cleft.

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week, but not return of vision after the IOP is lowered below 20 mmHg. Ophthalmoscopically, the ocular fundus cannot be visualized until the IOP is lowered and the corneal edema reduced. The optic nerve and retina may initially appear to be normal, although some vascular attenuation may be present. With the IOP maintained within the normal range after these acute increases, additional retinal and ONH degeneration may become apparent within a few weeks. In some of these dogs, the retinal degeneration may affect only limited areas, appearing as radiating or fan-shaped zones from the ONH and representing areas of retinal and choroidal degeneration caused by ischemia from the occlusion of individual short posterior ciliary arteries, apparently with high IOP levels. Because this breed often presents with its first affected eye with very high IOP and often irreversibly blind, prophylactic therapy of the fellow eye is very important.

The p.G661R *ADAMTS10* missense mutation responsible for Beagle POAG was excluded as a cause of primary glaucoma in the ACS (Kuchtey et al., 2013).

Glaucoma in the Basset Hound

In the Basset Hound, reports detailing inherited glaucoma are limited and based on a relatively small number of animals (Bedford, 1975; Boevé & Stades, 1985; Martin & Wyman, 1968; Wyman & Ketring, 1976). PACG with PLD (i.e., mesodermal dysgenesis) was documented in Basset Hounds during the late 1960s and investigated during the early 1970s (Martin & Wyman, 1968; Wyman & Ketring, 1976). In these reports, 63% of Basset Hounds had some degree of PLD, but fewer than 3% had glaucoma. In the most recent North American survey, glaucoma occurred very frequently in the Basset Hound at a mean age of 6.3 ± 1.30 years at first presentation. Prevalence has been increasing (1964–1973: 3.08%; 1994–2002: 5.44%) and appears to increase with increasing age (Gelatt & MacKay, 2004a). The gender ratio reflects the greater prevalence of the disease in females (1 : 2.4). Unlike the simple autosomal recessive inheritance pattern in the Beagle and equal gender ratio, the heredity of Basset Hound glaucoma is likely more complex. More recently a colony of glaucomatous Basset Hounds was established and the glaucoma classified as chronic angle-closure glaucoma with presumed autosomal recessive inheritance (Ahram et al., 2014, 2015; Grozdanic et al., 2010).

Basset glaucoma usually presents clinically as either unilateral, acute, congestive PACG or as chronic PACG with buphthalmia and eventual blindness (Fig. 20.13). In a study using periodic tonometry, a gradual rise in IOP occurred in glaucomatous Basset Hounds starting at 14 mmHg (8-month-old dogs), 15.5 mmHg (15-month-old animals), 17.5 mmHg (18-month-old dogs), 24 mmHg (24-month-old animals), and 36 mmHg (30-month-old dogs; Grozdanic et al., 2010). This suggests that progressive changes in the AH outflow pathways, probably within the trabecular meshwork, develop before IOP exceeds normal levels. When glaucomatous Basset Hounds are provoked with mydriatics, affected dogs treated with topical 1% tropicamide or 1% atropine develop significant elevations in IOP (35% and 50%, respectively). Anterior uveitis, with at least some of the corneal edema related to this inflammation, is present, which is unusual among breed-related canine glaucomas. It is not known at what point this inflammatory response develops or if the uveitis develops in response to the marked elevations in IOP and tissue damage. This inflammation complicates greatly the medical and surgical treatments of this form of

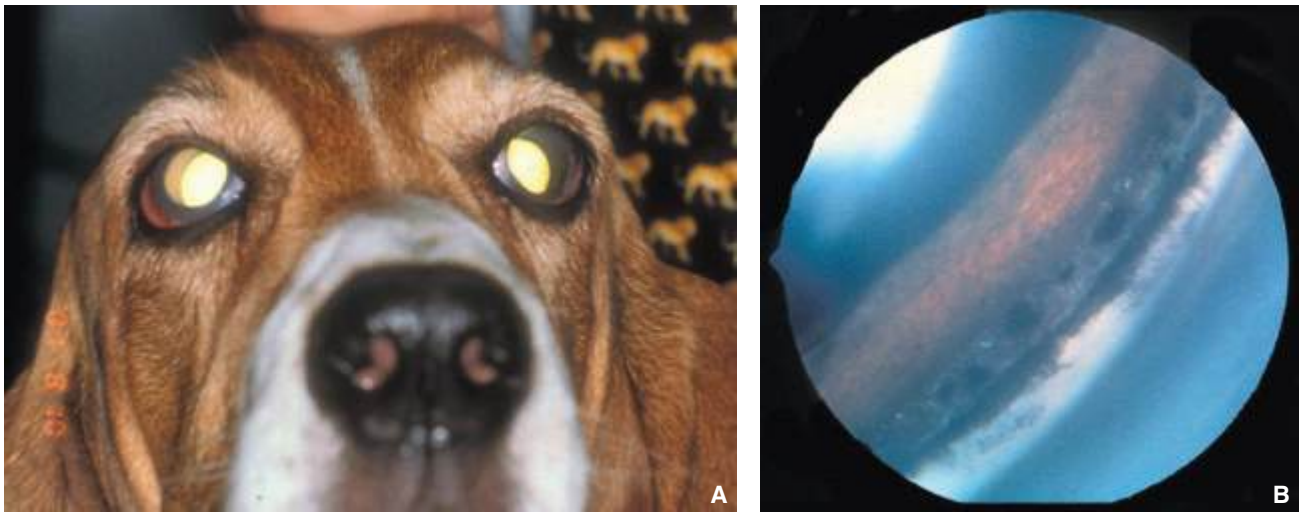


Figure 20.13 **A**. Basset Hound with bilateral advanced glaucoma. **B**. At gonioscopy, large, persistent mesodermal bands, rather than distinct, individual pectinate ligaments, are often visible. With extensive involvement, flow holes are present in these dysplastic pectinate ligaments. Because iridocyclitis is often present, these pectinate ligament anomalies must be differentiated from progressive, peripheral anterior synechiation of the aqueous outflow pathways in this type of glaucoma.

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glaucoma and requires concurrent anti-inflammatory therapy.

High-frequency ultrasonography indicates complete collapse of the ICA in dogs about 20 months old (Grozdanic et al., 2010). In the opposite, normotensive eye, and in the affected eye, gonioscopy usually reveals a narrow to closed ICA, and the opening of the ciliary cleft is spanned by varying sizes and numbers of consolidated thickened pectinate ligaments or mesodermal remnants, with varying numbers of "flow holes." There are usually some gaps in the regions of PLD, where the pectinate ligaments appear normal, and the gaps permit direct inspection of the trabecular meshwork and the ciliary cleft opening. Serial gonioscopy of some glaucomatous Basset Hounds suggests a gradual increase in the extent of the appearance of PLD with aging, suggesting possible formation of peripheral anterior synechiae with progressive narrowing of the ICA.

Results of histopathologic examinations of these affected eyes mainly involved the advanced form of the glaucoma. Short, stout pectinate ligaments span the collapsed ciliary cleft and, in the advanced glaucomas, are often in direct contact with the peripheral cornea, with the opening to the ciliary cleft being collapsed. The termination of Descemet's membrane in advanced cases is often enlarged, divided, and bulbous. Descemet's membrane and corneal endothelial cells may extend posteriorly along the trabecular beams. Specific changes within the trabecular meshwork in the early stages of this disease are unknown.

Schiøtz tonographic measurements of Basset Hounds with glaucoma revealed significantly impaired outflow (0.05 µL/min/mm Hg; Helper et al., 1974). In one of these Basset Hounds presenting with unilateral glaucoma, the flow rate in the affected eye was 0.03 µL/min/mmHg and 0.10 µL/min/mm Hg in the "normal" fellow eye, which subsequently developed glaucoma 1 year later.

While scotopic and photopic fERG does not reveal significant deficits in early-affected Bassets, PERG indicated significantly reduced amplitudes. Reduced PERGs can occur in dogs as young as 18 months of age and gradually declined from 3.5 ± 0.42 µV (18-month-old dogs) to 1.84 ± 1 µV (30-month-old dogs). There appeared to be a significant correlation between IOP levels and PERG amplitudes. This also suggests that functional vision deficits may precede significant elevations in IOP (Grozdanic et al., 2010).

Medical treatment of Basset Hound glaucoma is difficult because of the often acute and very high elevations of IOP, and the clinical signs of combined angle-closure glaucoma and iridocyclitis. Often the first presenting eye is moderately enlarged, the lens subluxated, the ONH cupped, and vision has been lost. Recent genetic reports on the Basset Hound are presented in "Genetics" in this chapter (Ahram et al., 2015; Grozdanic et al., 2010; Oliver et al., 2015). Most instances of glaucoma in the Basset Hound are attributed to PACG; however, there has been a discovery of a 19 bp mutation in exon 2 of *ADAMTS17* in Basset Hounds diagnosed with POAG in the United Kingdom (Oliver et al., 2015). The existence of different forms of glaucoma within a single breed confounds the study and expectations of the disease.

Glaucoma in the Boston Terrier

The prevalence of glaucoma is also increasing in the Boston Terrier (1964–1973: 0.97%; 1974–1983: 1.82%; 1984–1993: 2.6%; 1994–2002: 2.88%; Gelatt & MacKay, 2004a). It also increases with age (2–6 months of age: 0.88%; 6–12 months: 0.52%; 1–2 years: 0%; 2–4 years: 1.116%; 4–7 years: 1.99%; 7–10 years: 4.08%; 10–15 years: 5.64%; and 15+ years: 12.5%). Glaucoma presents in the middle-aged and aged Boston Terrier, with a mean age at initial presentation of 7.02 ± 1.24 years old. The male/female ratio is 1:1. There is no detailed report on glaucoma in this breed to date.

Glaucoma in the Bouvier des Flandres

In the Bouvier des Flandres, two reports of PLD and narrow-angle glaucoma have been published (Boevé & Stades, 1985; van der Linde-Sipman, 1987). Both reports were based on dogs in the Netherlands, where the breed is the most frequently affected purebred dog with glaucoma. In America, the Bouvier des Flandres is a relatively new breed of dog, and the number of glaucomatous animals in the survey report was limited to 23 animals (mean age of 5.43 ± 1.70 years old; Gelatt & MacKay, 2004a). The male:female ratio of affected dogs is 1:1. In addition to PLD and narrow ICA and ciliary cleft, histopathology of the affected secondary pectinate ligaments and trabecular meshwork contained significant amounts of PAS material, which may also affect AH outflow (van der Linde-Sipman, 1987). Ciliary clefts measured in 98 dogs by HRUS and divided into open, narrow, or closed revealed that a narrow or closed ciliary cleft was associated with the development of PACG (Dubin et al., 2017). Nine of the dogs with narrowed or closed clefts went on to develop PACG (9.8%), suggesting association but not causation. In the Bouvier des Flandres a recessive inheritance of PLD has been proposed (Rühli & Spiess, 1996).

Glaucoma in the Chow Chow

In the Chow Chow breed, the first report of glaucoma consisted of 18 glaucomatous animals (13 females and 5 males), with a mean age at initial presentation of 6.2 ± 2.2 years (Corcoran et al., 1994). That is similar to that noted in the North American prevalence survey, which reported a mean age of 6.45 ± 1.07 years on first presentation (Gelatt & MacKay, 2004a). The prevalence is increasing (1984–1993: 2.05%; 1994–2002: 4.70%) and the disease occurs more commonly in the aged animal (2–6 months of age: 0.46%; 6–12 months: 1.04%; 1–2 years: 0.35%; 2–4 years: 0.86%; 4–7 years: 5.92%; 7-10 years: 9.69%; 10–15 years: 5.22%). The male:female ratio in primary glaucoma in this breed is approximately 1:2.

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Primary glaucoma in the Chow Chow has been associated with ICA closure and limited PLD (Corcoran et al., 1994). Most animals presented with bilateral, acute congestive glaucoma. Results of gonioscopy, when possible, revealed narrow to closed ICAs, with short, stout pectinate ligaments. PLD, appearing as focal areas of solid pigmented sheets, was usually quite limited (< 1/16 the circumference of the angle). On the basis of clinical observations regarding the extent of PLD, the genesis of this form of primary glaucoma appears to be of the narrow- and closed-angle type.

Histopathologic results of a dog that had glaucoma for 18 months, as well as of four globes from three other Chow Chows with chronic glaucoma, revealed extensive retinal degeneration as well as deep cupping and gliosis of the optic discs. The pathology of the outflow pathways indicated collapse of the ciliary clefts and compression of the trabeculae. Endothelial cells and PAS-positive basement membrane material spanned the pectinate ligaments and occurred within the trabecular meshwork. The termination of Descemet's membrane had irregularities and nodular terminations. The Chow Chow is another breed with primary glaucoma that often retains functional vision until late in the disease, frequently despite elevated IOP, buphthalmia, and obvious, extensive ONH cupping and degeneration.

Glaucoma in the English Cocker Spaniel

Glaucoma in the English Cocker Spaniel may be more common in the United Kingdom, and there is but a single report including 16 glaucomatous dogs with a mean age of 9.8 years old (Bedford, 1980a). The prevalence of glaucoma in the English Cocker Spaniel in North America is fairly constant (1.16-1.35% between 1973 and 2002), and the disease primarily affects middle-aged and older dogs (2–12 months: 0%; 1–2 years: 2%; 2–4 years: 0%; 4–7 years: 0.66%; 7–10 years: 1.44%; 10–15 years: 3.36%). The mean age of initial presentation and diagnosis of glaucoma in the English Cocker Spaniel was 6.83 ± 1.34 years old. The male : female ratio for this breed's glaucoma is 1 : 2+. Bedford reported both narrow and closed ICAs and clefts as well as PLD in this breed (Bedford, 1977a). Breeding of only animals with normal ICAs led to a reduction in the presence and degree of ICA abnormalities in the English Springer Spaniel (Bjerkås et al., 2002).

Glaucoma in the English Springer Spaniel

The prevalence of primary glaucoma in this breed in North America is low (0.48% in 1974–1983) and the age at diagnosis varies (2–4 years: 0.48%; 4–7 years: 0.28%; 7–10 years: 0.72%; 10–15 years: 1.4%; Gelatt & MacKay, 2004a). This glaucoma, characterized as narrow ICA and PLD, was reported in 14 (5 males and 9 females) of 279 English Springer Spaniels in Norway (Bjerkås et al., 2002). While narrowing of the ICA in the hypertensive dogs seemed somewhat constant, the degree of PLD was more variable, with affected dogs generally more severely affected and more frequently in older dogs. About 25.5% of the normotensive Springers had some degree of pectinate ligament abnormality. Degree of PLD in this breed is graded based on the percentage (1/16 wedges) of angle circumference involved with PLD. Normal (i.e., normotensive) dogs in a series have been graded as normal (74.5%), grade 1 (15.8%), 2 (6.8%), 3 (1.8%), or 4 (1.1%), but no correlation has been made between presence or grade of PLD and development of glaucoma in this breed. Some narrowing of the ICA was present in 17.9% of English Springer Spaniels. This breed-related glaucoma appears to be inherited because related dogs were affected, and this possibility should be investigated more thoroughly.

Glaucoma in the Flat-Coated Retriever

Primary glaucoma also affects Flat-Coated Retrievers from the United Kingdom, but the condition has not been reported among those from the United States (Read et al., 1998; Wood et al., 1998). Flat-Coated Retrievers with the more extensive forms of PLD are predisposed to glaucoma. In one study, 16 had glaucoma (62.5%–100.0% of the ICA circumference affected) and 11 were normotensive (62.5%–87.5% of the circumference affected); Read et al., 1998). The onset of glaucoma has been postulated to develop as corneal endothelial basement membrane deposition within the ciliary cleft, or as gradual closure of the compromised cleft from lenticular enlargement with aging occurs, but no histopathologic examination findings have been described. The possible relationship between the corneal endothelium and the trabecular meshwork endothelia within the ciliary cleft in the pathogenesis of this glaucoma is unclear, but intriguing.

Repeated gonioscopic examinations of 96 dogs indicated that 39 (40.6%) developed progression in their PLD from the original observations (Pearl et al., 2015). Progression to the most severe form of PLD occurred in 12 (previously determined unaffected) of 96 dogs. Serial gonioscopic observations appear very important in this breed, particularly in older dogs. The role of secondary inflammation in the progression of these dysplastic pectinate ligaments over time and further closure of the opening of the iridociliary cleft is likely important.

Glaucoma in the Great Dane

PACG as it occurs in Great Danes from the United Kingdom has been described (Barnett & Mason, 1993; Wood et al., 2001). In that study 18 dogs were affected (11 females and 7 males), with an age range of 1–9 years (mean 4 years). Most dogs presented with unilateral acute congestive glaucoma, with 3- to 24-month intervals before the fellow eye developed clinical signs. Gonioscopy of the initially affected eyes, as well as of the opposite, normotensive eyes, revealed narrow to closed ICAs with PLD. No tonographic or histopathologic examinations of affected eyes have been reported. A subsequent study of 180 Great Danes compared depth of anterior chamber, presence of goniodysgenesis (PLD), devel-

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opment of glaucoma, and inheritance of goniodysgenesis (Wood et al., 2001). The estimated heritability of the degree of goniodysgenesis was 0.52, and there was a significant relationship between the angle abnormalities in the parents and their offspring. Anterior chamber depth of < 3.7 mm was a predictor of glaucoma. Shallow anterior chambers and extensive PLD appear to be risk factors in this breed.

Glaucoma in the Shiba Inu in Japan

The Shiba Inu is a relatively new breed in America, but its popularity is increasing. However, the Shiba Inu is a popular breed in Japan and demonstrates glaucoma with ICA narrowing and thickening of pectinate ligaments (Kato et al., 2006a, 2006b, 2007). The thickened pectinate ligaments range from very broad strands to small sheets and broad solid sheets, with or without flow holes. Of the primary glaucoma dogs in Japan, the Shiba Inu breed has the highest incidence (Kato et al., 2006b). Most Shiba Inu patients present with acute high IOP elevations, mydriasis, corneal edema, scleroconjunctival congestion, pain, and often loss of vision. This breed, like the Basset Hound, has considerable concurrent uveitis as part of the disease process and can maintain sight for longer than expected. Affected individuals are reported to respond better to surgical implantation of a gonioshunt compared to medical therapy alone, with a mean duration of vision retention of 58 months into the postoperative period (Kubo & Ito, 2019; Saito et al., 2017).

The genetics in this breed have been studied, but are not yet worked out. In a study involving glaucomatous, nonglaucomatous with open ICA, and nonglaucomatous with closed ICA Shiba Inu dogs, the exons of the canine *MYOC* gene were amplified and sequenced. A healthy Beagle dog was the control. Myocilin RNA was present in the ciliary body and trabecular meshwork, but the *MYOC* gene in this breed did not appear to be mutated (Kato et al., 2007). The G661R *ADAMTS10* missense mutation responsible for Beagle POAG has been excluded as a cause of primary glaucoma in the Shiba Inu (Kuchtey et al., 2013). In Shiba Inus (and Shih Tzus), *SRBD1* has been identified as a PACG risk gene (Kanemaki et al., 2013). It encodes for S1 RNA-binding domain and has been associated with human forms of primary glaucoma; however, its function remains unknown (Liu et al., 2014; Mabuchi et al., 2015; Writing Committee for the Normal Tension Glaucoma Genetic Study Group of Japan Glaucoma et al., 2010)

Glaucoma in the Miniature and Toy Poodle

Although the prevalence of glaucoma in Miniature and Toy Poodles in North America is not high and is relatively stable (Miniature: 1.49–1.86%; Toy: 1.06–1.2%), the popularity of these breeds results in very large numbers of glaucomatous animals (Gelatt & MacKay, 2004a). Glaucoma in these breeds tends to occur in middle-aged to older animals (Miniature Poodle: 2 months–4 years of age: 0%; 4–7 years: 0.42%; 7–10 years: 2.0%; 10–15 years: 2.37%; 15+ years: 3.78%; Toy Poodle: 2 months–4 years: 0%; 4–7 years: 1.07%; 7–10 years: 1.19%; 10–15 years: 1.79%; 15+ years: 2.34%). The mean age of initial presentation with glaucoma in Miniature Poodles was 7.31 ± 1.23 years. The affected male : female ratio for this breed is 1 : 1.4.

Glaucoma in the Samoyed

The first report of PACG in the Samoyed was in Europe and included 12 glaucomatous animals (mean age 6.6 ± 2.8 years) and 179 normotensive dogs (Ekesten 1993; Ekesten & Narfström, 1991, 1992; Ekesten & Torrang, 1995). In the North American survey, there were 148 glaucomatous dogs with a mean age at first presentation of 6.16 ± 1.39 years (Gelatt & MacKay, 2004a). Prevalence in North America is relatively stable (1.43% in 1974–1983; 1.57% in 1984–1993; and 1.59% in 1994–2002). In the Samoyed breed, glaucoma is presented in middle-aged and older dogs (2 months–4 years: 0%; 4–7 years: 3.15%; 7–10 years: 2.15%; 10–15 years: 0.61%), and the mean age of initial presentation with glaucoma was 6.16 ± 1.39 years. The ratio of males to females in the breed is 1 : 2.23.

PACG in Samoyeds has been investigated clinically in Sweden (Ekesten, 1993; Ekesten & Narfström, 1991, 1992; Ekesten & Torrang, 1995). This breed is another excellent example of members that have elevated IOPs (mid-30s mmHg) and advanced cupping of the ONH, but maintenance of vision. Results of gonioscopy indicated PLD to varying degrees in 47 of 210 eyes. The width (opening) of the ciliary cleft (as measured from goniophotographs) decreases with age. However, there was no significant correlation between IOP and degree of PLD of these animals. Interestingly, considerably narrower clefts were found in the eyes of dogs closely related to Samoyeds with angle-closure glaucoma. The heritability of the relative depth of the ciliary cleft opening was estimated at 56%. In affected animals, age-related shallowing of anterior chamber depth, increased lens thickness, increased vitreal axial length, and increased axial length of the globe are present before the onset of clinically detectable increased IOP in the fellow eyes of unilaterally glaucomatous Samoyeds (Ekesten, 1993; Ekesten & Narfström, 1991, 1992). These are frequent observations for primary narrow- or closed-angle glaucoma in humans as well (Ekesten, 1993). The glaucomatous eyes all had closed ICAs. Eyes with narrow ICAs had anteriorly positioned lenses and a longer vitreous body. The increase in globe axial length will increase the radial shearing forces at the scleral lamina cribrosa, to which the axons are exposed as they exit the globe, according to the equation

$$S = (DP * R) \div 2h,$$

where S is the radial shearing forces, DP the translaminar pressure difference, R the radius of the globe, and h the scle-

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ral thickness at the lamina (Fechtner & Weinreb, 1994). Increased susceptibility of ONH axons to IOP is the result.

The classic hypothesis concerning the pathogenesis of narrow-angle glaucoma is a relative block of AH passage through the pupil, which is caused by the greater tension applied by the iris against the central lens or, in Samoyeds, by the more anteriorly positioned lens. Increased resistance to the escape of AH into the pupil from behind the iris results in the more forward displacement of the basal iris, which could be associated with a narrow opening of the ciliary cleft. Over time, the outflow pathways become progressively more compromised and eventually close.

Glaucoma in the Shar-Pei

A relatively new breed to North America, the Shar-Pei exhibits primary or breed-related glaucoma with increasing frequency (1984–1993: 1.53%; 1994–2000: 4.40%) in later life (2 months–2 years: 0%; 2–4 years: 1.49%; 4–7 years: 7.58%; 7–10 years: 7.42%; 10–15 years: 3.17%; Gelatt & MacKay, 2004a). The breed has also been reported with hereditary lens luxation and POAG (Lazarus et al., 1998; Oliver et al., 2018), and how these two breed-related diseases interrelate remains to be defined. In the glaucoma study, males and females were affected with similar frequency and a male : female ratio of 1 : 0.89. In the dogs with PLL, the mean age of affected animals was 4.9 years (range of 3–6 years). This breed is another example that retains vision in the face of IOPs in the mid-30s mmHg and severe ONH cupping. A 6 bp deletion in exon 22 of the *ADAMTS17* gene has been implicated in the development of POAG and PLL in this breed (Oliver et al., 2018).

Glaucoma in the Siberian Husky

The prevalence of glaucoma in the Siberian Husky (1984–1993: 1.13%; 1994–2002: 1.88%) reflects the increased popularity of the breed in North America. PLD and progressive narrowing of the ICA have been associated with this form of ocular hypertension. Nell and colleagues reported that PLD in this breed may be inherited via an autosomal recessive mode of inheritance. She also reported that PLD was observed more frequently in the female and in blue irides (Nell et al., 1993). In these normotensive dogs, there was no relationship between the amount of PLD and IOP. Glaucoma in this breed affects mainly young and middle-aged dogs (2 weeks–2 months: 1.75%; 2–6 months: 1.24%; 6–12 months: 1.42%; 1–2 years: 1.0%; 2–4 years: 1.69%; 4–7 years: 2.59%; 7–10 years: 2.01%; 10–15 years: 0.86%). The mean ± SD age of initial presentation with glaucoma was 5.27 ± 1.64 years. In the Husky the ratio of affected males to females is 1 : 1.88.

Glaucoma in the Welsh Springer Spaniel

In Welsh Springer Spaniels from the United Kingdom, 28 cases of PACG have been reported (Cottrell & Barnett, 1988). Females were affected more frequently than males (ratio 4.2 : 1). Age of onset ranged from 10 weeks to 10 years (mean age 2.75 years). Four dogs were affected before 1 year of age. Time from the onset of glaucoma in the first eye to that in the second eye ranged from 6 days to 3 years. Clinical signs were either those of acute congestive glaucoma with pain, dilated and unresponsive pupils, episcleral congestion, corneal edema, and IOP as high as 80–100 mmHg, or those of chronic angle-closure glaucoma with enlarged globes, Haab's striae, lens subluxation and cataract formation, and advanced retinal and ONH degeneration. Gonioscopy of the affected dogs revealed eyes with regions of narrow and regions of closed ICAs and ciliary clefts, as well as other eyes with the angles totally closed. The Welsh Springer Spaniel has sparse and "wispy" pectinate ligaments. Scanning electron micrographs of the outflow pathways revealed closure of the ICA, complete absence of the pectinate ligaments, the iris root merging with the corneal endothelium, and partial collapse to complete closure of the ciliary cleft.

This form of glaucoma was familial, and the mode of inheritance appeared to be dominant (Cottrell & Barnett, 1988). Selected matings, however, were not performed. The affected animals with partially open or narrow angles were thought to be heterozygous, and those whose eyes had completely closed angles were thought to be homozygous. The defect may show variable expression as well.

Glaucoma in the Border Collie

Sudden-onset glaucoma has been recognized in Border Collies since the 1990s. Breed enthusiasts soon thereafter started a database to track affected dogs and the results of gonioscopic examinations, but a definitive association between PLD, or pectinate ligament abnormality (PLA) as it is referred to in the breed, could not be established with this alone (Pugh et al., 2019). Recent studies in Border Collies have identified and confirmed the association of a single variant in *OLFML3* with PLD and PACG (Oliver et al., 2020; Pugh et al., 2019). This variant consists of a change of arginine to glutamine in the OLFML3 protein encoded on canine chromosome 17. PLD and PACG have previously been considered to be complex diseases caused by multiple genetic and environmental factors. The results of these studies, however, are consistent with PLD and PACG largely being a monogenic, autosomal recessive trait, at least in Border Collies.

Other Breeds

Additional breeds also develop primary glaucomas (see Table 20.1A), but the specifics of the disease in most breeds have not been investigated. Primary narrow-angle glaucoma occurs in Golden Retrievers from the United Kingdom, with angle closure, cleft collapse, and PLD observed. Studies in the Eurasier breed in France have been reported (Boillot et al., 2014). Secondary glaucoma associated with pigmentary dispersion and anterior uveal cysts also occurs in this breed (see Chapter 21). Additional clinical studies using

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HRUS (20 MHz), UBM (50–60 MHz), OCT, ultrasound ocular measurements, and IOP diurnal recordings will hopefully document these glaucomas and their pathogenesis during the onset and early stages of these diseases. Once families of affected dogs are identified, DNA tests may reveal the causative gene defects. Accurate genetic testing may reveal potential glaucoma dogs before onset of the disease, enabling further documentation and classification of the disease (open/closed angle).

Secondary Glaucomas

The secondary glaucomas consist of diseases with increased IOP, open to closed ICAs and ciliary clefts, and detectable impairment of AH outflow. Both the medical and surgical management of secondary glaucomas in the dog have been overshadowed by those of the primary glaucomas. Clinical management of the secondary glaucomas is often more clear-cut, because the cause of the increased IOP can be ascertained (Table 20.4), and the prognosis for the glaucoma progression predicated.

Medical or surgical treatment of the secondary glaucomas is directed toward removing the cause of the elevated IOP. There may be additional or secondary changes (e.g., peripheral anterior synechiae) that may require application of the standard glaucoma filtering or cyclodestructive procedures. The most frequent cause of glaucoma in the dog requiring surgery is lens displacement, which is demonstrated as subluxation, anterior luxation, or posterior luxation and cataract formation. Dogs with *ADAMTS17* and *ADAMTS10* mutations likely have a component of POAG that is exacerbated by the complications and sequelae associated with lens displacement. Uveitis and intraocular tumors are also associated with secondary glaucoma in the dog.

Table 20.4 Summary of treatments for the secondary glaucomas in the dog.

Anterior Uveitis
Peripheral anterior synechiae
Pupillary obstruction
Iris bombé
Medical: Corticosteroids, Nonsteroidal anti-inflammatory agents, Mydriatics
Surgical: Coreoplasty, Iridencleisis
Lens-Associated
Cataract
Surgical: Lens removal
Displacement (Anterior luxation, subluxation, posterior luxation)
Surgical: Lens removal; other
Intraocular Neoplasms
Surgical: Iridocyclectomy; enucleation; laser
Hyphema
Surgical: Aspirate/tissue plasminogen activator
Melanocytic (Dog Only)
Surgical: Anterior chamber shunts; enucleation
Aphakic/Pseudophakic (Angle/Pupil Obstruction)
Surgical: Coreoplasty; Iridencleisis; anterior vitrectomy
Malignant
Surgical: Anterior vitrectomy
Silicone Oil
Surgical: Aspirate

Risk Factors and Secondary Glaucoma in the Dog

Lenses and the Glaucomas

Removal of the lens, though not commonly considered to be a surgical procedure for treatment of glaucoma, may be necessary in treatment of many of the canine lens-induced glaucomas. Lens removal may be indicated for secondary glaucomas associated with lens-induced uveitis and cataract resorption, intumescent cataracts, anterior and posterior lens luxations, and subluxations. When the lens is displaced from its patella fossa in a glaucomatous eye, maintenance of IOP within normal limits by surgical, medical, or some combination of these treatments may be impossible without lens removal. Lens removal has not been attempted in early PACG dogs to either prevent the onset and/or progression of angle closure or treat angle-closure eyes if IOP is already elevated. Lens luxations and cataract-induced uveitis account for nearly 80% of all secondary glaucomas.

Subluxated Lenses and Anterior and Posterior Lens Luxations

Lens luxations are the most common cause of secondary glaucoma in the dog, but they also can occur secondary to buphthalmia in primary glaucoma. It is important to recognize, however, that PLL and POAG may occur in combination in dogs with *ADAMTS17* and *ADAMTS10* mutations, which makes the designation of secondary glaucoma from a lens luxation complicated and potentially tenuous. Approximately 80% of all of the secondary glaucomas are associated with lens luxations in the dog. Most of the PLLs (presumed inherited) occur in younger dogs of the terrier breeds and occur bilaterally. Many breeds have glaucoma and lens luxations as inherited and concurrent traits. Lens luxations can also develop when the globe becomes enlarged, and the lens zonules become stretched and transected. Enlargement of the globe causes progressive stretching of the zonules, which eventually breaks their attachments to the equatorial lens capsule, or infrequently causes disinsertion of their attachments to the ciliary body. In the dog with bilateral buphthalmia and lens subluxation/luxation, it may be impossible to determine if the lens luxations are primary or secondary. The breed, age of onset, and presence or

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absence of cataract development may aid in making this determination. Total luxation with normal-sized globes is more common in primary luxation syndromes, with subluxations more commonly caused by the buphthalmia from glaucoma. Lens luxations in Terriers are common, especially in young dogs (3–5 years old; Table 20.5), and these dogs may present with either unilateral or bilateral and acute or chronic secondary glaucoma (Curtis, 1990). These younger dogs with PLL also have a higher rate of bilateral involvement (86% vs. 15% with secondary lens luxations; Betschart et al., 2014).

In a study on the prevalence of primary or breed-related and secondary glaucomas in the Wirehaired Fox Terrier, this breed was diagnosed with both the primary and secondary glaucoma types (Gelatt & MacKay, 2004a, 2004b). It is obvious that many veterinary ophthalmologists have difficulty establishing whether the initial ocular hypertension is primary or related to lens displacement in this breed. In the Wirehaired Fox Terrier, Formston first associated lens luxation to the glaucoma in 90 animals with a mean age of 4.96 ± 1.43 years. None of the dogs was less than 3 years old (Formston, 1945). In another study on lens luxation in dogs, Curtis and Barnett (1983; Curtis, 1990) reported that terrier breeds with PLL were relatively young (mean age 4.7 years), younger than dogs presenting with glaucoma without lens luxations. The PLL occurred in dogs between 3 and 5 years old, while the secondary lens luxations occurred in dogs over 8 years old (Curtis & Barnett, 1983).

The secondary glaucoma associated with lens instability or dislocations may be the result of iridocyclitis from microtrauma between the unstable lens and iris, with resultant increases of AH fibrin, proteins, and inflammatory cells, which can themselves interfere with aqueous drainage, and it also may aid in formation of preiridal fibrovascular pupillary membranes as well as anterior and posterior synechiae, which further compromise AH drainage (Fig. 20.14). Anterior lens movement can mechanically impair passage of AH through the pupil, thereby causing increased posterior chamber pressure, which in turn causes anterior ballooning of the peripheral iris and reduction in the area of the ICA outflow pathways. Such movement of the iris also contributes to the formation of permanent peripheral anterior synechiae, and posterior synechia that cause a condition known as iris bombé.

Table 20.5 Inherited and breed predisposition to lens luxation in the dog.

Inherited	Breed Predisposed
Border Collie	Australian Collie
Cairn Terrier	Basset Hound
Jack Russell Terrier	Beagle
Lakeland Terrier	Chihuahua
Manchester Terrier	German Shepherd
Miniature Bull Terrier	Greyhound
Norfolk Terrier	Miniature Poodle
Norwich Terrier	Miniature Schnauzer
Scottish Terrier	Norwegian Elkhound
Skye Terrier	Spaniel Breeds
Sealyham Terrier	Pembroke Welsh Corgi
Smoothhaired Fox Terrier	Welsh Terrier
West Highland White Terrier	Toy Poodle
Tibetan Terrier	Toy Terrier
Wirehaired Fox Terrier	

Lens subluxation is first apparent with a variable-size aphakic crescent (Fig. 20.15). With loss of the zonulary support, the lens becomes unstable (phacodonesis), as does the iris (iridodonesis). The vitreous may protrude through the aphakic crescent to variable amounts. Possible mechanisms by which these unstable lenses may produce ocular hypertension include microtrauma and iridocyclitis, peripheral anterior and posterior synechiae, formation of preiridal and ICA inflammatory membranes, pupillary blockage of AH flow, and vitreous pupillary blockage, among other factors.

The completely luxated lens can remain in the patella fossa, luxate into the anterior chamber, or move posteriorly through the torn anterior vitreal face and into the vitreous (Fig. 20.16). One report suggests that ocular hypertension occurs in 73% of canine eyes with anterior lens luxations, in 43% of those with subluxations, and in 38% of those with posterior lens luxations (Glover et al., 1995a). With anterior displacement of the lens from the patella fossa, vitreous adhering to the posterior lens capsule may occlude the pupil, thereby preventing pupillary flow of AH and ballooning the base of the iris, which in turn causes ICA and sclerociliary cleft closure. This type of iris bombé often masks the basal iridal and filtration angle changes.

With posterior or vitreal luxation of the lens, the torn anterior vitreal membrane allows both liquid and formed (i.e., gel) vitreous access into the pupil and the anterior chamber. Formed vitreous may cause pupillary blockage and secondary glaucoma. It can also adhere to the posterior cornea and ICA. Blockage of the ICA with formed vitreous sufficient to increase IOP is infrequent, but blockage of the pupil from vitreous sufficient to increase IOP occurs commonly.

In POAG and PLL and associated with *ADAMTS* mutations, the defect can affect the AH outflow pathways as well as the zonules. These defects may occur together clinically, or one defect may be dominant.

DNA studies have been reported in several breeds with lens luxations (Farias et al., 2010; Gould et al., 2011; Oberbauer et al., 2008; Sargan et al., 2007). A mutation located in a 6.3 Mbp region in the central part of the chromosome 3 (-logP (max) = 6.4) was first reported in Miniature

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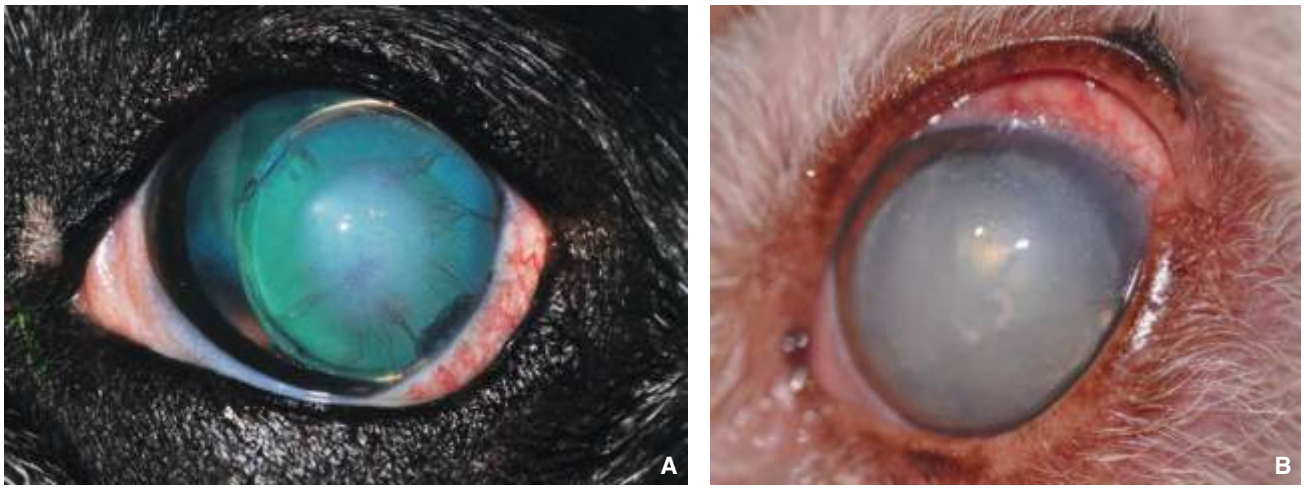


Figure 20.14 **A**. Glaucoma secondary to zonular dysplasia and an anteriorly luxated lens. The lens has migrated into the anterior chamber and is in contact with the corneal endothelium. The pupil is mydriatic and there is an obvious aphakic crescent nasal to the dislocated lens. Note the episcleral injection. **B**. Anterior lens luxation of a complete cataract with concurrent glaucoma.

Bull Terriers, Lancashire Heelers, and Tibetan Terriers (Farias et al., 2010; Sargan et al., 2007).

GWAS and fine mapping by homozygosity were used to demonstrate a GT->AT splice donor site mutation at the 5′end of intron 10 of the *ADAMTS17* gene in Miniature Bull Terrier, Jack Russell Terrier, and Lancashire Heeler (Farias et al., 2010). The predicted exon 10 skipping and resultant frame shift were confirmed with RNA derived from affected dogs. Subsequently, this c.147311G>A mutation in *ADAMTS17* was found in PLL-affected dogs of an additional 14 breeds, not all of them with terrier coancestry: Australian Cattle Dog, Chinese Crested Dog, Jagdterrier, Parson Russell Terrier, Patterdale Terrier, Rat Terrier, Sealyham Terrier, Tenterfield Terrier, Tibetan Terrier, Toy Fox Terrier, Volpino Italiano, Welsh Terrier, Wirehaired Fox Terrier, and Yorkshire Terrier (Gould et al., 2011). Genetic testing for this *ADAMTS17* mutation is currently available for at least 26 breeds (Komáromy & Petersen-Jones, 2015). *ADAMTS17* is one of 19 known mammalian members of the ADAMTS family of genes that encode secreted metalloproteases that proteolytically modify

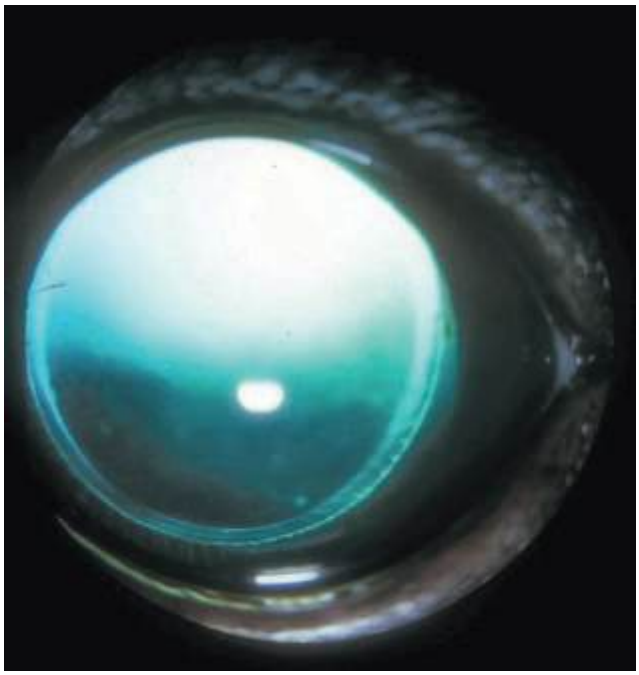


Figure 20.15 In lens subluxation, the cause of the ocular hypertension is less obvious. Intermittent pupillary obstructions of aqueous humor passage by the unstable lens and formed anterior vitreous, chronic iridocyclitis, and progressive iridocorneal angle and ciliary cleft closure, however, appear to be important.

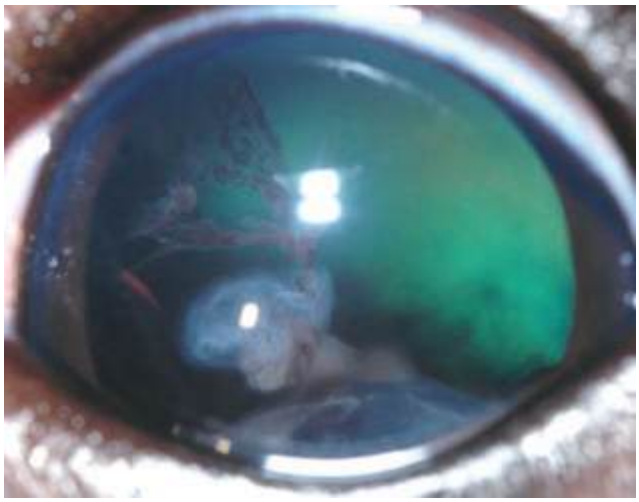


Figure 20.16 In posterior or vitreal lens luxation the lens often "falls" and lays on the floor of the vitreous body. Sometimes it adheres to the ventral retina. Often organized vitreous and even hemorrhage may be within the vitreous and its face.

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extracellular structural proteins. The exact mechanism(s) by which the *ADAMTS17* mutation affects the lens zonules remains to be determined. The nonpigmented (inner) ciliary body epithelium produces and secretes fibrillin 1, which is the important component of the zonules.

Cataractous versus "Clear" Lenses

Lens luxation may involve normal as well as cataractous lenses, but in most instances the mechanism for the zonular disinsertions differs. In terriers, Tibetan Terriers, and Border Collies, the zonules appear to possess structural malformations, and bilateral lenticular displacement occurs in dogs only a few years of age with clear lenses. IOP can remain normal or be associated with abrupt elevations (Curtis, 1990; Curtis & Barnett, 1983; Foster et al., 1986; Willis et al., 1979). In contrast, luxations of cataractous and often hypermature lenses tend to occur with inherited cataracts in older dogs (8–10 years old) of the nonterrier breeds. The zonular degenerations with advanced cataractous lenses appear to relate to the capsular and zonular changes associated with cataract hypermaturity and lens-induced uveitis. With focal zonular degenerations, small aphakic crescents develop, and partially liquefied vitreous may protrude through a defect in the anterior hyaloid membrane and into the pupil. This vitreous may also display pigment spots.

Early removal of displaced lenses, particularly in terriers, has the highest possibility of success for retention of vision and prevention of secondary glaucoma on top of POAG associated with *ADAMTS10* and *ADAMTS17* mutations. Delayed medical or surgical treatment of eyes with displaced lenses can result in secondary glaucoma. Surgical removal of subluxated lenses, anterior luxated lenses, and posterior luxated (i.e., intravitreal) lenses may be accomplished by extracapsular, phacoemulsification, or intracapsular techniques (Glover et al., 1995a; Nasisse & Glover, 1997; see Chapter 23). In contrast to the high success rate of cataract surgery in dogs by phacoemulsification, the *en bloc* removal of luxated lenses has a much higher risk of serious postoperative complications, including glaucoma and retinal detachment. If surgery is not possible, the medical approach to therapy typically involves chronic topical anti-inflammatories and anti-glaucoma medications and diligent monitoring of IOP for elevations. For eyes with posterior luxations, long-term therapy with potent miotic agents is advocated by some to keep the luxated lens behind the iris and in the vitreal chamber (Binder et al., 2007.

Zonular fiber morphology has been evaluated by light microscopy and special stains in dogs with glaucoma (Morris & Dubielzig, 2005). Zonular fibers are composed of microfibrils, whose primary components are the glycoproteins fibrillin-1 and fibrillin-2. In 63 dogs diagnosed with glaucoma secondary to lens luxation, two distinct forms of abnormal zonular fiber morphology were recognized and designated as zonular fiber dysplasia and zonular fiber collagenization. The dysplastic form had zonular protein tightly adherent to the nonpigmented ciliary body epithelium, exhibiting a distinct lamellar and cross-hatched pattern that was strongly positive to PAS and trichome stains, and staining negative to elastin stains. In the second form of zonular fiber collagenization, the abnormality was prevalent in the terrier and Shar-Pei breeds, and characterized by excessive zonular fiber that stains positive with PAS, trichrome (blue for collagen), and elastin stains, but was not tightly adherent to the nonpigmented ciliary body epithelium. The age of onset of glaucoma in these dogs also varied, with the zonular fiber dysplasia individuals developing lens dislocation at a much younger age (mean 5.2 years) compared to zonular fiber collagenization individuals (mean 8.9 years), supporting the likelihood of heritability of zonular fiber dysplasia (which has since been confirmed; see Chapter 22).

Phacomorphic Glaucoma and Intumescent Cataract

The intumescent (i.e., swollen) cataract has been associated with an acute pupillary block, phacomorphic glaucoma in the dog. This phenomenon occurs most frequently in the dog with diabetic cataracts, which may also develop anterior and equatorial capsular tears. The enlarged lens displaces the iris forward, thus increasing posterior chamber pressure and causing the base of the iris to shift forward. This in turn narrows the ICA and impinges on the ciliary cleft opening. If iridocyclitis is also present, peripheral anterior synechia may form. Treatment of this form of secondary glaucoma usually requires surgical extraction of the cataractous lens, usually by phacoemulsification, in addition to aggressive anti-inflammatory therapy.

Phacolytic Glaucoma/Resorbing Hypermature Cataracts and Lens-Induced Uveitis

Rupture of the lens capsule from ocular trauma and lens-induced uveitis from resorbing hypermature cataracts can cause the phacolytic form of open-angle glaucoma in the dog (Davidson et al., 1991a; Rubin & Gelatt, 1968). If the lens-induced uveitis is not carefully monitored and controlled medically, the filtration angle can eventually become obstructed with inflammatory cells, protein-rich AH, fibrin, and macrophages filled with lens-like material (Fig. 20.17 and Fig. 20.18). With chronic lens-induced uveitis, formation of anterior and posterior synechia, peripheral anterior synechia, and iris bombé may contribute to this phacolytic form of secondary glaucoma. The definitive treatment for phacolytic glaucoma is cataract extraction to eliminate the source of the lens protein obstructing the aqueous outflow pathways. Medical therapy with betablockers, carbonic anhydrase inhibitors (CAIs), and hyperosmotic agents is useful for reducing IOP in preparation for surgery.

Aphakic/Pseudophakic Glaucomas

The frequency of aphakic and pseudophakic glaucomas in humans after cataract surgery has gradually declined as surgical techniques have improved. In the 1950s and 1960s, the

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Figure 20.17 **A**. Glaucoma secondary to chronic lens-induced uveitis. Hypermature cataracts were present in both eyes, and the left eye has become buphthalmic and developed exposure keratitis. **B**. Glaucoma secondary to chronic lens-induced uveitis in a Labrador Retriever. The hypermature cataract is subluxated dorsally and a large aphakic crescent is evident. Note the mydriasis and episcleral injection.



Figure 20.18 Aphakic glaucoma may develop secondary to pupillary occlusion from annular posterior synechiae (iris to iris; iris to lens capsular/anterior vitreous adhesions or both), resulting in iris bombé.

incidence of these glaucomas in humans was reported to be from 0.7% to 7.0%, and even as high as 12%. In 1965, secondary glaucomas after cataract extraction were the most common cause for enucleation in humans (35% in 1954 and 31% in 1965; Tomey & Traverso, 1991). With the increased frequency of extracapsular and phacoemulsification cataract surgery and the intracapsular lensectomy for luxated lens in the dog, aphakic and pseudophakic glaucomas became more frequent as well (Biros et al., 2000; Davidson et al., 1991b; Lannek & Miller, 2001; Paulson et al., 1986). In one report, the incidence of aphakic glaucomas after cataract surgery was estimated to be 3% (Davidson et al., 1991b). In another study, in which extracapsular cataract extractions were used, aphakic glaucomas developed in 20% of the eyes (Paulson et al., 1986). Of these glaucomas, approximately 30% developed during the first 6 months after surgery; the remaining 70% developed later. Other studies have yielded a higher prevalence of secondary glaucoma after lens removal in dogs followed long term (Biros et al., 2000; Lannek & Miller, 2001).

In a report involving 172 dogs following phacoemulsification, the frequency of glaucoma increased with time, but remained under 10% overall (Sigle & Nasisse, 2006). The Boston Terrier, ACS, Cocker Spaniel–Poodle crosses, and Shih Tzus had increased risks of developing glaucoma. These same breeds are also predisposed to primary glaucoma. Also eyes with hypermature cataracts and anterior uveitis were most likely to develop glaucoma. Another report indicated about 15.8% of phacoemulsification patients may develop anterior uveitis and glaucoma in the long-term postoperative period (Johnsen et al., 2006).

These studies suggest that periodic reexamination after cataract surgery is critically important to monitor for the presence and degree of uveitis and changes in IOP. It appears that glaucoma can occur at any time following cataract surgery and its incidence may vary with surgeon experience and skill. The incidence will vary as well with duration of follow-up, as it appears that the risk of glaucoma does not disappear at any point in the postoperative period. As patient follow-ups are extended over time, a considerable number of patients are lost for a variety of medical and nonmedical reasons. In a study involving 247 dogs with 420 eyes operated, only 290 eyes were available for follow-up 3 months after surgery, 259 eyes 3–6 months after surgery, 200 eyes 6 months–1 year after surgery, 132 eyes 1–2 years after surgery, 80 eyes 2–3 years after surgery, 39 eyes 3–4 years after surgery, and 17 eyes 4 years or more after surgery (Sigle & Nasisse, 2006). This demonstrates the difficulty of conducting long-term studies, and the variable incidences of glaucoma following cataract surgery in the dog.

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Aphakic and pseudophakic glaucomas probably develop from multiple etiologies, especially occlusion of the pupil from inflammatory membranes and closure of the ICA and ciliary cleft by the formation of preiridal fibrovascular membranes and peripheral anterior synechia (Scott et al., 2013b). The glaucomas that occur secondary to pupillary blockage in the dog are usually characterized by a small pupil that is either adhered to itself or is obstructed by a membrane consisting of organized fibrin, inflammatory cells and fibrous tissue, anterior capsule remnants, artificial intraocular lens, posterior capsule, the anterior vitreous, or any combination of these. There may be iris bombé as well. The occluded pupil may be depressed and sometimes barely visible because of the iris bombé that bulges into the central and peripheral anterior chamber. IOP as measured by applanation or rebound tonometry is usually elevated, but this may not accurately reflect the profound IOP elevation in the posterior chamber behind the iris due to impaired flow of AH into the anterior chamber.

If the pupillary obstruction is acute (< 72 hours), intensive medical therapy consisting of potent mydriatics (such as 0.1% scopolamine, 10% phenylephrine), topical and systemic corticosteroids, topical and systemic nonsteroidal anti-inflammatory medications, and systemic CAIs can be attempted. Intravenous mannitol can be administered rapidly to reduce IOP, but its effects may be muted by the increased permeability of the blood–aqueous barrier due to iridocyclitis. Intracameral tissue plasminogen activator (tPA), 25–50 µg, can readily assist in the resolution of fibrin occlusion of the pupil of less than 2 weeks' duration (Martin et al., 1993).

If pupillary flow of AH is not possible, the occluded pupil can be opened by dissection with a sharp blade or hypodermic needle, laser iridotomy, iridectomy, or iridencleisis, but reformation of adhesions is common. Unsuccessful resolution of an occluded pupil and iris bombé results in chronic buphthalmia and blindness. Intraocular hemorrhage should be anticipated in these procedures, because the inflamed canine iris is highly vascular. During iridectomy, a radial (i.e., complete) or basal (i.e., peripheral) section of the iris is excised; unless they are large, these sites will eventually close, with iridal scarring and inflammatory membranes. The neodymium:yttrium-aluminum-garnet (Nd:YAG laser may be used to produce full-thickness iris holes (i.e., laser iridotomy); unfortunately, these holes will usually close within a few days.

Our impression is that aphakic glaucomas secondary to pupillary occlusion tend to occur early in the postoperative recovery period. The form of aphakic glaucoma characterized by angle closure, ciliary cleft collapse, and formation of peripheral anterior synechia develops in the dog several months or even years after successful cataract surgery. The onset of this glaucoma is usually slow and insidious, which is another reason for long-term monitoring of these patients after cataract surgery. Clinical signs may be either acute or chronic, but the elevation in IOP usually occurs over several weeks. Gonioscopic examination reveals large areas of peripheral anterior synechiae. Aggressive, long-term anti-inflammatory therapy may reduce the concurrent iridocyclitis and lower the IOP. Topical betablockers as well as topical and systemic CAIs can temporarily lower the IOP, but eventually an anti-glaucoma surgical procedure will be necessary. Aphakic glaucomas caused by either of these mechanisms may be difficult to reverse with intensive medical therapy; more often, they will require further surgery to relieve the pupillary occlusion and angle blockade.

Acute Postoperative Hypertension Following Cataract Surgery

Postoperative hypertension (POH) during the immediate postoperative period after cataract removal has been recognized for decades in both humans and dogs. In a report involving humans, the frequency of POH of > 30 mmHg 5 hours after surgery was 75%, and 21% for an IOP of 40 mmHg or greater (Vuori & Ali-Melkkila, 1993). In a clinical study involving 88 dogs undergoing cataract surgery, the incidence of postoperative hypertension of 25 mmHg or greater was 49%, of 30 mmHg or greater 34%, of 40 mmHg or greater 20%, and of 50 mmHg or greater 6% (Smith et al., 1996). Several studies have confirmed POH following lens removal; perhaps the most important variables are the times and frequencies of postoperative tonometry (Chahory et al., 2003; Miller et al., 1997). The average onset for POH of 25 mmHg or greater was 4.9 hours. The incidence of POH was not affected by lens removal technique (extracapsular or phacoemulsification); however, those eyes receiving phacoemulsification demonstrated a more rapid increase in IOP (mean 3.9 hours) than eyes receiving extracapsular techniques (mean 8.4 hours). Tonometry performed 6–12 hours after cataract surgery will miss the majority of POH occurrences. Intraocular lens placement may also cause a more rapid increase in postoperative IOP. Both older dogs and longer phacoemulsification times increase the likelihood of POH. Factors not found to correlate with development of POH included sex, stage of cataract, type of surgical procedure used, intraocular lens placement, preoperative lens-induced uveitis, posterior capsular tears, and anterior vitrectomy (Biros et al., 2000). Older Labrador Retrievers have a predisposition to both POH and subsequent glaucoma (Moeller et al., 2011).

The cause of POH is not known, but it seems to result from obstruction of AH outflow pathways. It is also unknown if dogs that develop POH will, at a future date, develop glaucoma. In an experimental study of normal dogs that underwent phacoemulsification, IOP peaked at the third postoperative hour, with a mean IOP of 49.9 ± 5.0 mmHg (Miller et al., 1997). Use of a viscoelastic agent, 2% hydroxypropyl methylcellulose, did not affect the peak or duration of POH. Results of computer-aided morphologic analysis indicated that increased IOP immediately after surgery may

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result from a significant reduction in ciliary cleft cross-sectional area and width.

The results of both of these studies confirm the value of postoperative tonometric monitoring in dogs undergoing cataract and lens removal. If the IOP exceeds "safe limits," topical or systemic CAIs (or both) or betablockers or some combination of these are recommended, because they reduce the rate of AH formation, but do not affect pupil size or increase the amount of iridocyclitis. Carbachol injected intracamerally during cataract surgery has been reported to prevent POH in dogs (Stuhr et al., 1998); however, the relative risk and benefits of a miotic agent to prevent this increase in IOP versus the intensification of postoperative uveitis must be weighted. Intracameral carbachol in Labrador Retrievers may exacerbate the incidence of POH and is not recommended for use in this breed (Moeller et al., 2011). When IOP exceeds 40 mmHg and is refractory to topical therapy and intravenous mannitol, anterior chamber paracentesis may be necessary.

Prophylactic prevention of POH (IOP 20 mmHg or higher) in 52 dogs (88 eyes) was attempted using either latanoprost, dorzolamide, or dorzolamide and timolol (Dees et al., 2017). IOP was measured 4 hours, 24 hours, 7 days, and 14 days postoperatively. IOP of 20 mmHg was recorded in 38% of the 88 eyes; IOP of 25 mmHg or higher occurred in 26% of 86 eyes. Topical anti-glaucoma medications did not change the frequency of POH significantly, but tPA administered intraoperatively appears to reduce the incidence of POH (Dees et al., 2017).

Malignant Glaucoma (Aqueous Misdirection)

Malignant glaucoma is a variation of pupillary block aphakic glaucoma, and it may develop after extracapsular extraction, phacoemulsification, or intracapsular extraction surgery (Denis, 2002; Strubbe, 2002). The pupil is usually of medium size and is obstructed with inflammatory membranes involving either the posterior lens capsule or the anterior vitreal face (with extracapsular extraction or phacoemulsification). The iris bombé may not be prominent centrally, but may place the peripheral iris in close proximity to the corneal endothelium. If the pupil is small, aqueous misdirection glaucoma may be detected by ultrasonography.

Rather than remaining in the enlarged posterior chamber behind the iris bombé, the AH is either misdirected or redirected into the vitreous body through a tear in its anterior face. As AH formation continues and the IOP rises, the AH is now misdirected into the vitreous body, thereby pushing the organized or formed vitreous further into the occluded pupil. This is a surgical condition in which the impermeable pupillary membranes must be removed by incisions with iris scissors followed by anterior vitrectomy. Once these impediments are removed, pupillary flow of AH is reestablished. Because peripheral anterior synechia may develop quickly with this disorder; however, iridencleisis may be considered.

Traumatic Glaucomas

Traumatic glaucomas, which occur secondary to blunt and penetrating trauma, are infrequent in the dog. Complete acute hyphema in the dog is usually associated with uveal inflammation and low IOP; chronic or repeated intraocular hemorrhage in the dog is more apt to increase IOP. Direct damage to the trabecular meshwork and angle recession, which occurs in humans and results in glaucoma months to years after the traumatic incident, has not been reported in the dog. Traumatic glaucomas in the dog are usually associated with intense iridocyclitis and are best managed clinically with aggressive treatment of the inflammation, prevention of peripheral anterior synechia, and control of the IOP (with CAIs). If peripheral anterior synechia develops, medical therapy becomes ineffective, and some type of anti-glaucoma surgical procedure is indicated. Intracameral tPA may be used to assist in resolution of anterior chamber fibrin following hyphema; however, recurrent hemorrhage can develop if tPA therapy is injected into eyes with acute (less than 7 days) or continuing/recurrent hemorrhages.

Uveitic Glaucomas

The iridocyclitides are a common group of intraocular diseases in the dog, and development of secondary glaucomas with these conditions is a serious complication. The inflammatory glaucomas may develop either with acute intense iridocyclitis associated with pupillary occlusion and iris bombé, with obstruction of the filtration angle with inflammatory cells, fibrin, and cellular debris, or with chronic iridocyclitis, usually from peripheral anterior synechiae, but infrequently from annular posterior synechia and iris bombé (Fig. 20.19). The most frequent cause of secondary glaucoma in the dog in North America is associated with cataract-induced uveitis that becomes chronic (Gelatt & MacKay, 2004b). The iridocyclitides may be associated with localized ocular diseases (e.g., corneal perforation, iris prolapse, iris bombé) or systemic infectious or inflammatory diseases (see Chapter 21 and Chapter 37, Part 1). Vogt-Koyanagi-Harada-like syndrome, or uveodermatologic syndrome, occurs in several Arctic breeds of dogs, and a recently discovered pigmentary dispersion and cyst formation in Golden Retrievers and Great Danes can occur as chronic intraocular inflammations. Their serious long-term complication is frequent cataract formation, which may further exacerbate secondary glaucoma (Deehr & Dubielzig, 1998; Holly et al., 2016; Sapienza et al., 2000; Spiess et al., 1998).

Several factors appear to be important in the pathogenesis of uveitic glaucomas (Moorthy et al., 1997). The trabecular meshwork may be plugged with inflammatory cells, fibrin, blood, and large molecular proteins, or it may be directly involved in the inflammation. The inflammatory cells within the trabecular meshwork may release cytotoxic substances such as arachidonic acid metabolites, cytokines, proteolytic enzymes, and oxygen metabolites (i.e., oxygen free radicals).

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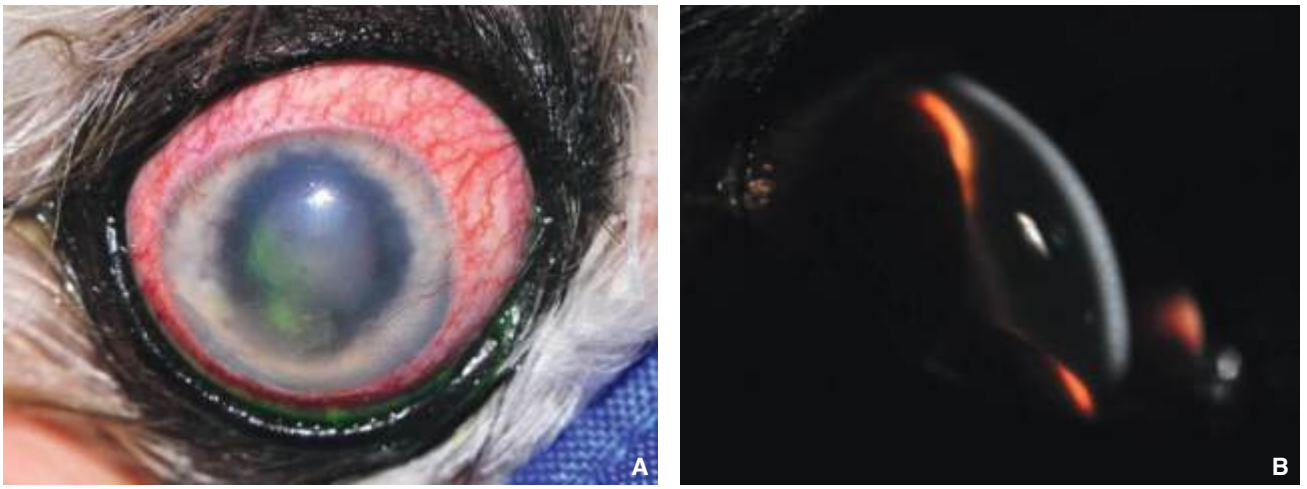


Figure 20.19 **A**. Anterior uveitis has resulted in glaucoma. There is diffuse severe episcleral injection, perilimbal corneal vascularization, diffuse corneal edema, and a superficial corneal ulcer. The pupil is mid-range in size due to the opposing influences of uveitis and glaucoma. **B**. Slit-lamp photograph of an eye secondary to anterior uveitis. Note the forward bow of the central iris. The pupil margin is directed posteriorly toward the anterior lens capsule, to which it has synechiated, while the ciliary zone of the iris is pushed forward with iris bombé.

Endogenous prostaglandins (PGs) lower the IOP by increasing the uveoscleral outflow of AH through the ciliary cleft during the first hours of an intraocular inflammation, but the prostaglandin-induced breakdown in the blood–aqueous barrier may briefly increase the IOP. Peripheral anterior synechiae may eventually occlude the filtration angle and the ciliary cleft. Posterior synechiae that encircle the pupil produce rapid development of iris bombé, which is caused by the lack of transpupillary AH flow, and increased IOP within the posterior chamber and segment. And lastly, chronic uveitis is very important risk factor.

Clinical signs of uveitic glaucoma are a combination of those of iridocyclitis and either acute or chronic glaucoma. The pupil may be normal (mid-range) in size, thus representing a balance between the effects of iridal inflammation and the IOP. Episcleral venous congestion, which is often present in the glaucoma, is partially masked by the conjunctival hyperemia (or ciliary flush) associated with the anterior segment inflammation. Likewise, corneal edema may represent a combination of the intensity of the iridocyclitis and the IOP elevation.

Elevations in IOP may be acute or may gradually elevate over several weeks or months. Tonometry is an important diagnostic tool for uveitis. Most often, iridocyclitis causes decreased IOP; however, the onset of acute iridocyclitis, within the first hours, actually produces a transient elevation in IOP associated with the release of PGs from the iris. Clinical signs of iridocyclitis with a normal IOP may indicate the early development of secondary glaucoma.

The treatment of uveitic glaucomas occurring in phakic eyes is targeted at the underlying uveitis and at controlling the IOP in order to minimize retinal and ONH damage and prevent permanent intraocular inflammation-induced adhesions. High concentrations and frequencies of topical and systemic corticosteroids and nonsteroidals are indicated. Because neither miosis nor mydriasis is desired, short-term mydriatics may be used to intermittently move the inflamed iris and pupil, and to discourage the formation of posterior synechiae. Systemic antibiotics may also be indicated if an infectious process is present or suspected. Topical antibiotics are generally not indicated unless a corneal ulcer is present concurrently. Topical and systemic CAIs are administered to, hopefully, maintain the IOP within normal limits. Surgical treatments, such as laser cyclophotocoagulation and anterior chamber shunts, may also be attempted. As in humans, however, lower success rates in uveitic glaucomas versus other types of glaucoma occur in the dog because of the inflammation and protein-rich AH.

Ocular Melanosis and Melanocytic Glaucoma

Originally described as pigmentary glaucoma in the Cairn Terrier by Covitz and colleagues (Covitz et al., 1984) and then by Petersen-Jones (Petersen-Jones, 1991; Petersen-Jones et al., 2007, 2008), the preferred term melanocytic glaucoma now seems to be more appropriate than glaucoma associated with ocular melanosis. Pigmentary glaucoma or pigmentary dispersion glaucoma in humans is characterized by a 360°, dense band of pigmentation in the trabecular meshwork, slit-like transillumination defects in the midperiphery of the iris, and a vertical band of pigment deposits on the central corneal endothelium (i.e., Kruckenberg spindle). In humans, the source of the pigment granules appears to be the posterior iris pigmented epithelium. In the dog, the pigmentation appears to relate primarily to the uveal melano-

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cytes and melanophages, not the extracellular melanin granules. Melanosis (also called pigmentary glaucoma) of the globe has been associated with this form of secondary ocular hypertension in Cairn Terriers. Glaucoma in this breed in North America has a prevalence of 1.33% (1984–1993) and 1.82% (1994–2002; Gelatt & MacKay, 2004b).

This unique glaucoma affects middle-aged to older Cairn Terriers, and it may affect one or both eyes (Fig. 20.20). It has also been reported in the Boxer and Labrador Retriever (Van de Sandt et al., 2003). In these eyes, large aggregations of melanocytes and melanophages occur within the filtration angle, episcleral and subconjunctival tissues, tapetal ocular fundus, and even in the meninges about the ONH. What initiates the unchecked proliferations of these melanocytes is unknown, but the condition may represent a diffuse type of benign iris melanin cell proliferation.

Reports focusing on ocular melanosis have provided insight (Petersen-Jones et al., 2007, 2008). In these reports, 114 Cairn Terriers were described (44 males, 67 females, and 3 dogs with gender unknown). Age of onset was quite variable and the first noticeable clinical sign was a dark-colored thickening of the basal iris. This was followed by the development of distinct episcleral and scleral pigment plaques, the release of pigment into the anterior chamber and AH, and the deposition of pigment into the AH outflow pathways (especially ventrally). Secondary glaucoma developed in the most severely affected dogs. A slow progression of pigmentation of the tapetal fundus occurred, probably from the posterior uveoscleral outflow of AH. In some dogs pigmentation adjacent to the ONH also developed. Pedigree analysis indicated a possible autosomal dominant mode of inheritance. Three affected Cairn Terriers eventually developed ocular melanomas and one mass metastasized widely. In the second report, 49 globes from Cairn Terriers with ocular melanosis were examined histologically, some by immunohistochemistry, and others by TEM. Large round pigment-laden cells were present within the anterior uvea, drainage angle, sclera, and episclera (Dawson-Baglien et al., 2019). In 39 of the 49 globes (80%) the structures of the ICA were obliterated by the infiltrating pigment cells. Some of these cells were also noted within the posterior segment (78% of choroid samples and 28% of retinas), optic nerve meninges, and periphery of the ONH. The posterior iris epithelium was present and did not appear to be involved in the proliferative process. About 20% of the affected globes also had a lymphocytic-plasmacytic infiltration of the anterior uvea and formation of preiridal fibrovascular membranes. Ultrastructurally, the pigment cells were mainly melanocytes with some macrophages. Many of the pigmented cells were immunoreactive to HMB45 (antibody for gp100 localized in stages II and III melanosomes), and some were MITF and vimnetin positive.



Figure 20.20 Pigmentary glaucoma in the Cairn Terrier. Note the hyperpigmented uvea and pigment deposition in the sclera.

Onset of chronic glaucoma appears to be slow and associated with the accumulation of pigmented cells within the filtration angle and scleral venous plexus. Some free melanin granules occur and are phagocytized by the wandering macrophages and trabecular endothelia within the outflow pathways. Medical and surgical treatment of this secondary glaucoma has not been successful in the long term, because the proliferating melanocytes and melanophages eventually completely obstruct any surgical anterior chamber bypass. Eleven potential candidate genes have been eliminated for ocular melanosis (Winkler et al., 2013). DNA studies to date have not identified the disease-causing genetic mutation.

A four-stage grading system of ocular changes occurring in this condition has been developed (Petersen-Jones et al., 2007). Stage 1 describes early-affected animals with a characteristic dark-colored, donut-shaped thickening of the iris root. Stage 2 includes animals with iris thickening and small pigment plaques on the sclera. These spots are initially spicule shaped, but progress to circular foci. Stage 3 consists of more extensive scleral pigment plaques accompanying a "lumpy, bumpy" ciliary iris and thinning of the pupillary zone. Some pigment may be noted on the ventral pectinate ligaments, and in some instances on the corneal endothelium. Some animals will exhibit signs of anterior uveitis and may have periods of IOP elevation. Progression to Stage 4 involves the development of overt and chronic signs of glaucoma and further increase of pigment deposition in the ICA and in the sclera.

Pigmentary Uveitis and Glaucoma in the Golden Retriever

An angle-closure/occlusion secondary glaucoma has been associated with pigment dispersion and iris and ciliary body cysts in Golden Retrievers (Deehr & Dubielzig, 1998; Esson et al., 2009; Sapienza et al., 2000). The mean age of the affected dogs is 7.6 years. Early in the disease, affected eyes demonstrate iridal hyperpigmentation, pigment deposition

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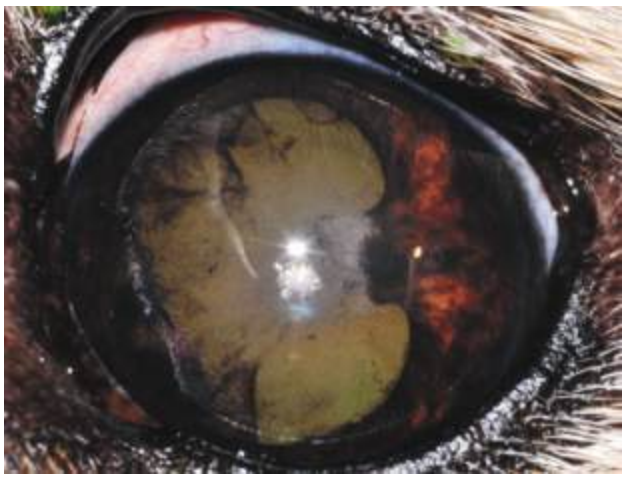


Figure 20.21 Glaucoma secondary to chronic pigmentary uveitis in a Golden Retriever. Note the multifocal posterior synechiae, pigment deposition on the anterior lens capsule, immature cataract, and corneal degeneration.

on the anterior lens capsule, cataract formation, and web-like strands of opaque material within the anterior chamber (Fig. 20.21). The clinical syndrome is characterized by the formation of thin-walled membranes within the posterior chamber, proteinaceous exudation, and pigment dispersion, which appears to cause the glaucoma and cataract formation. These membranes are typically light brown or red; some appear as collapsed cysts within the posterior chamber. Pigment is deposited on the lenticular, iridal, and corneal endothelial surfaces. The time from diagnosis of the syndrome to the development of overt glaucoma is generally about 5 months. All affected globes have free pigment within the trabecular meshwork.

In a study of 830 Golden Retrievers in western Canada, the prevalence of this disease was about 5% (iridociliary cysts in 4.8% and pigmentary uveitis in 5.9%). The incidence of pigmentary uveitis increased with age. Pigmentary/cystic glaucoma developed in 44.9% of the eyes with pigmentary uveitis. Pedigree analysis suggested an autosomal dominant mode of inheritance with incomplete penetrance (Holly et al., 2016).

Histopathologic examination revealed that the anterior uveal cysts were lined by thin cuboidal or simple squamous epithelium, PAS-positive basement membrane–like protein, and sometimes collagen or hyaluronic acid. Affected globes had little or no evidence of inflammation. Nearly all cysts remain in the posterior chamber. The thin cellular wall of the cysts stained positive with Vimentin, NSE, and S-100 in all globes. This staining pattern is consistent with a ciliary body epithelial cell origin; however, one in three of the cysts also stained weakly positive for cytokeratin, which could out rule out an iridociliary epithelial origin. They may be stretched across of the anterior face of the vitreous and some were attached to the anterior lens capsule. Peripheral anterior synechiae formation occurred in about 30% of globes; posterior synechiae were noted in about 50% of globes. Preiridal fibrovascular membranes were present in about 50% of globes.

The pigment dispersion seems to cause the elevation in IOP. The cysts may compress focally the ICA and ciliary cleft, or release their own contents to cause angle closure by mechanical and inflammatory means. The toxic effects of the contents within the iridociliary cysts upon the trabecular meshwork is unknown. Medical and/or surgical treatment of this syndrome may lower IOP and prolong vision for a period of time, but eventually fails. A secondary glaucoma occurs in the Great Dane and the American Bulldog, and is similar but perhaps not identical to the disease in the Golden Retriever (Pumphrey et al., 2013b; Spiess et al., 1998). Additional information on this syndrome can be found in Chapter 21.

It is important to recognize that not all Golden Retrievers that have anterior uveal cysts will develop or are at risk for the development of pigmentary uveitis. Many Golden Retrievers have anterior uveal cysts unrelated to this more serious condition. Careful examination looking for pigment sloughing and inappropriate pigment deposition is critical.

Intraocular Neoplasms and Glaucoma

The most frequently occurring primary intraocular neoplasms in the dog are melanomas (Wilcock & Peiffer 1986), followed by adenomas and adenocarcinomas of the ciliary body and iris. Not infrequently, the presenting clinical signs of these anterior segment tumors are those associated with secondary glaucoma, iridocyclitis, hyphema, or some combination of these (Fig. 20.22). Metastatic intraocular neoplasms, often lymphoma or an adenocarcinoma, also frequently involve the iris and ciliary body.

Glaucomas secondary to these neoplasms usually result from direct infiltration of the filtration angle, obstruction of the angle by tumor-associated inflammatory products and peripheral anterior synechiae, or secondary preiridal membrane formation. Rapidly growing neoplasms often produce glaucoma, and tumor-related necrosis may produce a secondary iridocyclitis.

In the clinical management of these patients, gonioscopy, indirect ophthalmoscopy of the peripheral ocular fundus, and ultrasonography with color Doppler imaging are used to carefully define the borders of the neoplasm. A systemic medical workup is performed to look for the presence of preexisting metastases. Most of these tumor-induced glaucomas are treated with enucleation, but local iridocyclectomy, either with or without scleral grafts, may successfully remove smaller neoplasms and preserve vision.

Glaucomas Secondary to Silicone Oil and Rhegmatogenous Retinal Detachments

Glaucoma may be observed in the dog occurring secondary to silicone oil in the anterior chamber that has migrated following surgical reattachment of rhegmatogenous retinal detachments. Silicone oil is used in the repair to tamponade

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Figure 20.22 **A**. Glaucoma secondary to an intraocular mass. Note the raised pigmented lesion posterior to the temporal iris that is displacing the lens. **B**. Glaucoma secondary to intraocular lymphoma. The iris is swollen with foci of hemorrhage and neovascularization. The dyscoria is suggestive of posterior synechiae. Diffuse corneal edema is also present.

the detached retina into contact with the RPE. Shifting of the oil from the vitreous into the anterior chamber, which occurs frequently in both aphakes and pseudophakes, increases the IOP by physically obstructing the aqueous outflow pathways. Treatment consists of removing the oil from the anterior chamber.

The association between rhegmatogenous retinal detachments and elevated IOP in humans was described in 1972 (Netland et al., 1994) and later reported in the dog (Smith et al., 1997). Nonrhegmatogenous retinal detachments in the dog are usually associated with normal or low IOP (i.e., ocular hypotony), presumably resulting from increased uveoscleral AH outflow. Canine rhegmatogenous detachments, however, especially in those dogs with giant retinal tears, may release rod and cone outer segment fragments into the subretinal fluids and vitreous, which eventually enter the anterior chamber. This cellular debris accumulates in the AH outflow pathways and elevates the IOP. Rod and cone outer segments may be demonstrated in the AH at the trabecular meshwork. Reattachment of these giant tears prevents further anterior movement of the outer segments and lowers the IOP; however, the risk of formation of preiridal fibrovascular membranes and subsequent secondary glaucoma remains high in these individuals.

Congenital Glaucomas

Extensive goniodysgenesis or trabecular maldevelopment is rare in the dog. When present, however, it may be unilateral or bilateral, and it occurs as an isolated defect or with other systemic anomalies. When present, elevations of IOP occur early in a puppy's life (usually 3–6 months of age), and the primary complaint is one of rapid and often dramatic globe enlargement (Fig. 20.23). This often severe buphthalmia occurs because of the abundance of elastin fibers within the immature sclera. If the IOP can be rapidly reduced to a normal level, the globe may return to near-normal size. The longer the buphthalmia persists, however, the less likely it is that a return to approximately normal globe size will result. This rapid buphthalmia somewhat protects the ONH and retina against the elevated IOP, and vision may be maintained longer than expected. Histopathologic results of the few globes available with canine congenital glaucomas have revealed multiple anterior segment and AH pathology abnormalities, including within the trabecular meshwork (Smith et al., 1993; Strom et al., 2011a).



Figure 20.23 Congenital glaucoma in a Parsons Russell Terrier puppy. Note the profoundly enlarged globe, episcleral injection, and keratitis. Young animals will often develop marked buphthalmia very quickly when intraocular pressure is elevated.

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Medical and Surgical Treatment of the Canine Glaucomas

The optimal plan(s) for clinical management and preservation of vision for the different forms of the canine glaucomas have not been developed. Lowering IOP remains the only available treatment. In primary or breed-related glaucomas, the genesis of the disease continues despite treatment, even in the face of control of IOP. Once medical control of IOP is achieved, there remains a great need for diligent regular monitoring, because these conditions do not remain static. The need to increase the frequency of medications or to institute combination therapy is expected. The choice of medical or surgical treatment, or most frequently a combination of both modalities, is based on the absence or presence of vision at initial presentation, the interest and ability of the owner to treat the glaucoma, the projected costs, and the temperament of the patient.

Target, Safe, and Diurnal Intraocular Pressure

IOP has been firmly established as the primary, only treatable risk factor for the development of glaucomatous optic neuropathy. Other factors are also important, but the higher and/or longer the IOP elevation, the greater the risk and severity of optic nerve damage. Lowering the IOP is critical for maintaining both vision and quality of life. Establishing a "target" or "safe" IOP for each canine eye implies an IOP reduction to levels that reduce the RGC loss from glaucoma to normal, age-related levels of RGC loss, and achieving an IOP that maintains the threshold number of RGCs necessary for vision (Jampel, 1997). Target IOP can be set by lowering the pressure to a given IOP, or it can be reduced by a given percentage. The greater the likelihood of future damage from glaucoma or the greater the amount of preexisting damage from glaucoma, the lower the target IOP should be set. The target IOP should relate to the maximum quality of life to be derived from preserving vision and comfort in the absence of side effects of therapy. A weakness of the target IOP concept is that because we are only able to obtain single, infrequent IOP tonometric measurements in the dog, we do not know the true IOP level. In the dog, setting the target IOP pressure at 20 mmHg or lower is reasonable, but if progressive loss of vision occurs it should be lowered, probably even lower than what is considered the normal range of IOP.

A reasonable population distribution of IOP (mean ± 2 SD) in the normal dog based on the two largest studies is 8–30 mmHg and, on clinical experience, is 12–25 mmHg (Gelatt & MacKay, 1998a). The mean and SD of IOP in the normal dog represent the real variation in IOP, variations in tonometers, and daily (i.e., diurnal) variation. Previous results in normal dogs indicate that diurnal IOP fluctuates by 2–4 mmHg, with the higher IOP occurring in the morning and the lower IOP in the early evening; in dogs with POAG, however, these diurnal IOP variations are greater, often ranging from 6 to 10 mmHg, even in dogs that have not yet expressed sustained IOP elevations in untreated eyes (Gelatt et al., 1981a).

What Is a "Safe" IOP?

The scleral lamina cribrosa is a zone of pressure transition for the optic nerve axons. The IOP largely affects optic disc tissue pressure over the most anterior 100 µm of the ONH tissue. The axoplasmic flow of these axons is tenuous at even normal IOPs. The axons leave the eye under the influence of the IOP and pass through the decreasing tissue pressures of the lamina to come under the influence of the retrolaminar tissue pressure (RLTP). The RLTP (mean canine RLTP 7 mmHg) directly relates to the cerebrospinal fluid pressure in the dog (Morgan et al., 1995).

The normal canine retina begins to show electrophysiologic evidence of effects from elevated IOP at 33 mmHg (under general anesthesia the baseline IOP is usually 10–12 mmHg; Hamor et al., 2000), and oscillatory potential parameters show changes in latency and amplitude at this IOP as well. Results of ONH autoradiography of normal dogs indicate that 10% of axons have mildly obstructed axoplasmic flow at an IOP of 25 mmHg (Williams et al., 1983), and this increases to near 100% at an IOP of 50 mmHg. Thus, the optic nerve axons are in a precarious functional state even at relatively normal IOPs in normal dogs. Beagles with hereditary glaucoma have mild to moderate obstruction of the axoplasmic flow of 87% of their optic nerve axons at an IOP of 30–35 mmHg (Samuelson et al., 1983). Settling for a goal of 30 mmHg in a glaucomatous eye will not often prevent damage to the optic nerve axons.

Medical Therapy for Intraocular Pressure Control

Therapy for canine primary glaucomas is difficult to rationalize and apply when we do not yet understand the initiating events that result in compromised outflow of AH, the mechanisms by which these events lead to aqueous outflow obstruction, or even the nature of the obstruction itself. Thus, it follows that we have, at present, no means of detecting the initiating events in clinical patients, nor do we have treatments to prevent the outflow obstruction and optic nerve atrophy. Therefore, at present, there is no cure for the glaucomas. An ideal treatment or "cure" would require treatment of the optic nerve damage sustained in glaucoma, with subsequent reversal of visual field defects. This is currently not possible, so the aims of therapy are to slow the progress of the disease, maintain vision as long as possible, and keep the patient comfortable, as glaucoma can be a profoundly painful condition.

Treatment of the different types of canine glaucoma has, as its paramount purpose, maintenance of vision and IOP within the normal range to prevent further damage to the

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optic nerve and retina. Elevated IOP is the risk factor that is necessarily the only target of therapy. Unfortunately, most canine glaucomatous patients present with the condition at an advanced stage in at least the first eye, and the therapeutic goal may simply be a pain-free eye that requires minimal medical care; the fellow eye may require the more intensive treatment regimen.

No single treatment regimen for canine glaucoma is possible, because there are so many different types of glaucoma with different etiologies and stages of presentation (Table 20.6). In secondary glaucomas, the initiating cause must be identified and, if possible, either removed or suppressed. Medical treatment of canine glaucoma is a critical aspect, because surgical procedures often still require concurrent medical therapy. Medical therapy for narrow- and angle-closure glaucomas is usually short term when employed alone, because eventually the outflow becomes so impaired that drug-associated changes in aqueous formation and outflow are inadequate. After anterior chamber bypass surgeries, however, some medical therapy may be necessary to maintain the IOP within a target zone. As with cataract surgery in the dog, results of some clinical studies suggest that the earlier in the glaucoma process the surgery is performed, the higher the long-term success rate at controlling IOP and maintenance of vision (Jampel, 1997). Medical therapy for the glaucomas can also be quite expensive; additional information on these drugs may be found in Chapter 8, Part 5.

Table 20.6 Treatment strategies for the canine glaucomas.

Initial Medical Intraocular Pressure (IOP) Control: Is the eye blind or visual?
Intravenous mannitol; anterior chamber paracentesis if mannitol fails
Prostaglandins
Miotics
Adrenergics – beta-blockers
Intravenous acetazolamide
Corticosteroids possibly
Neuroprotective drugs
Short-Term IOP Control
Prostaglandins
Miotics
Adrenergics – beta-blockers
Carbonic anhydrase inhibitors (CAIs) – topical and parenteral
Prostaglandins
Neuroprotective drugs
Surgery/laser
Long-Term IOP Control
Shunt surgery/laser cyclophotocoagulation
Supplement with medical control:
Miotics/prostaglandins
Adrenergics
CAIs – topical
Neuroprotective drugs

The mainstay of medical therapy for glaucomas is the lowering of IOP by targeting AH dynamics, either by increasing outflow or by decreasing the production of AH. More specifically, the targets of medical therapy include (1) improving conventional AH outflow (through the corneoscleral trabeculae); (2) improving unconventional AH outflow through the uveoscleral outflow pathways; (3) decreasing active AH production (direct action on the nonpigmented ciliary body epithelium); (4) decreasing IOP by an osmotic imbalance between the intraocular tissues (mainly vitreous) and intraocular fluids and the circulatory system; (5) decreasing blood flow to the ciliary body processes; and combinations of these. Medical treatment of primary glaucomas often includes short-term administration of a single drug, or combination of drugs, to maintain the IOP within normal limits (usually 20 mmHg or less) and the long-term administration of combinations of drugs to supplement available filtering surgeries and cyclodestructive procedures. Prophylactic treatment of fellow eyes in dogs presenting with unilateral primary glaucoma appears to delay the onset of glaucoma in these eyes for several months or longer, and is highly recommended (Miller et al., 2000). Treatment of normotensive fellow eyes in dogs presenting with unilateral PACG using either topical 0.5% beta-blocker (betaxolol) or 0.25% demecarium bromide with a topical steroid resulted in a median time to development of clinical signs of 30 months in one study (Miller et al., 2000). In a smaller study, treatment of fellow eyes with topical CAIs did not appear to delay IOP elevation (Stavinohova et al., 2015). While medical therapy of POAG in humans is generally quite successful, treatment of PACG in humans is less rewarding; vision is often impaired or lost on the initial presentation to the ophthalmologist (Aung et al., 2004). Outcomes in dogs are similar, although POAG canines have a greater risk of vision loss than do their human counterparts, due to delayed disease diagnosis and more rapid disease progression. PACG in the dog has a very poor prognosis for sight retention and IOP control overall. As glaucoma progresses, the intensity of medications will need to increase and eventually include a combination of drugs affecting different parts of the AH dynamics.

Drugs to Increase Conventional Aqueous Humor Outflow

Therapy for glaucomas has gradually changed in both humans and dogs, as more effective drugs with fewer side effects have been introduced. Parasympathomimetics or miotics can be used in most types of canine glaucomas, except for those associated with severe inflammations of the anterior segment. They are frequently combined with CAIs and beta-adrenergic antagonists in long-term medical treatment of the primary glaucomas. Cholinergic miotics produce pupillary constriction, ciliary musculature contraction, and

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increased outflow facility of the AH through the trabecular meshwork. Miotics also produce vasodilation of the blood vessels of the conjunctiva, iris, intrascleral plexus, and aqueous veins. Miotics can reactivate latent iritis, intensify concurrent iritis, and increase the protein content of the AH. The two most frequently used miotics in the dog are currently pilocarpine and demecarium bromide.

Pilocarpine has been used topically for the treatment of human glaucoma for more than a century, and in the 1950s through 1970s was the topical drug of choice. It was largely replaced by the introduction of beta-blockers in 1978–1979. Pilocarpine mimics acetylcholine at the iridal sphincter and ciliary body muscle end plates. The commercial solutions were available in many concentrations (0.25%–10%), even combined with 1% and 2% epinephrine, but are quite acidic (pH 4.0–5.5) and irritating, resulting in considerable blepharospasm, nictitans prolapse, and conjunctival hyperemia in the dog. The pH in the commercial solutions was used to prolong shelf life; pilocarpine solutions at pH 7 decrease IOP to a greater degree, but are not particularly stable (Carrier & Gum, 1989; Gelatt et al., 1983; Gwin et al., 1977; Whitley et al., 1980). Pilocarpine as sole therapy is no longer in favor nor recommended. Pilocarpine's side effects in the dog made drug instillations progressively more difficult long term. Carbachol is similar to pilocarpine but less lipid soluble, and never became very popular for topical use. It was available in 0.75%–3% solutions, and acted similarly to pilocarpine in normal and glaucomatous dogs. Since about 2000, the PGs have largely replaced this group of drugs. Now topical pilocarpine is very limited in its availability and must usually be compounded (thereby greatly increasing its cost).

Anticholinesterase miotics, such as demecarium bromide, inhibit the enzyme cholinesterase, thereby prolonging the action of locally produced acetylcholine at the motor end plates (Gum et al., 1993a). Demecarium bromide 0.125%–0.25% is a long-acting anticholinesterase inhibitor, and has been used in dogs to control IOP in eyes with posterior lens luxations long term (Binder et al., 2007). It is not currently commercially available and must be compounded.

Drugs to Reduce Aqueous Humor Formation

Adrenergics (beta-blockers and alpha-agonists) lower IOP in the dog, but they must be combined with other drugs to achieve maximal effect. Epinephrine, an alpha- and beta-adrenergic agonist, lowers IOP in normal as well as glaucomatous canine eyes when delivered as 1% or 2% solution (Gwin et al., 1978). Dipivalyl epinephrine, which is an epinephrine prodrug, is more lipophilic than epinephrine and possesses a greater ability to penetrate the cornea. Once in the cornea, dipivalyl epinephrine is converted to epinephrine and has both greater potency and less local toxicity than epinephrine. These agents are administered clinically 2–4 times daily and always combined with other topical drugs. Adrenergic agonists may produce local conjunctival irritation, as evidenced by tearing, conjunctival hyperemia, and occasional chemosis. Since the introduction of PGs in the 1990s, use of these adrenergic agonists has become very limited.

Topical beta-antagonists such as timolol, betaxolol, and levobunolol were introduced in the late 1970s and they quickly became the first-line therapy for the clinical management of POAG in humans. They are still used very frequently. In normotensive and glaucomatous Beagles, 0.5% timolol 2 times a day lowers IOP by approximately 5–7 mmHg (Gum et al., 1991b; Wilkie & Latimer, 1991). Timolol can adversely affect the cardiac and respiratory systems, and should be used with care, especially in very small dogs and cats with asthma. Timolol is usually combined with other drugs, often dorzolamide (Plummer et al., 2006), and instilled 2–3 times daily.

Apraclonidine, an α_2-adrenergic agonist, in normal dogs produced mydriasis with inconsistent decreases in IOP and bradycardia (Miller et al., 1996). This agonist lowers IOP by reducing the formation of AH through reductions in cyclic adenosine monophosphate formation and reduced blood flow to the ciliary body, with no effect on outflow facility. Brimonidine tartrate (0.2%) is another α_2-agonist that lowers IOP by reducing AH formation and increasing uveoscleral outflow. In the dog, brimonidine lowers IOP only slightly and must be combined with other ocular hypotensive agents if used (Gelatt & MacKay, 2002a).

Drugs to Increase Uveoscleral Aqueous Humor Outflow

PGs have been studied for nearly 30 years for their roles in ocular inflammation, but in the late 1980s it was discovered that very low concentrations of these drugs applied topically to the eye lowered IOP (Bito, 1986). Species differences in ocular hypotensive effects among humans, nonhuman primates, dog, cats, and other species have been demonstrated with topical PGA, PGE, and PGF and their analogues. PGF analogues are the most commonly employed topical antiglaucoma drugs, and they are effective in both humans and dogs (Gum et al., 1991a). PGs seem to lower IOP by increasing the uveoscleral or unconventional AH outflow, although there is tonographic evidence that trabecular or conventional outflow may be also increased in some species (Toris & Camras, 1997). PGF also produces miosis in dogs that is of shorter duration than the decline in IOP, which may change the trabecular or conventional AH outflow and be responsible for the acute IOP-lowering effect. Both PGA and PGF analogs can markedly lower IOP (decrease as high as 40–50%) in dogs (Gum et al., 1991a). With $PGF_{2\alpha}$ the reduction in IOP in normal dogs was about 9 mmHg (Studer et al., 2000) and in glaucomatous dogs 19 mmHg (Gelatt & MacKay, 2001b). In glaucomatous Beagles, latanoprost, travoprost, bimatoprost, and unoprostone significantly lower IOP (Gelatt & MacKay 2001b, 2002b, 2004c; Ofri et al., 2000). Recent investigations into this effective group of drugs have

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resulted in additional topical PGs, including tafluprost (Alario et al., 2015), PGE and PGA analogues, and latanoprostene bunod, a nitric oxide–releasing PG (Cavet & DeCory, 2018; Krauss et al., 2011).

Ocular side effects after chronic administration of latanoprost in humans, nonhuman primates, and pigmented rabbits include increased iridal pigmentation, hypertrichosis, and pigmentation of the eyelashes. The hypertrichosis results in thicker and longer eyelashes and a separate commercially available preparation has been marketed for cosmetic purposes (Giannico et al., 2013). As anti-glaucoma therapy in the dog often requires multiple drugs to lower IOP to acceptable levels, PGs can be combined with topical beta-antagonists and CAIs (both topical and systemic). Latanoprost seems to produce very few systemic effects, but is generally avoided in eyes with active anterior uveitis and anterior lens luxations.

Drugs to Reduce Active Aqueous Humor Formation

Systemic and topical CAIs reduce active AH formation by inhibiting the carbonic anhydrase enzymatic processes within the nonpigmented ciliary body epithelium (Skorobohach et al., 2003). These drugs do not have an effect on outflow facility. In the dog, systemic and topical CAIs can reduce IOP by 20%–30% (Gelatt et al., 1979; King et al., 1991). The maximal effect usually occurs 4–8 hours after oral administration, and the ocular hypotensive effects of these drugs do not depend on diuresis. Systemic CAIs have been used in the treatment of all types of glaucoma in humans, but in the 1990s were nearly discontinued in humans because of serious side effects. The systemic preparations have been replaced by equally effective topical CAIs that have considerably fewer adverse effects, including dorzolamide and brinzolamide. Topical dorzolamide is usually administered every 8 hours or every 12 hours. As intraocular penetration is slow, the maximum reduction in IOP may not occur until after 4–5 days of instillation (King et al., 1991). Low doses of systemic CAI may be used to supplement topical instillations of dorzolamide to ensure maximum reductions of IOP (Gelatt & MacKay, 2001a).

CAIs are useful for both short- and long-term management of canine glaucomas and are generally added to the topical treatment regimen of PGs, timolol, pilocarpine, epinephrine, or anticholinesterase miotics. The combined effects of these agents are additive, and in some cases synergistic, and can usually maintain IOP within the safe range for a period of time (Plummer et al., 2006). There are few reports of corneal thickening in the dog, probably due to slight corneal edema from reduced corneal endothelial active transport of water from the cornea stroma (Beckwith-Cohen et al., 2015).

Drugs to Lower Intraocular Pressure by Osmotic Effects

Hyperosmotic agents are used systemically in the initial treatment of acute high-pressure glaucoma in the dog to lower IOP as rapidly as possible, and before surgical procedures for glaucoma to ensure a hypotonic globe. Systemic hyperosmotic agents commonly used include intravenous mannitol and oral glycerol (Lorimer et al., 1989). With increased blood osmolarity, water is removed from the AH and the vitreous body, thus reducing the IOP and the volume of the vitreous body. Integrity of the blood–aqueous barrier is important for these drugs to be effective; presence of an iridocyclitis may reduce their ocular hypotensive effects. Ocular hypotension becomes evident within 30–60 minutes and lasts for at least 5 hours. The duration of effect relates to the rapidity of administration and the dose. These drugs are less commonly employed due to the rapidity of effect and ease of administration of topical PGs for acute congestive glaucoma.

Other Drugs

An additional group of drugs, not currently available for practice, are those that act centrally (acting on the brain), like the cannabis derivatives. The exact mechanism by which IOP is lowered with such a substance is not known. A topical formulation of 2% delta-9-tetrahydrocannabinol (THC) has been shown to lower IOP in normal dogs by between 15% and 21%, suggesting that there are active cannabinoid receptors in the eye that may alter AH dynamics. It is likely that THC would lower IOP to a greater extent in glaucomatous animals; however, this is unlikely to be an improvement over existing IOP-lowering medications (Fischer et al., 2013).

Antifibrin and Cytotoxic Drugs

Intracameral injections of tPA, 25–50 µg, will quickly dissolve fibrin of less than 10–14 days' duration within the anterior chamber and pupil (see Chapter 8, Part 4; Martin et al., 1993; Sidoti et al., 1995). The value of tPA in the different filtering and anterior chamber shunt surgeries for removing fibrin obstructions and postoperative ocular hypertension are unequaled, and tPA represents a major advance in the success of these surgeries.

While AH outflow occurs, in part, through the posterior supraciliary and choroidal spaces and does not incite inflammation, once AH enters the subconjunctival and/or retrobulbar tissues, an inflammatory response occurs. Control of this persistent inflammatory response may greatly increase the success of surgical AH bypasses. Cytotoxic anti-fibrosing drugs such as mitomycin-C and 5-fluorouracil may maintain the permeability and delay or prevent the scarring of subconjunctival aqueous outflow blebs adjacent to gonioimplants. Mitomycin, 0.2–0.4 mg/mL, is administered for 5 minutes intraoperatively to the episcleral surgical site via a surgical cellulose sponge, and then the area is profusely irrigated (Maggio & Bras, 2015; Tinsley et al., 1995). The conjunctival edges of the surgical wounds should not be touched with mitomycin, and high doses of mitomycin may diffuse through the sclera and lower the rate of AH formation by

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affecting the ciliary body. The loss of function of postsurgical gonioshunt blebs long term remains a major problem in the dog and requires further investigation. Control of this persistent inflammatory response may greatly increase the success of surgical AH bypasses.

Surgical Therapy for Intraocular Pressure Control

Surgical procedures for treatment of the primary glaucomas in the dog are divided into two types: those that construct alternate pathways of drainage within or to the outside of the eye, and those that decrease the formation rate of AH by destroying part of the ciliary body (Gelatt & Gelatt, 2011). Procedures to increase AH outflow include iridencleisis, corneoscleral trephination, cyclodialysis, combined iridencleisis and cyclodialysis, posterior sclerectomy, and anterior chamber shunts (i.e., gonioimplants). Techniques to reduce AH formation by partial destruction of the ciliary body include cyclocryothermy, cyclodiathermy, and transscleral or endoscopic cyclophotocoagulation. The most frequently used and effective procedures are anterior chamber shunts (i.e., gonioimplants) without or combined with destruction of the ciliary body processes by some form of laser cyclophotocoagulation (Bentley et al., 1999; Bras & Maggio, 2015; Cook, 1997; Garcia et al., 1998; Graham et al., 2017a, 2018; Maggio & Bras, 2015; Sapienza & van der Woerdt, 2005; Westermeyer et al., 2011). Other surgical techniques have fallen out of favor because of poor results. However, there is no gold standard surgical option that will be effective for all cases. Hence, the treatment strategy for canine glaucomas is constantly evolving.

All postoperative cases, regardless of the technique used, will require supplemental postoperative medical therapy. Anterior chamber shunts are usually reserved for glaucomatous eyes that are visual or have the potential for vision and are often combined with laser therapy. Laser cyclophotocoagulation may be performed via the transcleral route or the endoscopic approach. The transcleral approach is considerably less invasive, but also less precise. The endoscopic approach generally requires removal of the lens, cataractous or not, via phacoemulsification. Laser cyclophotocoagulation may be used in visual or blind glaucomatous eyes to reduce or eliminate the need for topical and systemic medications and to prevent pain, but the endoscopic route is usually reserved for visual globes or eyes with cataract that are considered high risk for the development of glaucoma in the postoperative period. The optimal canine candidates for anti-glaucoma surgery are visual patients with early glaucoma, no iridocyclitis or lens subluxation, and normal-appearing optic discs. Patients with vision and with IOP that is increasing despite maximum levels of medical therapy are also good candidates. Surgical treatments for advanced glaucomas not under adequate medical control and often without the possibility of restoration of vision require different strategies.

For enlarged blind and buphthalmic glaucomatous eyes, salvage procedures such as evisceration with placement of an intraocular prosthesis, chemical ablation with either gentamicin or cidofovir, or enucleation are recommended. Globes with exposure keratitis and corneal ulcerations should be enucleated, as they tend not to heal well following placement of an intraocular prosthesis.

Reasons to Operate Early

Higher success rates may result when filtering techniques and gonioimplants for the canine glaucomas are employed early in the disease process. Reasons for this apparently higher success rate include the following:

- Some AH outflow still remains.
- Damage to the retina and ONH is not advanced, and vision is present.
- The likelihood of lens subluxation, buphthalmia, peripheral anterior synechiae, and ciliary cleft collapse is reduced.
- The incidence of the complications of concurrent iridocyclitis, preiridal rubeosis, and vitreous within the posterior or anterior chamber (or both) is reduced.
- There is preliminary evidence that surgical treatment of early glaucomatous globes is more successful than for the advanced stages.

In addition, the AH of humans with primary glaucoma, as well as of those with uveitic glaucoma, seems to stimulate proliferation of the subconjunctival and sub-Tenon's fibroblasts more than normal AH does. This may relate to higher levels of growth factors and glycoproteins/glycosaminoglycans in chronically affected and perhaps inflamed eyes.

Preoperative Treatment

Preoperative considerations in treatment of the primary glaucomas include:

- Preoperative control of IOP to a near-normal level, if possible.
- Suppression of any concurrent anterior segment inflammation with corticosteroids and nonsteroidal agents.
- Maintenance of desired pupil size.
- Dehydration and reduction in size of the vitreous with osmotic agents.

IOP should be reduced to the low–normal range in patients before glaucoma surgery. Medical therapy and paracentesis may be necessary to lower the IOP to between 10 and 20 mmHg. If the IOP is 30 mmHg or greater after intensive anti-glaucoma medical therapy, anterior chamber paracentesis is recommended to prevent further damage to the ocular tissues (Fig. 20.24). Surgical procedures that abruptly lower the IOP can be associated with acute

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Figure 20.24 Anterior chamber paracentesis may be necessary as part of the initial medical therapy for refractory high intraocular pressure (IOP). It is indicated when IOP remains unchanged after a few hours of intense topical and intravenous osmotic therapy.

intraocular hemorrhage, exacerbated uveitis, and even retinal detachment.

Many types of canine glaucoma also exhibit concurrent iridocyclitis, which may also be a primary factor or secondary factor in the genesis of the glaucoma. Both topical and systemic corticosteroids and nonsteroidal anti-inflammatory agents are indicated to suppress inflammation and to reduce the levels of inflammatory cells and proteins in the AH. This inflammatory debris may compromise both short- and long-term, existing AH outflow pathways as well as the new surgical site.

Anterior Chamber Shunts (Gonioimplants)

The first report of anterior chamber shunts or gonioimplants in the dog was published in 1942, when the lacrimal canaliculi were transposed into the limbus of normal dogs as a new exit for AH from the anterior chamber (Gibson, 1942). In 1970, insertion of a silastic dacron tube through the limbus was attempted in normal dogs (Pritchard & Hamlet, 1970). In the early 1980s, the original Krupin–Denver valve was evaluated in normal Beagles as well as in Beagles with inherited glaucoma (Gum et al., 1981; Gelatt et al., 1987). This small scleral implant consisted of a small tube placed in the anterior chamber, a valve mechanism, and a short tube that extended only a few millimeters into the subconjunctival spaces. Without a broad area for reabsorption of the AH to occur, the exit of this implant became scarred and occluded in 50% of the dogs within 6 months.

A modified (i.e., nonvalved) Joseph implant was evaluated in 15 dogs (21 eyes) with primary glaucoma, and encouraging results were reported (Bedford, 1988, 1989). Additional reports have evaluated Ahmed, Baerveldt, and other anterior chamber shunts in limited numbers of normal dogs as well as in dogs with primary glaucomas (Gelatt & Gelatt, 2011; Glover et al., 1995b; Graham et al., 2017a. Recent reports with higher success rates evaluated alternate drainage sites (Håkanson, 1996) as well as combined gonioshunts and either diode laser cyclophotocoagulation or cryothermy (Bentley et al., 1999; Bras & Maggio, 2015; Cullen et al., 1998; Graham et al., 2018; Maggio & Bras, 2015; Sapienza et al., 2005).

Gonioimplants are divided into those with unidirectional valved systems, which are designed to permit passage of AH at approximately 10–12 mmHg, and those with bidirectional nonvalved systems, which have no pressure-regulatory devices except for the limited resistance in the shunt's tubing (Table 20.7; Gelatt & Gelatt, 2011; Gelatt et al., 1992; Hong et al., 2005). Typically, with the valved implants IOP immediately after surgery is about 10–12 mmHg; with the nonvalved implants, IOP is often below 5 mmHg. With fibrosis around the implant, which develops approximately 3–6 weeks postoperatively, the resistance for aqueous outflow with both types of implants is the same. The Ahmed valve,

Table 20.7 Anterior shunts reported in the dog.

Implant	Anterior Chamber Tubing	Scleral Explant	
Nonvalved			
"T" implant	Silicone ID 0.3 mm OD 0.6 mm	Silicone 7 × 30 mm 420 mm^2	
Baerveldt	Silicone	250/350/500 mm^2	
Valved			
Ahmed	Silicone ID 0.3 mm Valve opens/closes –8–10 mmHg	5-sided polypropylene-with silicone base – 500 mm^2	OD 0.6 mm
Joseph	Silicone ID 0.3 mm OD 0.64 mm Valve slit (side) 4–20 mmHg	Silicone strap 1 × 9 mm 8.5 cm long < 1600 mm^2	
Krupin	Silastic explant OD 0.64 mm Valve slit opens/closes 9–11 mmHg	Later #220 episcleral	ID 0.3 mm 180–360 mm long

Note: Implant dimensions are calculated for the entire surface area of each implant. ID, inner dimensions; OD, outer dimensions.

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which is much larger than a slit-shape valve, has been evaluated in an *in vitro* system at flows approximating the rate of aqueous turnover in the dog (Strubbe et al., 1997). IOP < 5 mmHg postoperatively in the dog can result in excessive fibrin in the anterior chamber, occasional hemorrhage, and even retinal detachments. To limit postoperative hypotony and shallow anterior chambers in the nonvalve systems, the anterior chamber tubing can be temporarily occluded intraoperatively with a nonabsorbable suture inside the tubing, a ligature (either absorbable or nonabsorbable suture) around the tube, or other techniques. Often, postoperative fibrosis around the shunt necessitates revision of the bleb and removal of scar tissue to allow continued drainage and resorption of the aqueous by the conjunctival vasculature.

Surgical Procedure for Anterior Chamber Shunts The surgical procedure for gonioimplants is similar for most of the episcleral devices. A 120–140°, fornix-based, dorsal bulbar conjunctival flap is created approximately 5 mm posterior to the limbus to leave some bulbar conjunctiva with which to manipulate the globe (Fig. 20.25**)**. Once the site is prepared, many advocate the use of topical mitomycin-C prior to placement and securing of the implant, in hopes of preventing the development of fibrotic capsules around the shunt that constrict the bleb (Westermeyer et al., 2011). The implant is usually positioned at or just posterior to the equator, with its rostral end approximately 8–12 mm from the limbus. The anterior border of the implant should be posterior to the extraocular muscle insertions. All anterior chamber shunts are checked before placement for both function and patency. A 25- to 27-gauge hypodermic needle is cannulated into the end of the anterior chamber tubing, and sterile balanced salt, lactated Ringer's solution, or tPA is injected to prime the tubing. Once the device is properly positioned, it is secured to the sclera and Tenon's capsule with 2–4 nonabsorbable 7-0 to 9-0 sutures, which are usually placed at the anterior border and near the extraocular muscle insertions. In some dogs with glaucoma, the sclera may be very thin in this area, and sutures with good holding abilities may be difficult to achieve. The overall length of the anterior chamber silicone tubing is carefully estimated by laying the tubing directly onto the cornea. Once in the anterior chamber, the tubing should not touch either the iris or the cornea, and it should avoid crossing the center of the pupillary axis. The tip is usually cut in a slightly beveled position to facilitate insertion into the anterior chamber. A beveled opening may be less subject to plugging with fibrin postoperatively as well. When the tubing end is beveled at 45° or less, however, it may be more easily plugged if contact with the corneal endothelium occurs.

A limbal-based, partial-thickness scleral hinge of 5 × 8 mm or a beveled hypodermic tunnel into the anterior chamber is prepared for the tubing to be inserted into the anterior chamber. The bend of the tubing as it enters the anterior chamber should be angled in the scleral tunnel or covered with a scleral allograft to prevent its erosion through the bulbar conjunctiva in dogs with "tight eyelids." Once the tubing is positioned in the anterior chamber, AH will generally be noted flowing through the device. The conjunctival flap wound is apposed using several simple interrupted or a continuous 6-0 to 7-0 absorbable suture. To treat any fibrin both in the AH and within the implant intraoperatively, tPA may be injected into the anterior chamber at the limbus.

Postoperative Management General postoperative management includes the following:

- Tonometry is used to evaluate the implant's function for the next several days postoperatively.
- Control and resolution of the iridocyclitis with use of topical and systemic corticosteroids and nonsteroidal anti-inflammatory agents are critical to success.
- Moderate pupillary dilation and encouragement of pupil movement with careful use of mydriatics (e.g., 1% tropicamide).
- Prevention of infection with use of topical and systemic antibiotics.
- Maintenance of normal IOP levels using CAIs and, if necessary, beta-blocker adrenergics (miotics and PGs may be counterindicated because of their effects on the episcleral fibroblasts and increased AH flare).
- The bleb and the gonioimplant can be imaged with ultrasonography, and the blebs characterized as small, medium, and large (Lloyd et al., 1993). The AH within the bleb appears as an echolucent area and the gonioplate appear as an echodense area. Although bleb size does not necessarily correlate with the level of IOP control, it does confirm that the implant's tube is patent.
- Continued topical medications that may lower IOP as well as control inflammation may be important postoperatively. Prednisolone acetate (1%) was recommended in one clinical series to reduce any inflammation and control the fibroblasts within the bleb surrounding the extrascleral implant (Westermeyer et al., 2011).
- Analgesics should be used in the immediate postoperative period and the surgical site should be protected from self-trauma.

Successful anterior chamber shunts will provide an IOP immediately after surgery of approximately 5 mmHg with nonvalved systems and of 10–12 mmHg with valved systems (Fig. 20.26). Occasional spikes of 5 or 10 mmHg may develop in the first few weeks if the shunt is temporarily plugged with fibrin. With development of a fibrous capsule about the base of the shunt, IOP will gradually increase to 12–20 mmHg several weeks later. Ultrasonography through the upper eyelid over the area of the shunt can demonstrate no surrounding AH "pool" if the tube or valve is occluded (Lloyd et al., 1993), or a very large bleb if the fibrosis around the implant

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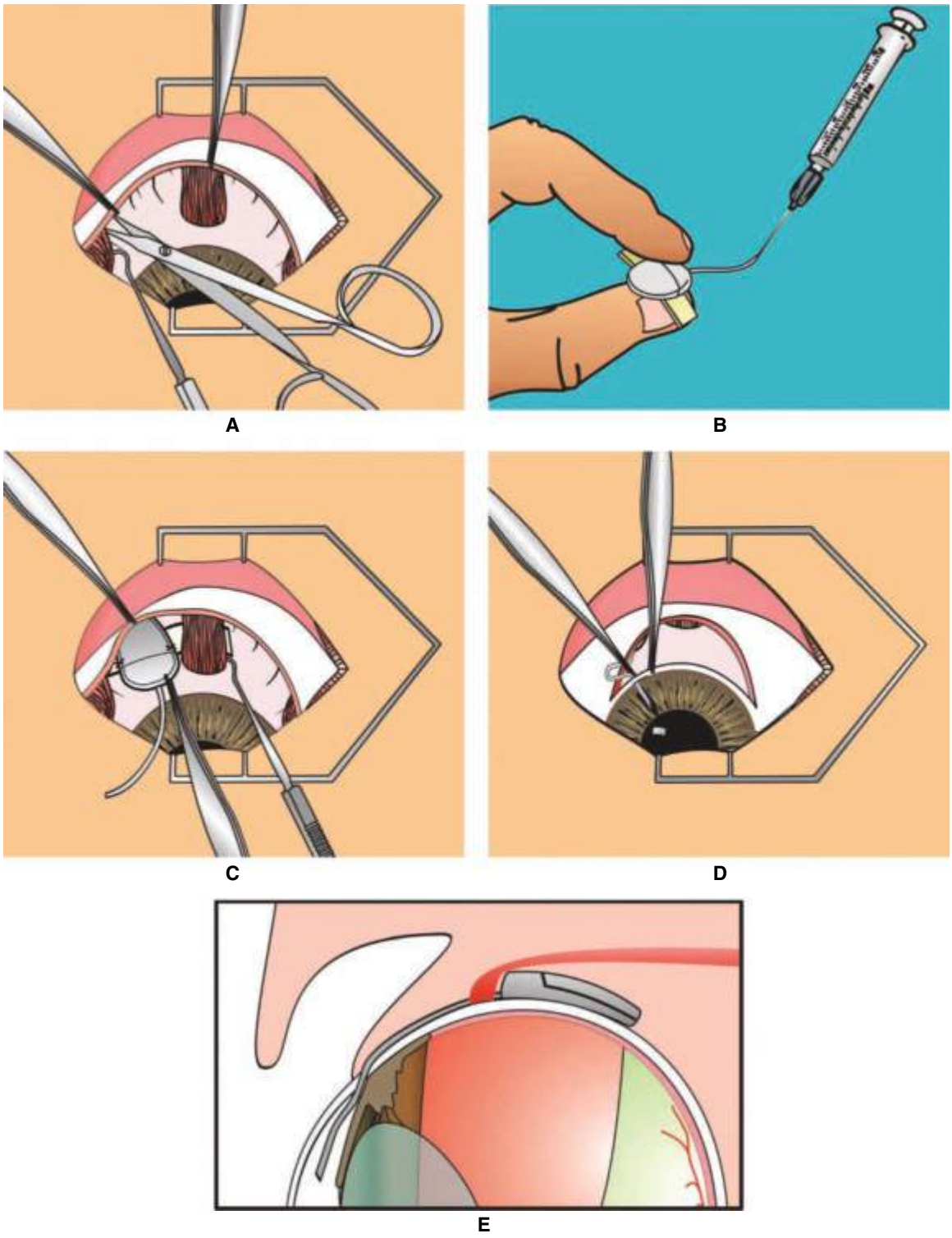


Figure 20.25 Surgical placement is similar for all the various anterior chamber shunts. **A**. Either the dorsolateral or dorsolateral quadrant is approached by scissor dissection under a fornix-based conjunctival flap. A space adequate to accommodate the episcleral base of the shunt between the dorsal rectus muscle and either the medial or lateral rectus muscle is prepared. **B**. The anterior chamber shunt must be primed with balanced salt solution before implantation. **C**. The anterior chamber shunt is positioned between the adjacent rectus muscles and, with some implants, under the rectus muscles. It is secured with simple interrupted, nonabsorbable sutures. **D**. After limbal puncture with a 20- to 22-gauge hypodermic needle and creation of the proper length and beveled end for the tube, the silicone tubing is inserted into the anterior chamber. The scleral aspect of this tube should be covered with either autogenous or homologous sclera to protect the overlying bulbar conjunctiva. **E**. Sagittal, postoperative view shows the proper position of the anterior chamber shunt, with its leading edge approximately 10–14 mm posterior of the limbus. (Modified with permission from Gelatt, K.N. & Gelatt, J.P. (2011) Surgical procedures for treatment of the glaucomas. In: *Veterinary Ophthalmic Surgery* (eds. Gelatt, K.N. & Gelatt, J.P.), pp. 263–303. Edinburgh: Elsevier-Saunders.)

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Figure 20.26 Ahmed gonioshunt in place in an eye with primary glaucoma. The shunt tubing is entering the anterior chamber at the 1 o'clock position.

has become resistant to aqueous exit. Topical corticosteroids (e.g., 1% prednisolone) are recommended postoperatively for several months to impede capsule formation about the base of the anterior chamber shunt. Needling or partial excision of the dorsal fibrotic capsule as well as the injection of 5-fluorouracil are used to address implant failure several months postoperatively (Sherwood 1990).

Complications of Anterior Chamber Shunts Failures of anterior chamber shunts may be grouped into three types (Sherwood, 1990). The immediate postoperative iridocyclitis can usually be controlled by routine anti-inflammatory medications. Any fibrin or blood in the anterior chamber that may occlude the tubing or valve usually resolves with one or two injections of tPA.

Long-term failure of anterior chamber shunts is usually associated with development of an impermeable capsule about the episcleral base of the device. More effective antifibrosis drugs are needed to markedly impede or totally prevent capsule formation about the extrascleral base of these implants long term. These drugs may be injected or inserted as time-release medications into the retrobulbar space either intraoperatively or 1–2 months postoperatively, after some capsule has formed about the implant and healing is complete. The Labrador Retriever seems to develop these fibrotic capsules very early (Moeller et al., 2011). Further improvements are necessary to minimize this complication.

Surgical Results Strategies for placing anterior chamber shunts in the dog are still evolving. The current anterior chamber shunts drain AH into the subconjunctival and retrobulbar spaces, but alternate sites, including the frontal sinus and other areas, have been attempted in the dog (Cullen et al., 1998; Gelatt & Gelatt, 2011; Håkanson, 1996).

The success rate for anterior chamber shunts has progressively improved with the refinement in the gonioimplant device, surgical procedure, and postoperative clinical management. In 1989, in a report involving 21 eyes in 15 dogs with the primary glaucomas that received the modified Joseph shunt, 20 eyes were normotensive at 4 weeks, and 17 eyes were still normotensive at 9–15 months (Bedford, 1989), with about 50% of these eyes receiving oral dichlorphenamide daily. Of the 9 eyes with vision preoperatively, 8 were still visual at 9 months. A larger series of studies in 1993, 1995, and 1998, involving 83 eyes in 65 dogs, compared three different anterior chamber shunts for treatment of primary glaucoma (Garcia et al., 1993, 1995, 1998). The criteria for success were maintenance of vision and IOP levels of 20 mmHg or less. The median time at which the IOP began to increase postoperatively depended on the shunt and ranged from 4 to 10–15 months. The median time for vision loss to develop postoperatively again varied by shunt and ranged from 4 to 6–9 months. At 1 year, 15 of the 22 eyes with an IOP of 20 mmHg or less were still visual. The most promising shunt was the large Ahmed shunt attached to a silicone band.

More recent reports have combined the gonioimplant with cyclophotocoagulation or cryotherapy. Bentley and coworkers reported on 18 glaucomatous dogs (19 eyes) treated with cycloablation and Ahmed gonioimplantation (7 eyes were treated with a diode laser and 12 were treated with cyclocryoablation; Bentley et al., 1996). One year after surgery, 11 of 19 eyes (60%) had vision and 14 of 19 eyes had IOP lower than 25 mmHg. The implant can prevent the IOP spikes that follow the cycloablation, as well as reduce the amount of energy or freezing for cryoablation. Sapienza and van der Woerdt (2005) reported their results using a combined diode laser cycloablation and the Ahmed gonioimplant in 48 dogs (51 eyes). Good control of IOP was achieved in 39/51 (76%) of the eyes, and IOP was poor or uncontrolled in 12/51 (24%) of the eyes. After 6 months 20 of 41 (49%) eyes maintained vision, and after 12 months 12/29 (41%) of eyes had vision.

In another series, temporalis muscle fascia or porcine intestinal submucosa grafts were used to cover the tube from the implant's base to the limbus, and topical 1% prednisolone acetate was instilled daily to control any intraocular inflammation, as well as to submit fibroblastic activity within the bleb's walls (Westermeyer et al., 2011). Mitomycin (0.25–0.50 mg) was administered by a trimmed cellulose sponge in the operative pocket for 5 minutes before implant insertion. The sides of the overlying conjunctival incision were not touched with the mitomycin solution-soaked sponge, and the entire area was rinsed with copious amounts of balanced solution for 5 minutes. Bleb revision was occasionally necessary and was performed by an incision on the top of the bleb. The fibrous tissue was excised and AH flow immediately returned. The bleb was then again treated with mitomycin using the same protocol. As an alternate

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approach, 5-fluorouracil (5 mg) was injected directly into the bleb twice at a 2-week interval. At 12 months postoperatively, 8 of the 9 dogs were still visual.

The 350 mm^2 Baerveldt nonvalve device was evaluated in both primary glaucoma (9 eyes, 7 dogs) and secondary glaucoma (23 eyes, 21 dogs). IOP was maintained under 20 mmHg in 24 of the 32 eyes (75%), with 43.8% receiving no additional therapy and vision retained in 18 of the 27 eyes with vision prior to surgery, with an average follow-up of 361 days. Postoperative complications were hypotony (81%), ocular hypertension (75%), and fibrin formation in the anterior chamber (63%; Graham et al., 2017a). When combined with transscleral cyclophotocoagulation, implantation of a Baerveldt drainage device resulted in greater control of IOP and vision retension than either transscleral cyclophotocoagulation or shunt placement alone (Graham et al., 2018).

Cyclodestructive Techniques Several noninvasive cyclodestructive procedures have been developed to treat glaucomas in small animals by decreasing AH formation through partial destruction of the ciliary body processes. Excessive heat, as with diathermy or lasers, or extreme cold, as with cryotherapy, is directed through the overlying sclera to the ciliary body processes. Proper positioning of the cryo and laser probes is critical; these probes must be directly over the ciliary body processes. In the dog, this area is approximately 5 mm from the limbus in the dorsal aspects of the globe. With globe enlargement, the ciliary processes of the pars plicata may shift an additional 0.5–1.0 mm posteriorly. Cyclodestructive procedures require some functional AH outflow to have an optimal IOP-reducing effect, because only partial destruction of the ciliary body will allow some level of minimal AH formation, which will continue to result in normal to subnormal IOP. Traditional cyclodestructive procedures can be refined only so much, in part because of the less than predictable regeneration of the ciliary body epithelium. Excessive application of these energies results in phthisis bulbi, with irreversible destruction of the ciliary body and permanent ocular hypotony.

Cyclocryothermy Cyclocryothermy is employed primarily in advanced glaucomatous eyes to reduce IOP in the presence of persistent pain or to induce phthisis bulbi, which may be more cosmetically acceptable than a buphthalmic eye (Merideth & Gelatt, 1980). This technique is also used in permanently blind glaucomatous eyes that are nonresponsive to intensive medical treatments. Cyclocryothermy is used infrequently in visual eyes, because prolonged periods of elevated IOP may follow the procedure.

The nitrous oxide or liquid nitrogen, 2.0–3.0 mm cryoprobe is applied 5 mm from the limbus directly onto the dorsal bulbar conjunctiva. Four to eight sites in the dorsal half of the eye are frozen for 120 seconds, each with the temperature of the cryoprobe reaching -60° to -80° C. The 3 and 9'clock positions are avoided to prevent direct damage to the long posterior ciliary arteries (Brightman et al., 1982).

Transscleral Laser Photocoagulation Transscleral cyclophotocoagulation uses energy developed by different types of lasers to destroy the ciliary body and to reduce AH formation. Both noncontact and contact Nd:YAG and diode lasers have been used in different animal species and, though costly, are promising treatments of canine glaucoma. Laser cyclophotocoagulation has been evaluated in the normal dog using the Nd:YAG and diode lasers (Nadelstein et al., 1997; Nasisse et al., 1988; Quinn et al., 1994; Sapienza et al., 1992). Using a noncontact Nd:YAG laser in 25 normal dogs, either 100 J or 238 J was delivered 5 mm posterior to the limbus to the canine ciliary body. In the 100 J group, IOP declined by 6 mmHg, but returned to prelaser levels within 7 days (Nadelstein et al., 1997). In the 238 J group, IOP declined by 10 mmHg throughout the 7 and 28 days of observation. Seven days after laser treatment, ciliary hemorrhage and ciliary necrosis were prominent; 28 days after treatment, ciliary atrophy and fibrosis were the primary histopathologic findings, though one eye developed extensive intraocular hemorrhage and phthisis bulbus. With the total pulse energy delivered 5 mm posterior to the limbus and varied at 126, 154, and 212 J, contact Nd:YAG laser cyclophotocoagulation in normal dogs produced a 1-month decline in IOP, except in the high-energy group, in which ocular hypertension developed 5–10 days after treatment (Sapienza et al., 1992). As the energy dose increased, the intensity of iridocyclitis and the possibility of acute iatrogenic glaucoma also increased. Focal cataract formation occurred in 75% of laser-treated eyes.

The diode laser was evaluated in a study of five normal dogs undergoing contact transscleral cyclophotocoagulation 3 mm posterior to the limbus (Nadelstein et al., 1997). The energy was delivered to 35 spots using 1.5 W at a duration of 1.5 seconds (i.e., 78.7 J per eye at 2.25 J/spot) and avoiding the 9 and 3 o'clock positions. Clinically, aqueous flare, conjunctival hyperemia, fibrin in the aqueous, miosis, limited hyphema, and in one dog intravitreal hemorrhage developed. IOP declined within 12–24 hours after treatment and remained low for the 28 days of observation. One dog's IOP spiked a single reading of 30 mmHg 1 hour after laser treatment. One hour after laser treatment, the treated areas in the dog appeared as white, blisterlike lesions, with adjacent hemorrhage, fibrin strands, and inflammatory debris. By 28 days, these areas appeared depigmented and slightly atrophied.

In another study, thermography was compared using the Nd:YAG and semiconductor diode laser among *in vitro*, normal canine eyes (Quinn et al., 1994). Histopathologic findings at the treated areas included a poorly demarcated, circular, hypereosinophilic focus of tissue coagulation that straddled the scleral–ciliary body interface. In this study, the Nd:YAG and diode lasers produced similar cyclodestructive effects.

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In a study using the noncontact Nd:YAG laser in 56 eyes of 37 dogs with glaucoma, promising results were obtained (Nasisse et al., 1990). Of these, 44 eyes had preexisting glaucoma, and 12 fellow eyes were treated prophylactically. The mean number of laser-treated spots were 35 ± 10. The mean energy per burst was 7.1 ± 2.6 J, and the mean total energy delivered to each eye was 228 ± 81 J. Treatment success was defined as an IOP of 25 mmHg or less. Information on vision was not reported. In the 44 treated glaucoma eyes, IOP was reduced to 25 mmHg or less in 83%. Three of the four failures were eyes devoid of uveal pigmentation (Nasisse et al., 1990). In lightly or nonpigmented eyes, such as those in the Siberian Husky or Old English Sheepdog, laser cyclophotocoagulation was not nearly as successful. Hyphema developed in 16% of those eyes, but it resolved without complications in all but 2. Cataract formation occurred in approximately 37% of treated dogs (i.e., 12 of 32 eyes; Nasisse et al., 1990).

A larger study using diode laser transscleral cyclophotocoagulation evaluated 176 eyes in 144 dogs with clinical primary glaucoma (Cook, 1997). The different breeds with these primary glaucomas were not analyzed separately, but approximately 50% were ACS. Laser treatments were administered 3–4 mm posterior to the limbus at 30–40 sites, for a mean dose of 85 J per eye. An immediate post-treatment IOP elevation of 11.3 ± 7.8 mmHg occurred (pretreatment IOP 45 ± 10 mmHg) and was treated by anterior chamber paracentesis. This immediate spike in IOP in 4 eyes was associated with loss of vision. An IOP of 30 mmHg or less occurred in 110 of 136 eyes at 8 weeks, 69 of 106 eyes at 6 months, and 45 of 88 eyes at 1 year following the procedure. Major complications included corneal ulcerations, cataract formation, intraocular hemorrhage, retinal detachments, and phthisis bulbi. Using the menace response as a test of vision, positive results were obtained in 21 of 37 eyes (57%) at 8 weeks, 11 of 30 eyes (37%) at 6 months, and 11 of 19 eyes (53%) at 1 year. Of the 45 eyes that tested positive with the menace test before laser therapy, only 10 (5.5%) were still evaluated as being visual at 12 months. The results of this study suggest that diode laser cyclophotocoagulation may be effective at lowering IOP for as long as 1 year (50% of the eyes), but is less effective at maintaining vision (22%).

In two studies from Australia, transscleral cyclophotocoagulation with the diode laser was evaluated in dogs with glaucoma following intracapsular lens extraction for displaced lenses and for the primary glaucomas (Hardman et al., 2001; O'Reilly et al., 2003). Approximately 16% of 99 patients with intracapsular lens removal for displaced lenses developed glaucoma. The diode laser probe with a spot size of 600 µm was applied perpendicularly (causing slight scleral indentation) to the globe in 20–25 sites 4 mm posterior to the limbus. A power of 1000 mW for 5000 ms delivered an average of 125 J per eye. Diode laser cyclophotocoagulation produced adequate control of IOP in 15 of 20 eyes (75%) without medications at 1 month post-therapy. After 12 months, 8 of 15 eyes (53%) had vision and 7 of 15 eyes (47%) were nonvisual.

A common protocol for visual eyes receiving contact diode laser cyclophotocoagulation is 1.2 W per site at a duration of 1.2 seconds with 35 sites (20 dorsal and 15 ventral), for a total of 50 J per eye (Fig. 20.27). The energy is delivered 3–4 mm posterior to the limbus. More energy can be delivered in eyes that are permanently blind. Medical treatment of glaucoma and anti-inflammatory therapy for post-treatment iridocyclitis should continue until the IOP is reduced and the inflammation subsides. It may take 3–4 weeks for the endpoint result (early postoperative IOP) of these surgical procedures to be known.

The newer micropulse transscleral cyclophotocoagulation (MP-TSCPC) seems to provide about a 70% success rate in IOP control, less postlaser inflammation, and fewer complications in humans, and shows early promise in its application in veterinary ophthalmology (Bras & Maggio, 2015; Sapienza et al., 2017; Sebbag et al., 2019a). The success rate of this modality at lowering IOP ranges from 50% to 65% depending upon the timeframe examined, with cases of primary glaucoma responding more favorably than those of secondary glaucoma (Sapienza et al., 2018). In dogs, corneal hypoesthesia is a common complication of MP-TSCPC and can be associated with qualitative and quantitative tear film deficiencies and neurotrophic corneal ulcers (Sebbag et al., 2019b).



Figure 20.27 Multiple sites of transcleral cyclophotocoagulation in a dog. With the contact diode laser, transcleral cyclophotocoagulation was 1.2 w per site for 1.2 seconds, with 35 sites treated (20 dorsal and 15 ventral) for a total of 50 J per eye.

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Diode Endoscopic Cyclophotocoagulation Endoscopic cyclophotocoagulation (ECPC) with a diode laser has been reported for therapy of the canine glaucomas (Bras & Maggio, 2015; Bras et al., 2005), and offers the advantage of highly selective laser ablation of the pigmented ciliary body epithelium while under direct observation. The microendoscope has three divisions: (1) wide cone viewing light; (2) image 10,000 pixel fiber bundle with 110° field of view; and (3) diode laser (810 nm) within 20-gauge diameter fiber bundle (30° curved or straight). The available integrated ophthalmic endoscopy systems provide both viewing and illumination (E4 and E2 consoles, Endo Optiks, Little Silver, NJ, USA) and include the video camera, light source, and video monitor. The surgical approach is either limbal for phakic, aphakic, and pseudophakic eyes using a 30° curved probe for as much as 300° from a single incision, or pars plana for phakic eyes treating 90–100° from a single incision (Fig. 20.28**).** During endolasering the ciliary process tissue quickly blanches (from black to light gray or white) and shrinks. Any tissue explosion (popping or bubble formation) is avoided. The ablation area is usually approximately 270° to achieve optimal ocular hypotensive effects. In phakic eyes, ECPC often affects the periphery of the lens and produces cataract formation, so most advocate concurrent removal of the lens via phacoemulsification followed by placement of an artificial intraocular lens. The limbal approach is generally used when concurrent phacoemulsification is performed. Overapplication of ECPC is associated with higher rates of complications. Color dilute breeds (Siberian Husky, Australian Shepherd, etc.) require higher levels of ECPC energy as the less pigmented ciliary body processes absorb less energy.

ECPC therapy in glaucoma patients is encouraging, but patient follow-ups are limited in both time and animal numbers. Studies to date report long-term IOP control and reduced need for topical glaucoma drugs in about 80% of treated cases for 12 postoperative months and maintenance of vision (of animals sighted at the time of surgery) in about 70% of cases. Three-year postoperative success rates decrease to about 50% with controlled IOP and sight (Lutz et al., 2013).

Treatment of End-Stage Primary Glaucomas

Because of the limited success of both medical and surgical therapies for glaucoma in the dog, salvage procedures to prevent ocular pain, to reduce the enlarged and blind globe to near-normal size to reduce corneal exposure, and to provide a cosmetically acceptable eye may be necessary. These procedures include pharmacologic destruction of the ciliary body with intravitreal injection of gentamicin or cidofivir, evisceration of the intraocular contents, followed by placement of an intrascleral or intraocular prosthesis and enucleation (i.e., surgical removal of the globe). Sometimes enucleation is the only viable option for certain patients and can even be used bilaterally to provide a happy pain-free companion animal (Fig. 20.29).

Pharmacologic destruction of the ciliary body with intraocular injections of gentamicin is a salvage procedure for advanced and blind canine glaucomatous eyes (Bingaman et al., 1994; Vainisi et al., 1983). Gentamicin is cytotoxic to the ciliary body epithelium and retina, thereby markedly reducing or even eliminating AH formation. In the original technique, 0.5–0.6 mL of liquefied vitreous was aspirated, and 25 mg of gentamicin sulfate and 1 mg of dexamethasone were injected into the vitreous space (Vainisi et al., 1983). Pharmacologic ablation of the ciliary body was successful in lowering the IOP in 65% of patients for treatment of absolute glaucoma in early studies. Of eyes that do not respond to the first injection of gentamicin, 50% fail again to respond after the second injection, and approximately 10% of the eyes will



Figure 20.28 Intraoperative image demonstrating blanching of the ciliary body processes during endoscopic laser cyclophotocoagulation. The red focus is the sight for the laser. The iris leaflet is located above the ciliary body in this image.



Figure 20.29 Postoperative appearance of bilateral intraocular prostheses following evisceration of the globes one year after the procedure.

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be phthisical after this method. This technique seems to work best when the preinjection IOP levels are less than 20 mmHg.

In another study, both anterior chamber and intravitreal injections were attempted (Bingaman et al., 1994), although a variety of protocols and dosages exist. The dose of gentamicin should not exceed the patient's total daily dose for this drug, and it has been reported to be absorbed systemically following intraocular injection (Rankin et al., 2016). The most recent report used between 25 and 40 mg of gentamicin per eye and had a success rate of approximately 86% (Rankin et al., 2016). Eyes treated with doses of gentamicin higher than 20 mg had a significantly lower IOP after injection. Post-injection inflammation is common, as is cataract formation in phakic eyes. There have been reports of intraocular sarcoma development in glaucomatous eyes of both cats and dogs following gentamicin ablation (Duke et al., 2013). Recent reports of the use of the antiviral agent cidofivir have shown promise with successful lowering of IOP in 85% of cases and describe less postoperative inflammation and cataract development (Low et al., 2014).

Evisceration and intrascleral prosthesis form another salvage procedure that may provide the most cosmetically acceptable result (see Chapter 14). This procedure treats the pain associated with absolute glaucoma, limits the corneal exposure from enlarged globes, and eliminates the need for anti-glaucoma treatments. The overall result is more predictable, and phthisis bulbus is not possible. Some corneal edema, fibrosis, and pigmentation occur postoperatively. Healing is prolonged in these eyes, likely because the large incision that must be made in the sclera to accommodate the intraocular prosthesis compromises the innervation to the fibrous tunic and the vascular supply to the interior of the globe is eliminated. The most serious short-term complications are the development of central corneal ulcerations and infections postoperatively. The most common long-term complication is the development of keratoconjunctivitis sicca (Lin et al., 2007). As these dogs often do not blink well in the immediate postoperative period, a temporary tarsorrhaphy is recommended for 10–14 days in all patients. If corneal ulceration occurs, a pedicle conjunctival graft can also be applied, because the corneal healing in these patients is slow. The overall success rate with intrascleral prosthesis is approximately 85%–95%.

New Developments in Glaucoma Therapy

Despite recent advances in the treatment of canine glaucoma, most affected dogs still go blind. There is no cure for glaucoma, but many forms of primary human glaucomas have become preventable with early diagnosis and intervention. Therefore, it is crucial that we gain a better understanding of canine glaucoma risk factors and disease mechanisms, which will allow earlier diagnosis and more effective, targeted treatment to prevent continued RGC loss and blindness (Komáromy et al., 2019). Recent and ongoing advances in canine genetics and ophthalmic diagnostic technologies, including high-resolution imaging and home monitoring of IOP, provide the necessary tools to aid in these efforts. Lowering IOP remains the main focus of glaucoma therapy, but other treatment options to protect and regenerate RGCs and their axons will hopefully become available in the foreseeable future.

Intraocular Pressure Control

Novel Medical Therapies to Lower Intraocular Pressure

Recent advances in IOP control of human patients include novel drugs and drug implants. More effective IOP control may be achieved by introducing novel, mechanistic-based medical therapies. Two newly approved topical IOP-lowering medications are latanoprostene bunod (Vyzulta™, Bausch & Lomb, Bridgewater, NJ, USA) and netarsudil (Rhopressa™, Aerie Pharmaceuticals, Bridgewater, NJ, USA and Research Triangle Park, NC, USA). Latanoprostene bunod is a nitric oxide–donating PG F2α agonist that showed improved pressure-lowering effect compared to latanoprost in glaucomatous Beagles (Borghi et al., 2010; Impagnatiello et al., 2011; Krauss et al., 2011). Compared to traditional PG analogues, latanoprostene bunod has a stronger therapeutic effect on the conventional outflow through the trabecular meshwork, in addition to an increase of uveoscleral outflow (Cavet & DeCory, 2018). Netarsudil is a Rho-Kinase (ROCK) and norepinephrine transporter (NET) inhibitor. ROCK inhibition reduces cell contraction and cell stiffness, and decreases expression of fibrosis-related proteins, resulting in increased trabecular outflow facility (Lin et al., 2018; Rao et al., 2017; Wang & Chang, 2014). Netarsudil's NET-inhibitory activity is likely responsible for the documented reduction of AH production and decrease in episcleral venous pressure, further contributing to the lowering of IOP (Kiel & Kopczynski, 2015; Lin et al., 2018; Rao et al., 2001). Netarsudil results in great reductions in IOP in rabbits and monkeys (Lin et al., 2018). Unfortunately, in clinical investigations to date in normotensive and glaucomatous dogs with *ADAMTS10* open-angle glaucoma, netardusil administrered topically twice daily has only demonstrated small, clinically unimportant reduction in IOPs (Leary et al., 2019; Yang et al., 2020).

One major factor responsible for the progression of glaucomatous optic neuropathy in human patients is poor adherence to eye-drop administration. It has been estimated that only 60%–70% of prescribed doses of eye drops for patients with glaucoma are taken (Friedman et al., 2007) and ~50% of patients have been found not to be adherent to their medica-

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tion over 75% of the time (Okeke et al., 2009). Because of this poor adherence, several drug companies have developed devices for long-term, sustained drug release, either onto the corneal surface or into the anterior chamber. Most of these implants release PG analogues, and some have already moved from preclinical testing into clinical application in human patients. Externally placed devices include the Helios™ bimatoprost periocular ring (Allergan, Dublin, Ireland) for placement into the conjunctival fornix (Brandt et al., 2017) and OTX-TP travoprost punctal plugs (Ocular Therapeutix, Bedford, MA, USA; Aref, 2017). Intracameral implants include Bimatoprost SR (Durysta, Allergan; Lee et al., 2018), ENV515 travoprost (Envisia Therapeutics, Durham, NC, USA; Aref, 2017), OTX-TIC travoprost (Ocular Therapeutix), and iDose travoprost (Glaukos, San Clemente, CA, USA; Aref, 2017). Intracameral, biodegradable latanoprost-, bimatoprost-, and travoprost-releasing devices have recently been tested in dogs (Komáromy et al., 2017; Lee et al., 2018; Navratil et al., 2015).

Novel Surgical Therapies to Lower Intraocular Pressure

Because newly developed glaucoma medications are emerging at a very slow rate and are generally optimized for the human rather than canine eye, a continued focus on improved surgical therapies is important. Improvement of surgical therapies includes the continued optimizing of current techniques, such as more effective inhibition of scarring to prolong goniomplant bleb function (Martorana et al., 2015; Saito et al., 2017; Yu-Wai-Man et al., 2017). A promising novel technique of cyclophotocoagulation uses a micropulse laser (MicroPulse® Cyclo G6, Iridex, Mountain View, CA, USA) for TSCP and will soon also become available for ECPC (Lee et al., 2017; Sapienza et al., 2017; Sebbag et al., 2019a, 2019b).

The most dramatic recent changes in the surgical treatment of primary glaucoma in humans are represented in the development of microinvasive glaucoma surgeries (MIGS). Because of their effectiveness and minimal invasiveness, these AH-draining techniques represent an attractive alternative to medical therapy for early stages of glaucoma (Fingeret et al., 2018). While these procedures are being developed for human patients, with some of them specifically targeting species-specific anatomic structures such as Schlemm's canal, selective MIGS may be applicable to dogs and have even been tested informally by veterinary ophthalmologists. Among the most commonly used MIGS are EXPRESS® Mini Glaucoma Shunt (Alcon, Fort Worth, TX, USA), SOLX® Gold Shunt (Solx, Waltham, MA, USA), InnFocus MicroShunt® (InnFocus, Miami, FL, USA), iStent® (Glaukos), and gonioscopy-assisted transluminal trabeculotomy (GATT). Another subconjunctival MIGS drainage device, the XEN® Gel Stent (Allergan), was successfully tested for safety in normal Beagles (Shute et al., 2016).

Novel Gene and Stem Cell Therapies to Lower Intraocular Pressure

The field of ocular gene therapy has enjoyed several recent successes, with treatments for retinal and optic nerve diseases being translated into clinical applications for human patients (Bennett, 2017; Campochiaro et al., 2017; Guy et al., 2017). These advances will likely also benefit human and animal patients with glaucoma – for the treatment of both the anterior and posterior segments of the eye. As we gain a better understanding of glaucoma genetics and the molecular disease mechanisms within the AH outflow pathways, gene therapies will allow us to specifically address and correct the pathogenesis for more effective, long-term IOP control. Targeting of transgene expression to trabecular meshwork has been successfully achieved in several animal species, including the dog, following intracameral injection of adenovirus, lentivirus, and adeno-associated virus (AAV) gene therapy vectors (Bogner et al., 2015; Buie et al., 2010; Dang et al., 2017; Oh et al., 2014; Wang et al., 2017). The recent expansion of the AAV vector toolkit combined with its excellent safety and efficacy record for use within the eye makes the AAV gene therapy vector a very attractive option for treatment of the trabecular meshwork and achieving long-term IOP control in open-angle glaucomas (Asokan et al., 2012; Bogner et al., 2015; Oh et al., 2014; Wang et al., 2017). Other tissues of the anterior segment, such as the ciliary muscle, may need to be targeted to address the disease mechanisms leading to PACG.

Recently, proof of concept has been provided that the trabecular meshwork can be regenerated in advanced stages of disease and trabecular outflow restored: trabecular meshwork–like cells were induced from induced pluripotent stem cells and injected into the anterior chamber of transgenic, *MYOC*-mutant mice (Zhu et al., 2016, 2017). As a result, the conventional outflow pathway was replenished with new cells, which resulted in improved outflow facility, IOP control, and halted RGC loss (Zhu et al., 2016, 2017). This type of stem cell–based therapy may become a promising possibility for long-term IOP control in dogs with primary glaucoma.

Neuroprotection and Neuroregeneration

One of the major challenges of treating glaucoma patients is the continued loss of RGCs and their axons despite effective IOP control. Considerable efforts have been made toward a better understanding of these IOP-independent disease mechanisms and the development of neuroprotective treatments to address them and prevent further RGC death. Some of these mechanisms that may or may not be triggered by an increase in IOP have been discussed earlier in this chapter: excitotoxicity caused by excessive excitatory amino acid release, such as glutamate and aspartate (Brooks et al., 1997; Seki & Lipton, 2008); neurotrophin deprivation due to blockage of retrograde

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axonal transport (Fahy et al., 2016; Knox et al., 2007; Pease et al., 2000; Salinas-Navarro et al., 2010); excessive intracellular calcium (Ward et al., 2014); compromised blood flow to the ONH and retina (Agarwal et al., 2009; Brooks et al., 1989a; Chung et al., 1999; Flammer et al., 1999; Gelatt et al., 2003; Gelatt-Nicholson et al., 1999; Michelson et al., 1998); oxidative stress (Liu et al., 2007; Mozaffarieh et al., 2008); inflammation and autoimmunity against retinal and optic nerve antigens (Bell et al., 2013; Pumphrey et al., 2013a; Wax & Tezel, 2009); and reactive gliosis (Bringmann et al., 2006; Inman & Horner, 2007, Neufeld & Liu, 2003; Son et al., 2010). A large number of compounds have been shown to address these disease mechanisms and protect RGCs effectively in experimental animal models of glaucoma, many of them being routinely used in the clinic for unrelated indications. Unfortunately, none of these drugs has been successfully moved into clinical application for glaucoma therapy.

The two neuroprotective therapies that have gone through clinical trial for glaucoma are memantine, given by oral route, and ciliary neurotrophic factor (CNTF), continuously released into the vitreous. Memantine, an Nmethyl-Daspartate receptor antagonist, is used for the treatment of Alzheimer's disease, and has been shown to reduce RGC death and functional loss by suppressing excitotoxicity in experimental glaucoma in rats and primates (Hare et al., 2004a, 2004b; Wolde-Mussie et al., 2002). Unfortunately, Phase 3 trials have failed to demonstrate protection of visual function by memantine in human glaucoma patients (Weinreb et al., 2018). The continuous release of CNTF by intravitreal encapsulated cell therapy has recently been tested in Phase 1 clinical trials in patients with POAG (ClinicalTrials.gov NCT01408472) and ischemic optic neuropathy (NCT01411657), but results have not yet been published. CNTF has previously been shown to slow RGC death in experimental glaucoma in rats (Pease et al., 2009). Because of its documented beneficial effect on ocular blood flow and its potential neuroprotective effect, the calcium channel blocker amlodipine is used systemically by some veterinary ophthalmologists on selected canine glaucoma patients (Källberg et al., 2003). The pursuit of neuroprotective therapy for glaucoma continues, including by gene and stem cell therapy (Jutley et al., 2017).

In addition to neuroprotection, the replacement of lost RGCs and the regeneration of RGC axons are high priorities in glaucoma research. For example, the National Eye Institute, which is part of the National Institutes of Health, predicts that these goals should be achievable within 10–15 years with adequate funding (Goldberg et al., 2016). Retinal and optic nerve regeneration is naturally possible in fish and amphibians, but not in mammals. However, several animal studies have shown that under the right circumstances, mammalian RGCs are able to regenerate their axons and connect to the appropriate target areas in the brain, resulting in visual recovery (Benowitz et al., 2017; Laha et al., 2017). Furthermore, transplantation of RGCs by intravitreal injection is one method that is being worked on to replace lost RGCs (Tanaka et al., 2015). Ultimately, even transplantation of whole eyes may become a realistic option with improvements in optic nerve regeneration.

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This book is dedicated to the memory of Dr. Gil Ben-Shlomo, an exceptional scholar, teacher, father and friend. The veterinary ophthalmology community has lost a gentle doctor and a gentleman.

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Preface

In 1965 when I entered veterinary ophthalmology, it became very quickly apparent that there was a very limited information base or knowledge in veterinary ophthalmology. If this new clinical discipline was to grow and develop into a respected clinical specialty, we would need to develop our own scientific base, and compete with the other emerging clinical specialties in veterinary medicine. And we have! With our limited English-language books of *Veterinary Ophthalmology* by R.H. Smythe (1956), W.G. Magrane's first edition of *Canine Ophthalmology* (1965; Lea and Febiger), and *Diseases of the Canine Eye* by F.G. Startup (1969; Williams and Wilkins), and the chapter in *Advances in Veterinary Science* called 'Examination of the Eye' and 'Eye Operations in Animals' by Otto Überreiter (1959; Academic Press), we needed to "roll up our sleeves" and get to work big time!

We have available now (2021) a large number of veterinary ophthalmology books concentrating on the dog, cat, exotic animals, horses, ophthalmic pathology, and ophthalmic surgery. Two veterinary ophthalmology journals have proven invaluable to our success as a discipline. The first journal, *Veterinary and Comparative Ophthalmology*, was published by Fidia Research Foundation and Veterinary Practice Publishing (1991–1998), and our second journal was *Veterinary Ophthalmology* (published by Blackwell and Wiley-Blackwell, 1998 to present); they greatly assisted our development and proved critical for the distribution of new scientific information. In fact, the current journal provides more than 90% of animal ophthalmic literature annually worldwide.

In the late 1950s and extending into the 1970s, professional groups of budding veterinary ophthalmologists organized scientific societies to gather and exchange their knowledge and clinical experiences, which rapidly evolved to Colleges of Veterinary Ophthalmologists whose primary missions were to train new veterinary ophthalmologists (termed residents), and foster (and fund) research to "grow" the clinical discipline long term and worldwide. Nowadays these significant changes have greatly enriched veterinary ophthalmology, and markedly improved the quality of our ophthalmic animal patients.

The advances in this text, *Veterinary Ophthalmology*, have paralleled and documented the changes in veterinary ophthalmology, and has become our symbol of where we are today. In 1981, the first edition was released, consisting of 21 chapters (788 pages) by 22 authors, and was well received. As a result, subsequent editions followed: second edition (1991; 765 pages and 19 authors), and then in 1999 our last single-volume release (1544 pages, 37 chapters, and 44 authors). The third edition was markedly expanded and had color illustrations throughout the text.

The last two editions were two-volume sets: for 2007, volume one 535 pages, 9 chapters, and 45 authors, and for the second larger volume 1672 pages, 20 chapters, and 36 authors; and in 2012 for volume one 789 pages, 12 chapters, and 26 authors, and for the second volume 1479 pages, 22 chapters, and 39 authors. All editions were well referenced; in fact, a great value of this text is that it documents the advances in veterinary ophthalmology during the past half of the twentieth century, and the first two decades of the twenty-first century!

The sixth edition again consists of two volumes, 37 chapters, and 64 contributors. Like the last two editions, the first volume contains the basic science and foundations of clinical ophthalmology chapters and the first part of the third section on canine ophthalmology. Basic vision science courses in veterinary medical colleges are often an afterthought, and our veterinary ophthalmic basic sciences are frequently documented by veterinary ophthalmologists (rather than anatomists, physiologists, pharmacologists, etc.).

The first volume of the basic sciences and foundations of veterinary ophthalmology is designed to provide the base of those subjects that underpin the clinical sciences. They include embryology, anatomy, ophthalmology physiology, optics and physiology of vision, and fundamentals of vision in animals. In the foundations of clinical ophthalmology section, the chapters include immunity, microbiology, clinical pharmacology and therapeutics, ophthalmic pathology, ophthalmic examination and diagnostics, ophthalmic genetics and DNA testing, fundamentals of microsurgery, and photography. The third section starts with the chapters for

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the first part of the canine ophthalmology including orbit, eyelids, nasolacrimal system, lacrimal secretory system, conjunctiva and nictitating membrane, cornea and sclera, and glaucoma.

The second volume focuses on clinical ophthalmology in the different species, and starts with the second part of canine ophthalmology (chapters- anterior uvea, lens and cataract formation, surgery of the lens, vitreous, ocular fundus, surgery of the posterior segment, and optic nerve), and continues with feline, equine, food and fiber-producing animals, avian, New World camelids, laboratory animals, pocket pet animals, and exotics, and concludes with comparative neuro-ophthalmology, ophthalmic manifestations of systemic diseases, and the index. The sixth edition more or less has devoted space relative to the amount of time based on different animal species encountered in veterinary ophthalmology practice.

Now, in 2021, the sixth edition of *Veterinary Ophthalmology* continues to document this discipline's advances. The magnitude of this edition has now required five associate editors, who devoted their time and expertise to make it happen. Like for me, I'm certain it was a learning experience! They are Drs. Brian C. Gilger, Diane V.H. Hendrix, Thomas J. Kern, Caryn E. Plummer, and Gil Ben-Shlomo. Each editor chose their authors and respective chapters, based on their expertise and preferences. A book like this is a huge undertaking, and all of us have devoted hundreds of hours to make it a successful product for the profession. Our 64 authors contributed hundreds of hours to this edition, taking time away from family and practice, and we thank them.

When all the chapters had been submitted and production had started, the COVID-19 pandemic spread across the world like a massive hurricane. Terms like "face masks," "social distancing," "isolation," and "quarantine or shelter at home" became common terms, and our daily personal and professional routines were markedly disrupted. But progress in the production of the sixth edition continued uninterrupted.

We thank Erica Judisch, Executive Editor, Veterinary Medicine and Dentistry, and Purvi Patel, Project Editor, of Wiley-Blackwell for their expertise and assistance in making the sixth edition of *Veterinary Ophthalmology* a reality. Our copyeditors, Jane Grisdale and Sally Osborn, and project manager Mirjana Misina were superb. And lastly, we thank and appreciate the continued support and encouragement of our spouses and family members who bear with us as we struggle to meet our time schedules and other life priorities.

Distinguished Professor of Comparative Ophthalmology, Emeritus

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About the Companion Website

This book is accompanied by a companion website:

www.wiley.com/go/gelatt/veterinary

The website includes:

- PowerPoints of all figures from the book for downloading
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Section IIIB

Canine Ophthalmology

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Diseases and Surgery of the Canine Anterior Uvea

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The uvea includes the iris, ciliary body, and choroid. The anterior uvea refers to the iris and ciliary body. The iris, because of the pupil, is responsible for regulating light entering the globe, and it is also important for normal esthetics. The ciliary body is contiguous with the choroid at its posterior aspect and is responsible for aqueous production and lens accommodation. The anterior uvea is the site of the blood–aqueous barrier, which normally prevents large, high-molecular-weight proteins from entering the aqueous humor, and it serves as the site for unconventional aqueous humor outflow. The rich blood supply and immunosensitivity of the anterior uvea make it the source for most of the inflammatory responses in the eye.

A complete ophthalmic examination, including use of magnification such as that provided by a slit-lamp biomicroscope, is important for diagnosing uveal disease. The size of the pupil can vary tremendously, and abnormalities in its size, shape, color, or responsiveness may indicate ocular or neurologic disease. Diseases such as anterior uveitis, glaucoma, retinal detachment and degeneration, and lesions along the afferent and efferent pupillary pathways can alter pupil size and function. Inflammation of the anterior uvea, termed anterior uveitis, is very common with both ocular and systemic diseases and often causes intense intraocular pain, alters pupillary function, and can lead to blindness. Intraocular neoplasia is not unusual in dogs and varies in its appearance. In addition to inflammatory and neoplastic disorders, developmental, degenerative, and traumatic disorders can all affect the anterior uvea. This chapter focuses on diseases that primarily involve the iris and ciliary body, but because the anterior uvea is contiguous with the choroid (or posterior uvea), several of the diseases often affect the posterior segment as well.

Developmental Conditions

Developmental abnormalities of the canine anterior uvea include disorders of incomplete development (e.g., coloboma), maldevelopment (e.g., anterior segment dysgenesis), and incomplete regression of embryonal tissues (e.g., persistent pupillary membranes, PPMs). Most anterior uveal anomalies in the dog occur sporadically, but some are heritable.

Normal anterior uveal development during embryogenesis occurs by invagination of the optic cup, resulting in a bilayered medullary epithelium. Continued differentiation of the innermost (i.e., more vitreal) layer forms the inner pigmented epithelium of the iris, the nonpigmented ciliary body epithelium, and the neurosensory retina. Differentiation of the outermost (i.e., scleral) layer forms the outer pigmented epithelium (and dilator and sphincter muscles) of the iris, the pigmented epithelium of the ciliary body, and the retinal pigment epithelium. Because normal ocular embryogenesis depends on initial development of the pigmented layers of the eye, several congenital defects relate directly to ocular color dilution and specifically to the merling gene. However, there is considerable variation of anterior uveal pigmentation in normal dogs, which accounts for the marked differences in eye color both within and among breeds.

Color Variants

Subalbinism

Subalbinism refers to dilution of ocular pigment. In contrast to complete albinism, in which the eye lacks all pigment, subalbinism is seen as a blue iris with a red fundus reflex. The neuroectodermal layer of the iris has normal pigmentation; however, the overlying stroma lacks pigment. These animals have a nonpigmented fundus that allows visualization of choroidal vessels. Tapetal presence is variable. Complete albinism results in a translucent iris with visible iris vessels, which gives a reddish hue to the iris stroma. Complete ocular albinism has not been reported in the dog.

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Figure 21.1 Heterochromia iridis in a mixed-breed dog.



Figure 21.2 This merle Great Dane has a typical iris coloboma. The ciliary processes are visible because of the absence of iris. An immature cataract is also present.



Figure 21.3 An iris coloboma is present in the nasal aspect of the iris in this Australian Shepherd.

Heterochromia Iridis

Heterochromia iridis refers to different colors within one iris or between the two irides. In the heterochromic eye, the iris is characterized by at least two distinct, solidly colored areas or by differently colored patches or spots (Fig. 21.1). Alternatively, each iris may be a different color.

Heterochromia iridis is often the sole manifestation of ocular color dilution in many breeds, including the Old English Sheepdog, Siberian Husky, American Fox Hound, American Cocker Spaniel, Malamute, and Shih Tzu. Apart from the variation in appearance, simple heterochromia iridis has no significance. Heterochromia iridis can be a component of ocular merling, which is often accompanied by multiple ocular anomalies such as dyscoria, corectopia, iris hypoplasia, PPMs, staphylomas, cataract, and retinal detachment (Gelatt & McGill, 1973; Gwin et al., 1981).

Iridal Changes Associated with Merling

Multiple ocular anomalies including iris anomalies occur in breeds affected by the merle gene (e.g., Australian Shepherds, Great Danes, Collies, and Dachshunds). The most severe ocular anomalies occur in homozygous merles with excessive white hair coat involving the head region. Affected animals also have varying degrees of congenital deafness (Gwin et al., 1981). Anterior uveal manifestations of the merling gene include heterochromia iridis, iris hypoplasia, a black-rimmed pupil from prominent iridal pigmented epithelium, and an eccentric pupil (i.e., corectopia). Both typical and atypical iris colobomas (Fig. 21.2 and Fig. 21.3) and mild to severe PPMs are also common in merle dogs (Gelatt & McGill, 1973). Anomalies caused by the merle gene have been studied most extensively in the Australian Shepherd (Bertram et al., 1984; Gelatt & McGill, 1973; Gelatt et al., 1981). Multiple ocular anomalies, including microphthalmia, irregular pupils, cataracts, equatorial staphylomas, retinal dysplasia, and retinal degeneration, occur as an autosomal-recessive trait in this breed. Severity of ocular lesions correlates with the amount of white in the hair coat. While the ocular disease is recessively inherited, the inheritance of merling appears to be dominant.

Persistent Pupillary Membranes

The pupillary membrane is a layer of primitive mesodermal tissue on the anterior face of the iris during fetal development. This membrane consists of fine blood vessels and connective tissue. Normally, the central vascular arcades regress first, beginning during the sixth week of canine development. The peripheral arcades that have their origins at the iris collarette regress last (Aguirre et al., 1972). This process continues through the final three weeks of fetal development and into the immediate postnatal period. In most puppies, the pupillary membranes completely atrophy by 6 weeks after birth. The rate of pupillary membrane dissolution

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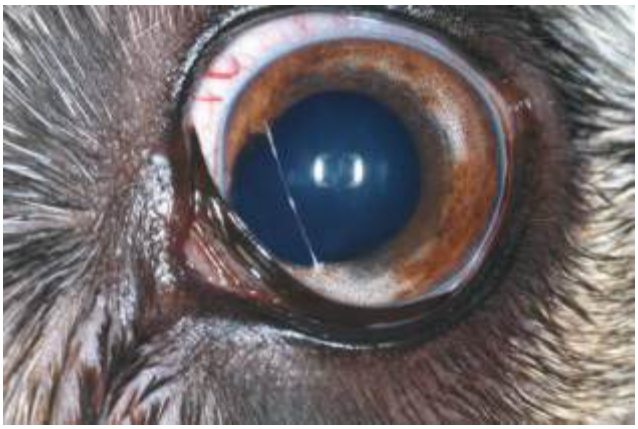


Figure 21.4 A single benign, persistent pupillary membrane can be seen crossing the pupil. A nasal iris colobomas is also present.

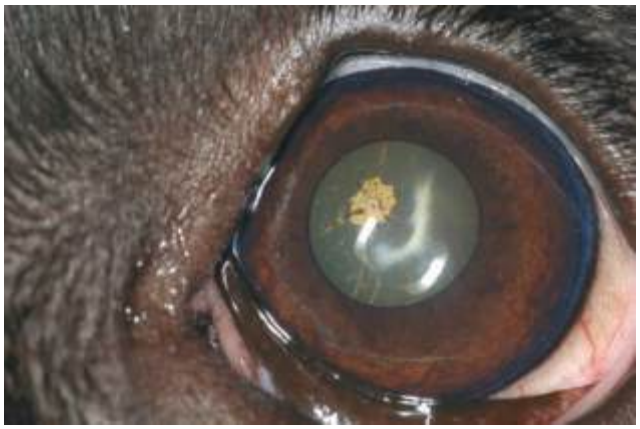


Figure 21.5 Persistent (dysplastic) pupillary membranes are present in this Rottweiler puppy. The membranes extend from the iris collarette to the lens, creating a circular opacity on the anterior lens capsule. They previously extended to the cornea, and an endothelial and deep stromal opacity remains.

varies, however, and it might not be completed for several months (Roberts & Bistner, 1968). Incomplete resorption of embryonal vasculature and mesenchymal tissues results in retained iris strands in both juvenile and adult dogs. These uveal remnants, which are termed persistent pupillary membranes, attach at the collarette region of the iris and usually retain the color of the adjacent iris. Total persistence of the fetal pupillary membrane with absence of the pupil is rare; when present, it is associated with other ocular anomalies (Martin & Leipold, 1974).

PPMs occur commonly in the dog and are usually an incidental finding. Iris-to-iris strands that bridge over the iris surface or cross the pupil and remnants with a single iris attachment that occur as small, free-floating tags are benign (Fig. 21.4). Iris-to-cornea strands and iris-to-lens strands frequently result in significant corneal or lenticular opacities that can compromise vision (Fig. 21.5). Because pupillary membrane contact with the lens and cornea is not normal, strands that contact the cornea or lens are classified as "dysplastic" rather than persistent (Grahn & Peiffer, 2007). PPMs occur either unilaterally or bilaterally, and different forms can exist in the same dog. Iridocorneal adhesions are associated with corneal edema, fibroplasia, and changes in Descemet's membrane causing a clinical leukoma (Roberts & Bistner, 1968). The corneal opacities often remain as the only sign of dysplastic pupillary membranes if the iris strands completely regress. Additionally, iridolenticular strands can extend from the iris collarette to the anterior lens capsule, with the adhesions resulting in capsular opacities or anterior polar subcapsular cataracts.

Persistent or dysplastic pupillary membranes are differentiated from anterior or posterior synechiae by observing the origin of a pupillary membrane at the iris collarette and the origin of a synechia at the pupillary margin. PPMs within the width of the iris are seen most easily when the pupil is constricted. Iris-to-iris PPMs that span the pupil are visualized more easily with mydriasis as the strands are pulled taut (Barnett & Knight, 1969). Magnification assists in visualizing small PPMs.

Heritable, clinically significant PPMs occur in the Basenji (Barnett & Knight, 1969; Bistner et al., 1971; Roberts & Bistner, 1968). The incidence of PPMs in this breed is high. Examination for PPMs should be performed before pharmacologic dilation of the pupils. The most common manifestation is small, iris-to-iris PPM remnants. Mild forms appear as small, linear, or Y-shaped strands originating from the iris collarette. These minor lesions may spontaneously disappear by 8 months of age. Such lesions have no clinical significance, but they do present a problem regarding genetic control of the disease (Rubin, 1989).

More severe PPMs in the Basenji manifest as cobweb-like strands of iridal tissue that cross the pupil, with or without attachments to the cornea or lens. In severe cases, corneal opacities are present axially or periaxially, secondary to disruption of the endothelium by the pupillary membrane attachment. Corneal opacities vary in size from discrete white dots to long, linear, or broad circular opacities. Slit-lamp biomicroscopy reveals an irregular and optically denser Descemet's membrane. A tail-like appendage or a complete band of pupillary membrane can extend from the opacities into the anterior chamber or iris. Multiple membranes inserting on the central or paracentral lens capsule often result in multifocal or diffuse anterior polar cataracts (Barnett & Knight, 1969; Roberts & Bistner, 1968).

Microscopically, PPMs are nests of connective tissue cells, some of which are pigmented. Areas of corneal opacification seen clinically correlate with defects in Descemet's membrane and the endothelium. Fibrous membranes in the area of the anterior lens capsule and disrupted, liquefied lens fibers are present in areas corresponding to anterior polar

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cataracts. Puppies with extensive pupillary membranes can be blind and have searching nystagmus (Roberts & Bistner, 1968). The mode of inheritance has not been determined, but it does not appear to be a simple recessive or dominant trait (Bistner et al., 1971).

Familial PPMs also occur in the Pembroke Welsh Corgi, Chow Chow, and Mastiff breeds; breeding dogs with any form of PPM other than iris to iris should be avoided (Genetics Committee of the American College of Veterinary Ophthalmologists, 2015; Rubin, 1989). PPMs and congenital cataracts of varying densities occur in the English Cocker Spaniel (Strande et al., 1988). Test matings have not been conclusive but suggest a complex mode of inheritance. A closely inbred line of Chow Chows had PPMs, cataracts, entropion, wandering nystagmus, microphthalmia, and multifocal retinal folds (Collins et al., 1992). Additionally, both minor and severe PPMs occur in many other breeds as well. The genetic implications have not been determined (Barnett & Knight, 1969; Collins & Moore, 1999; Genetics Committee of the American College of Veterinary Ophthalmologists, 2015; Rubin, 1989).

Therapy is rarely necessary for PPMs. Therapy might be beneficial in severely affected eyes, but options are limited. In cases of diffuse corneal opacities with considerable corneal edema, topical instillation of a hyperosmotic agent (i.e., 5% sodium chloride ointment) can be used 3–4 times daily for a trial period of 3–4 weeks. If this treatment is helpful, it can be continued indefinitely. Mydriasis is not recommended for dysplastic pupillary membrane-associated opacities, because pharmacologic dilation induces tension on the membrane attachments, thereby possibly aggravating the corneal or lens lesions. Surgically, the membranes attached to the cornea can be excised after entering the anterior chamber, and phacoemulsification can be done for an extensive anterior capsular or subcapsular cataract. Rarely is surgery indicated for PPMs, even in humans, but excision of the membranes with scissors after elevating the iris from the lens with sodium hyaluronate is effective (Oner et al., 2007; Sari et al., 2008).

Peters Anomaly

Peters anomaly refers to a condition in which a central corneal leukoma is associated with iridocorneal or corneolenticular adhesions that are often associated with other ocular and systemic malformations (Bhandari et al., 2011; Dubielzig et al., 2010; Zaidman et al., 2007). A Springer Spaniel puppy had a central corneal leukoma with cords of uveal tissue extending from the iris collarette to the posterior cornea. Microscopic evaluation corroborated the clinical findings and showed disruptions in Descemet's membrane at the sites of uveal adhesions (Swanson et al., 2001). Displastic pupillary membranes that disrupt the endothelium, leading to corneal opacities, fit the definition of Peters anomaly. In humans, Peters anomaly is categorized based on severity. This condition has been associated with several genetic mutations (Bhandari et al., 2011; Zaidman et al., 2007). Penetrating keratoplasty is often indicated in humans with Peters anomaly (Zaidman et al., 2007).

Aniridia and Iris Hypoplasia

Aniridia, iris hypoplasia, and iris coloboma all refer to incomplete iris development. Aniridia is a total absence of iris tissue, and it is exceedingly rare (Startup, 1966). In instances of apparent aniridia, a rudimentary iris base is usually present and would therefore be properly termed iris hypoplasia. Iris hypoplasia occurs as a partial- or full-thickness defect. Partial-thickness hypoplasia (i.e., incomplete iris coloboma) is a defect of one or more, but not all, layers of the iris. In cases of full-thickness hypoplasia, complete iris coloboma, the ciliary body processes, zonules, and equator of the lens can be visualized (Fig. 21.6). A complete iris coloboma is a result of localized developmental failure of all layers of the iris. These colobomas are located at the pupillary margin (i.e., notch coloboma), at the base of the iris (e.g., iridodiastasis), or within the iris body (i.e., pseudopolycoria; Barnett & Knight, 1969; Startup, 1966). Colobomas in the ventral aspect of the iris occur secondary to failure of closure of the optic fissure and are referred to as typical colobomas. Colobomas in other locations are referred to as atypical colobomas and are caused by primary abnormalities in the outer layer of the optic cup (Cook, 1995). Iris coloboma is a common feature of ocular merling (see Fig. 21.2 and Fig. 21.3).



Figure 21.6 This mixed-breed dog has unilateral iris hypoplasia. A complete lack of iris is seen clinically at the 7–9 o'clock position, revealing the ciliary processes and lens equator. No pupillary light response could be elicited in this dog. Vision and the remainder of the ocular examination were normal.

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Other Congenital Pupillary Abnormalities

Several other congenital pupillary abnormalities occur as sporadic abnormalities or in conjunction with previously described anomalies. Polycoria, an iris with more than one pupil with associated musculature, is extremely rare. More often, pseudopolycoria is present. Pseudopolycoria refers to multiple colobomas in the iris body that do not have associated pupillary musculature. Dyscoria is an abnormally shaped pupil, and corectopia is a pupil in an anomalous position. Microcoria is a congenital miosis resulting from absence of the dilator muscle.

Miscellaneous Congenital Abnormalities

Abnormal, lightly pigmented irides occur in beagles with hereditary tapetal degeneration (Burns et al., 1988). The melanosomes in the iris stroma and choroid of affected dogs are fewer in number than those found in the irides of unaffected beagles. The iris and ciliary body pigmented epithelium contain melanosome organelles, but no normal melanosomes. In addition, the melanin deposition is patchy and irregular. The condition might result from a defect in synthesis of the matrix component of melanosomes, resulting in absent or abnormal deposition of melanin and autophagy of these organelles (Burns et al., 1988).

A litter of Springer Spaniel pups had multiple ocular defects, including microphthalmia, PPMs, ciliary body dysplasia, lens luxation, and cataract. The puppies were blind and smaller than normal but were otherwise healthy. Microscopically, the pars plicata had irregular and thickened margins, and the zonules were organized but abnormal in length and shape (Dubielzig et al., 1985b). Ciliary body hypoplasia has been seen in dogs with multiple ocular defects (Gwin et al., 1981; Martin & Leipold, 1974).

Congenital uveal cysts occur alone or in conjunction with other ocular anomalies. Additionally, congenital cysts might not be observed until the dog is older, making the diagnosis of "congenital" questionable. One explanation for the development of an iris cyst is failure of fusion of the two layers of the primary optic vesicle. Failure of the two embryonal neuroectodermal layers to fuse allows fluid to accumulate between these otherwise contiguous epithelial layers. Cysts located at the pupillary margin are associated with a persistent or excessive development of the marginal sinus (Duke-Elder, 1963a). Another possible explanation for congenital cysts is entrapment of surface ectodermal epithelium, neuroectoderm, and mesodermal tissue during development (Deehr & Dubielzig, 1998; Grutzmacher et al., 1987).

Cysts often enlarge, suggesting that a limited proliferative or secretory activity of the epithelial cells remains (Duke-Elder, 1963b). Microscopically, the cysts are simply composed of heavily pigmented epithelial cells (Carter & Mausolf, 1970). Cysts are located caudal to the iris in association with the ciliary body or the posterior epithelium of the iris, at the pupillary margin, or free in the anterior chamber or vitreous. Uveal cysts are particularly common in retriever breeds, but they also occur in other breeds (Corcoran & Koch, 1993; Genetics Committee of the American College of Veterinary Ophthalmologists, 2015; Rubin, 1989; Startup, 1966). Anterior uveal cysts are discussed in more detail under "Degenerative Iridal Changes."

Anterior segment dysgenesis, which is an anterior chamber–cleavage anomaly syndrome, has been described in Doberman puppies (Arnbjerg & Jensen, 1982; Bergsjo et al., 1984; Lewis et al., 1986; Peiffer & Fischer, 1983). Affected eyes are blind and have variable microphthalmia and opaque corneas. Malformation of mesodermal, ectodermal, and neuroectodermal tissues is involved. The suspected cause is a primary defect in formation of the neuroectodermal optic cup (Peiffer & Fischer, 1983). Microscopically, anterior segment dysgenesis is characterized by a thinned corneal epithelium and stroma, absent Descemet's membrane and endothelium, undifferentiated anterior uveal tissue with lack of iridocorneal angle differentiation, and unencapsulated globules of lens material. Occasionally, rudimentary iris leaflets or elongated ciliary processes are present. Posterior segment anomalies include hyperplastic primary vitreous, hyaloid artery remnants, retinal dysplasia, and retinal detachment (Arnbjerg & Jensen, 1982; Lewis et al., 1986; Peiffer & Fischer, 1983). The mode of inheritance in Doberman Pinschers is thought to be autosomal recessive (Lewis et al., 1986). Unfortunately, there is no treatment. Similar multiple congenital ocular anomalies occur in St. Bernard puppies with some differences, such as acorea, aphakia, and optic nerve hypoplasia (Martin & Leipold, 1974).

Degenerative Iridal Changes

Senile Iris Atrophy

Spontaneous, progressive thinning of the stroma or pupillary margin of the iris is a common finding in older dogs and occurs in all breeds. Most commonly, the pupillary margin develops a scalloped, moth-eaten appearance (Fig. 21.7). In these dogs, atrophy of the pupillary muscles often results in dyscoria and may lead to a reduced or absent pupillary light response. Therefore, iris atrophy can be a cause of efferent pupillary abnormalities.

Senile iris atrophy often initially manifests as a subtle color change: the natural iris color fades, and foci of hyperpigmentation develop as stroma is lost and posterior pigmented epithelium is exposed. As degeneration progresses, additional thinning results in loss of pigmented epithelial layers. With transillumination, affected areas appear as translucent patches or openings within the iris, and are most striking when light is reflected from the tapetal fundus.

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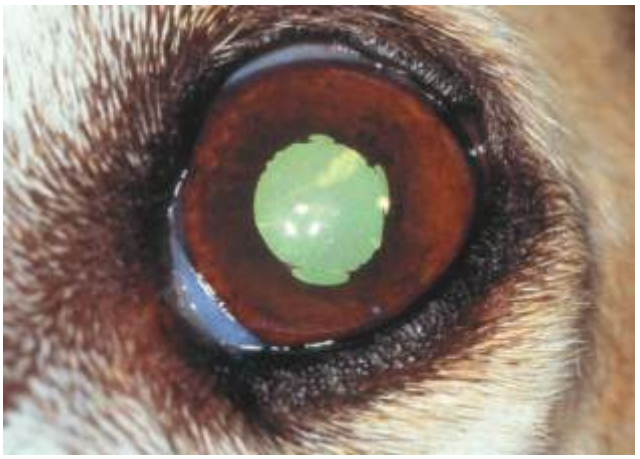


Figure 21.7 Iris atrophy at the pupillary margin of the iris is present in a geriatric dog.

These full-thickness defects should not be mistaken for congenital iris colobomas (Fig. 21.8). Vision is unaffected by iris atrophy; however, severe atrophy results in photophobia.

Secondary Iris Atrophy

Glaucoma and chronic uveitis often predispose to degenerative changes in the iris resembling those of senile iris atrophy. Signs of preexisting disease such as buphthalmia, lens subluxation, synechiae, or pigment dispersion on the anterior lens capsule aid in the diagnosis. As with senile iris atrophy, there is no specific treatment, but any active, concurrent glaucoma or uveitis should be treated.

Uveal Cysts

Uveal cysts are common in dogs. They arise either from the posterior pigmented epithelium of the iris or from the inner ciliary body epithelium and therefore are neuroectodermal in origin (Carter & Mausolf, 1970; Hildreth et al., 1991; Rush et al., 1982). Cysts are either congenital or acquired. They occur most commonly in Golden Retrievers, Labrador Retrievers, and Boston Terriers (Corcoran & Koch, 1993).

Cysts arise from the pupillary margin, the posterior iris face, or the pars plicata of the ciliary body. Examination through a dilated pupil facilitates visualization of cysts in the posterior chamber. Potential sequelae of larger cysts include vision impairment, corneal endothelial opacities, pigmentation of the anterior lens capsule, mechanical interference with iris function, and aqueous outflow obstruction with secondary ocular hypertension (Bedford, 1980; Deehr & Dubielzig, 1998; Spiess et al., 1998). Most cysts are first noted clinically in adult dogs and occur spontaneously; however, trauma and inflammation have also been proposed as initiating etiologies. When cysts occur without preexisting eye disease, it is possible that a defect was present at birth, and the cysts were not recognized until several years of age (see "Miscellaneous Congenital Abnormalities"; Duke-Elder, 1963a).

Uveal cysts are usually benign and incidental findings in dogs. Iridal or ciliary cysts can be unilateral, bilateral, single, or multiple. Size varies and the dark or translucent masses can be spherical, oval, or elongated (Fig. 21.9). Uveal cysts are usually brown or black, though light brown and amelanotic cysts occur (Fig. 21.10). They are often found free-floating within the anterior chamber or attached to the iris or ciliary body. Rarely, dislodged uveal cysts can move into the vitreous if the vitreous is degenerated or detached. Occasionally, the cysts are not visible unless the pupil is dilated, especially if they are located on the posterior iris surface or the ciliary body. A deflated uveal cyst appears as a round, thin layer of pigment on the corneal endothelium or the anterior lens capsule. In most cases, uveal cysts do not obstruct vision or cause lens or corneal opacities. The association with cysts and glaucoma in Golden Retrievers, Great



Figure 21.8 Severe iris atrophy involves the iris stroma in this geriatric dog.



Figure 21.9 A single large pigmented translucent uveal cyst and several smaller cysts are present in the ventral anterior chamber. An immature cataract is also visible.

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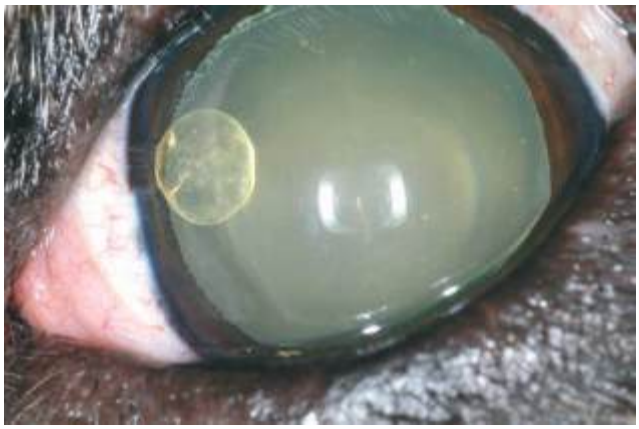


Figure 21.10 A single nonpigmented uveal cyst is present in the nasal aspect of the anterior chamber.

Danes, and Bulldogs is described later under "Pigmentary and Cystic Glaucoma." Uveal cysts are diagnosed based on clinical appearance. The most definitive diagnostic test is performed by transilluminating the cysts with a bright light source. Cysts should transilluminate, whereas neoplastic masses will not transilluminate. This test is not always reliable for very small cysts or cysts that are not within the pupil, as this location makes it difficult to generate a tapetal reflection through the cyst. Ocular ultrasound can be used in questionable cases, as cysts will not be hyperechogenic throughout as a mass would be.

Uveal Cyst Removal

Because most uveal cysts are benign and generally do not interfere with vision, they usually do not require treatment. However, attached or free-floating uveal cysts that occlude the pupil and compromise vision, or multiple cysts that might occlude the angle, can be aspirated with a small-gauge needle or deflated with a laser. Because these cysts generally arise from the posterior iris pigment layer, they are darkly pigmented and are easily visualized. Poorly pigmented cysts might not be amenable to diode laser therapy. Surgical removal or aspiration of the cysts might prevent progressive angle closure when identified and treated early (Spiess et al., 1998).

The use of semiconductor diode lasers for deflation and coagulation of anterior uveal cysts is effective. Perioperatively, mydriatics and corticosteroids are used topically. The operating microscope attachment and the indirect ophthalmoscope facilitate treatment of these cysts, because these two delivery systems emit a converging laser beam appropriate for transcorneal treatment of intraocular cysts and tumors. Topical anesthetic, sedation, or general anesthesia can be used. Discomfort or aqueous flare is not seen postoperatively (Gemensky-Metzler et al., 2004). Occasionally, remnants of the cyst remain attached to the corneal endothelium.

Alternatively, a straight, 25- or 27-gauge needle attached to a tuberculin syringe can be introduced into the anterior chamber at the limbus. The precise point of entry will vary with the cyst location and should facilitate comfortable hand positioning for the surgeon. The tip of the needle is directed toward the cyst. The thin cyst wall is readily penetrated by the beveled needle tip. After the cyst wall is punctured, slight negative pressure is exerted on the syringe plunger to collapse the cyst. The needle is then slowly withdrawn. Portions of the collapsed cyst often remain free in the anterior chamber or as a residual layer of pigment on the ventral corneal endothelial or anterior lens surface. Postoperatively, a single instillation of topical mydriatic agent and short-term use (e.g., 3 times daily for 7 days) of a topical antibiotic–corticosteroid solution is recommended.

Uveal Inflammation

Uveitis refers to inflammation of any aspect of the uvea. Uveitis occurs in conjunction with many intraocular and systemic diseases and is common because of the highly vascular nature of the tissue, its immunosensitivity, and its close proximity to other structures. Similar to inflammation elsewhere, inflammation in the uvea consists of three basic events: increased blood supply, augmented vessel permeability, and white blood cell migration to the injury site (Dalma-Weiszhausz & Dalma, 2002). Anterior uveitis refers to inflammation of the iris and ciliary body, posterior uveitis refers to inflammation of the choroid, and panuveitis refers to inflammation of all three portions of the uvea. More specifically, iritis and cyclitis may be used to describe inflammation of the iris and ciliary body, respectively. However, anterior uveitis is the term most commonly used, because differentiating between iritis and cyclitis clinically is very difficult and usually both tissues are inflamed simultaneously. Posterior uveitis, or choroiditis, can occur independently from anterior uveitis. A more advanced condition, termed endophthalmitis, is inflammation involving the ocular cavities and adjacent structures. Panophthalmitis is inflammation involving all tunics of the eye, and it may result in signs of orbital disease as well. Chapter 25 discusses posterior segment inflammation.

Etiopathogenesis of Uveitis

Uveitis occurs either independently of disease in other ocular structures or secondary to lens, corneal, or scleral disease. Additionally, uveitis can be associated with primary ocular disease or be secondary to neoplastic, infectious, or immune-mediated diseases. Elucidating the etiology of uveitis in the dog can be difficult. However, because uveitis can lead to blindness or be a sign of a potentially fatal disease, attempting to define the etiology is always warranted. Uveitis should be approached in a systematic fashion, evaluating for the most common diseases based on signalment, historical

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information including travel, ocular and physical examination findings, and locale.

Many etiologies for uveitis exist in all animal species. Most simply, causes can be divided into endogenous and exogenous. Endogenous causes originate from within the eye or spread to the eye from the bloodstream or from contiguous structures. Endogenous causes account for most cases of uveitis and include infectious, neoplastic, toxic, metabolic, and autoimmune diseases. Immune-mediated and autoimmune disease is the most rapidly growing group of diseases responsible for endogenous uveitis. Several endogenous antigens have been found to be associated with uveitis, including retinal-S antigen, melanin, and lens and corneal proteins (Bellhorn et al., 1988; Kanemaki et al., 2015; Morgan, 1989; Parma et al., 1985; Wilcock & Peiffer, 1987). Exogenous causes arise from outside the eye and most commonly involve various traumas but also include radiation exposure and chemical injuries (Jamieson et al., 1991; Martins et al., 2016; Tetas Pont et al., 2016). Trauma also includes surgical procedures and both perforating and nonperforating injuries, with or without secondary infection.

As stated previously, many diseases and conditions cause uveitis in the dog. Idiopathic uveitis is the most common diagnosis given to dogs with anterior uveitis (Gelatt & MacKay, 2004; Massa et al., 2002). One review found that an etiology for anterior uveitis could not be determined in 47% of the dogs. Infectious disease accounted for 18%, there was neoplasia in 25%, and uveodermatologic syndrome (UDS) or a vaccine reaction in 10% of the dogs (Massa et al., 2002). This study excluded dogs with anterior uveitis secondary to cataracts or trauma. Known causes of uveitis in the dog are listed in Table 21.1. Several reviews have also addressed uveitis in small animals (Crispin, 1988; Gwin, 1988; Hakanson & Forrester, 1990; Massa et al., 2002; Townsend, 2008).

General Uveal Inflammatory Responses

Most knowledge regarding canine uveitis has been derived from experimental and clinical observations in a variety of animal species, including humans. Clinicians must recognize that species variation exists and that some data is not applicable, and might even be contradictory to mechanisms occurring in the dog. Still, several unique aspects of uveal inflammation do cross species and play a role in the uveal response. These include (1) the blood–aqueous barrier, (2) the concentration of ascorbic acid and other antioxidants in the aqueous humor, and (3) anterior chamber-associated immune deviation (ACAID; Rosenbaum et al., 1999).

Uveitis is always initiated by tissue injury, often incited by trauma, bacteria, fungi, parasites, viruses, or immune-mediated disease. The ensuing clinical signs are attributed to disruption of the blood–ocular barrier and release of various chemical mediators after tissue damage. The blood–ocular barrier is composed of the blood–aqueous

Table 21.1 Diseases proved or suspected of causing uveitis in the dog.

Algal
Prototheca sp.
Bacterial
Brucella canis
Borrelia burgdorferi
Leptospira sp.
Septicemia of any cause
Fungal
Aspergillus fumigatus
Blastomyces dermatitidis
Candida albicans
Coccidioides immitis
Cryptococcus neoformans and *C. gattii*
Histoplasma capsulatum
Immune-mediated
Cataracts (lens-induced uveitis)
Immune-mediated thrombocytopenia[a]
Immune-mediated vasculitis
Lens trauma (phacoclastic uveitis)
Uveodermatologic syndrome
Metabolic
Diabetes mellitus (particularly diabetic cataract-induced uveitis)
Hyperlipidemia[a]
Systemic hypertension[a]
Miscellaneous
Coagulopathies[a]
Deep necrotizing or nonnecrotizing scleritis
Drug-induced (particularly miotic and prostaglandin agents)
Idiopathic
Idiopathic uveitis and exudative retinal detachment
Pigmentary and cystic glaucoma in the Golden Retriever[a]
Radiation therapy[a]
Snake bite (pit vipers) periocular and ocular
Trauma[a]
Toxemia of many causes (e.g., pyometra)
Ulcerative keratitis (any cause)
Miscellaneous Parasitic
Ophthalmomyiasis interna posterior (*Diptera* sp.)
Ocular filariasis *(Dirofilaria immitis; Angiostrongylus vasorum)*
Ocular larval migrans (*Toxocara* and *Balisascaris* sp.)
Neoplastic and Paraneoplastic Disorders
Histiocytic proliferative disease
Hyperviscosity syndrome[a]

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Table 21.1 (Continued)

Granulomatous meningoencephalitis
Primary and secondary neoplasms (lymphosarcoma most common)[a]
Protozoan
Leishmania infantum
Toxoplasma gondii
Neospora caninum
Trypanosoma evansi
Rickettsial
Ehrlichia canis or *E. platys*
Rickettsia rickettsii
Viral
Adenovirus infection (including postvaccinal "blue eye")
Herpes virus

[a] These etiologies often lead to aqueous flare or hyphema, but do not necessarily have an inflammatory component.

barrier anteriorly and the blood–retinal barrier posteriorly. Morphologically, the blood–aqueous barrier consists of tight junctions (zonulae occludens) between nonpigmented ciliary body epithelial cells, tight junctions and gap junctions in the iris vascular endothelium, and nonfenestrated impermeable capillaries in the iris (Freddo & Sacks-Wilner, 1989; Gabelt & Kaufman, 2011). Evolutionary divergence in ocular defense mechanisms has resulted in extreme differences of blood–aqueous barrier stability among different mammalian species. Primates have a very stable barrier, whereas the rabbit has an extremely labile barrier, which destabilizes in response to minute ocular irritants (Bito, 1984). Stability of the canine blood–aqueous barrier lies somewhere between these two extremes. Destabilization of the blood–aqueous barrier marks the onset of anterior uveitis.

Three phases of the ocular inflammatory response have been described: active, subacute, and chronic responses (Peiffer, 1980; Yanoff & Sassani, 2014). As with inflammation in other tissues, the acute phase has the five cardinal signs, including redness and heat, which are both caused by increased rate and volume of blood flow; increased mass, caused by exudation of fluid and cells; and pain and loss of function, which are both caused by outpouring of fluid and irritating chemicals. Immediately after injury, the arterioles contract for approximately 5 minutes and then gradually dilate because of histamine release from mast cells and factors released from plasma (kinin, complement, and clotting systems). The chemical mediators, which include histamine, serotonin, kinins, plasmin, complement, prostaglandins (PGs), and peptide growth factors, increase vascular permeability by causing the intercellular tight junctions in the vascular endothelial cells to open, allowing fluid to leak into the tissues. After several hours, the blood flow decreases to below normal because of increased viscosity of the blood resulting from fluid loss. Early after injury, various types of blood cells marginate (polymorphonuclear neutrophils, PMNs), then leave the vessels via emigration (PMNs), emperipolesis (PMNs, small lymphocytes, macrophages, and immature erythrocytes), and diapedesis (mature erythrocytes; Yanoff & Sassani, 2014). Additionally, plasma proteins, initially albumin and then larger globulins, leak through the vessel walls (Peiffer, 1980). Reported mean values for aqueous protein in the noninflamed canine eye using different assays range from 21 ± 1.2 mg/dL to 37.4 ± 7.9 mg/dL (Blogg & Coles, 1971; Brightman et al., 1981; Krohne & Vestre, 1987; Olin, 1977). In sharp contrast, aqueous protein values at various intervals after the onset of uveitis range from approximately 1200 mg/dL to as high as 6600 mg/dL in experimental and clinical cases, respectively. Additionally, flaremetry readings in clinically normal canine eyes range from 1.4 to 7.0 photon count (PC)/msec, with actual protein measurements ranging from 5 to 28 mg/dL. One eye with uveitis that was considered subjectively to have a 3+ flare had flaremetry readings as high as 246 PC/msec and a protein concentration of 729 mg/dL (Krohne et al., 1995).

The acute phase of the ocular inflammatory response is exudative. There are four types of exudates: serous exudate is composed primarily of protein; fibrinous exudate is composed primarily of fibrin; sanguineous exudate is composed primarily of erythrocytes; and purulent exudate is composed primarily of PMNs and necrotic products. These exudates are seen clinically as aqueous flare, fibrin clot, hyphema, or hypopyon, respectively (Yanoff & Sassani, 2014). In acute inflammation, the PMN is the predominant type of inflammatory cell present (Olin, 1977). The degranulation or death of PMNs causes additional tissue destruction and increases inflammation by inducing the chemotaxis of mononuclear phagocytes characteristic of the subacute stage (Yanoff & Sassani, 2014).

The subacute stage has special significance because during this period the immunologic reactions are initiated, healing occurs, or there is necrosis, recurrence, or chronicity (Yanoff & Sassani, 2014). If the inflammatory response is localized, the PMNs and mononuclear phagocytes can resolve the injury, and healing is possible with minimal scarring. If the inflammation is profound and uncontrolled, however, granulation tissue formation can result in excessive scarring, with subsequent ocular dysfunction. Granulation tissue is composed of leukocytes, fibroblasts, and proliferating blood vessels, which tend to be leaky when new. If healing ensues, the blood vessels involute, the leukocytes disappear, and the fibroblasts return to a resting state. If healing does not occur because of the inability to control both acute and subacute inflammatory events, the inability to eliminate the causative agent, or both, the inflammation

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becomes chronic (Yanoff & Sassani, 2014). Permanent alterations in uveal vascular structure, permeability, or both have been implicated as the cause of recurrent or chronic episodes of uveitis (O'Connor, 1983).

Distinguishing acute (< 4 weeks) from chronic (> 4 weeks) uveitis on the basis of aqueous protein and cellular determinations is possible. Dogs with acute uveitis have higher protein values (3.5 g/dL) than those suffering from chronic uveitis (1.8 g/dL). Polymorphonuclear cells are more typical of acute uveitis compared with a predominance of small and large mononuclear cells in chronic uveitis (Olin, 1977).

Chemical Mediators of Inflammation

Much effort has been directed to identifying the chemical mediators of ocular inflammation because of the direct therapeutic implications. While progress is always being made toward understanding inflammation, the variations in species' responses to inflammation and the varying diseases among species slow the progress.

PGs are the most widely studied mediators of ocular inflammation and are considered to be primary mediators of ocular inflammation (O'Connor, 1983; Wilkie, 1990b). Cyclooxygenase has been identified in all cell types, except for mature red blood cells (Kulkarni & Srinivasan, 1986), and PGs are produced by the irides of all species studied to date (Yoshitomi & Ito, 1988). The most notable pathologic ocular effects of PGs include miosis, hyperemia, changes in vascular permeability, and alterations in intraocular pressure (IOP), depending on the particular PG and species in question. Most of these effects are caused by direct action on the specific tissue. PGs disrupt the tight junctions between nonpigmented ciliary body epithelial cells and, to a lesser extent, the iridal vasculature, thereby allowing protein exudation and aqueous flare (Adler, 1992; Laties et al., 1966). In the dog, PGF_2 is a potent constrictor of the iris sphincter muscle, whereas PGE_1 and PGE_2 have little effect (Dziezyc et al., 1992; Yoshitomi & Ito, 1988). This action is independent of cholinergic or adrenergic innervations (Yoshitomi & Ito, 1988).

PGs also have normal physiologic functions such as moderation of inflammation, hypotensive effects, and other beneficial therapeutic effects (Bito, 1986; Havener, 1983). The PGs involved in uveitis, however, are present in excessive quantities. The eye has limited amounts of PG 15-dehydrogenase, which is the enzyme responsible for inactivation of PGs; therefore, PGs must be removed by active transport through the ciliary body for inactivation elsewhere. When uveitis is present, these active transport mechanisms are diminished (Bito, 1986; Eakins et al., 1974).

Arachidonic acid derivatives appear to play a key role in ocular inflammation. Arachidonic acid is released from damaged cellular membranes through phospholipases acting on cellular phospholipids (Boothe, 1984). It can then enter one of at least three metabolic pathways: the cyclooxygenase, lipoxygenase, or oxidation pathway (Millichamp & Dziezyc, 1991; Wilkie, 1990a). Each of these pathways has been identified in the eyes of various species, but the relative contribution of each in the genesis of uveitis is poorly defined (Collins & Moore, 1999). The cyclooxygenase pathway produces PGs, thromboxane, and prostacyclin, and the lipoxygenase pathway produces leukotrienes, hydroperoxy, and hydroxyeicosa-tetraenoic acids (Millichamp & Dziezyc, 1991; Wilkie, 1990a).

Leukotrienes are synthesized in the cornea, conjunctiva, anterior uvea, and lens. Species variations exist in the extent and duration of leukotriene production (Dziezyc et al., 1989). Leukotrienes are potent vasoactive substances and chemoattractants. Their chemotactic, humoral, and cellular activities are greater than those of PGs (Boothe, 1984). Leukotriene B_4 has almost no vasoconstrictive activity, but allows adherence of leukocytes to vascular endothelium; this may be an early mechanism for cell migration into the inflamed uvea (O'Connor, 1983). In a canine model of lens-induced uveitis (LIU), levels of leukotriene B_4 were increased during early inflammation (Dziezyc et al., 1989). In addition, dogs that received systemic lipoxygenase inhibitors did not experience the transient rise in IOP during acute uveitis often attributed to PGs, whereas the control dogs did. Another study that used a mild paracentesis model of uveitis concluded on the basis of similar results in treated and control dogs that leukotrienes are not important mediators of blood–aqueous barrier disruption in dogs (Ward et al., 1992a). Furthermore, it was suggested that leukotriene inhibitors might exacerbate uveitis through shunting of arachidonic metabolites to the cyclooxygenase and epoxygenase pathways.

Substance P, an undecapeptide normally present in sensory nerves, appears to be important in uveitis, particularly when associated with corneal irritation (O'Connor, 1983). Ulcerative keratitis causes varying degrees of uveitis, but it does so through a poorly understood "axonal reflex." With corneal irritation, antidromic impulses mediated by the trigeminal nerve (ophthalmic branch) reaching the iris and ciliary body are believed to stimulate release of substance P. This causes vascular dilation and altered permeability as well as PMN chemotaxis. These effects are transient and unlikely to result in permanent uveal changes. The role of substance P in canine uveitis is unclear (O'Connor, 1983; Unger & Tighe, 1984). One study indicated that PGs play a greater role than substance P in the canine ocular irritative response induced by rapid paracentesis, because inhibition of neuropeptide release by topical application of proparacaine did not affect the response of blood–ocular barrier breakdown and miosis (Ward et al., 1992a). However, when topically applied pilocarpine is used as a model for measuring aqueous flare and miosis, pretreatment with proparacaine or with nonsteroidal anti-inflammatory drugs (NSAIDs) inhibits the response equally (Krohne et al., 1998).

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The variation in results of the two studies might be due to the method of inducing aqueous flare. While the pilocarpine model does increase protein in the aqueous humor, it does not appear to do so by interfering with the blood–aqueous barrier (Freddo et al., 2006).

Tumor necrosis factor-alpha (TNF-α) is a cytokine that plays a role in inflammation and immune activation. Durieux et al. (2015) confirmed elevated levels of TNF-α in dogs with acute anterior uveitis and in chronic primary angle-closure glaucoma in comparison to normal controls. The levels were higher in dogs with uveitis than glaucoma (Durieux et al., 2015). Inhibition of TNF-α is used therapeutically in humans; unfortunately, its use is species specific.

Numerous other chemical mediators also have contributory, albeit largely undefined, roles in ocular inflammation. Histamine is important in the initiation of many inflammatory processes, and its release from mast cells leads to an increase in vascular permeability (Yanoff & Sassani, 2014), but histamine's role in canine uveal disease is poorly understood. Reactive oxygen metabolites, angiotensin-converting enzyme, and basic fibroblast growth factor may also play roles in uveitis (Abrams, 1989; Grahn et al., 1992; Mittag, 1984). For information on the direct functional impact of immune cells on the ocular microenvironment and mechanisms of ocular immune homeostasis, see Chapter 6.

Clinical Manifestations and Diagnosis

Anterior uveitis manifests many clinical signs. Some signs are specific for uveitis, such as aqueous flare and hypopyon, while others are general ocular responses, such as blepharospasm and ocular hyperemia. Anterior uveitis can also be a secondary component of other ocular diseases, such as corneal ulceration and glaucoma, demonstrating the need for a complete ophthalmic examination. The clinical signs of uveitis are listed in Table 21.2.

Excessive lacrimation, blepharospasm, and photophobia are readily observed. These signs suggest varying degrees of ocular discomfort not specific to uveitis. Acute uveitis tends to be more painful than chronic uveitis. The pain is referred to the ocular and periorbital regions. Pain and photophobia are caused by ciliary spasm. Excessive lacrimation might occur secondary to photophobia (Hogan et al., 1959).

Ciliary flush is hyperemia of the deep, perilimbal, or circumcorneal anterior ciliary vessels and is common with deep corneal and intraocular disease (i.e., uveitis and glaucoma). Congestion of the conjunctival vessels also commonly occurs with uveitis, and in severe cases uveitis can even lead to chemosis (Hogan et al., 1959). Ciliary flush must be distinguished from superficial conjunctival hyperemia, which is commonly seen with extraocular disease such as allergic conjunctivitis. Distinguishing between these vascular patterns is facilitated by topical application of a sympathomimetic agent (e.g., 1% epinephrine solution). The topical sympathomimetic agent will have a greater immediate vasoconstrictive effect on the superficial conjunctival vessels than on the deeper anterior ciliary vessels (Rubin, 1968). In addition, conjunctival vessels move with the conjunctiva on the surface of the globe, whereas the anterior ciliary vessels remain stationary within the sclera during movement of the conjunctiva over the globe.

Table 21.2 Clinical signs of uveitis.

Anterior Uveitis	Posterior Uveitis	Additional Adverse Sequelae
Aqueous flare	Vitreous opacity	Deep corneal vascularization
Fibrin in anterior chamber	Decreased vision	Ectropion uvea
Keratic precipitates	Chorioretinal granulomas	Iris atrophy
Hypopyon	Retinal detachment	Rubeosis iridis (or preiridal fibrovascular membrane)
Hyphema	Retinal hemorrhage	Secluded pupil and iris bombé
Miosis	Choroidal effusion	Secondary glaucoma
Decreased intraocular pressure	Optic neuritis	Cataract
Ciliary flush		Lens luxation
Corneal edema		Endophthalmitis/panophthalmitis
Iris color change (usually darker)		Phthisis bulbi
Iris swelling		
Pain		
Posterior synechiae		
Decreased vision		
Conjunctival hyperemia		

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Figure 21.11 Severe corneal edema, corneal vascularization, and conjunctival hyperemia are present in this dog with anterior uveitis secondary to blastomycosis.

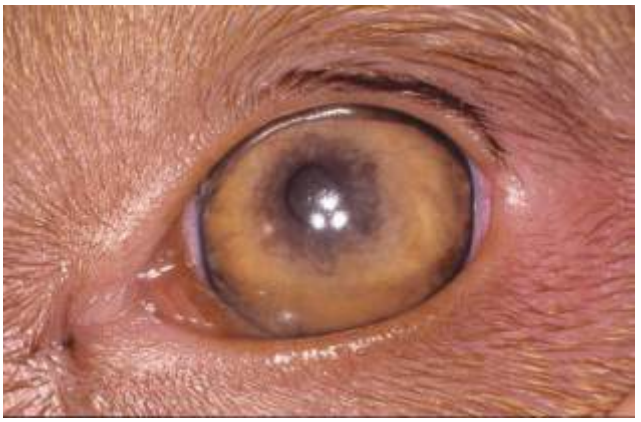


Figure 21.12 Congestion of iris vessels and miosis are evident in a Pharaoh Hound with anterior uveitis secondary to blastomycosis.

Corneal edema with an associated increase in corneal thickness develops with anterior uveitis secondary to both an increase in endothelial permeability and a decrease in Na/K ATPase pump site density (Fig. 21.11; MacDonald et al., 1987). Severe edema may result in bulla formation. Morphologically, edematous endothelial cells with disrupted intercellular junctions and a normal cell density are seen. The exact mechanisms for the damage to the endothelium probably include PGs, oxygen free radicals, and hydrolytic enzymes liberated in part by leukocytes. Persistent corneal edema may be followed by peripheral corneal vascularization. The use of steroids prevents these morphologic and physiologic changes. IOP determination helps to distinguish the corneal edema of uveitis from that of glaucoma, but the two often occur together. Peripheral corneal edema can also occur from extension of inflammation from the limbal circulation (Hogan et al., 1959).

Pupillary constriction, or *miosis*, is a very common sign with anterior uveitis. Miosis occurs in response to PGF_2 acting directly on the iris sphincter muscle (Fig. 21.12; Dziezyc et al., 1992; Yoshitomi & Ito, 1988). Inflammatory mediators also cause painful spasm of the ciliary body musculature, causing what is described as "brow ache" in humans. Subtle miosis is often more apparent when examining both eyes simultaneously in a darkened room using retroillumination with a penlight or Finoff transilluminator. The comparison of light reflected from the tapetal fundi in this technique readily allows detection of disparities in pupil size, or anisocoria. Iris swelling from edema and cellular infiltrates, in conjunction with inflammatory mediators, impedes normal pupil mobility. Subclinical uveitis often manifests with a pupil that dilates more slowly after short-acting mydriatic therapy (i.e., 1% tropicamide) compared with the normal eye. This observation is diagnostic. Conversely, the pupil often responds sluggishly to light. In addition, the pupil may be nonresponsive because of increased IOP seen with secondary glaucoma or synechiae.

Synechiae formation is one of the more serious complications of anterior uveitis. It results from inflammatory cells, fibrin, and fibroblasts leading to adhesions of the iris to the lens or peripheral cornea. Both posterior synechiae and peripheral anterior synechiae occur (Fig. 21.13). Peripheral anterior synechiae form because of anterior chamber shallowing as a result of pupillary block, secondary to organization of inflammatory exudates in the angle with gradual movement of the iris toward the angle structures, and with intense swelling of the iris root (Hogan et al., 1959). Posterior synechiae are a consequence of the lens shape, with the central portion of the lens extending more anteriorly than the peripheral lens. With miosis, the iris is in more intimate contact with the lens, increasing the surface area for synechia formation. Fibrin and other inflammatory products facilitate iris adherence to the lens capsule. Posterior synechiae can cause occlusion of the pupil leading to loss of sight, or seclusion of the pupil resulting in iris bombé with subsequent acute glaucoma (Fig. 21.14). Synechiae often result in a fixed miotic or mid-range pupil. With chronic synechiae, pigment frequently migrates from the surface of the iris onto the anterior lens capsule, which is more likely to interfere with vision if the pupil is miotic. Pigment clumps on the anterior lens capsule usually indicate previous uveitis; however, the pigment clumps can result from congenital remnants of the pupillary membrane. Lens capsular pigment from uveitis is generally darker than the pigment associated with pupillary membranes, and in the latter instance pigment is normally confined to the axial lens surface. Prolonged inflammation in the iris epithelium and stroma often eventually results in iris atrophy that is patchy or diffuse.

Aqueous flare, increased turbidity of aqueous humor, occurs as protein-rich aqueous humor and cellular components accumulate within the anterior chamber after the blood– aqueous barrier has been disrupted. Aqueous flare is

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Figure 21.13 Posterior synechiae is the only evidence of previous anterior uveitis in this eye that has a hypermature cataract.



Figure 21.14 Iris bombé developed secondary to 360 degrees of posterior synechiae, which led to anterior ballooning of the iris in this dog. Episcleral injection is also present.

visualized when particles suspended in the anterior chamber scatter the light, causing a continuous light reflection throughout the chamber. This continuous beam effect is called the Tyndall phenomenon, and it is analogous to shining a flashlight in fog or smoke. Observation of the Tyndall phenomenon is indicative of aqueous flare, and aqueous flare is pathognomonic for anterior uveitis (Berliner, 1966). Varying degrees of aqueous flare are possible, and though this scheme is highly subjective, some clinicians attempt to quantitate flare numerically as 1+ to 4+, with higher numerals indicating increased severity. One grading scheme describes the severity of flare as follows: 1+ indicates faint flare (barely detectable); 2+ indicates moderate flare (iris and lens details are clear); 3+ indicates marked flare (iris and lens details are hazy); and 4+ indicates intense flare (fixed, coagulated aqueous humor with fibrin; Fig. 21.15; Hogan et al., 1959). Flare is best detected with slit-lamp biomicroscopy, but other focal light sources (e.g., the small aperture of a direct ophthalmoscope) in a very dark room are also useful. Experimentally, laser flaremetry and fluorophotometry are used to assess the amount of protein in the aqueous humor. The flare meter quantitates the level of aqueous humor protein by measuring the photon count of scattered light, which is proportional to the amount of protein in the anterior chamber (Krohne et al., 1995). In experimental studies of uveitis, fluorophotometry, in which fluorescein concentrations in the anterior chamber are measured after intravenous injection of fluorescein, has also been used (Ward et al., 1991).



Figure 21.15 The visible haziness in this eye is caused by slight corneal edema and aqueous flare.

The term *fibrinous* (or *plasmoid*) *aqueous* refers to aqueous humor that has an increased level of protein, approximating that of normal plasma. This condition occurs most commonly in cases of acute, severe anterior uveitis. If fibrinous exudation is severe, fibrin clots form in the anterior chamber. Lipid-laden aqueous is also possible if the patient has concurrent hyperlipidemia, in which the aqueous assumes a milky-white appearance (Fig. 21.16; Olin et al., 1976). A specific cause-and-effect relationship between hyperlipidemia and uveitis is not well established; however, in most instances lipids simply enter the chamber with blood–aqueous barrier breakdown, as do large proteins.

Cells from the inflammatory process pass into the aqueous humor either from diffusion or from active migration from the uvea. They are either manufactured locally or egress through the capillary walls from the blood into the uveal tissue and into the aqueous humor (Hogan et al., 1959). Keratic precipitates (KPs) are accumulations of inflammatory cells, fibrin, and iris pigment that settle on the corneal endothelium (Fig. 21.17). KPs are usually located inferiorly on the cornea in a triangular shape, with the apex located superiorly. Convection currents in the anterior chamber that rise along the warm iris and fall along the cooler cornea create the characteristic formation (Tessler, 1989). KPs can be readily missed, however, if the examiner is not specifically looking for them. Detection of KPs is facilitated by magnification and

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Figure 21.16 Lipoid aqueous is visible in the anterior chamber of this Miniature Schnauzer.



Figure 21.17 Small keratic precipitates are visible on the ventral half of the corneal endothelium.



Figure 21.18 Hyphema, filling over half the depth of the anterior chamber, occurred secondary to systemic hypertension and retinal detachment in this Beagle.



Figure 21.19 Hypopyon is present in the ventral anterior chamber in this dog with lymphosarcoma.

gently tilting the animal's head downward, thereby facilitating upward rotation of the eye and ready examination of the ventral cornea. In painful eyes with protrusion of the nictitating membrane, KPs are especially difficult to observe. It is important to note KPs because their presence is always indicative of active or previous uveitis. In some granulomatous conditions, KPs tend to form as large, waxy-yellow deposits. Berliner (1966) notes that these deposits are made of plasma cells and macrophages typical of granulomatous inflammation, and that they have a greater tendency to agglutinate and adhere to the cornea than do lymphocytes and polymorphonuclear cells, which are typical of nonspecific uveitides. However, lymphocytes and polymorphonuclear cells can also form "nongranulomatous" KPs, which tend to be smaller (Whitcup, 2010). Varying amounts of pigment are present in KPs, with larger amounts seen with chronicity.

The deposits of red and white blood cells within the anterior chamber are the most marked examples of blood–uveal barrier breakdown and are termed *hyphema* and *hypopyon*, respectively (Fig. 21.18 and Fig. 21.19). In both instances, cellular components typically gravitate toward the ventral anterior chamber and settle in a homogenous layer. If bleeding was initially extensive or is continuous, complete (i.e., total) hyphema with filling of the entire anterior chamber occurs. Layering in the hyphema often indicates rebleeding. Occasionally, iridal hemorrhage occurs (Fig. 21.20). Clotted blood can also be observed. The term *eight-ball hyphema* has been used to describe complete hyphema of 5–7 days' duration, when the blood turns from bright red to bluish black. Blood staining of the cornea can occur, especially with large hyphemas, corneal epithelial damage, and elevated IOP (Brandt & Haug, 2001). Hypopyon can be a result of sterile inflammation, infection, or neoplasia. Hypopyon rarely occupies more than a third of the anterior chamber and is easily missed, because the ventral anterior chamber is often obscured by the third eyelid. Generally, hypopyon leaves the eye rapidly through the trabecular meshwork when treatment of the inflammatory processes is initiated.

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Figure 21.20 Iridal hemorrhages are present on the iris of this dog with immune-mediated thrombocytopenia.



Figure 21.21 A preiridal fibrovascular membrane is present on the surface of this iris. Because this iris was very lightly pigmented, the membrane can be seen as a fine meshwork of small vessels on the iris. The clinical term is rubeosis iridis. Areas of posterior synechiae are also present.

Preiridal fibrovascular membranes (PIFMs) arise from the anterior border layer of the iris and develop secondary to chronic ocular diseases such as uveitis, glaucoma, intraocular neoplasia, and retinal detachment (Peiffer et al., 1990). The clinical term for this condition is *rubeosis iridis*. Clinically, a haphazard array of very small vessels is seen on the iridal surface (Fig. 21.21). PIFMs can extend over the lens or pectinate ligaments and are differentiated from normally present but dilated iridal vessels by the haphazard organization, as compared to the radial orientation of normal iridal vessels. PIFMs are always preceded by ocular disease, and their development can lead to hyphema because of the vessel wall fragility, and to glaucoma because of membrane extension over the iridocorneal angle. Microscopically, cellular, vascular, and fibrous membranes are observed on the anterior face of the iris. Cellular membranes appear as a monolayer of plump to spindloid cells; fibrous membranes consist of fibrous tissue at varying stages of maturation; and fibrovascular membranes contain blood vessels that arise from the iridal vessels. Well-developed PIFMs consist of blood vessels with plump endothelial cells, spindle cells, inflammatory cells (primarily lymphoplasmocytic), and an extracellular matrix. Immunohistochemically, the extracellular matrix stains positive for collagen, mucins, and usually laminin. The vessels, which are CD31 positive, and spindle cells are both positive for laminin, vimentin, smooth muscle actin, vascular endothelial growth factor (VEGF), and COX-2 (Zarfoss et al., 2010). Another study found that both the cellular and fibrovascular membranes are negative for cytokeratin AE1/AE3 and positive for vimentin. The endothelial cells lining the vessels in the fibrovascular membrane are positive for factor VIII-related antigen, but the cellular membranes are not (Bauer et al., 2012). The pathogenesis of membrane formation is not known, but may be related to hypoxia and angiogenic and fibroblastic stimulatory factors from chronic inflammation and neoplasia (Peiffer et al., 1990; Yanoff & Sassani, 2014). These three types of membranes most likely represent a continuum of maturation, or the cellular membrane might arise from a separate mechanism (Bauer et al., 2012; Peiffer et al., 1990). Because of the positivity for VEGF, VEGFR1, VEGFR2, and COX-2 and similarities between all PIFMs regardless of the inciting ocular disease, in the future there may be a way to pharmacologically interfere with PIFM formation (Binder et al., 2012; Zarfoss et al., 2010).

In addition to rubeosis iridis, diffuse iris hyperpigmentation can occur with chronic anterior uveitis. This condition is more obvious in eyes with lightly pigmented irides and in cats.

Decreased IOP is one of the earliest and subtlest indications of uveitis. Proposed mechanisms for decreased IOP include both decreased aqueous humor production with breakdown of the blood–aqueous barrier and increased uveoscleral flow, mediated in part by PGs (Gabelt & Kaufman, 2011; Millichamp & Dziezyc, 1991; Toris & Pederson, 1987). IOP varies depending on the duration and severity of uveitis. In acute or subacute uveitis, IOP is usually decreased for the previously mentioned reasons; in chronic uveitis, fibrosis or atrophy (or both) of the ciliary body may contribute to decreased secretory function, with subsequent ocular hypotony. Marked ciliary body dysfunction and hypotony often result in phthisis bulbi.

Secondary glaucoma is a common manifestation of severe or protracted uveitis. The causes of secondary glaucoma include obstruction of the angle by inflammatory debris, iris bombé that occurs with formation of annular posterior synechiae, extensive anterior peripheral synechiae, and formation of PIFMs. An IOP of less than 10 mmHg is consistent with uveitis. A difference of more than 5 mmHg in IOP between the two eyes, even if the values obtained are in the

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normal range, is often significant and suggests that the eye with the lower IOP has uveitis or the higher has impending glaucoma. In one study, nonsurgical anterior uveitis was found to be the most common cause of secondary glaucoma (Johnsen et al., 2006). In another study, cataract formation, specifically, was found to be the most common cause of secondary glaucoma (Gelatt & MacKay, 2004). Some infectious diseases, such as blastomycosis, frequently lead to secondary glaucoma. Glaucoma can result from intraocular neoplasia; however, it is usually a late manifestation.

Cataracts, especially anterior subcapsular cataracts, commonly develop secondary to chronic anterior uveitis. They most likely arise from inflammatory mediators in the aqueous humor interfering with normal lens metabolism. Lenticular changes are not specific and include epithelial metaplasia or posterior migration and liquefaction, degeneration, or necrosis of lens fibers (Eagle & Spencer, 1996). Posterior synechiae can also result in cataract formation.

Diagnostic Tests for Uveitis

When uveitis is diagnosed, an attempt should be made to identify the etiology. Some causes are readily apparent, such as when anterior uveitis occurs in conjunction with a hypermature cataract. Conversely, extensive diagnostic testing and evaluation frequently do not lead to a specific etiology. Complete ophthalmic and physical examinations are always indicated. Regarding the ophthalmic examination, special attention should be paid to the cornea and lens of the affected eye and the fundi of both eyes (e.g., presence of chorioretinitis). Physical examination should include evaluation of the skin, looking for depigmented areas or draining lesions; lymph node palpation, auscultation, and abdominal and possibly rectal (especially in intact male dogs) palpation. A complete blood count and serum panel are usually indicated. Selected titers or antigen testing are run based on the endemic diseases in the dog's location and in areas where the dog may have traveled. Thoracic radiographs are also considered part of the minimal screening protocol when systemic disease is suspected. Radiographs are evaluated for evidence of metastatic or fungal diseases. Additional serologic tests and diagnostics are indicated according to the clinician's index of suspicion. Refer to "Uveal Manifestations of Selected Diseases" in this chapter as well as to Chapter 36, Part 1 for further discussion.

Cytologic evaluation of aqueous humor, bacterial or fungal culture of the aqueous, vitreous aspirates, or a combination thereof may be beneficial in determining the cause of uveitis. Aqueous aspirates yield useful and positive results most often in eyes with visible exudate or in animals with lymphosarcoma (Linn-Pearl et al., 2015; Olin, 1977; Wiggans et al., 2014b). Most commonly, aqueous aspirates yield nonspecific inflammatory cells. Because of the rarity of specific results and the exacerbation of existing uveitis, the procedure is not recommended in most cases. In patients with concurrent posterior uveal involvement, vitreous aspirates are more likely to yield positive results than aqueocentesis (see Chapters 24 and 25). This procedure should be considered for eyes with marked vitreous opacity, exudative retinal detachments, or panophthalmitis. Care must be taken not to puncture the lens. Intraocular hemorrhage following either aqueous or vitreous aspiration is possible.

Therapy for Anterior Uveitis

Topical anti-inflammatory therapy should be instituted immediately after the diagnosis of anterior uveitis is made, even in those patients with suspected systemic disease. Failure to initiate therapy early in the disease process could result in many adverse sequelae, including synechiae formation, cataract, secondary glaucoma, endophthalmitis, and phthisis bulbi. Topical therapy alone may suffice for mild anterior uveitis, but for severe anterior uveitis, posterior uveitis, and systemic disease, systemic therapy as dictated by the primary disease is also indicated.

Corticosteroids are the primary therapy for the treatment of anterior uveitis. Corticosteroids inhibit phospholipase and the release of arachidonic acid. They decrease cellular and fibrinous exudation and tissue infiltration, inhibit fibroblastic and collagen-forming activity, diminish postinflammatory neovascularization, and decrease vascular permeability (Duke-Elder & Ashton, 1951). Treatment with topical corticosteroids can be initiated in all cases of uveitis pending diagnostics, except in those cases with corneal ulceration. Prednisolone acetate, 1% suspension, is the most commonly prescribed ophthalmic corticosteroid because of its potency and availability. Dexamethasone is also a potent steroid; however, topically applied 1% prednisolone acetate is more effective than dexamethasone sodium phosphate in stabilizing the blood–aqueous barrier (Ward et al., 1992b). Both prednisolone acetate and dexamethasone are more potent than hydrocortisone, and are available as ophthalmic preparations either alone or in combination with antibiotics. An initial application frequency of 4–6 times daily is often required with solutions, compared with 3–4 times daily as recommended for ointments. Subconjunctival corticosteroids are administered in select cases as an adjunct to topical therapy, but they do not serve as a substitute. Triamcinolone acetonide and betamethasone are long-acting steroids that can be administered subconjunctivally. Risks include scleral perforation at the time of injection, granuloma formation, and extraocular muscle atrophy and paralysis (Pappa, 1994). Long-acting steroids should be used judiciously because the effects cannot be reversed in the case of corneal ulceration or infection.

Treatment with systemic corticosteroids or other systemic immunosuppressive drugs is not indicated until diagnostics have been completed. Systemic infectious disease often requires treatment with antibiotics or antifungal drugs.

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Systemic neoplasia frequently requires treatment with chemotherapeutic agents. Systemic corticosteroids are contraindicated in most cases of infectious systemic disease. When systemic prednisone is indicated, a recommended initial dosage is 1–2 mg/kg per day in divided doses per os, followed by gradual reduction.

Contraindications for the use of topical and systemic corticosteroids differ. In general, topical steroids are not used on eyes with corneal ulceration because of the inhibition of corneal healing and possible potentiation of infection and collagenolysis (Hendrix et al., 2002; Tolar et al., 2006). Systemic steroids can be used in dogs with simple, superficial, noninfected corneal ulcers; however, caution should be used, and the cornea should be monitored frequently for deterioration and collagenolysis. Systemic corticosteroids should be avoided in diabetic dogs if possible, and though topical therapy may alter an animal's glucose levels and subsequently its insulin requirements, the clinician must weigh the benefits against the risks. Topical steroids are frequently used to control uveitis after cataract surgery in diabetic animals with very few complications. Additionally, it is well known that systemic steroids suppress the hypophyseal–adrenal axis; topical steroids applied frequently cause a similar suppression (Glaze et al., 1988; Roberts et al., 1984). Therapy with either topical or systemic therapy is gradually reduced as the clinical signs of uveitis resolve and is then maintained at the lowest necessary dose.

Many topical NSAIDs are available for ophthalmic use. NSAIDs prevent intraoperative miosis, control postoperative pain and inflammation after intraocular surgery, control symptoms of allergic conjunctivitis, and alleviate signs of uveitis (Giuliano, 2004; Krohne et al., 1998; Ward, 1996; Ward et al., 1992b; Wilkie, 1990b). Most NSAIDs inhibit PG-mediated inflammation by interrupting the cyclooxygenase pathway (Opremcak, 1994). PGs generated via the cyclooxygenase pathway appear to have a greater effect on the blood–ocular barrier in the dog than do leukotrienes or sensory neuropeptides after anterior chamber paracentesis (Ward et al., 1992a). Additional anti-inflammatory actions may include suppression of polymorphonuclear leukocyte locomotion and chemotaxis, decrease in the expression of cytokines and mast cell degranulation, and action as a free-radical scavenger (Giuliano, 2004). The anterior chamber paracentesis model showed that flurbiprofen and prednisolone acetate were equally effective in preventing blood–aqueous barrier disruption (Ward et al., 1992b). In a laser capsulotomy model, flurbiprofen was more effective at preventing blood–aqueous barrier disruption than was prednisolone acetate (Dziezyc et al. 1995). Topical NSAIDs may be used either alone or in combination with corticosteroid therapy; the therapeutic effects of using both NSAIDs and corticosteroids are additive. Many ophthalmic NSAIDs are available and include indomethacin, flurbiprofen, suprofen, bromfenac, ketorolac, and diclofenac. Bromfenac is effective in human patients when dosed once daily, which is in difference to the other ophthalmic NSAIDs that are usually dosed four times daily; however, it is expensive (Henderson et al., 2011; Silverstein et al., 2011). One study showed that injectable flunixin meglumine (50 mg/mL) administered topically gave similar results to topical dexamethasone in dogs with naturally occurring anterior uveitis (Andrade et al., 2003).

An experimental study evaluating the relative blood–aqueous barrier–stabilizing effects of topical NSAIDs in dogs found that diclofenac and flurbiprofen appear to be more efficacious than suprofen (Ward, 1996). Although topical NSAIDs most likely delay corneal wound healing, they are commonly used to treat eyes with concurrent uveitis and corneal ulceration in dogs (Hendrix et al., 2002). However, dogs with corneal ulceration should be monitored judiciously, because a tenuous link with topical NSAID use and collagenolysis has been made in humans. Most cases appear to be associated with increased administration, diabetes mellitus, and the presence of concurrent ocular disease (Gaynes & Fiscella, 2002). The adverse corneal effects might be related to increased matrix metalloproteinase production and alterations in epithelial cell membranes and surface microvilli. Despite the possible adverse effects, the clinical risk–benefit of topical ophthalmic NSAIDs should be assessed. If a favorable response is not noted with treatment, reevaluating the therapeutic approach rather than switching NSAID classes is recommended. In addition, increasing the frequency of administration will not enhance the anti-inflammatory action of NSAIDs, and tapering NSAIDs might help avoid inflammatory rebound (Gaynes & Fiscella, 2002). Topical NSAIDs are applied as often as four times daily.

Relatively little research has been done evaluating the effect of systemic NSAIDs on anterior uveitis. In a repeated anterior chamber paracenteses model, dogs treated with carprofen had lower levels of PGE_2 than placebo-treated dogs, although the levels in both groups were low (Pinard et al., 2011). Results of an aqueocentesis model of induced anterior uveitis showed that flunixin meglumine and tepoxalin, which is no longer commercially available, decreased aqueous PGE_2 concentrations significantly more than carprofen and meloxicam, which did not have significantly lower concentrations than the control (Gilmour & Lehenbauer, 2009; Gilmour & Payton, 2012). Many other systemic NSAIDs are available, but their ocular effects have not been evaluated. Etodolac has been associated with the development of keratoconjunctivitis sicca and should be avoided (Klauss et al., 2007). For years, aspirin and flunixin meglumine were the mainstays of systemic NSAID therapy; however, use of these drugs has been replaced with newer and safer systemic NSAIDs. Systemic NSAIDs are not used in conjunction with systemic corticosteroids because of the greater potential for gastrointestinal complications, and their use is contraindicated when hyphema or generalized bleeding tendencies are present.

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Immunosuppressive drugs, such as azathioprine, are commonly employed in cases of uveitis that are deemed immune mediated and are unresponsive to conventional therapy. Azathioprine has been used most commonly in therapy for UDS in the dog (Morgan, 1989). Frequent blood and platelet counts as well as liver enzyme testing are recommended with this therapy because of potential hepatotoxic and myelosuppressive effects (Moore, 2001). Cyclosporine is another immunosuppressive agent that can be used systemically in the treatment of immune-mediated diseases. Cyclosporine primarily affects T-lymphocyte functions. Topical cyclosporine, as used in the treatment of keratoconjunctivitis sicca, has relatively poor intraocular penetration (Kaswan, 1987). Oral cyclosporine is used in the treatment of UDS; however, many complications have been reported in conjunction with the systemic use of cyclosporine, therefore close monitoring of the patient is imperative when this medication is used (Blackwood et al., 2011; Radowicz & Power, 2005; Steffan et al., 2005). Mycophenolate is also used for immunosuppression in dogs. Dosage adjustments may be necessary in dogs with renal disease. Vomiting, diarrhea, and lethargy are a few of the possible adverse effects (Plumb, 2015).

There are few indications for the use of topical antibiotics in the treatment of anterior uveitis, both because the intraocular inflammation is rarely bacterial in origin and because the intraocular penetration of topically administered antibiotics would not be adequate for treatment of an intraocular infection. Topical antimicrobial therapy is primarily used to prevent bacterial infection of corneal ulcers that may be present concurrently with anterior uveitis. If ulceration occurs during topical steroid therapy, treatment with an ophthalmic antibiotic preparation should be initiated. The topical steroid should be discontinued and initiation of treatment with an ophthalmic NSAID might be indicated. While ophthalmic antibiotics are often combined with corticosteroids, there is little indication for the use of this combination of drugs in the treatment of anterior uveitis. Frequently the greatest indication for the use of antibiotic–steroid combinations is when an ointment is needed because there are no commercially available ointments that contain only a steroid.

Systemic antimicrobial therapy for uveitis is indicated for treatment of specific systemic diseases, or for prophylaxis against infection in the case of corneal perforation or intraocular surgery. The blood–aqueous barrier is normally impermeable to many antibiotics, but during active uveitis the blood–aqueous barrier is compromised and drug permeability enhanced. Therefore, it is assumed that systemically administered antibiotics will reach the aqueous humor when trauma, infection, or ocular surgery dictates their use. Chloramphenicol penetrates the normal blood–aqueous barrier more effectively than do other antibiotics (Mauger, 1994). Recovery of infectious organisms by microbial culture of aqueous humor is unlikely in most instances, so antibiotic choice should be based on the odds of a certain bacteria causing the disease process (Olin, 1977). Fortunately, bacterial uveitis is extremely rare in the dog. A particular antimicrobial may be indicated in specific instances, such as doxycycline for the therapy of uveitis secondary to rickettsial diseases and itraconazole for the treatment of blastomycosis.

Parasympatholytic agents are important in uveitis therapy. Atropine is the most efficacious ophthalmic parasympatholytic drug. The two major benefits of parasympatholytic drugs are mydriasis and cycloplegia. Dilating the pupil decreases contact between the iris and lens, thereby minimizing the likelihood of posterior synechiae formation. Dilating the pupil also decreases the possibility of occlusion of the pupil resulting in vision loss. Parasympatholytic agents paralyze the iris (i.e., iridoplegia) and ciliary body (i.e., cycloplegia) musculature (Kachmer-McGregor, 1994). Intraocular pain is primarily derived from ciliary body muscle spasm. Atropine also stabilizes the blood–aqueous barrier by blocking the effect of acetylcholine, which dilates blood vessels (Van Alphen & Macri, 1966). Atropine is contraindicated when IOPs are elevated, with the rare exception of early iris bombé, for which atropine may be beneficial in breaking posterior synechiae. Atropine ointment or solution is the most commonly used parasympatholytic agent and is given to effect with mild uveitis requiring therapy once or twice daily, and more severe cases requiring more frequent application (e.g., four times daily) initially. The actively inflamed eye reacts much more slowly to atropine than does the normal eye, and the effects are shorter lived. The duration of mydriasis in the normal dog eye is 96–120 hours after administration of topical 1% atropine (Rubin & Wolfes, 1962). If synechiae are present at examination, repeated drops of atropine might help break them free. If the synechiae have been present longer than a few days, the continued application of atropine might break them down over several days. The addition of 10% phenylephrine could aid in breaking the synechiae.

Side effects of frequent treatment with topical atropine might include decreased tear production, tachycardia, decreased gut motility, and the potential to precipitate acute glaucoma (Moore, 2001). While the decrease in tear production is statistically significant, the levels do not typically drop below normal (Hollingsworth et al., 1992). However, caution should be used in dogs with borderline tear production and in dogs with ulcerative keratitis.

Tropicamide is a very weak parasympatholytic in comparison to atropine. It can be useful in treating cases of anterior uveitis in which the IOP is borderline high. Tropicamide can dilate the pupil just enough to prevent synechiation and tends to alter the IOP less than atropine. Tropicamide also has a greater mydriatic effect than cycloplegic effect; therefore, mydriasis does not necessarily indicate cycloplegia (Kachmer-McGregor, 1994).

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Uveal Manifestations of Selected Diseases

The following discussion summarizes selected diseases that are documented causes of uveitis in the dog. Complete ophthalmic and physical examinations are necessary in all cases of uveitis. Many ophthalmic and systemic diseases can lead to uveitis, and results from ocular and physical examinations in conjunction with ancillary diagnostic tests are necessary to confirm or rule out etiologies. Referral to textbooks on internal medicine and infectious diseases is recommended for detailed discussions of specific disorders, diagnostics, and systemic treatment. Refer also to Chapter 36, Part 1.

Lens-Induced Uveitis

LIU is a common complication of cataract in the dog (Dziezyc et al., 1997; Paulsen et al., 1986; van der Woerdt et al., 1992). LIU is typically associated with hypermature cataracts, but fluorophotometry, laser flaremetry, and IOP studies show that dogs with all stages of cataracts have evidence of at least subclinical uveitis (Dziezyc et al., 1997; Krohne et al., 1995; Leasure et al., 2001). Additionally, PGE_2 concentrations are similarly elevated in dogs with mature and hypermature cataracts in comparison to dogs without cataracts (Renzo et al., 2014). Lastly, the presence of D-dimers in the aqueous humor of diabetic dogs and nondiabetic dogs with cataracts and systemically ill dogs supports the presence of intraocular fibrinolytic activity in these dogs. The fibrinolytic activity is greater in dogs with diabetic cataracts than in those without cataracts and those with nondiabetic cataracts (Escanilla et al., 2013).

Most likely, small amounts of lens protein escape the normal lens and induce T-cell tolerance (Denis et al., 2003). Increased immune system exposure to lens crystallins by lens trauma, spontaneous lens resorption, or cataract extraction often overwhelms this tolerance and induces an intraocular or systemic cell-mediated and/or humoral immune response. A negative association between the presence and maturity of cataract and the presence of anti-lens crystallin serum antibodies has been shown. This negative association might occur because of the alteration of lens proteins with maturity of the cataract, affinity maturation of anti-crystallin antibodies, or ACAID (Denis et al., 2003).

Two distinct types of LIU occur in the dog (Fischer, 1983; Wilcock & Peiffer, 1987). Phacolytic uveitis occurs in dogs with rapidly developing or hypermature cataracts, in which soluble lens protein leaks through an intact lens capsule. This type of LIU is nongranulomatous and is characterized by mild lymphocytic-plasmacytic uveitis, not unlike that occurring with most idiopathic uveitides (Fischer, 1983; Wilcock & Peiffer, 1987). The diagnosis of this type of LIU is presumptive and is made on the observation of cataracts and the absence of other ocular or systemic disease. Phacolytic LIU may develop more rapidly in young dogs after the onset of cataract. While phacolytic LIU usually responds to conventional therapy, young dogs may respond more poorly to uveitis therapy, possibly because of higher concentrations of lenticular α-crystallin protein and faster cataract resorption in young dogs (van der Woerdt et al., 1992). LIU must be recognized and treated prior to cataract surgery. Long-term success rates of cataract surgery in dogs with LIU might be lower than in dogs without LIU (van der Woerdt et al., 1992). LIU also needs to be treated in dogs that are not surgical candidates because the uveitis is painful, and treatment may delay the onset of secondary glaucoma. Granulomatous LIU also occurs in dogs with an intact lens capsule but usually occurs in older dogs with rapidly progressing cataracts, especially Miniature Schnauzers, or longstanding cataracts (Fischer, 1983). These eyes have severe uveitis, often with large KPs, and are less responsive to therapy (Fig. 21.22).

Even when dogs undergo cataract surgery, anterior uveitis often persists for months, reducing postoperative success rates. There are many proposed mechanisms, including persistent blood–aqueous barrier breakdown, exposure of the uvea to sufficient amounts of intact lens protein to overwhelm the normal low-dose T-cell tolerance, acquired ability of vasculature endothelial cells to express major histocompatibility complex to antigens, and cross-reaction of anti-lens antibodies with uveal antigens (Strubbe, 2002). After surgery, uveitis can lead to cyclitic membranes, posterior synechia, or pigment migration across the lens capsule.

Phacoclastic uveitis occurs with sudden exposure of intact lens protein in amounts sufficient to overwhelm the normal low-dose T-cell tolerance to lens proteins (Davidson et al., 1991; Wilcock & Peiffer, 1987). Usually this occurs secondary to trauma. Septic implantation syndrome is a relatively new term that probably applies to many of the previously described phacoclastic uveitis cases. In these cases, there is



Figure 21.22 Large keratic precipitates, cataract, and posterior synechia are present in this diabetic Miniature Schnauzer.

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often recent or months-long history of ocular trauma (usually a cat scratch). The early clinical sign is uveitis with a slowly progressive course. Often, the eye is not examined until late in the course of disease, when the cause is not immediately apparent and puncture wounds have healed. Clinically, there is inflammatory exudate centered on the lens with a varying frequency of uveitis, cataract, glaucoma, and corneal disease. Microscopically, there is lens capsule rupture, cataract, and a lenticular abscess with neutrophils in the lens cortex. The inflammation is suppurative with fibrin; lymphoplasmacytic infiltrates are in the iris stroma; and bacteria or fungi are often present within the lens distant from the inflammatory infiltrates. The more common organisms are Gram-positive cocci and Gram-positive rods. Bell et al. (2013) suggest that the term phacoclastic uveitis might be better reserved for cases of sterile lens capsule rupture. Both medical and surgical therapies are used for phacoclastic uveitis (see "Traumatic Uveitis with Lens Rupture" and "Foreign Body Trauma," and Chapters 22 and 23).

Anterior Uveitis Secondary to Corneal, Scleral, and Periocular Disease

Anterior uveitis occurs commonly secondary to corneal ulceration. This response is much greater in horses and rabbits than in dogs. Miosis is the most common clinical sign of anterior uveitis seen in dogs with corneal ulceration, but decreased IOP and aqueous flare also occur. The purpose of topical atropine in the treatment of corneal ulceration is to decrease ciliary spasm, thereby decreasing pain. The mechanism for uveitis secondary to corneal disease was described in "Chemical Mediators of Inflammation."

Non-necrotizing scleritis in dogs is relatively common and does not typically involve the anterior and posterior segments of the eye. Necrotizing scleritis, however, can cause anterior uveitis, vitritis, subretinal masses, tapetal degeneration, hemorrhage, and edema. Scleral biopsies reveal an infiltration of lymphocytes, plasma cells, and macrophages with few neutrophils. Therapy with immunosuppressive dosages of prednisone and azathioprine is indicated, but may not be effective (Grahn et al., 1999).

Periocular snakebites from pit vipers typically cause pain, facial edema, chemosis, and conjunctival hyperemia. Uveitis is present in many dogs with periocular bites, as well in dogs with direct ocular bites. Pit viper venom contains many enzymes such as phospholipase A2 that most likely contribute to the influx of inflammatory cells to the eye and periocular area after a bite (Martins et al., 2016).

Uveodermatologic Syndrome

UDS, previously referred to as Vogt–Koyanagi–Harada (VKH)-like syndrome, is a canine disease that leads to anterior uveitis, chorioretinitis, poliosis, and vitiligo. The syndrome was initially termed VKH-like syndrome because of similarities to a disease in humans known as VKH syndrome. The term *uveodermatologic syndrome* was adopted to further separate the disease in dogs from that in humans because of the absence of neurologic signs in dogs. The disease was first reported in two Akitas in Japan (Asakura et al., 1977). Many case reports and case series reporting UDS in other breeds have followed.

The pathogenesis of UDS is not completely understood. VKH in humans is an autoimmune disease directed against melanocytes and is mainly mediated by cellular immune responses (Yamaki et al., 2005). Experimentally, Akita dogs have been immunized with tyrosinase-related protein, an enzyme involved in melanin formation that is expressed specifically in melanocytes. The Akitas developed clinical and histologic signs consistent with UDS, supporting the similarities between the canine and human diseases (Yamaki et al., 2005). Additionally, the canine leukocyte antigen DLA-DQA1*00201 has been associated with a significantly higher relative risk for UDS syndrome in American Akitas than other DLA Class II alleles (Angles et al., 2005).

UDS appears to affect primarily young adult dogs; the mean age from two reports was 3 years (Kern et al., 1985; Morgan, 1989). UDS also appears to occur more frequently in the Akita, Samoyed, Siberian Husky, and Shetland Sheepdog, but many other breeds are affected.

Ocular findings include bilateral anterior uveitis or panuveitis, iris or choroidal depigmentation, bullous retinal detachment, and blindness. Cataract, extensive posterior synechiae, iris bombé, and secondary glaucoma occur with chronicity. Dermatologic changes usually follow the development of ocular signs, and include vitiligo of the facial mucocutaneous junctions, nasal planum, scrotum, and footpads; however, generalized vitiligo may occur. Poliosis is confined to the facial region or is generalized. Alopecia occurs inconsistently (Kern et al., 1985; Morgan, 1989) (Fig. 21.23).



Figure 21.23 This black Labrador Retriever has poliosis secondary to uveodermatologic syndrome.

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General physical examination on affected dogs is normal. Clinically evident neurologic disease manifested as dysacusis and meningitis is common in humans with VKH; however, neurologic signs have not been confirmed in the dog, and this is thought to be due to the lack of pigment in the canine meninges. Analysis of cerebrospinal fluid (CSF) and postmortem examination of central nervous system (CNS) tissue has been normal in the few cases examined (Morgan, 1989).

Routine laboratory parameters are normal. Immune-function tests and titers for multiple infectious diseases have been negative (Kern et al., 1985; Morgan, 1989). Microscopically, the primary ocular change is a granulomatous panuveitis with prominent perivascular lymphoid aggregates and melanophages. The anterior chamber often contains many lymphocytes and plasma cells. Retinal detachment, destruction of the retinal pigmented epithelium, subretinal neovascularization, choroidal scarring, and signs consistent with secondary glaucoma are also seen frequently. Pigment-containing macrophages and melanophages are a prominent feature (Bussanich et al., 1982; Carter et al., 2005; Kern et al., 1985; Morgan, 1989). Histopathologic examination of the skin reveals interface dermatitis with a primarily lichenoid pattern. Large histiocytic cells, plasma cells, melanophages, and small mononuclear cells are characteristic (Kern et al., 1985).

Results of an immunohistochemical study of two cases suggested that the skin lesions were mediated by T-cells and macrophages (Th1 immunity), whereas the ocular lesions were more consistent with a B-cell and macrophage response (Th2 immunity; Carter et al., 2005).

Immunosuppressive drugs are the mainstay of therapy. Standard therapy for anterior uveitis with topical steroids, topical NSAIDS, and atropine (if the IOP is not elevated) is initiated. Oral prednisone at immunosuppressive doses is also used. Generally, there is a relatively rapid response to therapy. Unfortunately, many dogs have recurrence of clinical signs if the dose of oral prednisone is decreased and have the undesirable side effects of weight gain, polyuria, and polydipsia if it is continued. Therefore, other immunosuppressive drugs, such as azathioprine and cyclosporine, are often combined with corticosteroids or used alone in the treatment of UDS (Blackwood et al., 2011; Pye, 2009; Sigle et al., 2006). However, even with appropriate therapy, secondary glaucoma is a common sequela.

Mycoses-Associated Uveitis

Disseminated mycotic infections with ocular involvement are relatively common among dogs living in endemic areas. Even though mycotic infections typically involve multiple body systems, ocular disease is often the reason for presentation. The more common systemic mycoses include blastomycosis, coccidioidomycosis, histoplasmosis, cryptococcosis, and aspergillosis. Candidiasis occurs less frequently but can cause uveitis (Enders et al., 2017; Linek, 2004). Inhalation is believed to be the primary route of infection for all the major systemic mycoses, with later hematogenous spread to the eye. Both unilateral and bilateral ocular disease occurs, and infections of the paranasal sinus, orbit, and optic nerve occasionally affect the eye secondarily.

The diagnosis is made on the basis of concurrent clinical signs, which vary between mycotic organisms; identification of organisms in ocular or other tissue aspirates; or the results of fungal culture, histopathologic examination, or various serologic tests. The typical histologic pattern for all mycoses is granulomatous or pyogranulomatous inflammation characterized by variable numbers of neutrophils, lymphocytes, plasma cells, histiocytes, and occasionally epithelioid cells. Histopathologic identification of organisms is facilitated by special stains, such as Gomori's methenamine-silver, periodic acid–Schiff, and mucicarmine.

The preferred systemic therapy for each type of mycosis varies. Eyes that are potentially visual should be treated topically with corticosteroids and atropine if hypotensive or normotensive, but a painful, blind eye is best enucleated. Histologic evaluation of enucleated globes often facilitates diagnosis.

Blastomycosis

Blastomyces dermatitidis is the causative agent of blastomycosis. The endemic distribution is primarily the Mississippi, Missouri, and Ohio River valleys, the mid-Atlantic states, Quebec, Manitoba, and Ontario in North America, but it has been identified in other countries as well. Blastomycosis has a propensity for young, male, large-breed dogs (Albert et al., 1981; Bloom et al., 1997; Buyukmihci, 1982; Buyukmihci & Moore, 1987; Hendrix et al., 2004; Legendre, 2012). Ocular disease occurs in 30%–43% of dogs with systemic blastomycosis (Arceneaux et al., 1998; Brooks et al., 1991; Legendre et al., 1981). Anterior uveitis has been reported as the most common ocular sign, though anterior segment lesions often appear secondary to posterior segment lesions (Buyukmihci & Moore, 1987; Peiffer & Wilcock, 1991). Clinically, anterior uveitis, posterior segment disease, or endophthalmitis, with all of their sequelae, is commonly seen (Fig. 21.24; also see Fig. 21.11 and Fig. 21.12).

Microscopically, all tunics of the eye are usually involved. Infection appears to center in the choriocapillaris of the nontapetal choroid, with a relative sparing of the tapetal choroid. The most common findings are pyogranulomatous inflammation in the anterior and posterior segments, secondary glaucoma, and retinal detachment. Additionally, lens rupture, cataract, optic nerve inflammation, PIFMs, and periorbital cellulitis with extrascleral extension are seen (Buyukmihci & Moore, 1987; Hendrix et al., 2004). The yeast form is often seen on cytology or histology. The yeasts are 5–20 mm in diameter and have a

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Figure 21.24 This mixed-breed dog has blastomycosis. This eye has endophthalmitis with corneal edema, corneal vascularization, conjunctival hyperemia, and chemosis. Aqueous flare was visible on examination.

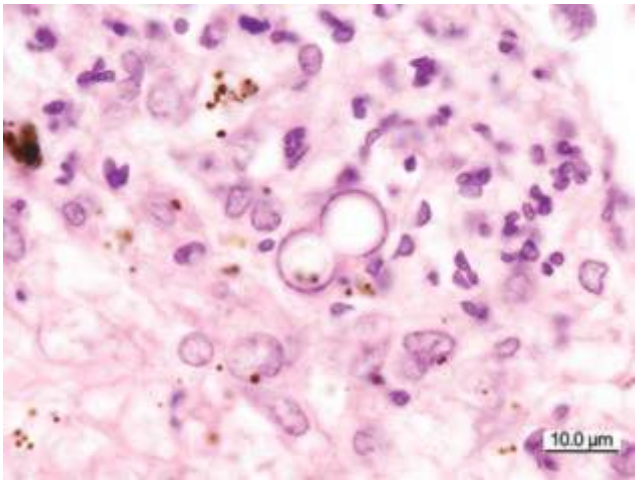


Figure 21.25 Pyogranulomatous inflammation and a budding *Blastomyces dermatitidis* organism are present in the posterior chamber of this dog with systemic blastomycosis.

thick, refractile, double-contoured cell wall (Fig. 21.25). The ease of diagnosing blastomycosis is variable. Infection commonly involves the lungs, skin, bones, lymph nodes, brain, and testes, in addition to the eyes (Legendre, 2012). Aspirates of enlarged lymph nodes, or vitreous when posterior segment disease is present, frequently yield organisms. Cytologic examination of impression smears from draining skin lesions can also be diagnostic. Antigen detection in urine is the preferred method of diagnosis if the organism itself is not seen cytologically or cultured. The sensitivity for the detection of antigen in urine is 93.5%, and the sensitivity of antibody detection is only 17.4% by agar gel immunodiffusion (AGID) and 76.1% by enzyme-linked immunosorbent assay (ELISA; Spector et al., 2008).

Itraconazole is considered to be the treatment of choice and is clinically very effective in most dogs with blastomycosis (Legendre et al., 1996; Mazepa et al., 2011). The typical dose is 5 mg/kg orally once daily for approximately 90 days (Legendre, 2012). Urine antigen levels decrease with itraconazole treatment and should be used to monitor disease resolution (Spector et al., 2008). Even with systemic itraconazole and topical therapy for anterior uveitis, the prognosis for vision in affected eyes is guarded. Brooks et al. (1991) showed that there is a positive response to treatment in 76% of dogs with posterior segment disease alone, 18% with anterior uveitis, and 13% with endophthalmitis. Many eyes that do not respond to treatment, continue to have uveitis, and develop glaucoma have *Blastomyces dermatitidis* organisms that appear to be thriving in the eye and/or may have lens rupture secondary to the severe inflammatory response (Hendrix et al., 2004). These findings may explain why the inflammation is intractable in many dogs.

Fluconazole is less effective and requires a longer treatment time than itraconazole, but it is less expensive (Mazepa et al., 2011). Dogs should be monitored for hepatotoxicity with both drugs. Parenteral amphotericin B is also effective, but renal toxicity is problematic with this drug (Aguirre, 1974). A combination treatment with itraconazole and amphotericin B–lipid complex has been used successfully in dogs at risk of losing vision from retinal detachment (Collins & Moore, 1999).

Studies have evaluated the use of corticosteroids via different routes to augment therapy with systemic antifungals. Oral prednisone has been administered with itraconazole or fluconazole in an attempt to preserve vision. In one study, the prednisone dosage ranged from 0.2 mg/kg/day to 1.4 mg/kg/day, and the mean duration was 3 months. The prednisone did not appear to adversely affect the survival rate. All eyes with mild or moderate lesions and half of the dogs with severely affected eyes were visual at their last recorded recheck examination (Finn et al., 2007). However, many clinicians do not advocate systemic corticosteroid treatment in dogs with mycotic infection (Collins & Moore, 1999), although topical prednisolone acetate should be used in the treatment of anterior uveitis secondary to blastomycosis. Topical atropine should be used in eyes without evidence of secondary glaucoma to increase comfort and decrease synechia formation. If IOP is elevated, dorzolamide and timolol should be used in conjunction with steroids.

Coccidioidomycosis

Coccidioidomycosis, caused by *Coccidioides immitis*, is endemic to the Lower Sonoran life zone, which includes the southwestern United States, Mexico, and areas of Central and South America (R.T. Greene, 2012). Ocular changes include keratitis, granulomatous panuveitis, endophthalmitis, chorioretinitis with retinal detachment, and orbital cel-

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lulitis (Angell et al., 1987). In one study 80% of dogs had uniocular lesions, and 43% of dogs demonstrated ocular disease alone (Angell et al., 1987). Similar to blastomycosis, anterior segment lesions are thought to be an extension of posterior segment disease.

Several tests are available for use in making a serologic diagnosis (R.T. Greene, 2012). The tube precipitin test measures immunoglobulin (Ig) M antibody levels; IgM both appears and disappears early in the course of disease. The complement fixation test measures IgG antibody, which persists longer. The complement fixation titer is indicative of the severity of infection: a titer of 1 : 64 or greater is indicative of disseminated disease. It is possible to have one test be positive and the other negative depending on the stage of infection; thus, the two tests should be performed in parallel. Latex agglutination, AGID, and ELISA are now also employed by some laboratories (R.T. Greene, 2012). Cytology and biopsy are often diagnostic as well. Oral ketoconazole, fluconazole, and itraconazole are all commonly used in the treatment of coccidioidomycosis (Angell et al., 1987; R.T. Greene, 2012).

Cryptococcosis

Cryptococcosis is typically caused by *Cryptococcus neoformans* or *Cryptococcus gattii*. *C. neoformans* commonly causes CNS, ocular, respiratory, and cutaneous signs. Fever, lymphadenomegaly, and lameness secondary to lytic bone lesions occur less frequently. CNS signs usually relate to meningoencephalitis and often include head tilt, nystagmus, facial paralysis, ataxia, mild paresis to complete paralysis, depressed reflexes, circling, and seizures (Berthelin et al., 1994a; Sykes & Malik, 2012). Ocular signs include optic neuritis, granulomatous chorioretinitis, exudative retinal detachment, anterior uveitis, and occasionally orbital abscess, cellulitis, or exophthalmos (Carlton, 1983; Carlton et al., 1976; Sykes & Malik, 2012; Trivedi et al., 2011; Wolfer et al., 1996). Anterior uveitis, though reported, is rare with cryptococcosis. As with other mycoses, even when anterior uveitis is present, organisms are rarely demonstrated in the anterior uvea. Posterior segment disease is the most common ocular manifestation, and funduscopic examination often reveals chorioretinitis characterized by single or multiple raised, gray, yellow, or white exudative lesions and retinal detachment. Rarely, anterior uveitis and retinal detachment occur without the presence of granulomas. The eye is involved secondary to hematogenous spread or extension from the brain along the optic nerve (Sykes & Malik, 2012). One report describes uveitis caused by *C. gattii* in a systemically affected dog (Gerontiti et al., 2017).

Cryptococcosis is diagnosed on the basis of clinical signs, identification or culture of the organism in ocular or other tissue aspirates including CSF, results of histopathologic examination, and results of serologic testing (Berthelin et al., 1994b; Sykes & Malik, 2012). The organisms are round to oval with a variably sized capsule and reproduce by budding. Because the daughter cells separate from the parent at varying sizes, the organisms vary in size. The latex cryptococcal agglutination test is considered to be the most reliable serologic test, because it can detect the presence of cryptococcal antigen in body fluids, including serum, urine, CSF, aqueous humor, and vitreous. The magnitude of antigen titers tends to correlate with severity of disease and response to therapy (Berthelin et al., 1994b; Fujita et al., 1983; Sykes & Malik, 2012). Molecular genotyping is used to differentiate *C. neoformans* and *C. gattii*.

The prognosis for dogs with cryptococcosis is generally poor because of the severity of meningoencephalitis, the difficulty of reaching organisms within large lesions, possible decreased immunity, and poor penetration of most antifungal drugs into the CNS. Variable responses have been obtained with systemic therapy with itraconazole, amphotericin B, flucytosine, ketoconazole, and fluconazole, either singly or in various combinations (Berthelin et al., 1994b; Sykes & Malik, 2012). One dog recovered without medical treatment after enucleation, suggesting localized disease (Berthelin et al., 1994b).

Histoplasmosis

Histoplasma capsulatum is widely distributed in soil in temperate and subtropical regions. In the United States, major endemic areas are associated with the Ohio, Missouri, and Mississippi rivers, but histoplasmosis has been identified in most states (Brömel & Greene, 2012). In the dog, clinical signs of disseminated histoplasmosis are most often referable to the gastrointestinal tract or liver. Reports of ocular involvement are relatively rare, but usually include chorioretinitis, conjunctivitis, blepharitis, retinal detachment, and optic neuritis (Brömel & Greene, 2012; Gwin, 1980). In experimentally infected dogs, peripheral granulomatous choroiditis was the most common finding (5 of 17 dogs; Salfelder et al., 1965). Diagnosis is via cytology, histopathology, or urine antigen enzyme immunoassay (Cunningham et al., 2015). The organisms in tissue are relatively small at 2–4 μm in diameter and are often located within cells of the mononuclear phagocyte system.

Aspergillosis

Systemic aspergillosis occurs less frequently than the preceding systemic mycoses. Dogs often have concurrent systemic signs, such as renal or neurologic disease, or they might present with only ocular signs. Ocular signs include panuveitis, retinal detachment, and secondary glaucoma. Microscopically, clinical signs are those of uveitis and its manifestations. However, *Aspergillus* sp. might have a propensity to invade the lens, as several reports describe lens capsule rupture with numerous hyphae within the lens (Gelatt et al., 1991; Wooff et al., 2018). Unlike other fungal infections described here, *Aspergillus* exists in hyphal form in tissue.

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Parasitic Diseases

Ocular Nematodiasis

Intraocular nematodiasis is reported infrequently in domestic animals. Ocular nematodiasis includes two distinct conditions: *ocular filariasis* and *ocular larva migrans* (OLM).

Ocular filariasis due to aberrant migration of immature *Dirofilaria immitis* occurs in dogs and humans. The condition occurs in dogs with and without concurrent microfilaremia. Uveitis and mild to severe corneal opacity are the predominant signs. Uveitis is commonly attributed to direct mechanical trauma or reaction to metabolic waste products of the parasite. In one case, it was speculated that antigen–antibody complex formation was an additional factor in uveitis when severe corneal scarring and pigmentation occurred after removal of the parasite (Bellhorn, 1973). Typically, one 5–10 cm filaria is seen undulating in the anterior chamber; migration between the anterior and posterior chambers and vitreous occurs. Light stimulation tends to increase the motility of the filaria and, subsequently, the discomfort to the patient. The prognosis is favorable with anti-inflammatory therapy and manual removal of the filaria (Carastro et al., 1992). Delay in surgical removal increases the likelihood of posterior segment migration, and with continued inflammation enucleation might be required (Miller & Cooper, 1987). Presurgical adulticide therapy is not advised, as the severe inflammatory reaction to the dead filaria leads to intractable uveitis. Microfilaricide administration caused increased activity of the filaria and transient exacerbation of clinical signs in one case (Lovers, 1968). *Angiostrongylus vasorum* is a metastrongylid nematode that infects the pulmonary artery and right ventricle. Adult nematodes reach the eye via aberrant migration. Clinical signs range from iris hyperemia to uveitis and hyphema. Diagnosis is suspected when an adult motile nematode approximately 10 mm in length is seen in the anterior chamber. The parasite can be removed via anterior chamber paracentesis or surgery, followed by appropriate systemic anthelmintic therapy. This parasite is primarily diagnosed in Europe (Colella et al., 2016; King et al., 1994; Rosenlund et al., 1991).

OLM generally refers to aberrant ocular migration of *Toxocara* spp.; *Toxocara canis* is suspected to be the most commonly involved (Hughes et al., 1987; Rubin & Saunders, 1965). *T. canis* is of public health significance because the nematode causes OLM and visceral larval migrans (VLM) in children. In dogs and humans, OLM resulting from *Toxocara* spp. is characterized by inflammation, primarily of the retina and vitreous. Ophthalmoscopy reveals areas of hyperreflectivity, hyperpigmentation, and vascular attenuation. Uveal involvement is rare and was seen microscopically in only one study (Hughes et al., 1987).

Infection with *Onchocerca lupi* most commonly causes subconjunctival pea- to bean-sized masses beneath the bulbar conjunctiva (McLean et al., 2017; Orihel et al., 1991; Sreter et al., 2002; Szell et al., 2001). Other signs include exophthalmos, conjunctival congestion, protrusion of nictitating membrane, uveitis, retinal detachment secondary to globe compression, and localized corneal edema and vascularization (Komnenou et al., 2003; McLean et al., 2017; Zarfoss et al., 2005). While intraocular infection is rare, an adult worm was seen and surgically removed from an eye that had concurrent uveitis (Komnenou et al., 2016). Microscopically, a pyogranulomatous or granulomatous reaction with eosinophils is associated with the adult worms. Lymphoplasmacytic uveitis, PIFMs, and evidence of secondary glaucoma are also seen (Zarfoss et al., 2005). Microfilariae are present in the uteri of females and in the surrounding tissues and can be isolated from skin biopsy specimens (Eberhard et al., 2000; Szell et al., 2001). The granulomas can be excised when they are easily accessible, followed by medical therapy including a filaricide. Some cases resolve with medical therapy alone, and medical therapy is indicated when lesions are not easily accessible or an identifiable granuloma is not visible. Treatment regimens include combinations of a filaricide agent (melarsomine), ivermectin, prednisone, and doxycycline (Komnenou et al., 2003, McLean et al., 2017).

Ophthalmomyiasis

Ophthalmomyiasis refers to aberrant ocular migration of fly larvae of the order *Diptera*. Some reported include *Cuterebra* sp., the sheep nasal botfly (*Oestrus ovis*), and the cattle warble (*Hypoderma bovis*; Edelmann et al., 2014; Gwin et al., 1984). Both intraocular and extraocular disease occur in domestic animals, but the intraocular disease *ophthalmomyiasis interna posterior* (OIP) has been reported most often in dogs, cats, and humans. As the name implies, OIP is primarily a disease of the posterior segment. The characteristic lesion has active or inactive roadmap-like subretinal tracts. Active disease is associated with uveitis, retinal detachment, and hemorrhage. Larvae have been identified in the anterior segment with concurrent uveitis. Increased numbers of migratory tracts in the retina appear daily in active infections (Gwin et al., 1984). Visible larva can be removed surgically via a keratotomy and larval extraction (Edelmann et al., 2014). Inactive infections require no therapy, whereas anti-inflammatory therapy is indicated in active disease. Organophosphates can be administered in an attempt to kill the larva, but a dead larva might exacerbate inflammation. The larvae also spontaneously depart from the globe.

Protozoal Diseases

Leishmaniosis

The flagellate organism *Leishmania infantum* is the most common cause of visceral leishmaniosis. The disease is endemic along the Mediterranean shore and in parts of East Africa, India, and Central and South America, and it is

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endemic in the United States in hunting dogs (Boggiatto et al., 2011; Pena et al., 2000; Vida et al., 2016). Domestic and wild members of *Canidae* serve as reservoir hosts, and the intermediate host is the sandfly (*Phlebotomus* spp.). In the United States and Canada, vertical transmission is the predominant means of transmission between dogs (Vida et al., 2016).

Ocular findings are present in the majority of dogs and include blepharitis, keratoconjunctivitis, uveitis, retinitis, and endophthalmitis (Ciaramella et al., 1997; Koutinas et al., 1999; Pena et al., 2000). Ocular disease is the only clinical sign in some dogs. The anterior segment is usually more severely involved than the posterior segment. Anterior uveitis developing during or after antiprotozoal therapy is attributed to treatment itself, an allergic response to death of the organisms, or to recurrence of disease (Di Pietro et al., 2016). Additional signs include lymphadenopathy, splenomegaly, hepatomegaly, renal failure, anemia, thrombocytopenia, and varying dermatologic conditions (Ciaramella et al., 1997; Koutinas et al., 1999).

Microscopically, vasculitis and intense granulomatous inflammatory zones are seen in the conjunctiva, fibrous tunic, uvea, optic nerve sheath, lacrimal duct, and both smooth and striated ocular muscles (Garcia-Alonso et al., 1996; Naranjo et al., 2010; Pena et al., 2008). The parasite has been found using immunohistochemical stains in 27% of affected eyes (Pena et al., 2008). Treatment usually consists of pentavalent antimonials and/or allopurinol. However, complete elimination of the organisms is rare, the clinical response to therapy is variable, and relapses are common (Baneth & Solano-Gallego, 2012; Pena et al., 2000).

Encephalitozoon cuniculi

Encephalitozoon cuniculi is an obligate intracellular, spore-forming, microsporidial parasite that has been associated with cataracts in rabbits, cats, dogs, and other mammals (Benz et al., 2011; Nell et al., 2015; Wolfer et al., 1993). Three young dogs had anterior uveitis, chorioretinitis, and focal posterior synechia with associated focal anterior cortical cataracts. All dogs had positive serum antibody titers for *E. cuniculi*. Two dogs maintained vision after undergoing phacoemulsification. Polymerase chain reaction on the lens material was positive for *E. cuniculi* strains II and IV. Evidence of microsporidia was seen via immunohistochemistry of the anterior lens capsule in one dog. All dogs were treated long term with topical and systemic steroids or other topical anti-inflammatory drugs and fenbendazole (Nell et al., 2015).

Toxoplasmosis

Toxoplasma gondii is a protozoan-obligate intracellular parasite that affects most warm-blooded animals. The cat is considered the only definitive host and is therefore integral to transmission of the disease. Dogs are infected by ingesting sporulated oocysts from cat excreta, ingesting tissue cysts in infected meats, or ingesting a transport host. Infection is usually subclinical (Bussanich & Rootman, 1985; Dubey, 1987), but neuromuscular, respiratory, gastrointestinal, or ocular signs do occur.

Ocular toxoplasmosis has been reported infrequently in dogs; when it is present, anterior uveitis, retinochoroiditis, and vitritis are seen (Bussanich & Rootman, 1985; Dubey, 1987; Piper et al., 1970; Wolfer & Grahn, 1996). Additional findings include optic neuritis and extraocular myositis. Even if signs of anterior uveitis are not seen clinically, microscopically inflammation of the iris can be seen (de Abreu et al., 2002).

Diagnosis of ocular toxoplasmosis is based on clinical signs, serologic testing, and histopathologic examination. Serologic evaluation is beneficial, but does not always correlate with clinical disease, as some subclinically affected dogs may have high antibody titers. A test that distinguishes IgM and IgG antibodies is necessary, and convalescent titers should be run (Dubey, 1987). Granulomatous or nongranulomatous inflammation is possible. Clindamycin is the drug of choice for treating toxoplasmosis (Dubey & Lappin, 2012).

Other Protozoal Diseases

Neospora caninum was diagnosed in four litters of puppies from one owner. The most common clinical sign was hindlimb paralysis. Some had generalized encephalomyelitis. Histopathology showed tachyzoites and tissue cysts in the brain and spinal cord. Lesions in the eyes included retinitis, choroiditis, nonspecific iridocyclitis, and myositis of the extraocular muscles (Dubey et al., 1990).

Trypanosoma evansi causes corneal opacities, conjunctivitis, and anterior uveitis in dogs. Therapy with subconjunctival steroids and intramuscular diminazene aceturate leads to corneal clearing and restoration of vision (Varshney et al., 2003). Parasitemia in peripheral blood smears and aqueous fluid confirms the infection.

Rickettsial Diseases

Ehrlichiosis

Ehrlichia canis is an obligate intracellular parasite transmitted by the brown dog tick, *Rhipicephalus sanguineus*. Pronounced clinical and laboratory abnormalities often occur with *E. canis* infections (canine monocytic ehrlichiosis) and include fever, lymphadenopathy, anemia, leukopenia, thrombocytopenia, monoclonal or polyclonal gammopathy, neurologic signs, and generalized bleeding tendencies (Stiles, 2000).

Ocular signs are common, and dogs can have ocular signs with no other apparent clinical signs. Ocular signs are most commonly bilateral and occur in both the acute and chronic forms of *E. canis* infections. Anterior uveitis and exudative retinal detachment are reported to be the most common

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ophthalmic signs. Other signs include conjunctivitis, conjunctival or iridal petechiations, corneal opacity, corneal ulceration, necrotic scleritis, low tear production, orbital cellulitis, panuveitis often with hyphema, diffuse retinitis or vasculitis, retinal hemorrhage, papilledema, and optic neuritis (Bayon et al., 1999; Harrus et al., 1998; Komnenou et al., 2007; Leiva et al., 2005; Oria et al., 2004; Stiles, 2000). The ocular hemorrhage associated with ehrlichiosis is thought to be related to thrombocytopenia, platelet dysfunction, and/or hyperviscosity (Harrus et al., 1998).

Experimentally, ocular signs consist of papilledema, perivascular retinal infiltrates, retinitis, and anterior uveitis. The ocular signs are evident 3 weeks after the onset of fever. The most consistent microscopic finding is a predominantly monocytic cellular infiltrate of the ciliary body and, to a lesser extent, the iris, choroid, retina, and optic nerve (Panciera et al., 2001; Swanson & Dubielzig, 1986).

Diagnosis is made on the basis of clinical signs, hematologic abnormalities, and serologic testing. Multiple intracytoplasmic subunits of *E. canis* (i.e., morulae) occur within monocytes. Serologic diagnosis is by immunofluorescent antibody (IFA) testing. Doxycycline and several other antibiotics are commonly used for systemic therapy (Harrus et al., 2012; Stiles, 2000).

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever (RMSF) is an acute infectious disease caused by *Rickettsia rickettsii* and transmitted by ticks of the *Dermacentor* spp. Vasculitis is the primary lesion, caused initially by direct infection of the vascular endothelium and perithelial smooth muscle, and later by immunologic phenomena. It is postulated that an Arthus-type reaction may be involved (Davidson et al., 1989; Keenan et al., 1977). Common clinical signs include fever, neurologic dysfunction, polyarthritis, thrombocytopenia, nonregenerative anemia, and ocular disease.

Ocular lesions are common in dogs with serologically confirmed RMSF. Anterior segment findings include subconjunctival hemorrhage, iris stromal petechiations, anterior uveitis, and hyphema. Posterior segment findings include retinitis characterized by perivasculitis, focal areas of edema, and petechiation. Because ocular disease is often confined to the retina, ophthalmoscopy should always be done when RMSF is suspected. Generally, ophthalmic lesions are mild with RMSF (Davidson et al., 1989).

The histologic appearance of RMSF is different from ehrlichiosis in that the most prominent lesion is necrotizing vasculitis, with perivascular accumulations of polymorphonuclear and lymphoreticular cells (Davidson et al., 1989; Keenan et al., 1977). Confirmation of the diagnosis of RMSF is made by a demonstration of rising serum IFA titers; therefore, a single titer is nondiagnostic (Greene et al., 1985). Doxycycline, tetracycline, chloramphenicol, enrofloxacin, and trovafloxacin are all effective systemic therapies (Breitschwerdt et al., 1991, 1999; Stiles, 2000). *Anaplasma platys* infection rarely causes anterior uveitis (Glaze & Gaunt, 1986; Harvey et al., 1978).

Viral Diseases

Infectious Canine Hepatitis

Infectious canine hepatitis (ICH) is caused by the canine adenovirus-1 (CAV-1). Natural infection is most common in unvaccinated dogs less than 1 year of age, in which the disease can be fatal. The virus replicates in reticuloendothelial, hepatic parenchymal, and vascular endothelial cells (Aguirre et al., 1975). Clinical findings include fever, vomiting, diarrhea, abdominal tenderness, hepatitis or hepatic necrosis, hemorrhagic diathesis, tonsillar enlargement, pneumonia, glomerulonephritis, and CNS and ocular disease (C.E. Greene, 2012).

Nongranulomatous anterior uveitis and secondary corneal edema (so-called blue eye) are reported in approximately 20% of dogs recovering from natural ICH. This keratouveitis may be the only abnormality in otherwise subclinically affected dogs. Persistent corneal edema, secondary glaucoma, and phthisis bulbi are possible sequelae of severe keratouveitis. The pathogenesis of ICH keratouveitis is related primarily to immune-complex deposition or to an Arthus-type reaction (Aguirre et al., 1975; Carmichael, 1965; Carmichael et al., 1975; Curtis & Barnett, 1981).

Keratouveitis occurs as a postvaccinal reaction in approximately 0.4% of dogs that receive the CAV-1 vaccine. An increased susceptibility of the Afghan hound to postvaccinal keratouveitis has been suggested (Curtis & Barnett, 1981). The CAV-2 vaccine is thought to cause ocular disease only when experimentally injected into the anterior chamber (C.E. Greene, 2012). However, anecdotal accounts exist of rare keratouveitis following subcutaneous administration of CAV-2 vaccines.

Therapy for dogs suffering from systemic disease with ICH is primarily supportive. Anti-inflammatory therapy of keratouveitis in dogs recovering from natural ICH infection or suffering postvaccinal reaction is debatable, since some consider the keratouveitis self-limiting. Corticosteroid therapy may be contraindicated and has been implicated in the prolongation of corneal lesions and even blindness in dogs suffering postvaccinal reactions (Carmichael, 1965). However, the potential for severe sequelae without therapy may be sufficient justification to treat affected eyes.

Bacterial Disease

Brucella canis is an aerobic, gram-negative coccobacillus that survives in mononuclear cells. Infection is by penetration of the organisms through mucous membranes of the oropharynx, genital tract, and conjunctiva. The concentration

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of the organism is highest in semen and vaginal discharge in infected dogs (Dziezyc, 2000). Abortion and infertility are common clinical signs that occur in breeding dogs, but neutered dogs are also affected (Greene & Carmichael, 2012; Ledbetter et al., 2009). Ocular signs occur in ~14% of dogs with brucellosis. The more common ocular findings include endophthalmitis, chronic uveitis, hyphema, and chorioretinitis (Ledbetter et al., 2009; Vinayak et al., 2004). Other signs include diskospondylitis, glomerulopathy, and meningoencephalitis, but overt systemic disease does not always occur. Diagnosis is made using the slide agglutination test in combination with AGID or by positive culture. Antimicrobial therapy is complicated and must be continued long term because of the intracellular nature of the organism (Ledbetter et al., 2009). Due to the zoonotic potential of brucellosis and the difficulty in eradicating the organism, euthanasia may be elected.

Bartonella vinsonii subsp. *berkhoffii* is one subspecies of a group of intraerythrocytic bacteria most likely transmitted by the brown dog tick, *Rhipicephalus sanguineus*. Clinical signs in dogs infected with this organism include lethargy, weight loss, muscle and joint pain, hindlimb paresis, endocarditis, myocarditis, lymphadenitis, and fever (Breitschwerdt & Chomel, 2012; Breitschwerdt et al., 2004). Various other neurologic and dermatologic signs also occur. Ophthalmic signs include anterior uveitis, chorioretinitis, hyphema, and retinal detachment (Breitschwerdt et al., 2004; Michau et al., 2003). Diagnosis is based on serologic testing. Multiple antibiotics have been used for treatment.

Leptospirosis is caused by a spirochete, a filamentous bacterium, belonging to the genus *Leptospira*, which includes many species and serovars. *Leptospira* organisms are most commonly transmitted through urine. Vasculitis and endotheliitis involving the kidneys, liver, spleen, muscles, CNS, and eyes occur. Anterior uveitis is infrequently seen (Dziezyc, 2000; Gallagher, 2011; Lajeunesse & DiFruscia, 1999; Thirunavukkarasu et al., 1995). *Leptospira* organisms have been cultured from the aqueous humor (Greenlee et al., 2004).

Algal Disease

Prototheca zopfii and *Prototheca wickerhamii* are achlorophyllic algae that are pathogenic in dogs and other animals. The primary clinical sign is usually hemorrhagic diarrhea; however, dogs often present with blindness or uveitis and chorioretinitis as the initial signs (Schultze et al., 1998; Stenner et al., 2007). Ocular signs are common and include anterior uveitis, hyphema, secondary glaucoma, chorioretinitis, and retinal detachment (Fig. 21.26). Neurologic signs rarely occur (Hosaka & Hosaka, 2004). Cytology or culture of vitreal or subretinal aspirates or CSF with appropriate clinical signs is often diagnostic (Fig. 21.27). *Prototheca* sp. are extracellular, round to oval single-celled 2–20 µm encapsulated



Figure 21.26 This dog has protothecosis. Iridal thickening and dyscoria suggestive of posterior synechia along with aqueous flare and hyphema were the primary findings of panophthalmitis. Other signs were corneal vascularization, conjunctival hyperemia, chemosis, and ocular discharge.

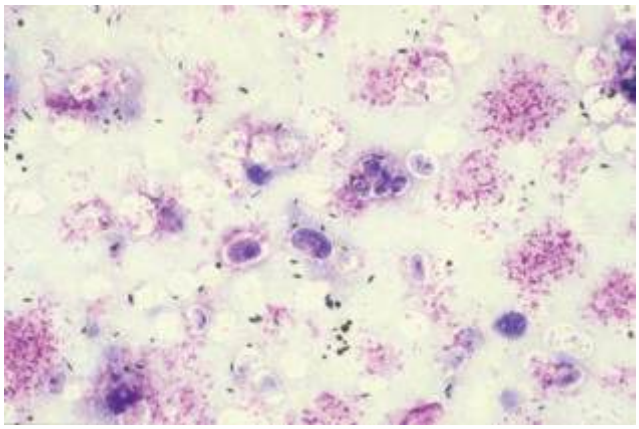


Figure 21.27 Multiple *Prototheca* sp. organisms are present in this vitreal aspirate.

organisms that contain sporangia with variable numbers of sporangiospores. Microscopically the most common findings are granulomatous chorioretinitis with retinal detachment and variable numbers of organisms within the inflammatory infiltrate. Signs associated with uveitis are also seen (Shank et al., 2015). Therapy with antifungal drugs has been attempted, but long-term survival is exceedingly rare.

Miscellaneous

Hyperlipidemia

Dogs with hyperlipidemia resulting from elevations in either cholesterol or triglycerides can have associated ocular abnormalities. Lipid-laden aqueous humor was discussed briefly under "Uveal Inflammation," as it occasionally occurs with anterior uveitis (see Fig. 21.16). Dogs' lipoproteins range

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from 50 to 350 Å in diameter (Olin et al., 1976). However, the iridal vascular endothelium and nonpigmented ciliary body epithelium normally prevent particles greater than 40 Å from entering the aqueous humor. Breakdown of the blood–aqueous barrier (i.e., anterior uveitis) concurrent with hyperlipidemia results in lipid-laden aqueous. Lipoid aqueous can occur in dogs with known uveitis, especially diabetic dogs following cataract surgery. However, it is seen in dogs without a history of ocular disease, suggesting that the lipids may also incite leakage of the blood–aqueous barrier.

Additional ocular manifestations of hyperlipidemia include lipid engorgement of retinal vessels and infiltration of the perilimbal cornea, conditions referred to as lipemia retinalis and corneal lipidosis (or arcus lipoides corneae), respectively (Crispin, 2016). Lipid-laden aqueous and lipemia retinalis are likely to resolve with resolution of the primary disorder. However, if anterior uveitis is the inciting cause, treating with topical anti-inflammatory drugs is indicated to help restore the blood–aqueous barrier.

Pigmentary and Cystic Glaucoma

Uveal cysts are generally considered benign; however, cysts associated with glaucoma occur in Golden Retrievers, Great Danes, and American Bulldogs. The syndrome that occurs in Golden Retrievers in the United States is referred to as both pigmentary uveitis, and pigmentary and cystic glaucoma (PCG; Esson et al., 2009; Sapienza et al., 2000; Townsend & Gornik, 2013). Pigment dispersion on the anterior lens capsule in a radial orientation is the most frequently observed early clinical sign (Fig. 21.28). Other clinical signs include thin-walled iridociliary cysts, spiderweb-like fibrinous debris in the anterior chamber, cataracts, and posterior synechia (Fig. 21.29). Secondary glaucoma occurs in the majority of eyes, and this disease is usually bilateral.

The disease progresses from thin-walled iridociliary uveal cysts as the only finding to radial pigment on the anterior lens capsule and finally glaucoma. In one study 62% of dogs made this transition within one year (Holly et al., 2016). The cysts might not be visible on every exam in the same dog, but this could result from variations in degree of mydriasis or in morphologic changes in the cysts. In eyes evaluated that had only a single cyst, the cyst was located nasally and rarely extended past the pupil margin. When multiple cysts are present, they are always located nasally, with extension dorsally or ventrally (Townsend & Gornik, 2013). Generally, the thin-walled cysts are seen in dogs 4–6 years of age, with the PCG developing several years later (Holly et al., 2016; Townsend et al., 2013). Pedigree analysis is most consistent with an autosomal-dominant mode of inheritance with reduced penetrance (Holly et al., 2016). When seen alone, the thicker-walled uveal cysts that are usually free within the anterior chamber are not necessarily associated with the development of PCG. One histologic study evaluating eyes enucleated because of glaucoma reported that all eyes had thin-walled iridociliary cysts (Esson et al., 2009). The cysts are lined with attenuated cuboidal epithelium and fill most of the posterior chamber, stretch across the anterior face of the vitreous, or attach to the lens capsule. Many cysts contain an Alcian blue–positive material, indicating that these cysts contain hyaluronic acid. Iris bombé, PIFMs, trichrome-positive collagen deposition on the lens capsule, mild uveitis, peripheral anterior synechiae, posterior synechiae, and free pigment within the trabecular meshwork are also seen in some cases (Deehr & Dubielzig, 1998; Esson et al., 2009).

Clinically, many dogs have mild visible turbidity (aqueous flare); however, microscopically, only about half of the eyes have evidence of very mild uveitis (Esson et al., 2009). The clinical appearance of aqueous turbidity in many cases is likely the result of protein and cellular material in the aqueous due to escape of cyst contents. Iridociliary epithelial



Figure 21.28 Multifocal areas of pigment in the classic radial pattern are present on the anterior capsule of this Golden Retriever with breed-related pigmentary and cystic glaucoma. An area of posterior synechia is also present.



Figure 21.29 This Golden Retriever had multiple iris cysts caudal to the iris and one anterior to the iris, which is part of the breed-related pigmentary and cystic glaucoma syndrome.

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cysts might not be clinically evident in dogs with microscopic evidence of cyst formation (Sapienza et al., 2000).

The mechanism of glaucoma secondary to iridociliary cysts appears to be multifactorial and could include mechanical angle closure by the cysts, plateau iris syndrome, heavy deposition of pigment in the filtration angle, secondary pigment dispersion syndrome, pupillary block, release of cyst contents, and inflammatory cellular infiltration blocking aqueous outflow (Deehr & Dubielzig, 1998; Lois et al., 1998). Progressive posterior synechia is common, leading to iris bombé. In humans, mucogenic glaucoma has been described in which mucus from cysts or an inflammatory reaction to mucus has obstructed the trabecular meshwork (Werblin et al., 1983). Ophthalmic NSAIDS, corticosteroids, and glaucoma medications are often used in affected dogs, but therapy does not prevent disease progression.

A syndrome similar to PCG of Golden Retrievers occurs in Great Danes. Consistent findings in Great Danes include ciliary body cysts, multiple cysts in the anterior and posterior chambers, and glaucoma. The cysts are variable in size, very poorly pigmented, and usually translucent. Often the entire posterior chamber is filled with cysts that push the iris forward. Microscopically, stacked cysts are seen in the area of the pars plicata and between the iris and ciliary body. The cysts originate from the ciliary body epithelium and are composed of a layer of epithelial cells that contain few melanin granules and are irregularly periodic acid–Schiff-positive. Commonly, a PIFM covers the drainage angle and the anterior surface of the iris. The mechanism of glaucoma is thought to be anterior displacement of the iris with narrowing of the angle and a possible contribution by PIFMs. Evidence suggests that both glaucoma and ciliary body cysts are inherited in the Great Dane (Spiess et al., 1998).

One report describes a series of American Bulldogs that had multiple cysts in the anterior chamber and iridociliary sulcus as well as glaucoma. Clinically and microscopically the dogs had cysts, PIFMs, narrow or closed iridocorneal angles with possible pectinate ligament dysplasia, and a perivascular mononuclear infiltrate in the iris and sclera. Any association between the cysts and the iridocorneal angle abnormalities was not clear. The Bulldogs do not have the radial pigment dispersion on the anterior lens capsule, cataracts, or fibrinous debris in the anterior chamber that is often present in Golden Retrievers, as already described (Pumphrey et al., 2013).

Solid Intraocular Xanthogranuloma in Miniature Schnauzer Dogs

Solid intraocular xanthogranulomas were identified in four globes from three older Miniature Schnauzers that all had a history of diabetes mellitus, hyperlipidemia, and bilaterally severe uveitis, with glaucoma that was believed to be lens induced. Grossly, all globes are filled with a heterogenous tan mass. Microscopically, intraocular contents are effaced by solid sheets of foamy macrophages admixed with hemorrhage, necrosis, and Alcian blue–positive refractile crystalline material in stellate patterns. Additionally, episcleral atherosclerosis is present, as evidenced by foamy macrophages within vessel walls (Zarfoss & Dubielzig, 2007).

Hyperviscosity Syndrome

Monoclonal gammopathy associated with lymphoproliferative disorders can result in hyperviscosity syndrome (HVS). HVS causes clinical signs referable to multiple organ systems, including the cardiac, renal, hemostatic, ocular, and central nervous systems (Kirschner et al., 1988; Lane et al., 1993). In the dog, HVS is associated with increased serum concentrations of IgG, IgM, and IgA (Center & Smith, 1982; Hendrix et al., 1998; Kirschner et al., 1988; MacEwen et al., 1977). HVS secondary to polycythemia vera has also been reported (Gray et al., 2003). Ocular anterior segment findings include conjunctival hyperemia, corneal edema, hyphema, and secondary glaucoma, all of which are likely related to concurrent anterior uveitis. However, ocular findings are most often referable to the posterior segment and include retinal vascular dilation, tortuosity, microaneurysms, retinal hemorrhage, retinal detachment, chorioretinitis, and papilledema.

Sulfonamide Hypersensitivity

Dogs with sulfonamide hypersensitivity often have multiple clinical abnormalities (Giger et al., 1985; Trepanier, 2004; Trepanier et al., 2003). Signs might include fever, arthropathy, blood dyscrasias, glomerulonephropathy, hepatopathy, skin eruption, uveitis, retinitis, and keratoconjunctivitis sicca.

Uveal Trauma

Ocular trauma often results in clinical signs that vary from mild miosis to disruption of the cornea or sclera. Often, blunt trauma manifests with flare, fibrin or hyphema, corneal edema, or iridodialysis, but rarely hypopyon. With sharp trauma or extremely severe blunt trauma, fibrin, hemorrhage, uveal prolapse, and perforation of the cornea or sclera can occur. Uveal prolapse occurs with globe rupture because the sudden decompression of the anterior chamber with aqueous outflow forces the iris into the wound, plugging it (Dalma-Weiszhausz & Dalma, 2002). Intraocular hemorrhage exhibits as hyphema, iridal stromal hemorrhage, or hemorrhage around the equator of the lens or in the vitreous. In all cases of trauma, careful examination with necessary additional diagnostics should be done to determine the extent of ocular and periocular damage.

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If the cornea is intact and the media sufficiently clear to permit examination of intraocular structures, the integrity of the iris, lens, vitreous, and retina can be determined by direct visualization of these structures. However, miosis, fibrin, or hyphema often precludes a thorough examination. In the case of globe rupture, uveal prolapse might be evident on examination if the rupture occurred in the cornea or anterior sclera, but a posteriorly located rupture is usually not evident. When ocular changes preclude a detailed direct examination, ultrasonographic imaging is an invaluable tool for assessing the extent of intraocular damage.

Emergency Management of Acute Ocular Trauma

Cases of acute ocular trauma must be handled on an emergency basis. When a dog is presented with ocular trauma, the dog should be restrained or sedated as needed to facilitate an ocular examination. Care must be used to prevent further trauma. If debris, exudates, or hemorrhage are present, they should be gently irrigated from the ocular surface with warm, physiologic saline solution (without preservative). If possible, the clinician should determine whether a laceration or rupture of the globe is present. Assessment of the extent of globe laceration or rupture is not always easy, but it is important as a prognostic indicator. Note that corneal lacerations frequently extend across the limbus under an intact but often hemorrhagic conjunctiva. If the globe is ruptured, further examination to assess the degree of rupture and foreign body examination should be delayed until the animal has been anesthetized. However, the appearance of intraocular contents (e.g., lens material or vitreous) within the wound or on the ocular surface is usually seen with minimal effort. It must be determined whether surgical repair is feasible or if enucleation or implantation of an intraocular prosthesis should be advised. This determination is made on the basis of the extent of intraocular damage, the likelihood of preserving vision, and cosmetic concerns. Systemic antibiotics should also be administered if the globe is ruptured. If the globe appears to be intact, topical anesthetic solution should be applied, and the ocular surfaces, including the conjunctival fornices and both sides of the nictitating membrane, should be inspected for foreign bodies.

Ancillary Diagnostic Procedures

Additional diagnostics are often required after the ocular exam to acquire more information. Radiography of the skull, including oblique views of the orbit or orbits, will confirm or rule out the presence of fractures and establish whether gunshot injury is involved. Brightness scan (B-scan) ultrasonography is specifically indicated when the normally transparent ocular media are opaque. Integrity of the lens and posterior sclera as well as the position of the lens and retina can generally be determined with B-scan ultrasonography. In traumatized eyes, echo-dense areas in the vitreous cavity usually indicate vitreal hemorrhage. Computed tomography (CT) and magnetic resonance imaging (MRI) are beneficial in assessing trauma, especially when intraocular foreign bodies (IOFBs) are suspected. Care should be taken with MRI, because metallic foreign bodies can incite additional damage.

Treatment of Blunt Injuries

Intense pressure exerted on the globe during blunt trauma results in vector forces reflecting off the posterior sclera and transferring anteriorly, causing a blowout rupture of the perilimbal cornea or anterior sclera. Some causes of blunt injuries are impacts by golf balls and baseball bats; commonly, the owner is not aware that the dog is in such close proximity when the accident occurs. Acute traumatic uveitis or hyphema from blunt injury is treated similarly to other causes of anterior uveitis and hyphema (see "Uveal Inflammation" and "Hyphema"). A ruptured globe resulting from blunt trauma is handled similarly to cases of penetrating corneal trauma with uveal prolapse (see Chapter 19). When globe rupture has occurred secondary to forceful trauma, retinal detachment with vitreal hemorrhage is a common complicating factor. Iris bombé, traumatic cataract, endophthalmitis, and phthisis bulbi can follow. Therefore, the prognosis following severe blunt trauma to an eye is guarded to grave.

Treatment of Penetrating Injuries

Focal punctures of the globe usually cause minimal damage to the cornea and often seal spontaneously. If the eye is examined within a few hours of the injury, it can be difficult to determine whether the cornea is completely penetrated or the extent of intraocular damage. Penetrating corneal injuries that seal spontaneously are treated with topical and systemic antibiotics and topical NSAIDs. Topical corticosteroids are usually not applied until the corneal epithelium has healed, unless the uveitis is severe. Systemic antibiotics are administered for a minimum of 10 days. In the absence of an IOFB, the primary concerns after such injuries are focal anterior or posterior synechiae, lens puncture with phacoclastic uveitis or septic implantation syndrome, traumatic cataract, secondary glaucoma, and infectious endophthalmitis.

Most penetrating injuries of the globe result in uveal prolapse, which appears as a protrusion of darkly pigmented tissue through the cornea or sclera. A grayish, fibrinous membrane typically covers the prolapsed uvea (Fig. 21.30). Sometimes the uvea abuts the penetrating wound and exudes fibrin, creating a mass of fibrin on the surface of the cornea. A shallow or absent anterior chamber, pupil loss, and hyphema are often present (Fig. 21.31). Traumatic uveal

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prolapse requires surgical repair that involves replacement or amputation of the prolapsed uvea. Specific steps in the repair of uveal prolapse are covered in Chapter 19. The prognosis after uveal prolapse repair varies depending on the time between injury and treatment, the extent of injury, concurrent infection, presence of a pupil opening, patency of the iridocorneal angle, and integrity of other intraocular structures (e.g., lens and retina).

Large lacerations or tears of the cornea or sclera with prolapsed uvea, total hyphema, and the presence of vitreous, lens capsule, or lens cortical material within the wound or on the surface of the eye indicate a very poor prognosis. In such cases, enucleation or globe evisceration with a prosthetic silicone implant are recommended alternatives to primary surgical repair. Severely injured eyes that are not repaired or enucleated will usually become phthisical within several days or weeks after the trauma. Even eyes that are repaired surgically might undergo phthisis if the uveal trauma is marked. Severely traumatized globes often become a source of chronic pain, because panophthalmitis and secondary glaucoma are possible sequelae.



Figure 21.30 Uveal prolapse secondary to a corneal laceration is present. Fibrin is exuding from the surface and is prominent on the corneal surface adjacent to the prolapse.

Traumatic Uveitis with Lens Rupture

Lens capsule rupture is most commonly caused by a penetrating foreign body or a cat claw injury. Lens capsule rupture allows the release of lens cortex into the anterior chamber, which often precipitates fulminating endophthalmitis (Davidson et al., 1991; Paulsen & Kass, 2012; Wilcock & Peiffer, 1987). Frequently there is a history of recent ocular trauma; however, lens penetration is rarely suspected. Often the corneal wound has sealed, and the anterior chamber has reformed by the time of examination. Capsular rents are generally difficult to detect, but overlying fibrinous or inflammatory cellular material is suggestive of capsular disruption (Davidson et al., 1991). Medical therapy of uveitis secondary to lens capsule rupture needs to be aggressive, with the use of topical and immunosuppressive doses of prednisone and topical atropine. Phacoemulsification might be necessary to treat lens rupture in some cases and, when indicated, it must be done early in the disease process (Davidson et al., 1991). However, medical treatment alone as above in conjunction with fluoroquinolones is often successful if the cornea has self-sealed. Many dogs also respond to medical therapy and surgical corneal repair without lensectomy (Paulsen & Kass, 2012). Small capsular rents often seal spontaneously and result in only a focal cataract (Fig. 21.32). Lens changes might even regress as the capsule is sealed with fibrosis (Paulsen & Kass, 2012). For additional information, see "Lens-Induced Uveitis" and Chapters 22 and 23.



Figure 21.31 A long fibrin strand is exuding from a laceration in the dorsal sclera. Hyphema is also present, obscuring the pupil and lens. The injury was caused by a cat's claw. The scleral rent was closed primarily.



Figure 21.32 Posterior synechiae and a focal cataract with overlying fibrin are present in this dog that had a penetrating trauma to sclera, iris, and lens. The anterior uveitis has resolved. This is the same dog as in Figure 21.31.

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Foreign Body Trauma

Corneal foreign bodies are common in dogs, but anterior segment foreign body trauma and retained foreign bodies are less common. Dogs less than 5 years old and hunting and working breeds are predisposed (Tetas Pont et al., 2016). Plant material is the most common type of ocular foreign body in dogs (Tetas Pont et al., 2016). Organic foreign bodies, such as splinters, thorns, and porcupine quills, are more likely to cause endophthalmitis than inorganic foreign bodies. Inorganic foreign bodies such as glass, plastic, and lead are nonreactive, while iron and copper foreign bodies are reactive and are more likely to cause direct toxicity to intraocular structures (Lit & Young, 2002; Mester & Kuhn, 2002; Schmidt et al., 1975). Diagnosing IOFBs can be difficult. A thorough history and a complete ocular examination including biomicroscopy, with special attention to evaluation of the lens and inspection of the conjunctival fornices, both sides of the nictitating membrane, and all remaining conjunctival surfaces, are essential.

The location, depth, size, and composition of the foreign body often correspond to the extent of associated tissue damage and the amount of uveal inflammation. Additionally, these factors dictate the method of removal (Tetas Pont et al., 2016). Small, inert foreign bodies can be left alone. In contrast, organic foreign bodies that remain inside the eye often stimulate severe, usually nonresponsive endophthalmitis; therefore, every effort should be made to remove all organic foreign material from the globe. Regardless of the type of foreign body, both septic and nonseptic endophthalmitis are sequelae that often necessitate enucleation.

A penetrating foreign body that is tapered, smooth, and relatively small in diameter can be removed directly after administration of general anesthesia. A hypodermic needle can be used to remove the foreign body. A single suture is placed at the site of penetration to seal the cornea and prevent aqueous leakage. Rough, jagged, or barbed penetrating foreign bodies often require a full-thickness incision adjacent to or over the top of the foreign body to facilitate removal.

For retained linear foreign bodies that have penetrated the globe tangentially, an oblique, full-thickness corneal or scleral incision directly over the foreign body is often necessary for removal. After incising the cornea or sclera with a pointed surgical blade (e.g., a No. 65 Beaver blade), the foreign body is removed, and the wound is irrigated liberally with balanced salt solution. The defect is sutured with 8-0 polyglactin 910. The associated uveitis is treated topically with fluoroquinolones, 1% atropine, and NSAIDs. Some cases require the judicious use of topical corticosteroids. Systemic treatment should include antibiotics (fluoroquinolones) and anti-inflammatory agents.

Unless there is a gaping corneal wound or an exceptionally large foreign body, a foreign body located completely within the anterior chamber should be removed from a site distant from the entrance wound to minimize scarring and damage to endothelial cells (Lit & Young, 2002). This positioning allows for visualization of an instrument as it approaches the IOFB, and minimizes obscuration from corneal edema if more manipulation is required than expected. The entrance wound should be closed, with reestablishment of IOP prior to creating a new surgical wound through which to remove the foreign body. Saline or viscoelastics can be used to dislodge foreign bodies that are located near the angle. Maintaining the anterior chamber with viscoelastics aids with visualization.

Possible complications of full-thickness corneal foreign body penetration include keratomalacia at the site of penetration, iridal abscess formation, septic endophthalmitis with secondary glaucoma, or retinal detachment. Minor lens involvement can result in an incipient cataract alone. If the anterior lens capsule is torn, uveitis is more severe, and cataract formation will be more advanced. However, with focal lens punctures the lens capsule often seals spontaneously. Rarely the foreign body is retained in the lens. Intralenticular hemorrhage or abcessation can also occur. Most cases of lens capsule rupture are successfully treated medically with mydriatics and topical and systemic antibiotics and anti-inflammatories. In the majority of those cases lenticular changes remain stable, but a very few dogs have long-term follow-up. Lensectomy using phacoemulsification is necessary for some cases of traumatic lens rupture. One study showed that the average number of days to referral in cases amenable to surgery was 3, versus 10 days in dogs that were not considered surgical candidates. Those cases seen later in the time course of disease had profound uveitis and extensive posterior synechiae (Davidson et al., 1991). Many of the cases that require phacoemulsification retain vision, but some develop secondary glaucoma, retinal detachment, or have chronic uveitis (Tetas Pont et al., 2016).

Risk factors for enucleation after foreign body trauma include full-thickness foreign body penetration, severe lens trauma, and severe uveitis (Tetas Pont et al., 2016). Ocular ultrasound is valuable to rule out retinal detachments when contemplating treatment options. Immediate referral to a veterinary ophthalmologist is advised in difficult cases to confirm the diagnosis, offer a prognosis, perform any necessary surgery, or treat any complications, which frequently arise.

While most foreign bodies need to penetrate deep into the cornea or enter the anterior chamber to cause significant uveitis, the setae from the pine processionary caterpillar, *Thaumatopoea pityocampa* (southern European and Mediterranean pine forests), causes anterior uveitis in 80% of affected dogs. In these eyes only a small superficial, crescent-shaped nonulcerative corneal lesion is present with the uveitis. The lesions might be caused by mechanical irritation, hypersensitivity, or a toxin. Generally, hydropulsion to remove the setae and medical therapy with topical antibiotics and NSAIDS are effective (Costa et al., 2016).

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Hyphema

Hyphema, or blood in the anterior chamber, occurs when uveal or retinal vessels are damaged or abnormally formed (see Fig. 21.18). Causes of hyphema in the dog include trauma, neoplasia, retinal detachment, blood dyscrasias, PIFMs, hypertension, infectious disease, severe uveitis, congenital anomalies, and canine ocular gliovascular syndrome (Bayon et al., 2001; Cullen et al., 2000; Grahn et al., 1997; Gray et al., 2003; Habin & Else, 1995; Heath et al., 2003; Kilrain et al., 1994; LeBlanc et al., 2011; Littman et al., 1988; Nelms et al., 1993; Oria et al., 2004; Peiffer et al., 1990; Stades, 1980; Treadwell et al., 2015; Trepanier, 2004; van de Sandt et al., 2004; Vinayak et al., 2004). Retinal detachment is the disease process most commonly associated with hyphema seen at referral institutions (Nelms et al., 1993). Chronic uveitis, chronic glaucoma, neoplasia, and retinal detachments often lead to the development of PIFMs, which can result in hyphema (Peiffer et al., 1990).

The prognosis for hyphema is dependent on the etiology and presence of posterior segment damage. Hemorrhage from damaged choroidal or retinal vessels can move anteriorly through the pupil to the anterior chamber. Vitreal, retinal, or choroidal hemorrhages with retinal detachment indicate severe intraocular disease and a poor visual prognosis. Also, the cause of hyphema influences whether blood clots in the anterior chamber. If the hyphema is secondary to a clotting abnormality, the hyphema is unlikely to clot. However, hyphema occurring secondary to trauma or iridocyclitis will usually clot. Hemorrhage resulting from neoplastic, retinal detachment, or congenital ocular diseases is often recurrent, and the hyphema in these cases frequently forms multiple layers within the anterior chamber.

A detailed history and complete physical and ocular examinations are essential. In young dogs with no history of trauma, congenital anomalies must be considered. Examining the eyes of littermates and being familiar with breed predilections to hereditary congenital ocular disease, such as Collie eye anomaly or persistent hyaloid artery, are helpful in making a diagnosis. Other differential considerations in young adult dogs with spontaneous hyphema include infections (e.g., ehrlichiosis) and toxic bleeding disorders. Neoplasia and systemic hypertension are causes that must be considered in older animals. Regardless of the animal's age, both genetic and acquired hemostatic diseases should be ruled out.

A complete ophthalmic examination including fluorescein stain and IOPs is indicated for all cases of hyphema. A full physical examination in association with a diagnostic evaluation, including appropriate laboratory tests, is indicated to rule out systemic disease in animals with atraumatic hyphema (see Chapter 37, Part 1). In many cases of hyphema, the most informative ancillary diagnostic procedure is ocular ultrasonography. Extensive hyphema prevents intraocular evaluation; therefore, intraocular masses, vitreal hemorrhage, retinal detachments, or scleral rupture are only detectable with B-scan ultrasonography. CT or plain-film radiographs of the skull and orbit are used to diagnose concurrent orbital fractures or foreign bodies. While MRI can be used, additional damage to the globe and contents from intraocular ferromagnetic foreign bodies is a risk with this imaging modality.

Thoughts on the best medical treatment of hyphema vary. Veterinary studies addressing medical management are lacking, in part because of the many common causes of hyphema. This contrasts with human medicine, where trauma is by far the most common etiology of hyphema. Gharaibeh et al. (2013) conducted a meta-analysis evaluating medical intervention for traumatic hyphema in humans. They found no evidence that the use of corticosteroids, cycloplegics, miotics, or nondrug interventions, such as bed rest, showed benefit. They also demonstrated that topical and systemic antifibrinolytics, such as aminocaproic acid and tranexamic acid, reduced the rate of secondary hemorrhage, but slowed the clearance rate. The authors concluded that treatment should be individualized (Gharaibeh et al., 2013). Following are the medications most commonly used in the treatment of hyphema and the reasoning behind their use. Topical dexamethasone or prednisolone acetate with or without systemic prednisone is typically used, assuming no contraindications, to reduce and control intraocular inflammation and to possibly reduce the incidence of rebleeding (Brandt & Haug, 2001; Walton et al., 2002). The use of pupilloactive drugs is somewhat controversial. Topical 1% atropine might be indicated initially to reduce the possibility of posterior synechiae formation, to decrease ciliary spasm, and to stabilize the blood–aqueous barrier. However, IOPs often increase with hyphema due to occlusion of the trabecular meshwork by clots, inflammatory cells, or erythrocytic debris, and the use of atropine can exacerbate ocular hypertension (Walton et al., 2002). Therefore, tonometry should be done regularly to monitor for changes in IOP. If an increased IOP is noted after the initiation of mydriatic treatment, atropine should be discontinued immediately and topical timolol and dorzolamide initiated to reduce the IOP (see Chapter 20). Tropicamide (1%) prevents synechia formation without having the risk of elevating IOP if used judiciously. Conversely, pilocarpine can be efficacious because it enhances the outflow of aqueous humor, facilitates the removal of blood through the trabecular meshwork, and increases the surface area of the iris (via miosis), thereby enhancing fibrinolysin activity (Havener, 1983). The potential disadvantages of pilocarpine or other miotics are that miosis predisposes patients to posterior synechiae and, subsequently, to iris bombé, and cholinergic agents might potentiate uveitis (Havener, 1983; Krohne et al., 1998).

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Tissue plasminogen activator (tPA) is effective in the treatment of hyphema when large blood clots and fibrin are present in the anterior chamber or the IOP is elevated secondary to fibrin blocking the iridocorneal angle (Gerding et al. 1992; Martin et al., 1993). An injection of tPA into the anterior chamber leads to rapid clot dissolution, and tPA is most effective when injected within 72 hours of clot formation. The recommended dosage for intracameral injection is 0.1 mL of a 25 mg/100 µL solution (Gerding et al. 1992; Martin et al., 1993). However, tPA should not be injected if recurrent bleeding is likely, although the risk of rebleeding is low due to clot specificity (Crabbe & Cloninger, 1987). Lastly, confining the dog's activity to a cage or small room in a quiet area might minimize the possibility of recurrent hemorrhage.

Establishing a prognosis or elucidating the cause of hyphema is not always possible. Evaluating the response to medical or surgical therapy (e.g., corneal laceration repair) helps to determine the extent of disease. Uncomplicated hyphema usually clears within 1 week (Walton et al., 2002). In cases of unexplained, nonresponsive, or recurring hyphema, the etiology must be reassessed. When intraocular neoplasia is present or strongly suspected to be the cause of hyphema, the affected eye should be enucleated and submitted for microscopic evaluation. The prognosis for vision is best with cases of small hyphema volumes not associated with retinal detachment, hypertension, or trauma. Initial exam findings of unilateral hyphema, complete hyphema, the absence of a dazzle or consensual pupillary light reflex, an elevated IOP, and retinal detachment, regardless of cause, are associated with permanent blindness (Jinks et al., 2018). Chronic hyphema can lead to all of the sequelae observed with chronic uveitis. Ghost cell glaucoma is a common complication of hyphema in humans that also occurs in dogs (Campbell, 1981). The prognosis for vision in dogs with hyphema secondary to retinal disease is grave, and most dogs develop secondary glaucoma (Nelms et al., 1993).

Non-neoplastic Iridal Proliferations

Ocular Melanosis (Pigmentary Glaucoma)

Abnormal ocular pigment deposition and glaucoma (ocular melanosis or pigmentary glaucoma) are described primarily in Cairn Terriers, but also in the Boxer and Labrador Retriever (Covitz, 1981; Petersen-Jones, 1991; van de Sandt et al., 2003). The disease appears to be familial and tends to occur in older dogs. This syndrome has been compared with the pigmentary dispersion syndrome in humans. Clinically, hyperpigmentation involves the iris, ciliary body, choroid, and filtration angle. Often the iris appears thickened, and pigment is dispersed in the aqueous humor. Additionally, patchy pigment deposition around the perilimbal zone of the sclera, progressive pigmentation of the tapetal fundus, and secondary glaucoma occur (Fig. 21.33; Petersen-Jones, 1991; van de Sandt et al., 2003). Affected dogs are poorly responsive to long-term therapy.



Figure 21.33 This Cairn Terrier has pigmentary glaucoma. Pigment is dispersed in the aqueous humor and is present on the anterior lens capsule. Additionally, there is pigment deposition in the perilimbal zone of the sclera. Secondary glaucoma has caused buphthalmia and lens subluxation.

Microscopically, many large, round, pigment-laden cells are seen infiltrating the anterior uvea, sclera, and episclera and obscuring the drainage angle. Fewer cells are present in the posterior segment of the globe, the optic nerve meninges, and the periphery of the optic nerve. Many globes have changes secondary to chronic glaucoma, and some have evidence of uveitis. While there has been debate as to whether the melanin-containing cells are melanophages or melanocytes, immunohistochemical ultrastructural characterization of the cells reveals that most of them are melanocytes, with fewer being melanophages. The melanocytes contain both immature and mature melanosomes (Petersen-Jones et al., 2008). The melanocytic infiltration can be so extensive as to simulate diffuse melanoma; however, this process is not neoplastic. Pedigree analysis suggests a possible autosomal-dominant mode of inheritance (Petersen-Jones et al., 2007). While this disease is not considered to be neoplastic, three dogs in one large study were subsequently diagnosed with uveal melanocytic neoplasms (Petersen-Jones et al., 2007).

Iris Freckles and Nevi

Non-neoplastic areas of hyperpigmentation are common on the canine iris. These are referred to as iris freckles or iris nevi (Trucksa et al., 1985). Iris freckles, benign melanosis, or pigment cell clusters are used to describe benign hyperplasia or increased pigmentation of normal melanocytes (Peiffer, 1981; Trucksa, 1983). These clusters of cells are located in the superficial iridal stroma and do not tend to distort the normal iris architecture, but are occasionally raised (Gelatt et al.,

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Figure 21.34 An iris nevus is present in the iris of this German Shepherd mix.

1979; Peiffer, 1981). Iris freckles infrequently coalesce to cause diffuse pigmentation, which can be bilateral. Observation of freckles in the opposite eye assists diagnosis (Peiffer, 1981). An iris nevus is a proliferation of melanocytes that forms a well-circumscribed, slightly elevated mass on the iris face (Fig. 21.34; Gelatt et al., 1979; Peiffer, 1981). Nevi tend to occur in young dogs. Microscopically, cells replace the iris stroma, and cystic areas may be present. Mitotic figures are not observed, and the cell population is relatively homogenous (Gelatt et al., 1979). Nevi have the potential to undergo malignant transformation; however, diffuse malignant melanoma of the iris rarely occurs in dogs, in comparison to cats, and usually the iris is thickened concurrently (Peiffer, 1981).

Anterior Uveal Tumors

Intraocular tumors are primary or secondary to metastatic disease or local invasion. The great majority of primary intraocular tumors have their origin in the anterior uvea. While distant metastasis from primary intraocular tumors is rare, local tissue destruction and secondary glaucoma occur commonly. Tumors must be differentiated from other intraocular masses, including iris cysts, granulomatous lesions, and staphylomas. Tumors must also be considered in any eye with secondary glaucoma or opaque media. Diagnosis is based on findings from complete ophthalmic and physical examinations and whether the masses are unilateral or bilateral, singular or multiple, raised or flat, and static or changing in appearance.

Primary Neoplasms

Melanocytic Neoplasms

Melanocytic neoplasia (i.e., melanoma) is the most common primary intraocular neoplasm in the dog (Saunders & Barron, 1958; Trucksa, 1983). Melanomas in veterinary medicine are often referred to as *benign* or *malignant*. Alternatively, melanocytoma can be used for benign melanomas. This is in contrast to human medicine, where melanoma implies malignancy. Larger studies of canine ocular melanomas classify canine uveal melanomas as melanocytomas and (malignant) melanomas (Giuliano et al., 1999; Nasisse et al., 1993; Wilcock & Peiffer, 1986). The term melanocytoma refers to benign anterior uveal melanomas, limbal melanomas, and choroidal melanomas. Melanocytomas are differentiated from (malignant) melanoma by nuclear pleomorphism, nuclear-to-cytoplasmic ratio, and mitotic index. Tumors are considered malignant if cellular morphology includes prominent nucleoli, a nuclear-to-cytoplasmic ratio greater than one, and more than four mitotic figures per 10 high-power fields (HPFs; Bussanich et al., 1987; Dubielzig, 1990; Giuliano et al., 1999; Labelle & Labelle, 2013; Wilcock & Peiffer, 1986). Most canine ocular melanomas arise in the anterior uvea, and both the iris and the ciliary body are common sites of origin. With large masses, the tissue of origin is often difficult to determine even microscopically.

Several large studies have provided the majority of the clinical and histologic information on canine uveal melanomas (Bussanich et al., 1987; Giuliano et al., 1999; Ryan & Diters, 1984; Wilcock & Peiffer, 1986). Intraocular melanocytic tumors are most common in older dogs, with a mean age of around 9 years and an age range of 2 months to 17 years. While German Shepherds and retrievers are the more commonly affected breeds reported in studies, population statistics have not been done to determine if breed is a risk factor. Inherited iris melanoma has been reported in a family of Labrador Retrievers, but the diagnosis was made on the basis of clinical examination with no microscopic confirmation (Cook & Lannon, 1997).

A color change or mass effect in the eye is often the first abnormality observed; however, if these initial changes go unnoticed, secondary uveitis or glaucoma develops. Melanomas in dogs tend to produce nodular growth rather than diffuse infiltration, as seen in cats and humans (Acland et al., 1980). At clinical presentation, melanomas are frequently focal and confined to the iris, or they can be extensive. Large masses often bulge through the pupil, displace the iris anteriorly, or cause dyscoria. Iris thickening, an irregular pupil, blindness, and ocular pain are the most common clinical signs (Fig. 21.35). Degree of pigmentation is variable, but amelanotic melanomas are rare (Dubielzig, 1990). Additionally, keratitis, anterior uveitis, hyphema, secondary glaucoma, buphthalmos, and retinal detachment frequently occur with chronicity. Anterior uveal melanomas are often locally invasive, extending to involve the choroid, sclera, filtration angle, cornea, and orbit. Lens subluxation occurs if the mass displaces the lens. Neoplastic melanocytes or melanophages (or both) are frequently free-floating in the

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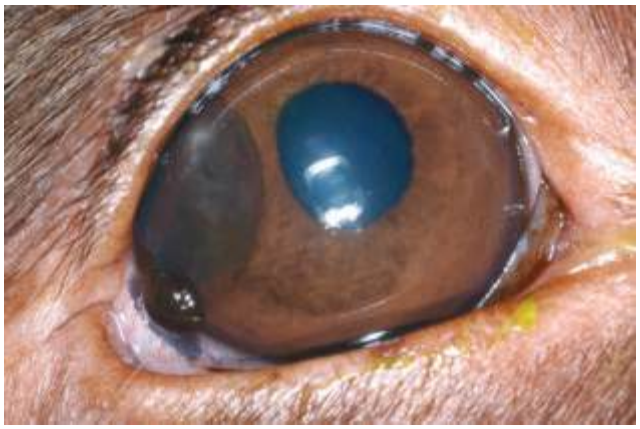


Figure 21.35 Melanocytic neoplasia is present in the nasal aspect of the iris. The tumor is protruding through the limbus.

anterior chamber, and their obstruction of the filtration angle contributes to secondary glaucoma. Uveal melanomas that penetrate the perilimbal sclera can simulate a limbal (i.e., epibulbar) melanoma.

Diagnosis is usually made on clinical examination. Possible differentials include uveal cysts, staphylomas, and limbal melanocytoma. Iris cysts transilluminate, and limbal melanocytomas are located on the external surface of the globe. Ultrasound can be used to differentiate between cysts and tumors and to help determine the extent of tumor growth when the cornea or ocular media is opaque. Gonioscopy facilitates differentiation between uveal and limbal melanocytomas. Uveal melanomas with extraocular extension often invade the filtration angle, whereas limbal melanocytoma, though extending deep into the sclera, will compress but less commonly invade the angle; still, invasion of limbal melanomas into the filtration angle and anterior uvea has been reported. Primary choroidal melanoma has been reported infrequently in the dog, and anterior uveal melanomas can infiltrate posteriorly into the choroid (Dubielzig et al., 1985a). It is important to rule out metastasis from a distant site by doing a thorough physical examination that includes examining the oral cavity, footpads, and nail beds.

The histopathologic descriptions of intraocular melanocytic tumors vary (Bussanich et al., 1987; Diters et al., 1983; Dubielzig, 2002; Ryan & Diters, 1984; Trucksa et al., 1985; Wilcock & Peiffer, 1986). Some authors use quantification of relative proportions of cell types (e.g., spindle, ovoid, epithelioid) to define benign or malignant qualities; however, even the criteria for certain cell types vary significantly. Spindle A and epithelioid cells are described by some but not by others. Most authors agree that plump or round pigment cells are a feature of canine uveal and limbal melanomas. These cells are typically polyhedral and heavily pigmented. Results of ultrastructural studies have revealed that plump cells are neoplastic melanocytes rather than melanophages. Plump cells occur with much greater frequency in microscopically benign melanomas; accordingly, these melanomas tend to be more heavily pigmented and lack mitotic figures. The plump cell is postulated to be a hypermature spindle cell that is amitotic and prone to lysis, whereas the cell types typical of microscopically malignant melanomas are thought to represent anaplasia rather than spindle cell maturation. In cases of a poorly pigmented or poorly differentiated melanoma, it might be difficult to make the histopathologic diagnosis, but immunohistochemical staining with Melan A can be beneficial. Additionally, monoclonal antibodies designed to detect melanoma-associated antigens in human tissues have been used with some success to diagnose canine melanomas, and such antibody markers might be useful in these rare instances (Berrington et al., 1994). While the Callender classification is used for correlating histopathologic features of uveal malignant melanomas with their metastatic potential in humans, its use is not deemed appropriate for use in dogs because many canine tumors are benign, are of the mixed or epithelioid-cell type, or have plump cells not seen in human uveal melanomas (Bussanich et al., 1987; Callender, 1931; Ryan & Diters, 1984; Trucksa et al., 1985; Wilcock & Peiffer, 1986).

Severity of intraocular destruction has also been used as a sole indicator of malignancy; however, most canine anterior uveal melanomas, though frequently invasive, do not conform to the strictest definition of malignancy, which includes metastasis having the potential to cause death (Ryan & Diters, 1984; Wilcock & Peiffer, 1986). Most primary ocular melanocytic neoplasms arise from the anterior uvea, with 79% of the benign lesions and 95% of the malignant melanomas arising from that site. Regardless of histologic characteristics, approximately the same number of tumors remained inside the sclera (-7%), invaded the sclera (-56%), or had extra-scleral extension (-28%; Giuliano et al., 1999). Most tumors arising from the anterior uvea grow expansively rather than invasively and occupy the filtration angle and deep stroma of the peripheral cornea and sclera (Wilcock & Peiffer, 1986). Malignant melanomas tend to be less pigmented and comprise 20% of intraocular melanocytic tumors (Dubielzig, 2002).

Metastasis occurs hematogenously and typically involves the thoracic and abdominal viscera, although other sites are sporadically reported (Bussanich et al., 1987; Giuliano et al., 1999; Ryan & Diters, 1984; Wilcock & Peiffer, 1986). Microscopically, neoplastic cells are identified in the scleral emissaria or the optic nerve, confirming the egress of neoplastic cells from the globe. Extraocular extension or glaucoma (or both) might predispose to metastasis (Trucksa et al., 1985). Metastasis to the contralateral eye has been reported once (Render et al., 1997). Metastasis to the eye from cutaneous or oral sites rarely occurs, so the primary tumor site may be difficult to determine (Ryan & Diters, 1984; Trucksa et al., 1985). Cytologic indices (i.e., mitotic

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index, nuclear pleomorphism, nuclear–cytoplasmic ratio) are sensitive and accepted indicators of malignant potential in many tumors. For all cases of canine anterior uveal melanomas in which metastasis has been confirmed, the neoplasms have shown morphologic characteristics easily recognizable as being indicative of malignancy. Specifically, the mitotic index has been suggested as being the superior criterion for predicting malignancy. A low mitotic index (< 2 per 10 HPFs) is typical of melanocytomas. For melanomas in which metastasis was confirmed, however, the mitotic index was higher (> 4 per 10 HPFs, and usually greater than 20; Bussanich et al., 1987; Dubielzig, 1990; Wilcock & Peiffer, 1986). Histologic criteria, such as necrosis, inflammation, degree of pigmentation, and presence of tumor cells in the cornea, filtration angle, or episclera, are not predictive of postsurgical biologic behavior (Wilcock & Peiffer, 1986). Cyclooxygenase-2 is expressed similarly in normal eyes and in eyes with benign and malignant melanocytic neoplasms; therefore, COX-2 expression is not useful in differentiating these tumors (Paglia et al., 2009).

Because of the need for enucleation for histopathology, the poor predictive value of histopathology, and the poor response of metastatic tumors to therapy, further studies have been undertaken. One study found that four genes (*HTR2B*, *FXR1*, *LTA4H*, and *CDH1*) that form part of a prognostic assay for human uveal melanomas demonstrate increased expression in metastasizing uveal melanomas in dogs (Malho et al., 2013). Another study by the same authors evaluated microRNAs (miRNAs), which not only have the potential to serve as markers but could also have a role in targeted therapy. This study found that 14 miRNAs exhibited statistically significant differences in expression between metastasizing and nonmetastasizing tumors, and of those, 9 categorized tumors with an accuracy of 89% (Starkey et al., 2018).

Dogs with malignant melanoma have shorter survival times than unaffected dogs and dogs with melanocytomas. Tumor extension, tumor size, and mitotic index are not specifically related to survival time. The metastatic rate for uveal melanomas in dogs has been reported to be 4% and 10% (Bussanich et al., 1987; Wilcock & Peiffer, 1986). One study showed evidence of metastasis with tumors deemed to be melanocytomas and malignant melanomas, with a lower metastatic rate in the dogs with melanocytomas (-4%) and a rate of 25% in dogs with malignant melanomas (Giuliano et al., 1999). The overall low risk of metastasis of canine uveal melanomas and unproven efficacy of enucleation at preventing metastasis make the decision to remove normotensive, noninflamed visual eyes difficult (Wilcock & Peiffer, 1986). Additionally, studies in humans with uveal melanomas have shown that dissemination of tumor cells at the time of enucleation may be a major risk for metastasis with small- and medium-sized tumors (McLean et al., 1982; Zimmerman & McLean, 1979).

Iridociliary Epithelial Tumors

Iridociliary epithelial tumors are the second most common primary intraocular tumor in the dog (Dubielzig et al., 1998; Peiffer, 1983a). These tumors arise from either the epithelial cells of the iris or the ciliary body (Dubielzig, 2002). Primary iridociliary epithelial tumors have one of the following criteria: noninvasive epithelial growth extending into the aqueous adjacent to the iris or ciliary body, pigmented epithelial cells, or thick basement membrane structures on the cell surface (Dubielzig et al., 1998).

Iridociliary epithelial tumors are more common in middle-aged to older dogs (mean age 9.0 years; Beckwith-Cohen et al., 2015; Dubielzig et al., 1998; Peiffer, 1983a; Peiffer et al., 1978). Labrador and Golden Retrievers appear to be overrepresented in a new study compared to older studies, suggesting that genetic traits may be related to this tumor occurrence in retrievers (Beckwith-Cohen et al., 2015). These tumors appear clinically as segmental or nonsegmental, solid or papillary, and invasive or noninvasive (Fig. 21.36). Generally they are pink with little to no apparent pigmentation. The incidences of adenoma (i.e., benign) and adenocarcinoma (i.e., potentially malignant) are approximately equal, and these tumors combined are suggested to have an incidence approximately half that of uveal melanoma. Distant metastasis of ciliary body adenocarcinomas has been reported sporadically (Bellhorn, 1971; Dubielzig et al., 1998; Peiffer, 1983a).

Adenomas are more often limited to the ciliary body, but can usually be visualized through a dilated pupil. Adenocarcinomas, on the other hand, are typically more invasive, extend through the iris base or pupil, but rarely metastasize. A cystic adenoma has also been reported (Peiffer et al., 1978). Rarely, iridociliary epithelial tumors are difficult to differentiate from melanomas (Peiffer et al., 1978).



Figure 21.36 A ciliary body adenoma can be visualized extending into the pupil in this Labrador Retriever.

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Microscopically, iridociliary epithelial tumors are papillary, solid, or cystic (Dubielzig, 2002; Dubielzig et al., 1998). Adenomas are composed of sheets and cords of well-differentiated epithelial cells with a tendency to form adenoidal structures with an eosinophilic secretory substance. Adenocarcinomas form fewer adenoidal structures, have less secretory substance, and have variable cellular pleomorphism and numbers of mitotic figures (Peiffer, 1983a, 1983b). The usefulness of correlating cellular morphology with metastatic potential in these tumors is unknown (Dubielzig, 1990). While pigmentation is present in about half of the tumors histologically, most have the clinical appearance of being nonpigmented. Invasion into the sclera or lens rarely occurs, and these tumors often have cellular features of anaplasia; therefore, they are designated adenocarcinomas (Dubielzig et al., 1998; Hendrix & Donnell, 2007). Most tumors stain positive for vimentin, S100, and neuron-specific enolase. Secretion of hyaluronic acid, which stains with Alcian blue, is further evidence of iridociliary epithelial origin (Dubielzig, 2002; Dubielzig et al., 1998). Other commonly seen histologic findings are PIFMs, retinal detachment, asteroid hyalosis, intraocular hemorrhage, and glaucomatous changes.

The great majority of eyes with iridociliary epithelial tumors are enucleated. However, some tumors are biopsied either incisionally or excisionally. Three of five eyes that underwent incisional biopsy lost vision. All 14 excisional biopsies in one study had dirty margins. Of the 14, 8 had tumor recurrence in a median of 5 months. The remaining had no recurrence clinically for a median of 21.5 months; however, of those 6 cases, 3 were blind postoperatively from surgical complications. Four of eight globes enucleated after biopsy had tumor cells within the corneal scars. Of 19 dogs with follow-up, 4 had vision with no recurrence at a median of 23 months. These findings suggest that the benefit of biopsying these tumors is limited. The authors also suggested close follow-up in older dogs with quiet, visual, nonglaucomatous eyes and presumed iridociliary epithelial tumors as a viable option rather than biopsy or enucleation (Beckwith-Cohen et al., 2015).

Intraocular tumors, primarily of the ciliary body, have been induced with intravenously injected ^{226}Ra and ^{228}Ra in Beagles. Most of the tumors were thought to represent a unique radium-induced neoplasm arising from the pigment epithelium of the ciliary body. In contrast to melanomas, these tumors were not of neural crest origin. Metastasis was rare (Taylor et al., 1972, 2000).

Medulloepitheliomas

Primary primitive neuroectodermal tumors arise from the germinal neuroepithelium of the neural tube (neuroectoderm). Medulloepitheliomas arise from the primitive medullary epithelium of the ciliary body, whereas retinoblastomas arise from the primitive neuroepithelium of the immature retina (Broughton & Zimmerman, 1978; Regan et al., 2013). The occurrence of retinoblastomas in dogs is controversial.

Clinically, medulloepitheliomas appear as a white or gray-white mass present in the pupil or extending through the iris in young dogs. Secondary glaucoma might be the presenting clinical sign (Dubielzig, 2002). Microscopically, medulloepitheliomas are composed of sheets and cords of primitive neuroectoderm. Reports vary, but describe rosettes, Flexner–Wintersteiner rosette-like structures, pseudorosettes, and canals and tubules. Additionally, structures resembling normal derivatives of neuroectoderm such as retina, ciliary epithelium, vitreous, and neuroglia are seen (Wilcock & Williams, 1980). Some tumors contain additional tissues not normally present in the globe, such as undifferentiated mesenchyma, cartilage, striated muscle, or tissue resembling brain. These tumors are *teratoid medulloepitheliomas* (Lahav et al., 1976; Langloss et al., 1976; McLean et al., 1994). Mitotic figures are frequent. The vast majority of these tumors have a clinically benign behavior, and the treatment is enucleation. One case with metastasis to the brain and kidneys has been described (Aleksandersen et al., 2004).

While the prevalent thought has been that retinoblastomas do not occur in dogs, an immunohistochemical study done on a series of primary primitive neuroectodermal tumors of the retina and ciliary body in dogs suggested a bimodal age distribution of very young dogs having retinoblastoma-like tumors and older dogs having medulloepitheliomas. While six of eight tumors arose from the ciliary body, two of those (in addition to one that arose from the retina and one in which the origin was undetermined) were described as retinoblastoma-like tumors because of positive staining for interphotoreceptor retinoid-binding protein. Positivity for other retinal differentiation markers was variable (Regan et al., 2013). Interpreting immunohistochemistry on tumors with pluripotent cells is difficult. By definition, retinoblastomas in humans contain mutations in the retinoblastoma suppressor gene (*RB1*), which has not been studied in dogs. Because of the rarity of primitive tumors in dogs, the controversy will need further study to be resolved.

Miscellaneous Primary Neoplasms

Reports of other primary intraocular neoplasms are extremely rare. A cavernous hemangioma of the iris was successfully excised by iridectomy (Magrane, 1954). Ciliary body hemangioma has also been reported, and iridal hemangiosarcoma was confirmed in one other instance following enucleation (Kirschner et al., 1986; Read, 1993). Iridal leiomyosarcoma, presumably arising from the pupillary constrictor muscle, has also been reported (Barron & Saunders, 1959). A myxoid leiomyoma appeared clinically as a nonpigmented mass on the peripheral iris. Microscopically, predominantly uniform, spindle-shaped cells were loosely

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packed and arranged in a swirling pattern, and the tumor involved the dilator pupillary muscle (Billson et al., 2003).

Ocular osteosarcomas are rare. Generally, extraskeletal osteosarcomas are highly aggressive tumors with a high rate of recurrence or metastasis (Langenbach et al., 1998; Patnaik, 1990). However, two dogs with ocular osteosarcomas that were enucleated did not appear to develop metastasis or recurrence (Heath et al., 2003; van de Sandt et al., 2004). Primary ocular osteosarcomas have histopathologic evidence of pleomorphic spindle or stellate cells, occasional multinucleated cells resembling osteoclasts, and an abundance of extracellular collagen matrix typical of osteoid.

Spindle cell tumors of the anterior uveal tract of dogs appear as nodular, nonpigmented masses of the anterior uvea. The majority of affected dogs have blue irides, and the Siberian Husky is overrepresented, hence the name uveal spindle cell tumor of the blue-eyed dog (Zarfoss et al., 2007). However, the tumor has also been diagnosed in a dog with a brown iris, leading the authors to suggest the name uveal schwannoma (Marlo et al., 2018). Microscopically, the masses occur in the iris with or without ciliary body involvement and are composed of pleomorphic spindle cells showing interdigitation with stromal collagen. Tumor cells often show nuclear palisading, with the spindle cells arranged in fascicles and whorls (variable Antoni A and B behavior; Dubielzig 2002; Klauss & Dubielzig, 2001). Tumors are positive when immunostained for vimentin and S-100, with variable immunopositivity to glial fibrillary acidic protein (GFAP) and other stains. These tumors are morphologically and immunohistochemically most consistent with schwannomas (Marlo et al., 2018; Zarfoss et al., 2007). Glaucoma and PIFMs are also common. A malignant uveal schwannoma with cartilage and peripheral nerve extension was diagnosed in a 12-week-old color-dilute Labrador Retriever. This tumor is similar to those already described, but the very young age, divergent mesenchymal differentiation, and interneural growth pattern are comparable to some aspects of human neurofibromatosis (Duke et al., 2015).

An intraocular sarcoma similar to those reported in cats was diagnosed in a dog with lens capsule rupture and persistent hyperplastic primary vitreous. Microscopically, there was a proliferation of large, spindle-shaped cells with large, irregular nuclei arising from the lens. The tumor was vimentin and S-100 positive (Graham et al., 2018).

Secondary Neoplasms

Secondary neoplasms infrequently metastasize to the eye from local or distant sites, or invade the eye by local extension from the ocular adnexa, cornea, orbit, paranasal sinuses, or nasal cavity. Hematogenous spread accounts for most secondary neoplasms, and of these, intraocular lymphosarcoma is the most common in the dog (Cello & Hutcherson, 1962; Krohne et al., 1994). Other metastatic neoplasms include hemangiosarcoma, cutaneous and oral melanoma, osteosarcoma, malignant histiocytosis, seminoma, transmissible venereal tumor, transitional cell carcinoma of the urinary bladder and urethra, neurogenic sarcoma, rhabdomyosarcoma, anaplastic fibrosarcoma, pheochromocytoma, mast cell tumor, and adenocarcinoma of mammary gland, thyroid gland, parotid salivary gland, adrenal gland (presumed), nasal, renal, pancreatic, and pulmonary origin (Barron et al., 1963a, 1963b; Bellhorn, 1972; Boostrom et al., 2014; Castellano et al., 2006; Dubielzig, 1990; Esson et al., 2007; Ferreira et al., 2000; Gelatt et al., 1970; Habin & Else, 1995; HogenEsch et al., 1987; Kirschner et al., 1986; Moore, 1984; Moore et al., 1980; Nyska et al., 1992; Pereira et al., 2000; Schmidt, 1981; Szymanski, 1972; Szymanski et al., 1984; Trucksa et al., 1985; von Babo et al., 2011; Yoshikawa et al., 2008).

Secondary neoplasms often have similar clinical presentations, regardless of the histopathologic type, and potentially are more likely to occur bilaterally than primary ocular neoplasms. Dogs with secondary ocular neoplasms might either have obvious concurrent systemic disease or signs referable only to the eye (Lavach, 1984). An intraocular mass is not always readily apparent. The uvea appears to be a predilection site for those tumors that metastasize hematogenously (Bellhorn, 1972). Therefore, ocular signs often include anterior uveitis, hyphema, and glaucoma. Hyphema of undetermined etiology can be a sign of a metastatic neoplasm; in those cases, ocular ultrasound often helps to delineate a mass (Moore et al., 1980). Additionally, signs associated with chronic ocular disease such as secondary glaucoma, keratitis, lens luxation, retinal hemorrhage or detachment, and extraocular extension are often present.

Ocular Lymphosarcoma

Ocular signs occur commonly with lymphosarcoma. The reported incidence of ocular involvement with lymphosarcoma in one prospective study was 37% (Krohne et al., 1994); while this incidence is higher than this author has experienced, ocular signs are common. With the high incidence of ocular signs and because ocular lymphoma can mimic inflammation, lymphoma should be considered as a differential for anterior uveitis and retinal disease, even in the absence of lymphadenopathy or other evidence of systemic disease (Cave & Billson, 2003). Most cases are bilateral. Anterior uveitis with thickening and a lighter color to the iris is commonly seen (Fig. 21.37; Cello & Hutcherson, 1962; Krohne et al., 1994). Panuveitis is also frequently diagnosed, whereas posterior uveitis alone is uncommon. Additional ocular signs include conjunctival infiltrates, corneal infiltrates, hyphema, hypopyon, intraretinal and subretinal hemorrhages, and glaucoma (see Fig. 21.19 and Fig. 21.38). The keratitis occurring with ocular lymphosarcoma is distinctive. It usually begins with corneal edema and vascularization,

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Figure 21.37 The misshapen iris in this dog is caused by iridal lymphoma. At presentation, the dog had cells and aqueous flare in the anterior chamber, but they resolved with topical prednisolone acetate.

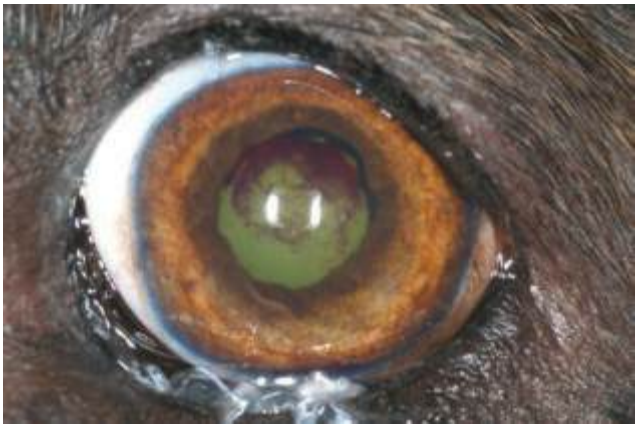


Figure 21.38 Hyphema and fibrin are seen in the anterior chamber of a dog with lymphoma.

followed 2–3 weeks later by perilimbal corneal infiltrates of neoplastic lymphocytes, which impart the appearance of a circumcorneal, dense white band (Cello & Hutcherson, 1962). Observation of a distinct intraocular mass is uncommon in the dog. Ocular lymphoma is most commonly associated with multicentric lymphoma, but there are rare cases of presumed solitary ocular lymphoma (PSOL) that have intraocular or conjunctival lymphoma with no other evidence of other sites of involvement at presentation. In one report of four dogs with intraocular PSOL, three dogs underwent chemotherapy and three had the eye enucleated. Two dogs also had uveitis in the less affected eye. All four dogs developed neurologic disease suggestive of CNS involvement prior to death or euthanasia. While results of such diagnostics have not been reported, MRI and CSF analysis should be considered in dogs with intraocular PSOL (Wiggans et al., 2014a). Additionally, uveodermatologic lymphoma was diagnosed in two young related Portuguese Water dogs. Both dogs had multiple skin nodules and bilateral ocular signs, including anterior uveitis, iris nodules, and secondary glaucoma (Escanilla et al., 2012).

Cytology of aqueous humor can be useful in making a diagnosis of lymphoma in dogs with anterior uveitis (Cave & Billson, 2003; Linn-Pearl et al., 2015; Ota-Kuroki et al., 2014; Pate et al., 2011; Wiggans et al., 2014b). Of the few uveal lymphomas that have been immunophenotyped, most have been B-cell lymphoma (Ota-Kuroki et al., 2014; Pate et al., 2011; Wiggans et al., 2014a). Microscopically, a diffuse uveal infiltration of neoplastic lymphocytes is present, and the anterior uvea is usually more heavily infiltrated than the choroid. Dense vascularity of the canine iris might be the reason for the increased incidence of anterior uveal involvement (Cello & Hutcherson, 1962). When present, retinal lesions range from mild retinal perivascular infiltrates to complete replacement of the retina by neoplastic cells (Cello & Hutcherson, 1962). Lymphocytic and lymphoblastic lymphosarcoma are the histopathologic types most often reported with ocular involvement, with the lymphoblastic type being slightly more common (Krohne et al., 1994). Intravascular lymphoma, also known as malignant angioendotheliomatosis, can also cause panophthalmitis, iridal swelling, and retinal detachment (Cullen et al., 2000).

Ocular signs are attributable not only to the neoplastic infiltrates, but also to associated abnormalities such as anemia, thrombocytopenia, and disseminated intravascular coagulation. These hematologic abnormalities, including leukemic blood profiles, are consistent with bone marrow involvement. Bone marrow involvement is more common in dogs with lymphosarcoma-associated ocular signs than those with lymphosarcoma and no ocular signs (Krohne et al., 1994).

Ocular examination of dogs with lymphosarcoma is useful in the clinical staging of the disease and as a predictor of longevity. In one study of 94 cases, the lifespan of dogs with ocular lymphosarcoma that underwent treatment was 60%–70% of that of those dogs without ocular involvement (Krohne et al., 1994). In this same study, all dogs presenting with uveitis and intraocular hemorrhage were classified as Stage V on the basis of other organ involvement and criteria. This finding may be particularly beneficial for immediate staging of those cases in which bone marrow biopsy has been nondiagnostic.

Diagnosis and Treatment of Uveal Neoplasms

Uveal neoplasms appear as either masses or anterior uveitis. Unilateral disease is more suggestive of a primary neoplasm, whereas bilateral disease is suggestive of secondary or metastatic neoplasia. A complete physical examination, serum biochemical profile, as well as thoracic and possibly abdominal radiography and ultrasonography are indicated when an intraocular neoplasm is detected or suspected, to determine

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the presence of metastatic disease. Disseminated neoplasia most commonly indicates that the neoplasm has metastasized from a primary site other than the eye, rather than a primary ocular tumor metastasizing.

Anterior uveal melanomas are the most common intraocular tumors and are often pigmented. As mentioned previously, transillumination to distinguish uveal cysts from melanoma or gonioscopy to distinguish limbal melanoma from uveal melanoma is often beneficial. The first indicators of intraocular neoplasia are commonly concurrent uveitis, hyphema, glaucoma, and ocular discomfort. Therefore, neoplasia should be considered in all such cases with an uncertain cause. Primary or secondary ocular neoplasia can mimic inflammation (masquerade syndrome) by shedding cells into the aqueous humor, by increasing the local blood supply, or by causing necrosis (Read et al., 2002). Ocular B-scan ultrasonography is often helpful in delineating a mass when opaque ocular media prohibit a thorough intraocular examination.

Cytologic evaluation of aqueous humor can be especially useful in diagnosing lymphosarcoma and mast cell tumors (Boostrom et al., 2014; Linn-Pearl et al., 2015; Olin, 1977; Wiggans et al., 2014b). All enucleated eyes or locally excised neoplasms should be evaluated histologically. Fine needle aspiration of intraocular masses has not been routinely used in veterinary ophthalmology.

Treatment of intraocular neoplasia depends on many factors, including the type of neoplasia, the overall health of the globe and the dog, the presence of metastatic disease, and the financial constraints of the owner. Treatment options include temporization, local excision, enucleation, orbital exenteration, and possibly euthanasia if metastatic disease is present. Given the seemingly benign biologic behavior of most uveal melanomas, some clinicians elect to simply observe the mass for progression, rather than hastily remove a sighted eye. Removal of a mass localized to the iris and not invading the filtration angle can be attempted by iridectomy. Masses that involve the iris and ciliary body can be excised via iridocyclectomy (see "Uveal Surgery"). A decision to perform local resection is made largely on the basis of clinical preference, the surgeon's technical proficiency in microsurgery, and the owner's financial constraints (see "Iridociliary Epithelial Tumors"). Diode laser photocoagulation of melanomas is an effective, less invasive treatment and is described in detail in "Photocoagulation of Iris Melanoma." Transscleral laser ablation and surgical excision of iris or ciliary body adenocarcinoma combined with chemotherapy using 5-fluorouracil have been reported (Clerc, 1996). In these latter instances, the diagnosis is presumptive, because histopathologic confirmation is usually not feasible.

From a practical standpoint, therapy in many instances is limited to enucleation or exenteration. Gentamicin injections for ciliary body ablation, which might be used in the treatment of end-stage glaucomatous eyes, are not recommended in eyes with intraocular neoplasia or inflammation. One study found that 40% of enucleated globes that had undergone chemical ciliary body ablation contained primary neoplasms. The majority were iridociliary epithelial tumors and melanoctyic tumors, and an unusually high percentage of the tumors had traits of malignancy. Many of these eyes had overt inflammation or suspect neoplasia at the time of the ablation. The authors suspect that the gentamicin selected for more malignant cells in preexisting tumors, or that inflammation was a predisposing factor for tumor development (Duke et al., 2013).

Naranjo found that 8% of evisceration samples contained a neoplasm and 39% of scleral shells contained a neoplasm. The most common tumor types were iridociliary epithelial tumors, melanocytomas, and malignant melanomas. Metastatic tumors were also identified (Naranjo & Dubielzig, 2014). Results of these studies support that the use of gentamicin for ciliary body ablation should be reserved for dogs that do not have ocular neoplasia nor disease that could mask its presence. Additionally, dogs that are diagnosed with neoplasia via evisceration sample should be followed up with enucleation, and if the tumor is metastatic, proper tumor staging should be undertaken. Enucleation is the preferred treatment for intraocular tumors when observation and follow-up are not appropriate. However, the curative potential of enucleation and the likelihood of inciting metastasis by performing such surgery remain controversial (McLean et al., 1982; Wilcock & Peiffer, 1986). Some clinicians recommend enucleation for primary tumors of any type when distant metastasis is not evident. Concurrent anterior segment inflammation or glaucoma is additional justification for enucleation. Orbital exenteration to completely remove the neoplasm is generally reserved for neoplasms that have extended outside the globe.

Enucleation or exenteration is often elected in the case of disseminated neoplasia when the goal is to reach a diagnosis or treat ocular discomfort. Systemic chemotherapy of secondary tumors, especially lymphosarcoma, often leads to resolution of ocular inflammation and regression of the intraocular mass. Topical corticosteroids alone frequently cause significant regression of anterior segment infiltrates associated with lymphosarcoma. Euthanasia may be more appropriate than enucleation (or exenteration) among select cases in which metastasis is present and the patient is debilitated, or the owner has declined therapy.

Uveal Surgery

Uveal surgery is indicated most commonly in the treatment of intraocular neoplasms and of pupillary abnormalities secondary to inflammation. Two other indications for surgery of the anterior uvea are the repair of globe perforations with

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prolapsed uveal tissue and the treatment of glaucoma refractory to medical therapy. These important areas of uveal surgery are addressed in Chapters 18 and 19.

General Concepts of Uveal Surgery

The anterior uvea is accessed through clear corneal, limbal, or scleral incisions. Entrance location into the anterior chamber is dependent upon the surgical procedure being performed and the location of the lesion within the uvea. Regardless of the entry point, several items need to be considered. The ora ciliaris retinae, the junction between the pars plana of the ciliary body and the peripheral retina, is located 8 mm caudal to the limbus superiorly and temporally, and only 4 mm inferiorly and nasally (Samuelson, 2007). An incision extending caudally to the ora may lead to retinal detachment or massive hemorrhage. The long posterior ciliary arteries enter the globe at the 3 and 9 o'clock positions from their scleral locations. These areas should be avoided when performing both surgical and laser therapies. Also, contact with the corneal endothelium and lens should be avoided in all procedures. Hemorrhage commonly occurs with uveal surgery, but can be minimized by avoiding surgery in actively inflamed eyes (which may not be possible) and by using electrocautery. Viscoelastic can be used to tamponade mild intraocular hemorrhage. If severe hemorrhage occurs, the surgeon can close the incision and reestablish the anterior chamber. After the blood clots, the clots can then be flushed or extracted.

Intraocular Surgery and Uveitis

All intraocular procedures incite some degree of anterior uveitis. Eyes with active uveitis at the time of surgery already have a compromised blood–ocular barrier and immunologically primed tissues, and are more likely to respond to surgical trauma rapidly and severely. Even when eyes with clinical uveitis are medically well controlled, the hypotony associated with decompressing the globe results in immediate passage of serum proteins and fibrin into the anterior chamber. When possible, intraocular surgery should be avoided in actively inflamed eyes. This most commonly applies to eyes with hypermature cataracts and LIU. In some cases, however, surgery is necessary or is justified (Davidson et al., 1991).

When intraocular surgery is performed on an eye with uveitis, it is essential that the affected eye be treated aggressively with appropriate topical and systemic anti-inflammatory medications both pre- and postoperatively. Indications for surgery on inflamed eyes might include annular posterior synechiae with pupillary seclusion and impending (or present) iris bombé, and phacoclastic uveitis caused by rupture of the lens capsule with release of lens protein into the anterior or posterior chambers. Intraocular surgery in an eye affected with uveitis might also be justified when complete hypermature cataracts (with associated phacolytic uveitis) have precluded vision and negatively affected the dog's quality of life.

Inflamed eyes have an increased likelihood of intraoperative complications, such as miosis, fibrin accumulation, and hemorrhage. Postoperative complications, including synechiae, pupillary membrane formation, secondary glaucoma, and phthisis bulbi, also occur more commonly in eyes that are inflamed at the time of surgery.

Preoperative therapy with topical prednisolone acetate is often initiated days to weeks prior to intraocular surgery. Mydriatics are usually indicated. Mydriasis and normalization of decreased IOP are good indicators of well-controlled anterior uveitis. Perioperative topical and systemic antibiotics are indicated for intraocular procedures. Additionally, preoperative NSAIDs and intraoperative heparin irrigating solution are usually indicated to reduce undesirable sequelae, such as recurrent synechiae and chronic uveitis. Preoperative NSAIDs or intraoperative heparin have the potential for intraoperative hemorrhage, but those used with routine cataract surgery are rarely problematic.

Topical corticosteroids, topical antibiotics, and mydriatics are used following most intraocular procedures. Systemic antibiotics and corticosteroids might also be indicated. Follow-up examinations that include fluorescein staining, IOP measurements, and complete light examinations are indicated frequently in the immediate postoperative period.

Mass Removal Procedures

Sector Iridectomy

Localized masses of the iris can be removed by sector iridectomy, although this procedure has largely been replaced with laser photocoagulation. This procedure is optimal for removing well-defined focal lesions of the iris that are located axially to the major iris blood vessels. The procedure is initiated by making a clear corneal incision adjacent to the iridectomy site. The incision is usually 90–180 degrees. After filling the anterior chamber with viscoelastic, the iris is retracted into the incision using a blunt iris hook. The iris, on both sides of the mass, is incised with iris scissors or cautery. The base is then incised. While there is limited hemorrhage with the radial incisions, more hemorrhage may occur with the base incision because of the major arterial circle that is present in the iris in 50% of dogs (Fig. 21.39). The iridectomy results in a keyhole-shaped pupil.

The main complications from this procedure include hemorrhage and incomplete excision of the mass. Use of electrocautery and avoidance of the major arteriolar circle help to minimize hemorrhage. Considerable or recurrent hyphema will cause significant postoperative problems. Determining

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the limits of the mass may be difficult during surgery, leading to the possibility of incomplete excision with subsequent recurrence. Surgical invasion of a neoplasm, with or without complete excision, could increase the likelihood of metastasis. In cases of iris tumor, the possible complications associated with iridectomy must be weighed against both cosmetic and functional loss of the eye, as the surgeon considers iridectomy versus laser photocoagulation or enucleation.

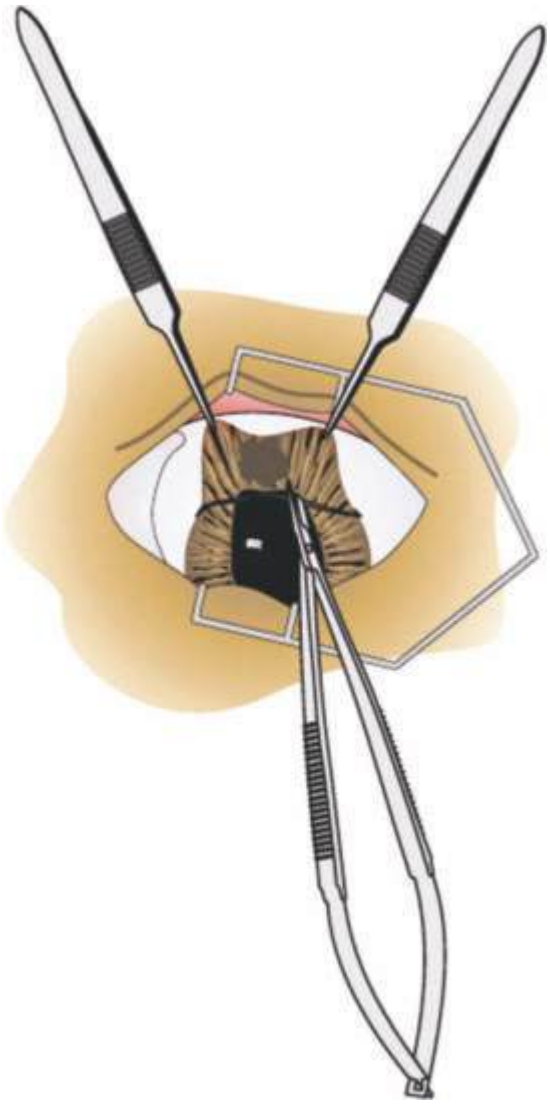


Figure 21.39 A sector iridectomy is initiated by making a clear corneal incision adjacent to the iridectomy site. The incision is usually 90–180 degrees. After filling the anterior chamber with viscoelastic, the surgeon retracts the iris into the incision using a blunt iris hook or thumb forceps. The iris, on both sides of the mass, is incised with iris scissors or cautery. The base is then incised. (Reproduced with permission from Gelatt, K.N. & Wilkie, D.A. (2011) Surgical procedures of the anterior chamber and anterior uvea. In: *Veterinary Ophthalmic Surgery* (eds. Gelatt, K.N. & Gelatt, J.D.), pp. 237–262. Philadelphia, PA: Elsevier.)

Iridocyclectomy

A sector iridocyclectomy is used when an anterior uveal tumor involves the ciliary body; however, this surgery is rarely performed and is often unsuccessful (see "Iridociliary Epithelial Tumors"). The surgery involves removing a portion of the iris and ciliary body. The ideal candidate has an uninvolved iridocorneal angle and a well-defined lesion confined to the anterior uvea. The presence of uveitis, glaucoma, or extension of the mass into the retina, choroid, or deep sclera jeopardizes the success rate of the surgery (Peiffer et al., 1988). The surgery should be limited to 90 degrees of the iris and ciliary body to minimize the occurrence of phthisis bulbi.

The iridocyclectomy involves making a limbal-based conjunctival graft and a 120–180 degree limbal incision over the mass. A full-thickness block of sclera is then excised over the affected area with a 6400 Beaver blade. Hemorrhage is controlled with point electrocautery. The affected iris and ciliary body are then excised with iris scissors (Fig. 21.40). A homol-

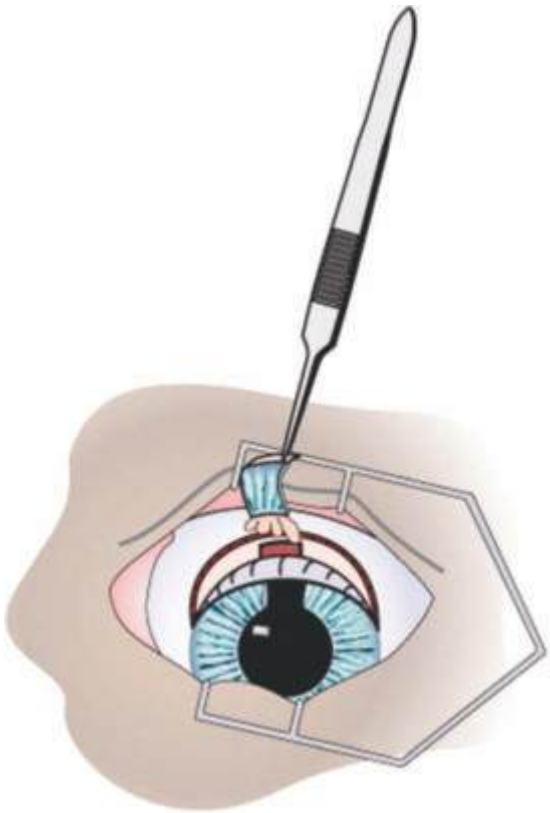


Figure 21.40 In the iridocyclectomy procedure, and after creating a limbal-based conjunctival flap, a limbal incision is made over the area of the neoplasm. A 6400 Beaver blade is used to excise a full-thickness block of sclera over the affected area. Hemorrhage is controlled with point electrocautery. The iris and ciliary body are then excised with iris scissors. (Reproduced with permission from Gelatt, K.N. & Wilkie, D.A. (2011) Surgical procedures of the anterior chamber and anterior uvea. In: *Veterinary Ophthalmic Surgery* (eds. Gelatt, K.N. & Gelatt, J.D.), pp. 237–262. Philadelphia, PA: Elsevier.)

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ogous graft of tissue 0.5 mm larger than the wound and the limbal defect are sutured using a simple interrupted pattern with 7-0 or 8-0 polyglactin 910. After the globe is reinflated, the conjunctiva is sutured using a simple continuous pattern (Gelatt & Wilkie, 2011).

Alternatively, the procedure can be initiated by making fornix-based conjunctival and scleral flaps. Then a perilimbal, clear corneal incision is made for approximately 100 degrees to allow access to the affected iris. A cyclodialysis spatula is used to separate the ciliary body from the sclera. The area of uvea to be removed is initially incised with electrocautery for hemostasis. Iris scissors are then used to complete the incision, allowing the block of affected uveal tissue to be removed. The scleral flap and corneal incision are sutured with 8-0 in a simple interrupted pattern, and the conjunctival flap is sutured to the limbus in a continuous pattern of 8-0 polyglactin 910 (Collins & Moore, 1999).

Severe uveitis is anticipated postoperatively. Therefore, intensive medical treatment is indicated to prevent a chronic, uncontrolled uveitis, which may result in phthisis bulbi. Other potential postoperative complications include hyphema, secondary glaucoma, and cataract formation. Enucleation is indicated when complications occur that do not respond to medical therapy or if tumor recurrence is noted. As stated previously, the possible complications associated with uveal surgery must be weighed against enucleation (see "Iridociliary Epithelial Tumors").

Laser Photocoagulation of Iris Melanoma

Diode laser photocoagulation can be useful in the treatment of presumed iris melanoma in dogs (Fig. 21.41). Selection criteria should include lesions isolated to the iris, with no evidence of complicating factors. The diode laser delivery system is used in a continuous mode, with either an operating microscope adapter or a laser indirect ophthalmoscope with a 20-diopter lens. Visualization of the lesion allows the surgeon to assess the surface changes, including shrinkage, surface disruption, and release of pigment cells into the aqueous humor (Fig. 21.42). Treatment is discontinued when no further shrinkage is observed, and surface changes are noted over the entire lesion.

<tx>Common postoperative findings include pigment dispersion on the anterior lens capsule, dyscoria, and diffuse iris hyperpigmentation. In most cases, the lesion is flattened and reduced in diameter, but persists (see Fig. 21.42). Occasionally, iris atrophy and corneal edema result. The postoperative corneal edema is suspected to occur because of collateral damage from heat generated when the laser is damaging the tumor. Some cases need more than one laser treatment (Cook & Wilkie, 1999).

Sphincterotomy, Synechiotomy, and Pupil Iridotomy

Occasionally, intraoperative mydriasis is inadequate to allow lens delivery during cataract surgery, or miosis occurs immediately after lens removal. In those cases, iridotomy of the pupillary sphincter (also termed sphincterotomy) might be necessary. Sphincterotomy is done by incising 1–3 mm of the pupil margin, usually at two to four positions in quadrants, with iris scissors. Limited hemorrhage and fibrin formation follow (Gelatt & Wilkie, 2011). One possible chronic postoperative complication of cataract surgery is the extensive formation of pupillary membranes, which is often secondary to progressive posterior synechiae. Extensive formation of pupillary membranes leads to vision loss by obliterating a functional pupillary opening, or to iris bombé with secondary glaucoma and resultant vision loss and loss of the eye. A pupil iridotomy might be considered in these cases. Pupillary membranotomy refers to a pupil iridotomy used in the treatment of postoperative pupillary membranes (Peiffer et al., 1988). Unfortunately, many fail because of reformation of the membranes.

Postoperative pupil iridotomy, or pupillary membranotomy, is done by making two small corneal stab incisions at



Figure 21.41 An iris melanoma is present at the temporal limbus. (Courtesy of Drs. Dennis Brooks and Kirk Gelatt.)



Figure 21.42 This is the same dog as in Figure 21.41 after diode laser therapy. The lesion is no longer elevated and is less pigmented. (Courtesy of Drs. Dennis Brooks and Kirk Gelatt.)

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the 10 and 2 o'clock positions to allow introduction of an infusion port and one needle that has its tip bent at a 90-degree angle. After the needle is directed through the stab incision and into the anterior chamber, it is rotated so that the tip engages iris tissue near the pupillary margin. The needle is then pulled across a portion of the membrane in either one or two locations, which usually results in an elliptical pupil opening. The anterior chamber is reestablished with physiologic irrigating fluid, and the corneal incision is closed with two interrupted 8-0 polyglactin 910 sutures (Collins & Moore, 1999; Peiffer et al., 1988).

The neodymium:yttrium-aluminum-garnet (Nd:YAG) laser is a noninvasive means of disrupting posterior synechiae (Brinkmann et al., 1992; Nasisse et al., 1990). This procedure is most effective in cases with limited numbers of clearly identified synechiae. Iris hemorrhage frequently occurs after laser therapy (Nasisse et al., 1990).

After pupil iridotomy, intensive medical therapy for anterior uveitis is initiated with ophthalmic steroids and atropine. Postoperatively, additional pharmacologic mydriasis may further dilate the pupil, thus enhancing the elliptical appearance. Unfortunately, the posterior synechiae often recur.

Iridotomy

Iridotomies are used for the creation of an alternative pathway for aqueous flow when flow through the pupil is not possible because of extensive annular posterior synechiae. By creating holes in the iris peripheral to the synechiae, aqueous flow bypasses the normal route through the pupil and goes directly from the posterior chamber to the anterior chamber. Full-thickness iris is incised with iris scissors or laser. After entrance into the anterior chamber via a 90-degree or 140-degree limbal incision, the middle third of the dorsal iris is incised with iris scissors. The middle third is incised to avoid the pupillary sphincter muscle and the greater arterial circle, which are located at the pupillary margin and base of the iris, respectively. Formation of full-thickness holes may be difficult in the inflamed iris. The inflamed iris of the dog is much thicker than the normal iris and frequently has a PIFM that will hemorrhage and exude more fibrin than the normal iris. Unfortunately, holes created via iridotomy are temporary and close within a few weeks (Gelatt & Wilkie, 2011).

The Nd:YAG and diode lasers have been used to treat pigmented irides with iris bombé in the dog (Brinkmann et al., 1992). Unfortunately, these procedures are not effective long term. While iridotomies created with the Nd:YAG laser are effective immediately postoperatively, all iridotomies eventually failed in one study (Brinkmann et al., 1992). In a study using the diode laser, a visible patent iridotomy could not be created. Ophthalmoscopically, the iridal pigment actually appeared to thicken as the adjacent iris contracted into the laser site (Nadelstein et al., 1996).

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22

Diseases of the Lens and Cataract Formation

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Introduction

The intraocular lens is the transparent, biconvex, avascular, and highly structured tissue that, located in the anterior segment of the eye, is partly responsible for the refraction of incoming light rays to a point source on the retina. The crystallin lens represents a unique tissue in light of its embryologic development, retention of old cells and nuclear make-up, transparent nature, immune privileged status, and metabolic restrictions. Its unique anatomic structure englobes a nucleus, cortex, and an external capsule composed of basement membrane, epithelia, and differentiated lens fibers. The lens is suspended by many dense zonular ligaments that, by directly connecting the ciliary body with the equatorial capsule, induce subtle changes in the lens curvature. Despite this simplistic anatomic structure, the lens has a highly refined and elegant series of biochemical processes that must function correctly throughout the life of the animal to maintain clarity. This transparency is a crucial property of the lens, which is achieved, in part, by the absence of light-scattering organelles within the lens fibers. New lens fibers are generated from the equatorial cells of the lens epithelium, which elongate, synthesize crystallins, and finally lose their nuclei as they become mature lens fibers. The crystallins, which make up over 90% of the proteins in the lens, are specially adapted to contribute to the maintenance of transparency by forming soluble, high-molecular weight aggregates that need to stay in solution for the duration of an individual's life.

Loss of transparency is an almost invariable common denominator of all lens diseases. Because of the high prevalence of heritable cataracts in dogs, this is considered the most common of all intraocular lesions and a leading cause of vision loss in this species. Primary lens displacement is the second most common vision threatening lens condition in dogs. In addition, congenital lenticular disorders, as well as lens conditions secondary to intraocular or systemic diseases, although less commonly seen, can also affect visual acuity. This chapter focuses on the clinical manifestations of congenital, developmental, and acquired diseases of the lens, and their appropriate medical management.

Special Techniques for Lens Examination

In the framework of a complete ophthalmic examination, complete lens evaluation can be achieved by a five-step slit-lamp biomicroscopy method. For this purpose, the light beam of the slit-lamp is initially angled at 30–45 degrees from the axis of the microscope, away from the muzzle, although during the course of the examination, the beam would swing from one side to the other. Firstly, diffuse illumination, with medium- to high-intensity light, is useful to obtain an initial gross overview of the lens and anterior chamber, revealing important clinical signs such as iridodonesis, phacodonesis, anterior lens luxation, and evident cataracts (Fig. 22.1A). Immediately after this, three direct illumination methods are performed: parallelpiped, optical section, and specular reflection. For all of them, the light source is placed at an angle of about 40–50 degrees from the microscope. Lens transparency can be grossly evaluated by means of a parallelpiped, which is obtained by using a broad slit beam (>0.5 mm), under minimal magnification and using medium light intensity. This step is particularly suitable for assessment of cataracts, although further, more precise direct illumination methods are needed for classification and location. The optical section is a very thin parallelpiped obtained with a thin slit beam (0.1–0.2 mm), under minimal or maximal magnification (10–17×) and using a high light intensity. This illumination technique can easily estimate anatomic distances, revealing changes in the anterior chamber depth. As an example, a shallow anterior chamber may be seen in cases of lens intumescence and anterior lens luxation, whereas a deep anterior chamber may be

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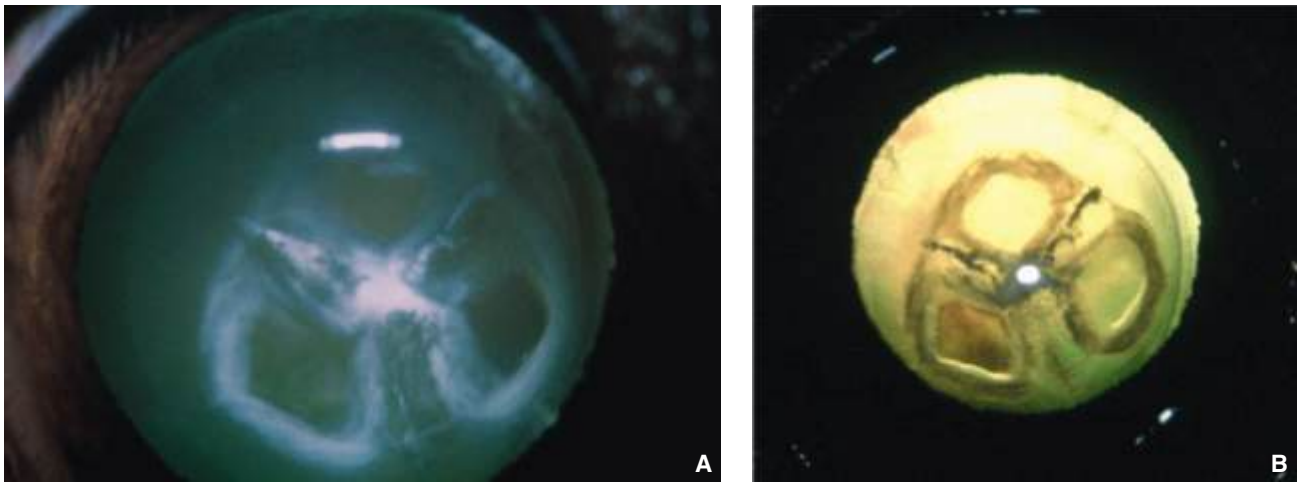


Figure 22.1 Early immature cataract seen by two illumination methods. **A.** Diffuse illumination. **B.** Retroillumination from the ocular fundus. Note the dark appearance of the lens opacities. (*Source*: Courtesy of Willows Referral Service.)

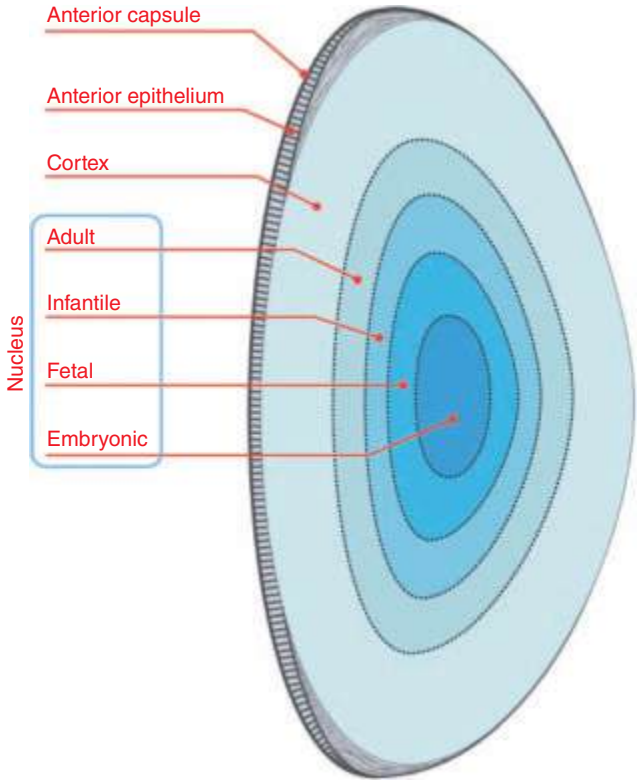


Figure 22.2 Schematic optical section of the adult canine lens, showing lens stratification (front to back): anterior capsule, anterior cortex, nucleus (adult, infantile, fetal, and embryonic), posterior cortex, and posterior capsule. Notice the significant size of the nucleus when compared with the rest of the lens layers. (*Source*: Scheme by A. Peña.)

associated with largely resorbed hypermature cataracts or posterior lens luxation/subluxation. The optical section evaluation is usually continued after inducing mydriasis, hence facilitating a complete assessment of the lens by showing a stratification into layers (Fig. 22.2). For this purpose, the ophthalmologist should keep the optical section always in focus (moving towards or against target) and should scan the lens completely (from one side to the other and back). This illumination technique allows for early detection of lens subluxation – when a mild aphakic crescent is seen peripherally – and for accurate location of the cataract. In addition, at this point, searching for vitreous strands in the anterior chamber should be done, indicating, if present, variable degrees of zonular rupture, and subsequently lens instability. Lens surface can be further evaluated by specular reflection, which is accomplished by separating the microscope and slit beam by equal angles from the central cornea (30 degrees, each). Angle of light should be moved until a very bright reflex is obtained from the lens surface (specular reflection). If the lens surface is smooth, the reflection will be also smooth and regular. Conversely, if irregular, the reflection will be broken or rough. Retroillumination from the ocular fundus is the last step of a complete lens examination and is performed by using the light beam (thin or broad), low to high magnification and a 0–10 degrees inclination of the beam light from the microscope. This step is better accomplished when the pupil is dilated. The image is obtained by reflecting the light of the slit beam into the ocular fundus, and thus placing the lens opacity against a bright background allowing it to appear dark or black. Water clefts and vacuoles are easily observed by this illumination technique (see Fig. 22.1B).

In addition, when corneal or anterior segment opacification precludes lens evaluation, the use of infrared imaging techniques and/or B-mode ocular ultrasound may be helpful in visualizing and classifying lens abnormalities (Fig. 22.3).

Normal Findings According to Age

Before examining a lens, the ophthalmologist should review the parameters of what is considered within the "normal

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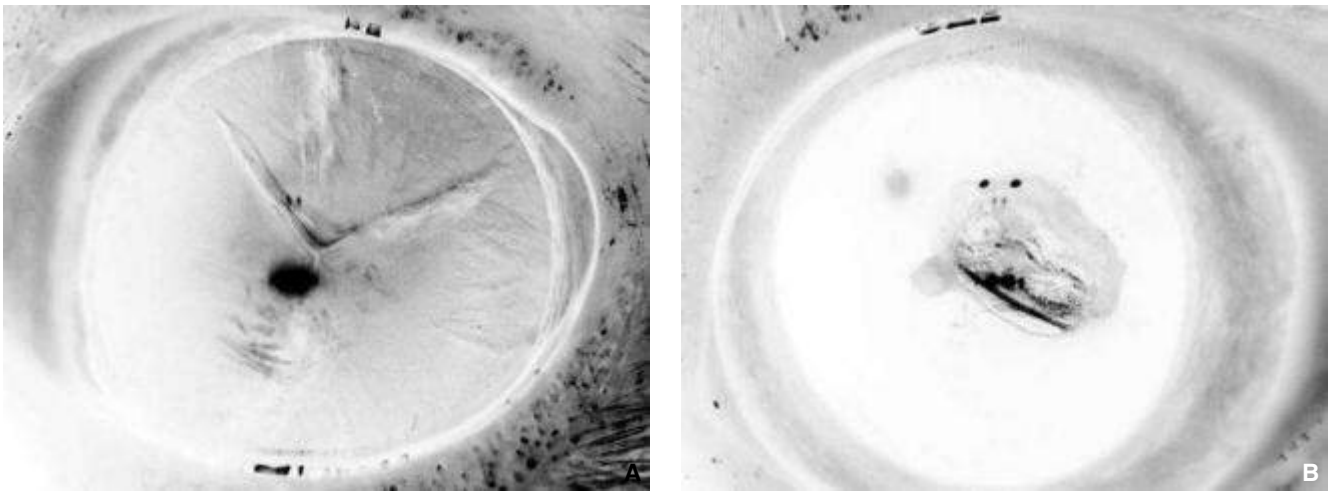


Figure 22.3 Digital infrared image of the lens through diffuse corneal edema. **A.** Mature, intumescent cataract showing marked anterior Y-sutures, peripheral vacuole formation, and pigment deposition in a 9-year-old Yorkshire Terrier. **B.** Traumatic anterior capsule rupture in a 1-year-old mixed-breed dog. Note the irregular anterior capsule and the perilesional cataract. (*Source*: Courtesy of J. Esteban.)

limits" in the species, so as to be able to distinguish those conditions from true disease processes.

In young animals, the suture lines of the lens, usually shaped as a "Y" anteriorly and as an "inverted Y" at the posterior pole, can often be observed as faint lines when examined under the biomicroscope. These lines, or arrowhead opacities, often disappear with age and should not be mistaken for congenital cataracts. In addition, in the very young dog, a visible nuclear ring can be occasionally seen and should not be mistaken for congenital cataracts. Occasionally, just after eyelid opening, condensed vitreous fibrils around the regressed *tunica vasculosa lentis* system can be temporarily seen on the posterior lens capsule, and should not be mistaken for persistence of *tunica vasculosa lentis*. Normally, no other opacities, apart from what is mentioned here, can be found when light is directed straight through the lens in young dogs.

Because lens transparency changes with age, understanding the aging lenticular changes in the dog is mandatory before issuing a diagnosis. In particular, nuclear sclerosis is a normal aging feature of the lens caused by the compression of fibers in the nuclear region. Although it has little or no effect on vision, the blue-gray appearance of the lens may prompt a misdiagnosis of cataract by unexperienced veterinarians. Besides biomicroscopy, ophthalmoscopy may also be helpful in the differentiation between the characteristic opacity of cataracts and the translucency of nuclear sclerosis. Whereas cataract results in a black shadow against the reflection from the fundus, nuclear sclerosis presents no barrier to the fundus reflection. Nevertheless, in some cases, the line between nuclear sclerosis and senile cataract is blurred and not easily discerned by biomicroscopy or ophthalmoscopy. If needed, a quantitative densitometric image analysis of slit-lamp images (obtained with a Zeiss Scheimpflug camera), may allow the exact measurement of the light scatter in the single lens layers, thus enabling the early recognition of disturbances in transparency (Vivino et al., 1993). For further specific details on nuclear sclerosis, the reader is referred to the appropriate section at the end of this chapter.

Congenital Lens Abnormalities

The lens is derived from the surface ectoderm and during its embryologic development is surrounded by a vascular envelope (Cook, 1995). Congenital anomalies of the lens can be mechanistically classified as: those that involve abnormalities in the formation and differentiation of the lens placode and subsequently the lens epithelial cells; those that are associated with anterior segment dysgenesis; those that are associated with abnormalities of the fetal vasculature; and those associated with the zonule formation (tertiary vitreous). The first group includes aphakia, microphakia, congenital cataract, and posterior lenticonus/lentiglobus. The second includes a spectrum of abnormalities related to incomplete or late separation of the lens vesicle from the surface ectoderm (Peters' anomaly), pigment flecks on the anterior capsule, and capsular/subcapsular cataracts associated with dysplastic pupillary membranes. The third includes posterior capsular opacities, posterior capsular defects, and retrolental choristomatous plaques (persistent embryonic vasculature). Finally, the latter group of congenital anomalies encompasses lens luxations, lens coloboma, spherophakia, and microphakia.

In addition, congenital abnormalities affecting the lens may be caused by genetic and/or exogenous factors. Because proper development of the lens is crucial in the orchestration of intraocular embryogenesis, eyes with lens anomalies often exhibit multiple ocular defects (Cook, 1995).

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Aphakia

Congenital aphakia or congenital absence of the lens is an extremely rare anomaly in the dog that occurs through failure of contact of the optic vesicle with the surface ectoderm during a critical inductive period of embryogenesis with subsequent failure of lens placode formation (Cook, 1995). In humans, congenital aphakia is classified as primary and secondary. In primary aphakia there is no lens induction of the surface ectoderm, whereas in secondary aphakia, lens development takes place, but later is resorbed or expelled *in utero* (Johnson & Cheng, 1997). Embryonic lens tissues have a major influence on the development of the optic cup, surface ectoderm, anterior segment cleavage, and vitreous. As a result, aphakia has been reported in association with multiple ocular defects such as microphthalmia, deformities of the anterior segment (e.g., Peters' anomaly, acorea), retinal dysplasia, retinal detachment, and staphylomas (Arnbjerg & Jensen, 1982; Bergsjø et al., 1984; Johnson & Cheng, 1997; Lewis et al., 1986; Martin & Leipold, 1974; Mikami et al., 2004; Peiffer & Fischer, 1983).

Microphakia and Spherophakia

Microphakia and spherophakia are rare congenital conditions; the lens may be either too small (microphakia) or spherical (spherophakia) when examined in cross section (Fig. 22.4). The abnormal shape may be caused by an underdeveloped zonule of Zinn (tertiary vitreous), which does not exert sufficient force on the lens to make it form the usual oval shape seen in cross section. In addition, microphakia may be also induced by abnormalities in the formation and differentiation of the lens placode. In both presentations, elongated ciliary processes may be present, and deficient lens metabolism may result in either congenital or juvenile cataract. Both conditions can be seen alone, combined (microspherophakia), or as part of other ocular syndromes, such as *persistent hyperplastic tunica vasculosa lentis* (PHTVL)/*persistent hyperplastic primary vitreous* (PHPV) or merle ocular dysgenesis (MOD) (Bayón et al., 2001; Gwin et al., 1981). Affected animals may additionally develop glaucoma.

Canine breeds reported to be affected with microphakia/spherophakia include the Beagle, Doberman Pinscher, English Springer Spaniel, Saint Bernard, Great Dane. and Miniature Schnauzer (American College of Veterinary Ophthalmologists [ACVO] Genetics Committee, 2015; European College of Veterinary Ophthalmologists [ECVO] Genetics Committee, 2017). The diagnosis of both disorders is made on the basis of clinical findings, supported if necessary by B-mode ultrasonography. Treatment includes benign neglect, medical management using a long-term miotic agent in order to minimize the risk of complete lenticular luxation, and/or surgical lens removal/replacement. Demecarium bromide and prostaglandin analogues may be used as miotic agents, although unwanted secondary effects may appear long-term with the latter.

Lens Coloboma

A coloboma of the lens is also a rare congenital condition characterized by equatorial notching (Fig. 22.5). Like lens spherophakia and microphakia, coloboma is related to problems of zonular development – local absence or marked deficiency of the zonular fibers (zonular aplasia or marked hypoplasia) – in a specific region, rather than to an incomplete embryonic fissure closure during development (Bavbek et al., 1993). Thus, when compared with other ocular colobomas (iris, optic nerve, scleral, etc.), a lens coloboma is not a true coloboma. As such, lens notching can occur secondary

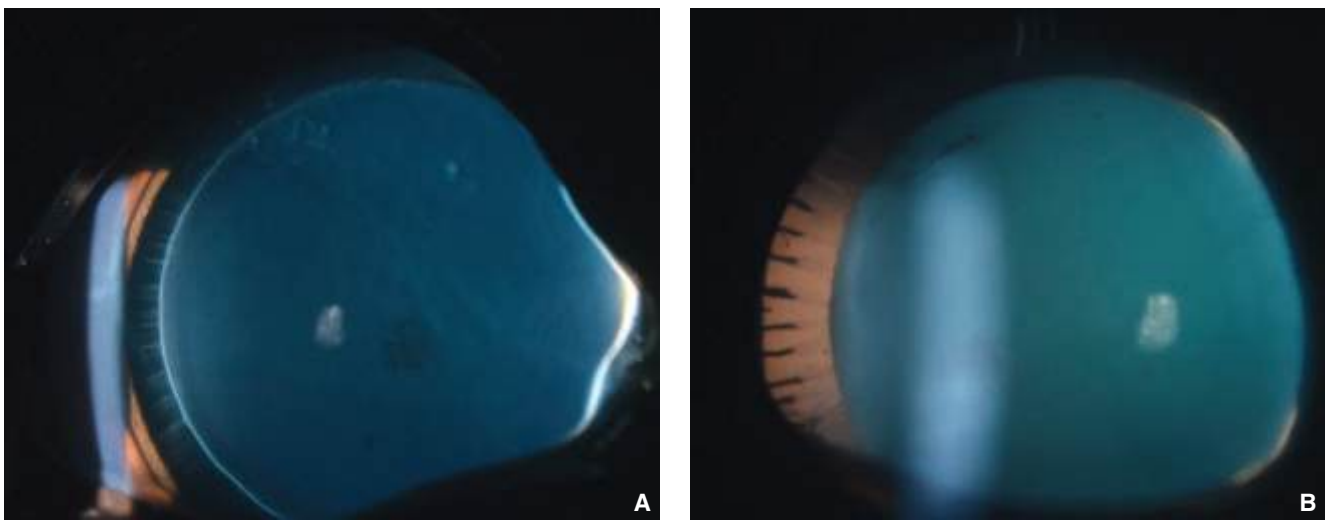


Figure 22.4 **A.** Microphakia and spherophakia in a crossbreed dog. Note the elongated zonules. **B.** Microphakia and spherophakia with elongated ciliary processes in a Miniature Schnauzer. (*Source*: Courtesy of A. Bayón.)

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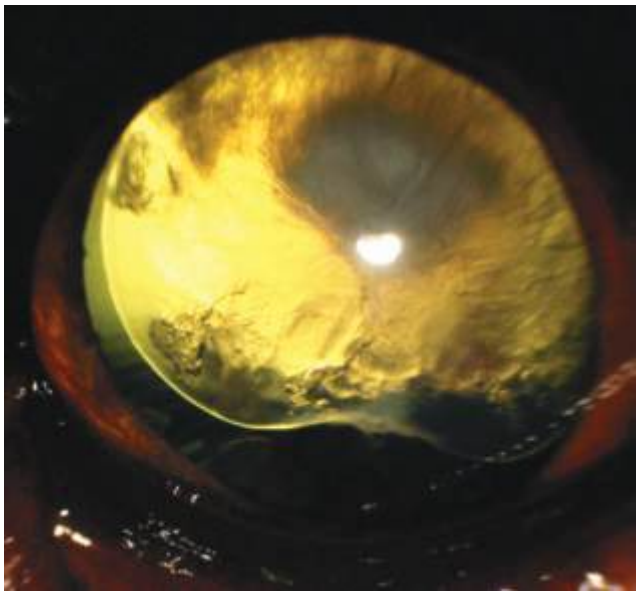


Figure 22.5 Focal typical lens coloboma (6 o'clock) and persistent hyaloid artery with posterior capsular and cortical cataract in a mixed breed dog. (*Source*: Courtesy of E. Gonzalez & A. Rodriguez.)

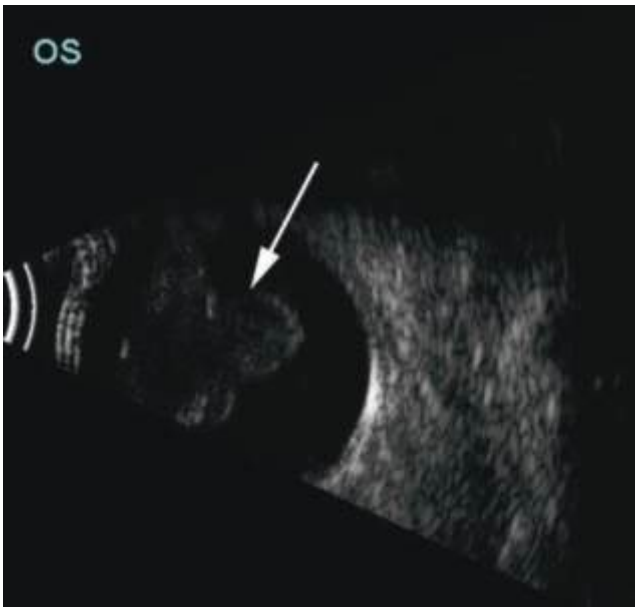


Figure 22.6 B-mode ultrasound of a posterior lenticonus (arrow) in a young, crossbreed dog. (*Source*: Courtesy of V. Espejo.)

to different etiologies causing weakened or deficient zonules. Despite not being clinically relevant, the classification of some equatorial defects induced by focal zonular hypoplasia can be challenging, as the line between colobomatous defects and spherophakia is not always discernible.

Colobomas can be either typical (6-o'clock position) or atypical (other location), the latter not always apparently associated with overt lens zonule defects. Based on size, colobomas can be further classified into focal or extensive. Furthermore, lens colobomas may be seen alone or associated with other congenital anomalies such as colobomas of the uvea, MOD or PHTVL/PHPV (Bertram et al., 1984; Gelatt & McGill, 1973; Martin, 1978; Priester, 1972). When alone and focal, they may go unnoticed until cataracts develop, but when extensive, they may be associated with lens displacement (Grahn et al., 2003). When treated with phacoemulsification, special attention to the size/type selection of the intraocular lens should be given, as depending on the size of the coloboma, it may preclude intracapsular lens implantation necessitating, in some cases, ciliary sulcus lens fixation.

Lenticonus/Lentiglobus

Lenticonus and lentiglobus are congenital anomalies in the shape of the lens with anterior or posterior protrusion of the lens in conical or spherical contours, respectively. The deformity occurs in late fetal development after normal formation of the lens nucleus, at the time of primary lens fiber elongation (25th day of gestation in dogs). Numerous theories on the pathogenesis have been proposed; the defect may relate to an abnormal embryonic remnant in the epithelial cell proliferation before the lens capsule forms or a hyperplasia of the lens accompanied by a thinning of the capsule over the defect. What is generally accepted is that lenticonus/lentiglobus are caused by a weakness of the lens capsule, which allows the cortex to protrude causing malformation at the anterior or, most commonly, the posterior pole. Rarely, cases may show rupture of the lens capsule with extrusion of lens cortical material into the vitreous, with varying degrees of secondary inflammation (Narfström & Dubielzig, 1984; Venter et al., 1996).

The diagnosis of lenticonus/lentiglobus is essentially a clinical diagnosis which is made by biomicroscopic examination. Biomicroscopically, *lenticonus* is characterized by a transparent, localized, sharply demarcated conical projection of the lens capsule and cortex, usually axial in localization and of variable size. In an early stage, retroillumination shows an "oil droplet" red reflex configuration. In a more advanced stage, the capsule in the affected area may show dysplastic or degenerative changes, which may influence associated subcapsular and cortical cataracts. If biomicroscopy of the posterior lens is not possible because of cataract formation, the condition may also be recognized ultrasonographically. A-scan ultrasonography may reveal an increased lens thickness and B-mode may show herniated lenticular material, suggestive of a lenticonus (Fig. 22.6).

Posterior lenticonus, first described in the Miniature Schnauzer and the Mastiff in 1973, may be unilateral or bilateral (Aguirre & Bistner, 1973; Gelatt et al., 1983a) and may occur in conjunction with other ocular anomalies. Lenticonus and secondary cataracts have been primarily

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reported in the Cavalier King Charles Spaniel (Narfström & Dubielzig, 1984), Akita Inu (Laratta et al., 1985), and Shih Tzu (Ori et al., 2000). In breeds such as Doberman Pinscher (Stades, 1980; Van der Linde-Sipman et al., 1983), Golden Retriever (Lavach & Severin, 1977), Bouvier des Flandres (van Rensburg et al., 1992), Bloodhound (Venter et al., 1996), Old English Sheepdog (Barrie et al., 1979), Labrador Retriever (ACVO Genetics Committee, 2015), Staffordshire Bull Terrier, and American Staffordshire Terrier (Curtis et al., 1984; Leon et al., 1986), *lenticonus* and/or *lentiglobus* have been also associated with retrolental fibrovascular plaques, microphthalmia, coloboma, retinal dysplasia, optic nerve hypoplasia, and intraocular hemorrhage. If visual acuity is affected, phacoemulsification with posterior continuous capsulorhexis and intraocular lens implantation is recommended. Intraoperatively, posterior lenticonus/lentiglobus may be suspected by the characteristic movement of the posterior capsule during phacoemulsification ("jellyfish sign") (Ganesh et al., 2017).

Lenticonus internum, rarely reported in dogs, occurs when the lens nucleus is abnormally shaped and extends into the posterior cortex (Lavach & Severin, 1977).

Embryonic Vascular Abnormalities

The vascular supply of the lens, present during prenatal development, derives from the intravitreal hyaloid vascular system. At about day 25 of gestation, the hyaloid artery (HA) branches to create a capillary network on the posterior surface of the lens capsule, the tunica vasculosa lentis (TVL). These capillaries grow toward the equator of the lens, where they anastomose with a second network of capillaries, called the pupillary membrane (PM), which covers the anterior surface of the lens. Once the ciliary body begins actively producing aqueous humor, the hyaloid vascular system is no longer needed and starts to regress. In the dog, the regression begins by day 45 of gestation, but the posterior part of the HA and the PM may remain until approximately 2–3 weeks after birth. The remaining parts of the PM-TVL-HA system that are still present by 8 weeks after birth will not undergo further regression and will persist throughout life, thus the term "persistent." Sometimes, a short remnant of the HA may be seen as a very small, white, spiral-shaped strand on the posterior pole of the lens (Mittendorf's dot).

Persistent PM (PPM) is a common congenital ocular anomaly seen sporadically in many breeds, presumably as a nonhereditary trait. Nevertheless, in breeds with a higher prevalence or more severe manifestations of PPMs (Basenji, Bloodhound, and English Cocker Spaniel, among others), a hereditary predisposition is likely although, unfortunately, its mode on inheritance has not been yet elucidated (Table 22.1) (ACVO Genetics Committee, 2015; Barnett & Knight, 1969; Bistner et al., 1971; ECVO Genetics Committee, 2017; Strande et al., 1988). Arising from the iris collarette, PPMs may show three different presentations that may affect the lens (dysplastic PPMs). First, they can be seen as pigmented strands attached to the anterior lens capsule, inducing varying degrees of focal or multifocal lenticular opacities (anterior capsular or subcapsular cataracts) (Fig. 22.7A, B). PPMs are differentiated from posterior synechiae by their appearance. Synechiae are common sequelae to uveitis and involve larger sections of iris, usually at the level of the pupillary margin, whereas PPMs are usually focal and arise from the iris collarette. PPMs may also appear as multiple, punctate pigment foci on the central anterior lens capsule, which are a common incidental finding in many breeds of dogs. They may be distinguished from pigment deposition from acquired posterior synechia secondary to inflammation, by generally being axial, punctate, and unassociated with other evidence of intraocular inflammation (Fig. 22.7C). In the authors' experience, these pigment foci are a common incidental finding in many breeds of dogs, do not evolve, and do not induce apparent visual disturbances. The last presentation of PPMs reported to affect the lens is the total PPM covering the entire pupil, which is extremely rare, although an unusual case of PPM with total anterior capsular pigmentation has been recently described (Yun et al., 2018).

Persistent tunica vasculosa lentis/persistent hyperplastic vitreous (PHTVL/PHPV) is the most severe congenital lesion associated with abnormal development of the intraocular vasculature leading, in most cases, to posterior or complete cataract (Fig. 22.8) (Boevé et al., 1992). The condition may occur unilaterally or bilaterally and appear alone or concurrently with microphthalmia (Bayón, et al., 2001; Kern, 1981; Stades, 1980) or other multiple inherited eye anomalies (Van Rensburg et al., 1992).

The first canine case was reported in 1969 in a Greyhound (Grimes & Mullaney, 1969). Since then, numerous cases have been described in several breeds (Arnbjerg, 1982; Barnett & Grimes, 1973; Bayón et al., 2001; Boroffka et al., 1998; Cullen & Grahn, 2004; Curtis et al., 1984; Gemensky-Metzler & Wilkie, 2004; Kern, 1981; Leon et al., 1986; Ori et al., 1998; Rebhun, 1976; Van Rensburg et al., 1992; Verbruggen et al., 1997) although detailed descriptions are restricted mainly to the Doberman breed. Incidence of PHTVL in the Doberman has been reported to be as high as 42.6% in the Netherlands (Stades et al., 1991), 14.5% in Norway (Bjerkås, 1990), 9% in Finland (Leppänen & Saloniemi, 1998), and 3.3% in Germany (Pfahler et al., 2015). In the former country, PHTVL/PHPV has been studied thoroughly, including its clinical, genetic and pathological aspects, as well as the surgical outcomes (Stades, 1980, 1983a, 1983b; van der Linde-Sipman et al., 1983). Based on morphologic severity, Stades classified the condition into six grades, of which only Grade 1 was unilateral and did not result in cataract formation. All the other forms (grades 2–6) were bilateral and eventually resulted in progressive cataract and, subsequently, severe impairment or loss of vision

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Table 22.1 Breeds predisposed to dystrophic persistent pupillary membranes causing secondary anterior polar cataract.

Airedale Terrier (b)	Grand, Briquet and Petit basset griffon vendéen (a1, b)
Akita (b)	Great Pyrenees (b)
Alaskan Malamute (b)	Havanese (b)
American Pit Bull Terrier (b)	Jack Russell Terrier (b)
Australian Shepherd (b)	Japanese Chin (Japanese Spaniel) (b)
Basenji (b)	Labradoodle (Australian) (b)
Basset Hound (b)	Lakeland Terrier (b)
Bearded Collie (b)	Leonberger (b)
Belgian Tervuren (b)	Lowchen (b)
Bloodhound (a1, b)	Mastiff (English) (b)
Border Collie (b)	Miniature American & Australian Shepherd (b)
Bouvier des Flandes (b)	Miniature Bull terrier (b)
Braque d'Auvergne (a1)	Norwegian Elkhound (b)
Bull Terrier (b)	Nova Scotia Duck Tolling Retriever (b)
Bullmastiff (b)	Old English Sheepdog (a1, b)
Chihuahua (b)	Pyrenean Shepherd (a1)
Chinese Crested (b)	Pembroke Welsh Corgi (b)
Chow Chow (a1, b)	Poodle (b)
Collie (Rough and Smooth) (b)	Portuguese Water Dog (b)
Dachshund (b)	Puli (b)
Doberman Pinscher (b)	Samoyed (b)
Dogue de Bordeaux (a1)	Scottish Terrier (b)
English Cocker Spaniel (b)	Shetland Sheepdog (b)
English Springer Spaniel (b)	Tibetan terrier (b)
French Bulldog (b)	Toy Australian Shepherd (b)
Fox Terrier (Wire & Smooth) (a1, b)	West Highland White Terrier (a1, b)
German Pinscher (b)	Whippet (b)
German Shorthaired Pointer (b)	Wirehaired Vizsla (b)
Golden Retriever (b)	Yorkshire Terrier (b)

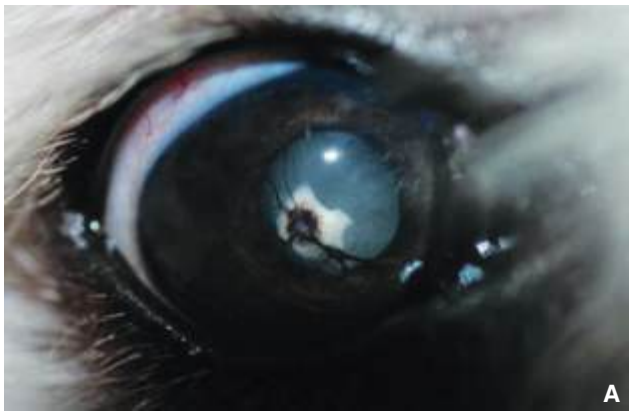
a1, Published studies referenced in the *ECVO Manual of Presumed Inherited Eye Diseases* (ECVO Genetics Committee, 2017). b, Published studies and nonpublished reports referenced in *Ocular Disorders Presumed to be Inherited in Purebred Dogs* (ACVO Genetics Committee, 2015).

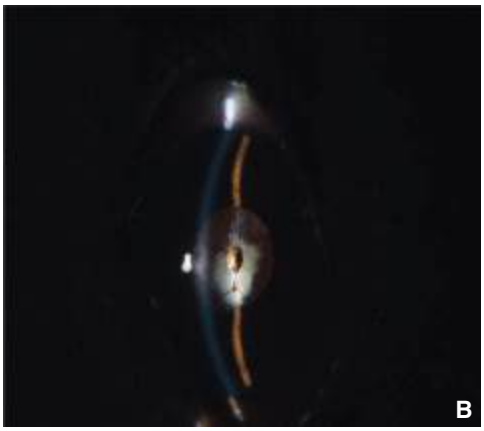
(Stades, 1980). Whereas the mildest presentation (*grade 1*) showed retrolental fibrovascular pigmented dots alone, *grade 2* presented in addition retrolental tissue proliferation attached to posterior lens capsule. *Grades 3* and *4* displayed posterior capsular plaque, combined with persistent parts of the vascular system (grade 3) or with posterior lenticonus (grade 4). *Grades 5* and *6* were defined as a combination of grades 3 and 4. However, lens coloboma, microphakia, and retrolental clots of pigment or free blood, were also observed in grade 6. Conversely, in the Staffordshire Bull Terrier, the condition has been rarely associated with progressive secondary cataracts (Curtis et al., 1984; Leon et al., 1986).

Although the disease has been suspected to be inherited in more than 35 breeds of dogs (ACVO Genetics Committee, 2015; ECVO Genetics Committee, 2017), its mode of inheritance has been elucidated only in five (Table 22.2); being considered as an incomplete autosomal dominant trait in Dobermans, English Toy Spaniels, and Staffordshire Bull Terriers (ACVO Genetics Committee, 2015; Curtis et al., 1984; ECVO Genetics Committee, 2017; Leon et al., 1986; Stades, 1983b), and suspected to be an autosomal recessive trait in German Pinschers (miniature and standard) and Miniature Schnauzers (Grahn et al., 2004; Leppänen et al., 2001). Breeding programs in the Doberman in the Netherlands resulted in a decreased incidence of severely affected dogs from 5% to 1% (Stades et al., 1991).

The histopathological findings in Dobermans with PHTVL/PHPV include retrolental dots and plaques composed of fibrous connective tissue on the posterior lens capsule that generally contained capillary structures and primitive melanocytes, as well as glial tissue on the vitreous side of the plaque (van der Linde-Sipman et al., 1983). The most important features in this breed are the broadening and irregularity or dissolution, and disappearance of the central posterior lens capsule, which is thought to be a degenerative process that may result in ingrowth of fibrous tissue into the lens (Boevé et al., 1993; van der Linde-Sipman et al., 1983). Iron pigments, calcium deposits, and neutrophils were

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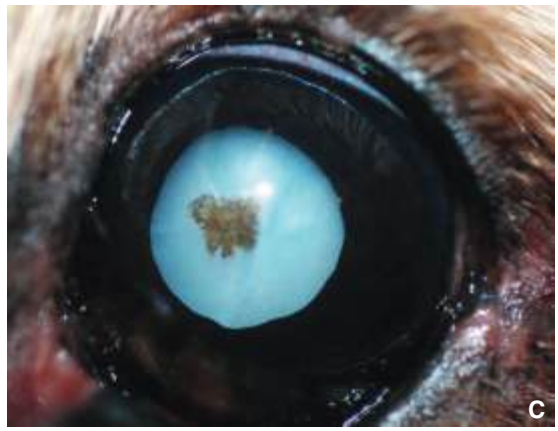


Figure 22.7 Two different presentations of PPMs in the dog. **A.** Pigmented dysplastic strands arising from the iris collarette get to the lens capsule, inducing a capsular cataract in a 6-month-old West Highland White Terrier with concomitant microphthalmia. **B.** Optical section of a pigmented iridal strand inducing anterior capsular cataract. (*Source*: Courtesy of A. Bayón.) **C.** Multiple punctate pigment deposition on the axial anterior lens capsule in a 9-year-old Yorkshire Terrier with mature cataract. Capsular pigment deposition is a common incidental finding in dogs.

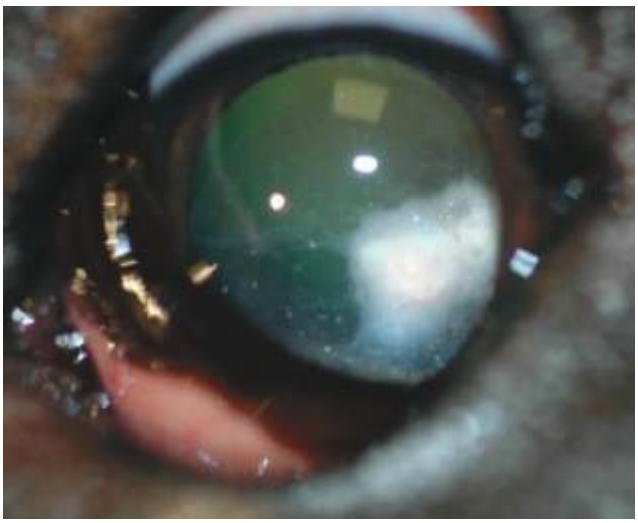


Figure 22.8 Spherophakia and persistent hyperplastic tunica vasculosa lentis inducing early immature posterior capsular cataract in a 9-month-old Doberman Pinscher. Note the reddish coloration of the lens opacification.

observed in some cases, possibly caused by small hemorrhages and secondary inflammatory reaction in the fibrous tissue extending into the lens through missing parts of the posterior lens capsule, leading to the hypothesis that the plaque may be also the result of lens-induced inflammatory reaction from the surrounding TVL (Boevé et al., 1993). Bergmeister's papillae and occasional localized rosettes of retinal dysplasia were present sporadically (van der Linde-Sipman et al., 1983). Histopathologic findings in Staffordshire Bull Terriers are similar to those seen in Dobermans; however, there were fewer, less progressive cataracts, no abnormalities of the posterior lens capsule, and fewer retinal folds (Leon et al., 1986). Histologic features of a retrolental plaque removed by capsulectomy during phacoemulsification on a Bloodhound puppy revealed coiled duplicated posterior capsule, dense fibrous connective tissue, blood vessels, free red blood cells, hemosiderin-laden macrophages, a pocket of neural tissue compatible with astrocytes, and perivascular mast cells (Gemensky-Metzler & Wilkie, 2004).

Pathomorphologic studies of prenatal ocular development of fetuses from Doberman dogs with severe PHTVL/PHPV

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Table 22.2 Canine breeds affected by persistent hyperplastic primary vitreous/persistent hyperplastic tunica vasculosa lentis (PHPV/PHTVL) causing lens opacification. Mode of inheritance and references are also included.

Canine breeds affected by PHPV/PHTVL	Inheritance	References
American Staffordshire Terrier	Unknown	ACVO Genetics Committee, 2015; Curtis et al., 1984; Leon et al., 1986
Australian Cattle Dog	Unknown	Chaudieu & Chahory, 2013
Basset Hound	Unknown	Boroffka et al., 1998; Verbruggen et al., 1997
Bouvier des Flandes	Not defined	ACVO Genetics Committee, 2015; Van Rensburg et al., 1992
Boxer	Unknown	Chaudieu & Chahory, 2013
Braque d'Auvergne	Familial predisposition	Chaudieu & Chahory, 2013
Bull Terrier	Unknown	French National Panel
Cavalier King Charles Spaniel	Unknown	French National Panel
Dobermann	Presumed dominant, incomplete penetrance	ACVO Genetics Committee, 2015; Boevé et al., 1988a, 1990, 1992; Stades, 1980, 1983a, 1983b; Stades et al., 1991; van der Linde-Sipman et al., 1983
Drentse Partridge Dog	Unknown	German National Panel
English Toy Spaniel (King Charles)	Presumed dominant/ incomplete penetrance	ACVO Genetics Committee, 2015; Chaudieu & Chahory, 2013
German Pinscher (Standard and miniature)	Presumed autosomal recessive	Chaudieu & Chahory, 2013; Leppänen et al., 2001
German Shorthaired Pointer	Unknown	ACVO Genetics Committee, 2015; Chaudieu & Chahory, 2013
Grand Anglo-Français (GAF), Anglo-Français de Petite Vénerie (AFPV)	Unknown	Chaudieu & Chahory, 2013
Great Dane	Unknown	ACVO Genetics Committee, 2015
Greyhound	Unknown	Chaudieu & Chahory, 2013; Grimes & Mullaney, 1969
French Pointing Griffon Korthals	Unknown	Chaudieu & Chahory, 2013
Grand Griffon Vendéen	Unknown	Chaudieu & Chahory, 2013
Japanese Chin	Unknown	ACVO Genetics Committee, 2015
Labrador Retriever	Unknown	ACVO Genetics Committee, 2015
Labradoodle (Australian)	Unknown	ACVO Genetics Committee, 2015
Leonberger	Unknown	Chaudieu & Chahory, 2013
Maremma Sheepdog	Unknown	Guandalini et al., 2016
Miniature Schnauzer	Autosomal recessive	Grahn et al., 2004
Neapolitan Mastiff	Unknown	Guandalini et al., 2016
Newfoundland	Unknown	Chaudieu & Chahory, 2013
Old English Sheepdog	Unknown	ACVO Genetics Committee, 2015
Pug	Unknown	Chaudieu & Chahory, 2013
Pyrenean Shepherd	Unknown	Chaudieu & Chahory, 2013
Schnauzer (standard)	Unknown	Chaudieu & Chahory, 2013
Shih Tzu	Unknown	Chaudieu & Chahory, 2013
Siberian Husky	Unknown	Ori et al., 1998
Staffordshire Bull Terrier	Autosomal dominant with incomplete penetrance	Curtis et al., 1984
Sussex Spaniel	Unknown	ECVO Genetic Committee, 2017
Tibetan Terrier	Unknown	Chaudieu & Chahory, 2013
Vizsla	Unknown	Chaudieu & Chahory, 2013
Welsh Terrier	Unknown	Chaudieu & Chahory, 2013
West Highland White Terrier	Unknown	Rubin, 1989

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have been also reported (Boevé et al., 1988a, 1988b, 1989, 1990). Developmental abnormalities were noted at day 30, when the hyaloid TVL system of affected eyes had developed further than in the reference fetus. From that stage onward, a retrolental fibrovascular membrane developed, and in some eyes, at day 37, posterior polar subcapsular cataracts and preretinal glial proliferations were observed (Boevé et al., 1988a). Capsular anomalies and distortions of the lens shape were not observed and are believed to be secondary entities. The antiangiogenic properties of normal vitreous and the fact that overdevelopment and subsequent incomplete regression of the hyaloid system plays a major role in the pathogenesis of the condition, gives rise to the hypothesis that a changed amount or effectiveness of humoral factors may play an important role in the etiology of this disease (Boevé et al., 1988a).

The diagnosis of PHTVL/PHPV is based on history, clinical examination with complete mydriasis, exclusion of other causes of leukocoria, and ocular ultrasonography (US). Color Doppler imaging and contrast-enhanced US can be useful to assess the blood flow in the vascular remnants and evaluate the likelihood of surgical complications (Bayón et al., 2001; Boroffka et al., 1998; Labruyere et al., 2011; Verbruggen et al., 1997).

Although surgical success rates for restoration of vision were low in the pre-phacoemulsification era (Stades, 1983a), surgical results have markedly improved in the recent years. Combination of phacoemulsification, posterior capsulectomy and placement of an intraocular lens has been successfully used for treating a non-patent hyaloid vessel in a Bloodhound puppy (Gemensky-Metzler & Wilkie, 2004). Although reports on the success of the surgical treatment for patent PHTVL/PHPV in dogs are scarce, in the authors' experience the above-mentioned steps, in combination with bipolar diathermy, enable the safe resolution of the condition in hands of an experienced intraocular surgeon.

Congenital Lens Luxation

The term lens luxation describes the displacement or dislocation of the lens from its normal position and implies lack or rupture of zonules. Occasionally, lens luxation may be seen as a congenital condition, which may occur alone or, more often, associated with other, usually multiple, congenital defects, such as lens coloboma, microphakia or spherophakia (Martin, 1978). There are no reports of inherited congenital luxations equivalent to congenital *ectopia lentis* in humans.

Congenital Cataract

Congenital cataract (CC) refers to a lens opacity present at birth or, in altricial animal species, when the eyes open for the first time. When presented as the only clinical sign, cataracts should be diagnosed prior to 8 weeks of age in order to be considered as congenital (ECVO Genetics Committee, 2017). Conversely, if there is distinct proof that the cataract is congenital in origin (e.g. associated PPM, PHTVL/PHPV), the age of the initial diagnosis is not mandatory for its classification.

CCs, whether unilateral or bilateral, have a broad spectrum of causative factors contributing to their formation, such as DNA mutations (random or hereditary), infectious diseases of the dam during pregnancy, teratogenic drugs, irradiation exposure, metabolic disease, and malnutrition during gestation (Carmichael et al., 1965; Koch & Rubin, 1967). Based on its triggering condition, CC may be classified into primary or secondary, depending on whether there is a direct or indirect effect to the lens, respectively.

Primary Congenital Cataract

Primary CCs can be classified into inherited or non-inherited, based on the mutation nature (inherited or random, respectively). Congenital cataracts may be an incidental finding in any dog breed. The causes of CCs have been the source of much speculation and research but, unfortunately, the majority have no identifiable cause, being usually the result of lens random dysgenesis (primary non-inherited CC). Making a distinction between unilateral and bilateral cataracts may be useful when considering etiology. Congenital cataracts suspected to be inherited may be diagnosed as the only clinical sign (primary inherited CC) or in association with other ocular anomalies (secondary inherited CC). However, when no distinct cause can be found (along with the fact that considerable inbreeding is common in many canine breeds), hereditary factors should always be suspected when a bilateral cataract is present in a puppy younger than 8 weeks. For these reasons, examination of the littermates and both parents is mandatory. In these cases, breeding of the affected animal, or its direct relatives, should be avoided.

Clinical and morphologic features of CCs vary among breeds. They may appear as small nonprogressive or slowly progressive opacities in the suture lines or in the fetal nucleus or as larger opacities in the posterior lens pole (ACVO Genetics Committee, 2015; ECVO Genetics Committee, 2017). This latter form may be nonprogressive or progressive, leading to complete blindness in some cases. To simplify understanding of its particularities, CC are grouped according to the dog's weight/size.

Clinical and Morphologic Features of Primary Congenital Cataracts in Small Breeds (<10 kg)

In small dogs, CCs were first reported in the Miniature Schnauzer (Rubin et al., 1969). In this breed, CCs are frequently bilateral and involve the nucleus and, to a lesser extent, the posterior cortex. Its progression is variable, but in some dogs may progress to complete cataracts as early as 6 weeks of age. Microphthalmia, microphakia and lenticonus

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are commonly associated findings (Gelatt et al., 1983a, 1983b; Rubin et al., 1969; Samuelson, 1987; Shastry & Reddy, 1994; Zhang et al., 1991). Non-progressive cataracts affecting the tips of the posterior "Y" suture lines have been described in West Highland White Terriers (Narfström, 1981). An autosomal recessive mode of inheritance has been postulated for these two breeds (Gelatt et al., 1983b; Narfström, 1981; Rubin et al., 1969).

In Cavalier King Charles Spaniels, CCs affecting the cortex and nucleus have been reported; however, although suspected to be inherited, the mode of inheritance has not been elucidated. In affected animals, a rapid progression to complete cataract was seen (Narfström & Dubielzig, 1984).

Clinical and Morphologic Features of Primary Congenital Cataracts in Medium Breeds (10–20 kg)

Congenital cataracts in American Cocker Spaniels have a central nuclear discoid shape, are bilateral, nonprogressive, and may be detected as early as 4 weeks of age. The nuclear distribution favors the lower proportion of cataractous to normal lens as the pups mature (Gelatt & MacKay, 2005; Yakely, 1978). Color variants of this breed manifest different and quite varied forms of primary CC with respect to location within the lens, even in closely related dogs, suggesting that the phenotype does not segregate according to familial lines (Engelhardt et al., 2007a, 2008; Olesen et al., 1974). Congenital cataracts in the American Cocker Spaniel seem to be genetically distinct from noncongenital inherited cataract (Engelhardt et al., 2007a). Similarly, English Cocker Spaniels also have congenital and noncongenital cataracts, but, in this breed, CCs are mainly located in the anterior capsule and commonly associated with microphthalmia and dysplastic PMs (secondary CC) (Engelhardt et al., 2007a; Gelatt & MacKay, 2005; Olesen et al., 1974).

Primary congenital capsular opacities have also been described in Beagle dogs, although they seem to represent a transient growth phase variant, as they gradually disappear by 6–8 months of age (Bellhorn, 1973). Conversely, congenital posterior cortical cataracts, concurrent with multiple dysplastic ocular abnormalities (e.g microphthalmia, lens luxation, dysplastic PM, choroidal hypoplasia, scleral thinning and atypical coloboma of the posterior segment), have been described in Soft Coated Wheaten Terriers (van der Woerdt et al., 1995), English Cocker Spaniels (Strande et al., 1988), and Red Cocker Spaniels (Olesen et al., 1974). Although suspected to be inherited, the mode of inheritance has not been yet established for any of the previously listed breeds.

Clinical and Morphologic Features of Primary Congenital Cataracts in Large Breeds (>20 kg)

In large dog breeds, CCs may show two distinct phenotypic presentations. The first presentation consists of small, white, dense opacities located in the suture lines, the embryonic or fetal nucleus, or at attachment points of associated anomalies (e.g *dysplastic PMs*, *PHTVL*). These cataracts are mostly nonprogressive or very slowly progressive and do not interfere with vision. The second phenotypic presentation consists of larger progressive opacifications located in the posterior pole.

Congenital posterior polar cataracts have been described in German Shepherds (Barnett, 1986) and Golden and Labrador Retrievers (Barnett, 1972, 1976, 1978, 1985b; Curtis, 1982; Curtis & Barnett, 1989; Gelatt, 1972; Rubin, 1974). These are generally bilateral and nonprogressive or slowly progressive, although occasional unilateral cataracts and extensive progression to complete cataract may be observed (Curtis & Barnett, 1989). Although suspected to be dominant with incomplete penetrance in Labrador Retrievers, the mode of inheritance for CC has been only definitively established in German Shepherds, being inherited as an autosomal dominant trait (von Hippel, 1930). Conversely, in the German Shepherd breed in England, an autosomal recessive trait has been reported and a severe progression of the posterior polar cataract to complete cataract and vision impairment has been described (Barnett, 1986). Concomitant microphthalmia has been described only in the Golden Retriever (Gelatt, 1972). In addition, cortical CCs have been described in Labrador Retrievers with appendicular skeletal growth retardation, persistent hyaloid remnants, and rhegmatogenous retinal detachment (Blair et al., 1985a, 1985b; Carrig et al., 1988), as well as in short-limbed dwarfed Samoyeds in conjunction with vitreal liquefaction, hyaloid remnants, and retinal detachment (Meyers et al., 1983).

Australian Shepherds affected by MOD may also show CC as one of the signs of their clinical picture (e.g. microphthalmia, microcornea, colobomas of the iris, retina, choroid and/or sclera, retinal dysplasia with or without detachment). This ocular syndrome is inherited as an autosomal recessive trait (Bauer et al., 2015; Bertram et al., 1984; Cook et al., 1991; Gelatt & Veith, 1970; Gelatt & McGill, 1973; Gelatt et al., 1981).

Nonprogressive congenital nuclear cataracts, in association with concurrent ocular signs (e.g. wandering nystagmus, entropion, microphthalmia, PPM, and multiple retinal folds), have been described in Chow Chows (Collins et al., 1992). Unfortunately, its mode of inheritance has not been yet elucidated. In addition, CCs have been associated with retinal dysplasia in breeds such as the Bedlington Terrier (Rubin, 1963, 1968), Sealyham Terrier (Ashton et al., 1968), Akita Inu (Laratta et al., 1985), Beagle (Heywood & Wells, 1970), Bloodhound (Venter et al., 1996), Samoyed (Meyers et al., 1983), Old English Sheepdog (Barrie et al., 1979), and Labrador Retriever (Carrig et al., 1988).

Finally, an autosomal dominant cataract has been reported in Norwegian Buhunds. The cataract appears as small dots in the fetal nucleus, and progresses over 4–5 years to assume a pulverulent ("candy floss") appearance (Bjerkås & Haaland, 1995).

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Secondary Congenital Cataract

Secondary CCs can be classified into inherited or non-inherited. The former group encompasses all the ocular congenital diseases that induce secondary cataracts (e.g. PPM, PHTVL/PHPV). Secondary non-inherited cataracts have been previously associated with infectious diseases of the dam during pregnancy, teratogenic drugs, irradiation exposure, metabolic disease, and malnutrition during gestation (Carmichael et al., 1965; Koch & Rubin, 1967).

Acquired Lens Abnormalities

Acquired lens abnormalities are common in the dog. These include cataracts, lens sclerosis, and lens displacement as the most commonly reported conditions.

Cataracts

Acquired cataracts are lens opacifications diagnosed after the arbitrary cutoff of 8 weeks of age in dogs. Nevertheless, an exception can be made for all those cataracts diagnosed after the cutoff which show distinct proof of being congenital in origin (e.g. associated PPM, PHTVL/PHPV).

Classification of Canine Cataracts

Cataracts are classified according to different criteria: age at onset, anatomical location, degree of maturation, and etiology. Based on the age of onset, cataracts can be graded as congenital, developmental, and senile. Based on location, cataracts are classified into capsular, subcapsular, cortical (these three areas are further divided into anterior and posterior), nuclear (embryonic, fetal, infantile or adult), and suture lines (see Fig. 22.2). Cataracts can be also categorized as axial, paraxial, or inferior/superior equatorial. Based on the degree of opacity and progression, cataracts may be further classified as incipient, immature, mature, hypermature, intumescent, and Morgagnian. Tapetal reflection is used as a classifying tool for most cataracts. An incipient cataract is the earliest stage of opacification and does not/minimally affects the tapetal reflection (<10%–15%) (Fig. 22.9). In this type of cataract, small lens opacities are often only seen under magnification with a dilated pupil, and vision is not noticeably affected. A more advanced cataract is described as immature, in which the tapetal reflection is reduced, but still present. Immature cataracts can be further categorized into early immature (affects 15%–50% of the tapetal reflection) or late immature (affects 50%–99% tapetal reflection) (Fig. 22.10). When vision no longer exists, no tapetal reflection is visible, and inspection of the fundus is no longer possible, the cataract is then referred to as mature (Fig. 22.11). Later, the cortex may liquefy (hypermature) and adopt a crystalline appearance with wrinkling of the lens capsule (Fig. 22.12). Limited vision and tapetal reflection may return. In the end stage, total liquefaction of the cortex allowing the nucleus to sink inferiorly may occur in some middle-aged/old dogs (Morgagnian cataract) (Fig. 22.13). In some young animals, the liquefied contents escape through the capsule, resulting in cataract resorption, which restores partial vision (Fig. 22.14) (Gelatt, 1975). Spontaneous cataract resorption is rarely seen in geriatric dogs (Gonzalez-Alonso-Alegre & Rodriguez-Alvaro, 2006). In cases in which the only abnormality is a cataract, the pupillary light reflexes should remain normal regardless of maturity. The last classification scheme distinguishes between primary and secondary cataracts, considering as primary cataracts those that develop independently of other ocular or systemic diseases.

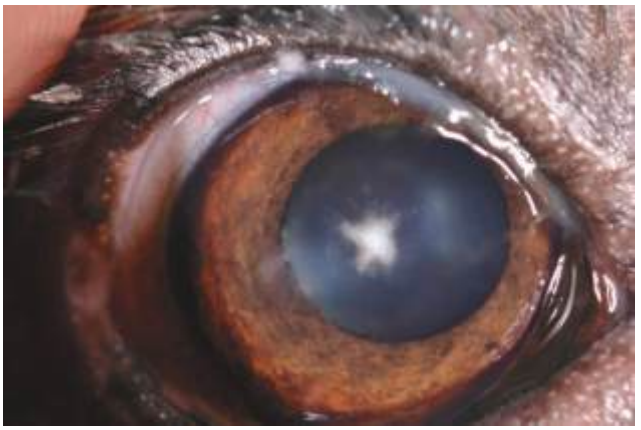


Figure 22.9 Incipient posterior cortical cataract in a 6-month-old German Shepherd with concomitant queratoconjunctivitis sicca.

Pathophysiologic Changes Associated with Cataract Formation

The lens is a unique structure composed entirely of lens epithelial cells (LEC). All stages of growth and decay are represented in an adult lens, because the older cells are never discarded, but rather are compressed into the center by younger cells. Thus, the lens increases in density throughout life and this, together with the loss of cell organelles, causes profound changes in cell protein and energy metabolism, leading to loss of transparency. Lens clarity is maintained by a number of complex factors including a highly organized arrangement of fibers with small interfibrillar spaces, low cytoplasm density, and small fluctuations of the cytoplasm refractive index. The high refractive index is accomplished by maintaining a structure with a low water content but a high protein concentration, both being characteristics imperative for lens transparency.

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Figure 22.10 Immature cataracts. **A.** Early immature cataract in diffuse illumination. Note the peripheral vacuole formation. **B.** Late immature cataract and lateral lens spherophakia seen with retroillumination.



Figure 22.11 Typical appearance of a mature or complete cataract seen in diffuse illumination. Note separation of the fibers and formation of a cleft along the anterior Y-suture.



Figure 22.12 Hypermature cataract seen in diffuse illumination. Note glistening, refractile appearance of lens material, as well as the beginning of the anterior capsule wrinkling.

The relative dehydrated state of the lens is dynamic and requires a continuous expenditure of energy to expel water that continually enters the lens, especially from the posterior aspect. The active transport of cations controls the lens fluid balance through a Na-K-ATPase pump that continuously removes water and sodium from the lens. On the other hand, the desirable protein concentration for maintaining lens transparency is achieved by lens proteins of high molecular weight (*crystallins* α, β and γ), high concentration and volume fraction of intracellular proteins, and the perfect organization of proteins within the cytoplasm. These factors, in turn, are influenced by cytoplasmic hydration, ionic strength, and other specialized metabolic pathways within the lens (Sreelakshmi & Abraham, 2016). Those pathways produce the energy necessary for maintaining transparency, synthesis and repair of LECs. The low levels of the enzymes associated with the aerobic oxidation of glucose restrict the lens metabolism mainly to anaerobic glycolysis, which metabolizes glucose to lactic acid.

Metabolic relationships among the four different pathways of glucose metabolism in the lens (Embden-Meyerhof, sorbitol and pentose phosphate pathways, and the citric acid cycle) are essential for maintaining its transparency (Beeve, 2011; Kinoshita, 1965). In addition, and based on oxidation being a key feature of cataract formation, antioxidative enzymes also play an important role in maintaining lens transparency. Expression of the lens antioxidative system varies considerably between species, with the glutathione-

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Figure 22.13 Morgagnian cataract seen in diffuse illumination. Note the complete liquefaction of the cortex allowing the nucleus to sink inferiorly. (*Source*: Courtesy of Màrian Matas.)

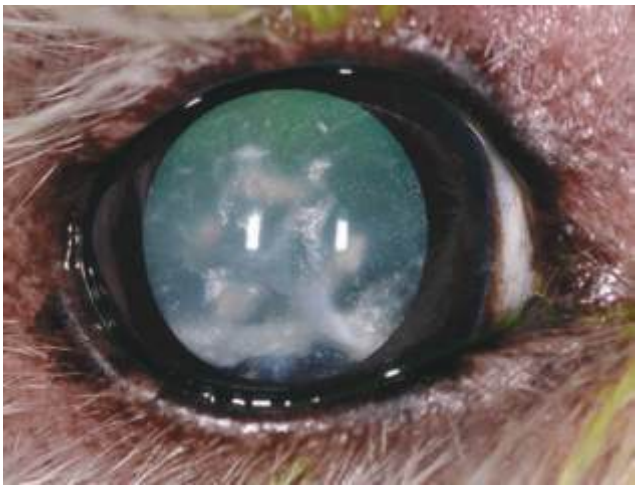


Figure 22.14 Nearly complete cataract reabsorption in a 2-year-old West Highland White Terrier. Note the capsular wrinkling and the crystalline appearance of the lens remnants.

S-transferase and glucose-6-phosphate dehydrogenase reported to be the most abundant in the canine lens (Slaughter et al., 2003).

Cataracts may be defined as a change in the lens refractive index so as to cause an apparent opacity by the scattering of light. Those changes can be induced by different situations such as localized lakes of water, formation of crystals, point-applied pressure or by aggregates of lenticular protein of higher than normal molecular weight, that although still soluble, will cause light scattering because their size approaches the wavelength of visible light. In fact, cataract should be considered as the common end-stage of a large collection of multiple disease entities affecting lens metabolism. The most common cataractogenesis mechanisms include metabolic pathways abnormalities, Na-K-ATPase pump dysfunction, shift on the relative concentration of lens proteins, and oxidative stress. Alteration of the percentage of energy obtained by each of the above-mentioned metabolic pathways may lead to cataract formation. As examples, the excess of glycolytic rate induces overproduction of lactic acid that may reduce the lens' pH, causing nuclear damage; on the other hand, an intumescent and fast-forming diabetic cataract is the result of the osmotic pressure increment induced by the sorbitol pathway (activated in cases of high lenticular glucose concentrations) (Basher & Roberts, 1995). Cataracts have been also associated with a decreased activity of the Na-K-ATPase pump which, in turn, causes an increase in intracellular sodium and calcium and a decrease in potassium content. Consequently, a decrease in oxygen consumption, ATP production, and antioxidant activity are observed. Cataracts, regardless of the etiology, are frequently associated with a shift in the relative concentration of lens proteins resulting from different mechanisms (e.g. gene mutation or oxidation) (Andley, 2006, 2009; Andley et al., 2000; Müller et al., 2006).

The most common imbalance seen is an increase in high molecular weight, insoluble proteins (*albuminoids*) that normally comprise 15% of the proteins of the lens and a decrease in the relative amount of soluble proteins (*crystallins*). Nevertheless, other imbalances have been also described. An increase in the relative proportions of α, and β-L crystallins and a decrease in the β-H and γ crystallins has been reported in the congenital cataract of Miniature Schnauzers (Daniel et al., 1984). In general, the disruption at any point of the exquisite metabolism equilibrium within the lens will influence all other pathways and, together, will induce cataract formation. All previously mentioned pathologic alterations, with progression and the increase of hydrolytic and proteolytic enzyme activity, produce cell membrane rupture and irreversible LEC damage. The loss of low molecular weight proteins increases the lens' water content, creating a shift in intralenticular colloid osmotic pressure that causes a further cation concentration shift of the lens toward equilibrium with the extralenticular fluid (increase in sodium content and decrease in potassium). Further degradation of proteins into amino acids and polypeptides allows small products of proteolysis to diffuse from the lens. The loss of water and nitrogenous material may cause the lens to shrink as with a hypermature cataract. The last of the most commonly reported cataractogenic mechanisms is oxidative stress that may induce cataracts through a combination of the three above-mentioned mechanisms in addition to others such as oxidative injury to lens lipids and proteins, and reduction of connexins (membrane proteins that form hemichannels between the cytoplasm and the extracellular space) (Ho et al., 2010; Retamal et al., 2011). In one study, plasma vitamin C levels were consistently lower in

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cataractous English Cocker Spaniels when compared with normal dogs (Barros et al., 1999). Glutamate and methionine are essential amino acids, the former being used extensively to form lens *crystallins* and glutathione, which is present at very high concentrations in the lens. Glutathione is a cofactor in numerous reactions and the substrate for the enzyme glutathione peroxidase, whose main biological role is to protect the organism from oxidative damage. Its depletion has been associated with congenital cataracts in Miniature Schnauzer pups (Gelatt et al., 1982). Similarly, another study documented decreased activity in the aqueous humor of the antioxidative enzymes superoxide dismutase, catalase, and glucose-6-phosphate dehydrogenase in Poodles with cataract when compared with those without (Barros et al., 2004). *In vitro* studies of canine LECs have documented the presence of *telomerase*, a ribonucleoprotein complex responsible for maintaining telomer length and repairing DNA strand breaks (Colitz et al., 1999). Telomerase activity and telomere length have been shown to increase with aging, being significantly greater in LECs from cataractous lenses when compared with normal lenses. It remains to be determined if this increase in activity is a primary dysregulation that may have a role in the development of the cataract or is secondary to cataractogenesis. In addition, it has been shown that UV radiation increases telomerase activity, which is believed to be necessary in normal LECs for protection against oxidative stress (Colitz et al., 2004, 2006). Differences in total *ferritin* lens concentration, the structures of its chains, and its ratio have been considered as an effect of oxidative stress in the canine lens. A study evaluating the distribution of ferritin chains in canine lenses with and without age-related cataracts yielded a significant increase in normal-sized ferritin H chains in the nucleus of cataractous eyes (Goralska et al., 2009).

Aberrant proliferation and migration of LEC occur during cataractogenesis and posterior capsule opacification in a process known as epithelial to mesenchymal transition. DNA damage, cell cycle and proliferation dysregulation were shown in LECs from diabetic cataracts but not inherited cataracts. It has been postulated that it may be related to the rapid onset of the diabetic cataract compared with the more chronic and slower-to-develop inherited cataracts (Bras et al., 2007).

Histopathologic Changes Associated with Cataract Formation

Histopathologic findings vary according to the extent of the lens opacification, as well as to its etiopathogenesis. In CCs, histopathologic findings include abnormal position or lysis of the nucleus, duplication, wrinkling or segmental changes in lens capsule, and posterior migration of LEC. Vascular or pigmented structures adhered to the capsule may indicate an association with abnormal development of the fetal vasculature (dysplastic PPM, PHPV, or PHTVL) (Collins et al., 1992; Dubielzig et al., 2010).

Specific capsular/subcapsular, cortical, and nuclear morphologic abnormalities are commonly seen with light microscopy, in almost all types of acquired cataracts. In subcapsular cataracts, LEC, normally positioned immediately adjacent to the lens capsule, proliferate to form localized aggregates of multilayered spindle-shaped epithelial cells (Fig. 22.15). In some cases, migration of these cells may pass their normal point of termination in the lens bow and spread along the posterior capsule. These cells, known as bladder or "Wedl" cells, are swollen, rounded and still nucleated (Fig. 22.16). Myofibroblastic differentiation of these posteriorly migrated cells may result in a plaque which is adherent

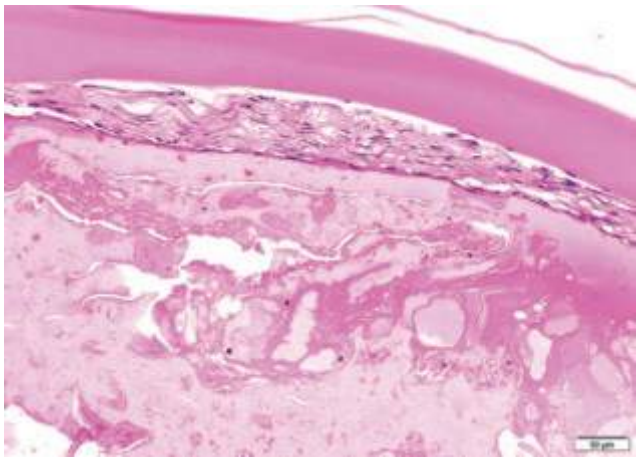


Figure 22.15 Lens epithelial cell proliferation and spindle cell metaplasia underneath the anterior lens capsule. A few "bladder" cells can be seen within the subtending cortex. (*Source*: Courtesy of Carolina Naranjo.)

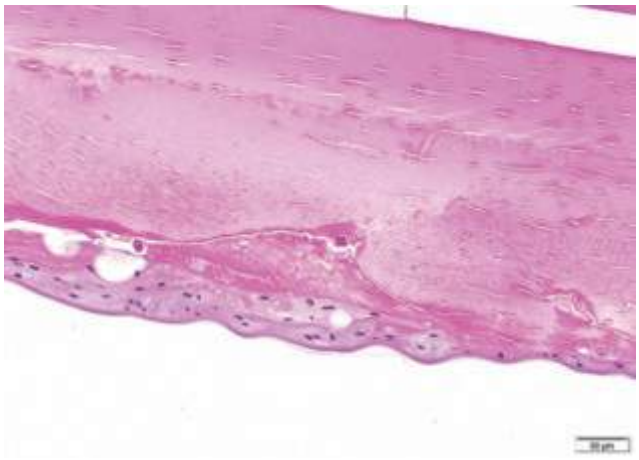


Figure 22.16 Swollen lens epithelial cells, known as "bladder" or Wedl cells are noted near the lens bow region. (*Source*: Courtesy of Carolina Naranjo.)

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to the subjacent capsule. These plaques are characterized by elongated spindle-shaped cells forming a placoid mass, embedded in an extracellular matrix containing collagen fibrils, often with duplicated or split basement membranes. TGF-beta and alpha-smooth muscle-specific actin are found in most of these cells and in some areas of the extracellular matrix, whereas fibronectin and tenascin are found in the extracellular matrix only (Bernays & Peiffer, 2000). Besides LEC migration, other commonly morphologic features seen in subcapsular cataracts include hyperplasia, fibrous metaplasia with secretion of surrounding collagen, mineralization, and loss of LEC, leaving behind cell-free collagen matrix.

Cortical and nuclear acquired cataracts do not have a perfect correlation between the clinical observation of lens opacity and the histologically observable changes, being difficult to determine the significance of observed morphologic changes (Dubielzig et al., 2010). Reliable morphologic indicators of cortical cataracts include a paucity or absence of lens epithelium (from degeneration or necrosis), particle aggregates within the cytoplasm, and increased eosinophilia. Eosinophilic fluid from lytic lens proteins may accumulate in small clefts formed between degenerative fibers and be associated with vacuolization of lens fibers and pyknotic nuclei. With advanced cell wall degradation, larger clefts and pockets of these degenerative proteins may be seen as small eosinophilic aggregates without a nucleus, called Morgagnian globules (Fig. 22.17). Similar changes may be seen with senile nuclear cataract, which should be differentiated from the more common nuclear sclerosis, characterized microscopically by a loss of concentric laminations producing densely eosinophilic staining with homogenous appearance (Eagle & Spencer, 1995; Monaco et al., 1985).

Hypermature cataracts have characteristic microscopic features, including advanced liquefaction and loss of cortical and sometimes nuclear lens contents, wrinkling of the lens capsule, dystrophic calcification, and the formation of multifocal, subcapsular plaques. In addition, capsular changes may be also seen in intumescent cataracts, showing significant capsular thinning. In cases of lens capsule perforation or rupture, the edges frequently curl and an associated inflammatory response with intralenticular leukocytes is often seen (Fig. 22.18). Lens mineralization can occur in long-standing cataracts (Dubielzig et al., 2010).

Cataract often occur secondary to other intraocular diseases, such as uveitis, glaucoma, neoplasia or advanced retinal degeneration. They can also occur as a result of trauma, electrocution, nutritional imbalance, exposure to toxins, or metabolic diseases, such as diabetes mellitus. Although concurrent intraocular diseases are easily seen with microscopic examination, no specific morphologic features distinguish metabolic cataracts from other cortical cataracts.

Detailed Description of Acquired Cataracts

Like CCs, acquired cataracts can be further classified into primary and secondary. Primary cataracts include lens opacifications induced by a lenticular metabolic abnormality (hereditary or not in nature) and those age-related (senile). Secondary cataracts are those induced by other ocular or systemic conditions, such as ocular trauma, glaucoma, uveitis, lens luxation, progressive retinal atrophy, nutritional or metabolic disorders, infectious diseases, and toxins.

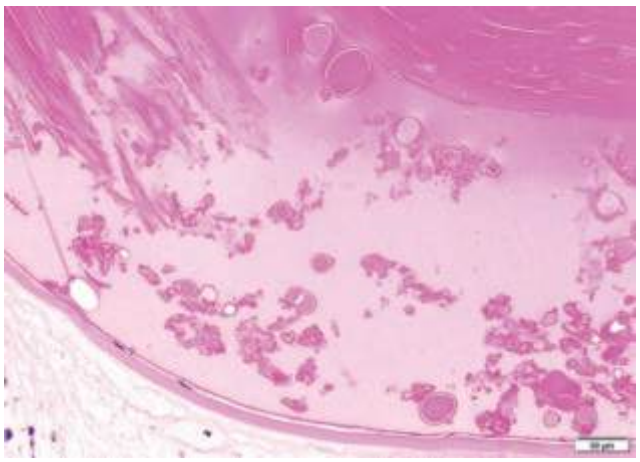


Figure 22.17 Morgagnian globules are rounded, swollen fragments of lens fibers present in the cortex. A few flattened lens epithelial cells have migrated to carpet the posterior lens capsule (posterior subcapsular cataract). (*Source*: Courtesy of Carolina Naranjo.)

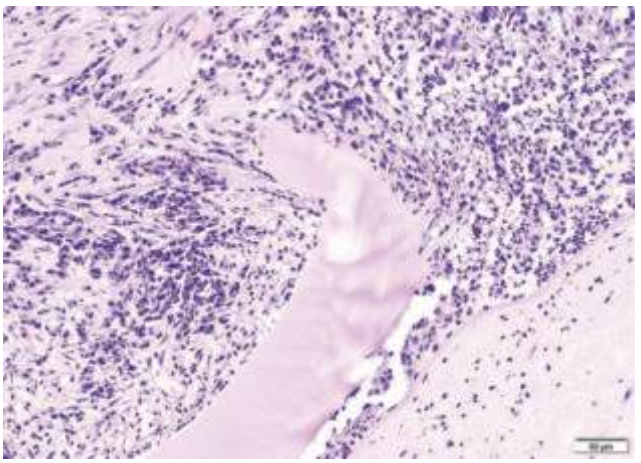


Figure 22.18 Ruptured lens capsule showing frayed eyes. A mixed inflammatory infiltrate is invading the robust fibrovascular membranes lining the external surface of the anterior lens capsule and extending into the collapsed capsular bag. (*Source*: Courtesy of Carolina Naranjo.)

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Acquired Primary Cataracts

Acquired primary cataracts are further classified into those appearing from 8 weeks of life to middle age, which in the dog is considered about 6–7 years of age (developmental cataract), and senile cataract, most commonly seen in dogs older than 8–9 years.

Developmental Cataracts

Developmental cataracts are defined as a primary opacification of the lens that displays a variable presentation among breeds but, at the same time, shows marked intrabreed specificity in their ophthalmoscopic appearance, age of onset, rate of progression, and degree of binocular symmetry, indicating their genetic homogeneity within a breed (Barnett, 1978; Barnett, 1982). They are considered nowadays as one of the most important causes of blindness in purebred dogs, with more than 180 breeds affected (Table 22.3). In some cases, more than one form of cataract for the same breed can be found (ACVO Genetics Committee, 2015; ECVO Genetics Committee, 2017).

Developmental cataracts may be classified into early form (juvenile) and late form, according to the age at which it is first diagnosed. Often, cataract changes develop early in life, at about 12 months of age. However, in some cases, the lens may be normal until advanced age; therefore, there is not an official upper age limit in which to stop re-examining a dog for inherited cataracts. The clinical and morphologic features of developmental cataracts have been described for many breeds of dogs. It should be noted that the phenotypic expression of heritable cataract in dogs, most notably age of onset and progression, can vary within a breed, and the expression can be influenced by other modifying genes or environmental factors. In many breeds, posterior polar cataract is the most common manifestation, primarily affecting the cortex and sparing the nucleus in the initial stages. Those cataracts might only progress a limited extent, rarely affecting the lens completely. Nevertheless, many different presentations have been described for developmental cataracts in the dog. The following descriptions should therefore be interpreted only as general guidelines on expected features of cataracts in the specific breeds. Although detailed information is given below, a summarized table is also included for better understanding and fast localization of the phenotypic and genotypic details (Table 22.4). For additional understanding of its particularities, developmental cataracts have been grouped according to the dog's weight/size.

Clinical and Morphologic Features of Developmental Cataracts in Small Breeds (<10 kg)

Grossly, developmental cataracts tend to occur most frequently in the smaller canine breeds (ACVO Genetics Committee, 2015; ECVO Genetics Committee, 2017; Gelatt & MacKay, 2005; Park et al., 2009). Among the affected breeds, it is worth noting the Miniature Schnauzer, Standard Poodle, Bichon Frise, Boston Terrier, and West Highland White Terrier, of which specific reports on phenotypic lenticular appearance and its progression, have been described.

In the Miniature Schnauzer, apart from the well-known congenital form, a juvenile developmental cataract has also been described. This form has an age of onset of 6 months and primarily affects the posterior lens cortex, with no nuclear involvement. Its progression is variable (Barnett, 1978, 1985b; Rubin et al., 1969). Juvenile cataracts have also been described in the Standard Poodle, in which lens opacification affects the equator and tends to impair vision by 6–18 months of age (Barnett & Startup, 1985; Gelatt & MacKay, 2005; Park et al., 2009; Rubin & Flowers, 1972). Bichon Frise shows a later-onset developmental cataract (2–8 years of age) that affects the anterior and posterior cortex (Adkins & Hendrix, 2005; Baumworcel et al., 2009; Gelatt & McGill, 2003; Gelatt & MacKay, 2005; Wallace et al., 2005). Although some authors suggested that retinal detachment is a common pre-/postoperative finding in Bichon Frise affected with developmental cataracts (Gelatt et al., 2003; Schmidt & Vainisi, 2004), others do not support this claim, thus discouraging prophylactic retinopexy (Braus et al., 2012; Pryor et al., 2016).

Two distinct types of developmental cataracts have been described in Boston and West Highland White Terriers. In the Boston Terrier, the first form, originally described in 1978 by Barnett, is bilateral and begins at the suture lines, affecting the nucleus, as well as the posterior cortex. Despite its early age of onset (8–12 weeks), it is considered as a developmental cataract and tends to progress to maturity (Barnett, 1978, 1985b; Mellersh et al., 2007). In 1984, Curtis described the second type of developmental cataract in this breed. This form has a later onset (3–4 years of age), involves the equator and anterior cortex, and has a very slow progression (Curtis, 1984; Mellersh et al., 2007). In the West Highland White Terrier breed in Sweden, the two types of developmental cataracts also clearly differ; one involves the tips of the posterior Y-sutures primarily, and the other affects the complete lens structure (Gelatt & MacKay, 2005; Narfström, 1981).

Clinical and Morphologic Features of Developmental Cataracts in Medium Breeds (10–20 kg)

Medium-breed dogs are also commonly affected by developmental cataracts (Baumworcel et al., 2009; Gelatt & MacKay, 2005; Park et al., 2009), but studies describing the disease in each breed individually are less common. The most frequently affected breeds include Staffordshire Bull Terrier, German Pinscher, and American and English Cocker Spaniel.

In Staffordshire Bull Terriers, developmental cataract is described as bilateral and symmetrical, located primarily in the nucleus and posterior capsule of the lens and progressing to blindness by 2–3 years of age (Barnett 1976, 1978,

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Table 22.3 Canine breeds affected by presumed hereditary cataracts (HC).

Affenpinscher (a1, b)
Afghan Hound (a1, b)
Airedale Terrier (a2, b)
Akbash dog (a2, b)
Akita Inu (a2, b)
Alaskan Malamute (a2, b)
American Cocker Spaniel (a1, b)
American Eskimo dog (a2, b)
American Hairless Terrier (b)
American Staffordshire Terrier (a1, b)
American Water Spaniel (a1, b)
Australian Cattle dog (a1, b)
Australian Kelpie (a2, b)
Australian Shepherd (standard, miniature and toy) (a1, b)
Australian Terrier (a2, b)
Barbet (a1)
Basenji (a2, b)
Basser Artésien-Normand (a1)
Basset Hound (a1, b)
Beagle (a1, b)
Bearded Collie (a1, b)
Bedlington Terrier (a1, b)
Belgian Malinois (a2, b)
Belgian Sheepdog (a2, b)
Belgian Tervueren (b)
Bernese Mountain dog (a2, b)
Bichon Frise (a1, b)
Black and Tan Coonhound (a1, b)
Black Russian Terrier (a2, b)
Bloodhound (a1, b)
Blue de Gascogne (a1)
Bolognese (a1, b)
Border Collie (a1, b)
Border Terrier (a2, b)
Borzoi (a1, b)
Boston Terrier (a1, b)
Bouvier des Flandres (a1, b)
Doberman Pinscher (a2, b)
Dogo de Bordeaux (a1, b)
Drentse Partridge dog (a2)
English Cocker Spaniel (a1, b)
English Pointer (a1, b)
English Setter (a1, b)
English Springer Spaniel (a1, b)
English Toy Spaniel (a1, b)
Entlebucher (a1, b)
Eurasier (a1)
Field Spaniel (a1, b)
Finnish Lapphund (a2, b)
Finnish Spitz (b)
Flat-Coated Retriever (a1, b)
Fox Terrier (Wire and Smooth) (a1, b)
French Bulldog (a1, b)
French shorthair pointer (a1)
French Spaniel (a1)
French Pointing Griffon Korthals (a1)
German Pinscher (a1, b)
German Shepherd dog (a1, b)
German Shorthaired Pointer (a1, b)
German Wirehaired Pointer (a1, b)
Giant Schnauzer (a1, b)
Glen of Imaal Terrier (a2, b)
Golden Retriever (a1, b)
Gordon Setter (a2, b)
Great Dane (a1, b)
Great Pyrenees (a1, b)
Greater Swiss Mountain dog (a1, b)
Greyhound (a2, b)
Groenendael (a1)
Harrier (b)
Havana Silk dog (b)
Havanese (a1, b)
Ibizan Hound (a1, b)
Icelandic Sheepdog (a2, b)
Münster Spaniel (a1)
Neopolitan Mastiff (a1, b)
Newfoundland (a1, b)
Norbottenspets (a2, b)
Norfolk Terrier (a1)
Norwegian Buhund (a1, b)
Norwegian Elkhound (a2, b)
Norwich Terrier (a1, b)
Nova Scotia Duck Tolling Retriever (a1, b)
Old English Sheepdog (a1, b)
Papillon (a1, b)
Parson Russell Terrier (a1, b)
Pekingese (a1, b)
Pembroke Welsh Corgi (b)
Petit Basset Griffon Vendeen (a1, b)
Pharaoh Hound (b)
Picard Spaniel (a1, b)
Polish Lowland Sheepdog (a1, b)
Pomeranian (a1, b)
Poodle (a1, b)
Polish Tatra Sheepdog (a1)
Portuguese Water dog (a1, b)
Portuguese Pointer (a1)
Pug (a1, b)
Puli (a1, b)
Pyrenean Shepherd (a1, b)
Rat Terrier (b)
Rhodesian Ridgeback (a1, b)
Rottweiler (a1, b)
Saint Bernard (a1, b)
Saluki (a1, b)
Samoyed (a1, b)
Sarloos Wolfhond (a1)
Sarplaninac (a1)
Schapendoes (a1)
Schipperke (a1, b)
Schnauzer Miniature and Standard (a1, b)

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Boxer (a1, b)
Boykin Spaniel (a2, b)
Bracco Italiano (a1, b)
Braque de l'Ariège (a2)
Braque d'Auvergne (a1)
Briard (a1, b)
Brittany Spaniel (a1, b)
Brussels Griffon (a1, b)
Bull Terrier (a1, b)
Bulldog (a1, b)
Bullmastiff (a2, b)
Cairn Terrier (a1, b)
Cane Corso Italiano (a1)
Canaan dog (b)
Cardigan Welsh Corgi (a2, b)
Cavalier King Charles Spaniel (a1, b)
Chesapeake Bay Retriever (a1, b)
Chihuahua (a1, b)
Chinese Crested dog (a2, b)
Chinook (b)
Chow Chow (a1, b)
Cirneco dell ´Etna (a1)
Clumber Spaniel (a2, b)
Collie (a2, b)
Coton de Tulear (a2, b)
Curly-Coated Retriever (a1, b)
Dachshund (a1, b)
Dalmatian (a1, b)
Irish Setter (b)
Irish Soft Coated Wheaten Terrier (a1, b)
Irish Water Spaniel (a1, b)
Irish Wolfhound (a1, b)
Italian Greyhound (a1, b)
Jack Russell Terrier (a1, b)
Japanese Chin (a1, b)
Jagdterrier (a1)
Karelian Bear dog (a2)
Keeshond (a1, b)
Kerry Blue Terrier (a1, b)
Komondor (a1, b)
Kuvasz (a1, b)
Labradoodle Australian (b)
Labrador Retriever (a1, b)
Lagotto Romagnolo (a1, b)
Lakeland Terrier (a1)
Leonberger (a1, b)
Lhasa Apso (a1, b)
Lowchen (a2, b)
Maltese (a1, b)
Manchester Terrier (a1)
Maremma Sheepdog (a1)
Markiesje (a2)
Mastiff (a2, b)
Mi-Ki (a2, b)
Miniature Bull Terrier (b)
Miniature Pinscher (b)
Scottish Deerhound (a1)
Scottish Terrier (a1, b)
Sealyhan Terrier (a1, b)
Segugio Maremmano (a1)
Shar-pei (a1, b)
Shetland Sheepdog (a1, b)
Shiba Inu (a1, b)
Shih Tzu (a1, b)
Siberian Husky (a1, b)
Silky Terrier (a1, b)
Skye Terrier (a1)
Soft-Coated Wheaten Terrier (b)
Spinone Italiano (a1, b)
Staffordshire Bull Terrier (a1, b)
Sussex Spaniel (a1)
Standard Schnauzer (b)
Swedish Vallhund (b)
Tibetan Spaniel (a1, b)
Tibetan Terrier (a1, b)
Vizsla (a1, b)
Volpino Italiano (a1)
Weimaraner (a1, b)
Welsh Corgi Pembroke (a1)
Welsh Springer Spaniel (a1, b)
Welsh Terrier (a1, b)
West Highland White Terrier (a1, b)
Whippet (a1, b)
Yorkshire Terrier (a1, b)

a1, Published studies referenced in the *ECVO Manual of Presumed Inherited Eye Diseases* (ECVO Genetics Committee, 2017). a2, Nonpublished reports considered in the *ECVO Manual of Presumed Inherited Eye Diseases* (ECVO Genetics Committee, 2017). b, Published studies and non-published reports referenced in *Ocular Disorders Presumed to be Inherited in Purebred Dogs* (ACVO Genetics Committee, 2015).

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Table 22.4 Canine breeds affected by hereditary cataracts (HC), in which the mode of inheritance has been described and/or a genetic test for its detection developed (ACVO Genetic Committee, 2015; ECVO Genetic Committee, 2017).

Canine breeds affected by HC	Inheritance	Available genetic tests	References
Australian Shepherd	Autosomal dominant with incomplete penetrance	*HSF4-2*	Mellersh et al., 2006, 2009
Border Terrier	Autosomal recessive	*HSF4-1*	ACVO Genetic Committee, 2015
Boston Terrier	Autosomal recessive	*HSF4-1* for early onset presentation	Mellersh et al., 2006, 2007
Chesapeake Bay Retriever	Autosomal dominant with incomplete penetrance	–	Gelatt, 1979
American/English Cocker Spaniel	Autosomal recessive	–	Engelhardt et al., 2007a, 2007b, 2008; Mellersh et al., 2006; Olesen et al., 1974; Yakely, 1978
Entlebucher Mountain dog	Autosomal recessive	–	Heitmann et al., 2005; Müller & Distl, 2008; Müller et al., 2006
French Bulldog	–	*HSF4-1*	ACVO Genetic Committee, 2015; ECVO Genetic Committee, 2017
German Shepherd Dog	Congenital: autosomal dominant Noncongenital: autosomal recessive	–	Barnett, 1986; Von Hippel, 1930
Australian Labradoodle	Autosomal dominant with incomplete penetrance Autosomal recessive Not defined	–	Curtis & Barnett, 1989; Kraijer-Huver et al., 2008
Labrador Retriever	Autosomal dominant with incomplete penetrance Autosomal recessive Not defined	–	Curtis & Barnett, 1989; Kraijer-Huver et al., 2008
Miniature Australian Shepherd	Autosomal dominant with incomplete penetrance	*HSF4-2*	Mellersh et al., 2006, 2009
Miniature Schnauzer	Autosomal recessive	–	Barnett, 1985b; Gelatt et al., 1983b; Monaco et al., 1985; Rubin et al., 1969; Samuelson, 1987
Norwegian Buhund	Autosomal dominant	–	Bjerkås & Haaland, 1995
Staffordshire Bull Terrier	Autosomal recessive	*HSF4-1*	Mellersh et al., 2006
Toy Australian Shepherd	Autosomal dominant with incomplete penetrance	*HSF4-2*	Mellersh et al., 2006, 2009
Welsh Springer Spaniel	Autosomal recessive	–	Barnett, 1980
West Highland White Terrier	Autosomal recessive	–	Narfström, 1981

1985a). German Pinchers in Finland are affected by a late-onset developmental cataract (9 years old at diagnosis) that primarily affects the posterior and subcapsular area (Leppänen et al., 2001). Conversely, in dogs bred in Germany, developmental cataracts can be found significantly earlier in life (median age 3.9 years) with a predisposition for the anterior cortical area followed by the posterior pole (Pfahler et al., 2015). The reason for these significant geographic differences is unknown.

The American Cocker Spaniel, apart from the previously mentioned congenital cataract, also shows a developmental cataract that affects the cortex, with the posterior aspect most commonly affected, with the anterior cortex and the equator involved less frequently (Yakely, 1978). They can appear as early as 6 months of age and have variable progression depending on age of onset. Progression tends to be rapid in dogs with early onset (<3.5 years of age) and slower in cases of late onset (>3.5 years of age). Both presentations seem to be genetically distinct (Engelhardt et al., 2007a). Both color variants of this breed manifest different and quite varied forms of cataract with respect to location within the lens, even in closely related dogs, suggesting that the

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phenotype does not segregate according to familial lines (Engelhardt et al., 2008). Similarly, English Cocker Spaniels also show congenital and developmental cataracts (Engelhardt et al., 2007a; Gelatt & MacKay, 2005; Olesen et al., 1974).

Clinical and Morphologic Features of Developmental Cataracts in Large Breeds (>20 kg)

Large breed dogs are commonly affected by developmental cataract, with the posterior polar area the most frequently involved (ACVO Genetics Committee, 2015; Baumworcel et al., 2009; ECVO Genetics Committee, 2017; Gelatt & MacKay, 2005; Park et al., 2009). In the Golden and Labrador Retriever, apart from the previously described congenital form, a later onset form of developmental cataract has been also described (Barnett, 1972, 1976, 1978, 1985a; Curtis, 1982; Curtis & Barnett, 1989; Gelatt, 1972; Rubin, 1974). In these breeds, cataracts are cortical, most commonly located in the posterior cortex, and progressive (Curtis & Barnett, 1989; Kraijer-Huver et al., 2008; Rubin, 1974). In the Labrador Retriever, dogs with posterior polar cataracts produce affected offspring with both focal and diffuse forms of cataract, suggesting the two forms cannot be considered totally separate entities (Kraijer-Huver et al., 2008). These cataracts could be phenotypic variations of the same genetic mutation or mutations, but it is also possible that there are different genetic mutations that occur simultaneously in this breed.

Equatorial and posterior subcapsular cataracts occur in the Siberian Husky. These cataracts are considered to be juvenile onset, as they appear at 6–18 months of age and are typically slowly progressive (Gentilini et al., 2008). Developmental cataracts suspected to be inherited have also been described in the Chesapeake Bay Retriever (Gelatt, 1979) and Labradoodle (Oliver & Gould, 2012), both showing multiple lens locations without a clear phenotypic predisposition.

In the German Shepherd breed in England, developmental cataracts have been reported at 8–12 weeks of age, as small dot opacities in the posterior cortex that can involve the Y-sutures and nucleus. With progression, by 1 year of age, nuclear and cortical cataracts with vision impairment can be present. No progression is noted after 1–2 years of age (Barnett, 1986).

Cataracts in the Norwegian Buhund were first described in 1988 by Barnett, who reported moderately large posterior polar cataracts with occasional extensions around the suture lines, as well as occasional vacuoles in the peripheral cortex and rapid progression to blindness (Barnett, 1988). In 1995, a clearly different type of cataract was described in this breed, which was termed pulverulent nuclear cataract (Bjerkås & Haaland, 1995). The term pulverulent means "dust like" and is commonly used in human ophthalmology (Reddy et al., 2004). The cataracts may be visible as early as 6.5 weeks of age as small dots parallel to the suture lines behind the nucleus. By the age of 4–5.5 years, the opacities progress to involve the fetal nucleus which then resembles a ball of candy floss. The adult nucleus and the cortex remain clear. More recently, a study on the prevalence and characteristics of hereditary cataracts (HC) in 250 Norwegian Buhund in Norway, confirmed that pulverulent cataracts are still very prevalent in the breed (52.4%), but there are also other common forms of cataracts (cortical, posterior polar, etc). Cataracts rarely cause loss of vision in this breed (Kristiansen et al., 2017).

In the Entelbucher Mountain Dog, developmental cataract is the most frequently observed hereditary eye disease with a prevalence of 23.5% (Heitmann et al., 2005). Most of the affected dogs develop bilateral symmetric opacifications, which are mostly capsular and subcapsular in the posterior polar part of the lens along the suture lines (Müller & Distl et al., 2006; Spiess, 1994). The first sign of cataracts can be seen at a mean age of 5.5 ± 2.6 years (Heitmann et al., 2005) and progressive retinal atrophy may be concurrent (Heitmann et al., 2005; Kuster et al., 2011).

Nuclear, posterior nuclear, and posterior polar subcapsular cataracts have been identified in closely related Leonbergers in the United Kingdom (Heinrich et al., 2006). Similarly, triangular-shaped polar (anterior and posterior) and complete cataracts have been described in Rottweilers of different ages, with the youngest at 10 months of age (Bjerkås & Bergsjø, 1991). In the Welsh Springer Spaniel, a bilateral, symmetrical, progressive cataract affecting the nucleus and posterior cortex has been described in a pedigree of three generations (Barnett, 1980). Equatorial cataracts can occur as early as 4 months in the Afghan Hound. Progression is rapid in this breed, with visual impairment often present by 2 years of age (Roberts & Helper, 1972). In the Old English Sheepdog, developmental cataracts have been also described, with the location of the opacity within the lens and the age of onset highly variable (Koch, 1972a, 1972b).

Mode of Inheritance and Affected Genes in Hereditary Cataracts

The paucity of canine cataract mutations reported in the literature, compared with those associated with, for example, inherited retinal degenerations in the dog, is testament to the fact that HC is probably a genetically complex disorder in most dog breeds, and studies to date have not included the analysis of sufficient numbers of cases and controls to identify DNA variants associated with the disease. Indeed, although presumed HC have been described in more than 180 canine breeds (see Table 22.3), the mode of inheritance has been established only in 17 breeds (Table 22.4) (ACVO Genetics Committee, 2015; ECVO Genetics Committee, 2017). Although an autosomal recessive trait has been reported as the most common mode of inheritance for hereditary cataracts (ACVO Genetics Committee, 2015;

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ECVO Genetics Committee, 2017), a presumed dominant mode has been described for the Australian Shepherd (Mellersh et al., 2006), Chesapeake Bay Terrier (Gelatt, 1979), German Shepherd (von Hippel, 1930), Australian Labradoodle, Labrador Retriever (Curtis & Barnett, 1989; Rubin, 1974), and Norwegian Buhund (Bjerkås & Haaland, 1995). In the remaining breeds affected by presumed HC not included in Table 22.4, a simple recessive trait with polygenic inheritance is highly suspected, although not proven (Yakely, 1978).

Because of its most prevalent mode of inheritance, HCs are difficult to control within canine populations. In affected breeding lines, asymptomatic carriers can only be identified retrospectively, once they have reproduced and affected offspring have been diagnosed. Extensive breeding from popular dogs (sire effect), inbreeding, and the difficulty in diagnosing carriers, all contribute to mutations responsible for recessive conditions becoming very prevalent within breeds at risk. Often, the only effective means of control is via DNA diagnostic tests and appropriate breeding programs. Unfortunately, despite the large number of breeds affected with HC, little is known about the molecular background and genetics of the condition. Since the availability of the canine genome sequence in 2004 (Lindblad-Toh et al., 2005), and after providing the radiation hybrid location of 21 cataract-associated genes and closely associated polymorphic markers (Hunter et al., 2006), the identification of associated and linkage genes in the dog has been greatly facilitated.

In humans and mice, several mutations in different genes have been linked to both autosomal dominant and recessive HC (Bu et al., 2002; Forshew et al., 2005; Fujimoto et al., 2004; Min et al., 2004; Nakai et al., 1997; Smaoui et al., 2004). Different studies have evaluated the role of these mutations in the development of HC in the dog. More than 21 candidate genes have been investigated in several canine breeds, but to date, only two genes, the heat shock transcription factor 4 (*HSF4*) (Mellersh et al., 2006, 2007, 2009) and the Sec1 Family Domain Containing 2 (*SCFD2*), have been associated with developmental HC in dogs (Ricketts et al., 2015).

HSF4 belongs to a family of heat shock transcription factors that regulate the expression of heat shock proteins in response to different stresses, such as oxidants, heavy metals, elevated temperatures, and bacterial and viral infections (Nakai et al., 1997). Mellersh and collaborators were the first identifying two different mutations in exon 9 of *HSF4* gene in three different breeds affected with HC (Mellersh et al., 2006). The study showed a nearly complete linkage with microsatellites adjacent to exon 9 of *HSF4* of chromosome 5 in Staffordshire Bull Terriers, Boston Terriers, and Australian Shepherds. The two gene mutations described in these breeds are predicted to alter the reading frame of the protein transcript and introduce a premature stop codon, which results in truncated and aberrant crystalline proteins (Shi et al., 2009). These abnormal proteins are the common final result of two possible *HSF4* exon 9 mutations: a 1-bp insertion seen in Staffordshire Bull Terriers and Boston Terriers (*HSF4-1*), and a 1-bp deletion detected in Australian Shepherds (*HSF4-2*). The mode of inheritance has been defined as autosomal recessive for the *HSF4* insertion mutation and autosomal incomplete dominant for the deletion mutation (Mellersh et al., 2006, 2009). However, some authors hypothesize that the deletion mutation is in fact a recessive trait, but when combined with an additional (as yet unidentified) mutation, may develop cataracts if they are homozygous for either mutation or heterozygous for both (Mellersh et al., 2009). Studies on HC indicate that in addition to *HSF4* mutations there are other genetic factors that can contribute to the development of the disease in the above-mentioned breeds (Mellersh et al., 2007; Ricketts et al., 2015). The insertion mutation in *HSF4* is responsible for the early HC, but not the late HC, seen in Boston Terriers; thus, proving that these two forms are genetically, as well as clinically, distinct conditions (Mellersh et al., 2007). It follows that genetic testing for the *HSF4* mutation in Boston Terriers cannot predict all forms of HCs in this breed.

The role of *HSF4* in HC should not be extrapolated to other breeds because *HSF4* has been excluded from involvement in the development of HC in a long list of breeds, including the Dachshund (Müller et al., 2007; Müller & Distl, 2009), Entlebucher Mountain dog (Müller et al., 2008), American and English Cocker Spaniel (Mellersh et al., 2006; Engelhardt et al., 2007b), wire-haired Kromfohrlanders (Engelhardt et al., 2007b), Siberian Husky (Gentilini et al., 2008), Golden Retriever (Mellersh et al., 2006), Jack Russell Terrier (Oberbauer et al., 2008), Alaskan Malamute, Bichon Havanais, Belgian Shepherd Tervueren and Groenendael, English Miniature Terrier, Finnish Lapphund, Griffon Bruxellois, Lapponian Herder, Miniature Schnauzer, Miniature Pinscher, Nova Scotia Duck Tolling Retriever, Rottweiler, Samoyed, Schnauzer, and Tibetan Mastiff (Mellersh, 2014).

More recently, a mutation in the intron 5 of the *SCFD2* gene on chromosome 13 has been associated with bilateral posterior polar cataracts in Australian Shepherd dogs (Ricketts et al., 2015). The *SCFD2* gene encodes a sec1 family domain-containing protein 2, a molecule that may be involved in protein transport, although very little is reported on its function.

Many other genes causing cataracts in humans have been tested in different canine breeds with no significant linkage or association (Mellersh, 2014; Müller & Distl, 2009; Shastry & Reddy, 1994).

Breeding Strategies and Genetic Tests Available for Hereditary Cataract

Advances in molecular biology have facilitated the identification of some of the causal DNA mutations underlying HC in several canine breeds (*HSF4-1*, *HSF4-2*, *SCFD2*) (Mellersh

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et al., 2006, 2009; Ricketts et al., 2015). In the near future, it is very likely that new mutations will be identified, and the list of DNA-based tests developed from these discoveries will be expanded. Because this is a rapidly changing field, consulting the websites of the individual laboratories offering DNA tests for the most current information is recommended.

Currently, there are only two DNA-based tests commercially available for the diagnosis of HC in dogs (see Table 22.4): the *HSF4-1* (exon 9 1-bp deletion in Border Terrier, Boston Terrier, French Bulldog and Staffordshire Bull Terrier) and the *HSF4-2* (exon 9 1-bp insertion in Australian Shepherd) (ACVO Genetics Committee, 2015; ECVO Genetics Committee, 2017). The high frequency of *HSF4* mutations and their significant association with HC in the above-mentioned breeds, call for careful planning of breeding strategies. It should be noted, however, that the high frequency of the *HSF4* mutations (1&2) in these breeds, warrants caution in the quickly/entirely eliminating carriers from the breeding population, as this could have adverse effects on the breeds as a whole. We must admit that based on a restrictive knowledge on modes of inheritance, breeding recommendations are usually limited to not breeding affected dogs.

Age-Related Cataracts

Cataracts are commonly seen in the aged dog and are often classified as age-related cataracts (ARC) or senile cataracts, if no other antecedent cause is apparent. The age of onset at which a cataract should be considered age-related is arbitrary and breed-related. In fact, different studies show that body size, life expectancy, and ARC incidence are interrelated in dogs; body size negatively correlated to longevity (Greer et al., 2007), and this in turn, positively correlated with the age at which prevalence of cataract is 50% (C50) (Urfer et al., 2011; Williams et al., 2004). Thus, the C50 value increases according to expected longevity of a breed; having lower values in larger breeds and higher values in small- and medium-size breeds. This suggests that ARC may have a connection to systemically acting factors controlling the rate of growth and scale of body size, which produce life-limiting events and also affect lens maintenance and health. Based on these findings, the authors generally use a cutoff age of 7 years for large breed dogs and 9 years for small breeds.

Although the clinical appearance and rate of progression of ARC can vary, they often can be found initially as an increase in relucency in the adult nucleus of the lens, generally occurring concurrent with or after dense nuclear sclerosis (Fig. 22.19). Cortical cataractous changes may also occur to varying extents, either concurrent with or separate from nuclear cataracts. A characteristic yellow to brown discoloration (*brunescence*) is often present in the ARCs of humans (Ranjan & Rao Beedu, 2006). The age-related chromophore



Figure 22.19 Typical age-related cataract in a 13-year-old Miniature Schnauzer seen in direct illumination. Note denser nuclear cataract with multifocal opacities in the cortices.

pigments responsible for this phenomenon have not been identified in canine lenses although the authors have identified a yellowish coloration in some chronic mature ARCs. The rate of progression of these classic ARCs in dogs is often slow, requiring many months to several years to result in demonstrable vision loss.

Often, cataracts with varying biomicroscopic features and rate of progression can be found in 6- to 10-year-old dogs of breeds that are at risk for heritable cataracts. The designation of these cataracts as either hereditary (based on the risk of the breed for cataract development), nonhereditary, or age-related, is often unclear. In some cases, the morphologic features of frequent initial and predominant nuclear involvement and the slow progression seen in ARCs may be useful to distinguish those from other types of primary acquired cataracts. Owing to breed predilection for these types of cataracts, it could be theorized that a genetic disorder of lens metabolism may be present and age-related changes in the lens, or other age-associated environmental factors, cause phenotypic expression or exacerbation of cataracts. Alternatively, some of these animals may simply suffer from heritable cataracts that have an atypical or late phenotypic onset with no environmental component.

The pathogenesis of ARCs in dogs is unknown. Much of the speculation regarding the pathogenesis of senescent cataracts in humans focuses on the photooxidative injury to the lens, the consequence of decades of exposure to ambient solar radiation and ultraviolet wavelengths of light (Spector, 1995; Taylor et al., 1988). Whether such photooxidative mechanisms are relevant in the dog lens, with an average life span only one-fifth that of humans, is speculative.

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Acquired Secondary Cataracts

Cataracts Associated with Medications, Toxic Substances, and Other Factors

A number of pharmacologic agents have been reported to produce cataracts in dogs. As this species is commonly used in toxicologic screenings of new pharmacologic agents and chemicals, numerous cataractogenic agents have been noted in laboratory dogs. Many of these agents have minor clinical significance, as they are typically produced during toxicologic studies, where the test compounds are administered chronically and/or in high dosages. Drug-induced cataracts tend to be bilateral and, although initially appear at a variety of locations within the lens, often begin in either the anterior and posterior cortical region near the equator or the Y-suture regions. This type of secondary cataract is often associated with lens vacuole formation and reported to be reversible if the drug insult is removed (Eagle & Spencer 1995; Heywood, 1971). It would appear that the majority of drug-induced cataracts are caused by specific interference with the lens enzyme system (Heywood, 1999).

In laboratory dogs, cataracts have been described with the chronic use of antihypertensive agents such as diazoxide (Schiavo et al., 1975; Schiavo, 1976) and phenylpiperazine (Susick et al., 1991). Induced lens opacities are progressive for phenylpiperazine, but transient and reversible for diazoxide. The administration of high dosages of cholesterol-lowering drugs such as hydroxymethylglutaryl-CoA (HMG-COA) reductase inhibitors (Gerson et al., 1990, 1991) or drugs inhibiting oxidosqualene cyclase (Funk & Landes, 2005; Pyrah et al., 2001) have also been described to produce cataracts, seen initially as accentuation of the suture lines that finally progress to anterior and posterior subcapsular areas. One exception from the HMG-COA reductase inhibitors group is atorvastatin, which does not seem to have cataractogenesis effects in the dog (Robertson et al., 1997). The hypocholesterolemic drugs are thought to have a cataractogenic effect by inhibition of cholesterol synthesis in the outer cortical regions of the lens, where cholesterol is critical for the newly synthesized lens fibers' cell membranes. Chronic and high doses of hypoglycemic agents, such as sulphonylurea glimepiride (Schollmeier et al., 1993), or quinolones, such as pefloxicin (Chist et al., 1985), have been also associated with experimental cataracts in dogs. Chronic topical and oral administration of dimethyl sulfoxide (DMSO) in dogs (dosage of 2.5–40 g/kg) has been associated with unusual lens changes with an unexplained pathogenesis. The lens alteration was characterized by a reduction in the refractive index of newly synthesized lens fibers in the cortex causing them to appear optically clear instead of relucent (Rubin & Mattis, 1966; Smith et al., 1969). Cataractogenesis in dogs has been also associated with the administration of oral contraceptives (Drill et al., 1975; Vessey et al., 1998) and with disophenol. This archaic antihelminthic drug produces reversible variable cataracts in young puppies, at both high and recommended doses (Martin et al., 1972; Martin, 1975). In addition, two fungicides have been reported to induce cataractogenesis in the dog, ketoconazole (Da Costa et al., 1996) and 2,6-dichloro-4-nitroaniline (DNCA) (Bernstein et al., 1970). Long-term therapy with ketoconazole has been associated with bilateral, progressive cataract formation, mostly in young, large-breed dogs. The pathogenesis of this imidazole-associated cataract is not known, but lens opacities appeared by 3.5–37 months after initiation of ketoconazole therapy for systemic mycoses.

A number of drugs have been associated with cataractogenesis in humans and other experimental laboratory animals besides dogs, and therefore would likely have potential to cause canine cataracts if administered in sufficiently high dosages. Systemic, topical, and inhaled corticosteroids are a leading risk factor for the development of drug-induced cataracts, increasing the risk with the amount of the daily dose and the duration of treatment, with individual susceptibility apparently also playing a role (Cumming et al., 1997; Manabe et al., 1984; McLean et al., 1995; Urban & Cotlier, 1986). Gender is not a factor, but young children may be at greater risk. Steroid-induced cataracts tend to be subcapsular and do not usually regress when the drug is stopped. Long-term use of miotics is also a leading risk for cataractogenesis, in particularly long-acting cholinesterase inhibitors, such as echothiophate, demecarium bromide, and disopropyl fluorophosphates (Kaufman et al., 1977; Khurana, 2007; Philipson et al., 1979). In dogs, cataracts are rarely observed, if ever, as a side effect of ocular corticosteroids or organophosphates use.

Although less frequently, lens opacities have also been reported after the use of neuroleptic drugs – chlorpromazine (DeLong et al., 1965) and carbamazepine (Fraunfelder & Meyer, 1982), busulfan (Kaida et al., 1999), allopurinol (Garbe et al., 1998), naphthalene (van Heyninger, 1976), ouabane, digitalis, diquat (Eagle & Spencer, 1995), hygromycine B (Sanford & Dukes, 1981), tetracyclines (Krejčí & Brettscheneider, 1983), deferoxamine (Wang et al., 1992), phenytoine (Bar et al., 1983), isotretinoin (Herman & Dyer, 1987), synthetics antimalarial agents (Drenckhahn & Lüllmann-Rauch, 1977), tamoxifen (Zhang et al., 1994). and sulfamides (van den Brûle et al., 1998).

Cataracts Associated with Toxic Substances

A number of toxic substances are known to trigger cataract, including: acetone, dinitrophenol, cresol, and paradichlorobenzol, as well as numerous chemicals and solvents (Gupta et al., 2014). Intraocular foreign bodies containing metals such as iron, copper, lead mercury, silver, gold, and thallium have been also associated with cataractogenesis (Parke et al., 2013). Accidental ingestion of an overdose of xylitol-containing chewing gum (estimated dose 0.7 g/kg)

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has been associated with acute bilateral cataract, retinal detachment, and hepatotoxicity in a dog (unpublished data).

Cataracts Associated with External Agents

Several external agents have been associated with cataracts in human and different animal species, including radiation, electricity, hypothermia, hyperthermia, and pH shifts. Ionizing, non-ionizing (microwave), ultraviolet and infrared radiation can cause cataracts by altering formation of new cells and differentiation of fibers (Cetinel et al., 2017; Ching et al., 1990; Lett et al., 1986; Lipman et al., 1988; Milroy & Michaelson, 1972; Yu et al., 2015). The likelihood of development of cataracts after ionizing radiation is related to the dose and the degree of exposure of the eye to the radiation beam (Jamieson et al., 1991; Roberts et al., 1987; Theon, 1993). In dogs, cataract was a common late finding (>6 months) when given 36–67.5 Gy in fractionated doses over 4 weeks using a 6 MV linear accelerator (Ching et al., 1990). Attempts should be made to exclude the ocular tissues from the radiation field or shield the globe with lead shields or other devices during cancer radiotherapy. Although there are some exceptions, in general, other collateral damage to the globe as a result of radiotherapy makes these dogs marginal candidates for cataract surgery. High doses of non-ionizing radiation (microwave) have also been associated with cataractogenesis in dogs (Michaelson et al., 1971). Its mechanism of action includes deformation of heat-labile enzymes, such as glutathione peroxide, that ordinarily protect lens cell proteins and membrane lipids from oxidative stress (Lipman et al., 1988).

Electricity-induced cataracts have been sporadically reported in both humans and dogs (Brightman et al., 1984; Long, 1963; Portellos et al., 1996; Reddy, 1999; Saffle et al., 1985; Thomas & Hanna, 1974). Bilateral anterior subcapsular cataract formation has been reported in a 3-year-old dog after biting an electric cord (Brightman et al., 1984). In humans, the incidence of electric cataract formation varies between 5% and 20%, and most patients develop initial loss of vision within 12 months of the injury, showing subcapsular cataracts that are often progressive (Fraunfelder & Hanna, 1972; Portellos et al., 1996). Patients at highest risk are those who have been exposed to voltages in excess of 1000 V and who have entrance wounds on the head or neck (Saffle et al., 1985). Although the morphologic and histological changes that evolve in the lens have been well described (Hanna & Fraunfelder, 1972; Long, 1963; Thomas & Hanna, 1974), exact pathophysiology of electrical cataracts remains obscure.

Hyperthermia and hypothermia have also been described as mechanisms for inducing cataracts in research laboratory animals, but to date, no description has been reported in dogs (Bermudez et al., 2011; Bollemeijer et al., 1989). In addition, low pH has been shown to directly affect crystalline proteins, causing its aggregation and thus, secondary cataracts (Wu et al., 2014). Cataract, in association with other intraocular and periocular inflammatory findings, was described in a dog secondary to an ocular snakebite (pit vipers). The pathogenic mechanism for the lens opacification is unclear, although severe anterior uveitis is the most likely (Martins et al., 2016).

Cataracts Associated with Other Ocular Diseases

A number of different intraocular diseases can cause secondary cataract in the dog. The most clinically relevant type of secondary cataract is undoubtedly that associated with progressive retinal atrophy (PRA) or other types of retinal degeneration. PRA-induced cataract is presumed to be of an endogenous toxicity nature. Degenerative rod outer segments may release water-soluble dialdehydes from peroxidation of photoreceptor lipid membranes that diffuse through the vitreous and are toxic to lens cellular membranes (Zigler & Hess, 1985). An organ culture lens system was used to show that toxic aldehyde products of lipid peroxidation can damage lens membranes and Na-K ATPase pumps (Zigler et al., 1983). Cataracts are commonly seen in dogs with moderate to advanced stages of PRA, often obscuring ophthalmoscopic detail of the fundus. Typically, the cataract is accompanied by dilated pupils with poor pupillary light reflexes and, if the retina can be examined, hyperreflectivity from the fundus. Questioning of the owner about onset, progression, vision in daylight and under reduced light conditions, as well as knowledge on the breed and the dog's age, is of essence to establish a clinical suspicion. The final diagnosis should be made by electroretinography. Although all the breeds genetically predisposed for PRA may develop secondary cataracts, some breeds, such as the Labrador Retriever, American Cocker Spaniel, and Miniature and Toy Poodle, have been suggested to most frequently develop PRA-induced cataracts (Adkins & Hendrix, 2005; Gaiddon et al., 1995). The reported incidence of PRA-induced cataracts varies between 12.4% (50/404 dogs with cataracts) (Donzel et al., 2017) and 27% (66/244) (Adkins & Hendrix, 2005). Although breeds of dogs at risk for PRA also have a high incidence of genetic cataracts, it is likely that the two disorders are not interrelated, but rather reflect two heritable disease states (Donzel et al., 2017; Heitmann et al., 2005; Koll et al., 2017; Kraijer-Huver et al., 2008; Kuster et al., 2011).

Cataract formation has also been associated with other intraocular conditions such as uveitis, glaucoma, and primary lens luxation. Uveitis may have different mechanisms of cataractogenesis; among those, posterior synechia, capsular deposition of inflammatory cells, and abnormal lens metabolism associated with diffusion of toxins into the lens should be considered. Primary glaucoma may induce cataracts directly by altering the lens metabolism (Akyol et al., 1990) or indirectly by inducing chronic mild uveitis or lens

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luxation. Similarly, primary lens luxation may induce cataract by inducing secondary uveitis or by a reduction of the nutritional support to the lens, caused by an alteration of the typically nourishing aqueous humor. Besides that, free movement of the lens inside the eye and the involuntary contact with other intraocular structures may also induce lens opacification. The three above-mentioned ocular conditions can be seen as a consequence of cataract or as its triggering condition. The initial disease, although not always easy to elucidate, is usually the most chronic or severe of the concurrent conditions.

Cataracts Associated with Systemic Ion Disturbances

Calcium Abnormalities (Hypocalcemia and Hypercalcemia)

Hypocalcemia, most commonly caused by renal failure or primary or secondary hypoparathyroidism in dogs, can be associated with characteristic cataracts manifested as multifocal, punctate opacities or coalescing lamellar cortical opacities (as a "field of stars"), that are bilaterally symmetric (Fig. 22.20) (Bruyette & Feldman, 1988; Kornegay et al., 1980; Russell et al., 2006). The opacities are thought to relate to hypocalcemic-associated defects in the active cation transport mechanism of the lens epithelium, causing an increase in sodium content and a loss of lens potassium. This derangement results in osmotic imbalance that leads to lens fiber swelling and rupture. In humans, hypocalcemic cataracts generally start in the posterior cortex, the site furthest from the ion regulatory pump mechanism in the anterior lens epithelium and, therefore, the area least able to compensate for alterations in the pump (Delamere et al., 1981; Evans & Kern, 1931; Pohjola, 1962). Treatment of hypocalcemic disease generally halts the progression of the cataract but does not reverse existing lens opacities. Although primary vitamin D deficiency, inducing hypocalcemia, and therefore secondary cataracts, has been described in humans (Brown & Akaichi, 2015), there are no reports in dogs.

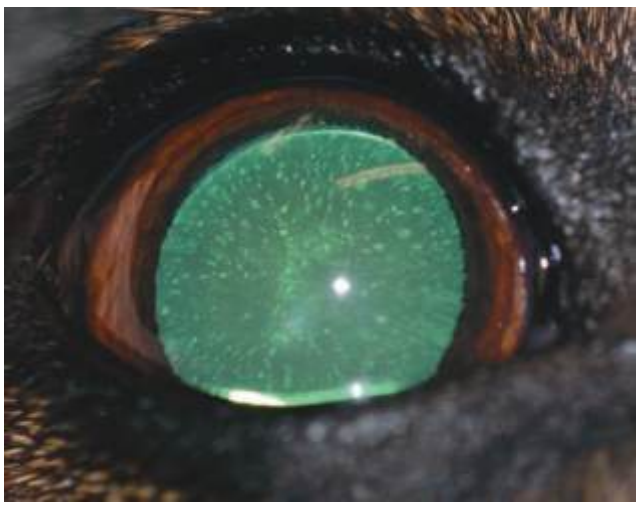


Figure 22.20 Multifocal, punctate cortical opacities with diffuse illumination in a dog with hypocalcemia. (*Source*: Courtesy of Màrian Matas.)

Hypercalcemia is rarely reported in dogs, with neoplasia being its most common cause, followed by primary hyperparathyroidism, chronic kidney disease, and hypoadrenocorticism (de Brito Galvão et al., 2017).

Paradoxically, both hypocalcemia and hypercalcemia have been associated with experimental cataract models and other forms of human cataracts (Ghahramani et al., 2015; Jedziniak et al., 1976; Kohart et al., 2017). Both calcium-induced cataracts have a very similar phenotypic presentation. Therefore, it is possible that causative factors fall into a bimodal distribution pattern, where one class of cataracts develops in subjects with hypocalcemia, and the other in animals with hypercalcemia.

Copper Abnormalities (Hypercupremia)

A characteristic, sunflower-shaped anterior subcapsular cataract is observed in humans suffering from Wilson's disease, and other noncongenital disorders causing derangement of copper metabolism (Lewis et al., 1975; Martin et al., 1983). Lens opacities have little effect on vision and clear after treatment with penicillamine (Dorland, 2012). A familial copper storage disorder, similar to Wilson's disease, has been described in Bedlington Terriers, West Highland White Terriers, Skye Terriers, Dalmatians, Doberman Pinschers, and Labrador Retrievers (Dirksen et al., 2017; Fieten et al., 2014; Fuentealba Aburto, 2003; Twedt et al., 1979). Despite this, cataracts have not been described in those animals, probably because, unlike the disease in humans, serum copper levels are generally normal, or only transiently elevated during hemolytic crises, and also perhaps owing to the relatively short life span of severely affected dogs. Interestingly, aqueous humor copper concentration has been shown to be increased in humans with glaucoma (Akyol et al., 1990). Its role in secondary cataract development remains unclear.

Cataracts Associated with Metabolic Systemic Diseases

Inborn Metabolic Diseases

A single case report of bilateral cataracts, keratitis, and small globes (possible microphthalmia) associated with congenital tyrosinemia in a German Shepherd is reported (Kunkle et al., 1984). In humans, cataracts have been described in inherited forms of tyrosinemia, in association with skin and surface ocular disease, presumably from an inflammatory response to tyrosine crystal deposits in tissues (Hunziker, 1980). The pathogenesis of the associated cataract is unknown.

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Ehlers–Danlos syndrome, a congenital inherited connective tissue disease, has been associated with bilateral cataract and lens luxation in a dog (Barnett & Cottrell, 1987). Similarly to humans, cataract is a rare presentation of this syndrome in dogs, and the pathogenic mechanism is unknown.

Congenital lysosomal storage diseases have been rarely associated with cataracts in humans and dogs (Chen et al., 2014). Only two, Niemann-Pick and Fabry diseases, have been associated with cataracts in humans (Chen et al., 2014). Although no descriptions of lens opacities have been reported in dogs with these two diseases, it is likely that cataracts may occur, because the enzyme deficiency is similar (Bundza et al., 1979; Chen et al., 2014).

Diabetes Mellitus

Diabetes mellitus is the most common cause of metabolic cataracts in the dog, and the second in numbers presented for cataract surgery (Basher et al., 1995; Beam et al., 1999). Cataracts are one of the most prevalent and important complications of the disease. A study evaluating incidence and estimated median time to cataract formation in 200 dogs found that half of the population had developed cataracts by the 170th day after diagnosis of diabetes mellitus, whereas 75% and 80% of the population developed cataracts by 370 days and 470 days, respectively (Beam et al., 1999).

The disease is commonly associated with rapidly developing, bilaterally symmetric complete cataract formation in dogs, from well-characterized alterations in lens metabolic pathways. In normoglycemic dogs, glucose is primarily phosphorylated to glucose-6-phosphate by hexokinase to enter the glycolytic and pentose phosphate pathways. With hyperglycemia, high glucose-6-phosphate levels inhibit hexokinase activity to prevent excess production of lactate. In addition, activity of the enzyme aldose reductase (AR) is increased, causing shunting toward an alternate energy metabolism, the sorbitol pathway (Chylack & Cheng, 1978). By utilizing nicotinamide-adenine dinucleotide phosphate (NADPH), AR reduces the aldehyde form of glucose to sorbitol, which is further oxidized to fructose by NAD-dependent sorbitol dehydrogenase. Accumulation of sorbitol (a polyol or sugar alcohol) results, which does not readily diffuse across the lens capsule. Water from the aqueous humor is imbibed into the lens because of osmotic forces, causing lens architectural changes, including fiber swelling and rupture, vacuole formation, and clinically evident cataract. Additionally, a series of biochemical changes occur, resulting in altered electrolyte concentrations, reduced ATP levels, amino acids, glutathione, myo-inositol and adenosine triphosphatase activity (Basher & Roberts, 1995; Sato et al., 1991; Wyman et al., 1988). The biochemical alterations provide some speculation that besides simple osmotic forces, other pathogenic mechanisms, such as a change in cell membrane permeability and oxidative forces may also contribute to diabetic cataract formation (Basher & Roberts, 1995). Evaluation of advanced glycation end-products in diabetic and inherited canine cataracts has revealed an increase in cell-cycle regulatory protein p21 and PCNA (proliferating cell nuclear antigen), suggesting cell cycle and proliferation dysregulation in diabetic cataracts but no increases in non-enzymatic glycosylation of lens crystallins (Bras et al., 2007). Recently, researchers have reported an increased expression of transforming growth factor beta 1 (TGF-β1) in serum and inconsistent expression of its receptors in the lens capsule of diabetic dogs with cataracts (Neumann et al., 2017). Although publications in human medicine have assumed a role of TGF-β1 in the pathogenesis of cataracts (de Iongh et al., 2001; Lovicu et al., 2002), its role in canine diabetic cataract has not been yet elucidated.

The prevalence of diabetic cataract formation is related to the level of hyperglycemia, lenticular AR activity, and sorbitol concentration (Chylack & Khu, 2000; Kubo et al., 2001; Lee et al., 1995; Lee & Chung, 1999). The dog is highly susceptible to diabetic cataract, and it has been assumed this may relate to the difficulty in controlling diabetes in this species and resulting chronic hyperglycemia. However, one study failed to identify a relationship between the development of cataract and the corresponding level of hyperglycemia in diabetic dogs (Salgado et al., 2000). Additionally, some diabetic dogs with a good therapeutic response to insulin and clinically acceptable blood glucose levels, still develop cataract (Richter et al., 2002). Species differences in susceptibility to diabetic cataract appear to more closely correlate with level of lenticular AR activity, rather than with the amount of AR. AR activity in canine lens is similar to humans (0.39 nm/min/mg lens protein), 3× lower than rat lenses (a species highly susceptible to sugar cataract), and much higher than the mouse lens (a species highly resistant to sugar cataract) which has almost undetectable levels (Sato et al., 1991). In another study, AR activity was found to be significantly higher in dog lens compared with lenses from cats older than 7 years of age (a species with a low incidence of diabetic cataract) (Richter et al., 2002).

Typical early clinical findings in diabetic cataracts include equatorial vacuoles (Fig. 22.21A) that progress rapidly (few weeks to months) to a mature intumescent cataract with broad and clearly visible suture lines ("water-cleft" formation) (Fig. 22.21B, C). The early presentation of cataracts is rarely reported in naturally occurring diabetes mellitus, probably owing to the rapid onset and progression of cataract or to the fact that equatorial vacuole changes may sometime dissipate after insulin therapy. Unfortunately, substantial cataractous changes with canine diabetes are not reversible with control of hyperglycemia. Canine diabetic cataracts are often so rapidly progressive and osmotically active that intumescence of the lens and phacolytic uveitis commonly ensues. Spontaneous lens capsule rupture, usually equatorial, and subsequent varying degrees of

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Figure 22.21 **A.** Typical appearance of a mature diabetic cataract. Notice the intumescent appearance, the separation of the fibers, and formation of a cleft along the anterior Y-suture. **B.** Incipient, equatorial cataracts in a dog with diabetes mellitus. **C.** Note lens vacuoles at the equator area characteristic of early cataractous changes.

phacoclastic uveitis have also been identified in dogs with diabetic cataract (Wilkie et al., 2006). Phacomorphic glaucoma is one of the possible clinical scenarios, induced by the large intumescent lens and the shallow anterior chamber.

Galactosemia

A similar mechanism of cataractogenesis can be found in experimental animals fed high levels of galactose. The clinical appearance and progression of these experimentally induced sugar cataracts is very similar to the diabetic-associated cataracts. Compared with glucose to sorbitol conversion, galactose is metabolized to galactitol more readily, and is not further reduced by sorbitol dehydrogenase. Thus, galactosemic dogs develop more rapidly progressive cataracts, generally within 3 months of onset of galactose feeding, which are characterized initially by Y-suture accentuation, followed shortly by equatorial vacuole formation. The opacification will progress to spoke-like cataracts in the anterior and posterior cortex and further accentuation of anterior and posterior Y-sutures. Then, punctate cortical cataract formation, progressing to complete cortical cataracts, follows. Interestingly, the cataract formation often decreases after 12 months of galactose feeding, causing new, superficial lens cortical fibers to appear clear. Light microscopic evaluation of canine lenses revealed the osmotic nature of sugar cataracts, with swollen, ruptured lens fibers, and vacuoles present near the lens bow (Sato et al., 1991; Wyman et al., 1988). The nature of galactosemic cataracts in dogs is also age dependent (owing to a decrease in AR activity with age), with young dogs more rapidly developing cataracts that also involve the lens nucleus, whereas in dogs older than 24 months, cataract development occurs less readily and is confined to the cortices (Lackner et al., 1997).

Other Metabolic Diseases

Liver dysfunction has been suggested as a risk factor for cataract formation in humans (Donnelly et al., 1995), but so far, no cases of cataract secondary to liver failure have been

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reported in dogs. Accidental ingestion of an overdose of xylitol-containing chewing gum (estimated dose 0.7 g/kg) has been associated with acute hepatotoxicity and bilateral cataracts in a dog (unpublished data).

Cataracts Associated with Infectious Diseases

Infectious diseases are rarely reported to directly induce cataract formation in the dog, with most cases secondary to anterior uveitis. *Encephalitozoon cuniculi,* a protozoan parasite of rabbits, has been described as cataractogenic in rabbits, cats, and dogs (Benz et al., 2011; Hartcourt-Brown, 2004; Nell et al., 2015). The description in dogs reports three mongrel dogs from Hungary and Serbia with focal uni/bilateral anterior cataracts. Affected dogs showed positive serum antibody titers against *E. cuniculi,* and the two that underwent cataract removal, positive PCR of the lens material (Nell et al., 2015). In addition, *Aspergillus spp*. panophthalmitis with intralenticular invasion and cataract has been reported in two dogs (Wooff et al., 2016).

Cataracts Associated with Dietary Deficiencies

Nutritional cataracts, resulting from a neonatal deficiency of certain vitamins and essentials amino acids or an excess of particular sugars, have been observed in different animal species, with the specific amino acid implicated varying from species to species. It has been postulated that a deficiency of the essential amino acids arginine and phenylalanine produces cataracts in dog, cat, and wolf puppies raised on commercial, as well as experimentally produced, milk replacers (Glaze & Blanchard, 1983; Martin & Chambreau, 1982; Remillard et al., 1993; Vainisi et al., 1981). Quantitative amino acid analysis of a commercial milk replacer showed an arginine content only half that found in milk of dams (Ranz et al., 2002). However, the pathogenesis of these opacities may be more complex than a single amino acid deficiency; other proposed mechanisms include deficiencies in tryptophan, phenylalanine and histidine, amino acid imbalance, and a relative protein or glucose deficiency induced by the diet (Martin & Chambreau, 1982; Remillard et al., 1993; Vainisi et al., 1981).

Early vacuolization of the equatorial fibers and Y-sutures and mild to moderate lens opacities located in the nuclear-cortical junction ring, were originally described in naturally occurring cases in puppies (Glaze & Blanchard, 1983) and timber wolves (Vainisi et al., 1981). Further description of the phenotypic appearance was performed in mongrel pups experimentally fed with milk replacements (Martin & Chambreau, 1982). In these puppies, lens opacities begin in the third week of life as a biomicroscopically visible brown colored lamellar zone that separates the anterior and posterior nuclear/cortical junctions and progresses to a dense white perinuclear opacity. Other less commonly described changes included: feathered appearance to the Y-sutures and a transient extra line of disjunction in the anterior and posterior cortex. The opacities were often mild and nonvision threatening, becoming less prominent or even resolving with age, although more advanced cataractous changes may persist into adulthood, necessitating surgical removal.

As the opacities appear to be most common and pronounced in pups totally deprived of dam's milk, or deprived during the first week of life, a suggested preventative effort, if practical, would be to attempt at least limited nursing of the pups during this time, supplemented with a high-quality milk replacement, as substantial variation in nutrition composition among milk replacers has been reported (Heinze et al., 2014). Moreover, some breeds may have a special need for certain amino acids that should be delivered (Backus et al., 2006). Therefore, the sooner puppies are started on equilibrated solid food, the sooner the lens can stabilize and improve.

Traumatic Cataracts

Physical injuries to the eye can be a serious threat, potentially causing devastating damage to the lens and, consequently, to the eye. Traumatic lens injuries can be classified into blunt trauma, sharp penetrating trauma, or intraocular foreign body penetration.

Blunt Trauma-Induced Cataract

Mild blunt injury to the globe rarely causes injury to the lens. Conversely, moderate force blunt injury may result in cataracts and posterior displacement of the iris, causing pigment imprinting on the anterior lens capsule in a fashion ring, commonly known as "Vossius ring" (Gipner, 1929). Blunt trauma-induced cataracts result from the coup and contrecoup ocular compressive forces (Wolter, 1963), causing damage to the lens epithelia, and rupture and disruption of spacing of lens fiber membranes in the underlying cortex. Variable degrees of subcapsular cataract formation, generally adjacent to the site of injury in the anterior superficial cortex, may ensue. Traumatic cataracts may sometimes initially manifest along the anterior and posterior lens sutures, producing a stellate shape.

The proposed pathogenesis of these Y-suture changes includes distortion and irregular alignment of the intercellular spaces, cellular fragmentation, or a combination of these two effects. With increasing time from the injury, a focal traumatic cataract may be displaced to deeper layers of the lens, as new lens fibers are formed. As fairly pronounced blunt trauma is necessary to induce cataracts, other signs of ocular injury are often concurrently present, such as hyphema. Cataract location, unilateral nature, and other concurrent ocular findings suggestive of blunt trauma help distinguish them from HC. In very severe cases of blunt ocular trauma, coup-contrecoup forces may induce grave ocular

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lesions such as globe rupture, diffuse intraocular hemorrhage, retinal detachment, lens luxation and lens capsule rupture. Rupture of the lens capsule from blunt trauma, in the absence of profound globe injury or rupture of the entire globe, is rare in dogs, but can occur (Gelatt, 1974).

Sharp Trauma-Induced Cataract

Traumatic anterior lens capsule disruption can be found most commonly in young animals from cat claw wounds (Braus et al., 2017; Denis, 2002; Spiess et al., 1996), although a variety of other sources of penetrating injury are possible. Penetrating ocular injury that perforates the anterior lens capsule would be expected to invariably cause focal to diffuse cataract formation, whose size and severity depend mainly on three factors. The first one is the size of the capsular rent: lacerations less than 1.5 mm long are associated with small focal nonprogressive cataract, whereas larger rents often cause progressive opacification of the lens and, in the dog, may be associated with severe phacoclastic uveitis, which results in vision-threatening sequelae (Davidson et al., 1991a). Conversely, there are some descriptions of larger rents that sealed spontaneously without clinically relevant consequences (Paulsen Kass, 2012). The extrusion of cortical material is the second factor to be consider when evaluating a sharp injury to the lens. If the perforation of the lens capsule is small, and no extrusion of cortical content is present, the lens can heal spontaneously by fibrous metaplasia of lens epithelia assisted by exudate from the uveal tract, leaving only a focal residual cataract (Buschmann et al., 1987). Dogs and rabbits appear to more readily seal small rents in the lens capsule when compared with humans owing to a fibrinous anterior uveitis (Buschmann et al., 1987). The likelihood and degree of progression of capsular and subcapsular cataracts from a penetrating injury sometimes is difficult to predict both in humans (Buschmann et al., 1987) and dogs (Paulsen & Kass, 2012). The third factor to consider is the potential septic implantation syndrome that may induce a slowly progressive or delayed-onset endophthalmitis (Bell et al., 2013). Intralenticular bacterial infection may exacerbate the injury, inducing a fibrinosuppurative inflammation centered on and extending into the lens, inducing, in some cases, a lenticular abscess. This finding, undoubtfully, increases the likelihood of progression and complicating uveitis (Bell et al., 2013).

Critical biomicroscopic evaluation after pharmacologic mydriasis is often necessary to detect and measure disruption of the lens capsule, which should be suspected when evidence of penetrating corneal or scleral injury is present concurrent with a focal fibrinous exudate on the lens capsule, with or without visible cataract formation. In cases where the anterior segment inflammation precludes the capsule examination, ocular B-mode ultrasound should be performed to evaluate the capsular integrity.

In 1991, Davidson and co-workers postulated the well-known *"gold standard"* approach to prevent globe-threatening complications in dogs affected by traumatic lens laceration (Davidson et al., 1991a). Lens capsule tears with only minor underlying damage to the cortex were recommended to be treated medically and carefully monitored for progression of cataract and phacoclastic uveitis. Conversely, in cases of capsule tears larger than 1.5 mm, and/or if substantial cortical cataract was present, lens removal was strongly recommended. More recently, this approach has been questioned by a study comparing the outcome of patients with corneal and lens laceration treated medically versus those treated surgically. In that study, all medically treated patients (15/15) were visual 6–12 months after the injury, compared with only 75% (3/4) patients being visual at the same time period after surgical removal of the lens. The authors therefore concluded that medical management was an appropriate therapy for patients of all ages and that patients managed by lens removal suffered vision-threatening complications approximately 3–4.5 times more frequently than patients treated by medical management (Paulsen & Kass, 2012). Unfortunately, there was no information regarding the size of the capsule laceration in either of the groups studied. As the conclusion drawn by Paulsen and Kass appeared to contradict the generalized impression that an excellent postoperative outcome is achievable after surgical management of lens laceration, a third study evaluated the results of phacoemulsification in sharp trauma-induced cataracts. This study yielded that phacoemulsification has a very good outcome in cases of traumatic capsular rupture and postulated that vision loss might develop more often because of complications associated with the initial corneal wound (Braus et al., 2017).

Foreign Body-Induced Cataract

Lens penetration with a metallic foreign body would be expected to result in at least a focal cataract, and more commonly, diffuse opacification from substantial disruption of fiber cells and lens metabolism. The effect of intraocular metallic foreign bodies not penetrating the lens but within the eye is dependent on inertness, position, composition, and size of the foreign body (Eagle & Spencer, 1995; Sansom & Labruyère, 2012). Most shot pellets are composed of lead, which are usually sterile because of high-velocity entry, and are surprisingly well tolerated by the globe, as they are usually covered with an insoluble carbonate which prevents diffusion of chemical reactivity (Schmidt et al., 1975). Lead shot retained within the globe, but which did not perforate the lens capsule, might not be expected to *de facto* cause cataract. Gold, silver, glass, and rubber are also relatively inert within the eye. Conversely, copper, zinc, iron, and brass foreign bodies have moderate oxidizing potential and often cause panophthalmitis. Iron and steel are most damaging,

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causing severe inflammatory reaction and secondary cataract (*siderosis lentis*) (Carter & Blevins, 1970). Intralenticular iron foreign bodies cause siderotic deposition, resulting in slowly progressive, focal red-brown or rusty-appearing lens opacities. Iron deposited outside the lens but within the eye may result in *siderosis bulbi*, with secondary lens epithelial degeneration and necrosis, and lens cortical degeneration (Eagle & Spencer, 1995).

In contrast to humans, in which foreign bodies are most commonly the result of industrial accidents involving metallic materials (Peate, 2007), plant material is the most frequently reported foreign body in dogs (Tetas, et al., 2016), followed by porcupine quills (Grahn et al., 1995). If affecting the lens, organic foreign bodies should be removed as soon as possible to avoid a severe diffuse pyogranulomatous intraocular inflammation. In the authors' experience many affected eyes are unfortunately diagnosed in advanced stages and enucleation/exenteration are often the most appropriate approach.

Medical Treatment of Cataracts

Despite the current availability of some therapeutic agents that claim to prevent or delay cataracts in different species, the only effective current treatment, once cataract has been diagnosed, is the surgical removal of the lens by phacoemulsification and intraocular lens implantation. In fact, medical therapy may actually decrease the chance for vision return by allowing the untreated lens-induced uveitis to cause further damage. In the early stages of cataract, especially if vision is not impaired, the use of mydriatics may allow the animal to see around the opacities, providing functional vision.

Drugs reported to delay or prevent cataracts can be grossly classified as those dedicated to avoid, reduce, or solve the consequences of lens proteins and lipids oxidation and those that focus on reducing the formation of sorbitol, and thus avoiding/delaying the formation of diabetic cataracts. The evaluation of the effectiveness of these drugs has been mainly performed in rodents, humans, and dogs. Unfortunately, from a clinical point of view, the rodent models are flawed by the relatively nonphysiologic nature of many of the cataract models and the unrealistically high levels of antioxidant supplementation. On the other hand, human and canine epidemiologic studies are complicated by the fact that, although close evaluation of cataract formation is possible, strict control on other external factors influencing the incidence of cataracts is impossible. In addition, clinical trials do not use accurate methods to quantitate lens opacity, and the onset of cataract maturity is unpredictable. The above-mentioned may be the main reasons why studies of cataract incidence in humans and dogs using antioxidant dietary supplements have had varied results depending on study design, although laboratory-based studies can give some relatively clear results.

Dietary Antioxidants

Several factors are postulated to be of importance in the generation of lens opacities, each having its etiopathogenic mechanism. Nevertheless, the final common pathway by which these different factors exert their influence is predominantly through oxidation of lens proteins and perioxidation of lipids (Williams, 2006). Thus, for many years the association between intake and cataract formation has been investigated in humans (Mares-Perlman et al., 2000; Taylor et al., 2002), but surprisingly, such investigations in dogs are scarce. In analyzing nutrients, human research has focused on antioxidants such as vegetable-derived nutrients and plant extracts, Nrf2 inducers, vitamins (C, E, B3 and B12), and carotenoids.

Vegetable-derived nutrients and plant extracts have been extensively studied as a source of antioxidants in humans and mice. Specifically, the beneficial effects of grape-derived phytochemicals on ocular structures have been widely studied in humans (Natarajan et al., 2017). In dogs, an *in vitro* study evaluating the effects of grape polyphenols in LEC documented inhibition of key components associated with cataractogenesis, reactive oxygen species production, and stress-induced cell signaling, suggesting grape polyphenols may warrant investigation for a therapeutic use for cataracts (Barden et al., 2008). Although when published, authors stated that *in vivo* studies were currently in progress, no reports on its clinical use have been reported to date. Diosmin, a plant-derived flavonoid, showed ameliorative effects on oxidative stress markers during diabetes in streptozotocin-induced type 1 diabetic rats (Wojnar et al., 2017). The authors of the study considered the drug as a promising compound in prevention and delaying cataract formation during diabetes. Unfortunately, no clinical studies objectively evaluating cataracts support this hypothesis to date. Curcumin has been shown to attenuated selenite-induced cataract through the reduction of the intracellular production of reactive oxygen species and the protection of cells from oxidative damage in rats (Cao et al., 2018).

Nrf2/Keap1/ARE (nuclear factor [erythroid-derived 2]-like 2/Kelch-like erythroid-cell-derived protein with CNC homology-associated protein 1/antioxidant response element) signaling system is one of the major cellular defense mechanisms against oxidative stress. Hence, the stimulation of this signaling pathway may prevent cataract formation. Nrf2 inducers such as tomatidine (abundant in tomatoes), rapamycin, hyperoside, morin, N-acetylcarnosine, DL-3-n-butylphthalide (NBP), sulforaphane (SFN), or *Rosa laevigata* Michx have been suggested as promising therapeutic targets

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for the design and synthesis of new agents for cataract treatment (Liu et al., 2017). Perhaps, the most studied Nrf2 inducer so far is N-acetylcarnosine (the prodrug of L-carnosine), being reported as an effective antioxidant in the management of ARCs reversal and prevention in human (Babizhayev, 2009; Babizhayev et al., 2004, 2009a, 2009b) and canine eyes (Babizhayev et al., 2004; Babizhayev & Yegorov, 2014; Williams & Munday, 2006). New formulated topical N-acetylcarnosine, with higher availability, has demonstrated improvement in vision in humans with senile cataracts (Babizhayev et al., 2009a, 2009b). In dogs, a non-placebo, controlled, unmasked study, administrating topical 2% N-acetylcarnosine three times a day for 8 weeks, resulted in a marginal but statistically significant reduction in lens opacification (as assessed by retroillumination photography) in mature cataract and nuclear sclerosis (Williams & Munday, 2006). The commercial drug used in William's study was combined with AR inhibitors and other antioxidants, such as glutathione, cysteine ascorbate, riboflavin, and taurine, which makes the objective evaluation of the results challenging. Although the drug has reached clinical trial in humans and seems to partially reverse and prevent cataract formation and progression in dogs (Babizhayev & Yegorov, 2014; Williams & Munday, 2006), further studies are needed before a clinically relevant therapeutic effect can be documented.

Reduced plasma and aqueous humor levels of Vitamin C, Vitamin E, carotenoids and glutathione have been shown in English Cocker Spaniels with senile cataracts (Barros et al., 1999), indicating a decrease in the antioxidant capacity of the aqueous humor as a possible cause of cataracts. Nevertheless, the role of vitamin C in cataractogenesis was put into question when the same research group found no differences in mean plasma or aqueous humor ascorbic acid concentration between cataractous poodles and noncataractous poodles (Barros et al., 2004). Lutein and zeaxanthin are the two carotenoids that have been most studied for cataract prevention (Christen et al., 2008; Maci & Santos, 2015). Although the ingestion of this xanthophyllic compound may help slow the aging process in the eye and protect against cataracts, there is not enough evidence to suggest that taking supplements containing these carotenoids lowers the risk for cataract formation. Glutathione is an essential antioxidant vital for maintenance of the tissue's transparency (Giblin, 2000). In humans, no benefits were described when applied topically in a 2% formulation, four times a day per 1-month period (Sharma et al., 1989).

Aldose Reductase Inhibitors

Sugar cataractogenesis is a complex process involving hyperglycemia/hyper-galactosemia and oxidative stress, which can be theoretically treated with both AR inhibitors and antioxidants, providing the former with the strongest evidence of potential efficacy as an anticataract agent. Aldose reductase inhibitors (ARIs) have been advocated for treating both diabetic and galactosemic cataracts (Kador et al., 2006, 2010; Lou et al., 1989; Sato et al., 1998; Takemoto et al., 2004). When first described in dogs, oral ARIs were shown to prevent galactose-induced cataracts in a dose-dependent manner, but unfortunately seemed not able to reverse cataracts past a critical point in their development (Sato et al., 1998; Takemoto et al., 2004). Historically, it was suggested that opacities resulting from lens fiber degeneration were irreversible and that only those opacities resulting from early vacuolation could be reversed. However, a more recent study using topical ARI formulation showed, for the first time, a reduction in opacities secondary to lens fiber degeneration (Kador et al., 2006) yielding that ARIs can be used not only to prevent, but also to reduce galactosemic cataracts in the dog. In addition, topical 2-methyl sorbinil (Kinostat®Therapeutic Vision, Inc., Elkhorn, NE, USA) applied three times a day over 1 year has shown to ameliorate the onset and progression of cataracts in dogs with naturally occurring diabetes mellitus (Kador et al., 2010). This topical ARI formulation will be commercially available in the near future and it is further being studied for its use to control diabetic keratopathies and retinopathies in both humans and dogs (Kador et al., 2016). Six years after its first description in dogs, a modified topical formulation with the same ARI, but in an improved gel-like emulsion carrier, showed the same results but with an improved bioavailability (Hao et al., 2016). Another prospective placebo-controlled double-masked study was done in diabetic dogs with oral alpha lipoic acid in a commercially available formulation including many different antioxidants (OcuGlo™, Animal Necessity, Key Largo, FL, USA). The formulation seemed to delay the onset of cataracts in this small series of diabetic dogs (Williams, 2017; Williams, et al., 2015). The percentage of the effects specifically caused by the alpha lipoic acid could not be elucidated, as the product was given in conjunction with antioxidants. In all cases, positive effects were directly related with the continuous administration of the drug.

Although no adverse effects resulting from long-term oral administration of ARIs have been published, it has been suggested that some ARIs may modify select hepatic enzymes associated with oxidative defense (Thomas et al., 2000). In contrast, this has not been observed with topical administration. Thus, topical administration may be preferred, particularly because hepatic junction may already be compromised in diabetic dogs.

Other Treatments

Despite that the majority of research has been focused on treatment of acquired cataracts, congenital cataracts have

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been also a target of study in humans. Mutation in the lanosterol synthase gene has been recently described to be responsible for causing congenital cataracts in children (Zhao et al., 2015). Lower levels of lanosterol have been directly associated with cataractogenesis in humans and dogs (Zhao et al., 2015). Although the first preliminary reports on the clinical treatment of congenital cataracts with lower lanosterol concentrations in humans were discouraging (Felici et al., 2018), treatment with lanosterol has been shown to reduce the severity of cataracts in dogs (Zhao et al., 2015). The results obtained after treating canine eyes over 6 weeks were very promising, reducing cataract severity, increasing lens clarity, and improving vision. Based on these results, higher concentration lanosterol drops may be tested in congenital cataracts in human.

Visual Consequences of Cataracts

There are no reports establishing the consequences of cataracts on vision in dogs. Visual deficits vary greatly depending on the severity and location of the cataract. Often, clinically apparent changes in behavior associated with diminished vision go unnoticed until the cataract is 40%–50% complete, and usually not unless both lenses are affected. Axial cataract would be expected to be associated with earlier and more profound visual deficits. Interestingly, those dogs are reported to have more visual difficulties in daylight vs. dim lighting (perhaps from a larger pupillary diameter in dim light). In addition, the same cataract may induce different demonstrable visual deficits among individuals, probably caused by factors such as the level and type of activity of the dogs, their acuity of other special senses, the owner's involvement in training the dog, etc.

Humans with cataracts may experience visual aberrations including a myopic shift (from hardening of the lens nucleus), diplopia, lenticular astigmatism, a shift in contrast sensitivity, glare, a color shift with absorption of the blue end of the spectrum, reduced light transmission, field loss, and visual acuity reduction (Beeve, 2011; Hurst, 1993). Symptoms such as field loss, glare, astigmatism, and visual acuity reduction may be also relevant in dogs with cataracts (Miller & Murphy, 1995). Motion detection, as in a response to a menacing gesture during an ophthalmologic examination, is often retained until the cataract is near complete. Complete, dense cataracts are associated with total loss of visual discrimination and motion detection but are not necessarily expected to cause total loss of the ability to discriminate photopic from scotopic lighting conditions, being associated with positive dazzle and pupillary light reflexes.

The consequences of advanced lenticular or nuclear sclerosis in dogs are also poorly defined. Generally, sclerotic changes seemingly do not interfere with functional vision in dogs, although similar changes in the human lens cause positive spherical aberration, defocus, glare, distortion, diplopia, a myopic shift, and a change in color spectrum (Beeve, 2011; Glasser, 2011; Hurst, 1993). A myopic shift has been reported in older-aged dogs (Murphy et al., 1992), presumably from a change in refractive status of the sclerotic lens' nucleus, as it has been described for humans with presbyopia (Glasser, 2011). It is possible that other alterations, as color perception, also occur in the aged dog; however, the ability to detect these subtle visual disturbances, especially in the less active older-aged dog, is limited.

Complications of Untreated Cataracts in Dogs

When cataract surgery is not performed, many canine cataracts will progress, and often result in intraocular problems such as lens-induced uveitis, glaucoma, lens luxation/subluxation, vitreal degeneration, and retinal detachment (Davidson et al., 1991b; van der Woerdt, 2000; van der Woerdt et al., 1993). Spontaneous resorption of cataractous lens material occurs most frequently in dogs less than 6 years of age. In those animals, cataract reabsorption may lead, in some cases, to improved vision, although the animal is rendered permanently hyperopic. The magnitude and duration of cataract resorption is highly variable in the dog, hypermature cataracts being a chronic finding in some of cases. The lifelong complication rate of untreated cataracts in dogs has not been studied, and therefore definitive statements cannot be made; however, one study of 77 cataractous dog eyes comparing the outcome of surgically treated, topically treated, and nontreated eyes, yielded that those receiving topical anti-inflammatory therapy had greater success than those with no treatment at all (Lim et al., 2011).

Lens-Induced Uveitis

Lens-induced uveitis is an inflammatory response of the uvea to lens proteins. Lens material may induce uveitis by two different well-known mechanisms: leakage of soluble lens proteins through an intact capsule (phacolytic uveitis) or direct extrusion of lens content into the anterior chamber caused by capsule disruption (phacoclastic uveitis). Phacolytic uveitis is usually a chronic condition, characterized by a mild unspecific lymphocytic–plasmacytic uveitis (Wilcock & Peiffer, 1987) that may display scleral injection, mild to moderate ocular discomfort, mild aqueous flare, and, eventually, darkening of the iris. In addition, the pupil is usually slightly miotic and the intraocular pressure moderately reduced (van der Woerdt et al., 1992). The condition has been described to accompany both cataract formation and resorption being usually milder when accompanying

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cataract formation. In fact, fluorophotometric studies (Dziezyc et al., 1997), D-dimers detection (a fibrin degradation product) (Escanilla et al., 2013), and prostaglandin E_2 concentration (Renzo et al., 2014) in aqueous humor of dogs with cataracts of different degrees of maturation, suggest that a blood–aqueous barrier breakdown might be present in all the eyes with cataract, regardless of degree of maturity. However, more clinically relevant uveitis may be present when hypermature cataract develops (Van der Woerdt, 2000; van der Woerdt et al., 1992). In this situation, leakage of soluble lens proteins through the lens capsule may increase cell and protein content of the anterior chamber fluid, inducing a moderate phacolytic uveitis (Leasure et al., 2001).

It is worth noting that phacolytic uveitis may cause a reduction in electroretinogram parameters including a reduction in b-wave amplitudes and b/a wave ratio (Maehara et al., 2007). The condition should be diagnosed and treated accordingly in early stages, as its presence prior to cataract surgery significantly reduces the success rate of phacoemulsification (Van der Woerdt, 2000), and its chronicity often induces, like in humans, secondary glaucoma (Kanski & Bowling, 2011; Van der Woerdt et al., 1992).

Unfortunately, the common occurrence of phacolytic uveitis and hypermature cataracts in dogs may be a diagnostic challenge in distinguishing primary cataracts from those occurring secondary to inflammation. Clinical history, signalment, anatomic location, and the typical mild nature of phacolytic uveitis are useful distinguishing features (Van der Woerdt et al., 1992).

Phacoclastic uveitis tends to be more acute and severe than phacolytic uveitis. It has been associated with spontaneous capsule rupture (in both, diabetic and nondiabetic dogs) (Graham et al., 2016; Wilkie et al., 2006) and traumatic lens injuries (sharp or blunt) (Braus et al., 2017; Paulsen & Kass, 2012). An equatorial location for the spontaneous rupture has been reported, making clinical diagnosis even more challenging (Wilkie et al., 2006). Surprisingly, histopathologic studies on lens rupture fail to show the typical granulomatous perilenticular inflammation considered as the hallmark of lens-induced uveitis in humans (Van Der Woerdt, 2000; Wilcock & Peiffer, 1987). The prominent fibroplasia and lessened tendency for granulomatous, perilenticular inflammation are features suggested to be somewhat different from the human counterpart after lens capsule rupture, although the histologic differences may reflect duration between injury and microscopic evaluation.

Diagnosis of the condition may need the use of ultrasound in some cases, as the degree of intraocular inflammation may preclude lens visualization. A combination of medical and surgical treatment is often indicated if vision is to be maintained.

The pathogenesis of both phacolytic and phacoclastic uveitis currently remains speculative (see Chapter 21). Because phacolytic uveitis in humans is rare, it has received virtually no investigation that might suggest a common pathogenesis with the disease in dogs. Lens-induced inflammation is proposed to occur after deviation of the normal low level of T-cell-mediated tolerance to lens proteins (crystallins) and other lens components (Simpson et al., 1989; Van der Woerdt, 2000). With phacolytic uveitis, only soluble lens proteins are presented to the immune system, whereas with lens capsule rupture, intact lens fibers, including soluble and insoluble proteins, are presented. Additionally, class II major histocompatibility encoded restricted T cells and macrophages are able to react with lens cell membrane proteins, soluble lens antigen, and other intracellular proteins (Marak et al., 1978). The sustained release (with hypermature cataracts) or massive release (with lens capsule rupture) of altered lens proteins, may exceed the normal anterior chamber-associated immune deviation (ACAID) phenomena, and result in a cell-mediated or delayed type hypersensitivity reaction, normally suppressed from anterior chamber presented antigens. Changes in the composition of lens fibers caused by aging tend to induce a more severe and rapid lens-induced uveitis in young dogs (more soluble protein content) than in adult/geriatric ones (less soluble protein content). ACAID has been shown to be overwhelmed with excessive antigen load or sustained exposure of antigens (English, 1992). The T-cell response may lead to macrophage production of IL-1 and chemotaxis of neutrophils causing release of other lymphokines (Marak et al., 1978).

Interestingly, a study in dogs with and without cataract found a negative association between serum anti-lens crystallin, serum antibody titer, and presence and maturity of cataract (i.e., dogs with advancing stages of cataract had a lower prevalence of anti-lens crystallin antibody). The same study found a negative association between severity of uveitis and anti-lens crystallin antibody for immature and hypermature cataract. The authors speculated that changes in crystallin epitopes during cataract maturation, affinity maturation of anticrystallin antibodies, and the ACAID phenomena may explain this negative association (Denis et al., 2003). Conversely, a more recent study suggested that increased reactivity by βA1-crystallin antibodies in serum may be associated with cataract formation in the American Cocker Spaniel (Kanemaki et al., 2015). Regardless, these controversial findings illustrate the complex and poorly understood nature of lens-induced uveitis.

Nuclear Sclerosis

The lens continues to grow throughout life, with progressive lens fiber formation and internal compression of older fibers, especially in the lens nucleus. Dehydration and condensation of old nuclear fibers induces light scattering and thus reduces transparency (Fig. 22.22). These changes are known

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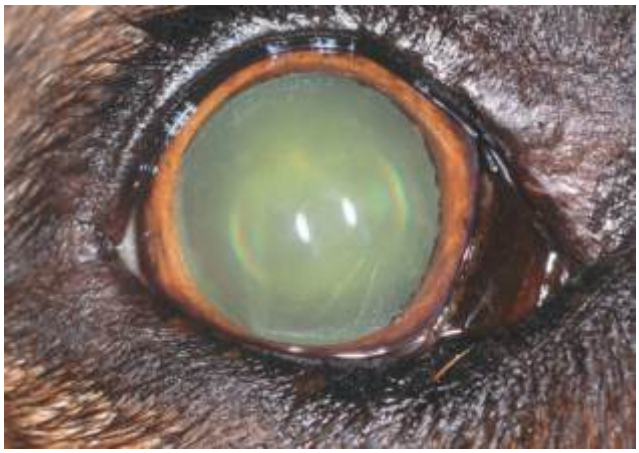


Figure 22.22 Lens sclerosis in a 10-year-old mixed dog, seen with diffuse illumination. Note the scattering of light induced by nuclear fibers.

as nuclear or lenticular sclerosis and are a consistent finding in dogs older than 7 years of age, although transmission of wavelengths in the UV-B/UV-A and visible ranges starts to diminish from 4 to 6 years. Indeed, the prevalence of nuclear sclerosis has been reported as high as 50% in dogs aged 9.6 ± 2.6 years (Williams et al., 2004). Furthermore, changes in lens reflection and transparency may be used as a predictive tool for calculating the age in dogs and cats (Tobias et al., 1998).

Biomicroscopic characteristics of nuclear sclerosis are as follows. On diffuse illumination, a clinically apparent whitish-blue appearance will be seen because of the light scattering induced by changes in optical properties of the nuclear fibers. On retroillumination, a tapetal or fundic reflection is still visible, and the outline or zone of the lens nucleus may be apparent. Funduscopic examination is still possible through the affected lens, although with advanced sclerosis, fine ophthalmoscopic detail is variably obscured. With mydriasis, the lens cortex will be clear. In dogs, nuclear sclerosis may be classified into four grades, the denser one often being indistinguishable from senile cataract, a pathologic condition, not considered as a normal aging process (Tobias et al., 2000).

Lens Luxation

The lens is surrounded by three anatomic landmarks. Anteriorly, by the posterior surface of the iris, posteriorly, by the vitreous that has rather firm hyaloid-capsular attachments, and equatorially, by the zonules, which are elastic filamentous structures that extend from both the anterior and posterior equatorial capsule, to blend with the internal limiting membrane of the ciliary body epithelium. Dislocation of the lens from its normal position within the patellar fossa is referred to as subluxation (partial dislocation) or luxation (total dislocation) and is related to a pathologic alteration in the ciliary zonules from abnormal development, degeneration, rupture, tearing, or a combination of these factors. Subluxation is the early stage in the process of luxation, in which there is partial breakdown or degeneration of the zonules, with the result that the lens, although slightly mobile, remains in its grossly normal position. Similar to canine cataracts, lens luxation has been classified according to different schemes, most commonly based on its etiology (congenital, primary, and secondary), and the segment to which the lens has been displaced (anterior or posterior).

Primary Lens Luxation

Primary lens luxation (PLL) is not a disease of the lens itself, but rather an inherited deterioration of the lens suspensory apparatus, the zonule, which is a system of fibers that suspend the lens from the ciliary body, maintaining it within the visual axis and in contact with the anterior surface of the vitreous body (Curtis, 1983b). In dogs affected with PLL, ultrastructural abnormalities of the zonular fibers are already evident at 20 months of age (Curtis, 1983c). Lens luxation typically occurs when the dogs are 3–8 years old as a result of progressive degeneration and breakdown of the zonules (Curtis, 1983a; Curtis & Barnett, 1980; Curtis et al., 1983; Foster et al., 1986; Gwin et al., 1982; Lazarus et al., 1998; Willis et al., 1979).

Zonular fiber proteome, although recently described in humans and bovines, has not been studied in dogs. In humans, zonular fiber proteome is surprisingly complex, with microfibrils composed of more than 50 components. Glycoproteins constitute the main structural component, with two proteins, fibrillin-1 and latent TGFβ-binding protein 2 (LTBP2) constituting 70–80% of the proteome. The composition among different fibers seems to be uniform (de Maria et al., 2017). Different studies focusing on anatomic, microscopic, and ultrastructural features of PLL-affected dogs have been performed (Curtis, 1983c; Martin, 1978; Morris & Dubielzig, 2005). Martin was the first to describe abnormal and haphazard lens equatorial attachment of zonules in two dogs with presumed PLL (Martin, 1978). Some years later, Gwin and colleagues documented inflammatory cells associated with zonular fibers in dogs with lens luxation cases, speculating that a primary inflammatory process involving the lens zonules was causative (Gwin et al., 1982). However, this contention was immediately questioned (Curtis, 1983b) and the inflammatory response considered to be secondary. Scanning and transmission electron microscopy studies performed in four litters of Tibetan Terriers, yielded zonular abnormalities consisting of a

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bizarre arrangement of fibrillary material associated with the ciliary processes, affecting the fibers inserting posteriorly at the lens equator (Curtis, 1983c). Interestingly, no abnormalities were found in the lens zonules arising at the *pars plana*, zonular attachments to the lens, and the ultrastructural form, diameter, or periodicity of the individual zonules. The dorsolateral quadrant was the most commonly affected. Similar ultrastructural zonular abnormalities were also noted in other Terrier breeds. The author suggested an abnormality in the fibroblast-like cell of the zonular fibers as the pathogenic mechanism (Curtis, 1983a). Light-microscopy evaluation of zonular fiber morphology in 63 dogs with PLL depicted two clearly distinct forms of abnormal zonular fiber morphology: zonular fiber dysplasia (ZFD) and zonular fiber collagenization (ZFC) (Morris & Dubielzig, 2005). ZFD was shown as a thick, lamellar protein layer tightly adherent to the nonpigmented ciliary body, whereas ZFC presented less pronounced nonlamellar protein, were more filamentous in nature, and not tightly adherent to the ciliary body epithelium. Furthermore, staining profiles differed among forms, showing negative Verhoeff's elastin staining for ZFD affected eyes, and thus suggesting an underlying protein abnormality within the zonular fiber structure. Whereas ZFC characterization results were nonspecific for lens luxation, ZFD characterization was unique to PLL (Morris & Dubielzig, 2005), most likely presenting a risk factor for PLL in dogs with breed predisposition. In addition, the authors believe that the extra stress that already-deficient fibers endure in highly active (barking) dogs may be another contributing factor inducing a premature rupture.

Presentation and Clinical Signs of Primary Lens Luxation

PLL most commonly manifests as an acute emergency, although onset and clinical findings vary depending on the severity and location of the dislocated lens. Its presentation is mostly bilateral, although not necessarily simultaneous. Primary lens displacement is documented most commonly in 3–8-year-old dogs (Curtis & Barnett, 1980; Curtis et al., 1983; Foster et al., 1986; Gwin et al., 1982; Lazarus et al., 1998; Willis et al., 1979) with the mean age reported to be 4.5 years in terriers and terrier-crosses (Curtis et al., 1983; Sargan et al., 2007) and 4.9 years for the Shar Pei (Lazarus et al., 1998). However, some variation in the age of onset may exist.

In primary lens instability, an increased mobility of the lens, manifested as phacodonesis (lens trembling) or iridodonesis (iris trembling) can be seen as early clinical manifestations. A change or asymmetry in the depth of the anterior chamber may be also evident in early stages, as well as the margin of the lens visible if pharmacologic mydriasis is induced. An inherent reduction in zonular tension would explain the tendency for the lens of an affected eye to assume a slightly more globoid form than normal, therefore allowing the visualization of the lens periphery when in full dilation. When the lens is subluxated, the margin may be easily visible without full pharmacological dilation, showing an aphakic crescent (area of the pupil devoid of lens coverage). Because the dorsolateral quadrant seems to be the earliest affected (Curtis, 1983c), most lens dislocations occur in a ventral direction (because of gravity), inducing generally a dorsolateral aphakic crescent. Degenerative vitreal strands, which appear by biomicroscopy as fine wispy fibers with increased relucency, are often displaced or prolapsed into the anterior chamber and may be apparent with gonioscopy in the iridocorneal angle (Fig. 22.23). Subluxated lens are generally associated with signs of mild uveitis, presumably related to an abnormal physical contact of the lens jostling against the uveal tissue. In the majority of cases, the subluxation progresses to luxation into the anterior chamber (anterior luxation) that tends to show acute clinical signs (Fig. 22.24).

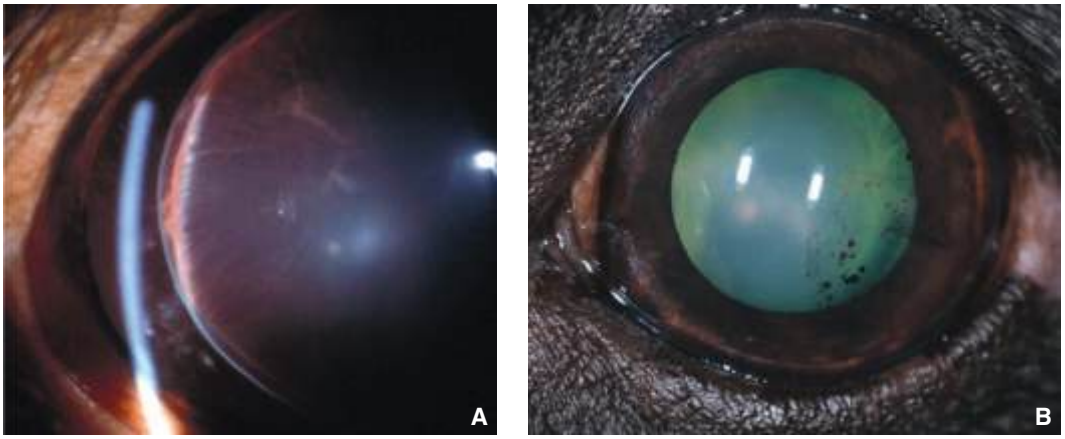


Figure 22.23 **A.** Lens subluxation viewed with optical section from left to right. The margin of the lens is visible as an aphakic crescent and early cortical cataract formation is present. Vitreal fibers that have displaced into the anterior chamber are observed as fine strands with increased relucency. **B.** Lens instability in an 8-year-old mixed breed dog. Note the presence of pigmented vitreous in the anterior chamber.

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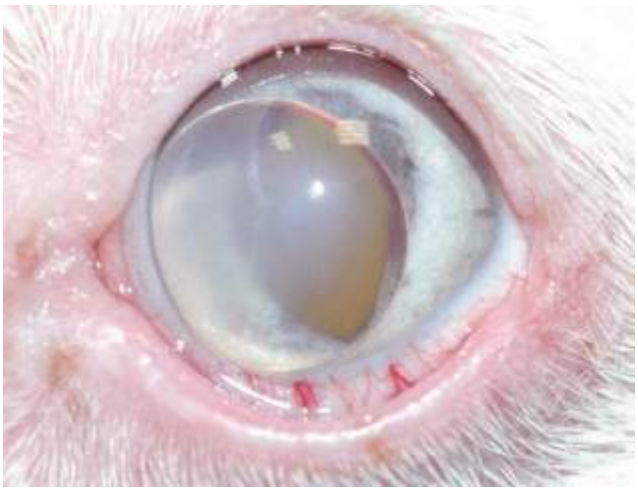


Figure 22.24 Primary anterior lens luxation in a 5-year-old dog, seen with diffuse illumination. Note the lens in the anterior chamber inducing corneal edema and discoria.

Individual subluxated lenses left without treatment have remained subluxated for up to 4 years (Curtis, 1990).

Pathophysiologic changes accompanying lens subluxation or anterior luxation often culminates in secondary glaucoma from several possible mechanisms. The first one is the occlusion of aqueous humor flow from the posterior chamber through the pupil because of the anterior shift in the lens and/or vitreal face, causing diversion of aqueous humor posterior to the lens or into the vitreous (pupillary block glaucoma). The second reported mechanism is associated with the substantial amounts of prolapsed vitreous that are often seen in the anterior chamber and iridocorneal angle that may theoretically cause mechanical obstruction to aqueous outflow. The last mechanism is the obstruction of the filtration angle caused by the presence of the lens in the anterior chamber (Curtis et al., 1983). In three retrospective studies on dogs with secondary glaucoma, lens luxation was the second most common cause, with incidences of 12% (779/9695), 15.2% (24/156), and 26.2% (49/217) (Gelatt & MacKay, 2004; Johnsen et al., 2006; Strom et al., 2011). Other secondary pathophysiologic changes seen in anterior luxated lens include transient or permanent corneal edema and mild anterior uveitis. The corneal edema, which is highly characteristic, has been associated with both intraocular hypertension and direct trauma of the lens to the cornea. Corneal edema is likely to remain even if the lens is subsequently removed surgically. In chronic anterior lens luxations, the cornea may become diffuse and irreversibly opaque and ultimately vascularized.

Posterior luxations are less frequently reported and show a more chronic onset than anterior PLL. These are commonly seen in old dogs with liquefied vitreous (syneresis). In syneresis-affected dogs, the absence of posterior physical restraint and the disruption of the anterior hyaloid face predispose posterior displacement of the lens. In those cases, lens luxations tend to occur ventrally toward the vitreous space, lying adjacent to or on the ventral retina and/or *pars plana* (Fig. 22.25). Complete posterior luxation is more innocuous than anterior luxation, and the complications of glaucoma, uveitis, or corneal edema are less prevalent. As syneresis is necessary for the lens to fully luxate posteriorly, mechanical obstruction glaucoma by vitreous strands is uncommon. Tractional retinal detachment may occur from changes in the vitreous or direct contact of the lens capsule with the retinal surface. It is worth remembering that it is common for a luxated lens to move freely between the posterior and anterior segments with change in head position and pupil size, and to undergo cataractous changes, which can progress to complete opacification with chronicity.

Breed Predisposition, Affected Genes, Genetic Tests, and Mode of Inheritance

PLL was first recognized as a canine familial disorder in 1909 by Gray, who later reported a predisposition for several terrier breeds (Gray, 1909, 1932). Since then, the number of canine breeds predisposed to this abnormality has increased significantly, nowadays being identified in nearly 50 different breeds, including terriers and nonterrier dogs (see Table 22.5).

ADAMTS17, one of the 29 known mammalian members of the ADAMTS family of gene encoding proteins, interacts with fibrillin-1 in some way to contribute to both the structural and regulatory roles of zonular microfibrils. In addition, other proteins of the same family, ADAMTS 4 and 10, have also been suggested to be involved with formation or maintenance of the zonule (Hubmacher & Apte, 2011). A mutation involving a nucleotide substitution in ADAMTS17 was initially associated with PLL in Miniature Bull Terriers, Lancashire Heelers, and Jack Russell Terriers (Farias et al., 2010). Subsequently, the mutation was identified in an additional 15 canine breeds, mostly terriers or breeds with terrier coancestry (Donner et al., 2016; Gould et al., 2011) (see Table 22.5). In addition, a recent study reported ADAMTS17 mutation inducing PLL and primary open angle glaucoma in Chinese Shar-pei dogs (Oliver et al., 2018). Mutations in ADAMTS17 in humans are associated with short stature and ocular anomalies, and the preponderance of PLL in terrier and other breeds with a miniature or short stature has led to speculation that selection for this body phenotype may have inadvertently led to selection of this mutation (Bellumori et al., 2013; Morales et al., 2009). In addition, PLL has been reported in Miniature Bull Terriers in association with pedal hyperkeratosis and abnormal foot and nail shape (Ghahramani et al., 2015). Considering that ADAMTS17 mutation has not been detected in all the tested breeds with inherited PLL, a genetically distinct form of PLL is suspected. A DNA-test for the detection of the mutation has been developed and is commercially available

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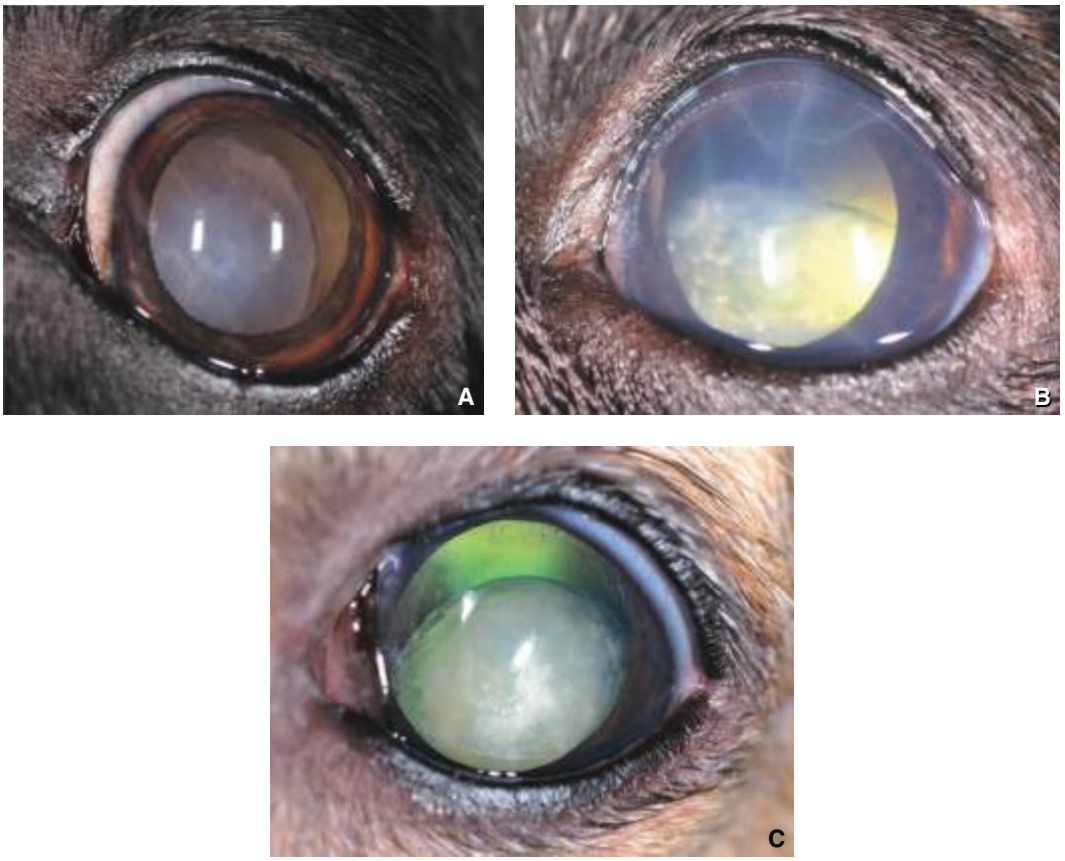


Figure 22.25 **A.** Age-related posterior lens luxation in an 11-year-old mixed breed dog. Note the aphakic crescent and the late immature cortical cataract. **B.** Posterior lens luxation associated with advanced primary glaucoma in a dog. Note the Haab's striae and the irregularly shaped aphakic crescent associated with hypermature cataract. **C.** Posterior lens subluxation associated with chronic cataract in a dog. Note the dorsal aphakic crescent and the zonular stretching.

(Oliver et al., 2018), allowing breeders to plan breeding strategies better.

Surprisingly, although PLL is suspected to be inherited in more than 50 canine breeds, its mode of inheritance has been suggested in very few, where it is considered as a simple autosomal recessive trait (see Table 22.5). The great majority of PLL-affected dogs are homozygous for the mutation, but a small minority are heterozygous (5%), leading to speculation that carriers, of some breeds at least (e.g., Miniature Bull Terrier), might be at increased risk of developing the condition compared with dogs that are homozygous for the wildtype allele (Gould et al., 2011). Some authors have suggested that PLL can be a polygenic disorder with a more complex inheritance pattern in breeds such as Jack Russell Terrier (Oberbauer et al., 2008) and Miniature Bull Terrier (Ghahramani et al., 2015).

Secondary Lens Luxation

Lens dislocation can appear secondary to damage to the suspensory apparatus of the lens, which can arise from senility, trauma, or be associated with ocular conditions such as chronic glaucoma, chronic uveitis, mature/hypermature cataract, or intraocular tumors (Pumphrey, 2015). When compared with PLL, secondary lens luxation does not usually have such an acute presentation and the direction of displacement is variable. In a retrospective study of 134 dogs with lens luxation, 36% dogs presented with secondary lens luxation. The most common causes for this condition were glaucoma (58%), cataract (19%), and trauma (17%) (Bestschart et al., 2014).

Age-Related Lens Luxation

Lens displacement, in the absence of other ocular disease, may also occur in older-aged dogs (>10 years of age), comprising various terrier and nonterrier breeds (see Fig. 22.25A). Senescent lens displacement in terrier breeds may represent a late-onset presentation of PLL. Older-aged dogs presumably develop lens displacement from undefined mechanisms that may reflect age-related degenerative process occurring in the zonules and/or anterior vitreous and vitreal base. Chronic exposure to ultraviolet light, even normal sunlight, induces expression of many types of matrix metalloproteinases (MMPs), including MMP-9. Though unproven, this

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Table 22.5 Canine breeds affected with primary lens luxation (PLL). Mode of inheritance and genetic test, when available, have been listed.

Canine breeds affected by PLL	Inheritance	Genetic tests available	References
American Eskimo Dog	Autosomal recessive	ADAMTS17	Farias et al., 2010; Gould et al., 2011
American Hairless Terrier	Not defined	No	ACVO Genetic Committee, 2015
Australian Cattle Dog	Autosomal recessive	ADAMTS17	Chaudieu & Chahory, 2013; Farias et al. 2010; Gould et al., 2011
Australian Terrier	Not defined	No	Chaudieu & Chahory, 2013
Border Collie	Autosomal recessive	No	Chaudieu & Chahory, 2013; Rubin, 1989
Brittany	Not defined	No	ACVO Genetic Committee, 2015
Brussels Griffon	Not defined	No	ACVO Genetic Committee, 2015
Bull Terrier (Miniature and Standard)	Autosomal recessive	ADAMTS17	Chaudieu & Chahory, 2013; Farias et al., 2010; Gould et al., 2011; Ghahramani, et al., 2015; Sargan et al., 2007
Cairn Terrier	Not defined	No	Chaudieu & Chahory, 2013
Cardigan Welsh Corgi	Not defined	No	Chaudieu & Chahory, 2013; Curtis, 1990
Chihuahua	Not defined	No	Chaudieu & Chahory, 2013; Rubin, 1989
Chinese Crested Dog	Autosomal recessive	ADAMTS17	Farias et al., 2010; Gould et al., 2011; Sargan et al., 2007
Chow Chow	Not defined	No	French national panel
Drentse Partridge Dog	Not defined	No	German national panel
English Pointer	Not defined	No	Chaudieu & Chahory, 2013
Brittany Spaniel	Not defined	No	Chaudieu & Chahory, 2013
French Spaniel	Not defined	No	Chaudieu & Chahory, 2013
Fox Terrier (Wire, Toy, and Smooth Haired)	Not defined	ADAMTS17	Curtis & Barnett, 1980; Gould et al., 2011
French Bulldog	Not defined	No	Chaudieu & Chahory, 2013
German Pinscher	Not defined	No	Chaudieu & Chahory, 2013
Grand Bleu de Gascogne	Not defined	No	Chaudieu & Chahory, 2013
Greyhound	Not defined	No	ACVO Genetics Committee, 2015
Grand and Petit Basset Griffon Vendéen	Not defined	No	Chaudieu & Chahory, 2013
Italian Greyhound	Not defined	No	ACVO Genetic Committee, 2015
Jack Russell Terrier	Autosomal recessive	ADAMTS17	Farias et al., 2010; Gould et al., 2011; Morris & Dubielzig, 2005; Oberbauer et al., 2008
Jagd Terrier	Autosomal recessive	ADAMTS17	Farias et al., 2010; Gould et al., 2011; Chaudieu & Chahory, 2013
Lakeland Terrier	Autosomal recessive	ADAMTS17	Chaudieu & Chahory, 2013; Farias et al., 2010; Gould et al., 2011; Rubin, 1989
Lancaster Heeler	Autosomal recessive	ADAMTS17	Farias et al., 2010; Gould et al., 2011; Sargan et al., 2007
Leonberger	Not defined	No	Chaudieu & Chahory, 2013
Manchester Terrier	Not defined	No	Chaudieu & Chahory, 2013; Curtis & Barnett, 1980; Curtis, 1990; Rubin, 1989
Norfolk Terrier	Not defined	ADAMTS17	Chaudieu & Chahory, 2013; Gould et al., 2011; Rubin, 1989

(Continued)

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Table 22.5 (Continued)

Canine breeds affected by PLL	Inheritance	Genetic tests available	References
Norwich Terrier	Not defined	ADAMTS17	Chaudieu & Chahory, 2013; Farias et al., 2010; Gould et al., 2011; Rubin, 1989
Parson Russell Terrier	Autosomal recessive	ADAMTS17	Gould et al., 2011
Patterdale Terrier	Not defined	ADAMTS17	Gould et al., 2011
Pekingese	Not defined	No	ACVO Genetics Committee, 2015; Rubin, 1989
Pyrenean Shepherd	Not defined	No	ACVO Genetics Committee, 2015
Rat Terrier	Not defined	ADAMTS17	Farias et al., 2010; Gould et al., 2011
Russell Terrier	Not defined	ADAMTS17	Gould et al., 2011
Scottish Terrier	Not defined	??	Chaudieu & Chahory, 2013; Rubin, 1989
Sealyham Terrier	Autosomal recessive	ADAMTS17	Curtis, 1990; Gould et al., 2011; Rubin, 1989
Shar Pei	Autosomal recessive	ADAMTS17	Lazarus et al., 1998; Oliver et al., 2018
Siberian Husky	Not defined	No	Rubin, 1989
Skye Terrier	Not defined	No	Curtis, 1990; Rubin, 1989
Tibetan Spaniel	Autosomal recessive	No	Chaudieu & Chahory, 2013; Rubin, 1989
Tibetan Terrier	Autosomal recessive	ADAMTS17	Curtis, 1983a; Curtis, 1990; Gould et al., 2011; Ketteritzsch et al., 2004; Sargan et al., 2007; Willis et al., 1979
Volpino Italiano	Autosomal recessive	ADAMTS17	Gould et al., 2011
Welsh Terrier	Not defined	ADAMTS17	ACVO Genetics Committee, 2015; Chaudieu & Chahory, 2013; Curtis, 1990; Curtis & Barnett, 1980; Gould et al., 2011; Rubin, 1989
West Highland White Terrier	Not defined	No	Chaudieu & Chahory, 2013; Curtis, 1990; Rubin, 1989
Yorkshire Terrier	Autosomal recessive	ADAMTS17	Farias et al., 2010; Gould et al., 2011

long-term exposure to normal sunlight has been suggested to explain part of the etiological basis for lens instability in some older dogs (Colitz & O'Connell, 2015). Fibrillin-1 is produced by the nonpigmented epithelium of the ciliary body throughout life, although the rate of production declines with age (Hanssen et al., 2001). These data indicate a very slow turnover of the zonular microfibrils which can be correlated with the appearance during aging of a new periodic fibrillar structure.

Traumatic Lens Luxation

Although lens luxation was historically suggested to result commonly from blunt trauma to the globe, this premise has not been substantiated with retrospective case studies. Blunt trauma with force sufficient to cause lens displacement generally would result in collateral and profound ocular injury. It has also been suggested that trauma may occasionally precipitate lens displacement in an animal predisposed to PLL (Curtis & Barnett, 1980).

Glaucoma and Secondary Lens Luxation

Lens displacement may be associated with chronic glaucoma, in which the high and sustained pressure will lead ultimately to stretching of the ocular tunics and enlargement of the globe (hydrophthalmos). As the eye enlarges, the physical stretching of the zonular fibers will eventually bring about their rupture, most commonly leading to subluxation, but in some cases liberating the lens allowing it to move freely. There may also be a direct effect of the pressure on the fibers themselves, but it is unusual to encounter lens luxation secondary to glaucoma in the absence of some degree of globe enlargement (Fig. 22.25B). However, the coexistence of increased intraocular pressure, subluxation of the lens, and an apparent normal globe size in some dogs on initial clinical presentation, sometimes makes determination of the primary or antecedent disease difficult. This may lead to speculation that, in some cases, ocular hypertension may precede and actually cause breakdown of the zonules through an undefined mechanism unrelated to a change in

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globe size. Subclinical changes in globe size with primary glaucoma may theoretically account for some of these cases. In addition, PLLs and primary glaucoma may coexist in some cases, because the terrier breeds appear to be at risk for both. It is also possible that PLL alters the anatomic and physiologic factors related to aqueous humor outflow in a yet undefined fashion. Further clinical studies would be necessary to confirm these observations.

Chronic Uveitis and Lens Luxation

Chronic uveitis, although rarely, may also induce lens luxation by different mechanisms. Chronic liberation of MMPs and inflammatory mediators may promote zonule degradation. MMPs are enzymatic proteins able to degrade the zonular fibrillin-rich structures that make up the lens zonules (Hindson et al., 1999). MMPs are increased in the aqueous humor of rabbits and humans with anterior uveitis (Di Girolamo et al., 1996). Therefore, the enzymatic degradation of fibrillin proteins likely plays a role in lens instability in eyes with uveitis and cataract.

Cataract-Induced Lens Luxation

Lens luxation occasionally results from advanced and chronic cataractogenesis. Several pathogenic mechanisms may facilitate this presentation. Lens luxation can be theoretically associated with chronic shrinking of the lens and secondary zonular stretching and breakage, or with the increased weight of a mature/hypermature cataractous lens (see Fig. 22.25C). Interestingly, MMPs are also increased in the aqueous humor of human cataracts, regardless of the type (Alapure et al., 2008), which could help in the zonular degeneration process. Zonular instability and/or an aphakic crescent are often present at the time of surgical removal of the hypermature cataract. A zonulolytic effect from any associated lens-induced inflammation may also contribute.

Lens Luxation Secondary to Systemic Disorders

Contrary to the situation in humans, there are virtually no reports on lens luxations occurring in association with systemic disorders. Bilateral lens luxation, in addition to a variety of ocular signs, including cataract and corneal edema, as well as fragility and laxity of the joints, has been described in a dog affected by Ehlers–Danlos syndrome (Barnett & Cottrell, 1987).

Diagnostic Approach and Medical Treatment of Lens Luxation

Diagnostic Approach for Lens Luxation

Clinical evaluation of the patient with lens luxation should include critical ophthalmic examination for any primary cause. Because PLL is almost invariably a bilateral disorder, the contralateral eye should be evaluated biomicroscopically after mydriasis for evidence of lens instability, or signs compatible with subluxation. Diagnosis of lens luxation is generally straightforward. Biomicroscopy is the gold-standard diagnostic technique for this purpose. Diffuse illumination of the eye may reveal phacodonesis or iridodonesis. On optical sectioning, the distance between Purkinje images 2 and 3 (P2 and P3) – representing the reflection from the inner surface of the cornea and the anterior capsule, respectively – may be increased or reduced. In cases of complete posterior lens luxation, absence of P3 and P4 (reflection from the posterior capsule) are commonly observed. In subluxated lens, only the very peripheral part of the reflected slit-lamp beam on the lens may be missing, highlighting an aphakic crescent. In lens instability, subluxation and posterior luxation, vitreal strands may appear as fine wispy fibers with increased relucency highlighted by the aqueous flare. Gonioscopy should also routinely be performed, especially if ocular hypertension is documented, in both the affected (if possible) and unaffected eye, to attempt to determine any causal relationship. In addition, vitreous strands may also be obliterating the iridocorneal angle in cases of severe vitreous displacement. In subluxation or lens instability, mydriasis should be routinely induced to allow complete biomicroscopic assessment of the lens. Fundic examination should be performed, when possible, to rule out posterior segment involvement. Other complementary imaging tests that can be helpful in the lens luxation diagnosis when opacification of the ocular media precludes complete intraocular examination are B-mode ultrasonography, high resolution ultrasound, and infrared evaluation.

Treatment Approaches for Primary Lens Luxations

Treatment strategy differs greatly between primary and secondary lens luxations. It is widely accepted that gold-standard treatment for primary anterior dislocated lenses is surgical removal by two-handed phacoemulsification (with removal of the lens capsular bag) or intracapsular lens extraction (ICLE), with or without sulcus intraocular lens placement (Glover et al., 1995; Nasisse & Glover, 1997; Wilkie et al., 2008). Anteriorly luxated lens may occasionally be successfully manipulated into the posterior chamber by transcorneal repositioning or reduction ("couching-like" technique), a change in head position, or by directing the lens posteriorly with a fine hypodermic needle inserted into the anterior chamber. The ophthalmic surgery referred to as "couching" or reclination, was first reported around 600 B.C. by an Indian surgeon (Grzybowski & Ascaso, 2013). Originally, couching was a surgical technique for treatment of cataracts, wherein a sharp lancet was used to pierce the sclera, then a blunt needle was inserted through the incision to induce posterior luxation of the cataractous lens into the vitreous to restore vision. Couching, as originally described, has not been previously reported as therapy for lens instability in dogs. However, a very

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similar technique, called "transcorneal reduction", was successfully described for the treatment of anterior lens luxation in dogs in 2014 (Montgomery et al., 2014). The authors performed the procedure in sedated or awake animals positioned in dorsal recumbency with ventroflexion of the neck. After applying topical anesthesia, one or two sterile, cotton-tipped applicators were utilized to apply pressure to the cornea and cause gentle depression of the corneal surface by rolling the applicator across the cornea. When combined with long-term topical 0.005% latanoprost administration every 12 hours, transcorneal reduction provides a nonsurgical alternative to ICLE or enucleation (nonvisual eyes). This technique should be considered in dogs with questionable vision or at high risk for general anesthesia; however, dogs are still at risk for re-luxation, retinal detachment, and glaucoma.

Conversely, the most appropriate management approach to lenses that are subluxated or posteriorly luxated is unclear. There is considerable diversity of opinions amongst veterinary ophthalmologists regarding when unstable lenses should be removed, with some individuals avoiding surgical intervention for as long as possible. Broadly speaking, management of subluxated or posteriorly luxated lens may include surgical extraction or a more conservative approach of waiting until anterior luxation occurs prior to surgical intervention. Advocates of surgical removal of subluxated lens refer to the potential advantages of lens removal prior to ocular damage related to anterior lens displacement or chronic posterior luxation (retinal detachment), as well as the advantage of avoiding unpredictable surgical timing forced by spontaneous anterior lens luxation (Glover et al., 1995; Nasisse & Glover, 1997). Other ophthalmologists advocate for conservative management, recommending topical administration of long-term miotic therapy in eyes with lens instability or posterior lens luxation (e.g., phospholine iodide, latanoprost, or demecarium bromide) (Binder et al., 2007; Montgomery et al., 2014), in an attempt to trap the lens behind the iris, thereby delaying or preventing anterior luxation. The rationale for this approach is to maintain the lens in the posterior chamber or vitreous, and prevent forward migration, where complications such as pupillary block glaucoma or corneal edema are more common. In one study of dogs with lens instability (subluxation or posterior luxation), conservative treatment with demecarium bromide maintained vision in 16 out of 20 dogs at 1 year and 11 out of 19 dogs at 2 years (Binder et al., 2007). It is worth mentioning that in the event of anterior lens luxation, a miotic agent may be contraindicated, as miosis can entrap the lens and attached vitreous humor, increasing the risk of pupillary block glaucoma development.

In cases of PLL, it is inevitable that the other lens will luxate; therefore, the prognosis is guarded and prophylactic treatment and long-term monitoring is required. In all PLLs, periodic evaluation of the fellow eye is required, but its treatment will depend on the ophthalmologist's preferences and the owner's wishes and finances. Unfortunately, there are no medical strategies reported to extend the time between PLL in one eye and subsequent lens luxation in the other eye. The reader is referred to Chapter 23 for further details on the surgical approach for anterior or posterior lens luxation and subluxation.

Treatment Approaches for Secondary Lens Luxations

Secondary luxations are treated according to the triggering condition, seldom necessitating surgical lens removal. Conversely to PLL, the fellow eye will not be at risk if the primary cause was trauma, unilateral cataract, or tumor; however, if primary glaucoma is present, the fellow eye might be predisposed and may need to be addressed accordingly. If there is no potential for vision, it would be indicated to enucleate the affected eye. Alternatively, evisceration with intraocular prosthesis implantation has proven to be a good and safe surgical procedure with minimal complications for end stage glaucoma (Lin et al., 2007).

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23

Surgery of the Lens

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Cataract Surgery

Cataract surgery is a routine procedure performed by veterinary ophthalmologists. Mirroring the changes occurring in cataract surgery in humans, rapid evolution of surgical techniques, ocular pharmacology, viscoelastic devices, phacoemulsification machines, and intraocular lenses (IOL) continues to develop. In addition to these developments, a successful outcome is dependent on attention to detail, surgeon skill and experience, and careful patient selection. Complications can be minimized by utilization of the most progressive equipment, smaller incisions, delicate tissue handling, shortened surgical times, adequate mydriasis, choice of IOL, and the use of viscoelastics and nondepolarizing neuromuscular blockade. Preoperative, intraoperative, and postoperative complications must be identified, treated, and minimized. Just as the intracapsular method of cataract extraction was replaced by phacoemulsification, the surgeon should always be prepared to adapt to the next evolutions in equipment and technique.

Patient Selection

Appropriate patient selection is essential to maximize a successful surgical outcome. Cataract surgery is an elective procedure in the majority of cases and many animals can adapt well to vision loss. Surgery is indicated in animals when impairment is associated with the cataract, or in animals with a progressive cataract for which vision loss is imminent. The development of lens-induced uveitis and intumescent cataracts with secondary glaucoma are more emergent indications for surgery. The primary question is always whether the surgery will benefit the patient. The owner and surgeon answer this question by considering together the age, breed, quality of life, activity of the patient, and other systemic and ophthalmic conditions present. Patient temperament and owner compliance are crucial, as the administration of postoperative medications, exercise restriction, and recommended follow-up are also essential to a successful outcome.

History, Systemic Evaluation, and Ophthalmic Examination

Both thorough ophthalmic and systemic histories are indicated. The visual history should identify when the cataract was first observed and when vision changes were noted. Vision loss prior to the onset of the cataract or a history suggestive of nyctalopia are concerning. A history of trauma to an eye or loss of a fellow eye to glaucoma is also relevant. Systemic disease related to the presence of the cataract (e.g., diabetes mellitus, trauma), that might affect anesthesia (diabetes, renal, hepatic, cardiac disease, systemic hypertension, etc.), that might impact postoperative outcome (systemic hypertension, coagulopathy), or that might impact life expectancy should be carefully examined for and addressed.

The ophthalmic examination is of paramount importance. Maze testing in photopic and scotopic conditions can help determine the degree of visual compromise. Poor maze navigation in scotopic conditions can indicate underlying retinal degeneration. The adnexa and globe should be evaluated for normal function and disease. Menace response, direct and consensual pupillary light reflexes, Schirmer Tear Test, and intraocular pressure (IOP) should be evaluated (Leasure et al., 2001). A low IOP may suggest lens-induced uveitis (LIU), while a high normal to elevated IOP could indicate early primary or secondary glaucoma. If IOP is normal, the pupil is then dilated with a mydriatic/cycloplegic and biomicroscopic and indirect ophthalmoscopic examination performed. The IOP should be measured again postdilation to detect elevations when challenged with mydriasis. The precorneal tear film should be examined for abnormalities such as qualitative and quantitative tear film deficiencies. The cornea is exam-

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ined for disease that may interfere with visualization of the intraocular structures intraoperatively or could lead to complications postoperatively. Corneal edema may indicate corneal endothelial dysfunction that can be exacerbated by surgery and can also interfere with visualization during surgery. Keratic precipitates indicate underlying LIU.

The anterior chamber is examined for the presence of aqueous or lipid flare. Vitreous strands in the anterior chamber could indicate lens instability. The chamber depth should be evaluated to assess for lens intumescence. Pupillary and iridal changes that could complicate surgery should be noted, such as posterior synechia. The presence of hyperpigmentation, synechia, or ectropion uvea is suggestive of chronic LIU. The lens opacity is characterized with respect to cause (i.e., congenital, age-related, secondary), stage (i.e., immature, mature, hypermature, Morgagnian), and location of cataract. The lens is examined for evidence of intumescence, lens resorption, capsular fibrosis or plaques, capsular wrinkling, lens capsule rupture, or lens instability. Axial lens opacities will result in a more significant visual disturbance, and anterior and equatorial cortical opacities are more likely to progress. Hypermature cataracts, cataracts in older dogs, cataracts in breeds of dogs predisposed to lens luxations, and vitreous in the anterior chamber are indications of potential lens instability that must be noted and factored into surgical planning. Iridodonesis, phacodonesis, and aphakic crescent are visual cues of lens instability that alter the surgical technique. Anterior capsule wrinkles, fibrosis, or plaques may also involve the posterior capsule and necessitate a planned posterior continuous curvilinear capsulorhexis (PCCC). Anterior capsule wrinkles and/or plaques can make the anterior capsulorhexis difficult. This is most common in chronic and hypermature cataracts (Bernays & Peiffer, 2000; Colitz et al., 2000).

The fundus should be examined by indirect ophthalmoscopy if possible. Vitreal changes that can affect surgery and the postoperative visual outcome include vitreal degeneration, vitreous present in the anterior chamber, asteroid hyalosis, vitreal bands, and posterior vitreal detachment (PVD). The fundic exam should evaluate the retinal vasculature, for possible retinal tears or detachments, tapetal reflectivity, and the optic nerve. If the retina cannot be clinically evaluated, further diagnostics are indicated (see "Additional Diagnostics in Patient Selection").

Signalment in Patient Selection

The age of the dog is important in decisions about whether to perform surgery or not. Young dogs that undergo cataract surgery are more at risk of cataract regrowth. Also, the lens capsules of younger animals are highly elastic and the capsulorhexis can expand equatorially in a flash, resulting in a radial tear, a capsulectomy that is too large, and therefore aphakia. Younger animals with cataracts that do not have surgery may go on to spontaneously resorb their cataract and regain aphakic vision. Spontaneous resorption of a diabetic cataract has been described (Gonzalez-Alonso-Alegre & Rodriguez-Alvaro, 2005). Similar to humans, there may be a connection between young age and postoperative retinal detachment (RD; Foote et al., 2018). There are multiple theories as to why younger patients may be more at risk of RD following phacoemulsification. The predominantly accepted theory in the human literature is the association between the posterior vitreous and the retina. Younger patients are less likely to have already experienced a PVD prior to surgery, and thus they are more at risk of developing a postoperative PVD and a subsequent RD (Clark et al., 2012). Regarding older dogs, they are more likely to suffer from systemic disease that may increase their anesthetic risk. Older Labrador Retrievers have been shown to be at increased risk of postoperative ocular hypertension (POH) and glaucoma (Moeller et al., 2011). Older dogs with cataracts may also be at increased risk for lens instability due to lens zonular degeneration.

The breed of dog can determine intraoperative and postoperative complications. Intraocular complications can include lens instability in dogs affected by primary lens luxation, cysts or pigmentary uveitis, and congenital abnormalities. Postoperative complications such as RD and glaucoma vary by breed (Boss et al., 2015; Braus et al., 2011; Foote et al., 2018; Lannek & Miller, 2001; Moeller et al., 2011; Pryor et al., 2016; Schmidt & Vainisi, 2004; Scott et al., 2013; Table 23.1).

Mixed-breed dogs have been reported to have a decreased risk of glaucoma compared to purebred dogs (Biros et al., 2000). The Labrador Retriever has a significantly increased risk (33%) of POH following cataract surgery compared to 18% in non-Labradors (Moeller et al., 2011). Estimated probabilities of postoperative glaucoma in Labradors were 23%, 25%, 30%, and 35% at weeks 4, 26, 52, and 104, respectively, compared with 5%, 6%, 7%, and 9% at weeks 4, 26, 52, and 104, respectively, in non-Labradors. POH was a risk factor for development of glaucoma in this breed. Boston Terriers, Shih Tzu, Cocker Spaniels, and Cockapoos have been reported to have a higher frequency of glaucoma after phacoemulsification than other breeds (Foote et al., 2018; Lannek & Miller, 2001; Sigle & Nasisse, 2006). Boston Terriers and Shih Tzu have a high occurrence of glaucoma – 38% and 29%, respectively – compared to previously reported non-breed-specific data (Foote et al., 2018). In one study, 50% of Boston Terriers and 34.9% of Shih Tzu developed glaucoma in at least one eye postoperatively (Foote et al., 2018). In contrast, there was no significant difference in visual outcome between Boston Terriers and non-Boston terriers within 1-year after phacoemulsification, but the incidence of glaucoma was not specifically recorded (Newbold et al., 2018). In addition to the Cocker Spaniel, other breeds of dogs with known primary glaucoma, such as the Bassett Hound, are likely at increased risk of glaucoma postoperatively as well.

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Table 23.1 Reported incidence of glaucoma and retinal detachment for specific breeds of dogs.

Breed	Complication	No. of Eyes in Study	% (No. of Dogs)	Length of follow-up	Reference
Labrador Retriever	Glaucoma	66	35 (42)	364 days (median)	Moeller et al. (2011)
		10	6.5	675 days (mean)	Scott et al. (2013)
	Postoperative ocular hypertension	66	33 (42)	24 hours	Moeller et al. (2011)
	Retinal detachment	79	3.8 (45)	804 days (mean)	Foote et al. (2018)
Shih Tzu	Glaucoma	123	29 (83)	804 days (mean)	Foote et al. (2018)
		8	5.8	675 days (mean)	Scott et al. (2013)
	Retinal detachment	8	63	675 days (mean)	Scott et al. (2013)
		123	8.9 (83)	804 days (mean)	Foote et al. (2018)
Boston Terrier	Glaucoma	91	38 (52)	804 days (mean)	Foote et al. (2018)
		16	10.5	675 days (mean)	Scott et al. (2013)
	Retinal detachment	16	56	675 days (mean)	Scott et al. (2013)
		Not reported	84.2 times more likely (10) (% not reported)	302 days (median)	Klein et al. (2011)
		70	17.6 (35)	675 days (mean)	Newbold et al. (2018)
		91	7.7	804 days (mean)	Foote et al. (2018)
Pug	Glaucoma	55	9 (32)	90 days	Boss et al. (2020)
	Retinal detachment	55	7 (32)	90	Boss et al. (2020)
Cocker Spaniel	Glaucoma	18	11.7	675 days (mean)	Scott et al. (2013)
	Retinal detachment	18	22 (18)	675 days (mean)	Scott et al. (2013)
Bichon Frise	Glaucoma	10	6.5	675 days (mean)	Scott et al. (2013)
	Retinal detachment	18	55	Only time to retinal detachment reported	Schmidt & Vainisi (2004)
		17	0 (11)	504 days (mean)	Sigle & Nasisse (2006)
		34	0 (20)	504 days (mean)	Braus et al. (2011)
		79	0.05 (42)	687 days (mean) Minimum 182 days	Pryor et al. (2016)
		264	13 (159)	Minimum 365 days	Pederson et al. (2015)
		311	15 (188)	504 days (mean) Minimum 182 days	Foote et al. (2018)
		10	50	675 days (mean)	Scott et al. (2013)
Jack Russell Terrier	Glaucoma	7	5.8	675 days (mean)	Scott et al. (2013)
Miniature Schnauzer	Retinal detachment	132	5.3 (73)	504 days (mean) Minimum 182 days	Foote et al. (2018)

Note: Scott et al. (2013) is a glaucoma histopathologic study.

Pugs have been reported to have a postoperative glaucoma rate of 9% within 3 months that was not significantly different from the reference population (Boss et al., 2020).

In a retrospective analysis on enucleated globes after phacoemulsification, Shih Tzu and Boston Terriers had the two highest percentages of RD (63% and 56%, respectively; Scott et al, 2013). Patients in this histopathology study were enucleated secondary to glaucoma; therefore, it was difficult to discern if the RD occurred before or after another postoperative complication (uveitis, glaucoma, etc.). Boston

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Terriers were 84.2 times more likely to develop RD than other breeds in another study (Klein et al., 2011). However, the number or percentage of Boston Terriers affected by RD was not stated, and only 10 Boston Terriers were analyzed in that report. In another report, 17.6% of 70 eyes of Boston Terriers were blind from RD (Newbold et al., 2018). This is in contrast to another study, where the cumulative incidence of RD following phacoemulsification in the Boston Terrier (7.7%) and Shih Tzu (8.9%) was in agreement with previously reported nonbreed-specific data (Foote et al., 2018). Pugs have been reported to have a short-term (3-month) postoperative detachment rate of 7% (Boss et al., 2020). The most significant complication and cause of vision loss following cataract surgery in this study was corneal ulceration (15%) and 75% of the Pugs had underlying pigmentary keratitis that can complicate the surgery (Boss et al., 2020).

In published studies, there have also been conflicting data regarding the incidence of RD in the Bichon Frise following phacoemulsification. Five studies have reported the complication of RD of the Bichon Frise, with frequency ranging from 0% to 55% (Braus et al., 2011; Foote et al., 2018; Pederson et al., 2015; Pryor et al., 2016; Schmidt & Vainisi, 2004). The original study reported the prevalence of RD following cataract surgery to be 55% without diode laser prophylactic laser retinopexy, and it decreased to 12% with prophylactic laser retinopexy (Schmidt & Vainisi, 2004). However, two subsequent studies showed no increase in RD rates (Braus et al., 2011; Pryor et al., 2016). In the most recent study, 159 Bichon Frises (without prophylactic retinopexy) were significantly more at risk to develop RD (13.6%) when compared individually to Labrador Retrievers (3.8%) and Miniature Schnauzers (5.3%), but not when compared to Boston Terriers (7.7%) and Shih Tzu (8.9%; Foote et al., 2018). The increased risk in this study compared to the two previous studies, while not much different from Boston Terriers and Shih Tzu, may be due to the increased number of dogs in the study and length of follow-up. The answer to what percentage of risk warrants the possible damage incited by a prophylactic retinopexy is unknown at this time (Goulle, 2016; Pizzirani et al., 2003a).

Additional Diagnostics in Patient Selection

Gonioscopy

The collection of preoperative gonioscopic abnormalities data in veterinary cataract surgery is warranted. However, gonioscopy only allows evaluation of the anterior face of the ciliary cleft and ultrasound biomicroscopy would provide more detailed cross-sectional information (Gibson et al., 1998). There is currently no documented correlation between the presence of preoperative iridocorneal angle (ICA) abnormalities detected via gonioscopy and POH (Dees et al., 2017; Matusow et al., 2016). Detected abnormalities may, however, still alter surgeons' recommendations, especially when combined with known breed predispositions.

Ultrasound

Brightness scan (B-scan) ultrasonography should always be performed preoperatively when the fundus cannot be examined clinically (Williams, 2004; Williams & Wilkie, 1996). B-scan ultrasound using a 10–12 mHz probe is used to evaluate for vitreal degeneration/asteroid hyalosis, RD (Fig. 23.1), posterior lenticonus (Fig. 23.2), persistent hyaloid artery (see Fig. 23.2), persistent hyperplastic primary vitreous/persistent hyperplastic tunica vasculosa lentis (PHPV/PHTVL), axial length of the lens and globe, and presence of spontane-



Figure 23.1 An 11 MHz ultrasound using a linear probe demonstrating a complete retinal detachment posterior to an advanced hypermature, cataractous lens.

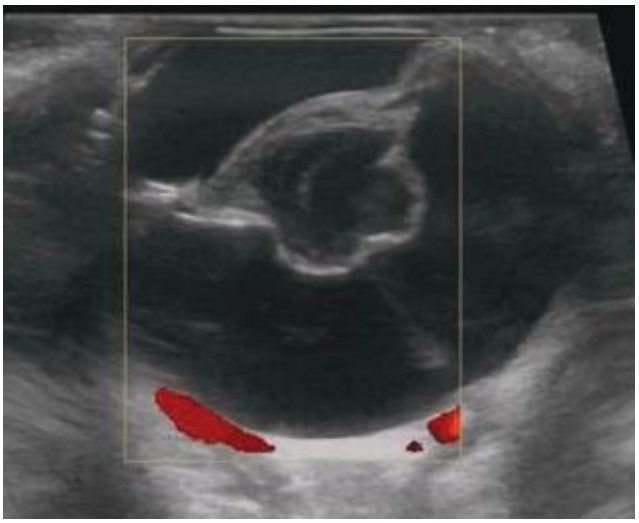


Figure 23.2 An 11 MHz ultrasound using a linear probe and color Doppler demonstrating a nonpatent persistent hyaloid artery posterior to the cataractous lens. Significant posterior lenticonus is also present.

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ous lens capsule rupture (Gemensky-Metzler & Wilkie, 2004; Ori et al., 2000; van der Woerdt et al., 1993; Wilkie et al., 2002, 2006). The prevalence of vitreal degeneration and RD increases as the cataract progresses (Park et al., 2015; van der Woerdt et al., 1993). Posterior vitreal detachments can also develop with age or disease (Fig. 23.3). Gray-scale B-mode ultrasound alone is neither sensitive nor specific for the diagnosis of PVD versus RD in canines (Labruyere et al., 2011). Diagnosing a PVD is challenging in humans as well and is best achieved with optical coherence tomography (OCT; Kuhn & Aylward, 2014). Contrast-enhanced ultrasonography with microbubbles has been proposed as a method for differentiating RD from PVD in the dog (Labruyere et al., 2011).

Evaluation of the ICA and angle opening distance (AOD) can be performed using high-resolution ultrasound (HRUS, 20 mHz; Bentley et al., 2003) and high-frequency ultrasound biomicroscopy (UBM, 35 MHz, 50 mHz, and 100 mHz; Hasegawa et al., 2015; Rose et al., 2008). It has been suggested that the ICA and AOD may correlate with the development of postoperative hypertension (Rose et al., 2008). B-scan ultrasonography (10 mHz) and UBM (35 MHz) have also been used to reliably assess lens equatorial dimension in dogs, and therefore could help guide choice of appropriate IOL size preoperatively (Barbe et al., 2017; Borroffka et al., 2006).

Electroretinography

Quantitative electroretinography (ERG) should always be performed when the fundus cannot be examined clinically. Both photopic and scotopic values should be determined. Normal values are dependent on the equipment used and are typically provided by the manufacturer. Low values must be interpreted based on signalment and ocular examination findings. Candidates with retinal degeneration can still have good visual outcomes. Patients with progressive retinal atrophy are not good surgical candidates. However, an older dog with mild senile retinal degeneration may be, provided that the owner understands the expectations for postoperative visual outcome. A thin degenerate retina may be more at risk of developing a retinal hole or tear. Some dogs with diabetes mellitus, LIU, and a mature cataract may have a dampened ERG preoperatively, but a normal fundic examination and vision testing postoperatively (Maehara et al., 2007). Thinning of the diabetic retina following cataract surgery has been documented by OCT in dogs (Braga-Sa et al., 2015).

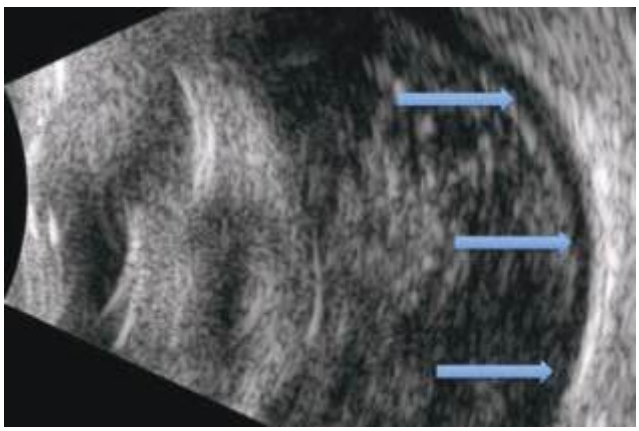


Figure 23.3 A 12 MHz ultrasound showing a posterior vitreal detachment (blue arrows).

Decision for Surgery, Timing, Prognosis, and Outcome

The decision to perform cataract surgery at all and, in the case of bilateral cataracts, whether to perform surgery on one or both eyes must now be made. These decisions are made after careful communication between the surgeon and the owner. They should reflect a balance between anticipated quality of life and visual improvement versus the risk of intraoperative and postoperative complications.

With the use of more advanced phacoemulsification equipment and techniques, both short-term and long-term outcomes for canine cataract surgery continue to improve (Davidson et al., 1991b; Klein et al., 2011; Magrane, 1960, 1969; Miller et al., 1987; Sigle & Nasisse, 2006; Wilkie et al., 2015). Emmetropia and a clear visual axis are expected. Successful outcomes range from 70%–95%, but depend on length of follow-up, stage of the cataract, and diligent postoperative care (Davidson et al., 1991b; Klein et al., 2011; Miller et al., 1987; Nasisse & Davidson, 1999; Sigle & Nasisse, 2006; Wilkie et al., 2015). Retrospective studies have documented a higher success rate with immature cataracts compared with those of mature and hypermature cataracts (Davidson et al., 1991b; Lim et al., 2011; Sigle & Nasisse, 2006). This has shifted the emphasis toward early, rather than late, removal of cataracts. Long-standing cataracts are more likely to be associated with LIU, capsular plaques, zonular instability, and increased phacoemulsification times, all of which can increase intraoperative and postoperative complications and decrease visual outcome. Hypermature cataracts are associated with increased prevalence of both pre- and postoperative rhegmatogenous RDs (see Fig. 23.1; Davidson et al., 1991a; Dziezyc et al., 1986; Miller et al., 1987) and postoperative glaucoma (Sigle & Nasisse, 2006). RD, secondary glaucoma, uveitis, and other complications may occur days to years following cataract surgery (Foote et al., 2018; Klein et al., 2011; Sigle & Nasisse, 2006).

Unilateral surgery in the presence of bilateral cataracts is sometimes elected due to less expense or not subjecting both eyes to the same intraoperative risk factors (e.g., endophthalmitis, toxic anterior segment syndrome or TASS), or surgeon recommendation due to underlying ocular or systemic factors. Postoperative complication rate between surgically treated eyes and nonsurgically treated eyes did not show a significant difference in a recent report, unless the eye was nonsurgical based on the surgeon's

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recommendations, and then the complication rate was significantly higher in that eye (Krishnan, 2020). Monocular phakic vision generally leaves the dog functional where monocular aphakic vision is less optimal. Bilateral surgery restores vision with a single anesthetic episode and convalescent period, and has a lower overall cost when compared with the cost of two unilateral surgeries (Davidson et al., 1990). Bilateral surgery is not associated with an increased risk of intraoperative or postoperative complications (Azaoulay et al., 2013; Davidson et al., 1990).

Diabetic dogs are more likely to have preoperative LIU (92%) compared to nondiabetic dogs (71%; Paulsen et al., 1986). Aqueous humor D-dimer concentrations, indicating fibrinolysis, are higher in diabetic dogs with cataracts than nondiabetic dogs (Escanilla et al., 2013). Diabetic dogs have a similar postsurgical outcome to nondiabetic dogs (Bagley & Lavach, 1994; Bouhanna, 2003), although these eyes are more likely to develop complicating postoperative uveitis that requires more aggressive and prolonged topical anti-inflammatory therapy. Inflammatory cell deposits on the IOL are more likely in human diabetics (Elgohary et al., 2006; Tognetto & Ravalico, 2001). The concurrent presence of Cushing's syndrome in diabetic dogs may have the opposite effect, in that postoperative inflammation can be less severe. Diabetic dogs are more likely to suffer moderate to severe hypotension due to hypovolemia secondary to hyperglycemia (Oliver et al., 2010). In addition, 44% of diabetic dogs had at least one episode of severe hyperglycemia while anesthetized. Corneal complications are more likely in diabetic dogs, as corneal sensitivity is decreased in the first 7 days following surgery and small-breed diabetic dogs are more likely to have keratoconjunctivitis sicca (KCS; Gemensky-Metzler et al., 2015; Rodriguez et al., 2017). Diabetic dogs are also more likely to develop peripheral neuropathies, such as facial nerve paralysis, Horner's syndrome, and neurogenic KCS, after phacoemulsification (Foote et al., 2019). Finally, diabetic dogs that undergo phacoemulsification with a foldable IOL implant have been shown to be at increased risk of POH compared to nondiabetic dogs (Rodriguez et al., 2016).

If the owner elects not to perform cataract surgery or performs cataract surgery on only one eye, the patient must still be monitored long term for lens-induced complications such as LIU, secondary glaucoma, RD, and lens luxation. Possible medical and/or surgical intervention in these eyes may negate any cost savings of performing cataract surgery on only one eye (Paulsen et al., 1986; van der Woerdt et al., 1992). Lens luxation is caused by an underlying cataract in 19% of dogs in one report (Betschart et al., 2014). In addition, another retrospective study looking at risk factors for canine secondary glaucoma found that nonsurgical uveitis (i.e., probable LIU) accounted for 44.9%, while cataracts accounted for 2.5% of cases (Johnsen et al., 2006). No treatment, topical medical management, and phacoemulsification were compared in a study of 44 dogs, which found that eyes receiving no treatment had failure rates 65 and 255 times greater than medically and surgically managed eyes, respectively, indicating that animals that do not undergo phacoemulsification should be managed with topical anti-inflammatories long term (Lim et al., 2011). In addition, failure was four times greater in eyes treated medically compared to those treated surgically (Lim et al., 2011). Failure included a painful globe, glaucoma, lens luxation, enucleation/evisceration, and, in surgical eyes, loss of vision (Lim et al., 2011).

Preoperative Complications

Prior to cataract surgery, complications associated with the cataract may occur and may interfere with surgical success intra- or postoperatively. These complications influence surgical technique and often result from the stage and duration of the cataract, underlying systemic abnormalities, age of the patient, and LIU. Preoperative complications include the development of corneal opacities and corneal disease, uveitis (LIU, lipid), posterior synechia, zonular instability and lens subluxation, vitreous presentation into the anterior chamber, lens capsule rupture, and glaucoma. While these changes will influence the approach to and success of cataract surgery, they do not need to eliminate the patient from surgery, nor do they need to decrease success or the ability to restore emmetropia in many cases. LIU is best treated by removal of the lens; posterior synechia can be broken down; vitreous in the anterior chamber can be tamponaded or removed via vitrectomy; lens instability can be managed using a two-handed approach and capsular tension rings (CTRs); and, with foldable IOLs and sulcus fixation, an IOL can still be placed. Additional preoperative concerns include congenital intraocular anomalies such as persistent pupillary membranes, persistent hyaloid artery, PHPV/PHTVL, posterior lenticonus, anterior lenticonus (Fig. 23.4), microphakia, lens coloboma, and microphthalmos (see Fig. 23.2). Adjustments of surgical technique may include a PCCC or alteration of IOL size and design. The presence of vitreal degeneration may influence a surgeon's decision on whether to perform a posterior capsulectomy. A partial RD would necessitate concurrent retinal surgery where indicated. Finally, abnormalities affecting the contralateral eye, such as elevated IOP or RD, may suggest the need for additional prophylactic interventions such as cyclophotoablation, glaucoma shunt placement, or retinopexy.

Spontaneous Lens Capsule Rupture

Spontaneous lens capsule rupture is a complication that occurs most commonly in association with the osmotic component of diabetic cataracts and rapid intumescence of the lens (Wilkie et al., 2002, 2006). The author has also encountered spontaneous lens capsule rupture in rapidly progressive juvenile cataracts. The axial length of the lens in dogs

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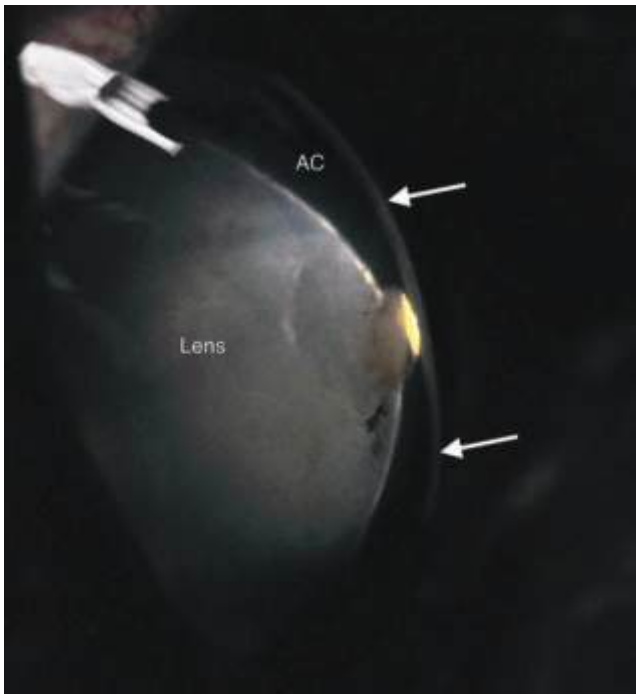


Figure 23.4 Biomicroscopic image of a presumed persistent keratolenticular attachment in a Miniature Schnauzer. The globe and lens were of normal size and no other ocular abnormalities were detected. Mature cataracts were present in both eyes. Cataract was present in both eyes. The lens capsule was carefully dissected from around the corneal attachment and routine phacoemulsification and intraocular lens implantation performed. A faint corneal opacity remained following surgery. The white arrows are pointing at the cornea. AC, anterior chamber. (Courtesy of Jessica Stine and Tammy Miller Michau, Blue Pearl Veterinary Partners.)

with spontaneous capsular rupture can range from 8 to 11 mm (mean of 9.3 mm; Wilkie et al., 2002) compared to a normal lens (7.1–7.6 mm; Samuelson, 2013). Most ruptures (> 95%) occur equatorially, but posterior capsule ruptures are also reported (Wilkie & Colitz, 2013). Clinical signs include an asymmetrically shallow anterior chamber, anterior movement of the iris and lens, posterior synechia in the location of the rupture, visibility of the edge of the capsule, signs of anterior uveitis, and secondary glaucoma (Fig. 23.5, Fig. 23.6, and Fig. 23.7**)**. The anterior uveitis is the result of phacoanaphylaxis or phacoclastic uveitis. The secondary glaucoma can be caused acutely by an angle-crowding mechanism when the iris is moved forward by the lens and also by inflammatory cells. Preoperative glaucoma can be alleviated by surgical removal of the lens and resolution of angle crowding.

The diagnosis of spontaneous capsule rupture is made preoperatively in over 90% of cases (Wilkie et al., 2006). Aggressive anti-inflammatory therapy combined with possible emergent surgical intervention is indicated. Postoperatively, long-term anti-inflammatory therapy may be required to control inflammation, but long-term visual outcome can be good (Wilkie et al., 2006). Depending on the size of the rupture, an IOL can sometimes still be placed inside the lens capsule, with the haptics directed away from the rupture. In some large equatorial ruptures, the anterior capsule can be removed while leaving the posterior capsule intact.

Penetrating trauma can also rupture the lens capsule. Small capsule tears may heal by lens epithelial cell (LEC) fibrous metaplasia and/or posterior synechia, resulting in coverage of the tear (Buschmann, 1987). Focal cataract formation is

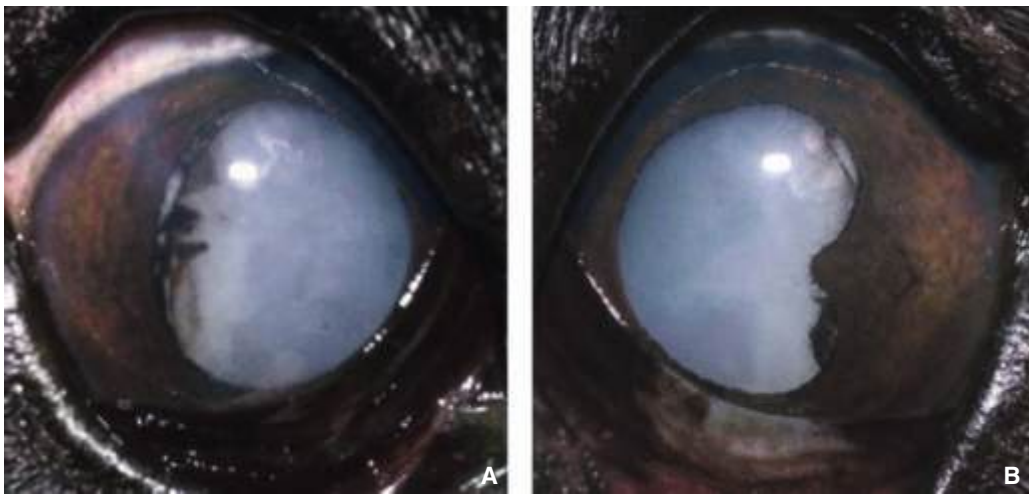


Figure 23.5 The preoperative right (**A**) and left (**B**) eyes of a diabetic dog with spontaneous lens capsule rupture in both eyes (OU). The rupture extends from 12 o'clock to 6 o'clock in the left eye (OS), but can only be visualized from 1 to 2 o'clock due to posterior synechia of the iris in the other clock hours. The rupture extends from 6 to 12 o'clock on the right eye (OD). The presence of keratic precipitates can be appreciated OD ventrally. Intraocular lenses were not placed and the dog was left aphakic OU.

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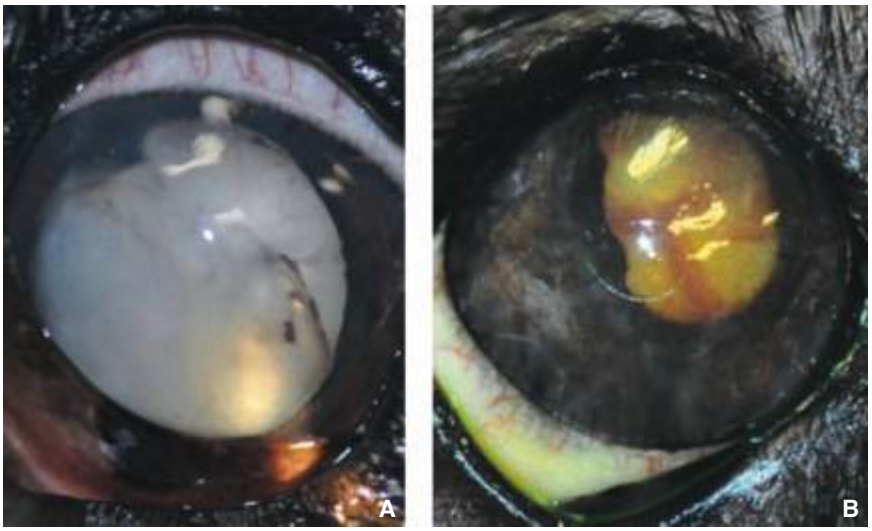


Figure 23.6 Spontaneous equatorial lens capsule rupture extending from 10 o'clock to 6 o'clock (**A**). The exposed lens cortex is visible. The lens capsule rupture cannot be visualized preoperatively (**B**), but red blood cells can be seen within the capsule tracking along the lens sutures.

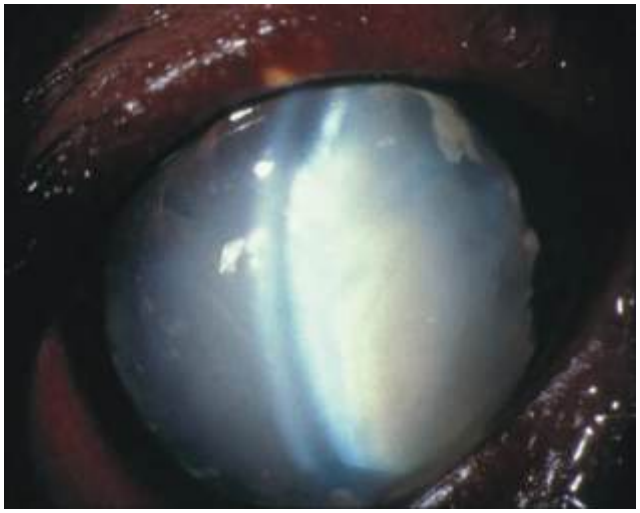


Figure 23.7 Diabetic intumescent cataract with forward movement of the lens, equatorial lens capsule rupture (not visualized until surgery), and emergent angle-crowding glaucoma.



Figure 23.8 Temporoventral luxation of an intraocular lens (IOL) and fibrous lens capsule in a 7-year-old Boston Terrier 6.5 years following phacoemulsification and IOL implantation subsequent to a lens capsule tear from a cat claw injury. Secondary glaucoma is present.

common (Buschmann, 1987). With more significant injury, the entire lens can become cataractous. Larger capsule tears can result in severe phacoclastic uveitis, massive fibroplasia, and secondary glaucoma (Davidson et al., 1991c; Wilcock & Peiffer, 1987). Small or large tears can be complicated by endophthalmitis and aggressive topical and oral antibiotic therapy is indicated in addition to anti-inflammatory therapy. Smaller tears can be managed medically, but surgery is indicated if the cataract progresses or inflammation develops (Davidson et al., 1991c). Phacoemulsification of the lens was previously recommended if the rupture was greater than 1.5 mm. A more recent study of 77 patients (67 dogs, 10 cats) with traumatic capsule rupture has suggested that medical management may be effective for many cases, even in ruptures larger than 1.5 mm (Paulsen & Kass, 2012). The complications, however, when they do occur, are globe threatening. Surgery can be complicated by corneal edema limiting vision of the surgical field intraoperatively. These dogs may be more at risk for long-term glaucoma and other complications as well (Fig. 23.8).

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Uveitis

Cataract is a common complication of chronic uveitis. These cataracts pose several challenges to the surgeon. Difficulties range from the preoperative control of inflammation to intraoperative problems like poor visibility due to corneal changes (degeneration, edema, keratic precipitates), small pupils, posterior synechia, pupillary membranes, bleeding from abnormal iris vessels, and unusual anterior capsules. The postoperative course can be complicated by the recurrence of inflammation and posterior capsular opacification (PCO). In spite of all these difficulties, modern surgical techniques and judicious use of anti-inflammatory therapy have helped improve the visual outcome in patients with cataracts complicated by preexisting uveitis (Sigle & Nasisse, 2006). At this time, there is no consensus on the optimal surgical procedures and perioperative therapeutic regimens for different etiologies of uveitis.

All stages of cataract have some degree of LIU, even if it is not clinically detectable (Gelatt & MacKay, 2004). Phacolytic uveitis is commonly seen in dogs with cataracts, with a reported prevalence as high as 71% and even higher in diabetic dogs (92%), and may lower long-term success rates (Miller et al., 1987; Paulsen et al., 1986; van der Woerdt et al., 1992). Clinical signs of LIU include hypotony, aqueous flare, iris hyperpigmentation, ectropion uvea, entropion uvea, keratic precipitates, delayed or incomplete pharmacologic mydriasis, and synechia. The severity of the LIU has some impact on success of surgery. Severe LIU with dense keratic precipitates, seen commonly in Miniature Schnauzers, can rapidly destroy the eye (Fig. 23.9). However, the author has aspirated hypopyon from the anterior chamber at the time of surgery with a successful outcome. Client communication is critical here. Pretreatment with topical and/or systemic anti-inflammatory therapy for a length of time consistent with the severity of and ability to control the inflammation, followed by phacoemulsification and use of intracameral steroids and epinephrine, is the most appropriate means to manage LIU and avoid long-term sequelae (Fisher, 1972; Gungor et al., 2014; Paulsen et al., 1986; van der Woerdt et al., 1992; Wilcock & Peiffer, 1987; Wilkie & Colitz, 2013). As a clinical sign of blood–aqueous barrier breakdown, diabetic dogs with high serum lipid levels and dogs with primary hypertriglyceridemia can develop lipid-laden aqueous during cataract development and postoperatively as well (Schechtmann et al., 2020).

Pigmentary uveitis (PU) or Golden Retriever uveitis (GRU) is an insidious disease leading to glaucoma and blindness in the Golden Retriever. Thin-walled iridociliary cysts are associated with the development of PU and then pigmentary and cystic glaucoma (PCG), and have also been described in Great Danes and American Bulldogs (Holly et al., 2016). The development of cataracts during the progression of GRU has been noted (Esson et al., 2009). Cataract progression to blindness before the onset of glaucoma in these dogs may occur, and a decision to perform or not perform cataract surgery is faced. Cataract surgery in these patients can present significant challenges due to pigment dispersion on the lens capsule, synechia of the thin-walled cysts to the lens capsule (Fig. 23.10), poor mydriasis, risk of hemorrhage, and fibrin-like deposition in the anterior chamber. The risks versus benefits of whether or not to place an IOL are unknown. The cysts predispose to significant posterior synechia and inflammatory membranes on the capsule and the presence of an IOL may complicate that even further. The author has experienced the development of "rock-hard eye syndrome" (Lau et al., 2014) during



Figure 23.9 A 10-year-old Miniature Schnauzer with a diabetic cataract and severe lens-induced uveitis. 360° posterior synechia and keratic precipitates are visible.



Figure 23.10 Intraoperative photograph of a 5-year-old Golden Retriever with extensive thin-walled ciliary body cysts attached to the anterior lens capsule peripherally and cataract.

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surgery on a case with concurrent PU. Following a primary posterior capsulotomy and vitrectomy, the eye subsequently developed an RD from vitreal bands and underwent retinal reattachment surgery. POH and glaucoma did not occur with a follow-up of 9 months at this time.

Elevated Intraocular Pressure

A high normal to elevated IOP is suggestive of impending or current glaucoma. Most eyes with cataracts have a low to normal IOP (Leasure et al., 2001). The glaucoma may be primary or secondary in origin. The IOP should be measured postdilation preoperatively to detect IOP elevations. Dogs with synechia from uveitis may have a lowered IOP following dilation. A recent report showed that there was no correlation between pre- and postdilation IOP with regard to the development of POH (Fritz et al., 2016). The initial predilation IOP ($\leq$ 20 mmHg) was a possible predictor for the potential for POH (Fritz et al., 2016). In the presence of primary or secondary glaucoma, the surgeon must also decide whether to perform concurrent glaucoma surgical intervention.

Perioperative Therapy

Cataract surgery is commonly facilitated by the use of medications before, during, and after the surgical procedure. These medications may include antibiotics, steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and anti-glaucoma medications to modulate IOP. Critical pre- and intraoperative goals include pupil mydriasis, suppression of ocular inflammation, minimization of ocular microbial flora, and akinesia and central fixation of the globe (Wilkie & Gemensky-Metzler, 2004). Postoperative goals include minimization of inflammation and synechia, control of IOP, and continued monitoring for signs of infection. While all cataract surgeons agree on the goals of perioperative therapy, no surgeons agree completely on how best to achieve these goals, which drugs to use, and the route and frequency of therapy.

Mydriasis

Rapid, adequate, stable mydriasis of limited duration is crucial in cataract surgery. Inadequate mydriasis can compromise the surgery by inhibiting view and increase the risk for both intraoperative and postoperative complications. Topical mydriatics are routinely used and include anticholinergic agents, sympathomimetic agents, or both. The most common topically applied drugs include 1% atropine, tropicamide, and 2.5%–10% phenylephrine (Park et al., 2010). While only a single dose is generally required 1–2 hours prior to surgery, some surgeons will choose to use it more frequently (e.g., every 30 minutes for 2 hours) or for an even longer period of time preoperatively. For atropine, this is not necessary, or advised. Protracted atropinization can cause receptor hyperplasia and contribute to intraoperative miosis (Smith et al., 1984). The systemic absorption of topically applied phenylephrine can also cause systemic hypertension in normal dogs and should be used with care in dogs with preexisting hypertension (Herring et al., 2004).

There are disadvantages to using topical mydriatics, including delayed effect and low bioavailability (Behndig & Korobelnik, 2015). The time to effective dilation can be longer than the procedure itself. In addition, although topical mydriatics might achieve good pupil dilation at the initial stage of cataract surgery, their effect can wear off during surgery, especially in patients with uveitis or heavily pigmented irides (Suan et al., 2017).

The use of intracameral mydriatics can serve as a solution to these problems. Intracameral preservative-free epinephrine, in conjunction with preoperative mydriatics or as the sole dilating agent, is routinely effective (Wilkie & Colitz, 2013). Epinephrine can be instilled intracamerally at the onset of surgery, or it can be placed in the irrigating solution in a lower concentration for continuous infusion. Single-use vials of preservative (chlorbitanol) and stabilizing agent (sulfite) free 1:1000 epinephrine are used and the concentration is diluted to 1:10,000 with balanced salt solution (BSS) for direct infusion (0.1–0.5 mL), or 0.4 mL is placed in 500 mL of irrigating fluid for continuous infusion (Packard & Buratto, 2003). Commercial intracardiac 1:10,000 epinephrine for direct infusion should be avoided, as it contains 0.1% bisulphate that due to its high buffer capacity is toxic to the corneal endothelium (Edelhauser et al., 1982). In addition to mydriasis, epinephrine will facilitate vasoconstriction, control potential bleeding, and decrease postoperative aqueous flare and fibrin (Wilkie & Gemensky-Metzler, 2004). The use of intracameral phenylephrine has been described and achieved similar results to topical mydriatics (Vazquez-Ferreiro et al., 2017). Other intracameral mydriatics include the use of lidocaine 1.0%, which also lowers isoflurane requirements (Park et al., 2010).

Anti-inflammatories

Both corticosteroids and NSAIDs are used perioperatively in dogs. They can be administered systemically, topically, or intracamerally. Topical corticosteroids are used every 6 hours starting at least 12–24 hours prior to surgery, and longer if LIU is present. The topical corticosteroid should be potent and have good corneal penetration. The corticosteroid of choice is 1% prednisolone acetate, or 0.1% dexamethasone can be used as an alternative. Topical 1% prednisolone acetate started 1 week prior to surgery versus 1 day prior to surgery did not decrease postoperative inflammation, but was associated with a greater incidence of POH (60%) versus 1 day (18%, McLean et al., 2012). A recent study showed no differential effect on diabetic regulation in the dogs treated with topical prednisolone acetate versus diclofenac sodium (Rankin et al., 2019). Systemic dexamethasone can be given at induction (0.1 mg/kg intravenously [IV]) and 0.4 mg

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preservative-free dexamethasone (4 mg/mL) can also be placed intracamerally. Intracameral preservative-free triamcinolone is also used (1–2 mg). Intracameral triamcinolone (2 mg) was more likely to result in elevated IOP postoperatively compared to dexamethasone in humans, but both were equally effective at controlling inflammation (Gungor et al., 2014).

NSAIDs have been proven to be a safe and effective alternative to corticosteroids in the topical prevention and management of noninfectious ocular inflammation in humans (Hoffman et al., 2016). NSAIDs both suppress inflammation and prevent miosis during surgery (Cillano et al., 1993; Holmes & Jay, 1991). Along with corticosteroids, topical NSAIDs can be administered every 30 minutes starting 1–2 hours preoperatively, and a systemic NSAID such as flunixin meglumine (0.5–1.0 mg/kg IV) or carprofen (2.2 mg/kg subcutaneously [SC]) can also be administered at or prior to induction, respectively, instead of dexamethasone. Topical NSAIDs available include bromfenac, diclofenac, flurbiprofen, ketorolac, and nepafenac. The topical NSAIDs ketorolac 0.4%, bromfenac 0.09%, and nepafenac 0.1% have been shown to be effective for the reduction of postoperative inflammation following phacoemulsification in humans (Sahu et al., 2015). Nepafenac was significantly more effective at 1 month postoperatively in reducing anterior chamber flare, as evidenced by decreased laser flare photometry. In humans, a recently approved combination of phenylephrine 1.0% and ketorolac 0.3% injectable solution, Omidria® (Omeros Corporation, Seattle, WA, USA), was designed to prevent intraoperative miosis and reduce intraoperative pain (Hoffman et al., 2016). It is added to the irrigating solution used during cataract surgery. Since ketorolac inhibits both cyclooxygenase (COX) enzymes (COX 1 and COX 2), it is able to dramatically reduce prostaglandin synthesis that occurs in the anterior chamber during surgery. In combination, phenylephrine and ketorolac function through two different mechanisms to promote pupillary dilation during cataract surgery. The use of Omidria in a canine model showed postsurgery therapeutic concentrations higher than that achieved with topical application of the drugs (Waterbury, 2018).

Antibiotic Prophylaxis

Postoperative endophthalmitis is a devastating inflammatory condition of the eye presumed to be due to an infectious process from bacteria. Bacteria gain access into the eye during surgery or postoperatively via the incision. Multiple measures for preventing endophthalmitis following cataract surgery have been studied. There is a lot of work looking at topical versus intracameral prophylaxis in humans. Intracameral use of antibiotics includes prepackaged intracameral formulation of cefuroxime in Europe, and the use of the fourth-generation fluoroquinolone moxifloxacin and vancomycin in the United States. Moxifloxacin has been used in small doses (0.05–0.2 mL) of either undiluted or diluted solutions varying from 0.1% to 0.5% from a commercially available preservative-free eye-drop container (moxifloxacin 0.5%, Vigamox®, Alcon Laboratories, Fort Worth, TX, USA) and shown to be safe (Braga-Mele et al., 2014; Lira & Lucena, 2017). However, there is increasing data to show bacterial resistance to moxifloxacin (Asbell et al., 2008; Lam, 2014). The intracameral use is also bacteriostatic and not bactericidal (de Miranda et al., 2015).

Corneal endothelial toxicity and TASS are potential concerns after intracameral injection of any medication. Toxicity might result not only from the drug itself, but also from preservatives and an abnormal pH or osmolality (Mamalis, 2013a). In a review study evaluating multiple methods of prophylaxis, high-certainty evidence showed that injection with cefuroxime with or without topical levofloxacin lowered the chance of endophthalmitis after surgery, and there was moderate-certainty evidence to suggest that using antibiotic eye drops in addition to antibiotic injection probably lowers the chance of endophthalmitis compared with using injections or eye drops alone (Gower et al., 2017). However, a systematic review and meta-analysis showed that intracameral antibiotics prevented endophthalmitis where there was little evidence that topical antibiotics had any effect (Kessel et al., 2015). The combination of preoperative povidone–iodine preparations and perioperative topical antibiotics is also commonly and effectively used as a prophylaxis technique (Inoue et al., 2008; Vazirani & Basu, 2013) and povidone–iodine may be the most important factor (Koerner et al., 2017; Nentwich et al., 2015).

Bacterial contamination of the anterior chamber has been shown to be a common occurrence in canine cataract surgery (Ledbetter et al., 2004). In one study, 57 of 398 samples tested positive for bacterial DNA, although this was not associated with significant postoperative complications (Fisher et al., 2016). Also, patients over 13 years of age were more likely to be positive. In veterinary patients, broad-spectrum bactericidal topical antibiotics are administered every 6 hours beginning 12–24 hours prior to surgery (Yu-Speight et al., 2005). In addition, many surgeons will administer an IV bolus of antibiotics at induction (e.g., cefazolin). Topical povidone–iodine solution is routinely used at induction to cleanse the eye and surrounding adnexa (Koerner et al., 2017; Roberts et al., 1986; Silas et al., 2017). Single-use povidone–iodine solution swabs are available (1%–10%). The ideal concentration of povidone–iodine has yet to be determined for clinical practice; however, the bactericidal effect of 5% povidone–iodine applied for 1 minute is superior to 1% povidone–iodine in cataract surgery patients, with a kill rate of 96.7% within 60 seconds (Ferguson et al., 2003). Care must be taken that the povidone–iodine does not enter the anterior chamber, as concentrations of 5% and higher are highly toxic to the endothelium (Alp et al., 2000).

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Akinesia, Analgesia, and Anesthesia

Most cataract surgeons choose a protocol of general anesthesia using standard premedication followed by inhalation anesthesia. To facilitate globe position and decrease external forces on the globe caused by extraocular muscle contraction (i.e., akinesia), systemic administration of a nondepolarizing neuromuscular blocking agent to paralyze the patient is routine. Although atracurium is widely used in veterinary medicine for akinesia of extraocular muscles, vecuronium and rocuronium use have also been described (Briganti et al., 2015; Lorenzutti et al., 2014; McMurphy et al., 2004, Wilkie & Gemensky-Metzler, 2004). These neuromuscular blocking agents, in addition to akinesia, cause paralysis of respiratory muscles, which requires positive-pressure ventilation and close monitoring of carbon dioxide levels and respiratory function. Significant residual neuromuscular block has been demonstrated with acceleromyography, even after spontaneous ventilation had returned to pre-vecuronium values (Martin-Flores et al., 2014). Monitoring spontaneous ventilation, including end-tidal carbon dioxide, expired tidal volume, peak inspiratory flow, or minute ventilation, cannot be used as a surrogate for objective neuromuscular monitoring, and this practice may increase the risk of postoperative residual paralysis. These agents can be reversed with neostigmine.

To avoid neuromuscular blockade, sub-Tenon and retrobulbar injection of lidocaine may be an alternative method for inducing akinesia of extraocular muscles, mydriasis, and intraoperative analgesia for phacoemulsification in dogs (Accola et al., 2006; Ahn et al., 2013a, 2013b; Bayley & Read, 2018; Hazra et al., 2008; Park et al., 2010). Like intracameral lidocaine, it allows for lower isoflurane requirements (Park et al., 2010). Cataract surgery may result in the priming of pain perception pathways and subsequent ocular pain during the postoperative period (Smith et al., 2004). In humans, 90% of patients undergoing vitreoretinal surgery after sub-Tenon injection of a local anesthetic did not require postoperative analgesia. It has not been shown to have an effect on postoperative pain scores in dogs (Ahn et al., 2013b). Systemic administration of lidocaine intraoperatively provides analgesia similar to systemic morphine in dogs undergoing cataract surgery (Park et al., 2010; Smith et al., 2004). Intracameral preservative-free lidocaine can also be used safely in the canine eye (Gerding et al., 2004; Park et al., 2009).

Postoperative Therapy

Topical antibiotics and corticosteroids are routinely continued every 6 hours in the immediate postoperative period and subsequently weaned. Topical antibiotics are frequently used due to the presence of corneal sutures and possible corneal postoperative complications. Changes in conjunctival bacteria and bacterial susceptibility to antimicrobials after cataract surgery in dogs have been demonstrated with the use of topical ofloxacin postoperatively (Sandmeyer et al., 2016). The frequency of positive culture results was significantly higher 6 weeks following surgery. The most frequently cultured organism was *Staphylococcus pseudointermedius* (26.9%), followed by coagulase-negative *Staphylococcus* spp. (24.4%). The number of bacterial organisms increased and the population of conjunctival bacteria was altered and had a higher proportion resistant to ofloxacin during the 6 weeks after cataract surgery (Sandmeyer et al., 2016). Topical NSAIDs are routinely continued every 12 hours in the immediate postoperative period. Some surgeons leave the patient on topical NSAIDs for extended periods of time (up to 6 months or indefinitely). This can vary depending on whether the patient is diabetic and the degree of inflammation present pre- and postoperatively.

Systemic antibiotics are commonly administered postoperatively, but their use in preventing endophthalmitis has not been studied in dogs. A course of systemic antibiotics is indicated (10–14 days) if the posterior lens capsule is opened and the vitreous face exposed (Beyer et al., 1985). Systemic antibiotics are also administered if a beginning surgeon is performing the procedure and when the patient is diabetic or immunosuppressed. Systemic anti-inflammatories, both corticosteroids and nonsteroidals, are also routinely prescribed following cataract surgery. There is insufficient evidence in the literature to inform practice for treatment of postoperative inflammation and it remains at the surgeon's discretion. Melatonin, a widespread free radical scavenger and antioxidant in different tissues, including ocular structures, has been demonstrated to have anti-inflammatory effects in both diabetic and nondiabetic dogs postoperatively when given orally (0.3 mg/kg twice a day, for 180 days) starting 7 days preoperatively (Sande et al., 2016).

Surgical Equipment and Devices

A successful outcome in cataract surgery depends on the preparation up until this point and now becomes dependent on the skill of the surgeon, the use of appropriate instrumentation, and the choice of technique. Microsurgical instruments, surgical microscopes, phacoemulsification machines, automated irrigation/aspiration (I/A), and vitrectomy capabilities are considered standard of care. Single-use instrumentation is preferable over multi-use instruments (e.g., cannulas, phaco needles, I/A tips, etc.) to minimize the risk of endophthalmitis or TASS (Stiles & Townsend, 2015).

There are five different parameters that the surgeon can control with the phacoemulsification machine: (1) power; (2) evacuation flow rate; (3) vacuum; (4) vacuum rise time; and (5) bottle height. These parameters are intertwined. The surgeon should be an expert in the specifics of the machine to be used and understand the indications and techniques needed to result in a successful outcome. For example, the surgeon must understand the effect of increasing flow versus

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increasing power, how to maintain a constant intraocular pressure to allow room for working and minimize motion of intraocular contents, and how to troubleshoot the equipment during cataract surgery.

Phacoemulsification Machine Parameters

The various functions of the phaco machine and their interrelationship are called phacodynamics. There are two basic functions of the machine: the delivery of ultrasonic power for emulsification and I/A for removal of the emulsified material. Thorough descriptions of phaco equipment and machine parameters exist and should be read extensively by everyone performing cataract surgery (Buratto & Zanini, 2003b; Fishkind et al., 2010; Gilger, 1997; Jaffe et al., 1997; Seibel, 2005; Steinert, 1995). The phacoemulsification systems in use today incorporate advanced technology and design elements that make cataract surgery safer and faster. Continuous technological advancements will only improve surgical outcomes. A phaco machine should deliver accurate and repeatable fluidic and ultrasound results as requested through its user interface. The goal is always less time, fluid flow, and energy used inside the eye.

Fluidics

Fluidics describes the principles that govern the flow of fluid into and out of the eye during phacoemulsification. This takes place in a closed system consisting of the irrigation bottle and line, anterior and posterior chambers, aspiration line, and machine (Zanini & Buratto, 2003). Fluidics affects the efficiency of the phaco handpiece and I/A procedure. The flow into the eye is determined by the bottle height and to a lesser extent by the compliance of the tubing. This will typically match what is flowing out of the eye, which is determined by leakage and flow regulated by the pump (i.e., evacuation or aspiration flow; Jaffe et al., 1997). Compliance is a measure of a hollow system's ability to expand or contract as a function of applied force. All other things being equal, greater compliance in phacoemulsification systems leads to slower vacuum rise and worse surge. The surgeon must understand the fluidics offered by the latest phacoemulsification systems (Han & Miller, 2009; Kent, 2017; Oakey et al., 2013; Solomon et al., 2016).

The type of pump used to generate the flow of fluid is the most important factor in determining fluidics. The IOP is directly proportional to the height of the infusion bottle and inversely proportional to the evacuation flow rate and incisional leakage. The bottle height should be between 65 and 75 cm and the corneal entry wound 2.8–3.2 mm (sized for a sleeved phaco needle in coaxial surgery) to correspond with the phacoemulsification needle selected. The bottle height can be increased if there is a need to deepen the anterior chamber or increase the evacuation rate to pull pieces of a hard nucleus closer to the tip. Bottle height can be lowered in the face of a posterior capsule rupture to minimize vitreous hydration and pressure on the rupture site (Jaffe et al., 1997). The bottle height is also lowered during vitrectomy.

The two main pump types used are flow-based pumps (peristaltic and scroll) and vacuum-based pumps (diaphragm and Venturi; Zanini & Buratto, 2003). The new phacoemulsification systems work predominantly in a peristaltic or flow-based mode. Flow-based peristaltic pumps consist of a roller that compresses plastic tubing against the circumference of a rigid cylinder. The rotation speed of the rollers will increase or decrease the aspiration flow rate and provide a fixed rate of flow (Jaffe et al., 1997). In reality the flow is not fixed, as the occlusion of the phaco tip with a cataract fragment increases the resistance to flow and therefore decreases the rate of flow (Jaffe et al., 1997). Aspiration flow builds up vacuum in the cassette and tubing. The peristaltic pump stops turning when the preset vacuum limit is reached. Machines can have a sensor that will increase the pump speed when the resistance at the tip is increased. In vacuum-based diaphragm pumps, a flexible diaphragm that moves backward and forward controlled by an electric motor via the foot pedal generates fluid flow. In vacuum-based Venturi pumps, vacuum results from a pressure differential (i.e., the Venturi effect) created when compressed gas (i.e., nitrogen) travels through a cylinder (Gilger, 1997; Zanini & Buratto, 2003). Pumps are primarily designed to create an optimal vacuum to attract and manipulate lens fragments inside the eye while minimizing pushing them away. The features of fluidics that are most affected by pump design are power, evacuation flow rate, vacuum, and vacuum rise time.

Power is what emulsifies the lens material and is dependent on the machine, handpiece, and tips. It is produced by the ultrasonic vibrations (29,000–60,000 cycles per second kHz) of the Quartz crystals in the handpiece. The number of crystals can vary and the higher the number of the crystals, the longer the stroke length of the tip and the higher the resultant power. The minimal amount of power needed to emulsify the lens should be used. Power is a source of heat and can result in corneal wound burn and endothelial cell and blood–aqueous barrier damage. The amplitude, duration, and delivery of power can all be altered. The same power settings between phaco machines do not mean the same power.

The evacuation flow rate is the volume of fluid made to flow through the tubing per unit of time (mL/min). More flow results in more movement of fluid into the phaco tip, which attracts fragments to the tip against the repulsive action of the ultrasound. This is termed *followability*. Distal followability brings a fragment to the phaco tip and is a function of flow into the aspiration port; it is adjusted directly on a flow pump and indirectly on a vacuum pump. Proximal followability refers to the efficiency with which carouseling phaco aspiration takes place, with poor function manifest by "chattering" or bouncing of the lens fragment on the tip. Poor proximal followability is an indication of insufficient

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attractive fluidic parameters (flow and vacuum) and/or excessive repulsive forces (traditional longitudinal ultrasound). Followability is a desired effect, but it is indiscriminate, in that anything in the path of the fluid is swept into the tip, including lens material, posterior capsule, and vitreous. Flow rate cannot be preset in the Venturi or diaphragm pumps, but is controlled by the foot pedal. The surgeon must be responsible for immediately stopping flow when the lens material occludes the tip, vacuum rises, and aspiration of the lens material occurs. Otherwise the high flow rate begins pulling other unwanted intraocular structures into the tip.

Vacuum is the "holding power" or actual aspiration force (millimeters of mercury, mmHg) created within the tubing during periods of fluid flow. Vacuum determines how well, once occluded on the tip, the lens fragments will be held. The importance of port size (i.e., 0.3 or 0.5 mm) and tubing size should also be understood when setting the vacuum limit. A system with smaller port and tubing sizes will be safer at a higher vacuum than a system with a larger port and tubing (Jaffe et al., 1997). While 0.3 mm openings are routine in human surgery, the 0.5 mm opening is more efficient for the harder, larger canine lens.

Vacuum rise time is the time the pump takes to reach the preset maximum vacuum pressure. When the port becomes occluded, how fast the vacuum builds is dependent on how high the flow rate is. With peristaltic pumps, complete occlusion of the needle tip must occur to obtain vacuum. As occlusion occurs, vacuum slowly rises within the tubing until the fragment is emulsified and aspirated. Peristaltic pumps have a longer vacuum rise time, allowing the surgeon a longer and safer reaction time (Zanini & Buratto, 2003). With diaphragm and Venturi pumps, no occlusion of the needle tip is needed to obtain vacuum. Vacuum pressures rise very quickly as the foot pedal is depressed because of the high flow rates. Due to this, these pumps are considered to be more "responsive" than peristaltic pumps (Nasisse & Davidson, 1999). Each pump has its own inherent advantages and disadvantages, and time and experience with the equipment are needed to determine surgeon preference.

Other variables are associated with equipment effect fluidics, including venting, reflux, and surge. Venting is the termination of vacuum in the line when the foot pedal is withdrawn from the active aspiration position. This is accomplished by allowing either air or fluid into the system to fill the volume of the reexpanding tubing. Both systems function effectively, but venting with air increases the rise time because of its high compliance (Nasisse & Davidson, 1999). Venting is needed when lens material occludes the needle, stopping flow. Venting results in the release of the occluding material and allows regrasping of the lens fragments for efficient fragmentation.

Reversing flow in the irrigation line is termed reflux and can be passive (i.e., gravity flow) or active (e.g., reverse revolution of the peristaltic pump; Nasisse & Davidson, 1999; Zanini & Buratto, 2003). Reflux creates positive pressure in the aspiration line and allows removal of fragments occluding the needle tip. It can also allow for quick release of the posterior capsule, iris, or vitreous that has inadvertently been pulled into the aspiration tip. Reflux is controlled by the surgeon via an accessory switch located at the top or side of the foot pedal.

Postocclusion break surge occurs when fluid outflow exceeds fluid inflow into the eye. It occurs when a lens fragment held by high vacuum is suddenly aspirated into the needle and a sudden and rapid influx of fluid follows it from the anterior chamber into the needle tip. This results in decompression of the elastic components of the phaco system. Surge effects are exaggerated in systems with less stiff, flexible tubing (increased compliance). Therefore machines that have decreased compliance (increased stiffness) would minimize surge. Surge can result in an excessive drop in IOP, collapse of the anterior chamber, and inadvertent suctioning of the posterior capsule and iris into the tip. Dangerous surge happens most often with larger-diameter phaco ports (>1.0 mm; Jaffe et al., 1997). Other variables affecting surge, besides compliance, include phaco power, aspiration rate, and vacuum, which can differ among machines. Typically surge decreases linearly with increasing bottle height and increases with increasing aspiration rate (Georgescu et al., 2007; Ward et al., 2008). Other methods to minimize surge in addition to decreasing compliance include lowering the flow and vacuum, and adding an aspiration bypass stabilizer. Surge is a known hazard of cataract surgery and failure to anticipate it is an important cause of posterior capsule rupture. For this reason, lens fragmentation should be performed away from the posterior capsule at the level of the iris. Beginning surgeons should also start out at lower vacuum settings and higher bottle heights. The newer phaco machines minimize surge through a variety of mechanisms.

Some commercially available phacoemulsification systems are summarized in Table 23.2. Alcon Laboratories' Centurion phaco systems feature "active fluidics technology," which allows the surgeon to set and maintain a target IOP during surgery, in comparison to gravity fluidics and fixed pressure irrigation (Solomon et al., 2016). This reduces surges due to occlusion breaks; increases IOP efficiency at lower, more natural settings; and eliminates the need to manually adjust fluid pressure (Nicoli et al., 2016). This system features both longitudinal and torsional (OZiL) ultrasound delivery using a Kelman bent needle that increases emulsification and cavitation efficiency without increased heat (Davison, 2005). Some form of curved needle is necessary to allow for the rotary movement of the tip. The torsional movement of the OZiL is similar to that of turning a doorknob. Although torsional phaco is delivered in a linear manner, it is measured differently from traditional phaco power. Torsional phaco power is recorded as cumulative delivered energy (CDE). The company recently introduced

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Table 23.2 Summary of some commercially available phacoemulsification systems.

Company	Pump style	Model	Next- Generation Model	Most Advanced-Generation Model	Phaco Movement
Alcon Laboratories	Peristaltic	Legacy	Infiniti (torsional; alone or in combination with longitudinal)	Centurion	Torsional Oscillating circular and side to side
Abbot Medical Optics	Peristaltic and Venturi	Whitestar Sovereign	Whitestar Signature	Whitestar Signature Pro	Transversal Elliptical lateral motion and longitudinal
Bausch & Lomb	Venturi	Millennium	Stellaris PC	Stellaris Elite	Longitudinal
An-Vision	Peristaltic			Alexos 3	Longitudinal

new software for the OZiL called Intelligent Phaco, which it describes as "adaptive software that continuously monitors and responds to" conditions during surgery. Increasing IOP with this system has been shown to improve efficiency and decrease chatter (Jensen et al., 2016). The Centurion also has a nontraditional peristaltic-style pump, which in effect acts as two pumps out of phase with one another, pulling in parallel from the same piece of tubing. The advantages of this are it allows for twice the flow rate achievable with a single pump and overcomes the resistance of the Centurion's smaller tubing (which helps to minimize postocclusion break surge) and, since the pumps are out of phase with one another, cancels out the small pulsations that a peristaltic pump produces. The Centurion also has stopcock-like rotary valves. Standard valves can cause motion in the eye when they close by pinching the tubing, which pushes fluid in both directions. Rotary valves stop the flow without causing a change in volume or creating a pulse, and can be opened or closed just partially, making the flow proportional.

Abbott Medical Optic's Whitestar Signature System®, and its upgrade, Whitestar Signature PRO®, feature Fusion Fluidics, with the CASE (chamber stabilization environment) system. There are two different pump technologies in the same machine, both peristaltic and Venturi. Peristaltic technology allows for great holdability and intraoperative control, which is advantageous early in the procedure. The Venturi pump allows for greater followability and bringing particles of the lens to the needle in the center of the eye, for fragment removal and also for I/A (Soscia et al., 2002). This minimizes the need for a second instrument to move fragments to the needle and improves efficiency in coaxial (single-incision) cataract surgery. The Signature system also senses that an occlusion at the tip has occurred and automatically implements changes to minimize surge when the occlusion breaks (Georgescu et al., 2008). This features both longitudinal and transversal (Ellips) ultrasound delivery using a straight or bent needle. Transversal motion is elliptical in nature. The technology generates less heat and requires lower vacuum settings.

Bausch & Lomb's older Millennium® and newer Stellaris Vision Enhancement System® (Rochester, NY, USA) features are vacuum-based Venturi systems (Kang et al., 2015). The Stellaris PC is also capable of performing vitrectomy surgery in addition to cataract surgery. The Stellaris Elite, featuring more than a dozen new innovations, has also been released. The Stellaris system allows the surgeon to control vacuum at the needle during phacoemulsification, as well as irrigation and aspiration. Like the Whitestar Signature in Venturi mode, the phaco needle does not have to be occluded to build vacuum, allowing for greater followability. Dual-linear foot pedal technology allows the surgeon to manage two parameters at once, such as aspiration and power. This is a longitudinal device that uses a straight or Kelman bent needle. Power modulation and pulse shaping are used to optimize longitudinal ultrasound delivery.

An-vision's Alexos 3 Phaco System is a portable system that has presets for equine and avian surgery in addition to canine, as well as elongated tips for use in the horse.

Phacoemulsification Handpieces and Needles

The vibrations of the phaco handpiece (Fig. 23.11) converting electrical energy to mechanical energy, thus emulsifying the lens, create ultrasonic power. The power achieved is dependent on the frequency of the handpiece and the resultant stroke length. Vibrations of the Quartz crystals in the handpiece range in frequency from 27,000 to 60,000 cycles per second (kHz). Lower frequencies are considered less efficient, while higher frequencies generate excess heat. A temperature of 50–70 °C is typically generated at the corneal incision by the phacoemulsification needle (Zacharias, 2016b). The optimal vibration frequency is between 35,000 and 45,000 cycles/second. The vibration causes the needle or tip to move a displacement distance, which at maximum power is termed the stroke length. Stroke length varies for different machines and normally ranges from 1.5 to 4 µm (Tognetto et al., 2012). The longer the stroke length, the greater the power, heat, and cavitation generated and the greater the physical impact on the lens. There are two basic

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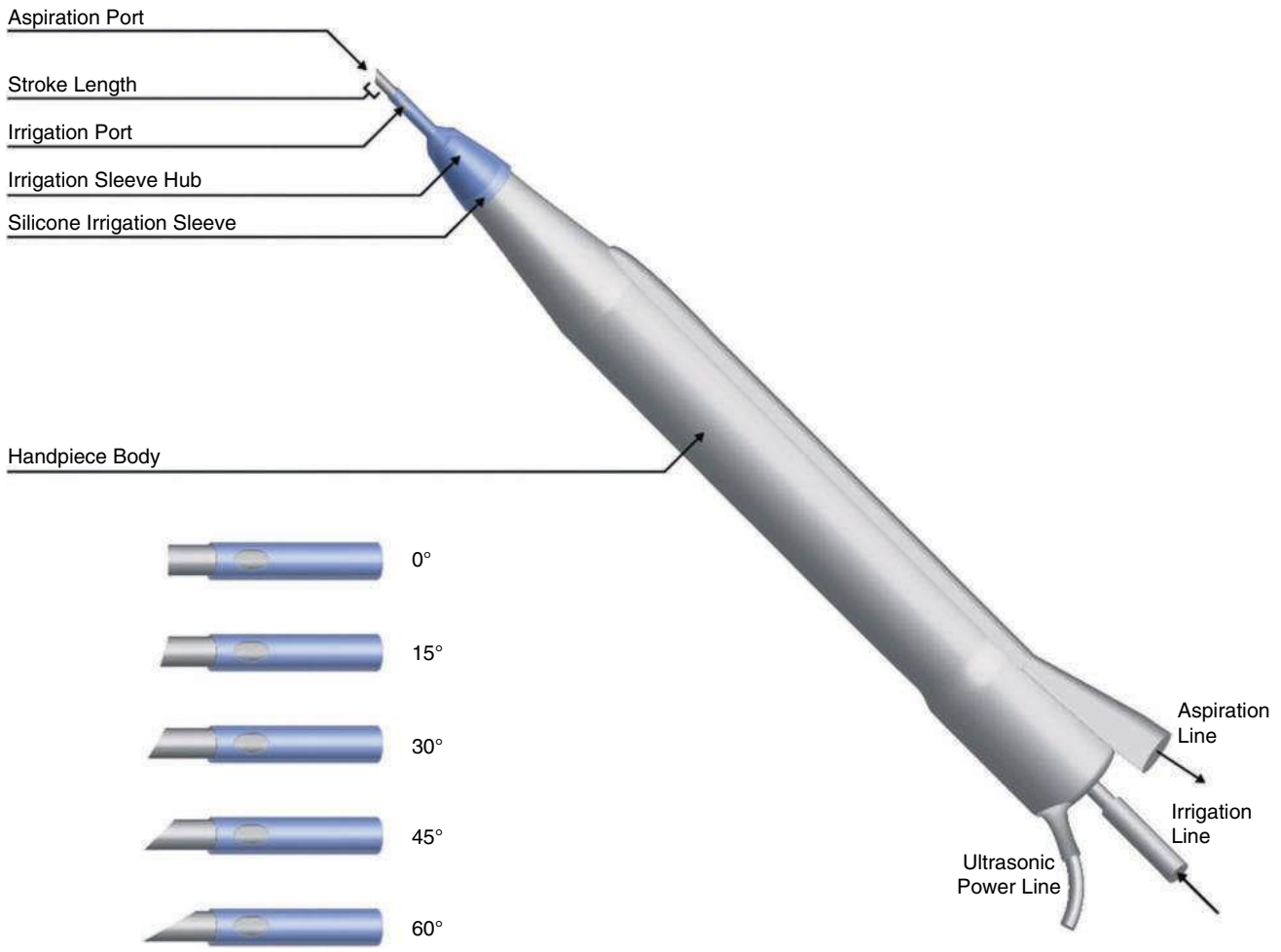


Figure 23.11 Diagram of a routine phacoemulsification handpiece shows the aspiration port (needle opening), one of the two irrigation ports in the silicone sleeve, aspiration line, irrigation line, and power cord. Needle openings come in 0, 15, 30, 45, and 60° bevels. The stroke length is the length the needle moves forward and backward in longitudinal phacoemulsification. (Courtesy of Brian Wilson.)

principles to consider regarding power modulation: the direction of phacoemulsification (i.e. longitudinal, transversal, or torsional) and timing (i.e. continuous, pulse, or burst).

Phacoemulsification tips or needles are a fundamental part of this process, as they attach to the handpiece, deliver the ultrasound energy, and aspirate the lens material from their open ends. The tips are usually made from titanium (Ti) alloys and should undergo rigorous quality controls to guarantee adequate sterilization. Single use of the tips provides the most efficiency (Demircan et al., 2016). The basic phacoemulsification handpiece and needle used a longitudinal, back-and-forth motion aligned with the longitudinal axis of the phacoemulsification tip. An acoustic conical-shaped wave and a fluid and particle wave are created in front of the phaco needle. Phacoemulsification occurs during the forward stroke of the tip as it impacts the lens material, and is the result of the "jackhammer effect" of the tip and cavitation (Zacharias & Claus-Dieter, 2013). Cavitation is created when the needle moves forward and then backward, resulting in the formation and subsequent collapse of microbubbles. The collapse releases energy in the form of heat (up to 13,000 °F) and a shock wave of 75,000 pounds per square inch (PSI; Fishkind, 2000). The collapse also causes "chatter" (i.e., repulsion of the lens fragments away from the aspirating port), decreasing the efficacy of aspiration as well as the followability of the lens fragments. Mechanical cutting dominates cavitation effects as the mechanism for emulsifying cataractous material (Zacharias & Claus-Dieter, 2013).

Newer, nonlongitudinal ultrasound technologies have been developed that use a torsional (oscillatory or lateral movement) or transversal motion (longitudinal movement combined with elliptical movement; see Table 23.2; Christakis et al., 2013). Differences in tip movement and microfluidics between longitudinal, torsional, and transversal phaco tips, alone or in combination with operational variables, such as flow rate, vacuum level, and ultrasound power, result in differential aspiration efficiency and

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attraction/repulsion of lens fragments (Zacharias & Claus-Dieter, 2013). An advantage of these technologies compared with standard longitudinal phacoemulsification is that they minimize chatter and improve followability, which allows for more efficient aspiration of the lens fragments (Zacharias & Claus-Dieter, 2013). A disadvantage may be that the lumen occludes more easily. Analysis of fluidics shows a characteristic fluid flow directed away from the tip's aspiration port in a forward direction with a longitudinal tip, regular fluid backflow into the aspiration port with a torsional tip, and multidirectional fluid flow with an elliptical tip (Zacharias, 2016a). Whereas with the longitudinal tip lens material can bounce off the tip, the torsional mode maintains a constant load attraction at the tip. With an elliptical tip, the material load rotates slightly and shows small movement away from the tip at irregular intervals (Zacharias, 2016a).

In addition to the direction of their movement, the shape and size of phaco needles influence efficiency and safety in the phaco procedure through their energy output, holdability, followability, and surge suppression. The choice of needle depends on surgeon preference, which is dependent on the equipment and surgical technique to be used. The standard tip has a 0.9 mm inner diameter and 1.1 mm outer diameter. Microflow tips, useful in soft cataracts, have an internal diameter of 0.45–0.6 mm, and result in decreased holding power for the same vacuum. Needles now come in straight, Kelman-style (downward angulation at 22–30°), flared, tapered, or "balanced" configurations (Fig. 23.12). They can also contain an aspiration bypass port that helps to minimize surge. A radiused edge tip (i.e., polished) as opposed to a traditional sharp-edge tip has been shown to significantly decrease the likelihood of posterior capsule breakage (Dewey, 2006).

Straight needles are typically used in longitudinal phaco. The addition of a flared end (1.1 mm tip opening vs. 0.9 mm opening) provides a greater surface area and increases holding power, while the narrower neck minimizes surge (see Fig. 23.12; Fishkind et al., 2010, 2013). Flared needles direct cavitation into the opening of the bevel of the tip, minimizing random emission of phaco energy. The reverse miniflared Kelman configuration needle was designed to aid surgeons using a bevel-down technique (Kim et al., 2011). The Kelman-style needle is bent at the tip anywhere from 12 to 22° (see Fig. 23.12). Traditional Kelman-style needles are widely used for both longitudinal and torsional phaco in humans and are excellent for use on very hard nuclei (Demircan et al., 2015). It can be difficult to visualize the tip of a traditional bent needle and they can "clog" easily with hard nuclei. However, with the development of newer ultrasound technology, the needles need to be optimized for newer motions. The Kelman-style angled needle amplifies the oscillatory movement of torsional ultrasound. Torsional phaco requires the Kelman-style needle opening to be angled at 30 or 45° to be effective. The needle end displacement is dependent on the degree of asymmetry of the shaft in torsional phaco. As the angle of bend increases, more movement of the needle end occurs. When used for torsional phaco, this results in significant motion of the shaft, which can lead to undesired corneal endothelial damage. A novel "balanced" needle has been specifically designed for



Figure 23.12 Examples of the needles available for phacoemulsification. **A**. Kelman® 30° needle (Alcon Laboratories, Fort Worth, TX, USA). **B**. Intrepid® balanced tip with aspiration bypass (Alcon Laboratories). **C**. Straight needle with 45° opening. **D**. Straight flared needle. (Courtesy of Brian Wilson.)

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torsional ultrasound and has enhanced sideways displacement at the needle end and greatly reduced action along the shaft (see Fig. 23.12; Intrepid®, Alcon Laboratories; Khokar et al., 2017; Zacharias, 2016b).

Needle openings come in angulations of 0, 15, 30, 45, and 60° (see Fig. 23.11). The higher the degree of opening angulation, the greater the surface area and the better the cutting efficiency (Helvacioglu et al., 2014). The bevel of the needle focuses the jackhammer and cavitational forces in the direction of the bevel. While a 0° needle generates greater cavitation, a 45° needle has a larger surface area for its opening and cuts better by the jackhammer effect, making it more useful in harder lenses. This greater surface area also allows for more holding power for lens fragments. At a vacuum of 100 mmHg, a 0° needle has a holding strength of 0.0019 lb, while a 45° needle has a holding strength of 0.0027 lb. Care should be taken when using a 45° needle near the posterior capsule by maintaining the bevel pointed upward, to direct surge effect toward the pupil rather than the posterior capsule (Nasisse & Davidson, 1999; Zanini & Buratto, 2003).

With coaxial phacoemulsification, needles are covered by a silicone sleeve that allows for irrigation around the needle, lowering the resulting temperature to protect the ocular tissues from thermal injury. A corneal incision that is too small compresses the sleeve against the needle and restricts fluid flow, resulting in thermal damage. Irrigation fluid typically exits the sleeve from two side ports. The amount of needle tip exposed by the sleeve and the alignment of the irrigation ports can be adjusted according to surgeon preference. The phaco handpiece is routinely oriented with the needle bevel up and the irrigation ports oriented horizontally. This aims the irrigation fluid sideways and not directly at the corneal endothelium.

Irrigation/Aspiration Handpiece

There are a range of I/A handpieces and vitrectomy handpieces available for most machines. They can be single use or reusable. The I/A handpiece may be straight, bent, or curved (45–90°) to allow for removal of the subincisional cortex. The tip will be rounded and the aspiration port placed on the side rather than the end of the tip. The I/A handpiece, when used in a coaxial method, has a 0.3–0.7 mm port and a silicone or metal infusion sleeve. A larger-aperture aspiration port (0.5–0.7 mm) works best for the canine cortex, which tends to be thick, sticky, and more difficult to aspirate compared to human cortex. A silicone sleeve will have less incisional leakage than a metal sleeve, but can be inadvertently occluded if the tip is manipulated too far laterally. The infusion ports should be directed perpendicular to the aspiration port. The pumps discussed in the fluidics section are also used for I/A, and the same principles apply. Peristaltic pumps are slower to build vacuum and less responsive compared to Venturi and diaphragm pumps, but are also more forgiving with respect to posterior capsular engagement and rupture. Again, vacuum will be linear, with tip occlusion resulting in an increase in vacuum according to the preset and foot pedal position. The foot pedal in I/A mode has two positions compared to the three positions in phacoemulsification mode.

Alternately, during bimanual I/A, one handle for irrigation is in one incision and another handle for aspiration in the second incision. This allows the surgeon to switch the aspiration handpiece to either entry port and makes removal of the subincisional cortex easier.

Foot Pedal

The foot pedal attached to the phaco machine is crucial. There are routinely three positions on most foot pedals. In foot position 1, only irrigation occurs. The flow of material in foot position 1 is *away from the phaco tip*. In foot position 2, both irrigation and aspiration occur. The flow of material in foot position 2 is *toward the phaco tip*. In foot position 3, irrigation, aspiration, and phacoemulsification all occur. Foot position 3 should be reserved for the emulsification of lens material when lens material is engaged at the tip. Sidekick functions of the foot pedal include reflux, as previously described, and on some models continuous infusion mode.

Machine Settings

Optimizing machine settings is an important factor in cataract surgery and can be challenging to understand. The surgeon can adjust and customize the phacoemulsification machine to suit their technique, preferences, and the particular lens to be emulsified. Using the same machine settings throughout every case is simple; however, the power and fluidic objectives change between the different stages of emulsification (i.e., sculpting, chopping, fragment removal, and epinucleus removal). This allows for changing the machine parameters to address issues such as weak zonules.

The amplitude, duration, and delivery of energy can all be controlled. The phacoemulsification power can be delivered in continuous or linear, pulse, or burst modes (Fig. 23.13).

In continuous phaco, there is no "off" period. Power increases linearly as the foot pedal is depressed, which allows the power to be applied at the surgeon's discretion. In general, the power is set to a preset maximum of 80% with the foot pedal fully depressed. Higher power is used for sculpting and lower power for excursions, as the bowl thins, and closer to the posterior capsule. With a very hard canine lens, routinely encountered in older dogs, the preset can be increased to 100%, providing more effective emulsification, but also creates more cavitation bubbles. In pulse mode, there is a fixed period of ultrasound with a fixed period of no ultrasound. Vacuum only is present during periods of no ultrasound. The pulse rate is how many pulses are delivered per second (pps). Traditional pulse mode is limited to 20 pps. The decreased energy expenditure of pulsed technology, which results from rapid on/off cycles, further reduces the dispersive forces that drive nuclear fragments away from the

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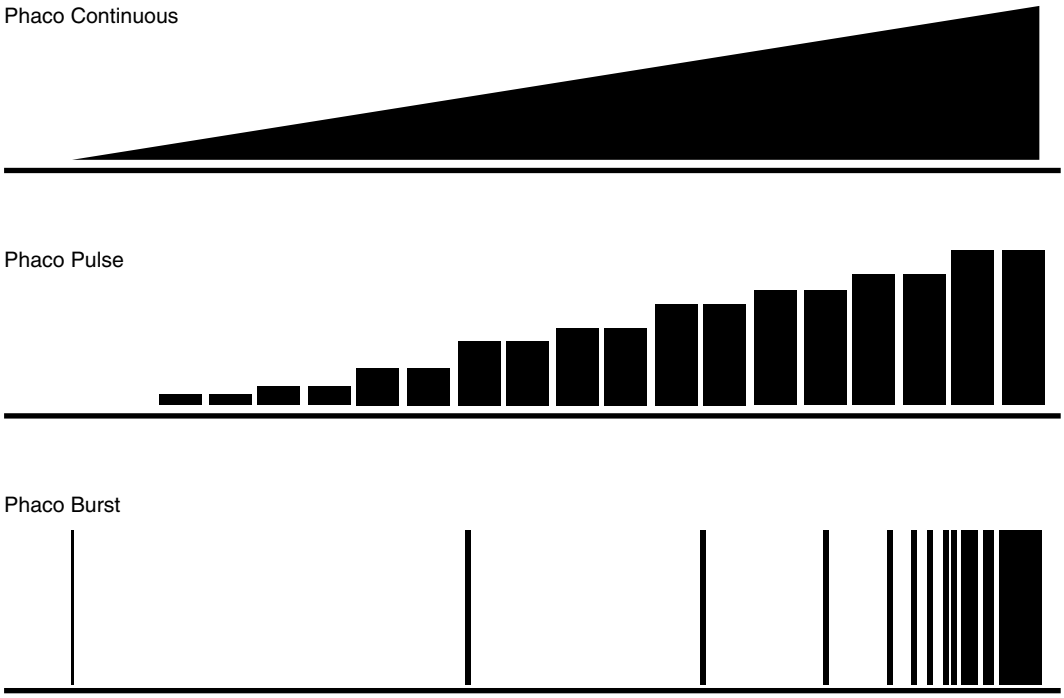


Figure 23.13 Continuous, pulse, and burst modes of energy delivery during phacoemulsification. (Courtesy of Brian Wilson.)

phaco tip. "Hyperpulse" allows for greater than 100 pps. The duty cycle is the ratio of the ultrasound "on" time to total time interval expressed as a percentage. Traditional pulse mode has a duty cycle of 50%, so that 500 ms of energy is delivered per second, which cuts down to 50% the energy delivered compared to continuous mode. Pulse mode decreases the overall phaco time, improves followability, and dissipates heat. Burst mode is where the time interval between each burst decreases as the foot pedal is depressed, and maximum foot pedal depression is equivalent to continuous phaco. Traditional burst mode is about 80 ms and hyperburst can shorten that to as low as 4 ms.

The vacuum setting for continuous phacoemulsification is typically set at 70 mmHg, but can be increased to 200–250 mmHg in the phacoemulsification pulse or burst modes. Some machines can set this even higher. High vacuum is not required when sculpting, since the lens is stable in the capsule. The higher vacuum in the pulse setting is used to grasp loose fragments prior to emulsification and to tear down and collapse a sculpted bowl. The pulse mode will allow the tip time to securely grasp fragments prior to emulsification. The vacuum can be increased in the I/A mode to 300 mmHg to facilitate removal of residual cortical material.

Settings for phacoemulsification have become somewhat more complex with the advent of transversal and torsional ultrasound systems (Assil et al., 2015; Wright et al., 2017; Zacharias 2016a). The roles of transversal and torsional energy, traditional coaxial energy, and pulse/burst modes are often intertwined in efficient, modern phaco systems.

Ophthalmic Viscoelastic Devices and Agents

Once the anterior chamber has been entered, aqueous humor effluxes from the wound and the chamber collapses. Viscoelastic materials, with the properties of both fluids and solids, are used to reinflate and maintain the anterior chamber before and after phacoemulsification and I/A. The viscoelastic agent is injected starting at the distal aspect of the anterior chamber, filling back toward the corneal incision, and expelling the aqueous humor.

Viscoelastics are so important that the term viscosurgery is used to describe surgical procedures using these materials, and they are commonly referred to as ophthalmic viscosurgical devices (OVD) in the human literature (Arshinoff et al., 2002). In addition to filling and maintaining the anterior chamber, the use of viscoelastic minimizes damage to and loss of corneal endothelial cells from turbulence, cavitation, ultrasound, free radicals, and lens fragments during phacoemulsification (Artola et al., 1993; Liesegang, 1990; Wilkie & Willis, 1999). Additional functions of OVDs include smoothing out the anterior lens capsule, preventing or repositioning iris prolapse, tamponade of hemorrhage, hydraulic breaking of posterior or anterior synechia, maintaining mydriasis, hydrodissection, tamponading posterior capsule tears, floating lens luxations, and repositioning vitreous.

There are many different commercially available OVDs for both human and veterinary surgery (Wilkie & Willis, 1999). The human choices are extensive and vary widely in cost. To select an appropriate OVD, the surgeon must understand the

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OVDs' properties and direct that choice toward a surgical goal. No one viscoelastic fulfills all needs. The commonly used OVDs are composed of one or combinations of the following three chemical components: (1) sodium hyaluronate; (2) chondroitin sulfate; and (3) hydroxypropyl methylcellulose (HPMC). The clinical behavior of an OVD is not the result of the specific chemical component, but of combinations of other components such its molecular size, weight, and concentration. This is defined primarily by the molecular chain length of the material, which characterizes the predictable changes in its properties and characteristics under different conditions of fluid movement within the eye.

The rheologic properties of viscoelastics determine the classification, behavior, and utility of each OVD. These include elasticity, viscosity, pseudoplasticity, and surface tension (Arshinoff & Jafri, 2005; Liesegang, 1990; Wilkie & Willis, 1999). Elasticity is the property of a substance to return to its original shape after being deformed. Viscous fluids possess molecular attractions that resist flow. Viscosity is the measure of this resistance to flow. The viscosity of an OVD changes with different flow rates, in contrast to water. The faster the flow of the OVD, the greater the decrease in the viscosity. Zero shear is a term used to describe a condition when there is no fluid movement within the eye (e.g., capsulorhexis performed in an anterior chamber filled with an OVD). High shear describes a condition when there is a high rate of fluid movement within the eye (e.g., I/A). Zero flow, or zero shear rate, represents the maximum viscosity of a viscoelastic, which determines the material's stabilizing effect. Medium viscosity occurs at medium flow of fluid, which describes the mobilizing effects of OVDs. Pseudoplasticity is a property of non-Newtonian fluids (e.g., sodium hyaluronate). It refers to the ease of ability of a material to change from being highly viscous at rest to being watery at higher shear rates. This is not to be confused with surgical retention, which is enhanced by three factors: (1) greater dispersive properties; (2) negative charge; and (3) the presence of hyaluronic acid. Chondroitin sulfate, like air and water, is a Newtonian substance and does not change its viscosity at different shear rates. The presence of chondroitin sulfate makes an OVD more dispersive. Coatability of an OVD describes the surface tension of the OVD itself and also the contact tissue, surgical instrument, or IOL.

OVDs must be sterile, nontoxic, nonpyrogenic, noninflammatory, and nonimmunogenic. In addition, OVD are balanced with respect to their electrolytes, osmolality, pH, and colloid osmotic pressure. There are now four main categories of OVDs depending on their rheologic properties: (1) dispersive; (2) cohesive; (3) viscoadaptive; and (4) viscodispersive. Cohesive and dispersive characteristics are outlined in Table 23.3.

Table 23.3 Summary of characteristics of classic cohesive and dispersive ophthalmic viscosurgical devices.

Type	Cohesive	Dispersive
Viscosity	High	Low
Molecular weight	Low	High
Molecular chain length	Long	Short
Surface tension	Higher	Lower
	Adhere to themselves through intramolecular bonds	Adhere to external surfaces, (e.g., tissues and instruments)
	Resist breaking apart	Easy to break apart
Pseudoplasticity	High degree of pseudoplasticity	Lower surface tension and lower pseudoplasticity
Maintain anterior chamber	+++	+
Flatten anterior lens capsule for capsulorhexis	+++	+
Protect corneal endothelium	–	+++
Ease of removal	Easy	Difficult
Contribute to postoperative ocular hypertension	+++	+/–
Prevent or treat iris prolapse	+++	–
Expand capsule bag for intraocular lens insertion	+++	–
	Avoid supercohesives as they will deflect the intraocular lens	

+++, very good; +, good; –, poor/none.

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Dispersive OVDs act like molasses and stick to and coat intraocular structures (e.g., corneal endothelium, IOL, etc.) and instruments (Kretz et al., 2014). They exhibit a low degree of pseudoplasticity and surface tension and tend to stay in place during the fluidics of phacoemulsification. Since they are retained when injected, they are good for partitioning spaces within the eye, such as after a rupture of the posterior capsule and protecting the cornea endothelium. Dispersives protect the corneal endothelium from the energy and heat of ultrasound power, I/A, cavitation bubbles, turbulence, lens fragments, hydroxyl radicals, instruments, the IOL, and shearing forces. However, they require more effort and time to remove. They are associated with less POH than cohesives and can be left in the eye postoperatively, if needed. Dispersive viscoelastics can also serve to lubricate injector cartridges to aid in IOL insertion. The disadvantage of a dispersive viscoelastic is its tendency to trap bubbles and lens fragments during surgery and thereby decrease visibility. The addition of chondroitin sulfate makes an OVD more dispersive and improves the protection of the endothelium (Bresciani et al., 1996). OVDs made from HPMC possess the lowest viscosity of all OVDs, so are highly dispersive. They are also poorly elastic and minimally pseudoplastic (lack of decline in viscosity with increased shearing rate), which causes them to require large-bore cannulas and increased infusion pressure for injection.

The long molecular chains of cohesive OVDs tend to interlock and intertwine, so they behave as a cohesive unit, like jam or jelly. They tend to leave the eye rapidly when I/A begins or the incision is opened and pressure is applied. This facilitates removal at the end of a procedure. However, removal within seconds of initiation of phacoemulsification leaves the endothelium exposed and predisposes to chamber collapse. Because they are more viscous and create space in their behavior, they are ideal for flattening the anterior and posterior capsule to facilitate planned capsulorhexis, placing an IOL, and for deepening a shallow anterior chamber. They offer low protection to the corneal endothelium. Postoperative IOP spikes have been repeatedly positively correlated to the amount of remaining OVD, particularly cohesive OVD, at the end of surgery (Berson et al., 1983). This is especially true with supercohesive viscoelastics. It is assumed that as the remaining OVD is gradually released into the aqueous humor, it mechanically obstructs the trabecular outflow pathway, and hence decreases the outflow facility. However, other factors have also been positively correlated with the incidence of IOP spikes, including patient predisposition as well as phacoemulsification time and power. For the techniques of removal, see "Ophthalmic Viscosurgical Device Removal" in "Surgical Techniques."

Viscoadaptive OVDs are different from dispersive and cohesive OVDs. They take advantage of both properties of viscoelastics, by being a substance that changes its behavior at different flow rates. At a low flow rate they are supercohesive and remain undisturbed while phacoemulsification continues (pseudodispersive). The higher the flow rate, the more pseudodispersive the viscoelastic is, allowing for better protection of the corneal endothelial cells. Like other OVDs, complete removal of viscoadaptives is essential to reduce the risk of POH. Viscoadaptives may be superior to other OVDs in protecting the corneal endothelium (Van den Bruel et al., 2011).

Viscodispersive OVDs are highly viscous dispersives, combining the advantage of both a cohesive and a dispersive OVD. They provide dual function, space maintenance (cohesive), and superior retention (dispersive) in the same syringe (Arshinoff & Jafri, 2005; Tognetto et al., 2017).

Not surprisingly, it is rheologically impossible to control the surgical environment with a single OVD. Realizing that two separate OVDs offer more versatility than a single agent, companies are now offering combination devices to the human market. Many surgeons prefer to use Healon® 5 (Johnson & Johnson Vision, Jacksonville, FL, USA) in combination with another, more dispersive viscoelastic, in the "soft-shell" technique (Arshinoff, 1999). This technique is based on the sequential use of higher-viscosity cohesive and lower-viscosity dispersive agents without mixing to take advantage of the positive attributes of both, while minimizing their drawbacks (Arshinoff, 1999). The dispersive OVD is placed first to coat the corneal endothelium, and then the cohesive OVD is injected centrally to flatten the anterior lens capsule, deepen the anterior chamber, and force the dispersive OVD toward the cornea. The ultimate soft-shell technique adds a third step of placing a layer of BSS between a viscoadaptive OVD and the anterior lens capsule (Arshinoff, 2002). This is particularly useful in mature/hypermature cataracts where a capsular dye, such as trypan blue, is used to stain the anterior lens capsule. The Tri-soft-shell technique is a unification and improvement of all the soft-shell techniques, from which basic specific applications to unusual circumstances are simple and intuitive (Arshinoff & Norman, 2013). There is no combination device yet marketed to veterinarians and the use of multiple OVDs during surgery has not yet been described.

For most veterinary ophthalmologists, a cohesive viscoelastic is used, with selection based on availability, cost, and volume supplied per syringe. There are a number of companies marketing veterinary OVDs in addition to the available human OVDs (Table 23.4). HPMC is typically lower in cost than sodium hyaluronate OVDs, but sodium hyaluronate is a superior OVD (Wilkie & Colitz, 2013). Single-use cannulas should be used for placement of the OVD or other intracameral substances, as the use of reusable cannulas has been shown to result in the introduction of toxic residues into the anterior chamber (Glasser et al., 1992; Mathys et al., 2008) and could be involved in the development of TASS (Stiles & Townsend, 2015).

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Table 23.4 Description of some OVD available for use in cataract surgery.

Veterinary Marketed	Name	Contents (mg/ml)	Molecular Weight (Daltons)	Viscosity mPa-s	Reported Classification
Addition Technology	VV14	SH 1.4%	2.4×10^6	15,000–20,000	Cohesive
Addition Technology	VV20	SH 2%	2.4×10^6	40,000–60,000	Cohesive
Addition Technology	VV30	SH 3%	2.4×10^6	160,000–200,000	Cohesive
Addition Technology	VVCELL	HPMC 2%	92,000	2,000–4,000	Dispersive
An-Vision	An-bfh 1.8%	SH 1.8%	$1.2–2.0 \times 10^6$	100,000	Cohesive
An-Vision	An-bfh 2.2%	SH 2.2%	$1.0–2.1 \times 10^6$	300,000	Cohesive
An-Vision	An-Viscose	HPMC 2%	Not applicable	4,000–5,000	Dispersive
I-MED	I-Visc	SH 1.0%	2.0×10^6	120,000	Cohesive
I-MED	I-Visc Vet	SH 1.8%	1.2×10^6	750,000	Cohesive/dispersive
I-MED	I-Visc Phaco	SH 2.5%	7.0×10^6	24,000,000	Viscoadaptive
I-MED	I-Cel	HPMC 2%	86,000	6,000	Dispersive
Human Marketed					
Abbott Medical Optics	Healon	SH 1%	4.0×10^6	300,000	Cohesive
Abbott Medical Optics	Healon GV	SH 1.4%	4.0×10^6	400,000	Supercohesive
Abbott Medical Optics	Healon D	SH 3%	645,000	40,000	Dispersive
Abbott Medical Optics	Healon Endocoat	SH 3%	800,000	50,000	Dispersive
Abbott Medical Optics	Healon 5	SH 2.3%	4.0×10^6	7,000,000	Viscoadaptive/ pseudodispersive
Alcon Laboratories	Viscoat	SH 3% CS 4%	500,000 25,000	40,000	Dispersive
Alcon Laboratories	Provisc	SH 1%			Cohesive
Alcon Laboratories	DuoVisc (Viscoat and Provisc) in dual syringe	SH 3%	5.0×10^5	40,000	Dispersive and cohesive
Alcon Laboratories	Dual syringe	SH 1%	2.5×10^6	50,000	Cohesive
Alcon Laboratories	DisCoVisc	SH 1.6% CS 4%	1.7×10^6	75,000	Highly viscodispersive
Bausch & Lomb	OcuCoat	HPMC 2%	> 80,000	4,000	Viscodispersive (very low viscosity)/viscoadherent
Bausch & Lomb	Amvisc	SH 1.2%	$1–2.9 \times 10^6$	40,500	Cohesive
Bausch & Lomb	Amvisc Plus	SH 1.6%	1.5×10^6	55,700	Highly viscodispersive
Zeiss	TwinVisc (combined)	SH 2.2%	1.0×10^6	14,000	Dispersive
		SH 1%	2.0×10^6	30,000	Cohesive

CS, chondroitin sulfate; HPMC, hydroxyl-propyl-methylcellulose; SH, sodium hyaluronate.

Surgical Approach

Every step in cataract surgery is crucial to the positive outcome of the following step. This starts with patient positioning. The operated eye should be facing up and the eyelids and cornea parallel to the floor. The patient and head position are immobilized and maintained using a vacuum pillow. Tape placed across the nose and anchored to the table will also minimize unexpected head movements. Care should be taken that the endotracheal tube does not kink during positioning and guarded endotracheal tubes that prevent this are recommended. The table, surgical chair, and armrest height, as well as the microscope, are positioned and adjusted for the surgeon and assistant. The patient should be routinely clipped and prepared for surgery according to the surgeon's preference.

A lateral canthotomy is indicated to increase exposure and to relieve globe-deforming forces caused by the eyelids and

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eyelid speculum. It may be unnecessary in most brachycephalic breeds and will increase postoperative discomfort. A canthotomy should always be performed when performing intracapsular lens extraction (ICLE) or suturing an IOL. If needed, a stay suture may be placed in the bulbar conjunctiva and Tenon's capsule using 5-0 to 6-0 suture material. Stay sutures are typically not needed with one-handed phacoemulsification or when neuromuscular blocking agents are used. The surgeon can stabilize the globe with forceps in one hand and perform phacoemulsification with the other. Neuromuscular blocking agents should be administered at this time.

Corneal Incision

Cataracts can be removed by phacoemulsification, extracapsular cataract extraction (ECCE), and intracapsular cataract extraction (ICCE). An ideal incision should provide adequate exposure for phacoemulsification and IOL implantation, minimize postoperative astigmatism, form a watertight seal when closed, and have negligible scarring (Glover & Constantinescu, 1997). The location, number, and length of the corneal incisions needed are dependent on the technique being performed. Phacoemulsification is the most commonly employed technique at this time and a clear corneal- or limbus-based incision is the most often used approach in veterinary ophthalmology. It is less time-consuming, results in minimal hemorrhage, and allows excellent visualization of the anterior chamber (Nelms et al., 1994).

In humans, the trend has been to move away from the limbus and into the sclera to reduce astigmatism and improve wound healing. Limbal or corneal incisions are easier to create and provide better access to the anterior chamber, but also are more likely to leak if wound apposition is not precise and heal with more visible scarring. Significant astigmatism does develop in dogs with clear corneal incisions and that error is reduced with a scleral incision (Nelms et al., 1994). However, the benefit of a scleral incision is lost as corneal curvature returns to near normal within 1 month of a clear corneal incision (Nelms et al., 1994). Scleral incisions are also associated with an increased risk of iris prolapse, excessive bleeding, difficulty aspirating the 12 o'clock cortex, and problems with delivering the IOL (Gilger, 1997; Nelms et al., 1994). A transcleral approach with success has been described in the dog (Pedro et al., 2017). An anterior-limbal incision (i.e., 0–1 mm anterior to the bulbar conjunctiva) is a compromise between the clear corneal and scleral incision (Fig. 23.14; Nasisse & Davidson, 1999).

Most veterinary ophthalmologists perform bi-plane two-step groove incisions, which serve to facilitate a watertight closure (Koch & Novak, 1995). However, a recent report showed no significant difference in leakage rates between *ex vivo* uniplanar and biplanar clear corneal incisions in dogs (Snyder et al., 2020). The globe is stabilized with fixation

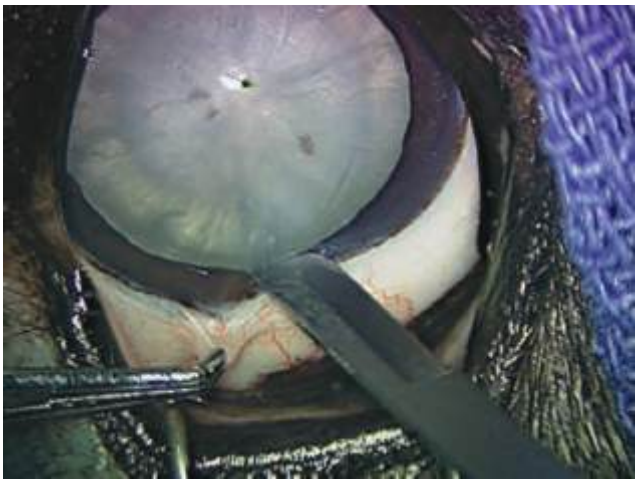


Figure 23.14 An anterior-limbal incision is made using a No. 64 Beaver blade such that the anterior edge of the incision is corneal and the posterior edge scleral.

forceps. Calipers can be used to make a more exact incision length. The incision is made in the dorsal quadrant slightly off the 12 o'clock position toward the side of the surgeon's dominant hand. A round diamond or sapphire knife or disposable No. 64 Beaver blade is used to make the initial corneal groove to a depth of 75%–80% along the distance required to insert the IOL. The length of the initial groove depends on the technique of lens removal planned and the size and type of the IOL for implantation. Foldable IOLs require smaller incisions in contrast to rigid polymethyl methacrylate (PMMA) lenses. If a PMMA IOL is to be implanted, the wound will subsequently be enlarged to 7–8 mm. Foldable acrylic IOLs and their injection cartridges only require enlarging the incision to 4 mm.

The anterior chamber is then entered with an angled keratome in the trough of the initial incision to create a two-plane incision (Fig. 23.15). Once the anterior chamber is entered, intracameral epinephrine (1:10,000) can be placed at this time to facilitate mydriasis and vasoconstriction. The width of this entry incision is critical and corresponds to the width required by the phacoemulsification needle and infusion sleeve. This ranges from 2.8 to 3.2 mm. If the incision is too large, fluidics will be disrupted and maintenance of a stable anterior chamber depth will be compromised. If the incision is too small, the handpiece sleeve can compress against the phaco tip, restricting irrigation fluid flow and generating heat. This subsequently leads to an inability to maintain a stable anterior chamber depth and corneal wound burn (Nasisse & Davidson, 1999).

If a two-handed approach is planned, the second approximately 1 mm incision should be made 70° away from the initial incision to the side of the surgeon's nondominant hand (Fig. 23.16). This incision can be made with a No. 67 Beaver blade or a keratome in a tunnel fashion. It can be performed

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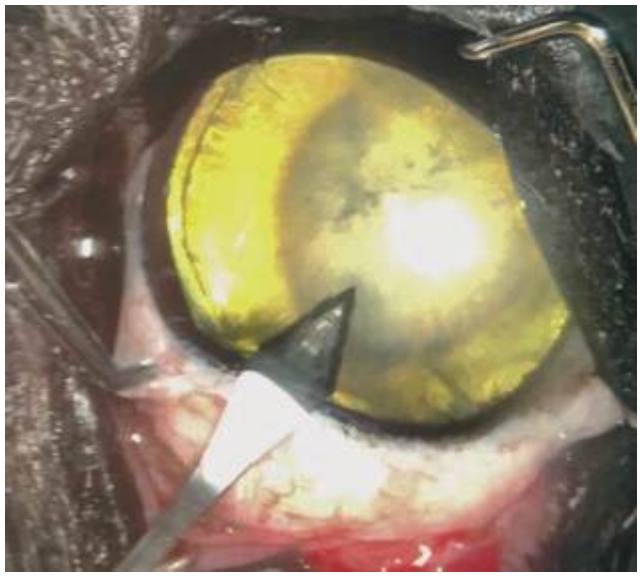


Figure 23.15 The corneal incision is completed and entry into the anterior chamber facilitated by the use of an angled keratome.

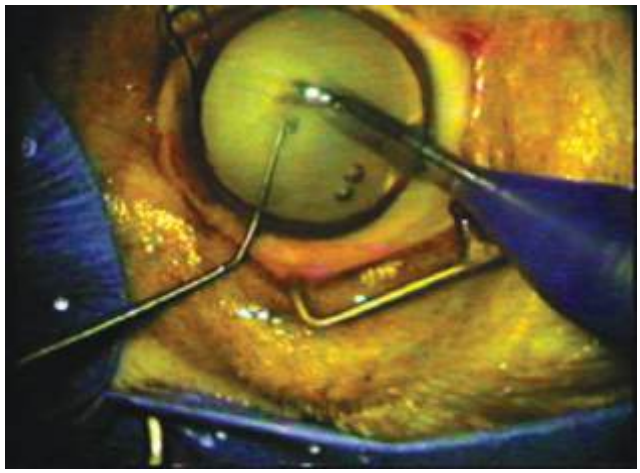


Figure 23.16 Two-handed approach where the second instrument is inserted through a 1 mm incision 70° away from the initial incision to the side of the surgeon's nondominant hand.

prior to entry through the primary incision or following insertion of the phaco tip with irrigation flow turned on. Comfortable performance of the second technique allows for conversion to a two-handed approach at any time during surgery.

Capsulorhexis/Capsulectomy

Following placement of an OVD to maintain the anterior chamber, the anterior capsule of the lens must now be opened in order to gain access to the nucleus and cortex during phacoemulsification. This is one of the most important steps in cataract surgery, especially if IOL insertion is desired (Neuhann, 2010). Increasing the magnification on the operating microscope is indicated at this time. A low-viscosity OVD, such as methylcellulose, can make this step more difficult and a high-viscosity OVD is preferred. Capsulorhexis should be performed prior to phacoemulsification, as this will decrease the chance of creating a radial tear (Arshinoff, 1992; Assia et al., 1991a, 1991b; Gimbel & Neuhann, 1990). Complications encountered or caused at this step, such as radial tears, can lead to significant difficulties downstream in the procedure. A radial tear results from the lens zonules exerting a major centrifugal force on the capsule, which tends to divert tears toward the periphery. The continuous curvilinear capsulorhexis (CCC) was developed to provide a consistent, regular, and reproducible surgical opening (Arshinoff, 1992; Assia et al., 1991a, 1991b; Gimbel & Neuhann, 1990) that did not predispose to radial tears. A CCC can withstand stretching without resulting in a radial tear (Krag et al., 1994). A correctly made CCC can withstand stretching by as much as 62% without tearing (Assia et al., 1991b). This increases safety during hydrodissection, fragmentation, I/A, and IOL implantation. In addition to its intraoperative advantages, a CCC has the postoperative advantage of uniform distribution of forces within the capsule, facilitating IOL centration (Zanini et al., 2003).

There is no right or wrong way to perform an anterior capsulorhexis. A smooth, round edge of appropriate size is the desired outcome. The anterior chamber should be filled with enough viscoelastic to create a positive pressure on the anterior capsule. Depending on the thickness and elasticity of the capsule, the CCC is initiated using a 25-gauge needle, cystotome, Vannas scissors, or using the angled keratome concomitant with entry into the anterior chamber (see Fig. 23.15). The CCC can be initiated at the 12 o'clock position (near the point of entry). If scissors are used to initiate the CCC, the incision is more controlled. Scissors can also be used to extend the entry in both left and right directions following any entry (Fig. 23.17).

Utrata capsulorhexis forceps are then used to complete the CCC, removing a circular portion of the axial anterior lens capsule in either a clockwise or counterclockwise direction (Fig. 23.18).

A surgeon should be able to perform both directions. Right-handed surgeons usually tear clockwise and left-handed surgeons may be more comfortable tearing counterclockwise. The lens can also be phacoemulsified through a small incision (endocapsular or intercapsular) and the capsulectomy is then completed after removal of the lens material. This technique likely protects the endothelium from damage and also allows for perfect entering of the capsulorhexis over the body of the IOL after insertion (Fig. 23.19; Gilger, 1997). However, this technique increases the risk of radial tears and prevents the use of a two-handed technique.

To maintain control of the CCC, it is necessary to grasp and regrasp the capsule every 2 to 3 o'clock positions near

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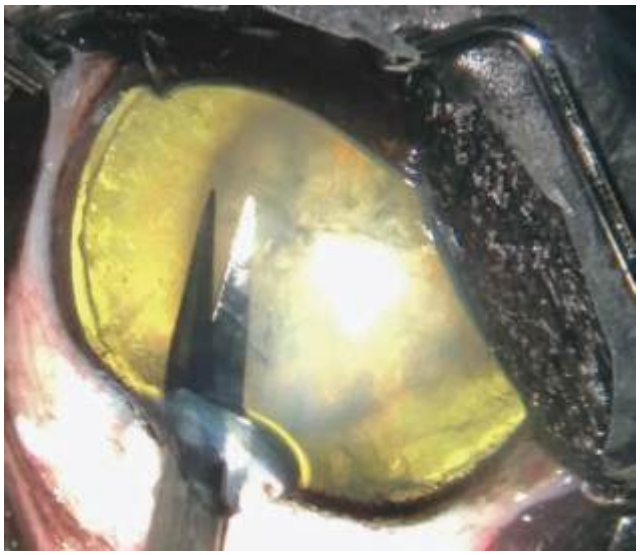


Figure 23.17 Curved Vannas scissors are used to extend the initial capsule entry clockwise and then counterclockwise.

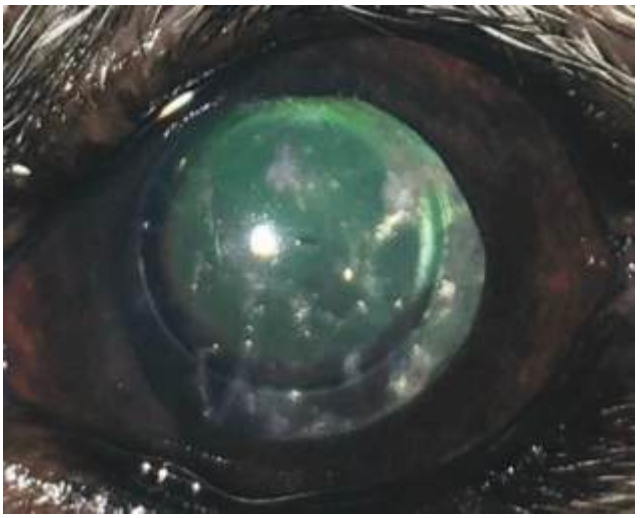


Figure 23.19 Four-month postoperative photo of a centered capsulorhexis over the body of the intraocular lens following endocapsular phacoemulsification. Anterior and posterior capsular opacifications were already present at the time of surgery.

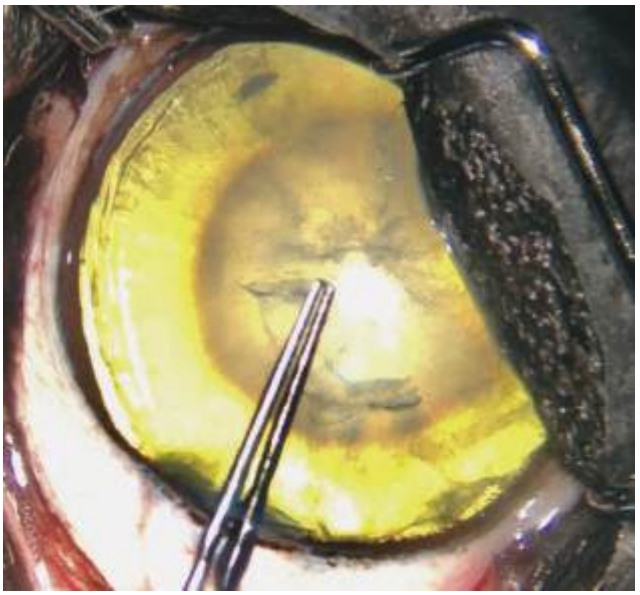


Figure 23.18 The anterior lens capsule is torn using Utrata forceps, folding it over and using shearing and ripping forces to create a continuous circular capsulorhexis.

the point of the tear. Visualization of the tear at all times is paramount. The procedure should be stopped if the surgeon loses sight of the CCC and problem solving initiated. In the face of miosis, OVD and/or a mydriatic agent can be injected near the problem location to attempt to move the iris. Remember, in young dogs with a highly elastic capsule, the force of the viscoelastic alone can uncontrollably extend the CCC and cause a radial tear.

It is critical to understand the physical forces that are harnessed to complete the circular tear. The two main forces used are shearing and ripping, and this is reviewed in detail in other publications (Gilger, 1997; Gimbel & Neuhann, 1990; Seibel, 2005; Fig. 23.20). In brief, the direction of forces applied results in the direction of a tear. A tear proceeds in the direction the capsule is being pulled if the vector of tension produced by that pull is parallel to the initial incision. Shearing forces stop when the instrument creating the forces stops and so allows the direction of the tear to be easily controlled (see Fig. 23.20). Shearing is only accomplished easily if the capsule is folded over or under and onto itself. Ripping forces do not stop when the instrument causing them stops. Ripping forces also result in more tension on the capsule and can easily lead to a rapid tear in an unpredictable direction (Assia, 1991b; Nasisse & Davidson, 1999; Zanini et al., 2003). Ripping also places excessive tension on the lens zonules and should be avoided in zonular instability. Ripping does allow for more abrupt changes in direction when required. Shearing forces should be employed to tear the majority of the circle. When the circle is almost completed, ripping forces are then employed to finish it (see Fig. 23.20). A capsulorhexis will often spiral inward as the circle is completed, resulting in a "Q" sign that is a radial tear off the circle (Fig. 23.21). "Q" signs should always be rectified prior to performing the phacoemulsification. To accomplish this, the tear should be propagated in the opposite direction using the larger-diameter side of the capsulorhexis to turn the tear back into a complete circle.

The size of the capsulorhexis should be approximately 1 mm smaller than the diameter of the IOL optic to be implanted (see Fig. 23.19). A smaller initial CCC may be made and then enlarged following phacoemulsification to minimize the risk of lens herniation into the anterior

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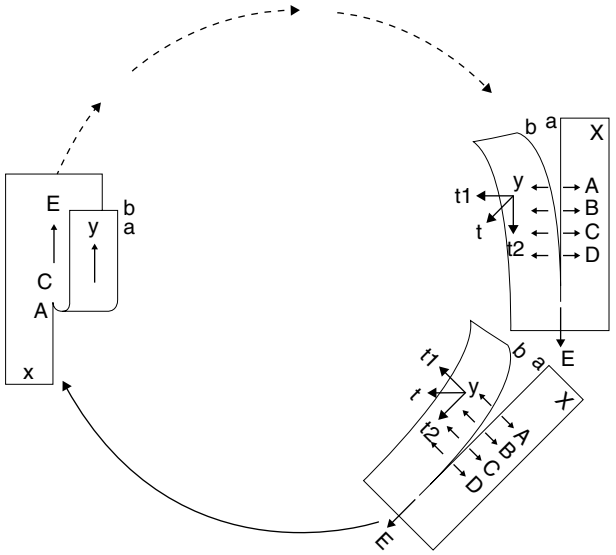


Figure 23.20 The physical forces used to initiate and complete the capsulorhexis in all quadrants. On the lefthand side, shearing forces are demonstrated. Area x remains stationary while area y is folded over and torn from point a to point b. The tear propagates from A to C to E only when the instrument is in motion. On the righthand side in a clockwise direction, ripping forces are initiated. Area x remains stationary as the vector force is pulled in the direction from a to b with vector force t. The component vector t1 is the direction that pulls the capsule apart, while the component vector t2 directs the rip. The arrows going to the right indicate the counterforce of the lens zonules. Stress and then strain increase progressively from A to B to C to D until the strain passes the capsule's breaking point and ripping begins toward E. Ripping can progress uncontrollably in a flash, even when the instrument is held stationary. More force is required to initiate ripping as it is distributed over a larger area (A, B, C, D). (Courtesy of Brian Wilson.)

chamber, and can improve visualization for the final enlargement. To enlarge a capsulorhexis, a cut is made using Vannas scissors to the diameter of the desired rhexis. A tangential cut and not a perpendicular cut to the original capsulorhexis is critical to minimize the risk of a radial tear (Fig. 23.22). Utrata capsule forceps and shearing forces are then used to enlarge the rhexis grasping, and for regrasping as it progresses (Packard & Buratto, 2003; Zanini et al., 2003).

The presence of anterior capsular wrinkling and plaques can result in difficulty performing the CCC and extreme, uncontrollable forces that risk radial tears and unwanted tension on the zonules. The CCC can be propagated through these areas by the use of long, curved Vannas scissors or other scissors. The use of numerous stains to better visualize the capsule during capsulorhexis, including Indocyanine green, trypan blue, fluorescein, crystal violet, gentian violet, and Brilliant Blue G, has been described. Only trypan blue is approved by the US Food and Drug Administration (FDA; Mohammadpour et al., 2012). TASS has been reported to be associated with their use, and care should be taken when placing anything intracamerally (Matsou et al., 2017). Use of radiofrequency diathermy has also been described for performing the capsulorhexis (Luck et al., 1994; Morgan et al., 1996; Speiss et al., 1996). This technique results in significant loss of strength and stretching capability of the capsule margin (Luck et al., 1994; Morgan et al., 1996). Most complications that occur during the capsulorhexis result from a lack of understanding of the forces applied, inadequate visualization, failure to use OVD to pressurize the capsule, capsular plaques/fibrosis, and zonular instability (Gilger, 1997). Newer techniques being employed in human cataract surgery include a disposable automated precision pulse capsulotomy

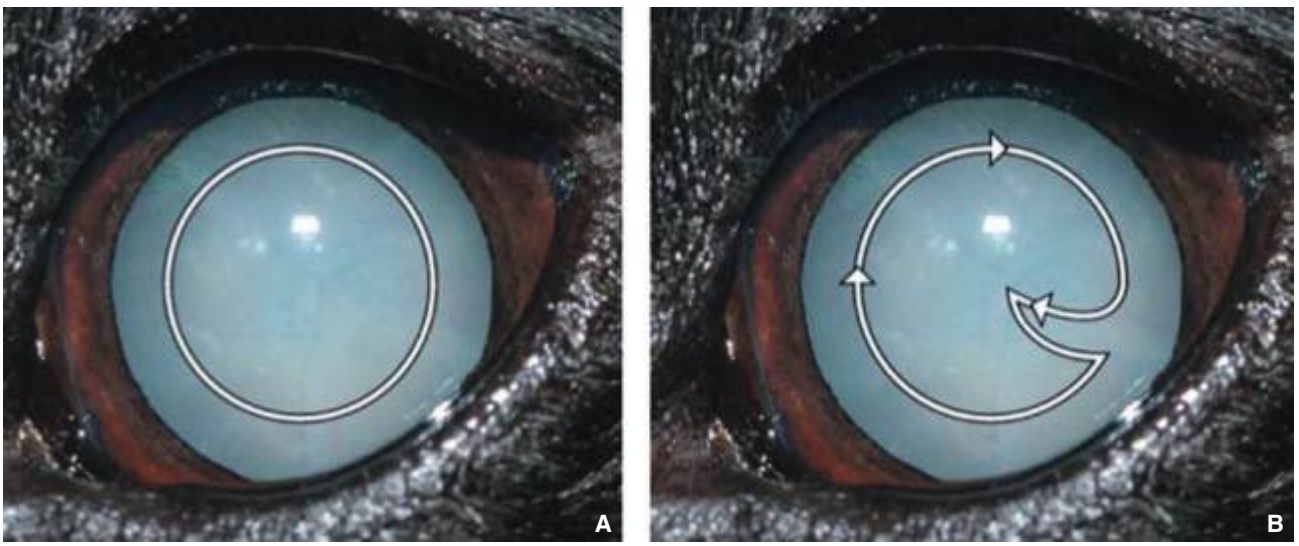


Figure 23.21 **A**. A correctly made anterior continuous curvilinear capsulorhexis (CCC). **B**. An incorrectly made anterior CCC. The clockwise tear (indicated by the blue directional arrows) has spiraled inward, leaving a radial tear and creating the "Q" sign. This is corrected by using the larger-diameter side of the capsulorhexis to turn the tear back into a complete circle. (Courtesy of Brian Wilson.)

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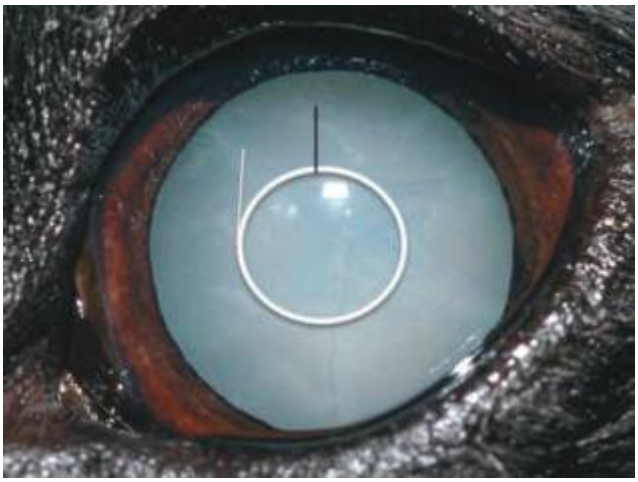


Figure 23.22 The correct location to start a tangential cut to enlarge the capsulorhexis (white line) compared to an incorrect perpendicular location (black line).

device that employs a nitinol filament (Zepto™, Mynosys Cellular Devices, Bloomington, MN, USA) and femtosecond laser capsulotomy (Thompson et al., 2016). Femtosecond equipment is likely cost prohibitive in veterinary surgery at this time, but the disposable capsulotomy device could prove useful in the dog in the future. At this time, the energy it employs is too low for thickened capsules and plaques frequently found in the dog (personal communication, Enry Garcia). Increasing the energy outside the safety data in humans for use in the dog is not recommended.

Phacoemulsification Techniques

Phacoemulsification, automated I/A, and implantation of an IOL to restore emmetropia are the standard of care for cataract surgery in veterinary ophthalmology (Gaiddon et al., 1988; Gilger, 1997; Glover & Constantinescu, 1997; Ozgencil, 2005; Sigle & Nasisse, 2006; Williams et al., 1996). At all times the surgeon must look to maximize efficiency and minimize time and trauma inside the eye. Trauma to the eye associated with the duration of surgery, volume of irrigating fluid, amount and time of ultrasound energy used, turbulence, bounce or collapse of the anterior chamber, and choice of and insertion of the IOL can lead to intraoperative and postoperative complications. Newer phacoemulsification machines, sharp single-use needles, appropriate needle choice, two-handed techniques, and foldable IOLs all contribute to this goal. An operating microscope, knowing when to increase or decrease magnification, and a well-equipped microsurgical pack are also essential to success. Beginning surgeons often hold the instruments too far up the handle and this results in less control, translating small hand movements into larger displacements at the instrument tip. Utmost care must be given to tip position within the eye to avoid contact or energy directed at delicate tissues within the eye.

The four main goals of any cataract surgery are to break the nucleus into fragments, emulsify those fragments, aspirate those fragments, and control surge. These can be accomplished using a variety of techniques that are described in the human literature. These techniques are accomplished using either one-handed, coaxial endocapsular phacoemulsification or a two-handed approach. Two-handed techniques include a second incision where the instrument introduced is a chopper or manipulator, or true bimanual phacoemulsification where the second instrument is also an irrigator and the phacoemulsification handpiece has only ultrasound and aspiration (Buratto & Zanini, 2003b). The advantage of the two-handed technique is that it allows the surgeon more options to crack and divide the lens. This results in decreased total phacoemulsification time and energy. It is especially advantageous in hard cataracts and unstable lenses. The disadvantage of the two-handed technique is the learning curve. The surgeon must now be spatially aware of and account for two instruments within the eye, increasing the risk of damage to intraocular structures.

Techniques described in the human literature include "divide and conquer," "four-quadrant divide and conquer," "phaco chop," "chip and flip," "stop and chop," "stop chop and stuff," and "bevel-down phaco chop." Most are applicable to the dog. The surgeon should be familiar with these techniques to plan their approach, as well as have at their fingertips the ability to face challenges that present intraoperatively.

One-Handed Phacoemulsification

Most beginning veterinary cataract surgeons learn the technique of endocapsular phacoemulsification using a one-handed, coaxial technique. This allows them to focus their attention on a single instrument within the eye. The nondominant hand can then be used to stabilize the globe with forceps. Hydrodissection is not performed, because the lens-capsule adhesion stabilizes the lens so that a second instrument for this purpose is not needed (Buratto & Zanini, 2003b). The goal of this technique is to remove the bulk of the nuclear top, center, and rim (i.e., sculpting) so that the remaining posterior nuclear plate is small enough to be freely attracted to the phaco tip for safe carouseling and emulsification axially at the iris plane. The three phases include central sculpting, nuclear rotation, and removal of residual central and deep nucleus (Buratto & Zanini, 2003b). The foot pedal is engaged to position 2, activating I/A. With the bevel up, the ventral edge of the phaco tip engages the near cortex and nucleus at the proximal edge of the CCC. Foot pedal position 3 is then engaged, activating the ultrasound. The phaco tip is advanced across the lens, sculpting a long groove or "trench" in the lens (Fig. 23.23). The length of the initial trench should be just short of the CCC or slightly beyond, but always keeping the tip visible.

The power needed will depend on the hardness of the nucleus and the needle angle. Too little power, too low of a

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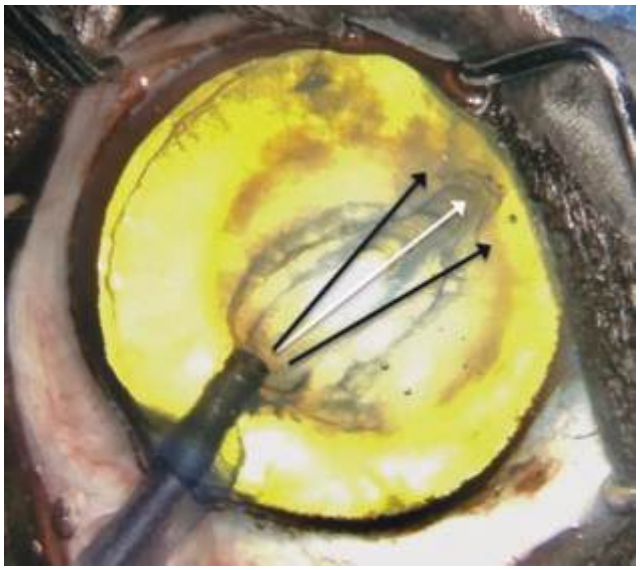


Figure 23.23 The phacoemulsification needle is advanced bevel up across the lens, sculpting a groove in the lens (white arrow). The needle is retracted to the starting point, and the area immediately adjacent to the initial groove is engaged, and a second groove is cut and then a third (black arrows).

needle angle, or moving the probe too fast results in pushing without cutting, leading to zonular stress. The speed of the probe should match the rate of emulsification. The ultrasound power employed using the foot pedal may only be 30%–40% (soft lenses in young dogs or diabetics) or maximum preselected power (hard lenses in old dogs) The lens is "shaved" during sculpting and the tip is never fully occluded. Embedding the tip in the lens nucleus (i.e., lollipop effect) should be avoided. Advance as far as the surgeon feels comfortable, decreasing power as the far quadrant is reached. The needle is then retracted to the starting point, and the area immediately adjacent to the initial groove is engaged (see Fig. 23.23). During retraction only irrigation is used. Aspiration and ultrasound should only be used with lens material in the needle; otherwise energy is released unnecessarily into the eye. This procedure is repeated, sculpting an ever larger, wider, and deeper "bowl." Once the central trench is made, it can be widened by also tilting the probe with the bevel facing toward the center to allow for a more circular track around the edges. The nucleus must be rotated in the bag in 90° increments to allow for sculpting 360°. The nucleus is rotated while irrigating only (Buratto & Zanini, 2003b). The remaining posterior bowl protects the posterior lens capsule. The bowl must now be collapsed or flipped over to continue safely. Suture lines, usually readily apparent in diabetic dogs, should be used when identified to collapse the bowl into quadrants. The use of a Venturi pump or switching to pulse or burst mode with a high vacuum preset (200–250 mmHg) can be initiated at this time. The high vacuum is used to engage an edge of the bowl and pull the wall of the bowl axially with gentle traction. Collapsing and fragmenting the lens can then be accomplished. If these techniques do not result in the collapse of the bowl, the phaco tip can be used to flip the lens over within the lens capsule (Arnold, 1991). The phaco tip is used to engage the proximal aspect of the deep bowl, and gentle pressure is applied slightly downward and peripherally, until the lens flips over into the capsulotomy, opening axially at the iris plane. This should be done with care, as the posterior lens capsule can be lacerated with the edge of the lens or the phaco tip. A handheld disposable nitinol filament loop (miLOOP, Precision Lens, Bloomington, MN, USA) has been designed for human use that achieves full-thickness fragmentation of the nucleus independent of phaco energy. The filament is only about 7 mm long and a modification with a longer filament length may be needed for use in the dog (personal communication, Enry Garcia).

Two-Handed or Bimanual Phacoemulsification

The standard concept of two-handed phacoemulsification uses a second instrument introduced through a 1 mm incision 70° away from the initial incision to the side of the surgeon's nondominant hand. These instruments vary and can range from simple rotators to specially designed chopping devices. The second incision can be made at the start of the surgery or any time during the procedure where indicated. In addition to dividing and chopping, the second instrument can be used for manipulating the lens material, stabilizing the globe, rotating the nucleus, and "feeding" the needle.

There are a variety of techniques or maneuvers discussed in the following sections. The most popular methods are divide and conquer, phaco chop, or a combination of the two; that is, stop and chop. In addition to divide and conquer, phaco chop procedures subdivide the nucleus into smaller fragments that can be emulsified close to the center of the pupil and away from the posterior capsule. Stop and chop starts with a trench as in divide and conquer, stops after the first trench, and then proceeds with chopping techniques. Phaco chop has been described in the veterinary literature (Warren, 2004).

Bimanual microincisional phacoemulsification (B-MICS) is another technique performed through two incisions. The infusion is removed from the phacoemulsification handpiece and attached to the second instrument. The phaco needle can now be used sleeveless and a smaller corneal incision (<1.5 mm) is therefore required. Without a sleeve, pulsed phacoemulsification energy is required to cool the needle. The addition of the infusion to the second instrument also allows the infusion to be directed where the surgeon chooses and improves movement of lens fragments to the aspiration port.

Hydrodissection

Hydrodissection uses a pressurized fluid wave to disrupt adhesions between the lens capsule and cortex. It is routinely

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employed for the technique of two-handed phacoemulsification and it allows the lens to be freely rotated within the capsular bag to facilitate its fragmentation. The need for cortical I/A is also reduced (Gilger, 1997). This technique is not advised for one-handed phacoemulsification, as the lens will be too unstable to fragment efficiently without a lens-capsule adhesion.

Hydrodissection is performed immediately after the capsulectomy, using BSS or a dispersive OVD through a 25- to 27-gauge blunt cannula attached to a 3.0 cc syringe. The cannula should be inserted under the distal edge of the capsulorhexis and immediately adjacent to the anterior capsule. Multiple injections in different quadrants may be required. A fluid wave should be visualized as the injection occurs (Buratto & Zanini, 2003a). It is possible to rupture the lens capsule if too much force is used.

Divide and Conquer

The divide-and-conquer method was initially popularized by Gimbel (1991) and Shepherd (1990) and modified by Nagahara (1993). The essence of this technique is to create a space in the middle of the nucleus where it can be emulsified after breaking it into pieces. It is the safest, but often the slowest technique. The classic technique was intended as a two-handed procedure after hydrodissection, but it can be modified for a one-handed technique in which pie-shaped lens sections are trenched, typically along suture lines, as described previously in basic techniques (Pacifico, 1992). In four-quadrant divide and conquer, the lens is divided with the formation of two trenches at 90° to each other, intersecting centrally. This allows for the cracking of the nucleus into four separate quadrants (Fig. 23.24). Another similar technique termed the "V-shaped or Victory trench" also does not require hydrodissection (Klemen, 1993). In this technique, two deep trenches are made from the 12 o'clock position to the 4 and 8 o'clock positions, respectively, to isolate a central fragment, which can then be safely removed.

The trenches should be 70%–90% of the depth of the nucleus and the width should be twice as wide as the phaco tip (Buratto & Zanini, 2003b). After the trench is made, the phaco tip and lens manipulator or chopper are inserted deep into the groove next to each other. This is done with the foot pedal in irrigation mode only. The instrument in the right hand engages the left side of the groove, while the left instrument inserts against the right side (see Fig. 23.24). The two instruments are moved apart with gentle pressure to crack and separate the posterior rim. The rim will hinge instead of crack if the instruments are not placed deep enough in the groove. The lens is rotated 90° and the second trench is then created. The nucleus is again cracked to obtain quadrants of nuclear material that can be brought to the "safe zone" and emulsified. Quadrant removal should be performed with higher aspiration and vacuum settings than sculpting. The quadrant being targeted should be opposite the wound.

Phaco Chop/Stop and Chop

The bimanual technique of phaco chop was first presented in 1993 by Dr. Kunihiro Nagahara (Nagahara, 1993). This concept uses the phaco tip to impale and hold the nucleus in the central "safe zone" and then uses a chopping instrument to split it into pieces, using forces directed toward the tip. Phaco chop is the basis of a wide variety of chopping techniques, including horizontal chopping and vertical chopping (see Fig. 23.24). Phaco chop has been modified for the dog

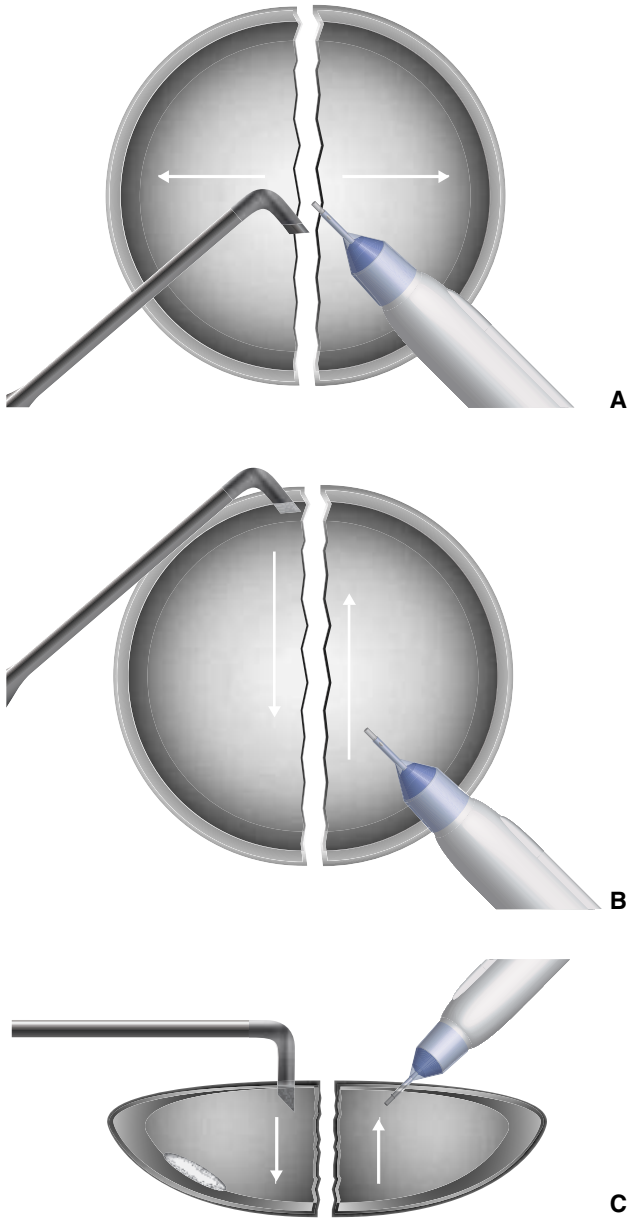


Figure 23.24 **A**. Divide-and-conquer technique, where the forces used are radial and centrifugal. Only the initial trench is shown for the four-quadrant technique. **B**. Horizontal chop technique where the forces are radial and centripetal. **C**. Vertical chop technique where the forces are anterior–posterior and centrifugal. (Courtesy of Brian Wilson.)

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(Warren, 2004). Instead of the typical nucleus rotator, the second instrument for this procedure is a chopper with a 90° angled 1–2 mm tip for humans (Buratto & Zanini, 2003b) that is modified to 4 mm for use in the dog (Warren, 2004). The length of the chopper tip should be approximately 50% of the axial lens thickness (Warren, 2004). After the CCC and hydrodissection, the phaco needle is engaged in the superior portion of the nucleus immediately adjacent to the rhexis. A short burst of ultrasound with high vacuum is used to embed the phaco tip in the lens to hold it. The tip should be 30° or less, as these are easier to occlude. Placing the needle bevel down will improve tip occlusion (Buratto & Zanini, 2003b). The chopper is then introduced under the anterior lens capsule and extended equatorially, rotated 90° to engage the lens, and gently pulled toward the phaco needle. When the chopper nears the phaco needle, it is moved slightly left while the phacoemulsification tip is moved right, splitting the nucleus into two parts (Buratto & Zanini, 2003b; Warren, 2004). The nucleus is rotated and a second chop performed, creating a pie-shaped wedge. Some surgeons will remove this wedge and continue to chop and fragment as they progress, while others will rotate and chop the entire lens into small sections before removing any portion. If the first option is chosen, the vacuum should be high (150–250 mmHg) to engage the wedge and pull it toward the axial pupil for emulsification. The advantage of the second technique is that the lens sections remain in place as the lens is rotated and chopped, thereby maintaining the capsular bag and protecting the posterior lens capsule.

A variation of this technique is Koch's stop and chop, which begins with two to three passes of the phaco tip to remove the axial superficial cortex and epinucleus and create a groove that will be fractured using the divide-and-conquer technique (Buratto & Zanini, 2003b; Koch & Katzen, 1994). This allows for some space to manipulate lens fragments for emulsification, compared to the Nagahara technique that leaves fragments locked together in a puzzle fashion with less space to engage the tip.

Incomplete hydrodissection or a failure to embed the phaco tip or the chopper deep enough into the lens results in difficulties performing the phaco chop technique. Significant dexterity of the nondominant hand is required (Buratto & Zanini, 2003b). The advantages of phaco chop compared to a divide-and-conquer technique include less phaco time and energy, reducing endothelial cell damage, and reduction of zonular and capsular stress (Buratto & Zanini, 2003b).

Chip and Flip/Crack and Flip

The chip-and-flip method is most effective with a soft nucleus (Fine, 1991). In this technique, both hydrodissection and hydrodelineation are performed. Hydrodilineation is performed first to cleave the endonucleus and epinucleus from each other, followed by hydrodissection. The epinucleus shell will protect the posterior capsule while the nucleus is fragmented. A central trench and bowl are sculpted to create a space to flip the nucleus. The rim of the inner nuclear bowl is then chipped at the 5 to 6 o'clock position. The bowl is rotated, and the procedure is repeated until the entire nuclear rim is removed. The inner nucleus is then lifted to the center with the second instrument and removed. The soft epinucleus is now removed by pulling the bowl toward the 12 o'clock position with the nucleus rotator, which allows the 5 to 6 o'clock rim to be safely emulsified. The 5 to 6 o'clock rim is then captured with the phaco needle and pulled, whereas the nucleus rotator is used to depress the proximal extremity so that the outer nuclear bowl is flipped over, thereby allowing it to be easily fragmented and emulsified. The crack-and-flip method is a modification where sectorial nuclear division is added to facilitate removal of a hard nucleus (Buratto & Zanini, 2003b; Fine et al., 1993; Nasisse & Davidson, 1999).

Another modification of the flip-and-chip technique that does not require hydrodissection and hydrodelineation can be used to remove the harder canine lens (Nasisse & Davidson, 1999). First, a large bowl is sculpted in the central nucleus and epinucleus, and a central trench is made. The nucleus is then fractured with the phaco needle and the nucleus rotator. The nuclear bowl is rotated and fractured again to isolate a pie-shaped fragment in the 5 to 6 o'clock position. After the nuclear rim is purchased with the phaco needle, the nucleus rotator is used to depress the apex of the segment so that it flips over and into the superficial capsular bag, where it can be easily fragmented and emulsified. This is repeated as necessary with the remaining nucleus.

Irrigation/Aspiration

Once the nucleus is emulsified, all the residual cortical material must be removed, and this is best performed using the automated I/A handpiece (Fig. 23.25). Manual I/A can be accomplished using a routine or J-shaped Simcoe cannula in certain situations. Residual cortical material most commonly remains adhered to the posterior, equatorial, and possibly anterior lens capsule. Removal of all cortical material lessens postoperative inflammation, PCO, IOL decentration, and capsular sac distortion and folding (Apple et al., 1992, 2000b; Buratto & Zanini, 2003b). Once a surgeon becomes proficient with phacoemulsification, most posterior capsular tears occur during this step.

After the I/A tip is inserted through the incision, irrigation is initiated to deepen the chamber and capsular bag. The I/A port is directed equatorially to the cortex and away from the posterior capsule. Position 2 on the foot pedal is engaged with enough vacuum to grasp but not aspirate the cortex. The tip is rotated up in an ice-scream scoop motion or moved slowly toward the mid-pupil, peeling the cortex off the equatorial lens capsule (Nasisse & Davidson, 1999). In general,

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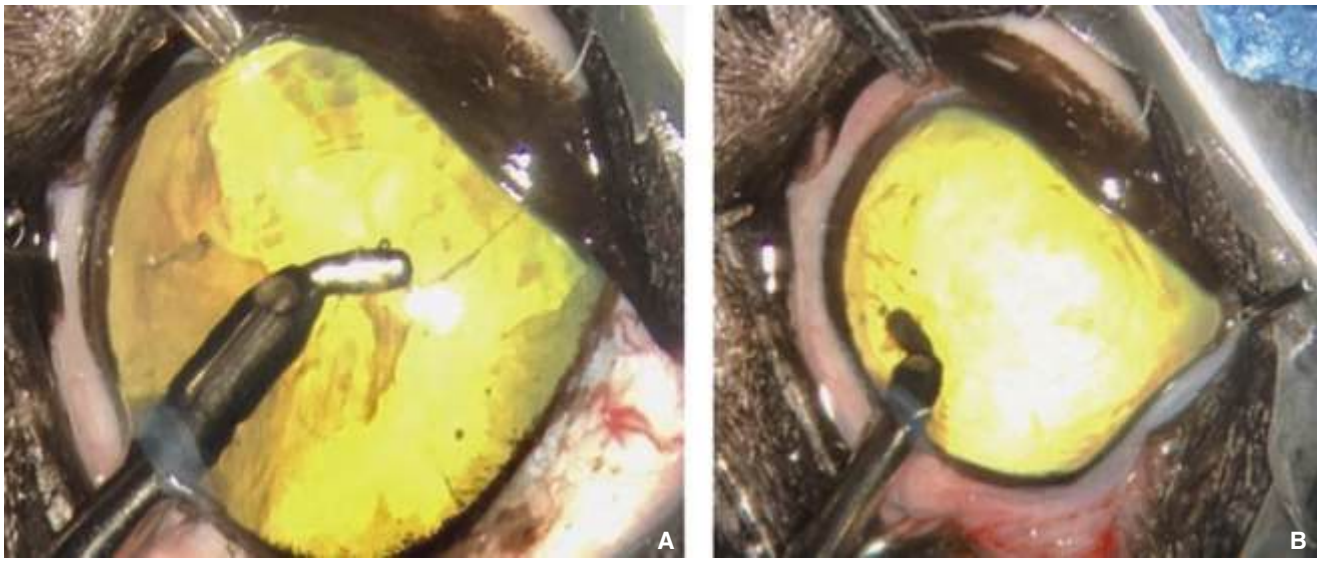


Figure 23.25 **A**. The irrigation tip engages the cortex and then is rolled upward toward the pupillary opening as the cortex is aspirated. **B**. Cortex at the 12 o'clock position should be engaged on either side (11–1 o'clock) and removed first if possible.

vacuum of 100–150 mmHg is used to grasp and peel the cortex, with a preset maximum of 300–400 mmHg used to aspirate the cortex. Aspiration should be initiated when the tip has rolled upward and the aspiration port should be visible at all times. Movements of the tip should be slow and care taken to avoid inadvertent aspiration of the posterior capsule. If the posterior capsule is engaged in the tip, all movement should stop and aspiration reflux be used to disengage it. Evidence of engagement of the posterior capsule is numerous wrinkles or folds directed toward the I/A tip.

The subincisional cortex should be removed first, as this is the most difficult to grasp and easiest when adjacent cortex remains to help grasp and roll or "carousel" it out. A bent, curved, J-shaped, or flexible I/A tip facilitates access to the subincisional capsular bag. Alternatively, the subincisional cortex can be removed after IOL implantation if preimplantation removal fails. The IOL can be used to protect the posterior lens capsule and rotating the IOL in the bag can dislodge the cortex as well.

Lens Capsule: Polishing, Opacities

Following removal of the cortex, capsule washing and polishing using the I/A handpiece constitute the next essential part of cataract surgery. The main purpose of this is to remove LEC, residual cortex, and areas of capsular fibrosis, and to minimize PCO. Capsule polishing should be performed using 12–14× magnification and on both the anterior and posterior lens capsule. It is easiest to use a 0.3 or 0.5 mm I/A opening at a low vacuum setting for the posterior capsule (5–40 mmHg) and a higher vacuum setting for the anterior lens capsule (50–100 mmHg). A low vacuum preset or gentle pressure in foot pedal position 2 can achieve low vacuum. Silicone I/A tips are safer and can be used more aggressively than metal I/A tips. The polishing consists of a combination of vacuum and mechanical abrasion. The I/A port is directed toward the capsule and the capsule engaged using low vacuum. The I/A tip is moved gently back and forth with this procedure, "vacuuming" the capsule. The posterior capsule will wrinkle as it is vacuumed into the I/A port. Great care must be taken to prevent inadvertent posterior capsule tearing during movement of the I/A tip.

If additional polishing and LEC removal are desired, further polishing can be performed. There is some controversy in human ophthalmology as to how much this is required. One study showed a decrease in PCO development following posterior lens capsule polishing (Palik et al., 2012). Another study showed that anterior capsule polishing did not decrease residual cell growth and may actually enhance cell proliferation in capsular bag cultures (Liu et al., 2010), but it did decrease anterior capsular opacification and phimosis (Baile et al., 2012). Capsules with significant plaque formation are frequently encountered in canine cataract surgery and additional polishing is likely beneficial. Further studies are warranted. If the posterior capsule is the target, the lens capsular bag should be distended with OVD to make the posterior capsule as taut as possible. Instruments with angled paddle-like blades such as the Singer sweep capsule polisher, or ring-like or curette-type ends such as the Rentsch capsular curette (Geuder®, Heidelberg, Germany) or Shepherd capsule polishing curette (Katena Eye Instruments, Denville, NJ, USA), are available and listed for use on the anterior or posterior capsule or both. Cannulas such as the Terry Squeegee (Alcon Laboratories) can be attached to the OVD syringe and used to safely polish the posterior capsule.

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Not all capsular opacities can be removed by I/A or with the use of polishing instruments. If they cannot be removed at the time of surgery, are not in the visual axis, or are insignificant in size, they may be left in place. Larger opacities in the visual axis may require removal by a planned posterior continuous capsulorhexis (PCCC) (Fig. 23.26). PCCC is also indicated for management of a nonpatent persistent hyaloid and PHPV/PHTVL (Gemensky & Wilkie, 2004). Posterior capsulotomy can be performed easiest prior to IOL insertion using a cohesive OVD to extend the capsule and prevent vitreous presentation through the capsular opening. Magnification on the operating microscope should be increased to 12–14×. The axial posterior lens capsule can be incised with a 25-gauge needle and/or Vannas scissors. The capsule should then be elevated from the vitreous face using OVD. The PCCC is completed by removing the indicated diameter of the capsule using Vannas scissors, Utrata forceps, or by use of a guillotine vitrector (Castaneda et al., 1992; Gemensky-Metzler & Wilkie, 2004). It is not recommended to have a larger diameter than the body of the IOL being inserted.

Intraocular Lens

The placement of a 41 diopter (D) IOL and return to emmetropia following phacoemulsification is considered standard of care in the dog at this time (Gilger, 1997; Glover & Constantinescu, 1997; Ozgencil, 2005; Sigle & Nasisse, 2006; Williams et al., 1996). The surgeon should consider all variables when deciding to place an IOL or not. As newer lenses become available, the risks of innovative or nonvalidated procedures should always be discussed with the owner.

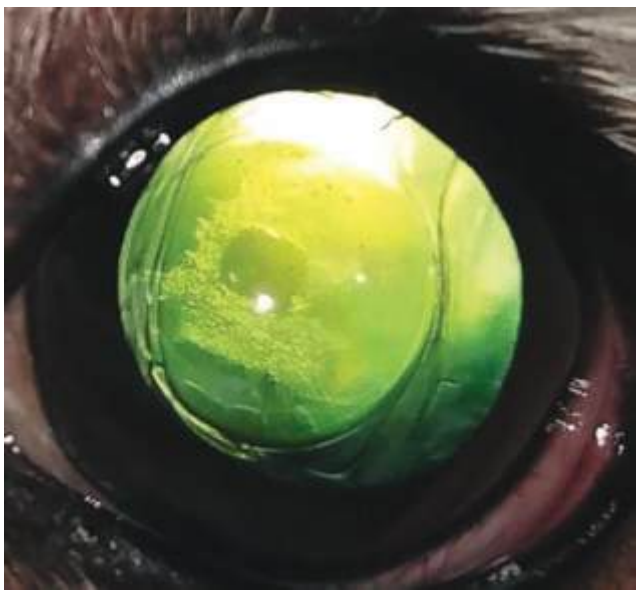


Figure 23.26 A very small primary posterior capsulorhexis in a 3-year-old dog with juvenile-onset cataracts and plaques on the posterior capsule. This continuous curvilinear posterior capsulorhexis (CCPC) could safely be at least 2 times larger. The fibrous changes on the posterior lens capsule surround the CCPC.

Intraocular Lens Design/Material

PMMA was the first biomaterial used in the manufacture and implantation of IOLs in humans by Dr. Harold Ridley in 1949. Significant revolutions in IOL design, construction material, and location of implantation have occurred since then. The materials should be as inert as possible to minimize postoperative inflammation and the design targeted at minimizing PCO, the surgical incision size, and bacterial biofilm formation. The IOL should also be easy to handle and insert. The most common biomaterials used in IOL construction are divided into two major categories: acrylic and silicone (Werner, 2008). Acrylic lenses can be further divided into rigid and foldable IOLs. Rigid IOLs are manufactured from PMMA, and foldable IOLs are manufactured from hydrophilic acrylic (hydrogel) and hydrophobic acrylic. Foldable IOLs were developed to allow for smaller incisions and silicone was replaced with acrylic when it was thought to cause significant intraocular inflammation, although improved versions of silicone IOLs do not show this (Samuelson et al., 2000).

It is apparent that the physical characteristics of the IOL are also important, and it is difficult to differentiate between IOL material and the physical characteristics of the lens when evaluating postoperative changes such as inflammation and PCO (Vock et al., 2009). The uvea's reaction to the IOL is its biocompatibility. Proteins and cells are released in the aqueous humor following cataract surgery and IOL implantation. These proteins then adsorb on the IOL surface and subsequently influence immunologic foreign-body reactions on the IOL (Werner, 2008). Monocytes and macrophages subsequently migrate into the aqueous humor and onto the IOL surface. Monocytes (lymphocytes) transform into small round cells and macrophages into epithelioid and foreign-body giant cells that are responsible for the phagocytosis of debris, bacteria, and foreign material. Giant cells usually degenerate and detach from the IOL surface, and only an acellular proteinaceous membrane remains, isolating the IOL from the surrounding ocular tissues.

The material, size, shape, angulation, and other modifications of the IOL impact the degree of PCO that occurs after surgery. With PMMA IOLs, the biconvex optic and forward haptic angulation designs encourage optic–posterior capsule contact and help to reduce the severity of LEC migration and PCO (Hansen et al., 1988). Acrylic IOLs are designed with single or multiple sharp or squared edges to the optic to inhibit LEC migration and PCO (Kohnen et al., 2008; Kugelburg et al., 2010; Nishi et al., 2000; Ursell et al., 1998; Werner et al., 2005). Additional advantages of a foldable IOL are a smaller incision, ability to implant an IOL in instances of capsular tears, expanding vitreous, and some instances of zonular instability.

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Veterinary cataract surgeons now have the choice of a variety of biocompatible IOL materials and IOL designs. The most commonly employed are PMMA or foldable acrylic IOLs implanted in the capsular bag. Both hydrophilic and hydrophobic IOLs are available. Implantation of silicone IOLs has also been described in the dog (Gaiddon et al., 1997; Neumann, 1991). The average canine lens diameter is approximately 12 mm. The haptic lengths are 15–17 mm for single-piece PMMA IOLs and 12–14 mm for acrylic IOLs in the dog. The length chosen depends on surgeon preference, size of the patient's eye, and degree of memory of the haptics. Most canine IOL optics are 7 mm in diameter with a power of 41 D (Gaiddon et al., 1991). Dogs are 14 D hyperopic if left aphakic after cataract surgery (Davidson et al., 1993). Dialing holes in the optic or haptics, which are designed to facilitate insertion and manipulation of the lens, or in certain instances to attach sutures for fixation, are available in some designs (Fig. 23.27).

The FDA regulates IOL design and manufacturing in human ophthalmology. Veterinary ophthalmologists should hold manufacturers of canine IOLs to the same standards to avoid problems associated with poor manufacturing, inadequate surface polishing, defects at the haptic–optic junction, improper sterilization, or presence of residual polishing compounds (Olivero et al., 1993; Wilkie & Colitz, 2013). In addition, surgeons should record the IOL manufacturer, lot number, and date of implantation to allow tracking if problems arise (Wilkie & Colitz, 2013). It may also be prudent to use two different lot numbers in bilateral cataract surgery. Prior to insertion, the surgeon should aggressively rinse the IOL with sterile BSS to remove any residue that could contribute to TASS or PCO.



Figure 23.27 A foldable acrylic intraocular lens (Acrivet 60-V). The right side of the capsulorhexis is not as circular in the area where a ripping force was used to complete the capsulorhexis.

Basic Intraocular Lens Implantation

OVD is placed to distend the capsular bag and anterior chamber to provide space for implantation and maneuvering of the IOL. The corneal incision is elongated using corneal section scissors to a size dependent on the type of IOL and technique used. This is approximately 8 mm for a 7 mm PMMA IOL and 3.5–4 mm or smaller for foldable acrylic IOLs. The use of an injection cartridge minimizes the incision size needed.

To insert a PMMA IOL, the optic is grasped using IOL forceps (e.g., Shepherd forceps). The haptics are oriented at 6 and 12 o'clock, sweeping counterclockwise with the IOL forceps passing over the 12 o'clock haptic to grasp the optic. The ventral haptic and optic are advanced through the corneal incision and into the lens capsular bag, moving toward 6 o'clock. The angle of insertion of the ventral haptic must be flattened as it enters the bag to avoid traumatizing the posterior lens capsule. The optic is advanced to the midpoint of the capsulorhexis and the IOL forceps removed. The IOL is then dialed in a clockwise direction with an IOL manipulator. This brings the dorsal haptic into the lens capsular bag and completes implantation. The IOL is centered in the visual axis and the haptics should be placed at 3 and 9 o'clock. Alternately, the dorsal haptic can be folded toward the optic with forceps, tucking it into the bag.

Foldable IOLs are implanted using IOL folding forceps or an injection cartridge. Every IOL company has its own injector system, with a cartridge either fitted to or free from the injector. Some IOLs come preloaded in the cartridge. Using the cartridge minimizes iatrogenic trauma and incision size. If using folding forceps, the IOL is grasped with the forceps held in the dominant hand. The IOL is turned 90° from its final orientation and inserted through the corneal incision. The forceps are then rotated upright, and the ventral haptic placed in the capsular bag with the optic oriented axially over the capsulorhexis. The haptics are typically oriented at 12 and 6 o'clock (see Fig. 23.27). The forceps are opened slowly to avoid rapid unfolding of the IOL, and moved posteriorly in the bag to allow the IOL room to unfold. The superior haptic is then positioned in the capsular bag using an IOL manipulator.

If an injector is used, the IOL is loaded according to the manufacturer's directions. A lower-viscosity dispersive viscoelastic or BSS can be used to lubricate the cartridge, but is not always necessary and specific manufacturer instructions should be followed. Examine the injector under the microscope to look for evidence the IOL has pieces caught in the injector. The IOL should slide with no resistance once the plunger is depressed, and advancing it slightly into the injector

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tip to test this is best performed prior to entering the anterior chamber. The tip of the cartridge is passed through the corneal incision, into the capsular bag centrally, and directed toward the ventral capsular equator. The IOL is injected slowly and as the ventral haptic is positioned in the capsular bag, the injector is withdrawn as the IOL emerges to avoid pressure on the equatorial capsule. The superior haptic is then positioned in the capsular bag using an IOL manipulator. Hydrophilic IOLs unfold more quickly than hydrophobic IOLs. The IOL may "roll over" during expression from the injector, and this is suboptimal with IOLs that have a "posterior" side. Care must be taken when flipping it back over not to tear the posterior lens capsule. It is also possible for the haptic to shear and break during injection. The severity of the shear and how much it decenters the IOL affect the decision to remove it, with the attendant possible trauma, or leave it in position.

Implantation of an IOL in instances of lens capsular instability, subluxation, or complete luxation requires modification of the basic technique. This is discussed in the lens luxation section of this chapter.

Ophthalmic Viscosurgical Device Removal

The decision to remove the OVD at the end of surgery is based on the type used (cohesive, dispersive, etc.), preoperative gonioscopy/breed concerns, need for space occupation in the postoperative period (e.g., tamponade, posterior capsular tear, etc.), manipulation and trauma associated with removal, and ultimately surgeon preference. Removal of the OVD is preferred to minimize POH and the risk of postoperative endophthalmitis, and is usually completed after placement of the IOL. Bacteria or the exoskeleton of bacteria can be attached to the IOL, and removal of the OVD and cleaning around the IOL may minimize this (Miller et al., 2011).

Removal can be performed following placement of the IOL using the automated I/A system or manual irrigation. Removal of a cohesive OVD can be accomplished by placing the I/A tip in the central anterior chamber. The I/A tip should then be placed on the anterior surface of the IOL and the lens gently displaced posteriorly, to express any viscoelastic that remains between the IOL and the posterior lens capsule. Removal of dispersive viscoelastics is more difficult, requiring manipulation of the I/A tip, and complete removal may not be possible without inducing trauma. OVD trapped behind the IOL can be removed by multiple techniques, including (1) placement of the I/A tip on the anterior optic of the IOL with no further manipulation; (2) alternately pressing the I/A tip near the edge of the IOL optic anterior surface on one side and then the other to tilt the IOL back and forth without rotation (modified rock-and-roll technique); and (3) placement of the I/A tip behind the IOL. The average amount of OVD retained inside the capsule after using technique 2 or 3 was significantly lower than after using technique 1 (Mitani et al., 2014).

Time of I/A required for removal of an OVD varies by type. Healon and Healon GV were completely aspirated within 20–25 seconds, while removal of OcuCoat® (Bausch & Lomb) took 1–3 minutes, and Viscoat® (Alcon Laboratories) required 3.5 minutes of automated I/A to remove (Assia et al., 1992). In addition to removal from the anterior chamber and capsular bag, it is important to remove an OVD, especially the cohesive types, from the corneal incision prior to closure. Failure to do so can result in poor wound apposition, wicking of aqueous humor outward or contaminants inward, and epithelial downgrowth. Indications to leave the viscoelastic following surgery would include iris prolapse into the corneal incision, intraocular hemorrhage, posterior capsular tear and vitreous presentation, vitreous expansion, or IOL instability.

Wound Closure

Closure of the corneal incision should result in a watertight seal with minimal astigmatism. In veterinary surgery, this is still predominantly accomplished by suturing. The smallest suture that is strong enough to ensure a successful closure and result in minimal suture reaction should be used, and this is typically 8-0 to 10-0 nonabsorbable polypropylene type or absorbable polyglactin 910 (Vicryl™, Johnson & Johnson Medical). Polyglactin 910 comes as a monofilament (9-0), the most commonly used, or braided (8-0) size. The monofilament is easy to handle, results in minimal tissue reaction, and is of sufficient strength. Both the 8-0 and 9-0 come double-armed swaged to spatula needles. A simple or double continuous sawtooth pattern is most common (Fig. 23.28). The latter is preferred for its increased wound strength and decreased astigmatism.

A single suture may be required for the second entry point in a two-handed approach, if the tunnel entry is not self-sealing. A nonwatertight seal can result in aqueous humor efflux and hypotony, fibrin efflux to the incision (Fig. 23.29), IOL decentration, and a possible entry point for bacteria postoperatively. A leaking clear corneal incision on the first day postoperatively was associated with a 44-fold increased risk of endophthalmitis in humans (Wallin et al., 2005). A watertight seal has been associated with POH in humans (Hildebrand et al., 2003).

Intraoperative Complications

The best way to manage intraoperative complications is take steps ahead of time to minimize or avoid their occurrence and be prepared when a setback occurs. Some intraoperative complications can be anticipated based on the preoperative examination, including shallow anterior chamber, anterior capsular fibrosis, vitreous in the anterior chamber, lens instability, synechia, spontaneous lens capsule rupture, lens coloboma, lenticonus, and PHPV/PHTVL. The surgeon should be prepared for intraoperative complications that

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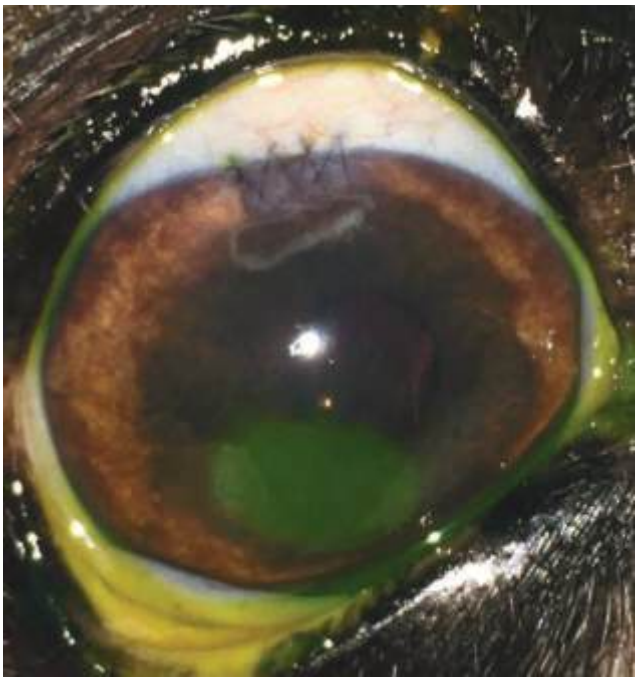


Figure 23.28 A double continuous sawtooth pattern for corneal wound closure following phacoemulsification. A superficial corneal ulcer is also present 2 days postoperatively in a diabetic dog.

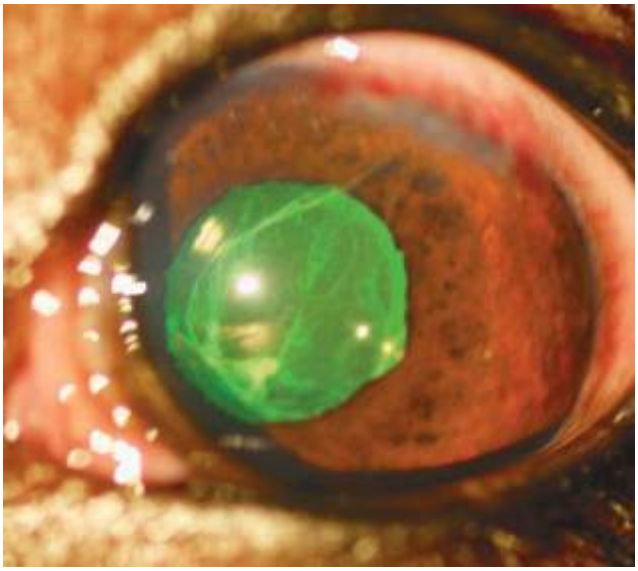


Figure 23.29 A complex of fibrin is surrounding the intraocular lens in the pupillary aperture and strands can be seen coursing toward the dorsal corneal incision 2 weeks postoperatively following routine phacoemulsification.

cannot be predicted ahead of time and should remain calm. Intraoperative complications that occur with little warning can include corneal wound burn, acute fluid misdirection syndrome, iris injury, iris prolapse, pupil constriction, radial tears, zonular issues, posterior capsule rupture, and lens fragment loss, to name a few.

Corneal Injury

Damage to the cornea at the point of incision can occur during construction and usually consists of traumatic stripping of Descemet's membrane. Recognition of a detachment is important and care should be taken not to enlarge it further when positioning instruments into and out of the eye. Iatrogenic trauma can also occur with inadvertent or uncontrolled hand movements resulting in instrument contact, especially near the limbus where the globe is stabilized with forceps during a one-handed technique. The cornea should be irrigated with BSS approximately every 30 seconds during the procedure to minimize epithelial injury.

Corneal incision contracture (CIC) or corneal wound burn is an uncommon but potentially serious complication when temperatures at the incision reach 50–60 °C (Bradley & Olson, 2006; Olson & Miller, 2005; Sorenson et al., 2012). However, thermal injury can occur at lower temperatures (Olson & Miller, 2010, Jun et al., 2010). Thermal injury is caused by heat transferred from the phaco needle to the incision leading to collagen contracture and distortion of the incision. Factors that contribute to CIC include higher energy used to divide the nucleus, OVD choice, and an incision that is too small for the phaco sleeve causing compression against the needle and restricting irrigation inflow (Sorenson et al., 2012). The lowest incidence is seen when prechopping is employed and the highest incidence with divide-and-conquer, stop-and-chop, and carousel techniques (Bradley & Olsen, 2006). The amount of heat transferred is also dependent on the OVD used and has been reported to be higher with the use of Healon 5, followed by OcuCoat and Viscoat (Sorenson et al., 2012). An aspiration bypass port present in the needle can decrease the risk of thermal injury. Signs of CIC include flash whitening of the cornea at the incision and gaping of the incision. Performing phaco under too high magnification will not allow the surgeon to visualize the incision site during the procedure and should be avoided. Ultrasound should be stopped immediately when changes are noted and the underlying issue addressed. CIC can result in corneal melting, wound gape, aqueous leakage, hypotony, synechia, and bacterial entrance into the anterior chamber (Sorenson et al., 2012).

Anterior Chamber Depth Abnormalities

The degree to which a diabetic dog's lens can swell, especially with concurrent capsule rupture, can be profound (see Fig. 23.7). The resulting loss of anterior chamber depth can be so great that the initial paracentesis risks capsule entry and/or corneal endothelial damage. Care must be taken to enter the chamber without penetrating the lens capsule in an unwanted location. The anterior chamber can be inflated

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as much as possible with a higher-weight cohesive viscoelastic. The anterior lens capsule can also be punctured in the center or slightly dorsal, but still within the planned CCC, with the 45° tip of the phaco handpiece or Vannas scissors, allowing for liquid cortical material removal, a deeper anterior chamber, and a controlled CCC (Genc et al., 2016). The forces required to perform a manual CCC are typically not possible if the capsule is ruptured. Intraocular Vannas scissors or diathermy capsulectomy can also be used. If the anterior lens capsule is not stable enough to hold an IOL or is protruding through the pupillary opening, the anterior or entire lens capsule may need to be removed. Hydrodissection with a dispersive viscoelastic should be avoided, as the posterior "wave" may push lens material out of the rupture.

Acute fluid misdirection syndrome or acute intraoperative rock-hard eye syndrome has been reported in the human literature, but has not been reported in the veterinary literature (Grzbowski & Kanclerz, 2018). The author has experienced something similar to it during phacoemulsification in a Golden Retriever with extensive iridociliary cysts and posterior synechia.

Intraoperative Miosis

Adequate initial pupil dilation as well as maintenance of dilation during surgery are necessary for safe and efficient phacoemulsification. The mechanical expansion of the iris with OVDs and intracameral bolus use of various mydriatics can augment the preoperative mydriasis. Constant irrigation during the procedure of mydriatic combinations usually prevents intraoperative miosis. If intraoperative miosis occurs, intracameral use of 1:10,000 epinephrine as previously described (0.1 mg/ml) or 1–2% lidocaine will usually result in mydriasis (Park et al., 2009).

Pupil expansion devices are still needed in up to 10% of human cases (Malyugin, 2007; Zarei-Ghanavati & Bagherian, 2015). Iris Hooks (MST Microsurgical Technology, Redmond, WA, USA) and pupil expansion devices of various designs (e.g., Malyugin ring, etc.) can also be employed in canine surgery. These devices vary in materials, pupillary margin fixation mechanisms, and ease of manipulation during implantation and removal.

Iris Prolapse

Iris prolapse through the corneal incision can result from vitreous expansion, incorrect size and topography of the corneo-limbal incision, inadequate dilation of the iris, presurgical iritis, intraoperative iris trauma, excessive irrigating fluid velocity, and overfilling with OVD posterior to the iris. A more anteriorly placed incision, decreasing infusion velocity, care with OVD placement, and gentle tissue handling will minimize the occurrence of iris prolapse. If iris prolapse occurs, a cohesive viscoelastic can be used to reposition it, facilitating closure and reforming the anterior chamber. Once the incision is closed, a 30-gauge cannula can be inserted through the incision and the iris gently irrigated with BSS or an OVD and mechanically displaced from the corneal wound. Intraoperative miotics are of limited reported benefit (Wilkie & Colitz, 2013).

Intraocular Hemorrhage

Intraocular hemorrhage can occur for a variety of reasons, including preoperative uveitis, intraoperative tissue trauma, and tension on the zonules. Intraoperative use of epinephrine, gentle tissue handling, and use of viscoelastic agents decreases the likelihood of hemorrhage. If hemorrhage occurs, a small amount of epinephrine directed at the site of the hemorrhage and then a dispersive OVD followed by a cohesive OVD over this can tamponade it (Rypniewska et al., 1993). I/A can also be used to clear hemorrhage as it forms, making it less significant to intraoperative visibility. Postoperatively, use of tissue plasminogen activator (tPA) can be considered to prevent fibrin clot formation (Gerding et al., 1992). However, there is a possibility of rebleeding when tPA is used intraoperatively.

Anterior Capsule Fibrosis

Capsular wrinkling and fibrosis can make completion of a CCC using forceps difficult. Capsule entry may require a sharp stab with a 23–25 g needle or the use of intraocular scissors. Long, curved Vannas capsulotomy scissors can then be used to extend and/or complete the capsulectomy. Defects in the capsule at the point of scissor tip closure can predispose to a radial tear. A two-handed capsulorhexis technique using Duet® microsurgical forceps and scissors (Microsurgical Technologies, Redmond, WA, USA) will facilitate a capsulorhexis in cases of severe fibrosis or with lens instability (Wilkie & Colitz, 2013). Alternately, the capsulorhexis can be completed after phacoemulsification is performed through a small capsulotomy or using bipolar radiofrequency diathermy.

Lens Capsule: Continuous Curvilinear Capsulorhexis too Small

The initial CCC can be too small, either intentionally or unintentionally. A small intentional CCC may prevent displacement of the lens material into the anterior chamber during phacoemulsification. However, too small a capsulorhexis can lead to radial tears when tension is placed on the capsulorhexis edge during phacoemulsification. The CCC can be enlarged to the desired size before or following phacoemulsification and IOL implantation performed as described in the section on capsulorhexis.

Lens Capsule: Radial Anterior Tears

Anterior capsular tears or radial tears should be prevented, rather than managed (Fig. 23.30). They most commonly occur during capsulorhexis, followed by during phacoemulsification. Many factors play a role in the occurrence of a

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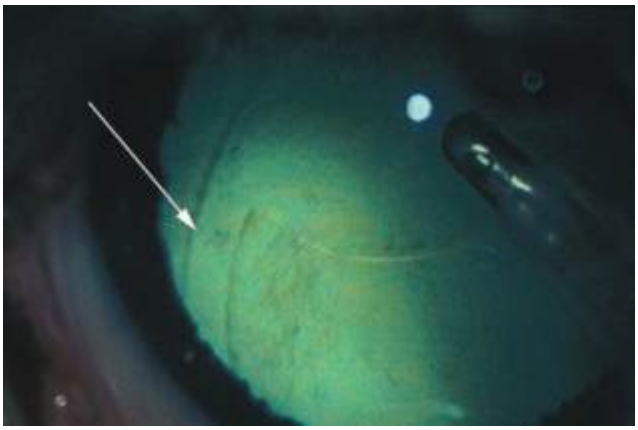


Figure 23.30 A large radial tear extending equatorially (arrow).

radial tear, including a shallow anterior chamber due to inadequate OVD, weak zonules, high positive vitreous pressure, intumescent and hypermature cataracts, fibrosis or plaques on the capsule, pediatric cataracts with elastic capsules, and inexperienced surgeons. Radial tears can then lead to further serious complications that include zonular rupture, extension to a posterior capsular tear, insufficient capsular support for the IOL, displacement of the IOL haptic out of the capsular bag, IOL decentration, and lens material loss into the posterior chamber (Assia et al., 1991a, 1991b, 1993). The most common reason for IOL decentration is the presence of a radial tear (Assia et al., 1993).

If a radial tear is discovered, the rhexis should be stopped immediately and a plan formulated to rescue it if possible. Bringing it back into the central circular capsulorhexis as if you were making a larger CCC is optimal. This will most likely need to be performed from the opposite direction to avoid extending the tear. Tension directed away from the tear will enlarge it. Carefully refill the anterior chamber with OVD to increase positive pressure. Do not attempt to manipulate a radial tear in a location in which it is not visible (i.e., under the iris). Vannas scissors should be used in this situation to complete the CCC where it is visible. Hydrodissection should be avoided, as it will expand the capsule and extend the tear (Packard & Buratto, 2003). An IOL can still be placed depending on the number and extent of a radial tear. The haptics should be directed as far from the radial tear as possible. The IOL should also have maximal haptic–capsule contact to increase IOL stability and a decreased likelihood of haptic displacement from the capsule into the sulcus. Acrylic IOL appear less likely to migrate and displace out a radial tear (Wilkie & Colitz, 2013). Appropriate sizing of the IOL is crucial to minimize tension on the tear.

Lens Capsule: Posterior Tears

Posterior capsular tears (PCTs) should be prevented, rather than managed (Gimbel, 2001). If a PCT does occur, it is essential to stop and stabilize before proceeding. These tears can occur at any time during cataract surgery, including during nucleus fragmentation (41%; Mulhern et al., 1995; Osher & Cionni, 1990), during I/A (Gimbel & Neuhann, 1990), during posterior capsule polishing (28%; Osher & Cionni, 1990), during hydrodissection, and during IOL implantation. Factors implicated in PCTs include deep sculpting, sharp nucleus edges, excessive pressure, and continued extension of an anterior capsular radial tear (Packard & Buratto, 2003). Other factors implicated in posterior capsule tears include the active vacuum at the needle tip, flow rate, needle gauge, sharpness of the needle, and burrs on cannula tip use during polishing (Meyer et al., 2010). In humans, the incidence of PCT has been reported at 0.45%–5.2% across all levels of surgical experience (Hong et al., 2015). In veterinary cataract surgery, the incidence of planned or accidental PCT has been described to occur in 14%–16% of cases (Johnstone & Ward, 2005; Nasisse et al., 1991).

A PCT can be associated with significant morbidity. Consequences of PCT include retained lens fragments, vitreous prolapse or traction, RD, endophthalmitis, ocular hypertension, uveitis, hemorrhage, and corneal edema. An increase in IOP has been shown to occur with a PCT in dogs during both the sculpting and IA portions of the surgery (Kang et al., 2018). All cataract surgeons should be prepared with a structured disaster plan if they occur. The three main steps are: (1) identify it; (2) stop and stabilize it; then (3) choose your surgical strategy. This will depend on when it occurs during surgery, its size, and its location. Surgical strategies should be focused on maintaining further capsular integrity, stabilization of lens fragments in the anterior chamber if possible, removal of retained nuclear and cortical lens material, prevention and management of vitreous prolapse and traction, placement of an IOL if possible, and protection of the corneal endothelium. A PCT is still compatible with an excellent postoperative result when managed appropriately.

Suspicion or evidence of a PCT includes loss of controlled capsulorhexis, increased depth of the anterior chamber, abrupt disappearance of lens material, lack of nucleus followability into the phaco tip, vitreous visualized in the bag, and visualizing the tear. The irrigation rate should be decreased and the irrigating fluid directed away from the PCT to prevent pushing lens material into the vitreous as well as enlarging the tear. In many instances, it may be best to convert to a bimanual technique, placing a separate infusion port into the anterior chamber, directing the infusion away from the capsular tear/vitreous face, and thereby minimizing further progression of the tear. Decreasing the ultrasound power and increasing the vacuum may also be indicated (Packard & Buratto, 2003). A dispersive viscoelastic should be placed over the tear and then covered with a cohesive viscoelastic to stabilize the tear, tamponade the vitreous, and elevate lens fragments as far anterior as possible (Chiu, 2014; Packard & Buratto, 2003). Overinflation with

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viscoelastic will expand the tear and viscoelastic should be injected slowly and moderately (Packard & Buratto, 2003). At this time if possible, a small linear or triangular PCT is best converted into a circular tear by means of a planned PCCC (Castaneda et al., 1992) using Utrata forceps and or Vannas scissors. It has been demonstrated that this will minimize the progression of the capsular tear and facilitate IOL insertion. Phacoemulsification can be reinitiated away from the PCT when lens fragments have been liberated from vitreal attachments and the tear stabilized. The use of a Sheet's glide has not yet been described in the dog (Michelson, 1993). Lens fragments should be engaged with the phaco tip only after occlusion has been achieved. If the capsular tear occurs during capsule polishing, continued polishing may be ill advised. Remember, "the enemy of good is better" and a good surgeon will know when to stop (Wilkie & Colitz, 2013). All further movements should be directed toward the tear to avoid enlarging it.

In general, if vitreous is present in the anterior chamber, a partial vitrectomy is indicated. Most phacoemulsification machines include an oscillating and/or a guillotine vitrector and conversion is simple and rapid. In general, it is preferred to perform either a dry vitrectomy that uses viscoelastic agents to maintain the chamber, or a low-flow bimanual vitrectomy that uses a separate infusion port, rather than coaxial infusion to minimize further disruption of the posterior lens capsule and vitreous. The single-port I/A sleeve provided with some vitrectors should not be used, as this will direct infusion into the vitreous, exacerbating the problem by hydrating and expanding the vitreous (Gimbel, 1990).

In humans with PCT, anterior vitrectomy was required in 44% of cases (Mulhern et al., 1995). Vitreous will follow the path of least resistance down a pressure gradient into the anterior chamber and out of the corneal incision. Identification of the location of any vitreous is paramount. The off-label use of preservative-free intracameral triamcinolone (Triesence®, Alcon Laboratories) diluted 10:1 with BSS has been reported to more easily identify prolapsed vitreous through the tear (Arbisser et al., 2016; da Silva, 2017; Vasavada et al., 2013). Viscoelastic in the anterior chamber can prevent dispersion of the triamcinolone. Complications of triamcinolone staining are uncommon, but its use is associated with higher rates of ocular hypertension and, rarely, endophthalmitis (Gungor et al., 2014; Jonas et al., 2005; Kasbeckar et al., 2013; Lee et al., 2007). Triamcinolone can cause delayed ocular hypertension, which can persist for several months after surgery (Angunawela et al., 2009). A newer technique using an endoilluminated infusion cannula can also help identify vitreous in the anterior segment during bimanual technique (Nichamin, 2012).

If vitreous prolapses into the corneal wound, great care should be taken not to allow further prolapse or traction. The topic of whether to clear corneal incisions of vitreous by performing dry vitrectomy with a cellulose (Weck-Cel®, Labtician Ophthalmics, Oakville, Ontario, Canada) sponge is controversial (Arbisser et al., 2016). Pulling the vitreous with a cellulose sponge by itself risks retinal injury and severing vitreous strands internally with automated vitrectomy may be indicated first. However, Weck-Cel vitrectomy may be warranted to avoid entanglement of externalized vitreous in subsequent surgical maneuvers. Weck-Cel sponges should never enter the anterior chamber or contact the iris. To minimize vitreoretinal traction, any vitreous that adheres to a sponge should be cut immediately, without pulling or stretching (Chiu, 2014).

IOL placement depends largely on the stability of the anterior and posterior capsule and the size of the tear. If a small PCT is present, but the remaining capsular bag is intact and stable, an endocapsular IOL is preferred. An acrylic IOL of appropriate size that does not require dialing will improve lens placement and minimize vitreous presentation. Careful distension of the capsular bag with OVD provides space for IOL insertion without further capsule damage. Placement of even a slightly too large IOL in the bag may propagate the tear and result in loss of the IOL posteriorly. When possible, the IOL haptics should be positioned away from the tear, but once the IOL is settled in the bag, further attempted manipulation may be ill advised. If the capsule disruption is severe, then options include aphakia versus suturing a posterior chamber IOL in the ciliary sulcus using an *ab interno* or modified *ab externo* approach (Nasisse & Davidson, 1999; Nasisse & Glover, 1997; Wilkie et al., 2008). One study reported that IOL placement occurred in 76% of canine eyes without a PCT, but in only 31% of eyes with a posterior capsular tear (Johnstone & Ward, 2005). This decreased to 15% when the PCT was accidental (Johnstone & Ward, 2005). Displacement of the IOL into the vitreous is extremely rare, but could occur immediately following placement. A method for sectioning and removal of an acrylic IOL in the vitreous has been described (Vilaplana & Prazos, 2013). Any manipulation of IOLs or lens fragments in the posterior chamber can predispose to RD.

Displaced/Dislocated Lens Fragments

The sudden disappearance of a lens fragment may be the first jarring sign of a PCT. Complications associated with retained lens material include elevation in IOP, corneal edema, inflammation, and retinal tears and detachments (Borne et al., 1996; Mulhern et al., 1995; Vanner & Stewart, 2011). Postoperatively, systemic NSAIDs or corticosteroids and antibiotics may be indicated in these patients.

Options for removal of displaced lens material include manual removal, floating the posteriorly displaced lens fragments anteriorly with OVD, and automated vitrectomy (Arbisser, 2012; Hong et al., 2015). Important questions to answer include whether the retained material is cortical or nuclear, whether it is still within the bag or now in the vitreous, what amount of lens material is in the vitreous, and

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what is the consistency of the vitreous. A small amount of residual nuclear lens material can be left in the vitreous with possibly minimal reaction (Mulhern et al., 1995). Retained cortical material is more reactive, and should be removed if possible. However, a small amount can be resorbed (Gilliland et al., 1992). In humans, long-term visual acuity is better if the material is removed via par plana vitrectomy (Gilliland et al., 1992; Mulhern et al., 1995). In veterinary medicine, the majority of cataract surgeons do not have the equipment to perform a pars plana approach. Removal of the lens fragments can be performed through the limbal incision provided that care is taken to avoid further disruption of the vitreous.

Manual retrieval of lens material requires enlargement of the corneal incision. Active irrigation should be avoided, as it will cause further vitreal prolapse. Kansas nucleus-removal forceps are also useful in removing lens fragments. Viscoelastic material may be used to float posteriorly displaced lens fragments into the lens bag if the vitreous is liquefied, or, in instances of more solid vitreous, after the overlying vitreous is removed using a vitrector. Alternately, a vitrector can be used to cut and aspirate smaller pieces of lens material in the vitreous body. This is especially effective for cortical material, and a guillotine vitrector works best. When performing a vitrectomy, a low-flow bimanual technique is best, or viscoelastic material is used to vault the chamber and a dry vitrectomy is performed (Borne et al., 1996). Although cortex can be removed with the vitrector handpiece in irrigation-aspiration-cut mode, manual aspiration of cortex with a cannula may be more controlled. Displaced lens material is also another appropriate situation to keep in mind that the "enemy of good is better" (Wilkie & Colitz, 2013).

Expanding Vitreous Syndrome/Vitreous Presentation

Spontaneous expansion of the vitreous (i.e., expanding vitreous syndrome) may occur in eyes with an intact or disrupted posterior lens capsule. Causes include external forces on the globe, brachycephalic anatomy, or overhydration of the vitreous body by irrigation fluids or systemic intravenous fluids. Clinically, the intact posterior lens capsule moves anteriorly and in some instances will protrude through the anterior capsule opening and into the anterior chamber. Expansion while lens material is still present that requires phacoemulsification is a dangerous situation, with posterior capsule tearing and lens fragment loss imminent.

Solutions, in the presence of an intact posterior capsule, include relieving external forces on the globe by repeat administration of a nondepolarizing neuromuscular blocking agent if indicated, performance of a lateral canthotomy, and enlarging the eyelid speculum. A high-viscosity cohesive OVD should be introduced in an effort to vault the capsule posteriorly. The IV fluid rate may also be lowered. If the vitreous expansion cannot be controlled, it may prevent insertion of the IOL or the IOL may extrude following implantation, especially if the anterior capsulorhexis is too large. There is currently no evidence to show that premedication with carbonic anhydrase inhibitors or osmotic diuretics to prevent vitreous expansion is efficacious.

Lens Capsule: Zonular Dehiscence

Zonular instability is the bane of any cataract surgeon and can range from mild to severe. Many times it can be clinically identified prior to surgery, but not always. Older animals and breeds of dogs predisposed to zonular disease are at increased risk. The stage and chronicity of the cataract also increase the risk, as more chronic hypermature cataracts are more likely to have zonular issues. In cases of severe capsular instability, conversion to an open-sky extracapsular or ICLE may be indicated (see "Surgery for Lens Instability"). Phacoemulsification is always preferred and zonular dehiscence of 180° or less should still be amenable to phacoemulsification with a two-handed technique (Coret & Elies, 2003; Por & Lavin, 2005). Some surgeons will perform phacoemulsification with even larger areas of dialysis (up to complete luxation) if the vitreous is stable. With zonular dehiscence, phacoemulsification should be performed with a minimum of lateral movement. The capsulotomy is completed with scissors and not by ripping or shearing. If a ripping force is needed, it should be directed at the area of zonular instability, not away from it. Use of a two-handed technique is advised, with the second instrument used to stabilize the lens and aid in fragmentation. A basket, such as the Sabet lenticular safety net (Rhein Medical, St. Petersburg, FL, USA) can also be introduced under the lens through a second port to elevate and stabilize the lens.

It is possible to perform phacoemulsification on a dangling lens where the vitreous is not supportive. The author has personally performed phacoemulsification on dangling lenses; the capsule is manually removed upon completion and the animal left aphakic. It is helpful to enter the lens capsule on the opposite side of the remaining attachments. No capsulorhexis is performed and an entry is made with Vannas scissors or a 25-gauge needle if possible. Great care should be taken to avoid entanglement with the vitreous.

Placement of an endocapsular IOL in the presence of zonular instability is possible, and an ideal lens is one with a large optic and increased haptic–capsular contact (C loop or 360° haptic). The IOL should be inserted by pressure on the superior haptic and not by dialing, so avoid a PMMA IOL (Mulhern et al., 1995). In addition, use of a CTR placed prior to or after phacoemulsification will facilitate lens capsule stability (Ahmed et al., 2005; Wilkie et al., 2015). CTRs are indicated with zonular dehiscence of less than 180° and can be left in place to avoid decentration of the IOL (Por & Lavin, 2005). The use of Iris Hooks has been described to stabilize the lens and to secure the capsular bag for CTR insertion (da Silva, 2017).

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Cavitation/Bubbles

Motion of the needle during phacoemulsification through a liquid medium results in zones of high and low pressure. The low pressure that occurs with backward motion of the needle pulls dissolved gases out of solution, producing cavitation bubbles (Fig. 23.31). The threshold for bubble formation varies with the handpiece, and as the needle surface area increases, the power threshold for cavitation decreases (Svensson & Mellerio, 1994). Cavitation bubbles are formed at the probe tip during phaco, and at the shoulder of the probe where it joins the handpiece by infusion along the silicone sleeve. The threshold for bubbles at the shoulder of the probe is considerably less than at the probe tip (Svensson & Mellerio, 1994). The streamlining of this shoulder in newer needles reduces the effect of cavitation.

Once formed, the bubbles migrate to the highest point within the anterior chamber due to buoyancy or remain trapped midchamber due to the OVD in use. Wherever their location, they can obscure the surgeon's view. They also reduce cutting power by interfering with probe–lens contact. The bubbles also store energy, and they release that energy when they implode with forward motion of the needle. This high-pressure, high-temperature "shock wave" can induce free radicals, all of which can result in cell death (Svensson & Mellerio, 1994). The ease of removal of the bubbles is dependent on the OVD in use. Rotating the phaco irrigation port so it is facing the bubbles and then irrigating and aspirating can dislodge them.



Figure 23.31 Cavitation bubbles evident in the axial anterior chamber have floated up to the corneal endothelium due to buoyancy.

Postoperative Complications of Phacoemulsification and Intraocular Lens Implantation

Postoperative complications can be minimized by adequate therapy and follow-up examinations.

Immediate Postoperative Complications

Corneal Incision Dehiscence and Infection

Wound dehiscence is uncommon, but can occur due to many reasons, including incisional weakness, improperly placed sutures, spike in IOP, and blunt or self-trauma (Matossian et al., 2015; Miller et al., 1997). One study in dogs reported its incidence at 1.14% (Dees et al., 2017). Clear corneal incisions in cats are stable at 60 days, whereas limbal incisions are stable at 7 days postoperatively (Ernest et al., 1998). In the dog, perilimbal corneal wounds are stable at 16 days postoperatively using 9-0 nylon or 9-0 polyglactin 910 (Vicryl®, Ethicon, Somerville, NJ, USA; van Ee et al., 1986). Both types of sutures showed similar inflammatory responses at all time periods and similar wound strengths. Canine corneas heal faster than rabbits, cats, and humans (van Ee et al., 1986). Wound dehiscence in humans is decreased with the smaller incision required for foldable IOLs, but has not yet been evaluated in dogs (Kumar et al., 2001). The postoperative prevention of self-trauma by confinement and the use of an e-collar are paramount in veterinary patients.

Wound dehiscence should be addressed promptly to minimize short-term sequelae, including hypotony, hyphema, and influx of microorganisms and long-term sequelae including endophthalmitis, excessive scarring, epithelial downgrowth, and fibrous ingrowth (Khurshid & Fahy, 2003; Ledbetter et al., 2018; Nichamin et al., 2006; Wallin et al., 2005). Epithelial downgrowth has been documented in a dog following intracapsular lens extraction and following cataract surgery in two dogs and is also a rare complication of human cataract surgery (Koch & Novak, 1995; Kostuik, 2007; Ledbetter et al., 2018). A small amount of wound leakage, evidenced by fibrin strands pulled to the incision in the face of a maintained anterior chamber and IOP and a negative Seidel test, can be managed conservatively (see Fig. 23.29). Actively leaking incisions, evidenced by protrusion of fibrin through the incision, broken sutures, and significant dehiscence of the incision, should be immediately addressed surgically. Intracameral antibiotics, if not already administered, may decrease the risk of intraocular infection/endophthalmitis (Hashemian et al., 2016). Topical and oral antibiotics may be of use, but there is limited data to support this. Infection of the corneal incision site is typically associated with sutures (Lee et al., 2009; Nichamin et al., 2006). This is also more likely to occur in human diabetic patients and, in the author's experience, in diabetic dogs (Matossian et al., 2015).

Surgery-Induced Corneal Astigmatism

Normal dogs have varying amounts of mild astigmatism, but it is usually minimal (Kim et al., 2008; Nelms et al., 1994;

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Pollet, 1984). The corneal incision associated with cataract surgery induces astigmatism, with the degree dependent on the sharpness of the blade used, location, size, and whether suture is used or not. Human surgery has moved to scleral-based incisions to minimize this. Sutureless clear corneal incisions may induce less astigmatism and this has been evaluated in the dog (Kim et al., 2008; Mahmood et al., 2014). The sutured clear corneal or limbal incisions used in veterinary cataract surgery produce some astigmatism that remains long term following surgery (Kim et al., 2008; Nelms et al., 1994). The corneal curvature of normal dogs prior to, immediately following, and 1 month following a 9 mm clear corneal or scleral incision has been evaluated (Nelms et al., 1994). Preoperative average mean astigmatism was 0.82 D or 0.75 D in the corneal or scleral incision groups, respectively. Significant astigmatism resulted immediately following the clear corneal approach (4.44 ± 3.4 D) compared to the scleral approach (1.3 ± 1.56 D). One month postoperatively, astigmatism in the corneal approach group (2.35 ± 1.3 D) was not significantly higher than the scleral approach group (1.36 ± 1.3 D; Nelms et al., 1994). Smaller incision surgery reduces astigmatism in humans (Kumar et al., 2001). The astigmatism resulting from smaller incisions (less than 4 mm) used with foldable IOLs in dogs has been reported at 1.39 ± 0.48 D for sutured and 0.02 ± 0.07 D for sutureless clear corneal incisions (Kim et al., 2008). The larger incisions necessary for ECCE, and presumably for ICCE, cause more astigmatism than the small incision approach (Fig. 23.32; George et al., 2005).

Corneal Ulceration

Ulceration of the cornea can occur postoperatively in the dog. One report had an incidence of 5.68% (Dees et al., 2017). A higher incidence of 13% has been reported in a brachycephalic breed (i.e., Pugs) within 3 months of surgery and was the most common cause of vision loss following surgery in that breed (Boss et al., 2020). Causes include decreased tear production and exposure secondary to anesthesia (Herring et al., 2000), KCS, decreased blinking rates, iatrogenic, toxicity associated with topical betadine solution, damage to the corneal nerves from the incision resulting in focal neurotrophic keratitis, self-trauma, and impaired healing. Impaired healing is more likely in diabetic patients and in brachycephalic breeds (Boss et al., 2020; Foote et al., 2019; Gemensky-Metzler et al., 2015; Yi et al., 2006). Most of these ulcers are superficial and heal within 2 weeks (see Fig. 23.28). Topical antibiotics are indicated and a balance must be found when treating postoperative uveitis. Topical corticosteroids should be discontinued due to their inhibitory effect on corneal epithelialization and risk of infection. Oral corticosteroid medications or NSAIDs can be used to decrease the need for topical corticosteroids until the ulcer has healed. In addition, topical corneal protectants such as viscous tear solution or gel and contact lenses can aid in corneal healing. Diabetic dogs are more at risk and, due to immunosuppression, are more likely to develop infections, especially when on postoperative topical steroids (Fig. 23.33).

Corneal Edema and Endothelial Decompensation

Corneal edema can be a short-term and/or a long-term postoperative complication of cataract surgery (Fig. 23.34). Some loss of endothelial cells occurs even in the most routine of cataract surgeries (Ventura et al., 2001). This has been minimized by the continued revolution of the techniques and equipment used (George et al., 2005). However, the reported endothelial cell losses still vary between 4% and 25%



Figure 23.32 A 160° clear corneal/anterior-limbal incision for intracapsular lens extraction. Significant scarring occurs.



Figure 23.33 A bacterial stromal corneal ulcer in a diabetic dog 6 weeks following phacoemulsification. Vascularization from the dorsal limbus has occurred in response to the ulceration. This ulcer is more likely to leave an opacity in the visual axis once healed.

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Figure 23.34 Corneal endothelial degeneration that progressively worsened over 5 years following phacoemulsification and intraocular lens implantation in a 10-year-old Bichon Frise.

(Storr-Paulsen et al, 2006). The period of increased postoperative endothelial cell loss remains unknown, but could be up 10 years or for life (Bourne et al., 2004; Storr-Paulsen et al., 2006).

In humans, endothelial cell density decreases at a greater rate than in healthy, unoperated corneas (Lesiewska-Junk et al., 2002; Mencucci et al., 2006). The amount of loss depends on factors including the technique used, the type of OVD used, the type of IOL implanted, corneal incision size, and intraoperative and postoperative factors such as corneal deformation, lens fragment endothelial contact, amount and time of irrigation, turbulence of the fluidics system, thermal effect of the phaco needle, cavitation and release of oxygen-free radicals, uveitis, and increased IOP (Cameron et al., 2001; Dick et al., 1996; Hayashi et al., 1996). Iatrogenic damage can include inadvertent contact of the endothelium with surgical instruments, the IOL, or lens fragments (Steinert, 1995).

Longer irrigation times, higher flow rates (up to 50 ml/min), and larger volumes are more traumatic to the corneal endothelium (Hejny & Edelhauser, 2003). The ideal irrigating fluid for endothelial function should contain (1) adequate bicarbonate as a buffer to maintain proper pH (between 6.7 and 8.1) and osmolality (between 270 and 350) to maintain the endothelial transport system; (2) a substrate such as calcium and glutathione to maintain junctional stability and the blood–aqueous barrier; and (3) an energy source such as glucose (Edelhauser & Ubels, 2003).

Ultrasound power required for traditional or longitudinal phacoemulsification is a risk factor for endothelial cell loss and tissue damage. Modern technology has aimed to reduce ultrasound power and improve efficiency for this reason (Hayashi et al., 1996). Ultrasound oscillation alone has been shown to cause corneal endothelial damage in a rabbit model (Murano et al., 2008). Reduction of ultrasound energy with power modulations (pulse, burst, etc.), improved pump systems, and improved infusion systems all help minimize the impact on the endothelial cells (Atas et al., 2014). Conversely, one study showed that torsional versus longitudinal phacoemulsification, with a mean ultrasound time, cumulative dissipated energy, and percentage total equivalent power significantly lower compared to longitudinal phacoemulsification, did not differ in endothelial cell loss (Reuschel et al., 2010). Directing the ultrasound power away from the endothelium, a bevel-down technique, spares endothelial cells (Bourzika et al, 2012).

Free radicals are generated by the high-intensity ultrasound energy associated with phacoemulsification (Gardner & Aust, 2009; Holst et al., 1993; Takahashi, 2005; Topaz et al., 2005). They can also be present in intracameral agents used during surgery (Lockington et al., 2010). This leads to apoptosis of endothelial cells and potentially transient or permanent edema (Geffen et al., 2008). The addition of superoxide dismutase to the irrigation buffer decreased endothelial damage in phacoemulsification in rabbits (Holst et al., 1993). Ascorbic acid added to the irrigation solution reduces endothelial cell loss by 70%, presumably by its free radical–scavenging properties (Rubowitz et al., 2003). Another study comparing BSS, BSS Plus, as well as BSS with glutathione or with ascorbic acid found that corneal endothelial cells were significantly protected by the inclusion of antioxidants (Nemet et al., 2007). Ascorbic acid demonstrated the lowest endothelial cell loss (0.9%), and glutathione had a 5.2% loss, compared with BSS (19.3%) and BSS Plus (10.6%). Ascorbic acid was measured in the aqueous humor of dogs following extracapsular lens extraction; ascorbic acid was reduced until day 15 following surgery (Barros et al., 2003). The effects of intracameral ascorbic acid on the corneal endothelium of dogs undergoing phacoemulsification have recently been evaluated (Padua et al., 2018). Dogs receiving ascorbic acid showed less severe losses of endothelial cells. There were no differences in corneal thickness. Hexagonality decreased significantly and coefficient of variation of cell size increased significantly in dogs receiving only BSS. Torsional phaco has shown a significantly higher proportion of the hydroxyl radicals formed outside the phaco tip compared to inside the tip, but only generated one-fourth the malondialdehyde compared to longitudinal phaco (Aust et al., 2011).

Corneal edema was present in 3% of eyes in 6–24-month follow-up groups postphacoemulsification (Sigle & Nasisse, 2006). In the dog, there is an average endothelial cell loss of 22% centrally and a 13% loss peripherally following phacoemulsification (Gwin et al., 1983). Another canine study

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found a significant transient increase in central corneal thickness postoperatively using spectral-domain OCT (Lynch & Brinkis, 2006). Uveitis may transiently reduce endothelial cell pump function (Lynch & Brinkis, 2006). Older dogs that already have fewer endothelial cells due to normal attrition are more at risk (Gwin et al., 1982). Breeds such as the Boston Terrier, which suffer from primary endothelial disease, may be at higher risk of corneal edema, as are dogs that develop chronic uveitis or glaucoma (Sigle & Nasisse, 2006).

More endothelial cell loss occurs in diabetic patients undergoing small incision surgery than in nondiabetic patients (Morikubo et al., 2004). This has also been demonstrated in the dog, where corneal thickness was more significant in diabetic patients and took longer to return to normal in animals receiving a foldable acrylic IOL, as compared to aphakic and PMMA pseudophakic eyes (Lynch & Brinkis, 2006).

The minimization of endothelium damage during phacoemulsification is the guiding impetus behind the development and use of OVDs (Rosado-Adames et al., 2012). The best protection is the use of dispersive and viscodispersive OVDs (Ho & Afshari, 2015; Takahashi, 2016). The corneal endothelium of dogs following use of various OVDs (i.e., 1% sodium hyaluronate, 4% sodium chondroitin sulfate, 3% sodium hyaluronate, 2% hydroxypropyl methylcellulose) was evaluated compared to BSS (Gerding et al., 1990). No changes in endothelial cell density or morphology occurred. The mean corneal thickness increased the most in the 3% sodium hyaluronate group, but was not statistically significant. OVDs containing hyaluronic acid have free radical–scavenging effects (Artola et al., 1993a, 1993b; Takahashi, 2005). OVDs with the highest retention rates were most effective at this (Takahashi, 2016). A dispersive hyaluronate OVD allows for protection of the endothelial cells while also suppressing the formation of free radicals (Storr-Paulsen et al., 2006).

Most cases of postoperative corneal edema will resolve over time. Edema associated with primary underlying corneal disease may be permanent or worsen over time. Edema secondary to uveitis and glaucoma will resolve with treatment of the underlying cause.

Postoperative Ocular Hypertension

POH is a distinct clinical syndrome characterized by a transient increase in IOP in the acute postoperative period. By definition, the increase in IOP during POH spontaneously decreases or responds to pressure-lowering drugs and resolves in 24–48 hours (Biros et al., 2000). POH occurs in anywhere from 0% to 100% of cases, with the average incidence around 35% (Biros et al., 2000; Chahory et al., 2003; Crasta et al., 2010; Crumley et al., 2009; Dees et al., 2017; Klein et al., 2011; Lannek & Miller, 2001; Mancuso et al., 2019; Matusow et al., 2016; McLean et al., 2012; Miller et al., 1997; Moeller et al., 2011; Rodriguez et al., 2016; Rose et al., 2008; Smith et al., 1996; Stuhr et al., 1998; Yi et al., 2006). The IOP elevation in POH can be mild or severe and is generally defined as an IOP > 25–27 mmHg (Chahory et al., 2003; Crasta et al., 2010; Dees et al., 2017; Klein et al., 2011; Lannek & Miller, 2001; Miller et al., 1997; Moeller et al., 2011; Smith et al., 1996; Yi et al., 2006), with one study including a group with an IOP of 20–25 mmHg (Dees et al., 2017). Reported time frames to peak occurrence vary and range from 2 to 4.9 hours after phaco (Chahory et al., 2003; McLean et al., 2012; Miller et al., 1997; Smith et al., 1996; Yi et al., 2006). Multiple reports have also described POH 2–48 hours following cataract surgery (Gerding et al., 1989; Harooni et al., 1998; Henry & Olander, 1996; Jurgens et al., 1997; Miller et al., 1997; Smith et al., 1996; Stuhr et al., 1998).

The exact cause of POH remains unknown, but is likely multifactorial. Possible contributing factors to POH include insufficient aspiration/residual OVD, inflammation, residual lens particles, intracameral carbachol, rapid aqueous humor production in combination with watertight wound closure, and viscous plasmoid aqueous (Dees et al., 2017; Miller et al., 1997). Histologic structural changes in the trabecular meshwork have been shown to persist even after IOP normalization, and this may account for patients experiencing POH further out from surgery (Dees et al., 2017; Miller et al., 1997). Those histologic changes included blood refluxed into the collecting channels and corneoscleral trabecular meshwork, decrease in ciliary cleft cross-sectional surface area and width, and structural alterations and swelling in the trabecular meshwork (Miller et al., 1997). The authors hypothesized that release of tension on the lens zonules, along with cycloplegia due to atropine, may result in peripheral movement of the ciliary body and compression of the trabecular meshwork. The residual increase in IOP would then further compress the ciliary body and exaggerate the ciliary cleft collapse. Residual lens material was not seen in the trabecular meshwork or anterior chamber and was not thought to contribute to POH (Miller et al., 1997). How the IOP returns to normal despite the fact that the changes have not resolved by 24 hours postoperatively is not understood.

A recent study looking at ultrasound biomicroscopy (UBM) changes after phacoemulsification showed shifting of the iris diaphragm backward, resulting in changes in the ICA that should structurally increase aqueous humor outflow, not decrease it (Park et al., 2016). Another study using UBM evaluated the ICA and AOD of dogs with cataracts prior to and following pharmacologic mydriasis preoperatively, and also at 1 and 3 hours following phacoemulsification (Rose et al., 2008). Dogs with larger ICA and AOD predilation before surgery were at a greater risk of developing POH. Conversely, a weak inverse relationship between AOD preoperatively and POH 1 day postoperatively was

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found in another study (Crumley et al., 2009). These somewhat conflicting results indicate that further work using UBM is warranted to correlate the changes of the ICA and development of POH (Dees et al., 2017). It was also determined that preoperative IOP did not significantly correlate with POH (Rose et al., 2008).

Factors previously shown to be associated and not associated with POH after cataract surgery in the dog are shown in Table 23.5. Interestingly, in one study dogs that did not receive an IOL did not develop POH (Crumley et al., 2009).

In a recent study, the Labrador Retriever appears to have an increased incidence of POH compared with non-Labrador Retrievers: 33% compared to 18%, respectively (Moeller et al., 2011). In addition, Labradors were at increased risk for glaucoma and blindness compared with non-Labradors (Moeller et al., 2011). It appears that increasing age and POH are risk factors in Labradors for the development of postoperative glaucoma (Moeller et al., 2011).

The effect of preoperative, intraoperative, and postoperative medications on POH and secondary glaucoma after cataract surgery in the dog has been evaluated. It is well accepted that retained viscoelastic materials inhibit aqueous outflow and result in increased IOP, and their complete removal will reduce the incidence of POH (Arshinoff, 2004; Assia et al., 1992; Berson et al., 1983; Morgan & Skuta, 1994; Wilkie & Willis, 1999). Multiple studies comparing different viscoelastic materials are found in the literature (Arshinoff, 2004; Arshinoff et al., 2002). If not completely removed, all OVDs cause postoperative increases in IOP (Arshinoff, 2004). High-viscosity cohesive OVDs are associated with higher postoperative IOPs compared with lower-viscosity dispersive OVDs (Arshinoff et al., 2002). However, low-viscosity OVDs are generally more difficult to remove from the eye completely. Changes in IOP due to intracameral injection of various OVD in dogs have been evaluated (Gerding et al., 1989). A comparison of all three OVDs (1% sodium

Table 23.5 Individual patient and intraocular factors previously associated.

Not Associated*	Associated**
Age	Older dogs
Gender	–
Neuter status	–
–	Breed
–	Diabetes
Cataract stage	Hypermature cataract stage
Initial intraocular pressure	–
Phaco power	–
Phaco time	Longer duration of phaco
Residual lens fragments/anterior chamber debris	–
Intraocular lens (IOL) placement	IOL placement
–	Foldable IOL in diabetics***
–	High-viscosity ophthalmic viscosurgical device (OVD)
–	Residual OVD
Preoperative lens-induced uveitis (LIU)	Preoperative LIU
Type of topical anti-inflammatory	–
Type of oral anti-inflammatory	–
Posterior lens capsule tears	–
Vitrectomy	–
–	Postoperative uveitis
–	Intraoperative hemorrhage
–	Retinal abnormalities

* Biros et al. (2000); Dees et al. (2017); Johnsen et al. (2006); Lannek et al. (2001); Matusow et al. (2016); Sigle & Nasisse (2006); Smith et al. (1996); Wilkie & Willis (1999); or not associated.
** Dees et al. (2017); Rose et al. (2008); Smith et al. (1996); Stuhr et al. (1998); with postoperative ocular hypertension after cataract surgery in the dog.
*** Rodriguez et al. (2016).

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hyaluronate, 4% sodium chondroitin sulfate, and 3% sodium hyaluronate) caused an increase in IOP at 2 hours postinjection. Removal of 2% hydroxypropyl methylcellulose from the anterior chamber prevented the previously reported mild IOP increase seen at 2 hours following intracameral injection (Miller et al., 1997).

Intraoperative miotics such as acetylcholine (Miochol®, Bausch & Lomb) or carbachol (Miostat®, Alcon Laboratories) are advocated in human cataract surgery to prevent POH (Solomon et al., 1998; Wedrich & Menapace, 1992). Both miotics have a similar onset of action, but carbachol has a longer duration of action. In veterinary ophthalmology, carbachol has been advocated to decrease the incidence of immediate POH (Stuhr et al., 1998). The potent miosis seen in dogs following latanoprost use (Studer et al., 2000) prohibits its use preoperatively, and it may potentiate postoperative uveitis. The effect of intracameral carbachol on IOP at 3 and 6 hours and the morning following surgery was evaluated (Stuhr et al., 1998). None of the dogs that received intracameral 0.01% carbachol developed POH, whereas 75% of control dogs that did not receive carbachol did develop POH. Carbachol was also shown to decrease POH in non-Labrador breeds, but significantly increased the risk of POH in Labrador Retrievers (Moeller et al., 2011). Conversely, another study showed that intracameral carbachol increased the incidence of POH as well as the IOP at 2 hours postoperatively in the study population (Crasta et al., 2010). This study also showed no significant effect of routine postoperative administration of latanoprost on the occurrence of POH in treated (29%) and untreated (33%) dogs. Also, the use of perioperative miotics may be associated with increased postoperative flare, fibrin, miosis, and pain. In the same study, topical 0.005% latanoprost or intracameral injection of 0.3 mL of 0.01% carbachol did not increase intraocular inflammation (Crasta et al., 2010). Use of topical latanoprost decreased it substantially in another study; however, that decrease did not reach statistical significance (Dees et al., 2017). The use of these agents may require postoperative mydriatics where indicated, but can be complicated by the POH. Overall, it is difficult to draw conclusions on the appropriate use of miotics in preventing or minimizing POH due to the conflicting results in the literature.

The use of topical carbonic anhydrase inhibitors and beta-blockers perioperatively has also been evaluated in an effort to avoid POH. Dorzolamide/timolol decreased the incidence of POH when administered three times, at 14 and 2 hours preoperatively and at corneal incision closure (Matusow et al., 2016). When POH did develop, eyes that had been treated with dorzolamide/timolol were significantly more likely to have an acceptable clinical response to one drop of 0.005% latanoprost solution than were eyes that received the sham treatment (Matusow et al., 2016). Another study showed that dorzolamide and dorzolamide/timolol applied immediately after surgery and then for 2 weeks had no effect on decreasing the incidence of POH (Dees et al., 2017).

Hyaluronidase has been shown to have efficacy with Healon, Healon GV, and Viscoat, but not with OcuCoat, in avoiding the postoperative pressure rise seen following cataract surgery (Harooni et al., 1998). While there has been concern over the possibility of intracameral drug binding by the OVD and subsequent alterations in efficacy or toxicity, this does not appear to be a significant concern (McDermott & Edelhauser, 1989). This has not been evaluated in the dog.

The intracameral administration of tPA (25 µg) immediately after incision closure had no effect on the incidence of POH (Mancuso et al., 2019). Conversely, in another study, the use of intraoperative intracameral tPA decreased the incidence of POH (Dees et al., 2017).

A retrospective study did not reveal an effect of immediate preoperative and postoperative topical, systemic, or intracameral steroids and nonsteroidals on the incidence of POH (Dees et al., 2017). However, previous reports have identified IOP elevations following the use nonsteroidals in the dog (Lu et al., 2017; Millichamp et al., 1991; Pirie et al., 2011). An increase in outflow resistance from the inhibition of endogenous PG synthesis is presumed (Millichamp et al., 1991). In a prospective study, the use of topical steroidal anti-inflammatories topically for 1 week prior to cataract surgery in the dog increased the risk of POH compared to use of the medication just 1 day prior (McLean et al., 2012). Another study showed that both bromfenac and flurbiprofen, in combination with dexamethasone, elevated postoperative IOP, especially at 2 hours (Lu et al., 2017). A higher percentage of eyes receiving bromfenac (23%) had therapy discontinued over concerns of elevated IOP compared to eyes receiving flurbiprofen (9.8%) during the study. The risk of having elevated IOP with bromfenac is 1.04 times higher than with flurbiprofen, and bromfenac-treated eyes were more likely to require intervention for elevated IOP (Lu et al., 2017). Conversely, another canine study showed that there was no association between COX-2 inhibitor (bromfenac and Celecoxib-treated IOLs) administration and POH (Brookshire et al., 2015).

In one report, 59%–69% of POH cases occurred within the first 24 hours after surgery, consistent with previous findings (Dees et al., 2017). However, 24%–27% of POH cases occurred 1 week following surgery, indicating that one out of every four POH cases does not fall within the typical timeframe. Evaluation of postoperative IOP should be performed at 1, 2, and 4 hours following corneal closure and POH managed as needed (Smith et al., 1996). If POH develops, medical management should be initiated immediately. This management varies greatly between surgeons. If the IOP is above 20 mmHg but below 40 mmHg, one drop of a topical carbonic anhydrase inhibitor (CAI) is warranted. There is no data to support the use of an oral CAI in POH. The IOP should then be reevaluated 1 hour later to evaluate whether the IOP is

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decreasing or increasing. If the IOP is greater than 40 mmHg, one drop of topical 2% pilocarpine or 0.005% latanoprost as well as the CAI is indicated. Some surgeons also employ IV mannitol. If the IOP remains below 15 mmHg, no further anti-glaucoma medications are usually needed. However, if the IOP increases to or remains above 15–20 mmHg, then topical and/or oral CAIs are used until the 1–2 week reevaluation and the IOP should be rechecked in 24–48 hours. Topical mydriatics such as tropicamide should not be used postoperatively if the IOP remains above 15–20 mmHg. In a published report, eyes with IOPs of 26–45 mmHg were treated with one drop of 0.005% latanoprost solution and reassessed in 1 hour. A positive response was defined as a subsequent IOP of <25 mmHg. Eyes not responding to latanoprost and those with an IOP of >45 mmHg were treated according to surgeon preference, including use of some combination of topical 0.005% latanoprost, oral or topical CAIs, topical beta-adrenergic receptor antagonists, aqueous paracentesis, or manual leakage of fluid via the corneal incision with a cannula (Matusow et al., 2016).

Continued diligent monitoring of IOP during the first few weeks after cataract surgery in the dog is warranted (Dees et al., 2017). POH can also uncommonly recur after discontinuation of anti-glaucoma medications (Wilkie & Colitz, 2013). The effect of POH on the canine eye is currently unknown. It is possible that the potential initiating factors of POH could cause long-term ocular changes that may contribute to the progression of POH to eventual secondary glaucoma after cataract surgery (Dees et al., 2017). The higher the IOP elevation, the more likely it is for damage to be done to the retina and optic nerve. Clinical signs can include no clinical signs, temporary loss of vision, blepharospasm, and corneal edema (Gelatt & Brooks, 1999). The rapid rise in IOP postoperatively may be more detrimental to the optic nerve than slower elevations in IOP (Bito, 1992).

Intraocular Hemorrhage

Hyphema and/or vitreal hemorrhage can occur in the immediate postoperative period, but are relatively uncommon. The reported prevalence in dogs is 7%–12.3% (Klein et al., 2011; Sigle & Nasisse, 2006; Yi et al., 2008). It occurs in 9.4% of patients less than 3 days postoperatively (Yi et al., 2008), 12.3% of patients a median of 10 days postoperatively (Klein et al., 2011), and 7% within the first 3 months postoperatively (Sigle & Nasisse, 2006). Possible causes include hypotony, underlying uveitis, underlying coagulopathy, iridociliary cysts, breakdown of iridal synechia during surgery, sudden changes in IOP, tension on the ciliary processes during surgery, an oversized IOL, unidentified intraocular masses, and RD or tears. Tension around the patient's neck postoperatively should be avoided and a body harness is recommended instead of a collar. Restricting the patient's activity and minimizing stress and barking are optimal for the first 2 weeks (Wilkie & Colitz, 2013). Diabetic retinopathy or systemic hypertension are more likely to cause retinal hemorrhage and not hyphema (Kern & Engerman, 1995; Landry et al., 2004; Lane et al., 1993; Wyman et al., 1995), but all cataract surgery candidates should have their blood pressure checked preoperatively. Mild hyphema should resolve without further complications (Nasisse & Davidson, 1999; Yanoff & Fine, 2015b; Yi et al., 2008). Significant hyphema or vitreal hemorrhage can result in long-term complications. These include persistent corneal edema, fibropupillary membranes that lead to posterior synechia and dyscoria, hemolytic glaucoma from hyphema due to obstruction of the outflow tract with hemoglobin aggregates and/or hemolyzed red blood cells (ghost cells), and vitreal traction bands (Nasisse & Davidson, 1999; Yanoff & Fine, 2015a). Vitreal traction bands can then lead to retinal tearing and/or detachment. Intracameral tPA can be administered for fibrin or clot resolution up to 2 weeks following hemorrhage once the fibrin clot has stabilized and further hemorrhage is not expected (Siatiri et al., 2005). tPA has resolved clots present for greater than 2 weeks (Wilkie & Colitz, 2013), with 0.1–0.2 mL of tPA (25 µg/100 µL) being injected intracamerally (Wilkie & Gemensky-Metzler, 2004). Possible side effects of intracameral tPA include corneal edema, increased IOP, and rebleeding. A study in dogs showed no changes in corneal thickness or IOP following intracameral injection of tPA (Gerding et al., 1992).

Uveitis

Cataract surgery is now minimally invasive, decreasing the associated risks. However, it is still associated with varying degrees of postoperative uveitis. This can range from mild uveitis or fibrin formation only to severe uveitis with sterile hypopyon (TASS), or endophthalmitis. Some level of postoperative uveitis is always expected and has been clinically reported in 29%–82% of cases (Klein et al., 2011; Moore et al., 2003). Control of anterior uveitis both preoperatively and postoperatively is imperative due to the dogs' amplified uveal inflammatory response, compared to that in humans (Bito, 1984). In the study looking at eyes enucleated or eviscerated due to complications from glaucoma, uveitis was diagnosed on histopathology in 62% of cases (Moore et al., 2003). Preoperative LIU can be exacerbated by surgery. Clinical signs of uveitis include blepharospasm, conjunctival hyperemia, scleral injection, corneal edema, aqueous flare, fibrin, hyphema, hypopyon, and miosis. A retrospective study found a 16.2% incidence of uveitis following phacoemulsification (Klein et al., 2011). Flare grades in dogs increased from 0/3 up to 1.5/3 at 3 days postoperatively and then decreased to 0 again by 14 days postoperatively in another clinical retrospective (Yi et al., 2008). A study in normal dogs demonstrated a 72-fold increase in anterior chamber protein 24 hours postphacoemulsification that remained significant at 15 days (De Biaggi et al., 2006). In addition, the total antioxidant capacity and the ascorbic acid concentration

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of the aqueous humor were decreased for 7–15 days postoperatively (De Biaggi et al., 2006). Excessive uveitis, characterized as cellular flare and hypopyon, was diagnosed in 3.14% of postoperative cases in a recent study (Dees et al., 2017). In a histopathologic study, Boston Terriers and Jack Russell Terriers had an increased incidence of postoperative uveitis, characterized by posterior synechia and fibrovascular membranes (Scott et al., 2013).

Topical anti-inflammatory medications are routinely started preoperatively and continued postoperatively with the expectation of postoperative inflammation. Oral steroidal or nonsteroidal anti-inflammatory medications may also be necessary to manage uveitis, depending on the severity. Uveitis should be managed aggressively and monitored frequently, as severe or chronic uveitis can result in preiridal fibrovascular membrane (PIFM) formation, PCO, permanent corneal edema, secondary glaucoma, and RD (Fig. 23.35; Lannek & Miller, 2001; Moore et al., 2003). A recent study showed that eyes receiving Celecoxib-treated IOL and prednisolone acetate had better initial control of inflammation (Brookshire et al., 2015). Bromfenac was equally effective compared with prednisolone acetate in controlling inflammation. Another study compared the use of oral melatonin (0.3 mg/kg twice a day) to oral NSAIDs in diabetic dogs and oral dexamethasone in nondiabetic dogs, and showed a decreased occurrence of clinical signs of uveitis in the dogs treated with melatonin (Sande et al., 2016). Subconjunctival triamcinolone acetonide (Kenalog-40, Bristol-Myers Squibb, Princeton, NJ, USA) can also be employed in more severe or persistent cases, but should be used with caution in diabetic dogs and dogs with corneal disease. The use of an intravitreal device for slow release of dexamethasone has been evaluated in the dog and did not show any benefit in control of postoperative inflammation (Lima et al., 2015). A mydriatic–cycloplegic strong enough to dilate the pupil in the face of inflammation, such as atropine, should be used to prevent posterior synechia, but weighed against the presence of elevated IOP.



Figure 23.35 Long-term complications of chronic uveitis, including anterior synechia (dorsal temporal and ventral), dyscoria, corneal edema, and glaucoma 10 months following surgery in a diabetic dog. Topical anti-inflammatories were stopped for over 1 month immediately postoperatively due to an infected corneal ulcer.

Fibrin

Intraocular fibrin development can occur with uveitis or without other signs of inflammation 1–3 weeks postoperatively in up to 50% of patients (see Fig. 23.27; Dees et al., 2017; Mancuso et al., 2019; Yi et al., 2008). It can be mild, and require no intervention as it resolves with topical therapy, or it can be severe and require additional intervention. The incidence in the dog has been reported at 4.55%–34% (Dees et al., 2017; Pizzirani et al., 2002; Yi et al., 2008). The incidence in human surgery is reported at 2% and can be 4%–54% with diabetes, uveitis, pseudoexfoliation syndrome, glaucoma, and pediatric cases (Heilingenhaus et al., 1998; Siatiri et al., 2005; Sterling & Wood, 1986). Possible causes of this formation include late-onset TASS, endophthalmitis, retained cortical material, and factors associated with the inflammatory response in the canine eye (Bito, 1984). While there is concern that fibrin formation may be related to specific IOLs, there is no evidence yet to support this. Proteins adsorb on the surface of all IOLs and subsequently influence an immunologic foreign-body reaction (Werner, 2008). Clinical studies have compared the inflammatory reaction after the implantation of IOLs manufactured from different biomaterials (Abela-Formanek et al., 2002a). One study evaluated hydrophilic acrylic, hydrophobic acrylic, and silicone IOLs, and the hydrophobic acrylic IOLs showed the highest incidence of late foreign-body cell reaction, followed by the hydrophilic acrylic and silicone (Abela-Formanek et al., 2002a). Postoperative flare values are not clinically different among foldable biomaterials in human patients with or without underlying uveitis (Abela-Formanek et al., 2002b). One study looking at hydrophobic foldable IOLs compared to PMMA IOLs showed comparative postoperative inflammation (Pizzirani et al., 2003b). Bacterial biofilm formation and distribution on the various biomaterials used to manufacture the IOL could also have an impact. A recent study showed no difference in bacterial counts between PMMA, hydrophilic acrylic, hydrophobic acrylic, heparinized PMMA, and silicon at 72 hours (Mazoteras & Casaroli-Marano, 2015). However, bacterial counts were lower at 3 hours for hydrophilic and PMMA lenses. Heparin modification of the IOL surface may reduce inflammatory cell adhesion to the IOL and decrease the risk of reaction (Roesel et al., 2008). Other causes of fibrin formation in the eye can be related to the OVD used and may be associated with

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manufacturer quality (personal experience). Fibrin formation was also more likely to occur with hypermature cataracts in one study (Yi et al., 2008). Heparin surface modified hydrophilic canine lenses are available.

Fibrin and fibrinogen degradation products promote chemotaxis and activation of intraocular inflammatory components (Rowland et al., 1985). If significant, or located in the area around the IOL in the capsular bag, it can result in decreased vision, as it can lead to opacity of the IOL or more severe PCO (Heilingenhaus et al., 1998). It may also contribute to POH and glaucoma. Intracameral tPA should be administered at a concentration of 25 µg/100 µL with a volume of 0.1–0.2 mL injected into the anterior chamber using a 30-gauge needle (Hellignenhaus et al., 1998; Wilkie & Gemensky-Metzler, 2004). This may be performed on an awake patient using only topical anesthesia, but sedation is safer to prevent iatrogenic intraocular trauma. Intracameral administration of tPA immediately after incision closure in dogs had no effect on the incidence of anterior chamber fibrin formation postoperatively (Mancuso et al., 2019).

Toxic Anterior Chamber Syndrome versus Endophthalmitis

TASS is an intense, anterior segment, sterile inflammatory reaction usually described 12–48 hours following surgery (Monson et al, 1992). Clinical signs include severe corneal edema, fibrin, and hypopyon. The main differential diagnosis is postoperative infectious endophthalmitis, which is rare (0.28%) in the dog (Ledbetter et al., 2018). The onset of TASS is typically more acute than infectious endophthalmitis, in which symptoms more commonly develop 2–7 days postoperatively, but has been reported up to a median of 18 days after surgery (Ledbetter et al., 2018). However, subacute and late-onset forms of TASS as far out as 2–3 months following surgery have been reported (Miyake et al., 2015). A higher incidence of TASS has been reported in patients with diabetes, systemic hypertension, hyperlipidemia, and renal disease (Yazgan et al., 2017). Gram stain and cultures from aqueous and vitreous in cases of TASS are negative. Negative cultures could also occur in endophthalmitis when the sample is inadequate or bacterial cell counts are low. The effect of intraocular irrigating solutions, instrument-related contaminants, and intraocular drugs on corneal endothelium have been studied (Breebaart et al., 1990; Parikh & Edelhauser, 2003; Parikh et al., 2002). The initial rupture of endothelial cell junctions and the acute loss of its barrier function are the cause of the corneal edema seen with TASS.

The etiology of TASS includes any substance used during or immediately postoperatively in surgery that causes toxic injury to intraocular tissue. Causes of TASS reported in the literature are roughly categorized into two types: (1) extraocular agents introduced into the eye such as topical antiseptics, preservatives, or stabilizing agents used in topical medications, ointments placed topically, and talc from gloves; and (2) abnormalities associated with substances or instruments used intraocularly. The second category includes improperly sterilized instruments, insufficient cleaning/flushing of the surgical instruments, metal degradation in the surgical instruments, IOLs or toxic substances on the IOL, reusable items such as cannulas and phaco needles, fluids and additives used for irrigation, errors in intracameral antibiotic concentration or pH, residues of OVDs, OVD in a prefilled syringe, use of trypan blue or Indocyanine green, and gram-negative endotoxins in ultrasonic bath water (Althomail, 2016; Bodnar et al., 2012; Buchen et al., 2012a, 2012b, 2012c; Cutler Peck et al., 2010; Hellinger et al., 2007; Leder et al., 2012; Mamalis, 2007, 2013a; Mamalis et al., 2006; Matsou et al., 2017; Tandogan et al., 2016). One study found sulfate, copper, zinc, or silica impurities in the autoclave steam moisture, especially when the maintenance of the autoclave and water composition used in the autoclave were poor (Hellinger et al., 2007). Contamination of the trypan blue was implicated in another report (Matsou et al., 2017). Elevated levels of endotoxin above the allowable limits (0.5 endotoxin units per mL) in BSS also caused an outbreak of TASS (Kutty et al., 2008). Benzalkonium chloride (BAK) is toxic to the corneal endothelium and caused significant corneal edema when used as a preservative in an OVD (Eleftheriadis et al., 2002; Liu et al., 2001). Methylparaben, another preservative used in lidocaine, should be avoided. Bisulfites or metabisulfites, used to stabilize epinephrine, should be avoided (Avisar & Weinberger, 2010). Glove powder can result in TASS, but some powder-free gloves release a compound that causes TASS when contact is made with the IOL (Diez et al., 2013).

Inadequate cleaning of the phaco and I/A handpieces was the most common cause in one survey (Cutler Peck et al, 2010). Residual OVD, debris, or chemical substances used in the cleaning protocol can deposit on the inner and outer surfaces of reusable instruments. Both enzymatic and nonenzymatic detergents used in cleaning can deposit in the lumen of these instruments (Jun & Chung, 2010; Parikh et al., 2002). Enzymatic detergents appeared to elevate the risk for TASS without providing any additional offsetting benefits (Mamalis, 2016). During sterilization, OVDs are denatured and become a source of toxin (Mathys et al., 2008). However, endotoxin can enter the manufacturing process of OVDs at any time (Althomail, 2016). Gram-negative bacteria can be found in water baths, ultrasound baths, and autoclave reservoirs. Bacteria are destroyed during heat sterilization, but their heat-stable bacterial wall endotoxins and biofilms remain intact and can deposit on instruments (Holland et al., 2007; Kreisler et al., 1992; Sorenson et al., 2016). Delayed-onset TASS is usually caused by issues associated with the IOL such as chemicals used in packaging, polishing, cleaning, or sterilization of the lens (Diez et al., 2013; Hernandez-Bogantes et al., 2019; Oshikia et al., 2017).

The broad spectrum of etiologies of TASS makes it difficult to determine the cause in many cases. TASS outbreaks

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in human ophthalmology have been trending down and this is due to adequate irrigation of handpieces, decreased use of reusable cannulas, increased use of distilled/deionized water for final rinse, and use of fewer additives (Mamalis, 2013b). TASS is likely underreported (Myrna et al., 2009) in the veterinary literature and only a single outbreak has been reported (Stiles & Townsend, 2015). Two factors determined to have been the most underlying cause were high levels of endotoxin in water sources and inadequate cleaning of cannulated instruments (Stiles & Townsend, 2015). Veterinary ophthalmologists should establish and maintain a similar program to the FDA's proactive TASS program to track and determine the underlying etiology of outbreaks (Eydelman et al., 2012).

Eyes affected with TASS should be treated aggressively with topical and oral anti-inflammatory therapy. Surgical intervention (e.g., IOL removal, irrigation of the anterior chamber) is indicated as soon as the hypopyon is noticed (Wilkie & Colitz, 2013). The hypopyon should be removed with antibiotic-spiked fluids and copious irrigation. Dispersive OVDs have protective effects on the corneal endothelial cell damage in TASS (Song et al., 2012). If a contaminated IOL is suspected, the IOL should be removed or replaced with an IOL from a different lot number. Culture and sensitivity and cytology should be performed on the aqueous humor. Since endophthalmitis cannot be definitively ruled out, aggressive antibiotic therapy should also be instituted. Oral NSAIDs are more appropriate than oral corticosteroids and the decision to use a corticosteroid should be weighed against the severity of the inflammation (Wilkie & Colitz, 2013). Intracameral tPA is indicated if fibrin is present. Intracameral dexamethasone can also be employed here. A polymerase chain reaction (PCR) test can also be performed and interpreted for bacterial and/or fungal DNA (Wilkie & Colitz, 2013). TASS typically responds to therapy much better than endophthalmitis. Systemic dexamethasone has been shown to decrease the levels of prostaglandin E2 in aqueous humor in a rat model of TASS (Eom et al., 2014).

Long-Term Postoperative Complications

Corneal Complications

Corneal lipidosis or degeneration was the second most commonly reported complication (19%) after POH in one study, occurring a median of 135 days postoperatively (Klein et al., 2011). Progressive and severe degeneration can lead to visual compromise. Corneal ulceration has been shown to occur as a complication in 0%–5% of cases throughout long-term follow-up (Sigle & Nasisse, 2006). In a study looking at eyes enucleated or eviscerated due to complications from glaucoma, corneal ulceration was diagnosed in 13% and corneal perforation in 10% of the cases (Moore et al., 2003). In a second histopathologic study looking at eyes enucleated or eviscerated due to complications from glaucoma, corneal complications included cellular inflammatory infiltration, endothelial cell loss, duplication of Descemet's membrane, and retrocorneal membrane formation (Scott et al., 2013). Duplication of Descemet's membrane is a relatively common morphologic change observed following intraocular surgery, anterior lens luxation, or blunt trauma (Scott et al., 2013). It leads to reduced visual outcome by causing a corneal opacity or edema. Endothelial separation and reattachment in response to trauma or chronic inflammation may induce this phenomenon (Kafarnik et al., 2009).

Corneal stromal abscesses can be seen weeks to months after cataract surgery, predominantly in diabetic dogs. Beta-hemolytic *Streptococcus* sp., *Staphylococcus aureus*, *Escherichia coli*, and fungal organisms have been reported as underlying causative organisms (Wilkie & Colitz, 2013). Surgical intervention may be indicated. Medical management with topical chloramphenicol and a poor response to fluoroquinolones has also been reported (Wilkie & Colitz, 2013). Diabetic dogs and dogs on chronic topical corticosteroids are at increased risk.

Epithelial inclusion cysts or epithelial downgrowth is a rare complication of human cataract surgery (Koch & Novak, 1995). Epithelial downgrowth leading to incision nonunion has been reported in the dog and may be associated with the development of postoperative infectious endophthalmitis (Ledbetter et al., 2018). In humans, epithelial downgrowth can manifest as corneal decompensation, glaucoma, chronic anterior uveitis, and a retrocorneal membrane with a demarcated leading edge (Koch & Novak, 1995).

Endophthalmitis

Postoperative endophthalmitis after cataract surgery, although rare, is a devastating sight- and globe-threatening complication. The recent incidence of endophthalmitis in human cataract patients is reported to be between 0.04% and 0.2% (Packer et al., 2011). This incidence has changed over time, with conflicting evidence that it was related to the type of incision used (clear corneal vs. scleral or limbal based; Fintelmann & Naseri, 2010; Lundtsrom et al., 2007). The prevalence in the canine literature is higher compared to humans (0.28%–1.4 %) and can be infectious or sterile (Azoulay et al., 2013; Klein et al., 2011; Ledbetter et al., 2018; Sandmeyer et al., 2016; Sigle & Nasisse, 2006). In one study, positive bacterial cultures from the aqueous humor occurred in 24% of dogs undergoing cataract surgery (Taylor et al., 1995). In another study, endophthalmitis developed in 1.4% of cases within the first 3 months postoperatively, and no cases were reported after 3 months (Sigle & Nasisse, 2006). Two histopathologic studies have reported the diagnosis of frequency of endophthalmitis following enucleation or evisceration for glaucoma postoperatively in 27% and 9% of cases (Moore et al., 2003; Scott et al., 2013). One study revealed that 27% were diagnosed histologically with endophthalmitis

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and the average time until enucleation following cataract surgery was less than 1 month (Moore et al., 2003). Endophthalmitis was associated most often with suppurative keratitis, incisional dehiscence or nonunion, and corneal perforation away from the incision site (Ledbetter et al., 2018; Moore et al., 2003). The second study reported a lower but still relatively high occurrence of 9% (Scott et al., 2013). In a histopathologic study of enucleated or eviscerated globes following cataract surgery for glaucoma, Bichon Frise had the highest proportion of globes demonstrating endophthalmitis, and Boston Terriers and Jack Russell Terriers also showed a significant frequency of it (Scott et al., 2013).

Aqueocentesis should be performed in the suspicion of endophthalmitis for cytology, culture and sensitivity, and PCR testing. Antibiotic therapy should be commensurate with those results, but aggressive intervention should be started immediately.

Intraoperative risk factors for endophthalmitis include vitreous presentation, silicone and PMMA IOLs compared to acrylic, nonuse of intracameral antibiotic, possible use of a clear corneal incision, and male gender (Barry et al., 2006; Fintelmann et al., 2010; Hashemian et al., 2016). The use of an injector cartridge is associated with a lower risk of endophthalmitis in comparison with forceps-delivered IOLs (Weston et al., 2015). The absence of injector systems for foldable IOLs and the need for a larger incision for a nonfoldable PMMA lens can confound this association (ESCRS Endophthalmitis Study Group, 2007; Fintelmann & Nasari, 2010).

Numerous fungal and bacterial agents can cause endophthalmitis postoperatively. Gram-positive, coagulase-negative staphylococci, *Staphylococcus aureus*, and *Streptococcus* are the most commonly reported agents in humans (Fintelmann & Nasari, 2010; Hashemian et al., 2016). However, a systematic review showed that gram-negative organisms accounted for 65% of cases and 51.8% of those were *Pseudomonas aeruginosa* (Pathengay et al., 2012). The surface ocular flora are the most common source of bacterial contamination, and potential routes of infection include incisional dehiscence or nonunion, externalized vitreous strands, movement into and out of the eye of surgical equipment, and full-thickness corneal sutures (Ledbetter et al., 2004, 2018; Sandmeyer et al., 2016; Taylor et al., 1995). Other sources of bacterial entry include contaminated irrigating fluids or equipment, bacterial adhesion to the IOL, and airborne and hematogenous bacteria (Kodjikian et al., 2004; Ledbetter et al., 2004; Pathengay et al., 2012). Phacoemulsification cataract surgery has a significantly lower incidence of anterior chamber contamination than nonphacoemulsification cataract extraction in both humans and dogs (Egger et al., 1994; Taylor et al., 1995).

Pathogenic bacteria are found in the meibomian glands of humans, and this may also be a source of infection in dogs (Lacerda et al., 2018; Yoshitomi, 2005). In a study looking at bacterial isolates from aqueous humor and conjunctival surface samples in dogs, the genetic diversity of bacterial isolates from the aqueous humor after surgery indicated that anterior chamber contamination from the conjunctiva occurred, but also from other sources (Lacerda et al., 2018). According to the rep-PCR analysis, 16.6% of *Enterobacter* spp. isolates from conjunctival surface were genetically similar to those from aqueous humor. The rest of isolates encountered in aqueous humor were genetically distinct from those of conjunctival surface. Isolates from the conjunctival surface were *Enterobacter* spp., *Staphylococcus* spp., and *Staphylococcus aureus*, and from aqueous humor samples were *Enterobacter* spp., *Pantoea* spp., *Streptococcus* spp., and *Staphylococcus* spp., respectively, in decreasing order of prevalence (Lacerda et al., 2018). Another study in dogs undergoing cataract surgery showed that 22.7% of eyes grew bacterial or fungal organisms consistent with the conjunctival flora cultured preoperatively (Ledbetter et al., 2004). The most common bacterial organisms grown in that study from the conjunctiva and eyelid margins were *Bacillus* sp., *Staphylococcus* sp., and *Clostridium* sp. Bacterial organisms from the aqueous humor were *Bacillus* sp., *Staphylococcus* sp., and *Pantoea* sp. (Ledbetter et al., 2004). *Staphylococcus* or *Streptococcus* spp. were recovered from aqueous and vitreous humor samples in another study (Ledbetter et al., 2018). Despite what seems to be a relatively common occurrence of intraoperative contamination of the anterior chamber during cataract surgery, the actual incidence of endophthalmitis is lower (Egger et al., 1994; Ledbetter et al., 2004; Taylor et al., 1995). Rabbits are able to clear live bacteria from the anterior chamber, so other factors such as inoculum size and organism virulence must be relevant (Maylath & Leopold, 1955; Shockley et al., 1985).

There are numerous studies in human surgery focused on preventing endophthalmitis and the majority of them now involve the use of intracameral antibiotics. Endothelial toxicity and TASS are potential concerns after intracameral injection of any medication (Cakir et al., 2015). Intracameral vancomycin is associated with serious complications (Witkin et al., 2015). Rare events such as anaphylactic reaction have been reported several minutes after intracameral injection of cefuroxime at the end of cataract surgery (Moisseiev & Levinger, 2013). However, the risk for postoperative endophthalmitis has been shown to be decreased 80%–90% by the use of intracameral cephalosporins (Arshinoff & Modabber, 2016; Barry et al., 2006; Montan et al., 2002). This led to widespread adaptation of intracameral cefuroxime in Europe. There is no FDA-approved intracameral antibiotic in the United States, and with the increasing finding of cefuroxime-resistant gram-negative isolates, the focus has shifted to finding more appropriate candidate drugs for intracameral use. Alternative antibiotics, such as the fourth-generation fluoroquinolone moxifloxacin, are under study. Moxifloxacin has been used in concentrations varying from 250 mg/mL to 500 mg/mL from a commercially available, preservative-free eye-drop container (moxifloxacin 0.5%, Vigamox; Braga-Mele et al., 2014; Cavalcanti Lira et al., 2017). Intracameral moxifloxacin safety

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also stems from its near-neutral pH and isotonicity. Because medication turnover after intracameral administration is rapid, intracameral moxifloxacin, which is concentration dependent, may be more effective than cefuroxime, which is time dependent (Matsuura, 2015; Matsuura et al., 2013). A single infection in 3,430 cases occurred with a moxifloxacin-resistant strain of *Staphylococcus epidermidis* when moxifloxacin 100 µg in 0.1 mL was used. Increasing the dose prepared by dilution of 3 mL of moxifloxacin 0.5% (Vigamox) with 7 cc BSS and with the administration of 0.3–0.4 cc (450–600 µg), and changing the administration technique resulted in no infections in 4,601 cases and no detrimental side effects or complications (Arshinoff & Modabber, 2016). Moxifloxacin was placed as the final step in surgery via the side port after the main incision has been sealed. Intracameral moxifloxacin was more effective than cefuroxime in reducing bacterial adhesion of *Staphylococcus epidermidis* on hydrophobic IOLs (Benbouzid et al., 2016). No optimum dose of intracameral moxifloxacin has been established. Intracameral moxifloxacin at more than 500 mg/mL could damage the cell membranes (Haruki et al., 2014). However, many studies have used undiluted solutions up to 0.5% with no reports of toxicity. The dosage in the present study was 150 mg in 0.03 mL; taking into account that the anterior chamber has a volume of approximately 0.4–0.6 mL in pseudophakic patients, the final drug concentration was 250–375 mg/mL. Randomized clinical trials of the safety of intracameral moxifloxacin are recommended. Current concerns with the use of moxifloxacin are a growing resistance to it and its infrequent, but serious, adverse effects (Asbell et al., 2008; Ullman et al., 2016; Yannuzzi et al., 2017). The use of the IOL itself, or an attached drug delivery device to decrease endophthalmitis, has also been evaluated and may be promising (Kleinmann et al., 2006; Shaw et al., 2010; Tsuchiya et al., 2008).

Other methods of endophthalmitis prophylaxis include the use of periocular topical antibiotics and preoperative povidone–iodine or chlorhexidine. Most veterinary ophthalmologists begin administering topical antibiotics 2–24 hours prior to surgery in addition to using perioperative antibiotics. Human studies have shown no clear benefit with the use of preoperative antibiotics (Barry et al., 2013). With the increasing rate of bacterial resistance to antibiotics, antiseptic solutions preoperatively may be the only and best way to decrease the incidence of endophthalmitis (Gryzbowski et al., 2016; Nentwich et al., 2015). The use of 10% povidone–iodine on the skin and 1%–5% povidone–iodine on the conjunctiva significantly reduces the risk of postoperative endophthalmitis (Nentwich et al., 2015; Wu et al., 2006). The relationship of bactericidal activity of povidone–iodine with its concentration is not a simple one. Release of free iodine becomes more difficult as the povidone–iodine concentration increases, and diluting the solution facilitates iodine release. Because of this, 0.1%–1.0% povidone–iodine might require a shorter time to show bactericidal activity (15 seconds) than 2.5%–10.0% povidone–iodine (30–120 seconds; Berkelman et al., 1982). The possible toxicity of the povidone–iodine to both corneal epithelium and endothelium is concentration dependent and it should be used with this in mind (Alp et al., 2000; Freitas et al., 2002).

Patients at higher risk for developing endophthalmitis should receive postoperative oral antibiotics. These risk factors include patients that undergo longer phacoemulsification times, posterior capsular tear and vitreous presentation, diabetics, and dogs with skin allergies or dermatitis, especially in the periocular area and ears. The last group may benefit from preoperative oral antibiotics as well, and care should be taken that these infections are as controlled as possible prior to surgery.

Posterior and Anterior Capsule Opacification

PCO is the most common long-term postoperative complication after phacoemulsification (Fig. 23.36). Even with the most careful and meticulous lens removal, some LECs are always left behind within the capsule. The development of capsular opacification involves proliferation, migration, and differentiation of the LECs. The wound healing response consisting of cell proliferation and migration occurs along all interior surfaces of the capsule, but predominantly posteriorly. The proliferation of residual LECs is highest within 3–4 days postoperatively (McDonnell et al., 1985a). Some of these cells also undergo epithelial to mesenchymal transition (EMT), from cuboidal cells to migratory myofibroblast-like cells that overexpress alpha-smooth muscle actin and COX-2 (Chandler et al., 2006, 2007; de Longh et al., 2005; Marcantonio & Vrensen, 1999; McDonnell et al., 1983, 1985b). Increased expression of alpha-smooth muscle actin results in LEC contraction with resultant capsule wrinkling, folds, and possible IOL decentration (Apple et al., 1992). This fibrous PCO, if it occurs around the anterior lens capsulotomy, is termed Soemmering's ring. Other cells, especially equatorial LEC, undergo lens fiber cell differentiation in an attempt to regenerate the lens (Findl et al., 2010; Wormstone et al., 2009). They form large, balloon-like bladder or Wedl cells, also known as Elschnig's pearls (Fig. 23.37; Apple et al., 1992; Findl et al., 2010; Kappelhof & Vrensen, 1992). Clinically, PCO can decrease visual acuity by blocking the visual axis. Wrinkles and plaque formation worsen this even further (Apple et al., 1992). This also leads to an increasing inability to monitor the posterior segment for complications such as RD, therefore delaying timely intervention.

Factors that may influence PCO formation include patient age, stage of cataract, the size of the capsulorhexis, hydrodissection, composition of the irrigating solution, viscoelastic material used, capsule polishing, IOL biocompatibility and design, and other systemic and local host factors, including species (Apple et al., 1992; Bras et al., 2006; Chandler et al., 2007; Davidson et al., 2000; Haeussler et al., 2010; Pandey et al., 2002). The disruption of lens fibers during cataract

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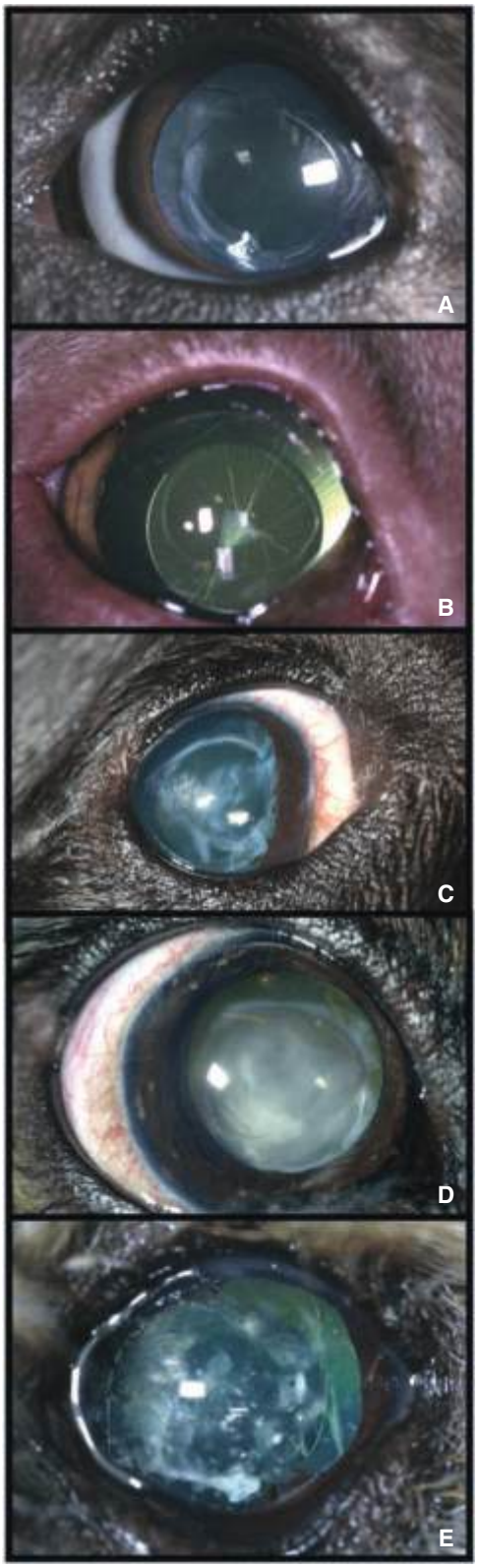


Figure 23.36 Appearance of posterior capsular opacification (PCO) in canine patients after phacoemulsification and intraocular lens implantation. Clinical examples of PCO grading scores (0–4+) in canine patients. **A**. A faint haze or minimal opacity of the posterior lens capsule that permitted a thorough evaluation of the retina was graded as 1/2+ PCO. **B**. A focal plaque, or diffuse haze, or mild opacity on the posterior lens capsule that slightly impaired evaluation of the retina was graded as 1+ PCO. **C**. More than one plaque, or dense haze, or moderate opacity of the posterior lens capsule that mildly impaired the fundic examination was graded as 2+ PCO. **D**. Numerous dense posterior lens capsular plaques or severe opacification that moderately impaired the fundic examination was graded as 3+ PCO. **E**. PCO that completely obstructed the view of the retina was graded as 4+.

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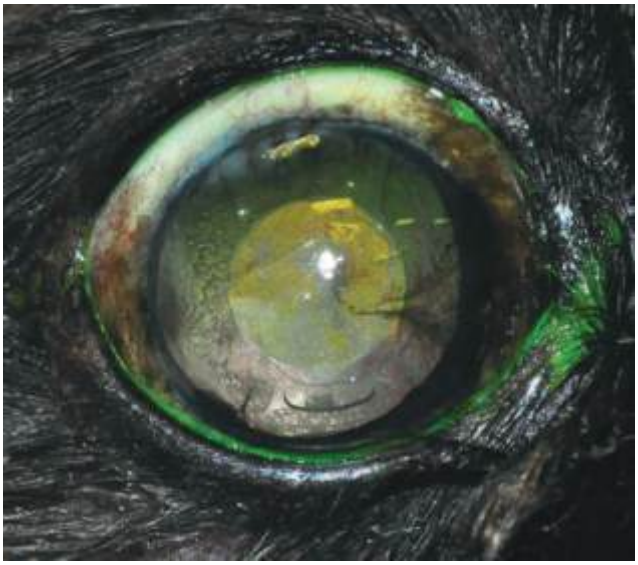


Figure 23.37 A patient that underwent phacoemulsification and foldable acrylic intraocular lens (IOL) implantation. Elschnig's pearls are visible around the body of the IOL and under the haptic ventrally.

surgery alters the local environment and induces the proliferation of LECs (Rakic et al., 1997). Residual cortex and melanocytes from the iris may also induce proliferation (Cobo et al., 1984). Breakdown in the blood–aqueous barrier following surgery can also increase the expression of growth factors and cytokines in the aqueous humor, promoting EMT (Chandler et al., 2010; Cobo et al., 1984). The presence of a foreign material such as the IOL may exacerbate this response.

The residual LECs can secrete various cytokines that regulate the behavior of LECs and the development of PCO (Iyengar et al., 2009; Wallentin et al., 1998; Wormstone, 2002; Wormstone et al., 2001, 2009). These cytokines can include fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), epidermal growth factor (EGF), insulin-like growth factor (IGF), transforming growth factor beta (TGFβ), and interleukin 1 and 6 (Iyengar et al., 2009; Wallentin et al., 1998; Wormstone, 2002; Wormstone et al., 2009). Some of these growth factors can induce EMT through the Akt pathway (Yao et al., 2008). Phorphylated Akt (pAkt) interacts with and phosphorylates telomerase in canine LECs that have undergone EMT, but not in normal canine LECs (Barden et al., 2004; Colitz et al., 2009). It is possible that induction of pAkt results in increased lenticular telomerase activity, thus promoting PCO formation (Chandler et al., 2010). The effect of inhibiting signal transduction through Akt on PCO formation in an *ex vivo* canine lens capsule explant model has been evaluated (Chandler et al., 2010). Telomerase activity decreased in a dose-dependent manner with inhibition and decreased PCO formation. TGFβ induces EMT of LECs and leads to the production of extracellular matrix (de Longh et al., 2005). The use of pirfenidone, an anti-inflammatory and anti-fibrosis agent, inhibits TGFβ-induced proliferation, migration, and EMT transition of human LECs (Yang et al., 2013). TGFβ initially decreases after surgery, and this allows proliferation of LECs due to the action of basic fibroblast growth factor (bFGF) and other growth factors (Meacock et al., 2000; Wallentin et al., 1998; Wormstone, 2002). Intracellular calcium signaling pathways can also be associated with PCO development (Collison et al., 2004). Several proteins are overexpressed in LECs that have undergone EMT, as in PCO, including COX-2, estrogen receptor alpha and telomerase (Colitz et al., 1999, 2004), aromatase (Colitz et al., 2005), as well as other proteins. COX-2 expression in canine cataracts in an *ex vivo* PCO model showed increased expression compared to normal canine LEC (Chandler et al., 2007). Unfortunately, the effect of inhibition of specific components of the signaling pathway on PCO prevention is unsatisfactory or has shown inconsistent results, which suggests that PCO develops through multiple redundant pathways involving various factors (Davis et al., 2012).

In human surgical patients, anterior capsular opacification occurs 1–6 months postoperatively (Kimura et al., 1998). PCO occurs in 20%–60% of patients within 5 years postoperatively (Apple et al., 2000b, 2001; Leysen et al., 2006; Mootha et al., 2004; Sundelin & Sjostrand, 1999, Wormstone et al., 2009). In dogs, PCO occurs in 62%–100% of patients (Bras et al., 2006; Sigle & Nasisse, 2006). The average time to significant clinical PCO in humans is 26 months after surgery, with a range of 3 months to 4 years (Apple et al., 1992). A similar amount of PCO develops in dogs by 12 months postoperatively (Bras et al., 2006). Small and medium-sized breeds seem to develop more PCO than larger breeds (Bras et al., 2006). A younger age predisposes to increased severity of PCO in humans, but that has not been consistently reported in dogs (Bras et al., 2006; Moisseiev et al., 1989).

Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser posterior capsulotomy is the most commonly used therapeutic modality for the treatment of PCO in humans (Apple et al., 2000a). Potential complications of the procedure include damage to the IOL, IOP elevation, cystoid macular edema, RD, IOL luxation, or endophthalmitis (Apple et al., 1992; Lane, 2004). A study evaluated the effect of Nd:YAG laser energy on PMMA and acrylic IOLs in normal dog eyes (Beale et al., 2006). There was a therapeutic margin between capsulotomy threshold (2.6–2.7 mJ) and IOL damage threshold (4.9–5.7 mJ) that reliably achieved capsulotomies with minimal IOL damage for both acrylic and PMMA IOLs (Beale et al., 2006). Hypermature cataracts or excessively thickened or wrinkled posterior capsules may reduce the therapeutic effect of the laser procedure, as the energy necessary to disrupt the posterior capsule would damage the IOL. Further studies are warranted.

Three surgery-related factors and three IOL-related factors are important in the prevention of PCO in humans (Apple

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et al., 1998, 2000a, 2000b, 2001, 2011; Schmidbauer et al., 2001). The three surgery-related factors are a small CCC with the edge on the IOL surface, hydrodissection, and in-the-bag fixation (Schmidbauer et al., 2001). Creating a capsulorhexis that is slightly smaller (0.5 mm) than the optic is the accepted standard in human cataract surgery (Zanini et al., 2003a). This achieves a tight fit of the anterior capsule and helps to sequester the optic in the capsular bag away from the aqueous humor and its macromolecules and inflammatory mediators (Schmidbauer et al., 2001). The second technique, hydrodissection, is an important technique used in humans to reduce PCO (Peng et al., 2000a). A modification of traditional hydrodissection, cortical cleaving hydrodissection, permits the cleavage of the cortex from the posterior capsule, which allows more efficient and thorough removal of most or all of the cortex and LEC during phacoemulsification (Buratto et al., 2003; Schmidbauer et al., 2001). The routine use of a one-handed technique by veterinary ophthalmologists diminishes the ability to use hydrodissection. The third surgery-related factor is in-the-bag placement of the IOL. The primary function of this factor is enhancing the IOL-optic barrier effect, which is maximal when the IOL directly contacts the posterior lens capsule (Peng et al., 2000b). In humans, the rate of in-the-bag fixation was only 60% prior to foldable IOLs and increased to 90% with their use. The rate of in-the-bag fixation in veterinary medicine has not been evaluated, but has been estimated to be greater than 98% (Wilkie & Colitz, 2013).

The three IOL-related factors that decrease PCO include biocompatibility, maximal IOL optic–posterior capsule contact, and a mechanical barrier effect of the IOL optic (Fig. 23.38). Lens material biocompatibility is often defined as the ability to inhibit postoperative stimulation of LEC proliferation (Apple et al., 2000a; Zhao et al., 2017). There are numerous reports in the human literature regarding the biocompatibility of numerous IOLs, but few in the veterinary

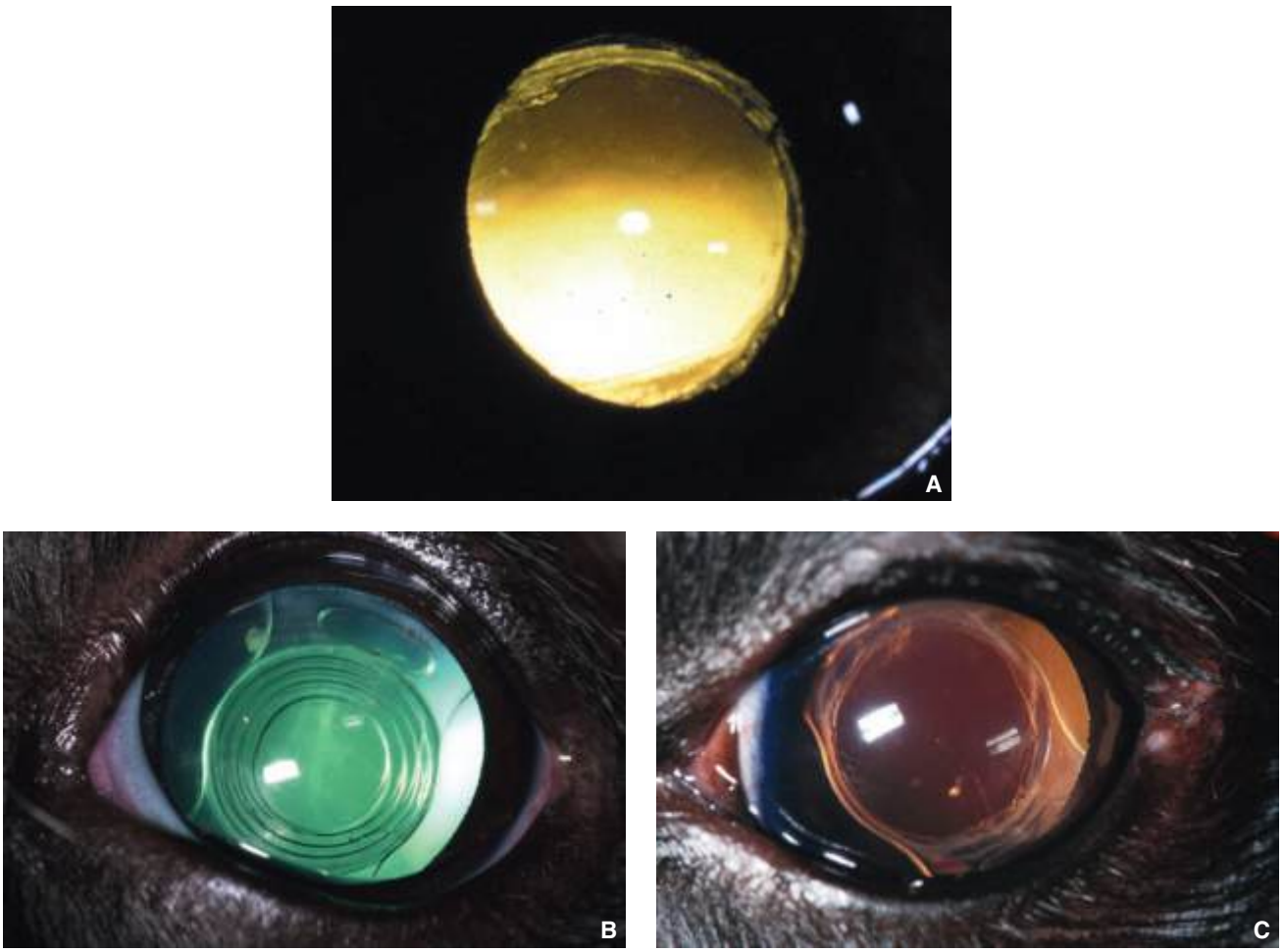


Figure 23.38 **A**. A polymethylmethacrylate intraocular lens (IOL) 2 years postoperatively. The axial IOL and capsule remain transparent, and peripheral anterior capsular fibrosis is evident. **B**. 30-V acrylic (Acrivet) IOL 1 year postoperatively. The IOL and lens capsules remain clear. **C**. 60-V acrylic (Acrivet) IOL 18 months postoperatively. Posterior capsule opacification is noted at the edge of the optic, but the central optic remains clear.

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literature. The biologic effects of different IOL materials on the adhesion, migration, morphology, and EMT of human lens HLEB3 cells have been reported (Wang et al., 2017). Four different IOL materials were tested (i.e., PMMA, silicone elastomer, hydrophilic acrylic, and hydrophobic acrylic). The highest levels of HLEB3 cell adhesion and migration were found for the hydrophobic acrylic IOL cultures, which also had the lowest incidence of EMT. In contrast, while the PMMA IOLs had a low level of cell adhesion, the percentage of these cells undergoing EMT was the highest compared to the other groups. The hydrophilic IOLs were also associated with an extremely low level of cellular adhesion, which ultimately prevented any further analysis. Finally, while the HLEB3 cells cultured with silicone IOLs were similar to those cultured with hydrophobic acrylic IOLs in terms of morphology and EMT levels, they had significantly lower adhesion and migration profiles. So IOL composition greatly affected lens cell behavior during PCO development, and hydrophobic IOLs may be the best option to limit the effects of PCO after cataract surgery (Chang & Kugelberg, 2017; Wang et al., 2017). Clinically, with PMMA IOLs the incidence of PCO in humans ranges from 30.4% up to 50% (Apple et al., 1992; McDonnell et al., 1983; Schmidbauer et al., 2001; Wilhelmus & Emery, 1980). Consistent with the cell culture study, acrylic IOLs with hydrophobic surfaces were associated with the lowest PCO score (Zhao et al., 2017). Acrylic IOLs with either hydrophobic or hydrophilic surfaces are associated with lower overall PCO scores than silicone or hydrogel (Findl et al., 2005; Hollick et al., 1999). Foldable acrylic hydrophobic IOLs have shown long-term ability to decrease the amount and density of PCO (Chang & Kugelberg, 2017). Foldable hydrophobic (e.g., Alcon AcrySof®) IOLs have been implanted following phacoemulsification in two captive lowland gorillas. The younger gorilla (17 months) developed PCO and required an Nd:YAG laser capsulotomy (de Faber et al., 2004). Both hydrophobic and hydrophilic IOLs are available for use in dogs.

The second IOL factor, maximal IOL optic–posterior capsule contact, uses the posterior angulation of the IOL haptic and posterior convexity of the optic to create a tight fit of the IOL optic with the posterior capsule. It has been suggested the optic biomaterial may also create an adhesion of the capsule to the IOL optic, termed bioadhesion (Apple et al., 2000a; Schmidbauer et al., 2001).

The third IOL factor, the IOL optic barrier effect, is the second line of defense against PCO. Nishi et al. (1998) first showed this effect in rabbits, followed by Apple et al. (1998) in humans. This concept puts the phrase "no space, no cells" into action by creating a physical barrier against LEC migration under the IOL and onto the posterior capsule. A square edge on the posterior optic surface appears to be the most important IOL design feature for PCO prevention (Buehl & Findl, 2008; Buehl et al., 2005). According to various studies, the preventive PCO effect associated with the square edge may be due to a mechanical barrier effect (Werner et al., 2005), the contact inhibition of migrating LECs at the capsular bend created by the edge (Nishi & Nishi, 1999), the higher pressures exerted by IOLs with a square-edged optic profile on the posterior capsule (Boyce et al., 2002), or combinations of all three factors. A study of canine IOL design and PCO suggests that squared-edge foldable acrylic IOLs show a tendency toward less PCO than round-edged PMMA IOLs in the early postoperative period (Gift et al., 2009).

In addition to IOL design and material, surface modifications of the IOL have been studied in an attempt to prevent PCO with variable degrees of success (Farukhl et al., 2015; Krall et al., 2015; Kramer et al., 2015; Pot et al., 2009; Vyas et al., 2007; Werner et al., 2000, 2004; Wormstone et al., 2009). Exposure of the IOL to ultraviolet light and placing a smooth or a patterned silicone protective membrane into the capsular bag prior to placement of the IOL have also been evaluated and show promise for decreasing PCO in humans (Farukhl et al., 2015; Krall et al., 2015; Kramer et al., 2015). The heparin modification of a PMMA IOL changed its surface properties from hydrophobic to hydrophilic, which resulted in a reduced inflammatory cell adhesion and better uveal biocompatibility (Roesel et al., 2008). However, modifying the surface with heparin did not reduce PCO (Krall et al., 2015). Coating the lenses with selenocystamine did decrease PCO in a canine model (Pot et al., 2009).

Numerous pharmacologic agents have been evaluated for the prevention for PCO (Davis et al., 2012; Nibourg et al., 2015). These agents can be delivered directly into the anterior chamber at the time of surgery, placed in the irrigating fluids used during surgery, delivered via impregnation of the IOL or capsule tension ring device. Mitomycin-C, 5-fluorouracil, lidocaine, carbachol, and osmotic agents have been shown to be effective in the inhibition of PCO *in vitro* (Biwas et al., 1999; Nishi, 1999; Pot et al., 2009; Walker, 2008; Wormstone et al., 2009). However, *in vivo* concentrations high enough to inhibit LEC proliferation had a toxic effect on the surrounding intraocular tissues, especially on the corneal endothelium, thus limiting their clinical use (Davis et al., 2012; Nishi, 1999). The use of the IOL itself, or an attached drug delivery device, to decrease PCO and postoperative inflammation has been evaluated (Kugelberg et al., 2010; Morarescu et al., 2010; Siqueira et al., 2006). Studies have demonstrated success in the delivery of drugs to the eye after incubating with indomethacin (Nishi et al., 1995), dexamethasone (Kugelberg et al., 2010), or rapamycin (Liu et al., 2009). For the IOL–drug incubation/sustained release to be effective in the prevention of PCO, sufficient concentrations need to be released for an appropriate duration to inhibit LEC growth without causing toxicity to the eye (Wormstone et al., 2009). One prospective randomized multicenter human study found that tPA might also diminish PCO (Heiligenhaus et al., 1998). No further studies have shown this result.

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The effect of various COX-2 inhibitors in preventing PCO has been evaluated. Topical diclofenac 3 times daily for 1 year postoperatively decreases PCO in human patients (Seki et al., 1992). However, topical flurbiprofen once daily for 6 months following cataract surgery in the dog did not appear to lead to a decrease in PCO formation (Newbold et al., 2017). In an *ex vivo* canine LEC model, COX-2 inhibition (Celecoxib) prevented EMT and, as a result, may decrease PCO (Chandler et al., 2007). This inhibition of LEC growth was shown to be a pharmacologic effect rather than nonspecific toxicity, and LEC growth did not resume when these cultures were continued without Celecoxib for another 7 days (Chandler et al., 2007). This may be clinically applicable, as COX-2 inhibitors could be administered intra- or postoperatively. In another study, canine eyes receiving a Celecoxib-impregnated IOL and topical prednisolone acetate had better initial control of inflammation than eyes receiving topical bromfenac or prednisolone acetate (Brookshire et al., 2015). Bromfenac was equally effective compared with prednisolone acetate in controlling inflammation. Celecoxib-impregnated IOL eyes showed better initial control of PCO (up to 12 weeks), while eyes receiving bromfenac had better long-term control of PCO (56 weeks; Brookshire et al., 2015). In a third study evaluating Celecoxib effects, a 4-day treatment of canine lens capsules with a concentration of 20 µM effectively prevented PCO (Davis et al., 2012). IOLs incubated in Celecoxib for 24 hours resulted in a sustained release of the drug *in vitro* at levels sufficient to inhibit LEC growth in the *ex vivo* model of PCO (Davis et al., 2012).

Introduction of exogenous hyaluronic acid into the canine lens capsule can induce lenticular migration and upregulate CD44 expression (Chandler et al., 2012). CD44 expression increases during migration of LEC and it is found in human cataracts and PCO material (Saika et al., 1998). OVDs containing 2% hyaluronic acid viscoelastic (Acrivet, Hennigsdorf, Berlin, Germany), 1.2% hyaluronic acid viscoelastic (Acrivet), or HPMC viscoelastic (Acrivet) were compared. The hyaluronic acid–containing OVD increased CD44 expression and LEC migration. As the concentration of hyaluronic acid within the OVD increased, the rate of PCO increased. These results suggest that surgeons should remove viscoelastic material from the anterior chamber and lens capsule when possible to help minimize PCO (Chandler et al., 2012).

Another study evaluated cyclosporine A (CsA) dose and minimum drug delivery time needed to prevent PCO and the mechanism of CsA-induced cell death in an *ex vivo* canine model (Chandler et al., 2015). Lens capsules treated with 5, 6, or 7 days of 10 mg/mL CsA showed a significant decrease in *ex vivo* PCO formation; 6 days of drug delivery prevented PCO. Morphologic changes, formation of acidic vesicles, and increased expression of LC3-II supported the hypothesis that CsA mediates LEC death via autophagy (Chandler et al., 2015).

Pulsed fluid lens capsule washing, using the AquaLase® liquefaction handpiece, a component of the Alcon Laboratories' Infiniti phacoemulsification machine, has also been shown to be capable of removing LECs and delaying PCO formation in canine eyes following phacoemulsification *ex vivo* (Hughes et al., 2005; Lutz et al., 2015). This capsule-washing technology has also been proposed to pose a decreased risk of posterior capsule rupture when compared with conventional phacoemulsification needles due to its smooth polymer tip (Mackool, 2005).

Capsular bag irrigation with trypan blue dye decreased PCO at 6 and 12 months postoperatively in a human study (Sharma & Panwar, 2013). In contrast, another study showed decreased PCO at 6 months in humans, but no effect at 36 months (Joshi & Hussain, 2017). Although it induced low levels of LEC death, it was also not effective in reducing PCO in an *ex vivo* canine model (Brash et al., 2019).

Placement of a CTR delays the onset of PCO and decreases its overall severity in humans (Kim et al., 2005). Placement of a CTR alone and in combination with an IOL resulted in decreased PCO in a study in dogs (Morales et al., 2015). The CTR mechanically prevents LEC proliferation, migration, and PCO formation in multiple ways (Wilkie et al., 2015). The CTR provides 360° circular capsule contact and mechanical barrier with the IOL optic by creating radial capsular distension forces. Haptics may angulate the IOL such that irregular or discontinuous contact is made between the IOL and capsule if no CTR is implanted (Menapace et al., 2000). It stretches the capsular bag, decreasing space between the posterior lens capsule and IOL optic, inhibiting LEC migration between the capsule and optic by increasing the barrier effect (Findl et al., 1998). The stretching can also minimize or eliminate capsular folds that allow for cell proliferation and migration (Menapace et al., 2000). The PMMA CTR, used in human ophthalmic surgery, has now been specifically redesigned for veterinary ophthalmic use (Wilkie et al., 2015). The canine PMMA CTRs have a compressible open-ring circular shape with a square cross-section, sharp edge, and angled rounded eyelets on each end of the open ring to facilitate manipulation and implantation (Wilkie et al., 2015). It was determined that 12.5, 13.5, and 14.5 mm closed CTR diameters would appropriately distend the canine capsule equator without CTR ends overlapping or gaping for lens capsules receiving 12, 13, and 14 mm 30 V 41 D, acrylic IOLs, respectively (Wilkie et al., 2015).

A CTR injector was also designed and manufactured, lengthening the injector tip for ease of implantation of the canine CTR into the capsular bag (S&V Technologies/Acri.Vet Veterinary Division, Hennigsdorf, Germany). The injector serves to prevent CTR contact with contaminated extraocular surfaces *in vivo*. The injector contains a hook designed to engage the CTR eyelet, which then draws it back into the injector upon release of the plunger. The plunger is depressed to extrude the CTR into the equatorial aspect of the capsular.

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CTR implantation may be performed prior to phacoemulsification following hydrodissection, after phacoemulsification and I/A, or any time in between (Wilkie et al., 2015). Optimal timing for CTR placement is after phacoemulsification if possible (Wilkie et al., 2015). Less traction or stress is placed on the zonules when the capsular bag is empty than when the cataractous or unstable lens is still in place (Ahmed et al., 2005; Wilkie et al., 2015). Complete distension of the capsular bag with a viscoelastic device to reduce the risk of CTR drag on the capsule and subsequent traction on the zonules or capsular rupture is recommended (Wilkie et al., 2015).

Intraocular Lens Decentration/Luxation

IOL problems following cataract surgery were reported in 6.3% of dogs (Yi et al., 2006). These issues can include IOL or haptic dislocation, both in and out of the bag (see Fig. 23.8), as well as IOL decentration (Fig. 23.39 and Fig. 23.40). Possible causes of IOL decentration include an excessively large lens capsule (i.e., intumescent diabetic cases), the IOL is too small in diameter for the lens capsule, a too large anterior capsulotomy, radial tears, and capsule contraction from PCO that displaces the IOL. Capsule contraction syndrome is an exaggerated reduction in anterior capsulotomy and capsular bag diameter as a complication of CCC (Davison, 1993; Hanson et al., 1993; Tadros et al., 2005). It is caused by the anterior LEC undergoing EMT, which causes expression of alpha-smooth muscle actin and contraction and wrinkling of the anterior capsule (Tanaka et al., 2004). Elevated aqueous humor TGF-beta2 concentration and increased receptors in the LEC may also contribute to it (Zhu et al., 2016). This syndrome can result in reduction and malposition of the capsulotomy opening; IOL decentration, tilting, or displacement; zonular traction leading to IOL dislocation; and RD (Davison, 1990; Tadros et al., 2005). Anterior capsular opacification and capsule contraction syndrome usually occur earlier, within 3–6 months, than PCO (Werner et al., 2001). Foldable IOLs do not decentrate or dislocate as often

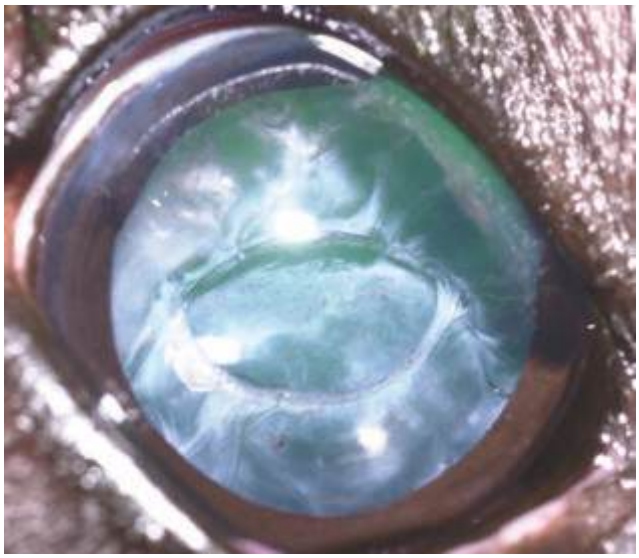


Figure 23.39 The right eye of a dog that underwent phacoemulsification and polymethylmethacrylate intraocular lens (IOL) implantation. The IOL is ventrally decentered and the capsulorhexis is contracted around the dorsal edge of the body of the IOL. Posterior capsule opacification is also evident.

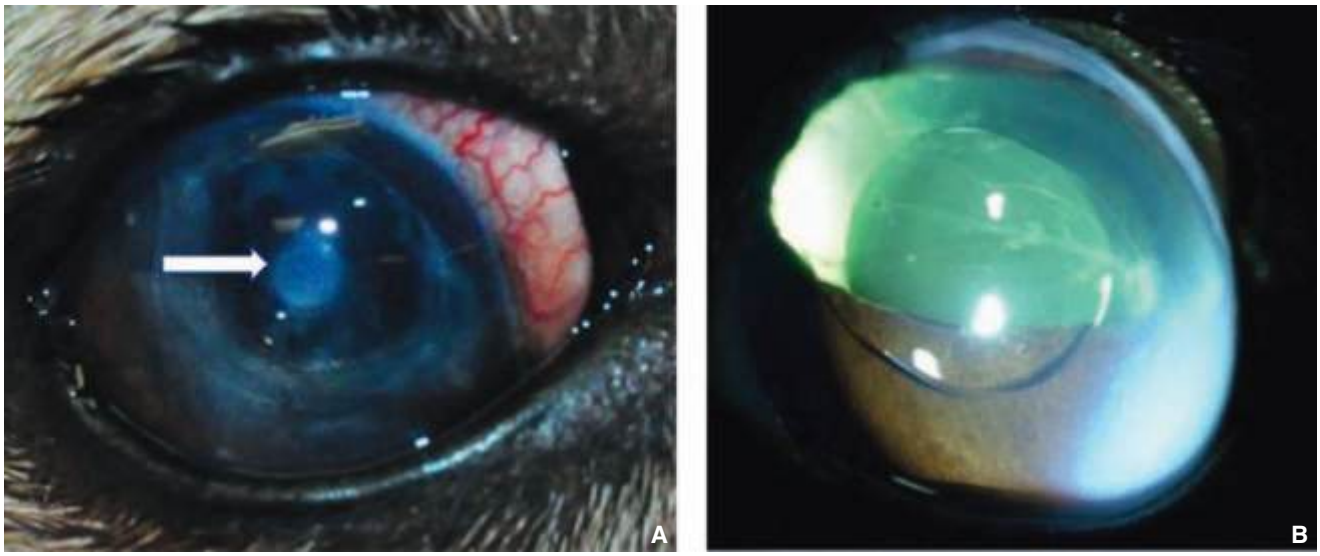


Figure 23.40 **A**. The intraocular lens (IOL), in the bag, luxated into the anterior chamber in a 10-year-old Jack Russell Terrier 4 years following phacoemulsification and foldable IOL implantation. Posterior capsule opacification is evident around the IOL body. The axial circular area (white arrow) is the pupil behind the IOL. **B**. The ventral haptic of a polymethylmethacrylate lens is displaced anterior to the iris and entrapping it. Pigment has proliferated over part of the haptic. There is focal ventrotemporal corneal edema.

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as the PMMA IOLs, but it is reported (Wilkie & Colitz, 2013; Yi et al., 2006).

Constructing a CCC that is as large as possible for the IOL to be implanted and removal of anterior subcapsular LECs by aspiration or scraping can help prevent capsule contraction syndrome (Tadros et al., 2005). Curettes or diamond-finished tips used to polish the anterior capsule are probably preferable to vacuuming by the I/A handpiece (Sacu et al., 2004). The use of a CTR centers the capsular bag despite weak zonules and may prevent capsular shrinking and IOL decentration (Cionni & Orsher, 1998; Hara et al., 1991). However, a nonsutured CTR does not guarantee protection against progressive zonular dehiscence occurring. Primary zonular instability in certain breeds of dogs may also predispose to IOL dislocation (see Fig. 23.8).

Irritation to the iris or ciliary processes results in low-grade uveitis and possibly fibrin formation and increases the risk of permanent corneal edema, PIFM formation, secondary glaucoma, and RD in dogs (Lannek & Miller, 2001; Moore et al., 2003; Sigle & Nasisse, 2006; Zarfoss et al., 2010). Therefore, removal or replacement of a dislocated IOL is indicated. Replacement should be attempted if a better fit can be achieved, a foldable IOL can be implanted, or the lens can be sutured in place.

Glaucoma

The development of glaucoma postoperatively is a significant contributor to the failure of phacoemulsification in dogs. In a study looking at eyes enucleated or eviscerated due to complications from glaucoma, glaucoma accounted for 76% of those cases (Moore et al., 2003). Glaucoma secondary to cataract was present in 19.3% of dogs in a retrospective study over 39 years (Gelatt & MacKay, 2004). Glaucoma as a sequela to cataract surgery occurred in approximately 5.1% of dogs. One study that did not differentiate between POH and glaucoma reported the incidence at 38.2% (Lim et al., 2011). A similar incidence to the Gelatt and MacKay study has been reported in a study with a short median follow-up of 5.8 months, which found that 16.8% of eyes developed postoperative glaucoma (Biros et al., 2000). A second study with a longer follow-up time of 31.7 months showed an incidence of 18.8% (Lannek & Miller, 2001). A more recent retrospective study evaluating 179 eyes following phacoemulsification found a lower glaucoma prevalence of 6.7% (Klein et al., 2011). The incidence of glaucoma with foldable IOLs has been reported at 6.7%, with vision loss from glaucoma in 76% of those cases at last evaluation (Rodriguez et al., 2016).

Risk factors for glaucoma postoperatively include breed, age, stage of cataract, aphakia, preexisting uveal and retinal abnormalities, and intraocular hemorrhage (Biros et al., 2000; Lannek & Miller, 2001; Scott et al., 2013; Sigle & Nasisse, 2006; Smith et al., 1997). An increased risk of glaucoma was found in eyes with hypermature cataracts (Biros et al., 2000), preexisting uveal or retinal abnormalities (Lannek & Miller, 2001), and intraoperative hemorrhage (Lannek & Miller, 2001). Anterior uveitis secondary to phacoemulsification accounted for 15.8% of secondary glaucoma cases of 156 dogs evaluated in one study (Johnsen et al., 2006). The presence of LIU, placement of an IOL, or POH were not risk factors for developing glaucoma in another study (Lannek & Miller, 2001). The likelihood of glaucoma has been shown to increase 1.88 times for each year of increasing patient age (Klein et al., 2011). A lower risk of glaucoma was found in eyes that had IOLs placed in another study (Biros et al., 2000).

Mixed-breed dogs have been reported to have a decreased risk of glaucoma compared to purebred dogs (Biros et al., 2000). The most frequently represented breeds identified as being enucleated or eviscerated as a result of glaucoma following routine phacoemulsification were the Cocker Spaniel (11.7%), Boston Terrier (10.5%), Labrador Retriever (6.5%), Bichon Frise (6.5%), Shih Tzu (5.8%), and Jack Russell Terrier (5.8%; Scott et al., 2013). The Labrador Retriever has a significantly increased risk (33%) of POH and glaucoma following cataract surgery (Moeller et al., 2011). The Boston Terrier, Shih Tzu, Cocker Spaniel, and Cockapoo have been reported to have a higher frequency of glaucoma after phacoemulsification than other breeds (Foote et al., 2018; Lannek & Miller, 2001; Moore et al., 2003; Sigle & Nasisse, 2006). Boston Terriers and Shih Tzu are reported to have an overall glaucoma incidence of 38% and 29%, respectively (Foote et al., 2018). In that study, 50.0% of Boston Terriers and 34.9% of Shih Tzu developed glaucoma in at least one eye postoperatively (Foote et al., 2018). In contrast, in another study there was no significant difference in visual outcome between Boston Terriers and non-Boston terriers within 1 year post-phacoemulsification, but the incidence of glaucoma was not specifically recorded (Newbold et al., 2018). In addition to the Cocker Spaniel, other breeds of dogs with known primary glaucoma, such as the Bassett Hound, are likely at increased risk of glaucoma postoperatively as well. Pugs have been reported to have a postoperative glaucoma rate of 9%, which is consistent with non-breed-specific data (Boss et al., 2020). In a retrospective analysis on enucleated globes after phacoemulsification, Shih Tzu and Boston Terriers had the two highest percentages of RD (63% and 56%, respectively; Moore et al., 2003). Patients in this histopathology study were enucleated secondary to glaucoma; therefore, it was difficult to discern if the RD occurred before or after another postoperative complication (uveitis, glaucoma, etc.).

Reevaluations following phacoemulsification should be consistent and frequent to monitor for the development of glaucoma. Medical intervention and management should be aggressive and imitated as soon as it is identified. Topical carbonic anhydrase inhibitors and/or topical prostaglandin analogs are frequently used. The proinflammatory effects of topical prostaglandin analogues should be considered

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whenever starting therapy postoperatively (Fechtner et al., 1998). Surgical intervention consists of endoscopic laser cyclophotocoagulation, transscleral diode cycloablation, and placement of drainage valves with or without transscleral cyclophotoablation (Bras & Maggio, 2015; Bras et al., 2005; Cook et al., 1997; Garcia-Sanchez et al., 2005; Gomez-Guajardo et al., 2006; Lutz & Sapienza, 2008). Endoscopic cyclophotocoagulation performed at the time of phacoemulsification and IOL implantation is an approach being evaluated to delay or postpone the onset of secondary glaucoma in high-risk cases (Bras & Maggio, 2015; Bras et al., 2005). If retinal function is acceptable, it may be possible to improve outcomes with concurrent diode endolaser cyclophotoablation (Bras et al., 2005). This is discussed further in the section on surgery on unstable lenses.

Retinal Detachment

RD is a devastating complication following phacoemulsification. RDs can occur by two mechanisms postoperatively: (1) tractional RDs occur when tension forces in the vitreous (hemorrhage, inflammatory bands, direct tension form surgical manipulations) pull the retina away from the RPE (Vainisi et al., 2013); and (2) secondary rhegmatogenous RDs occur when fluid from the vitreous cavity enters the subretinal space through a tear in the retina. Secondary rhegmatogenous RDs occur most commonly due to cataract surgery, but can also be a sequela of trauma, glaucoma, lens luxation, and surgery involving the ciliary body. Specific risk factors that have been identified for RD include breed, hypermature cataracts, and vitreal degeneration (Davidson et al., 1991a; Dziezyc et al., 1986; Foote et al., 2018; Miller et al., 1987). Spontaneous PVD that occurs with age may decrease the incidence of RD in older animals (Foote et al., 2018).

Retinal detachment rates in dogs following phacoemulsification, without focusing on breed, have been reported as 1%–2% (Sigle & Nasisse, 2006; Wilkie et al., 2015), 4.7% (Davidson et al., 1991b), 4.8% (Miller et al., 1987), and 8.4% (Klein et al., 2011). In one of the two studies with low RD rates, all cases of RD occurred prior to 3 years postoperatively, and it was speculated that patient selection or a few intraoperative variables may have contributed to this lower prevalence (Sigle & Nasisse, 2006). It is possible that fewer hypermature cataracts overall are undergoing surgery or fewer breeds predisposed to RD were included in those studies (Wilkie & Colitz, 2013). In the study with a prevalence of 8.4%, RD was the most common cause of blindness with an average of 1 year of follow-up (Klein et al., 2011). Phacoemulsification cataract surgery in humans has a similar low rate of RD of between 0.75% and 1.65% (Ramos et al., 2002).

In contrast, RD was observed on histopathology in up to 64% of globes and retinal tears in 24% of globes enucleated following phacoemulsification complications (Moore et al., 2003). In another retrospective analysis on enucleated or eviscerated globes after phacoemulsification, Shih Tzu and Boston Terriers had the two highest percentages of RD (63% and 56%, respectively; Scott et al., 2013). However, patients in this histopathology study were enucleated secondary to glaucoma; therefore, it is difficult to discern if the RD occurred before or after another postoperative complication (uveitis, glaucoma, etc.; Scott et al., 2013). Shih Tzu, Boston Terriers, and Bichon Frises may have a predisposition to primary rhegmatogenous RD, and Shih Tzu are at increased risk specifically for giant retinal tears (Itoh et al., 2010; Vainisi et al., 2013). Boston Terriers were reported to be at increased risk of RD in one study, specifically 84.2 times more likely than other breeds (Klein et al., 2011). However, the number or percentage of Boston Terriers affected by RD was not stated and only 10 Boston Terriers were analyzed in their report. This is in contrast to a study where there was no increased risk of RD following phacoemulsification in the Boston Terrier (Foote et al., 2018). In that study, looking at Boston Terriers, Shih Tzu, Labrador Retrievers, Miniature Schnauzers, and Bichon Frises, the total frequency of RD was 9.4% (64 of 681 dogs; Foote et al., 2018). The breeds of interest in this study, the Boston Terrier and Shih Tzu, had RD prevalences of 7.7% and 8.9%, respectively, and follow-up time ranged from 3 months to 9 years (mean 2.2 years). The median time to RD was 106 days for the Boston Terrier, compared to 242 days for the Shih Tzu. This is in contrast to a median time of onset of 98 days in the Klein et al. (2011) retrospective analysis. In 2006, Sigle and Nasisse reported a trend for RD to occur more frequently in patients with longer follow-up; that is, the incidence was 1 of 290 (0.34%) at 3 months but 1 of 180 (1.25%) at 2–3 years. However, in humans, pseudophakic RD has been seen to be highest in the first 6 months after surgery (Bjerrum et al., 2013). The incidence declines slowly until 5 years after surgery then levels off, but remained significantly higher than the fellow eye up to 10 years postoperatively (Bjerrum et al., 2013). Although no statistical analysis was run due to the small sample size and follow-up pool, no specific trend for RD incidence was seen in either breed (Foote et al., 2018).

In the past decade, there has also been conflicting data regarding the frequency of RD in Bichon Frises following phacoemulsification. It has been suggested that prophylactic retinopexy should be performed to prevent this complication (Schmidt & Vainisi, 2004; Vainisi & Wolfer, 2004). Five studies have evaluated RD prevalence, with results ranging from 0% to 55% (Braus et al., 2011; Gelatt et al., 2003; Pederson et al., 2015; Pryor et al., 2016; Schmidt & Vainisi, 2004). The original retrospective study reported the prevalence of RD following cataract surgery in 18 nondiabetic breed-related Bichon Frise eyes to be 55% without diode laser prophylactic laser retinopexy, and it decreased to 12% with prophylactic laser retinopexy in another 39 eyes (Schmidt & Vainisi, 2004). In that study, 58 eyes from nondiabetic Bichon Frise

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dogs with breed-related cataracts were divided into four groups (Schmidt & Vainisi, 2004). In Group 1, dogs that did not undergo prophylactic random transscleral retinopexy or phacoemulsification had a 60% incidence (12 of 20 eyes) of rhegmatogenous RD. In Group 2, dogs that did not undergo prophylactic random transscleral retinopexy but had phacoemulsification had a 55.5% incidence (10 of 18 eyes) of rhegmatogenous RD. In Group 3, dogs that underwent prophylactic random transscleral retinopexy but no phacoemulsification had a 10.5% incidence of rhegmatogenous RD. In Group 4, dogs that underwent prophylactic random transscleral retinopexy and had phacoemulsification had a 5.1% incidence of rhegmatogenous RD. This study showed that prophylactic retinopexy significantly diminished the risk of RD in this breed. However, two subsequent studies showed no increase in RD rates (Braus et al., 2011; Pryor et al., 2016). In the first study looking at a population of 34 dogs in the United Kingdom, 0% of 34 dogs developed RD following phacoemulsification with a mean follow-up of 16 months (Braus et al., 2011). It is possible that hereditary differences exist between Bichon Frises in the United Kingdom and Bichon Frises in the United States. The second study, where phacoemulsification was performed without retinopexy in 79 eyes (42 dogs) and with prophylactic retinopexy in 23 eyes (12 dogs), reported an incidence of RD of 0.05% in the non-retinopexy group compared to 0% in the retinopexy group (Pryor et al., 2016). The ratio of diabetic dogs in each group was approximately the same. At final reexamination, RD occurred in 4 of 79 eyes without retinopexy, compared to 0 of 23 RDs in the retinopexy group. There was no statistically significant difference in RD rates between the two groups. This study suggested that prophylactic transscleral diode retinopexy did not prevent and may in fact increase the risk for postoperative RD (Klein et al., 2011).

In the most recent study looking at the largest number of dogs with the longest follow-up time, 159 Bichon Frises (without prophylactic retinopexy) were significantly more at risk to develop RD (13.6%) when compared individually to Labrador Retrievers (3.8%) and Miniature Schnauzers (5.3%), but not when compared to Boston Terriers (7.7%) and Shih Tzu (8.9%; Foote et al., 2018). The incidence of RD post-phacoemulsification was 13% in 264 eyes with at least 1 year of follow-up, affecting 18% of 158 patients in the previous study (Pederson et al., 2015). When dogs with 6–12 months of follow-up were included, the RD rate decreased to 11% of 311 eyes, or 15% of 188 dogs. Diabetes mellitus was a negative risk factor, and postoperative glaucoma was significantly associated with RD. RDs occurred at an average of 456 days postoperatively (Pederson et al., 2015). The increased risk (13.6%) compared to the two previous studies, while not much different from Boston Terriers and Shih Tzu (Foote et al., 2018), is also similar to reported rates of RD post-phacoemulsification with prophylactic retinopexy (12%–20%; Klein et al., 2011; Schmidt & Vainisi, 2004). In the Klein et al. (2011) study, the rate of RD in all breeds was higher in the prophylactic retinopexy group (20% compared to 4.4%). This suggests that the potential benefit of prophylactic retinopexy does not outweigh the risks (Pryor et al., 2016). However, this rate is higher than in the Pryor et al. (2016) study (0%) and the answer as to what percentage of risk warrants the possible damage incited by a prophylactic retinopexy is still unknown at this time (Goulle, 2016; Klein et al., 2011; Pizzirani et al., 2003a).

The histopathology study of globes enucleated following phacoemulsification showed that a large number of RDs were not identified clinically prior to enucleation; therefore, the clinical diagnosis of RD may be underestimated (Scott et al., 2013). Possible causes affecting the underestimation of RD include the loss of patients to follow-up and decrease after surgery in ocular transparency through corneal opacities and PCO. For example, patient follow-up in Foote et al.'s (2018) analysis dropped considerably after the first year of surgery, from 70% of patients at 1 year to 43.7% at 2 years and 28.9% at 3 years. This makes data interpretation more challenging and potentially biased. It is possible that patients with continued follow-up years after surgery could be skewed to be the ones with complications, but patients with nonobvious complications (i.e., unilateral RD) can also be missed if not presented for follow-up by their owners.

Therapy for RD and/or tears detected following cataract surgery includes transpupillary barrier retinopexy or pneumatic retinopexy, depending on the severity of the detachment or tear (Spatola et al., 2015; Steele et al., 2012; Sullivan, 1997; Sullivan et al., 1997; Vainisi & Wolfer, 2004). Transpupillary retinopexy can be challenging in the face of significant PCO. A recordable preoperative electroretinogram (ERG) is a favorable prognostic indicator for return of vision in canine patients (Hoffman et al., 2018).

Peripheral Ocular Neuropathies

Diabetes causes a wide variety of acute, chronic, focal and diffuse neuropathy syndromes in humans (Juster-Switlyk & Smith, 2016; Murphy et al., 2004). Tear and epithelial barrier dysfunction, recurrent epithelial defects and erosions, delayed epithelial wound healing, corneal edema, superficial punctate keratitis, endothelial dysfunction, corneal nerve tortuosity, and decreased nerve density have also been documented (Saghizadeh et al., 2005). Corneal sensitivity following phacoemulsification in humans does not return to presurgical levels until 3 months postoperatively, and tear function recovers by 30 days postoperatively (Khanal et al., 2008).

Postphacoemulsification, diabetic dogs have been shown to be more likely to develop peripheral neuropathies, such as facial nerve paralysis, Horner's syndrome, and neurogenic KCS than nondiabetic dogs (Foote et al., 2019). The Labrador Retriever and the Miniature Pinscher, while not achieving statistical significance, are overrepresented. Spontaneous

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resolution of disease is also possible. Diabetic dogs also have significantly reduced corneal sensitivity (Good et al., 2003; Rodriguez et al., 2017). As in humans, glycemic control and estimated duration of diabetes have not been correlated with the decreased corneal sensitivity (Good et al., 2003; Murphy et al., 2004). Corneal complications are more likely in diabetic dogs, as corneal sensitivity is decreased in the first 7 days following surgery, and small-breed diabetic dogs are more likely to have KCS (Cullen et al., 2005; Gemensky-Metzler et al., 2015; Rodriguez et al., 2017; Williams et al., 2007). A study evaluating tear production and quality, corneal sensitivity, tear glucose concentrations relative to ocular microflora, and conjunctival changes in diabetic and nondiabetic canine patients with or without cataracts showed decreased tear production and tear film breakup times in diabetic cataractous dogs (Cullen et al., 2005). Histologic evidence of reduced goblet cell density higher tear glucose concentrations were also documented. The conjunctival microflora was not different between groups (Cullen et al., 2005). Prophylactic tear replacement should be aggressively pursued in postoperative canine diabetic patients.

Atonic Pupil

An atonic pupil, defined as a dilated pupil of unknown origin, is a rare postoperative complication of ophthalmic surgery with an incidence in the human literature of 0.0067% (Ishii et al., 2010). Another study reported that 60% of cataract surgeons had seen at least one case of it (Golnik et al., 1995). The clinical signs can include ocular pain and headache, and the nonresponsive dilation occurs weeks after surgery. This has not been reported in the veterinary literature, but the author has experienced it following routine phacoemulsification and IOL implantation bilaterally in a 9-year-old Miniature Poodle, and it likely occurs in our canine patients. The Poodle exhibited photophobia. Pharmacologic testing has localized the lesion to the iris sphincter in humans (Lam et al., 1989).

Surgery for Lens Instability

Lens instability can occur as a congenital, primary, or secondary abnormality. The decisions about surgical intervention for lens instability can be difficult. Once the lens is luxated completely, intervention depends on whether it is located anteriorly or posteriorly and whether glaucoma is present already or not.

There is considerable diversity of opinion among veterinary ophthalmologists regarding when unstable lenses should be removed, and some individuals avoid surgical intervention for as long as possible or completely. It has been advocated that unstable lenses should be removed as soon as the instability is detected (Nasisse & Davidson, 1999). A retrospective comparing the outcome of 23 dogs (26 eyes) that were treated medically with prostaglandin analogues (i.e., latanoprost, travaprost) twice daily for lens subluxation were compared with 26 dogs (29 eyes) that underwent phacoemulsification for lens subluxation on presentation (Hayton-Lee, n.d.). Results of statistical analysis demonstrated that there was a significant increase in time remaining visual for dogs treated surgically compared to those treated medically when age was not taken into account. When age was included in the model, the type of treatment was no longer statistically significant, but indicated that the effect of treatment varied with age, with younger dogs benefiting most from surgery. However, only 30% of medically treated eyes and 45% of the surgically treated eyes were reported still visual at the end of the study. Medical management of unstable lenses offers a similar outcome to ICLE, neither of which is very satisfactory (Binder et al., 2007).

The prognosis for vision after ICLE is poor if glaucoma is present at surgery (Glover et al., 1995). The mechanisms by which unstable lenses cause glaucoma have not been identified, but some believe this begins early in the course of lens instability and then rapidly become irreversible. Secondary glaucoma was the most common cause of vision loss in dogs with lens instability treated medically (Binder et al., 2007). In another retrospective study of secondary glaucoma evaluating risk factors, it was found that lens dislocation accounted for 15.2% of secondary glaucoma cases, while glaucoma secondary to ICLE only accounted for 3.8% of the 156 dogs evaluated (Johnsen et al., 2006). Another retrospective evaluation of secondary glaucoma in 217 dogs found that lens luxation was the cause in 22.6% of dogs (Strom et al., 2011). Mechanical irritation from an unstable lens may result in hypertrophy and/or hyperplasia of the posterior pigmented iris epithelium, and subsequent cellular exfoliation and release of melanin (Alario et al., 2013). An inflammatory reaction directly or indirectly related to melanin release may obstruct the outflow pathways, ultimately leading to glaucoma and loss of vision. Therapy with topical steroids may be warranted in dogs with primary lens instability (Alario et al., 2013).

Many breeds of dogs with primary lens instability have a mutation in the *ADAMTS17* gene and a genetic test is now available (Farias et al, 2010; Gould et al, 2011; Oliver et al., 2018). These dogs will experience lens instability between the ages of 2 and 6 years. Early surgical intervention using phacoemulsification with or without IOL implantation in dogs homozygous for the mutation should possibly be considered (Wilkie & Colitz, 2013). The use of CTRs may also be beneficial to improve long-term outcomes (Wilkie & Colitz, 2013). All options and the pros and cons of each intervention should be discussed with the owner.

Medical Management of Lens or Cataract Luxations

A posteriorly luxated lens is more difficult to remove surgically than an anteriorly luxated lens. The lens must be floated anteriorly for removal, increasing interaction with the vitreous and risk of RD. Alternatively, a topical prosta-

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glandin analogue or other miotic can be used as a therapeutic approach in managing the luxation without surgery. Potent miosis occurs in dogs as well as a concurrent antiglaucoma effect (Gelatt & MacKay, 2001; Studer et al., 2000). The use of demecarium bromide 0.25% topically twice daily showed a median vision retention time of 1,313 days (Binder et al., 2007). Those without miotic treatment had a median vision retention time of 1,454 days, revealing that treatment did not significantly affect the time to vision loss. However, treated eyes showed a significant delay in time to anterior lens luxation in eyes with lens instability (Binder et al., 2007). Treatment did not significantly affect the time from anterior lens luxation in one eye to anterior luxation in the other eye, or time to onset of glaucoma in eyes with an unstable lens (Binder et al., 2007). Of the 34 dogs with lens instability managed medically, vision was maintained in 80% at 1 year and 57% at 2 years (Binder et al., 2007).

Once medical therapy has been instituted, a posterior luxation is more likely than an anterior luxation long term, which the surgeon then faces a choice of indefinite medical therapy to avoid posterior chamber surgery or earlier surgical intervention, before the lens luxates. An anteriorly luxated lens is frequently an emergency due to pupillary block glaucoma, and surgical versus medical decisions must be made quickly. Transcorneal reduction (couching) of anteriorly luxated lenses with good outcome has been described (Montgomery et al., 2014). Continuous use of miotics and anti-glaucoma medications are then indicated. This procedure itself can be painful if not performed correctly and result in corneal damage (e.g., ulcers, endothelial damage) and intraocular hemorrhage (Colitz & O'Connell, 2015). The more chronic an anterior lens luxation is, the more difficult it can be to couch. Some surgeons will abort surgery if an anteriorly luxated lens falls posteriorly in the process of surgery, and then maintain the patient on topical miotics twice daily indefinitely.

Surgical Management of Lens Luxations

The technique for removal of an unstable lens will depend on the degree of instability, location of the lens, equipment availability, health of the vitreous, and surgeon preference. Surgical techniques for lens extraction include ICLE for lens luxation, two-handed phacoemulsification (with or without removal of the lens capsular bag), and/or CTRs for mild to severe lens instability (Wilkie & Colitz, 2013). Small incision phacoemulsification is the preferred method of extraction if the lens is stable enough to allow it. This may allow for significantly improved outcome compared with large incision ICLE. With improvements in viscoelastics, use of two-handed techniques, and CTRs, many unstable lenses can now be safely removed by phacoemulsification (Wilkie et al., 2008).

Since a posteriorly luxated lens has increased surgical risks, its removal may be controversial. A vitrectomy may be required to remove the vitreous overlying the lens, allowing it to be elevated. This is dependent on the state of the vitreous (i.e., semisolid or in strands vs. liquefied). Posterior segment manipulations increase the risk of retinal holes and detachment. The lens is floated into the anterior chamber by using a highly cohesive OVD, filling from underneath it. Once the lens is in the anterior chamber, it can be removed using a standard intracapsular technique. These patients are at high risk for RD and postoperative glaucoma. Some surgeons will also place an intracameral miotic at this time and perform phacoemulsification of the lens in the anterior chamber. Capsulorhexis is not performed and the capsule is opened with Vannas scissors. This technique is best performed using a cohesive OVD to protect the endothelium. The lens capsule is removed through the small incision.

Perioperative Medications in Instability

Most veterinary ophthalmologists, with the exception of mydriasis, use a similar preoperative medical plan to that of phacoemulsification. Mydriasis could allow the anteriorly luxated lens to drop into the vitreous chamber and should be avoided if surgical removal is desired. If the lens still has some zonular attachments, a weak mydriatic such as tropicamide or intracameral 1:10,000 epinephrine may be used to allow for visualization of the edges and movement forward. Use of alpha-chymotrypsin to induce zonulolysis has been described in normal dogs (Maggs et al., 2010). Alpha-chymotrypsin (75 U diluted to 1:5000 with sodium chloride) was placed in the posterior chamber for 7 minutes prior to ICLE (Maggs et al., 2010). When administered in this manner, alpha-chymotrypsin facilitated ICLE without adverse effects (Maggs et al., 2010). Manual breakdown of intact zonules can cause intraocular hemorrhage; alternatively, they can sometimes be transected with Vannas scissors.

Standard Surgical Approach

The traditional approach to an ICLE has not substantially changed over time. A 160°, two-thirds depth, corneal groove is made with a No. 64 Beaver blade or a sapphire blade. The incision is made by repositioning the forceps, stabilizing the globe halfway through the incision, without lifting the blade from the incision. The incision should not be extended under the nictitating membrane, as this makes suturing difficult. Paracentesis is performed using a No. 65 Beaver blade or an angled keratome. Care should be taken not to penetrate the lens capsule. If necessary, a small amount of OVD can be injected to make room for entry. OVD should then be injected to protect the corneal endothelium and to vault the anterior chamber. Overinflating the anterior chamber at this time may displace the lens posteriorly and should be avoided. OVD is then placed behind the lens to prevent posterior displacement. Right and left corneal section scissors are used to extend the incision. The tip of the blades should be elevated at all times and not closed completely until the end of the incision. If a few zonules are still adhered to the lens, they

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can be broken down with an IOL dialer or Vannas scissors. The lens is then extracted by the cryoprobe method or via OVD use.

In the cryoprobe method, the anterior surface of the lens should be freed of any vitreous before placement of the probe. A single suture can be placed in the distal corneal wound edge at 12 o'clock using polyglactin 910 with attached beads. This enables lifting of the cornea during lens extraction; the bead is then resected and the suture used to start closure of the corneal wound. Tissue markers can be used to allow for perfect alignment of the corneal wound. Once the cornea is lifted and the lens safely exposed, a 2 mm, curved nitrous oxide cataract probe is used to engage the anterodorsal aspect of the lens. A 3–4 mm diameter ice ball is made, and the lens is slowly extracted from the globe. The probe and ice ball should never contact the cornea. A lens loupe can also be employed to deliver the viscoelastic-coated lens.

The use of lens loupe cannulas has been described to remove the lens, where viscoelastic is delivered beneath the lens while elevating it anteriorly (Wilkie & Colitz, 2013). The final method is using the OVD to float the lens completely out through the corneal incision. Once the lens has reached the level of the corneal wound, Wescott tenotomy scissors should be used to tease or cut any posterior capsule vitreal attachment by the hyaloideocapsular ligament. This attachment is more common and stronger in younger dogs than in older dogs with vitreal degeneration. Teasing versus cutting will minimize disruption of the vitreal face, thus potentially avoiding the need for a vitrectomy. In addition, leaving the vitreous face intact will allow a sulcus IOL to be better positioned, minimizing tilt, decentration, and rotational instability (Nasisse & Glover, 1997). The globe is then reinflated with OVD and the closure of the incision completed in both directions, beginning at the 12 o'clock position. Vitreous in the incision must be removed by manual or automated vitrectomy or by visco displacement of the vitreous. Failure to clear the incision of vitreous will result in wound dehiscence and possible vitreal traction bands. A continuous or double continuous pattern using monofilament 8-0 or 9-0 polyglactin 910 is used for wound closure.

Surgical Management of Lens Subluxations

The degree of zonular instability influences the need for an ICLE versus attempted phacoemulsification. Zonular instability during phacoemulsification is associated with an increased incidence of intraoperative complications and is more technically challenging. The degree of lens instability may preclude placement of an intracapsular IOL, and other options include leaving the patient aphakic or suturing an IOL in place (Glover et al., 1995; Nasisse & Glover, 1997; Nasisse et al., 1995; Stuhr et al., 2009; Wilkie et al., 2008).

Several surgical devices to manage zonular instability have been described, including an open-ring PMMA CTR previously described to minimize PCO (Weber & Cionni, 2015; Wilkie et al., 2015). The CTR is designed to stabilize the capsule both intraoperatively and postoperatively (Hara et al., 1991; Nagamoto & Bissen-Miyajima, 1994; Weber & Cionni, 2015). A CTR is described as having two diameters, one in the open position and the other in the compressed position. Because the diameter of the open CTR is greater than the diameter of the capsular bag, tension will occur across the capsular bag, recruiting the strength of the intact zonular fibers. The CTR automatically expands as it enters the fornix of the capsular bag to its largest possible diameter based on its size and spring constant (Kurz & Dick, 2004; Wilkie et al., 2015). The CTR thus supports the capsule by maintaining the circular contour of the bag and distributing the forces equally over all zonular fibers (Cionni & Osher, 1995; Hara et al., 1991). If the lens has up to a 180° (6 o'clock) instability, the CTR can be left in place to prevent decentration of the IOL (Por & Lavin, 2005).

A potential complication associated with the insertion of the CTR includes damage to zonular fibers during deployment into the capsular bag. CTR insertion produces zonular stress and elongation, even with careful insertion (Ahmed et al., 2005; Jacob et al., 2003). This can result in extension of the zonular dialysis or the creation of iatrogenic dialysis (Jacob et al., 2003; Wilkie et al., 2015). The angle and point of initial contact of the CTR with the capsular bag relative to the zonular disruption need to be carefully planned to avoid any additional zonular damage (Wilkie et al., 2015). The bag is displaced in the direction of the torque of the CTR. Stress on the zonules occurs 180° away from the point of lens capsule contact as the CTR is deployed (Page, 2015). For example, if the leading eyelet gets entangled in the bag and the CTR bends out into the bag at 6 o'clock (area of torque applied), the zonules at 12 o'clock have undue stress placed on them. Adequate distention of the capsular bag with an OVD helps minimize the risk for potential complications of CTR deployment, including capsule entanglement with the leading eyelet of the CTR and posterior capsular tear (Wilkie et al., 2015).

Both standard and modified implantation techniques for CTR insertion have been described (Weber & Cionni, 2015; Table 23.6).

When zonular instability is mild to moderate, standard CTR is typically performed. Standard CTR insertion was described in the section on PCO. When the zonular instability is severe, modified CTR techniques are performed (Li et al., 2016). A suture can be placed in the leading eyelet of the CTR and allows for removal of the CTR in the event of posterior capsule rupture during phacoemulsification (Moreno-Montanes et al., 2004). Another technique describes a suture-guided insertion following phacoemulsification that maintains the intended shape of the CTR and direction of implantation. The technique enables precise control of the leading eyelet with a 10-0 suture, thereby reducing the risk for capsule entanglement and iatrogenic

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Table 23.6 Comparison of capsular tension ring (CTR) insertion techniques.

Technique	Potential Advantages	Potential Disadvantages
Standard CTR insertion (Hara et al., 1991; Wilkie et al., 2015)	Can be used with inserter or forceps to rotate the CTR into the capsular bag	Displacement of the capsular bag may occur Leading eyelet may become entangled in capsular fornix during insertion, causing further zonular damage Leading eyelet can cause a posterior capsular tear
Fishtail technique (Angunawela & Little, 2007)	Eliminates rotation of the CTR, minimizing entanglement and bag displacement	Significant bending and potential damage to the CTR Precision control of the leading eyelet during insertion is lost Increased possibility of introducing bacteria into the anterior chamber without use of an inserter
Fishtail on a line technique (Rixen & Oetting, 2014)	Suture in leading eyelet to achieve fishtail configuration places less torque on CTR	Significant bending of CTR inside the anterior chamber Precision control of the leading eyelet during insertion is lost
Suture-guided CTR technique (Page, 2015)	Suture in leading eyelet guided by a microforceps enables surgeon to dial in the CTR, mitigating torque and entanglement Allows precision control with intended CTR shape and direction of insertion	Requires an inserter and second micro instrument in the anterior chamber to guide the suture in the leading eyelet

Source: Modified from Page (2015).

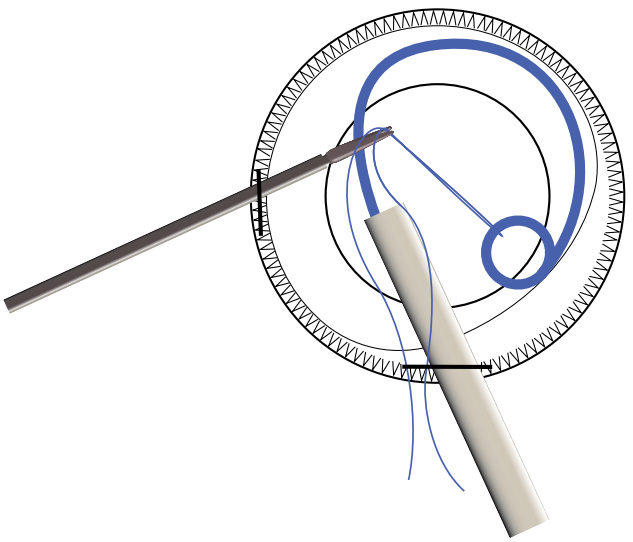


Figure 23.41 Suture-guided insertion of a capsular tension ring following phacoemulsification. The technique enables improved control of the leading eyelet with a 10-0 suture, thereby reducing the risk of capsule entanglement and iatrogenic zonular dialysis. (Courtesy of Brian Wilson.)

zonular dialysis (Fig. 23.41; Page, 2015). The suture can be gently pulled with a microforceps to guide the leading eyelet centrally, mitigating the risk for extending a dialysis or creating an iatrogenic dialysis. To reduce the risk for extending a dialysis by minimizing tangential and shearing forces, the fishtail technique for CTR insertion has been described (Angunawela et al., 2009). This technique introduces the CTR through the incision without an inserter. It limits further zonular damage because the CTR is not dialed into position. Instead, the CTR is folded until the trailing loops overlap, forming a fish-like configuration. The apex or mouth of the fish is inserted through the incision into the capsular bag, and the remaining arms of the CTR are then placed in the bag. The technique requires no further manipulation or rotation of the CTR (Angunawela et al., 2009). Since the use of an inserter for IOLs diminishes the risk of endophthalmitis, it is possible that inserting a CTR without an inserter could increase it. Other surgical devices that have been described to stabilize the lens in humans include the Ahmed segment and Cionni ring to fixate the capsular bag to the sclera (Kim et al., 2014), microhook retractors to stretch and stabilize the loose capsule–zonule complex (Mackool, 1984), and the Malyugin device (Malyugin 2007).

Two-handed phacoemulsification in cases of severe to total lens instability to minimize trauma to the globe may be successful (Wilkie & Colitz, 2013). This is preferable to the 160° incision necessary for ICLE. Depending on the degree of lens instability, an IOL may be placed with or without a CTR, or the lens capsule can then be removed via the small incision. If an IOL cannot be placed in the capsular bag, a sutured IOL can be considered. It has been advised that if the zonular instability is less than 180° in the dogs, a CTR can be implanted and a foldable acrylic IOL may be placed in the bag (Wilkie

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et al., 2008, 2015). It is best if the CTR can be placed prior to phacoemulsification to provide increased stability during two-handed phacoemulsification. If the instability exceeds 180°, then the entire lens capsule should be removed. Vitrectomy is performed only in cases where the vitreous is disrupted and has potential for complications. If an IOL is not going to be sutured into the sulcus, then the small incision is closed and medical management is continued as usual.

Sulcus Intraocular Lens Fixation

Suturing of an IOL into the ciliary sulcus has been described in the dog (Nasisse & Davidson, 1999; Stuhr et al, 2009; Wilkie et al, 2008). The standard *ab interno* and *ab externo* approaches to suturing an IOL into the ciliary sulcus have not changed substantially (Nasisse & Davidson, 1999). The location where the suture will exit or enter the sclera is marked, depending on whether an *ab interno* or *ab externo* approach is used, respectively. Small conjunctival flaps should be made 1.5 mm posterior to the limbus in these marked locations prior to making the clear corneal incision, to facilitate entry or exit of the needle and to allow suturing to the sclera at the end of the procedure. To avoid the nictitating membrane, approximate landmarks are 2 o'clock and 8 o'clock for the right eye and 10 o'clock and 4 o'clock for the left eye. Both nonfoldable PMMA IOLs and foldable acrylic IOLs that have an eyelet(s) in the haptic for attaching the suture are available. These lenses are specific for the technique of sutured IOLs and differ in size and design from the standard endocapsular IOL. The most commonly used suture type is 10-0 polypropylene or 9-0 nylon. The needle type used is dependent on the surgeon's preference and planned technique. A straight needle on the 10-0 polypropylene or a curved spatula needle on the 9-0 nylon is typical. Suture placement should be accurate to minimize refractive error and tilt of the IOL. A two-point fixation does not prevent lens rotation and tilt and a three-point fixation is optimal.

In the *ab interno* method, the suture is tied to the IOL haptics prior to making the corneal incision. A 160–180° corneal incision is necessary to suture an IOL into the eye using this method. Once the lens is extracted, the first needle is passed into the anterior chamber, behind the iris, and through the ciliary sulcus in the ventrolateral position, exiting through the sclera where the conjunctival window was made (Fig. 23.42). If the straight needle is used, it is bent to 110° preinsertion; if a curved spatula needle is used, its proximal half is straightened leaving the distal curve, which makes driving it through the sclera easier. The second needle is then passed at the same level through the sclera where the conjunctival window was made 180° across from the first suture. The IOL should be rinsed with BSS and coated with OVD to protect the corneal endothelium while it is inserted. The haptics are gently guided under the iris and into the ciliary sulcus while placing tension on the sutures until the IOL is centered. A vitrectomy should be performed when indicated. If the vitreous face has been disrupted or the vitreous has degenerated, then vitrectomy should be performed to remove the vitreous in the anterior chamber. Vitreous present in the anterior chamber may cause postoperative complications such as dyscoria, secondary glaucoma, or decentration of the sulcus IOL. After the corneal incision has been closed and the globe reinflated, the lens-anchoring sutures are gently pulled taut to position the lens in the axial pupil opening and tied to the sclera. The conjunctival window is then closed using 7-0 to 8-0 Vicryl. A drawback of this technique is that the lens-anchoring sutures are placed into the ciliary sulcus blindly. A retrospective study of ICLE by cryoextraction followed by a placement of a sutured IOL using the *ab interno* technique reported vision in 70% of eyes (Stuhr et al., 2009). The mean time to vision loss was 41 months and most commonly occurred secondary to glaucoma and/or RD (Stuhr et al., 2009).

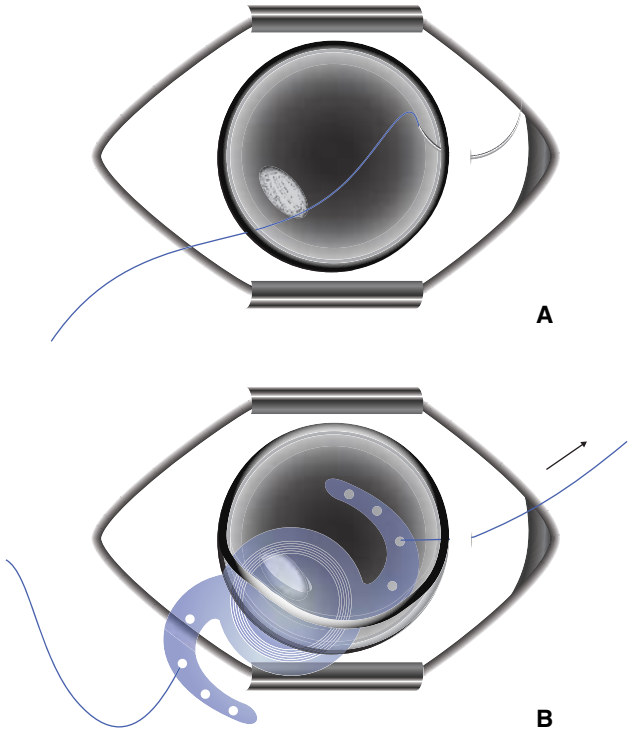


Figure 23.42 **A**. In the *ab interno* method of sulcus intraocular lens (IOL) fixation, the suture is passed beneath the iris to exit the sclera 2 mm posterior to the limbus. **B**. The IOL haptic is then pulled into the ciliary sulcus as tension is placed on the suture. (Courtesy of Brian Wilson.)

The *ab externo* method places the lens-anchoring suture through the sclera prior to entering the eye (Nasisse & Davidson, 1999; Nasisse & Glover, 1997; Wilkie et al., 2008). This technique can only be performed if the lens is posteriorly luxated or if the lens has been extracted at a prior time; therefore, it is uncommonly performed (Fig. 23.43). After the conjunctival windows are made over the sites of needle

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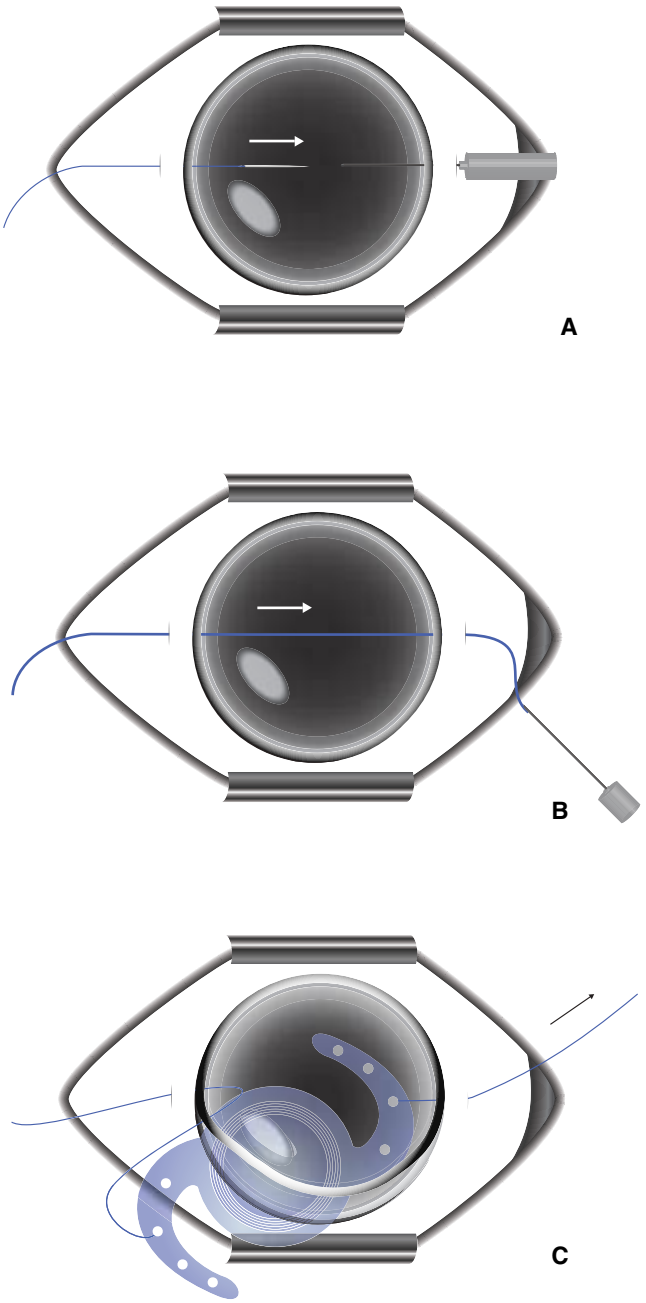


Figure 23.43 **A**. In the *ab externo* method, the suture is first preplaced by threading the suture needle through the ciliary sulcus and into the lumen of a hypodermic needle. **B**. The lens-anchoring suture is then pulled into the posterior chamber. **C**. After the lens has been extracted, the lens-anchoring suture is pulled through the incision, cut, and tied to each haptic of an intraocular lens (IOL). The IOL is then positioned within the eye. After the incision is closed, the IOL anchoring sutures are tied to the external sclera. (Courtesy of Brian Wilson.)

placement 1.5 mm posterior to the limbus, a partial-thickness score incision is made at the site of each proposed needle placement. A 27-gauge hypodermic needle is inserted through one of the score incisions, the sclera, and the ciliary sulcus, and allowed to rest in the center of the pupil. A straight needle swaged onto 10-0 polypropylene is then inserted in the opposite score incision, the sclera, and the ciliary sulcus, and into the tip of the 27-gauge hypodermic needle. Once secure in the needle lumen, the hypodermic needle is withdrawn from the eye, taking the suture with it as it exits the globe. The corneal incision is then made and the lens-anchoring suture is pulled from the eye through the stab incision. The lens-anchoring suture is cut, and each end is sutured to the eyelet of the sulcus IOL. The IOL is introduced into position, the sutures are pulled taut to center the IOL, the incision is closed, the anterior chamber is reinflated, and the sutures are secured to the sclera.

A modification of the a*b externo* technique allows for a sutured IOL placement with small incision phacoemulsification (Wilkie et al., 2008). The original report uses a rigid PMMA IOL, but the use of a foldable acrylic IOL is now available. The conjunctival flaps and sclera are prepared as previously described. Prior to entry into the eye, the IOL is prepared by attaching 9-0 nylon suture to the haptic eyelets for either two- or three-point fixation. The needles are then removed from the suture. Following phacoemulsification, either the entire capsule is removed or, if the posterior lens capsule is stable enough to be preserved, just the anterior lens capsule is removed. Preservation of an intact posterior lens capsule occurs in some diabetic patients with lens capsule ruptures, and it can be left to keep the vitreous face intact and the entire anterior capsule removed. The anterior chamber is reformed with OVD. A 30-gauge needle is passed from outside of the globe, at the site of the ventral suture placement. This needle enters the sclera 1.5 mm posterior to the limbus, passes into the eye at the level of the ciliary sulcus, and is directed toward and out of the 3.2 mm corneal incision (Fig. 23.44). The 9-0 nylon suture is passed into the lumen of the needle and the needle withdrawn so that the suture exits the sclera. Next, a 30-gauge needle is passed through the dorsal sclera in a similar fashion and the second suture passed into the lumen and the needle withdrawn (see Fig. 23.44). If three-point fixation is planned, the third suture is now positioned in the same fashion as the first two. The corneal incision is opened to a distance of 8 mm for a PMMA IOL using corneal section scissors and the IOL positioned in the ciliary sulcus. The original opening of approximately 3.2 mm can be used with a forceps folded acrylic IOL. The corneal incision is closed, the anterior chamber reformed, and the IOL sutures fixed to the sclera as previously described. The advantage of this technique is that it allows removal of the lens and placement of the suture through a 3.2 mm incision, and suture placement is more accurate and less traumatic than with the *ab interno* approach.

Intraoperative and Postoperative Complications

Intraoperative and postoperative complications of ICLE/ICCE include those described in the sections for routine phacoemulsification, including fibrin accumulation,

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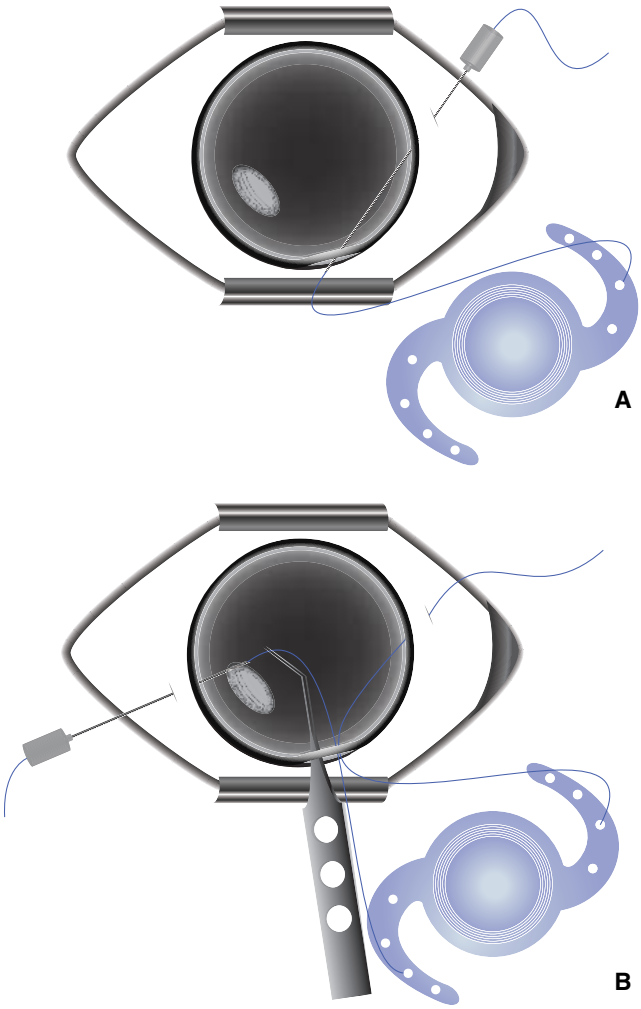


Figure 23.44 In the modified *ab externo* technique the lens and lens capsule are removed through a 3.2 mm incision. **A**. A 30-gauge needle is passed 1.5 mm posterior to the limbus, anterior to the vitreous, and emerges from the corneal incision. A 9-0 nylon suture, attached to the intraocular lens haptic, is passed into the lumen of the needle. **B**. The second suture is passed into the anterior chamber and into the lumen of the 30-gauge needle. Microsurgical tying forceps are used to pass the suture while in the anterior chamber. (Courtesy of Brian Wilson.)

hemorrhage, and vitreous expansion with or without presentation. Some differences are relevant. The larger incision, longer surgical duration, and increased incidence of uveitis may predispose these patients to an increased risk of complications. Only a few of the complications will be discussed, as they have unique differences from those occurring following phacoemulsification.

Corneal Incision Dehiscence and Infection

Corneal ulceration is more common in large incision surgery, and in the face of topical anti-inflammatory use, is as likely to become infected (Fig. 23.45). The larger incision (160°) required for ICLE also increases the risk of incisional dehiscence with trauma over the smaller incision used for phacoemulsification. In a retrospective human study evaluating outcome following traumatic wound dehiscence after ICCE, factors associated with a worse visual outcome included hyphema, IOL dislocation or loss, vitreous hemorrhage, scleral rupture, and a long interval (>8 weeks) from surgery to trauma (Chowers et al., 2001). This complication must be addressed as soon as it is identified. Replacing the suture(s) or oversewing the suture line to repair the defect should be performed if the incision is not watertight to minimize the chance of hypotony, hyphema, endophthalmitis, and RD.



Figure 23.45 Corneal stromal ulcer with cellular infiltrate and bacterial infection 5 weeks after intracapsular lens extraction in a 10-year-old Boston Terrier. The incision was closed in a single continuous pattern with 9-0 polyglactin 910. A suture knot is visible at 10–11 o'clock in the heavily vascularized suture line.

Hemorrhage

Hemorrhage is more likely to occur with ICLE/ICCE and sutured lens placement. It can arise from the ciliary processes as tension is placed on them while extracting the lens with some persistent zonular attachment. It may efflux from the ICA as the IOP is acutely lowered upon entering the eye when glaucoma is already present preoperatively. Finally, it may result from needle placement into the ciliary sulcus when suturing an IOL. Hemorrhage from needle placement is uncommon, but can be encountered if the needle is dull, if the direction of passage is changed as the needle is advanced, or if the eye is inflamed. Hemorrhage is controlled as previously described with intracameral epinephrine and OVD tamponade or viscoelastic material.

Refractive Error

In addition to the refractive error introduced by a large corneal incision, perfect placement of a sulcus IOL is nearly

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impossible; therefore, some additional refractive error is expected. A 0.5 mm increase in anterior chamber depth will result in 4–6 D of hyperopia (Nasisse & Glover, 1997). IOL tilt results in oblique astigmatism and IOL tilt of greater than 5° will induce refractive error (Por & Lavin, 2005). Significant lens tilt of greater than 10° occurs in 11.4%–16.7% of human patients with sutured sulcus IOLs (Hayashi et al., 1999). Dogs will adapt to most errors, though if the IOL is tilted or is improperly positioned, they may have subtle signs of visual impairment (Wilkie & Colitz, 2013).

Secondary Glaucoma

Glaucoma is the most common postoperative complication after ICLE, occurring in as many as 81% of cases (Glover et al, 1995; Nasisse & Davidson, 1999). Preoperatively, 73% of eyes with anterior luxations had secondary glaucoma, compared to 43% with subluxations and 38% with posterior luxations (Glover et al., 1995). Eyes with glaucoma preoperatively had a lower success rate (66%) than eyes without (82%; Glover et al, 1995). Transcleral cyclophotocoagulation (CPC) following ICLE surgery has been reported (O'Reilly et al., 2003). Newer techniques include diode endoscopic CPC and micropulse CPC (IRIDEX, Mountain View, CA, USA; Bras et al., 2005). Endoscopic CPC is reported to cause less inflammation than transcleral CPC (Bras et al., 2005). Micropulse CPC allows the tissue to cool between laser pulses, minimizing or preventing tissue damage. These procedures can be performed after surgery or at the time of ICLE. Average settings for endoscopic cyclophotocoagulation are 0.4 mW (0.25–0.5 mW) in a pigmented eye with continuous duration (Bras et al., 2005). The average treated area was 160° (90°–180°) and a minimum of 180° of the ciliary processes should be lasered for maximal effect (Bras et al., 2005). Prophylactic endolaser performed at the time of ICLE in the face of a normal IOP has shown no significant benefits (personal communication, Dineli Bras). When glaucoma is present, endolaser or micropulse CPC is indicated and should be discussed with the owner. Further work on these procedures needs to be performed.

Retinal Detachment

RD following ICLE is the second most common postoperative complication after secondary glaucoma and has been reported in 38% of cases (Glover et al, 1995; Nasisse & Davidson, 1999). This is thought to be due to preexisting retinal tears that enlarge following surgery (Nasisse & Davidson, 1999), and disruption of the anterior hyaloid face may predispose eyes to this complication (Por & Lavin, 2005). The incidence of RD in humans is 0.4%–3.6% of cases (Ramos et al., 2002). Performing ICLE soon after the luxation occurs may decrease the incidence of this complication (Wilkie & Colitz, 2013).

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24

Diseases and Surgery of the Canine Vitreous

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The vitreous, also called the vitreous body or corpus vitreum, is a transparent, elastic hydrogel accounting for approximately 80% of the volume of the canine globe (Evans & de Lahunta, 2013). The volume of the canine vitreous humor has been quantified to an average of 1.7 mL (+/− 0.86); (Gilger et al., 2005). Posteriorly, the vitreous is bordered by the retina, for which it provides support, and the optic disc, and at the anterior side by the posterior lens capsule and the ciliary body and Zinn zonules of the uvea. It is composed of water (about 99%), collagen fibrils, hyalocytes, hyaluronic acid, and other glycosaminoglycans.

Development and Anatomy

To understand vitreous pathology, some basic knowledge of vitreal ontogenesis is important. In the dog, the lens vesicle becomes separated from the surface ectoderm from which it originated by day 16–24 of gestation (Aguirre et al., 1972; Boevé et al., 1988a). During the same period, ectodermal and mesodermal fibrillar material extends into the space between the lens vesicle and presumptive retina, thus forming the primitive vitreous. Later, the primitive vitreous is concentrated centrally, in the optic cup, while the definitive or secondary vitreous develops around it (Aguirre et al., 1972; Balazs, 1975; Boevé et al., 1988a; Gloor, 1973b; Mann, 1964).

After formation of the lens vesicle, the hyaloid artery, which is of mesodermal origin, penetrates into the primary (or primitive) vitreous through the optic fissure and grows toward the posterior pole of the developing lens.

Just retrolentally, the hyaloid artery branches, generally into three main trunks, which subsequently develop into a vascular network around the primitive lens, thus forming the tunica vasculosa lentis. More proximally in the vitreous space, the hyaloid artery branches into the vasa hyaloidea propria. On the anterior side of the lens, the primitive vascular system anastomoses with the annular vessel at the rim of the optic cup, which is the location where the iridal base will later be formed.

In the dog, the hyaloid system is at its maximal development by day 45. At this stage, the hyaloid system has developed into an elaborate vascular network. After approximately day 45 the hyaloid system starts to regress, and between the second and fourth weeks after birth, the entire vitreal vascular system has degenerated (Gloor, 1975). Eventually, only a small, short, usually corkscrew-shaped, rudimentary string of the hyaloid artery remains, which is attached retrolentally to the posterior lens capsule just ventral to the posterior pole between the two ventral suture lines. Through a slit-lamp microscope, this rudiment can be observed in most normal canine eyes; the site of attachment to the posterior lens capsule is named Mittendorf's dot. Remainders of the primitive vitreous concentrate around the hyaloid artery. After regression of the latter, a channel-like structure (i.e., Cloquet's channel) remains, but this structure is only barely observable in normal adult canine eyes.

Some authors regard the hyaloid system as part of the primitive vitreous, while others do not. This, in part, accounts for the existence of two names, persistent hyperplastic primary vitreous (PHPV) and persistent hyperplastic tunica vasculosa lentis (PHTVL), for the same disease.

The vitreous forms one of the refractive ocular media, and provides the necessary pressure to hold the neuroretina properly positioned against the pigment epithelium. The two main solid components of the vitreous are hyaluronic acid and collagen. Approximately 1% of the vitreous consists of a network of polygonal, hydrated fibrils of hyaluronic acid and collagen (Type II, with a helical structure of $\alpha_1(II)_3$; McLaughlin & McLaughlin, 1986; Snowden & Swann, 1980). These polymers are electronegative, thus causing expansion of the gel. Introducing electropositive ions into the vitreous may cause the gel to collapse (Osterlin & Jacobson, 1968). Such collapse has been described for ferrous ions in the rabbit (Hui et al., 1988). As a cellular component, a few hyalocytes, which

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originate from blood macrophages, are mainly located peripherally, near the ciliary body (Gloor, 1973a). The hyalocytes are believed to be responsible for the production of glycosaminoglycans, especially hyaluronic acid (Sebag, 1993). The remaining 98%–99% of the vitreous consists of water (Balazs, 1961).

The outer limits of the vitreous do not consist of membranes; rather, they consist of condensations of fibrils that are firmly attached to the ora ciliaris retinae and the pars plana ciliaris (Tolentino et al., 1976).

The anterior portion of the vitreous is strongly attached to the posterior lens capsule, which has given rise to the confusing term hyaloidocapsular ligament (i.e., Weiger's ligament, Egger's line). The vitreous is also attached to the region of the ora ciliaris retinae and to the prepapillary area (Evans & de Lahunta, 2013). The vitreoretinal interface consists of outer part of the vitreous, anchoring fibrils of the vitreous body, and the inner limiting membrane of the neuroretina (Fine & Tousimis, 1961; Gartner, 1964; Heegaard, 1997). Vitreous detachment is a condition whereby the vitreous shrinks and pulls away from the retina, impairing the vitreous attachment. This condition is common in humans, but has not been described in the dog. In humans, vitreous detachment rarely leads to serious problems, although it can cause macular puckers, retinal tears, or holes that may be vision threatening.

Physiology

The most essential (patho-)physiologic relationships and functional aspects of the vitreous can be summarized as follows (Lund-Andersen & Sander, 2003):

- Support function for the retina and filling-up function of the vitreous body cavity (prevention of retinal detachment, absorption of external forces, reduction of mechanical deformation of the globe).
- Diffusion barrier between the anterior and posterior segments of the eye (the gel structure contains a barrier function for bulk movement of substances).
- Metabolic buffer function (dilution of substances produced in the retina, and supplementation of the retinal metabolism, especially during anoxic conditions).
- Establishment of an unhindered path of light (specific structural aspects, low concentration of macromolecules).

Aging

Both the fibrillar condensations and the colloidal state of the vitreous provide for maintenance of the water contents, and both seek to prevent penetration by "strange" cells (e.g., inflammatory cells) or microorganisms. In addition, the gel structure acts as a barrier against the movement of solutes. Some increase in vitreal density occurs with age, and the stability of the colloid decreases with age as well, thus leading to liquefaction of the hydrogel (Eisner & Bachmann, 1974). As a consequence, fine, white, fibrous structures may become visible in the vitreous of older dogs during slit-lamp microscopic examination.

During life, the vitreous goes through considerable physiologic changes that are significant for its function (Lund-Andersen & Sander, 2003). The most fundamental aging-determined change consists of a disintegration of the gel structure (liquefaction; syneresis), which is especially notable in the center of the vitreous, where the collagen concentration is lowest (Swann, 1980; Swann & Constable, 1972). Common aging processes, such as the cumulative effect of light exposure, possibly photooxidative stress, and nonenzymatic glycosylation, are considered to be important factors in the mechanism behind liquefaction (Kasai et al., 1983; Stitt, 2001). Concerning signs of aging, see also "Degenerative Vitreal Disorders and Reactions."

Diagnostic Procedures

To facilitate clinical observation and evaluation of the vitreous, the pupil should be dilated using a short-acting mydriatic agent, such as tropicamide. In puppies, however, tropicamide may not cause adequate pupil dilation in all cases; the use of atropine may be indicated. The part of the ophthalmic examination dealing with the posterior segment of the globe should be performed in twilight conditions.

Focal Light

The eye is both illuminated and inspected from a distance (≈40–60 cm). The light source should be powerful and focal, such as a penlight of good quality, a direct ophthalmoscope, or an otoscope, to allow any vitreal opacities or condensations to be visualized by indirect illumination (i.e., by light reflected from the tapetal fundus, also known as the tapetum lucidum). Because opacities will either partly or completely block the reflected light, they will be seen as dark structures against a bright tapetal reflectivity. Movement of vitreal structures following motions of the globe or lagging behind ocular motions may be determined more easily in this way.

Slit-Lamp Biomicroscopy

A slit-lamp microscope is a highly useful and necessary tool for examination of the vitreous, even though such inspection using a slit-lamp microscope will be limited to the anterior part. A slit-lamp microscope is therefore especially useful to evaluate disorders at the lens/vitreous interface, such as persistence of parts of the tunica vasculosa lentis (TVL) posterior, persistent hyaloid artery (PHA), PHTVL/PHPV, as well as posterior lental pathology (e.g., lenticonus/lentiglobus posterior).

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Ophthalmoscopy

A direct ophthalmoscope may be used as previously described. By decreasing the distance between the light source and the eye, direct illumination of vitreal structures will increase, enabling better visualization of their morphology. Vitreous liquefaction and floaters may also be visualized with an indirect ophthalmoscope, and use of a fundus contact lens to eliminate the refractive power of the ocular lens enables observation of the vitreous/fundus interface with a slit-lamp microscope. Thus, proliferations or excavations at this location can be positively identified.

Diagnostic Imaging

Ultrasonography

Ultrasonography, using a high-resolution ultrasound machine, is a highly useful and noninvasive means of vitreal examination. This is especially true in eyes with opacities of the anterior segment of the globe that exclude visual examination of the vitreous. Examples of abnormal structures in the vitreal cavity that may be visible ultrasonographically (Boroffka et al., 1998) include persisting parts of the hyaloid vascular system (Fig. 24.1), severe congenital lenticular malformation (Fig. 24.2), a luxated lens (Fig. 24.3), vitreal hemorrhage, vitreous degeneration (Fig. 24.4), retinal detachment (Fig. 24.5), and intraocular neoplasia. In a study by Labruyere et al. (2008), the sensitivity and specificity of ophthalmoscopy using ultrasonography as a golden standard were 39% and 100%, respectively, concerning the detection of signs of vitreous degeneration. Use of color-flow Doppler may be useful to indicate fluid/blood flow in suspected structures. Contrast-enhanced ultrasonography has been described to be a useful tool in the differentiation of retinal detachment and vitreous membranes in dogs and cats (Labruyere et al., 2011). The mean sound wave velocity in the canine vitreous has been described to be 1.535 m/s at 36 °C, increasing linearly with temperature (Görig et al., 2006).

Computed Tomography/Magnetic Resonance Imaging

In addition, computed tomography (CT) and magnetic resonance imaging (MRI) may contribute to the evaluation of vitreal disease. In a publication by Salgüero et al. (2015), the CT dimensions of the vitreous of normal canine eyes were studied. The mean anteroposterior distance of the vitreous chamber was described as measuring 0.96 cm. The mean vitreous humor density in CT was calculated at 11.20 Hounsfield units.

Hyalocentesis

In diagnostic vitreal paracentesis (i.e., hyalocentesis), a small amount of liquid vitreous is aspirated for analysis, most often cytologic examination or microbiologic culturing (Gelatt & Gelatt, 2011). Hyalocentesis is performed after instillation of a short-acting mydriatic agent, preferably under general anesthesia, and after antiseptic pretreatment

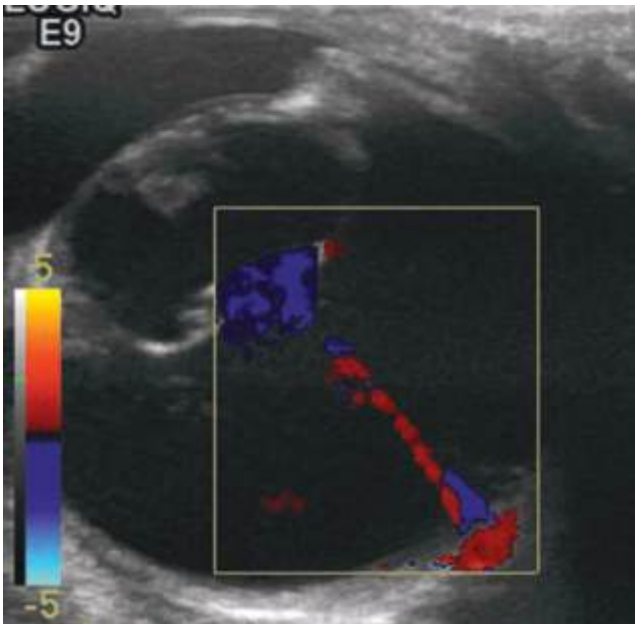


Figure 24.1 Ultrasonography with color-flow Doppler imaging of the eye of a dog with cataract. A persisting and patent hyaloid artery is visible in the vitreous, running from the optic disc to the posterior pole of the lens. (Courtesy of Dr. Elena de Ferrari.)

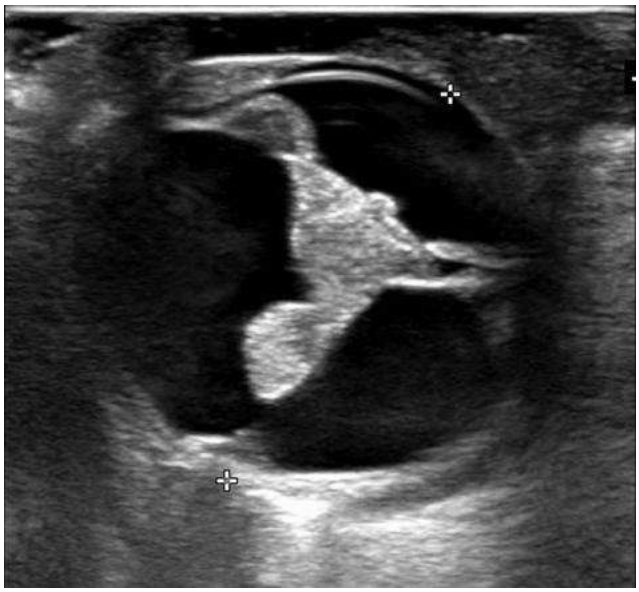


Figure 24.2 Canine eye with severe congenital lenticular malformation. The cataractous lens is irregular and protrudes caudally into the vitreous. A very short hyaloid artery derives from a conical optic disk (Bergmeister's papilla) and connects with the most posterior part of the "lens."

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Figure 24.3 Ultrasonography of this canine eye shows part of the contour of a luxated lens in the vitreous. The anterior chamber is deep and degenerated vitreous material can be seen in the pupillary region, posterior to the pupil, and in the anterior chamber.

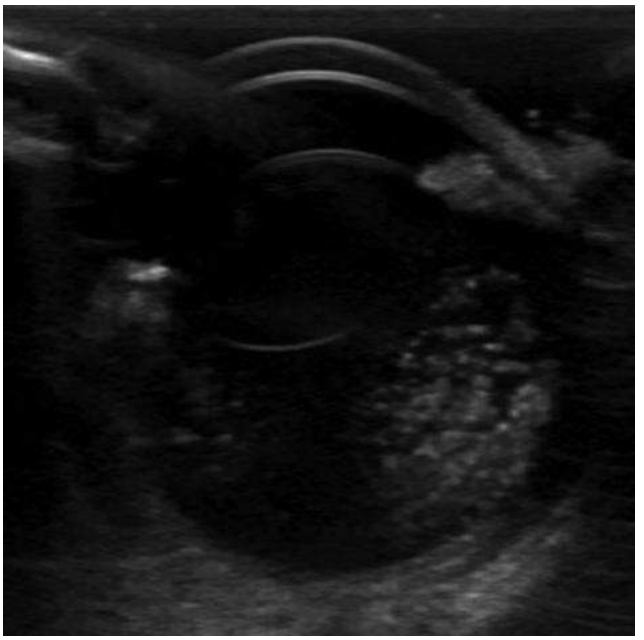


Figure 24.4 Ultrasonographic image of a canine eye, showing the granular appearance of asteroid hyalosis.

of the conjunctival sac (e.g., with a 0.5% povidone–iodine ophthalmic solution). A 22- to 26-gauge (0.70–0.45 mm) needle is used to penetrate the sclera, and the exact location of needle penetration is of great importance (Fig. 24.6). The eye should be penetrated via the anterior or medial region of the pars plana ciliaris (Smith et al., 1997). The corresponding external sites in medium-sized mesocephalic dogs are 7 mm (i.e., superotemporal quadrant), 6<thin>mm (i.e., inferotemporal quadrant), 5 mm (i.e., inferonasal quad-



Figure 24.5 Linear hyperechogenic structures in the vitreous space, indicating retinal detachment. (Courtesy of Dr. S. Boroffka.)

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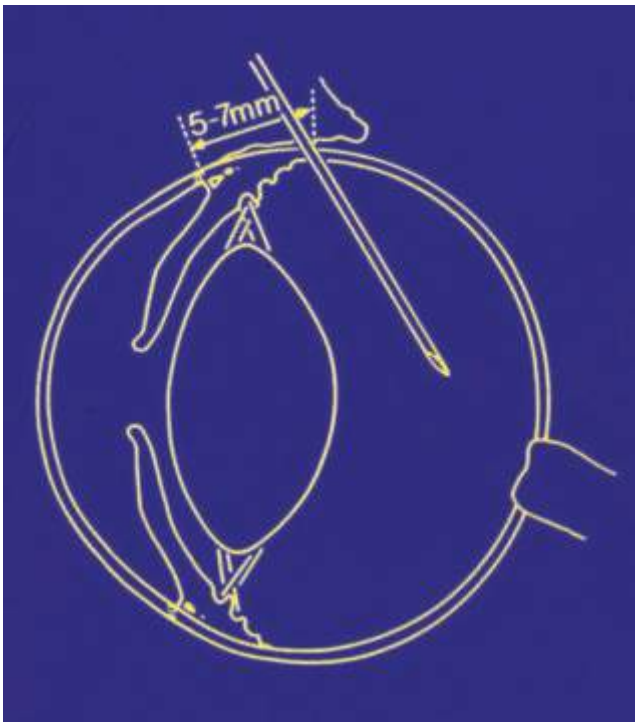


Figure 24.6 Hyalocentesis. The point of insertion of a 22- to 26-gauge needle (0.70–0.45 mm), 5–7 mm posterior to the limbus, depending on the ocular quadrant and globe size as determined by calipers or ultrasonography, is of utmost importance. Copyright Frans C. Stades.

rant), and 4–5 mm (i.e., superonasal quadrant) posterior to the limbus (Smith et al., 1997). There are indications that these sites will be more posterior in larger dogs with larger eyes (Smith et al., 1997). Needle penetration through the *pars plicata ciliaris* will result in considerable intraocular hemorrhage, whereas penetration posterior to the *pars plana ciliaris* will cause punctures of the retina. For these reasons, hyalocentesis should be performed only when essential.

The needle should be directed toward the posterior pole of the globe. Great care should be taken to avoid touching the lens in the process. Under observation via an indirect ophthalmoscope through the dilated pupil, the needle can be directed to the opacities under investigation. If the vitreous at the needle tip is gelatinous instead of liquefied, it may obstruct the needle. In that case, the needle should be gently flushed to remove the obstruction and repositioned for another attempt. An amount of balanced salt solution (BSS) or other vitreal substitute equal to the volume of aspirated vitreous should be injected at the same site to restore the vitreous volume and intraocular pressure (IOP). Conversely, if drugs are injected, the same volume of vitreous should be aspirated. In endophthalmitis, diagnostic hyalocentesis is believed to have a higher sensitivity than aqueous paracentesis (Brightman et al., 1986).

Therapeutic Procedures

Medical Treatment

Because the vitreous is avascular in adult dogs greater than 8 weeks of age, penetration of systemically administered drugs is poor. When the blood–aqueous barrier is compromised, such as occurs in uveitis, accessibility of the vitreous for drugs increases. Hence, systemic administration of drugs, even though relatively safe, is of limited use in reaching the vitreous. The most direct way to achieve high drug concentrations in the vitreous is by intraocular injection. The canine globe only tolerates rather low doses and volumes, however, and large dosages may produce severe ocular damage (Gelatt, 1978). This latter phenomenon is used by injecting gentamicin into the vitreous as a treatment in globes with absolute glaucoma and in which enucleation is contraindicated. For therapeutic intravitreal injections, hyalocentesis is performed. Topical or subconjunctival administration of drugs is indicated only in ciliary body–dependent vitreal pathology; such administration is of limited value in the treatment of other posterior segment disease (Gelatt, 1978).

Surgical Treatment

Surgical treatment is necessary when the vitreous is displaced within the pupil during anterior segment surgeries, anterior lunation of the lens, and in the treatment of retinal detachments. Details on vitreous surgery are provided in Chapter 26.

Vitrectomy

Vitrectomy is generally indicated when vitreous presentation or protrusion occurs during anterior segment surgery. Another indication for vitrectomy is during vitreoretinal surgery for the treatment of retinal detachments and vitreal traction bands.

Anterior Vitrectomy

Anterior vitrectomy is indicated when formed vitreous protrudes into the pupil or the anterior chamber during anterior segment surgery. During intracapsular lens removal, presentation of vitreous may be prevented by trying to carefully separate the posterior lens capsule from the anterior surface of the vitreous. In humans, this is thought to be practically successful only in patients older than 50 years (McLeod, 1987). In most cases involving dogs, protrusion occurs during or directly after intracapsular lens removal. If the posterior lens capsule is perforated during cataract surgery, the vitreous may protrude into the capsular bag, pupil, anterior chamber, or even the corneal incision. Protrusion of vitreous in the pupil or the anterior chamber may physically impair or obstruct the flow

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or drainage of aqueous, resulting in an increased IOP. In addition, vitreous touching the corneal endothelium may cause persistent corneal edema. Left untreated, vitreous protrusions may cause the development of traction bands, with the risk of subsequent retinal detachment.

Anterior vitrectomy is generally performed through an (intraoperatively) already existing corneal or corneoscleral incision or, seldom, through a traumatic perforation. A second corneal incision in a different area occasionally is necessary for adequate access to the pupil. In selected cases, a pars plana vitrectomy through a newly made surgical entrance (i.e., pars plana posterior vitrectomy) may be indicated. Anterior vitrectomy should be performed automatedly.

Manual vitrectomy was used in open-sky surgical techniques, which presently are generally considered superseded. In this technique, formed vitreous is touched with a microsurgical sponge, to which it will adhere (i.e., Kasner technique). The adherent vitreous gel is then carefully retracted and cut using iris or vitreous scissors. Abrupt movements or traction, however, can result in retinal detachment. All vitreous matter in the anterior chamber and attached to the margin of the pupil should be removed. Liquefied vitreous, if present, can be aspirated by using a blunt cannula and is generally located at the highest point.

In automated vitrectomy, the use of "guillotine" vitrectomes is common in veterinary ophthalmology. In a rabbit model, inhibition of postvitrectomy intraocular fibrin formation with the use of hirudin has been demonstrated (Liu et al., 1997).

Pars Plana Posterior Vitrectomy

In pars plana posterior vitrectomy, part of the vitreous is removed using a vitrectome. Successful use of this method requires considerable experience. The surgical entrance is where the dorsolateral sclera is positioned over the pars plana ciliaris (see above). This procedure is commonly included in the surgical treatment of complicated retinal detachment and vitreal traction bands. For a description of vitreoretinal surgery, see Chapter 26. Other indications for this procedure include ophthalmomyiasis interna posterior (Ollivier et al., 2006) and uveitis (mainly used in horses with equine recurrent uveitis).

For surgical procedures concerning the vitreous, the same pre- and postoperative measures and anesthesiologic considerations that are valid for other intraocular surgeries are applicable.

Vitreal Diseases

Developmental Disorders

Developmental disorders form a group of relatively rare ophthalmic anomalies. Usually, these anomalies are part of syndromes associated with persisting intraocular vasculature or with other ocular developmental disorders, such as microphthalmia, Collie eye anomaly (CEA; Roberts et al., 1966), and retinal dysplasia (Rubin, 1974; Saunders & Rubin, 1975). Their causes are not well understood, but these anomalies may result from a chance error during embryogenesis or have a hereditary cause, as has been determined for several canine breeds.

Persistent Hyaloid Artery

The anomaly PHA results from failure of part, or all, of the hyaloid artery to regress (Fig. 24.7). The artery may have persisted as a string (in some cases containing blood) situated in the vitreous space, between the optic disc and the lens (Duddy et al., 1983). In PHA, only a small, dense, white, connective tissue string usually remains adhered to the posterior lens capsule. The optic disc may have a conical shape (i.e., Bergmeister's papilla), and during ocular movements PHA structures lag slightly behind and thus may show a "waving" motion. In addition, there may be scar-like lesions in or against the posterior lens capsule where the PHA is in contact with or attached to the capsule and in the immediately surrounding area. In some cases, such "scars" may lead to cataract formation in the adjacent lens fibers. PHA has been suggested to be hereditary in the Sussex Spaniel (Stades & Boevé, 1989) and the Doberman (Stades, 1980).

PHA alone rarely requires surgical treatment. If the associated cataract formation leads to visual impairment,

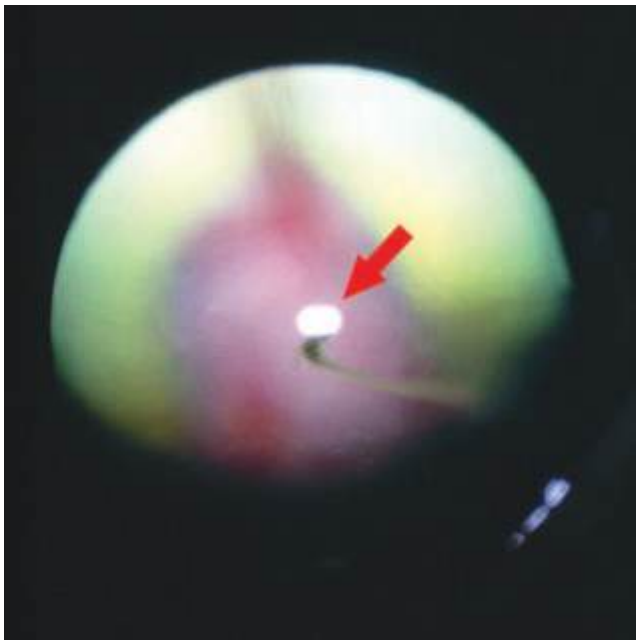


Figure 24.7 Persistent hyaloid artery in a Golden Retriever. The hyaloid artery is visible as a white string (arrow). The optic disc in this patient had the shape of a Bergmeister's papilla. Copyright Frans C. Stades.

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however, surgery may be indicated. In these cases, the risk of complications is increased compared to "routine" cataract surgery, because in PHA-related cataracts, axial fenestration of the posterior lens capsule and anterior vitrectomy are usually indicated. This is especially hazardous when the hyaloid artery is still patent. This can preoperatively be diagnosed by using Doppler ultrasonography. In such cases, the hyaloid artery must be closed by wet-field coagulation before transection.

Persistent Tunica Vasculosa Lentis

In persistent tunica vasculosa lentis, there are fine, white, strand-like deformities (i.e., "spiderweb"), or parts of vascular structures, attached to the posterior lens capsule (i.e., persistent tunica vasculosa lentis posterior). These structures are the remainder of the tunica vasculosa lentis (posterior), retrolentally connected to, or "printed" to, the posterior lens capsule. Fine strands may also extend from the equator through the pupil to the "collarette" on the anterior surface of the iris (persistent tunica vasculosa lentis anterior). These structures generally have no clinical significance, and they may be observed incidentally during routine ophthalmic examinations. Slit-lamp microscopy, using a very narrow light beam, will reveal their presence as well as their typical retrolental-capsular location. The lens contents should be free of any opacity.

Persistent Hyperplastic Tunica Vasculosa Lentis/Persistent Hyperplastic Primary Vitreous

In this group of apparently rare and generally unilateral disorders (Grimes & Mullaney, 1969; Kern, 1981; Rebhun, 1976; Venter et al., 1996), parts of the hyaloid system and primitive vitreous have become hyperplastic during early fetal development, combined with a subsequently incomplete regression. This anomaly has been described in many species. In the dog, PHTVL/PHPV has been described in the Basset Hound (Verbruggen et al., 1997), Bloodhound (Gemensky-Metzler & Wilkie, 2004), Bouvier des Flandres (van Rensburg et al., 1992), Doberman (Stades, 1980), Samoyed and Spanish Pachon (Bayón et al., 2001), Siberian Husky (Ori et al., 1998), Staffordshire Bull Terrier (Curtis et al., 1984), and Golden Retriever (Graham et al., 2018).

PHTVL/PHPV and its development have been studied extensively in the Doberman (Boevé & Van Zoelen, 1989; Boevé et al., 1988b, 1990). In Doberman fetuses with PHTVL/PHPV, the hyaloid system and tunica vasculosa lentis posterior have been described to be hyperplastic as early as day 30 of gestation, compared to the development in normal Beagle fetuses as controls.

The clinical relevance of this condition is its association with cataract formation and, hence, visual impairment (Stades, 1980). In both the Doberman and the Staffordshire Bull Terrier, PHTVL/PHPV generally occurs bilaterally, is inherited (likely because of an incomplete dominant gene in the Doberman), and hence has a higher prevalence in these breeds compared to other breeds (Boevé et al., 1992; Curtis et al., 1984; Stades, 1980, 1983a).

The pathophysiology of this anomaly has not been determined. Mice lacking arf and p53 tumor suppressor genes as well as Norrie disease pseudoglioma and ARP5, or Norrie disease and FZD4 genes, suggest that at least these genes are needed for hyaloid vasculature regression (Shastry, 2009).

Signs include very small, retrolentally positioned fibrovascular dots on the posterior lens capsule that represent minor remnants of the tunica vasculosa lentis vasculature (i.e., Grade 1; Fig. 24.8 and Fig. 24.9). The pathologic findings in the different grades of PHTVL/PHPV are depicted in Table 24.1. The retrolental dots alone (Grade 1) cause no further ocular changes during life, and they do not demonstrably impair vision. These dots are generally only visible with the aid of a slit-lamp microscope. The severe grades, as in the hereditary forms of PHTVL/PHPV, occur bilaterally and usually lead to visual impairment. In Grade 2, a retrolental plaque of white fibrovascular tissue, which is sometimes combined with glial tissue components, is centrally located against the posterior capsule and is accompanied by Grade 1 dots peripherally. In the more severe grades (i.e., 3–6), there may be larger parts of the hyaloid system (Grade 3), which are sometimes accompanied by glial tissue, lenticonus (Grade 4), or some combination (Grade 5). Grade 6 comprises the most severe ocular malformations resulting from PHTVL/PHPV, such as intralental or retrolental pigment or hemorrhage, lental coloboma, microphakia, or spherophakia, with or without microphthalmia.

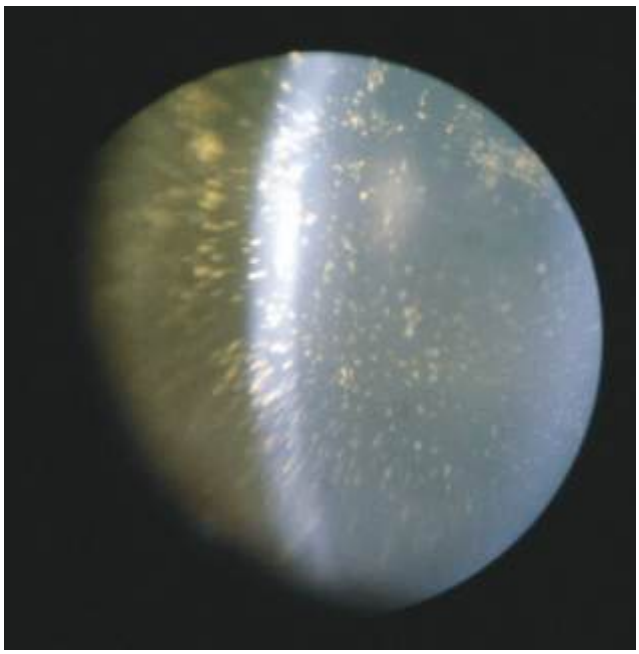


Figure 24.8 Slit-lamp micrograph of the posterior lens capsule of a Doberman with Grade 1 persistent hyperplastic tunica vasculosa lentis/persistent hyperplastic primary vitreous. Yellow-brown pigment dots are visible on the posterior capsule. Copyright Frans C. Stades.

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Figure 24.9 Postnatal persistence of vasculature belonging to the hyaloid system, including the tunica vasculosa lentis posterior, as seen in the right eye of a Doberman puppy with Grade 3 persistent hyperplastic tunica vasculosa lentis/persistent hyperplastic primary vitrous. Copyright Frans C. Stades.

In eyes with Grades 2–6 PHTVL/PHPV, the posterior capsule may be involved as well, showing such signs as "dilution," "dissolving," or capsular rents. These qualities result in central-posterior cataract and the penetration of blood, iron pigment, and calcium deposits into the lens (Rebhun, 1976). The presence of blood components or iron pigment in the lens may be recognized as a dark red or deep brown cataract. Cataracts may be present at birth, but they may also be minimal at that time and progress postnatally.

In the anterior form of PHPV in humans, elongated ciliary processes are considered to be pathognomonic (Haddad et al., 1978; Reese, 1955). In dogs with PHTVL/PHPV, however, these are a rare finding. Large retinal folds, or preretinal glial proliferations that are pathognomonic for posterior PHPV in humans (Manschot, 1958; Pruett & Schepens, 1970), are also observed in dogs, though infrequently (Van der Linde-Sipman et al., 1983). The nomenclature PHPV in humans was coined by Manschot in 1958 and was primarily based on the presence of neuroectodermal components. Findings in dogs support the use of PHTVL as a primary nomenclature and, for the sake of completeness, PHPV as a secondary term when describing this entity in this species.

The differential diagnosis of PHTVL/PHPV includes cataracts resulting from other causes, microphthalmia alone, and other solitary dysplastic disorders of the lens. In severely affected blind eyes (i.e., Grades 2–6), cataract surgery with fenestration of the posterior capsule and transection of the hyaloid artery, if applicable, combined with anterior vitrectomy may be indicated. The prognosis for surgery in severely affected cases of PHTVL/PHPV is less favorable than that in routine cataract surgery because of the higher complication risks (Stades, 1983b). Especially in cases with a patent PHA or when extensive vitrectomy is indicated, the prognosis is less favorable because of complications such as intra- or postoperative vitreal hemorrhage, formation of traction bands, and retinal detachment. The owner should be well informed about these risks.

Preventive examinations for PHTVL/PHPV can be performed in puppies. Preferably, the puppies should be older than 6 weeks and be positively identifiable by microchip (or tattoo). Because the globes are still small at this age, fine dots (Grade 1) may easily be overlooked. Hence, the result of a litter examination should always be regarded as preliminary. On the other hand, early examination prevents new owners from receiving severely affected puppies.

Dogs with severe PHTVL/PHPV (Grades 2–6) should be excluded from breeding. The prevalence of severe forms of PHTVL/PHPV in Dobermans in the Netherlands has decreased significantly after implementation of an adequate breeding program (Stades et al., 1991) and no severe cases of PHTVL/PHPV in Dobermans have been diagnosed in recent years.

Other Anomalies

The vitreous may be involved in diseases of its bordering structures as well. In CEA, a partial failure of vitreal development, which is only recognizable by use of a slit-lamp microscope, has been described (Tolentino et al., 1965). Vitreal syneresis, vascular anomalies, hemorrhages, and retinal detachment may also be found in CEA. These anomalies may include preretinal vascular loops penetrating into the vitreous, and such vessels may cause vitreal hemorrhage. In case of retinal detachment, the neuroretina is partially or totally detached into the vitreous.

In the focal and geographic forms of retinal dysplasia, the retina folds slightly into the vitreous. In severe forms of retinal dysplasia, as has been described for the Bedlington Terrier (Rubin, 1968), the Yorkshire Terrier (Stades, 1979), and the Labrador Retriever (in combination with skeletal abnormalities; Barnett et al., 1970; Blair et al., 1985a; Carrig et al., 1977), the retina is partly or totally detached and dislocated into the vitreal space. Syneresis may be present in retinal dysplasia as well.

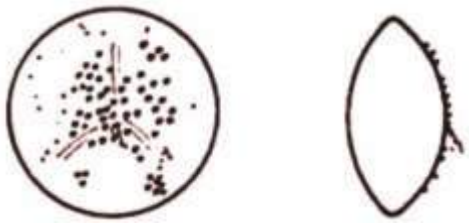
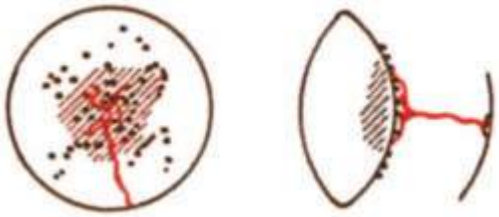
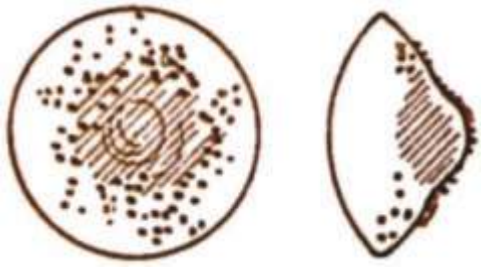
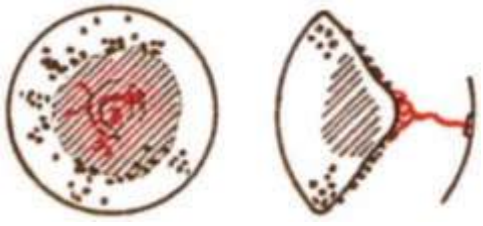
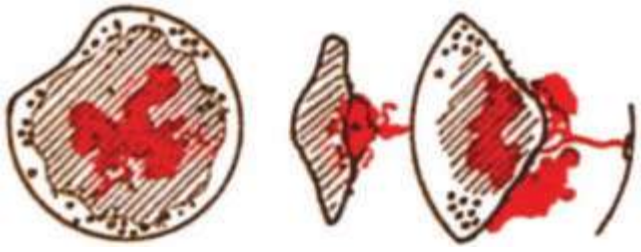
Acquired Disorders

Trauma

Penetrating trauma, such as caused by air-rifle or shotgun pellets, easily causes floaters of blood in the vitreous. The penetration tunnel is usually marked by prolapsed lens material, blood residues, traction bands, and other scars, and the foreign body itself may still be present in the vitreous.

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Table 24.1 Classification of the lental and retrolental anomalies in Dobermans with persistent hyperplastic primary vitreous/persistent hyperplastic tunica vasculosa lentis (PHTVL/PHPV).* Copyright Frans C. Stades.

Grade	Clinical Findings	Appearance
1	Limited posterior capsular cataract with capsular/retrolental pigment dots, about 0.5 mm in diameter.	
2	More extensive central-posterior capsular cataract with yellow-brown capsular/retrolental fibrous tissue. Multiple pigment dots in the central part as well as in the periphery of the posterior capsule. In cross-section the appearance of persistent pupillary membrane occurred frequently in Dobermans with PHTVL/PHPV.	
3	Persistent tunica vasculosa lentis–hyaloid system vessels appearing as a meshwork combined with Grade 2 abnormalities.	
4	Lenticonus of varying extent combined with more or less extensive elevation and Grade 2 abnormalities.	
5	Combination of Grade 3 and Grade 4 abnormalities.	
6	Combinations of the first five grades, such as lens coloboma, microphakia, larger (retro)lental clots of pigment, or red material like free blood.	

* Cataract formation is depicted in the frontal and sagittal views. Cataract progression may occur in Grades 2–6 based on the extent of the retrolental anomalies, and mature cataracts may develop in Grades 2 and higher.

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Less often, blunt trauma causes vitreal hemorrhage. Dogs that show ophthalmic problems of sudden onset that include signs of trauma such as corneal edema, hyphema, uveitis, and vitreal hemorrhage should additionally be examined with diagnostic imaging techniques, especially ultrasonography, for the presence of foreign bodies, vitreal changes, and retinal detachment. Survey radiography alone will be sufficient for demonstrating radiopaque (e.g., metallic) foreign bodies.

Depending on the severity of the concurrent uveitis, therapy in such patients consists of topical antimicrobial treatment/prophylaxis, mydriatics/cycloplegics (e.g., 1% atropine), and dexamethasone (4–6 times daily), as well as systemic prophylactic antimicrobial and extensive anti-inflammatory treatment (e.g., corticosteroids or nonsteroidal anti-inflammatory drugs). In cases of ocular hypertension, the IOP should be reduced as well, in which case the use of parasympatholytic mydriatics, and especially atropine, is contraindicated.

Surgical trauma may influence the vitreous as well. Kang et al. (2015) evaluated fluid leakage into the canine vitreous humor during phacoemulsification. They concluded that high fluidic parameters lead to greater fluid passage through the zonules, increasing fluid passage into the vitreous. According to these authors, intraocular tissues may be adversely affected by longer phaco durations as well.

Degenerative Vitreal Disorders and Reactions

The term vitreous degeneration is clinically used to indicate vitreous changes that are consistent with breakdown of the vitreous hydrogel. Signs may comprise liquefaction (syneresis) and opacities (floaters, asteroid hyalosis, and synchysis scintillans). However, in "normal" dogs, a wide variety of vitreous gel consistencies can clinically be noticed.

Over the last decade, an entity called primary vitreous degeneration has become an issue in a number of breeds, such as Brussels Griffon, Chihuahua, Chinese Crested, Havanese, Italian Greyhound, Lowchen, Papillon, Shih Tzu, and Whippet. However, there still is a lack of scientific support concerning this entity in dogs. Further research in these and other breeds will have to confirm or deny this condition as a separate, primary entity.

Small or large opacities that consist of conglomerates of calcium and lipids, condensations of vitreous fibrils, groups of erythrocytes, or pigment cells (including remnants of the hyaloid system) may persist or develop in the vitreous (see above). Such opacities may move as well, following the movements of the eye ("lag behind"). In older animals, further degeneration of the vitreous can lead to liquefaction, in which case the opacities have a greater tendency to lag behind ocular movements or whirl up. Ultrasonography forms an important diagnostic tool in the detection of signs of vitreous degeneration (Labruyere et al., 2008; see Fig. 24.1, Fig. 24.2, Fig. 24.3, Fig. 24.4, Fig. 24.5, and Fig. 24.10).

The etiology and pathophysiology of vitreous degeneration is diverse. Other than possible breed predispositions as mentioned before, a hereditary etiology has not been determined in the dog. In humans, mutations in the collagen *COL2A1* and *COL11A1* genes have been reported to cause vitreous degeneration. Vitreous degeneration has been described to be related to the rate of oxygen consumption and ascorbate concentration in (human) samples obtained by vitrectomy (Shui et al., 2009). Ascorbate in the vitreous decreases exposure of the lens to oxygen. The gel state of the vitreous preserves ascorbate levels, thereby sustaining oxygen consumption. Vitrectomy or advanced vitreous degeneration may increase exposure of the lens to oxygen, promoting the progression of nuclear cataracts (Shui et al., 2009).

An association of vitreous degeneration, on ultrasonography, with more severe cataract grades in dogs has also been indicated for the dog (Park et al., 2015).

Syneresis

Syneresis is a degenerative breakdown of the vitreous gel that separates its liquid from its solid components, resulting in liquefaction and development of fluid-filled cavities within the vitreous. This breakdown may occur with age, but it can also be the result of inflammatory reactions or unknown causes (Okun et al., 1961). For human and bovine vitreous fibrils, it has been described that the shielding of Type II collagen from exposure on the fibril surface by Type IX collagen decreases with age. This predisposes the vitreous collagen fibrils to fusion, which may lead to liquefaction (Bishop et al., 2004). Another pathophysiologic momentum of age-related vitreous liquefaction might be the increase in potential degradative activity in (human) vitreous (Voughan-Thomas et al., 2000).

Syneresis predisposes to posterior vitreous detachment. Foss and Wheeler (1982) reported a strong correlation between vitreous liquefaction and posterior vitreous detachment in humans. Posterior vitreous detachment rapidly progresses into total vitreous detachment, separating the posterior vitreous cortex from the neuroretina by traction, thus potentially leading to a retinal tear and to rhegmatogenous retinal detachment. For the dog, this was recently suggested in a publication by Itoh et al. (2010), in which the development of rhegmatogenous retinal detachment in the Shih Tzu was suggested to occur through primary retinal degeneration and secondary vitreous degeneration (syneresis).

In humans, loss of vitreous gel has been described to increase the risk of age-related nuclear cataracts (Harocopos et al., 2004). The process of syneresis usually starts retrolentally. It can be recognized by the presence of fine, cloudy structures whose slow movements follow the movement of the globe during slit-lamp microscopic examination.

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Vitreous Floaters

Vitreous floaters, muscae volitantes, or "flying flies" are larger flakes or streaks in the vitreous that may lag behind ocular movements. If these structures are very movable, especially against bright light, they can give the impression that something resembling a fly is passing by. In the past, this was thought to cause the "fly-biting syndrome," but today this behavior is generally suspected to result from nonophthalmic causes, such as temporal or occipital lobe dysfunction (Chrisman, 1991). Conversely, a recent case report described "light chasing" of a dog diagnosed with a marked degree of vitreous syneresis, several large clumps of vitreous that were mobile with patient head movement, and some vitreous plication in one (left) eye. The cause for this dog's light- and shadow-chasing behavior was finally determined to be multifactorial (Bain & Good, 2015). Vitreous floaters are uncommon and rarely require surgical treatment.

Asteroid Hyalosis

Asteroid hyalosis (see Fig. 24.4 and Fig. 24.10) is characterized by many small and sometimes slightly pigmented particles (i.e., "asteroid bodies" from 0.03–0.10 mm in diameter) in the vitreous of one or both eyes (Miller et al., 1983; Rubin, 1963; Schaeffer, 1985).

These particles move both during and following movements of the globe, but they also return to their initial position. They generally have no to low influence on vision by their presence alone; however, asteroid hyalosis may be associated with posterior uveal changes or (progressive) retinal atrophy.

Asteroid hyalosis has been described to occur in experimentally galactose-fed Beagles that develop the advanced stages of diabetes-like retinopathy (Wang et al., 2006). Comparisons of vitreous humor containing asteroid bodies collected from these Beagles and vitreous samples from age-matched normal Beagles have indicated that asteroid bodies contain calcium and phosphorus (Kador & Wyman, 2008). Further analyses resulted in the identification of the quasimolecular ion of 1,2-dipalmitoyl-glycero-3-phosphoetanolamine (DPPE) as the main component of asteroid bodies (Kador & Wyman, 2008). In the same publication, it was suggested that these lipid components diffuse into the vitreous originating from a degenerating retina.

Synchysis Scintillans

Synchysis scintillans is characterized by numerous cholesterol particles in a more or less liquefied vitreous. Especially after eye movement, they can resemble a snow flurry behind the lens, and against bright light they may cause dazzling. The abnormality is rare and seldom causes recognizable problems in dogs. It may be associated with retinal atrophy (Barnett, 1966a, 1966b; Leon, 1988) or with posterior uveitis (Hogan & Zimmerman, 1962). Synchysis scintillans and asteroid hyalosis may be difficult to differentiate clinically.

Intravitreal Membranes

Intravitreal membranes are associated with intravitreal hemorrhage. In one study on ocular pathology, intravitreal membranes were determined to be of glial origin predominantly (Zeiss & Dubielzig, 2004). Additional common findings in that study included epiretinal membranes, retinal neovascularization, preiridal fibrovascular membranes, and glaucoma. The authors state that vitreal membranes may not be clinically apparent unless associated with more severe ocular lesions.

Vitreoretinopathy

Vitreoretinopathy is a highly uncommon condition in the dog. It was first reported in the Labrador (Blair et al., 1985b), and has recently been described for the Shih Tzu (Papaioannou & Dubielzig, 2013). These authors described the histopathologic and immunohistochemical features of

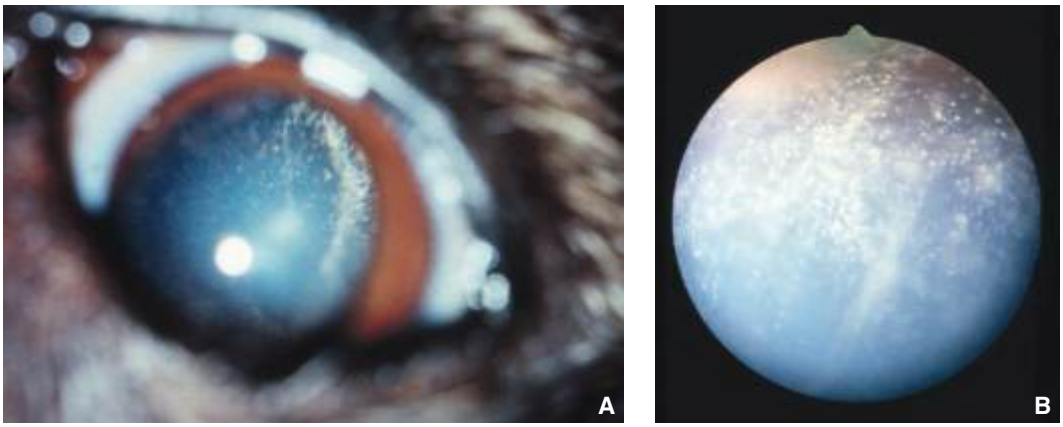


Figure 24.10 Asteroid hyalosis in a dog. **A**. External appearance. **B**. Ophthalmoscopic appearance. Copyright Frans C. Stades.

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this entity in 50 Shih Tzu dogs. The major pathologic changes in this condition were retinal detachment and extensive retinal tears, as well as collagen deposition in the vitreous body. Additionally, extracellular, eosinophilic matrix material admixed with few spindle cells, and preiridal fibrovascular membrane, goniodysgenesis, secondary glaucoma, hypermature, and subcapsular cataract were detected. Affected dogs were middle-aged to older, consistent with previous descriptions of vitreous degeneration. There are no clinical reports of vitreoretinopathy in dogs. Most of the examined globes in the study of Papaioannou and Dubielzig (2013) had been enucleated because of glaucoma.

Vitreal Inflammation and Hemorrhage

Because the adult vitreous has no intrinsic vasculature, nor nerve supply, the possibilities of reaction to noxae are limited. Hence, inflammation of the vitreous itself (i.e., hyalitis, vitritis) will almost always be secondary to inflammatory reactions of adjacent structures. Floaters of hemorrhagic or other exudate in the vitreous, especially if diffuse or bilateral, often result from exudative uveitis, chorioretinitis, retinitis, or optic neuritis. Vitreal exudates may also be secondary to perforating, iatrogenic, or blunt trauma, to retinal detachment, or to intraocular neoplastic or paraneoplastic diseases (e.g., lymphosarcoma, malignant histiocytosis). Therefore, the history as well as further examinations in such cases should be directed at revealing both the direct and any possible underlying causes.

Free blood in the vitreous is relatively uncommon (Fig. 24.11). Hemorrhage may result from congenital anomalies, such as the persistence of fetal vasculature (e.g., PHA, PHTVL/PHPV), CEA, trauma, infection, or systemic diseases (e.g., coagulopathies, vasculitis, systemic hypertension, neoplasms). Blood in the vitreous has been described to have a destructive effect on the gel structure: vitreous adjacent to a hemorrhage is prone to liquefaction (Forrester et al., 1978). The presence of macrophages induces an inflammatory reaction, which results in the formation of vitreal fibrinous membranes and traction bands (Fig. 24.12; Burke & Smith, 1981; Miller et al., 1986).

Spontaneous intraocular hemorrhage has been described in the Beagle (de Lahunta & Anderson, 1963).

Depending on the geographic location of the patient, various infectious agents are known to induce vitreal exudates. Infections reported to cause vitreal exudates include blastomycosis, cryptococcosis, histoplasmosis, brucellosis, as well as many other diseases (Gwin et al., 1980; Legendre et al., 1981; Moore et al., 1985).

In these cases, therapy should be directed primarily at the underlying cause. If signs of infection are present, high doses of antimicrobial agents with high intraocular penetration are indicated. In such severe cases, vitreous culturing and biopsy may be indicated, followed by intravitreal administration of antimicrobials, if necessary. At present, the types of vitreal surgery advocated in such cases among humans, including extensive vitrectomy, have found only limited application in veterinary ophthalmology.

The prognosis of vitritis strongly depends on the underlying cause. Small amounts of blood or exudate may be slowly resorbed, but larger amounts usually cause visual disturbances, even if the inflammatory reaction can be controlled. Vitreal membranes and traction bands may develop. In turn,

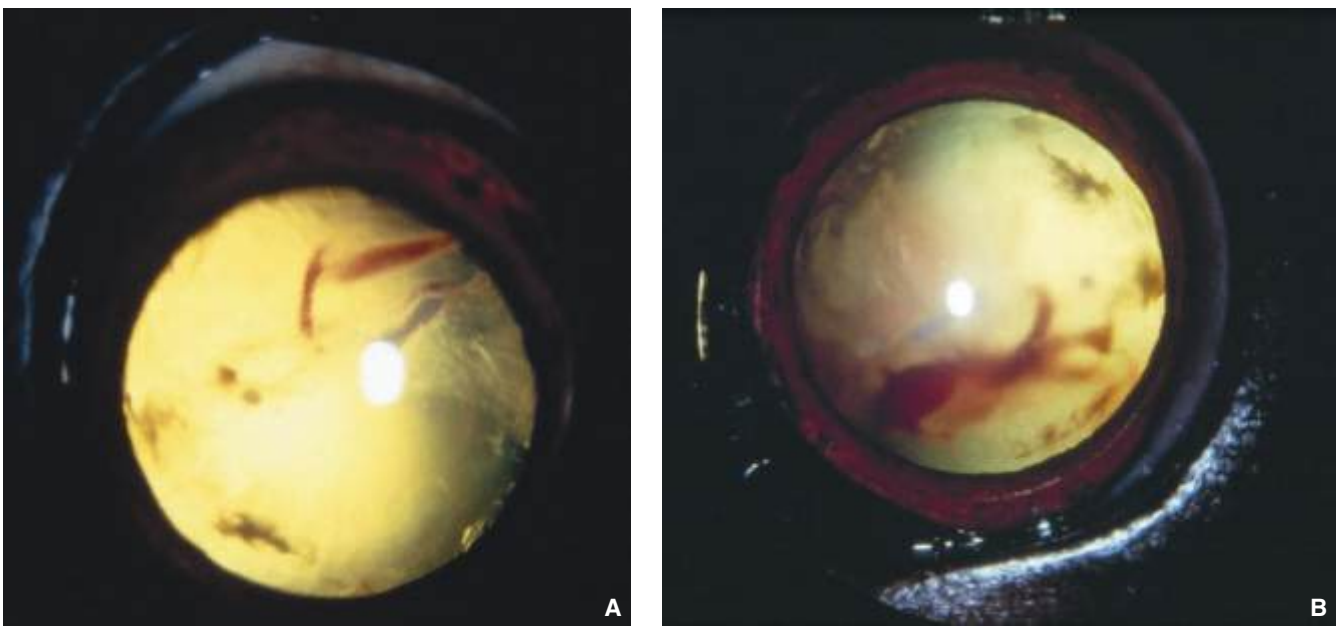


Figure 24.11 Vitreal hemorrhage following trauma in a dog. **A**. Limited hemorrhage. **B**. More extensive vitreal hemorrhage.

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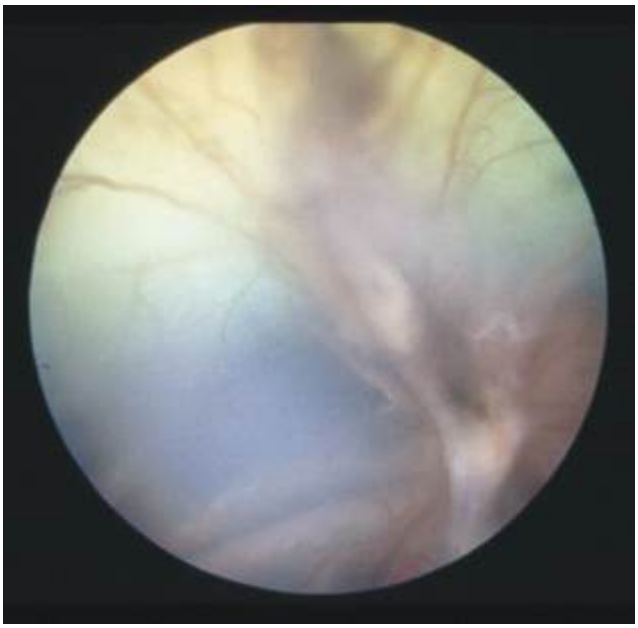


Figure 24.12 Preretinal fibrinous membranes of unknown cause in a dog.

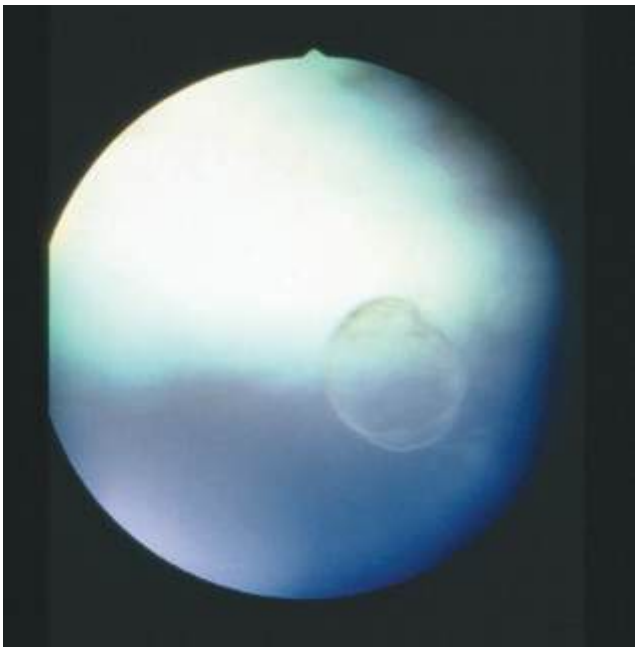


Figure 24.13 A cyst in the nasal portion of the vitreous of a 6-year-old, male Labrador Retriever.

vitreal displacement, prolapse, herniation, and traction caused by traction bands or membranes may cause secondary retinal detachments even months after the primary disorder has resolved.

Cysts

Cysts, most likely originating from the pigmented epithelial layer of the iris or the ciliary body, may extend into the vitreous (Leon, 1988). These cysts are much less common than anterior or posterior chamber uveal cysts. In humans, the use of miotic agents has been described to cause cysts of uveal origin (Shields et al., 1984); however, this has not been determined for the dog. Cysts may also be caused by parasites.

Vitreal cysts have the appearance of spherical or oval, translucent bodies that may be stationary or move slowly in liquefied vitreous following movements of the globe (Fig. 24.13). Depending on their size and location, they seldom interfere with vision.

Parasites

Migrating larvae of *Dirofilaria immitis*, *Toxocara canis*, the larvae of flies (i.e., ophthalmomyiasis interna), and *Echinococcus* sp. may penetrate the vitreous (Berliner, 1949; Blanchard & Thayer, 1978; Johnson et al., 1987). Living or dead intraocular parasites may cause local irritation, uveitis, or cyst formation. Killing intraocular dirofilaria by medication is sometimes possible (Westerhof, 1992). However, the intraocular presence of a dead parasite generally induces severe immunogenic uveitis, with possible subsequent endophthalmitis. Therefore, if the parasite can be reached without an unacceptable risk, surgical removal is to be preferred.

Neoplastic Disease

Intraocular neoplasms generally arise from the uvea and may occupy part or almost all of the vitreous space. Neoplasms may be primary, metastatic, or systemic/multicentric. Depending on location and size, a vitreal tumor may cause more or less displacement of the vitreous and lens as well as posterior uveitis and retinal detachment.

Primary neoplasms of the retina, choroid, and optic nerve are extremely rare in the dog, and neoplasms originating from the anterior uvea are relatively uncommon in this species. Uveal neoplasms mainly comprise malignant melanomas, but other neoplasms have been reported (Barrie & Gelatt, 1981; Langloss et al., 1976; Meyerholz & Haynes, 2004; Saunders & Barron, 1958).

Retinoblastoma, which is a well-known tumor with vitreal extension in humans, is virtually nonexistent in the dog (Hogan & Albert, 1991) and has only once been positively identified according to the criteria used in humans (Syed et al., 1997). The prognosis for an eye affected by a neoplasm extending into the vitreous depends on both the type of neoplasm and its extension, but such a neoplasm generally should be considered an indication for enucleation.

Tumors located in the vitreal space generally appear as a retrolental mass of grayish, red, or darkly pigmented tissue, often containing wildly arranged vasculature. Patients suspected of having intravitreal neoplasms should be examined

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clinically by diagnostic hyalocentesis and diagnostic imaging techniques (i.e., ultrasonography, CT, MRI), and referred for oncologic evaluation. Treatment and prognosis depend on the underlying cause, the range and locations of the affected areas, and the existence of related neoplasms in other parts of the body.

The Vitreous in Relation to Other Ophthalmic Disorders

Lens Luxation

The lens may dislocate when its suspension system is compromised by degeneration or rupture of the Zinn zonular fibers. The zonular fibers may have developed abnormally or have degenerated; in exceptional situations they can rupture from external trauma (Curtis, 1990; Martin, 1978). Chapters 22 and 23 address lens luxation and its implications in detail.

If several zonular fibers have ruptured, vitreous may leak into the anterior chamber along the lental equator and through the pupil. If the fibers have ruptured over a greater area, subluxation of the lens will occur. If the lens becomes completely unattached, it may remain more or less in its normal position, be displaced toward anterior or posterior, or topple. Because of its volume and the strong attachment of the posterior lens capsule to the vitreous, a dislocated lens will dislocate part of the vitreous as well. Subsequently, vitreous may prolapse or herniate in the pupil, thus impairing, or even blocking, drainage of aqueous between the posterior surface of the lens and the anterior surface of the iris (if the lens has become dislocated into the anterior chamber) or, at the level of the drainage angle, causing secondary glaucoma in all cases.

The earliest recognizable sign of a lens luxation is the presence of slight vitreous protrusions, which are recognizable on slit-lamp microscopy as thin, white clouds along the pupil margin. These protrusions are visualized best when illuminated from the front and inspected from the side, over the surface of the iris. In most cases, there will also be syneresis, resulting in waving movements of vitreous that are visible in the slit-lamp beam.

Lens Capsule Rupture

The majority of lens capsule ruptures occur posteriorly, because the posterior lens capsule is much thinner than anteriorly. Especially in diabetic dogs, with intumescent cataracts, an equatorial lens rupture is possible. Clinically such cases are presented with signs of an acute phakogenic uveitis. On ultrasonographic examination, protrusion of lens material into the vitreous can be detected.

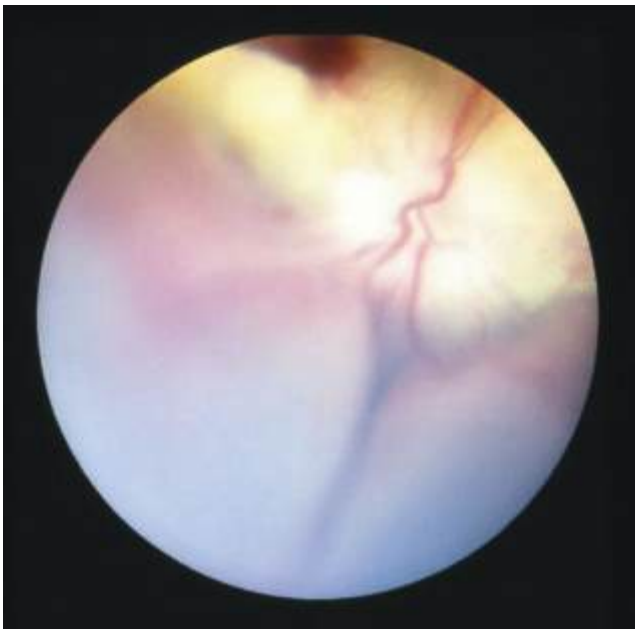


Figure 24.14 Bullous retinal detachment in the left eye of a Bernese Mountain dog suffering from systemic hypertension.

Retinal Detachment

A retinal detachment may occupy part or almost all of the vitreous space (Fig. 24.14). A small retinal detachment is observed as an indistinctly bordered, grayish blue "cyst" or fold of the retina. Large detachments look more like grayish blue to red, parachute-shaped, vascularized bullae positioned either directly behind the posterior lens capsule or deeper in the vitreous. Depending on the type of detachment, the optic disk may be obscured. Also, dark sheets of blood, pigment, or other inflammatory signs may be found. The combination of intraocular (intravitreal) hemorrhage and retinal detachment may be indicative of systemic hypertension. Diagnostics should therefore include an internistic work-up including blood pressure measurement.

In retinal detachments, the outer layer of the neuroretina (i.e., photoreceptors) and the pigment epithelium have separated. Only the aspects directly related to the vitreous have been discussed in this chapter. Chapters 25 and 26 address retinal detachment and its implications in detail. Retinal detachments of vitreal origin may develop because of vitreal traction bands (e.g., after perforating trauma or lens luxation), by dissolution of the vitreous (i.e., syneresis), or as a complication following vitreal surgery or hyalocentesis. Vitreous prolapse, or traction caused by secondary strings or membranes in the vitreous, resulting from posttraumatic uveitis, including postoperative uveitis after intracapsular lens extraction, may cause secondary retinal detachment even months after surgery. Surgical techniques to reattach the retina are described in Chapter 26.

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Diseases of the Canine Ocular Fundus

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Methods of Examination

The ocular fundus is examined with various direct and indirect diagnostic methods. Several methods are routinely used clinically, while others are more investigative.

Behavioral Testing

A history of visual impairment may be described by a diligent owner, particularly if the dog performs tasks (such as herding or agility) that require optimal visual ability. However, in a familiar environment, dogs can rely on other senses or memory to guide them, and visual deficits, particularly when subtle, can be missed by owners. Assessment of visual navigation ability in a clinical situation can therefore be beneficial.

A simple maze can be constructed, in which several objects such as chairs and buckets can be used as obstacles, set up in a room unfamiliar to the dog. The time taken to navigate and the extent of "mistakes" (colliding with objects) can be subjectively or objectively assessed, and different lighting conditions can be used to assess dim and bright light vision. However, isolation of pure rod-mediated vision requires a very low light intensity, which may not be achievable in a clinic setting. Although typically both eyes are left uncovered, if there is debate regarding unilateral visual ability, vision from one eye could be obscured. The test should be repeated to ensure reproducibility and objects in the maze should be rearranged frequently to prevent the patient learning the layout of the maze. A more standardized obstacle course testing method has been recently described (Garcia et al., 2010) and a novel, reproducible, four-choice method for standardized and objective vision testing has been developed for dogs (Annear et al., 2013; Gearhart et al., 2008).

It should be noted that in certain disease conditions, such as in day blindness, vision testing in normal room light may not be sufficient to diagnose a cone disorder, as rod-mediated vision may contaminate the test (Ropstad et al., 2007a). Outside, in bright daylight, however, the clinical changes in regard to the cone system are more obvious, such as difficulties in negotiating the maze and, in some cases of day blindness, marked miosis (Hurn et al., 2003).

Vision may also be assessed from the dog's response to falling objects (visual tracking) that do not create a noise or current of air (e.g., small cotton balls). The balls can be dropped both in front of the dog and to the sides to get an impression of central and peripheral vision. The results should be interpreted with some caution, however, because of patient indifference. Some diseases that affect the retina also affect the central pathways, including the visual cortex.

Testing Reflexes and Responses

The pupillary light reflex (PLR) requires a functional retina, but also depends on postretinal transmission of signals. Loss of the PLRs is not a definite sign of retinal dysfunction or even of loss of vision. They can also be partially inhibited in an apprehensive patient because of an increased sympathetic tone. Furthermore, residual PLRs are often present in dogs even with advanced retinal degeneration, such as in progressive retinal atrophy, especially if the inner retina is preserved. The reason for this phenomenon is that the PLRs are driven by the photoreceptors at low light levels and have been shown in various species to be driven by the melanopsin-containing ganglion cells at high light-intensity stimulation (Guler et al., 2008; Kardon et al., 2009; Semo et al., 2003). The presence of the PLRs is therefore not a guarantee of a healthy retina in dogs with opaque media (e.g., preoperatively in those with dense, extensive cataracts) that prevents ophthalmoscopic examination. A totally unresponsive pupil might suggest any kind of generalized retinopathy, glaucoma, or lesion involving the reflex pathway, including the pupillary sphincter muscle. The direct and indirect PLRs are routinely tested in mesopic conditions using a

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strong focal light. For investigational and research purposes, the PLRs are often tested in both scotopic and photopic conditions, using either a custom-made or a commercially available pupillometer (Thompson et al., 2010; Yeh et al., 2017).

The menace response (i.e., the reaction to a sudden, threatening object coming into the near field of view) may also be used to assess vision. This cortical response requires both a functional sensory pathway from the photoreceptors to the visual cortex and an intact motor pathway, including the facial nerve. Blinking and, possibly, withdrawal of the head is the normal response. Objects the dog can smell or that cause air currents will incorrectly stimulate senses other than vision. It is noteworthy that absence of a menace reaction may be caused by pathologic conditions other than severe visual impairment (such as cerebellar dysfunction), and sympathetic drive during stress can also partially impair the menace response. It should be remembered that this is a learned response and not present in young puppies.

Structural Visualization of the Fundus

Ophthalmoscopy

Direct, panoptic, and indirect ophthalmoscopy are all used in veterinary ophthalmology to visualize the fundus. The ophthalmoscopic examination is performed in a darkened room using short-acting mydriatics, such as 0.5%–1.0% tropicamide (Mydriacyl™, Alcon Laboratories, Fort Worth, TX, USA). Direct ophthalmoscopy, in general, provides the observer with a smaller field of view that is of greater magnification and detail than that with indirect ophthalmoscopy. Direct ophthalmoscopy is mainly used to examine the central parts of the fundus, especially the region of the optic nerve head (ONH), but it is considered inadequate to examine the peripheral fundus of domestic animals. Indirect ophthalmoscopy allows a more wide-angle, less magnified examination of the fundus, therefore a screen of the entire fundus can be achieved in a short time. Moreover, it allows stereopsis (with the use of a binocular indirect headset), which is useful in appreciating the topographic features of the retinal surface such as when appraising retinal detachments, colobomas, and papillary edema. Different indirect lenses can be selected to allow for a more highly magnified view when required. Also, indirect ophthalmoscopy optimizes examination when the fundus is partly obscured by opacities of the ocular media (e.g., cataracts). Panoptic ophthalmoscopy utilizes an indirect lens incorporated into the instrument, combined with mirrors to revert the image to the correct orientation. It offers an intermediate field of view and magnification, between direct and indirect ophthalmoscopy. All techniques have advantages that complement each other when used together.

Scanning Laser Ophthalmoscopy

Scanning laser ophthalmoscopy (SLO) is a diagnostic imaging technique developed for very precise and detailed fundus visualization. Lasers of different wavelengths allow the examiner to obtain information about specific tissues and layers on the basis of their reflection and transmission characteristics (Cideciyan et al., 2005b; Rosolen et al., 2001; Seeliger et al., 2000, 2005). The laser beam is used to scan the fundus, thereby allowing examinations with low levels of light, high resolution, and high contrast of retinal details as well as simultaneous video display of the fundus. The SLO can also be utilized in an angiography mode in order to correlate functional with morphologic aspects in disease processes affecting the retinal and/or the choroidal vasculature. Adaptive optics SLO has been described in humans (Williams, 2011), with the capability of imaging individual photoreceptors *in vivo*. To date, there has not been a description of this technique in dogs, although there is potential to utilize it as both a clinical and a research tool in the future.

Optical Coherence Tomography

Optical coherence tomography (OCT) has been developed and used both in research and for clinical purposes to evaluate *in vivo* retinal structure (Cideciyan et al., 2005a; Drexler & Fujimoto, 2008; Jacobson et al., 2004; Panzan et al., 2004). High-resolution, cross-sectional images of optical reflectivity are obtained. The technique is based on the principle of low-coherence interferometry, in which distance information concerning various ocular structures is extracted from time or light spectrum delays of reflected signals. This *in vivo* microscopy technique gives information about retinal organization and structural integrity. For example, photoreceptor-layer thickness can be quantified using OCT. The technique is mainly used for evaluation of retinal layers in disease processes and can be used in the determination of therapeutic progress (Jacobson et al., 2005). Instrumentation has also been developed that utilizes both OCT and SLO techniques simultaneously. Angiography using OCT techniques has been recently described in physician medicine (Spaide et al., 2018), although to date there have been no reports of its use in dogs.

Autofluorescence Imaging

Fundus autofluorescence (FAF) is described in humans as a monitoring tool for macular geographic atrophy (GA), a subform of age-related macular degeneration in which retinal pigmented epithelial (RPE) cells die. FAF relies on autofluorescent characteristics of fluorophores in the RPE, predominantly from the metabolite lipofuscin (Yung et al., 2016). To date its use in dogs has not been described, but it may have utility as a clinical or research tool in the future (Fig. 25.1).

Ultrasonography

Ultrasonography is a valuable aid in detecting and monitoring pathologic conditions in the canine posterior segment (Dziezyc et al., 1987; van der Woerdt et al., 1993). In patients with opaque media (e.g., dense cataracts, intraocular hemorrhage),

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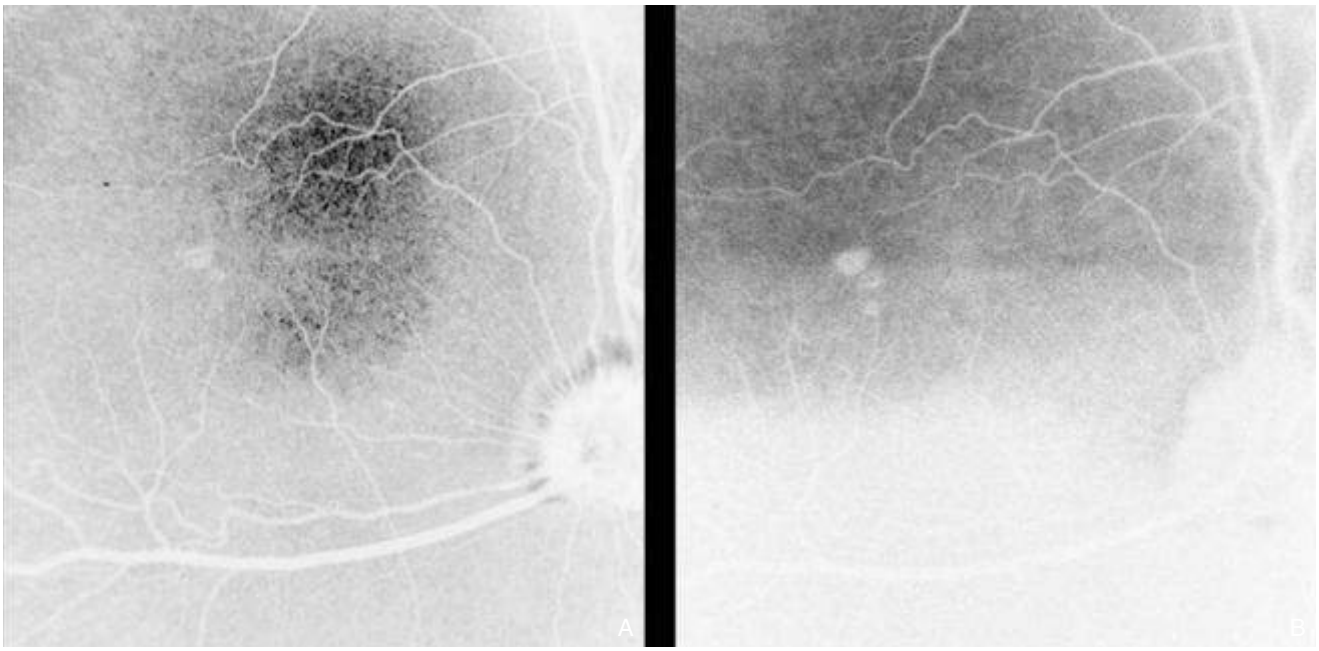


Figure 25.1 Infrared (**A**) and autofluorescence (**B**) fundus images of a dog, in which an area centralis hypoautofluorescent lesion has developed. (Courtesy of North Carolina State University Ophthalmology Service.)

ultrasonography can be used to detect, for example, a detached retina or posterior segment neoplasm. Furthermore, ultrasonography can be used to study space-occupying conditions that are difficult to examine because of their location (e.g., neoplasms in the choroid close to the ciliary body).

Angiography

Angiography is used to delineate the vasculature of the retina and choroid, and can be used to evaluate disease processes affecting the posterior segment. The procedure is performed in either sedated, anesthetized, or conscious dogs, depending on the preference and need of the examiner. Although the use of dyes to delineate vasculature is currently the only option in veterinary ophthalmology, with the advent of OCT angiography in physician medicine that does not require intravenous delivery of dyes, this may become an option in veterinary medicine.

Fluorescein angiography is used primarily to evaluate retinal blood vessels, ONH perfusion, and choriocapillaris (in the tapetal fundus where the pigment epithelium is nonpigmented). Fluorescein sodium solution (FL) 10% is given as an intravenous bolus into the cephalic vein. Fundus photography is then performed using a fundus camera or confocal scanning laser ophthalmoscope (cSLO; Pirie et al., 2012; Seeliger et al., 2000, 2005) that generates the correct excitation spectrum and collects the correct emission spectrum for fluorescein. This is achieved in fundus photography by using barrier filters; the excitation filter is recommended to be a maximum of 492 nm, and that of the barrier filter 575 nm, for good visualization in the dog (De Schaepdrijver et al., 1996). SLO uses lasers for excitation. The phases of fluorescein angiography include choroidal, retinal arterial, arteriovenous, venous, and late phases, with all but the last phase occurring within the first 15 seconds. Because of the risk of anaphylaxis, it is recommended to pretreat dogs with an antihistamine such as diphenhydramine, and to monitor patients carefully during the procedure. In humans, the most common manifestations of anaphylaxis are hypotension, nausea, and vomiting (Ha et al., 2014).

In pigmented animals, short-wavelength lasers provide the highest-quality images of the retina, but do not penetrate the RPE and choroid well. In contrast, infrared lasers, used in indocyanine green (ICG) angiography, show less retinal detail but also reveal choroidal structures clearly, down to the sclera. Therefore, FL provides the most detailed images of retinal capillaries, whereas ICG adds information about choroidal vessels but shows less detail of the retinal vasculature (Fig. 25.2). The two dyes behave differently because of the difference in their affinity to large plasma proteins: ICG is bound more than 98% to such proteins, while FL is bound to only about 70% (Destro & Puliafito, 1989). Therefore, ICG diffuses very slowly out of the vascular lumen, while FL tends to leak rapidly, particularly from choroidal vessels.

Functional Testing of the Retina

Electroretinography

When the retina is stimulated by light, an electrical response is generated by neuronal and nonneuronal cells that can be recorded as the electroretinogram (ERG; Gouras, 1970). This

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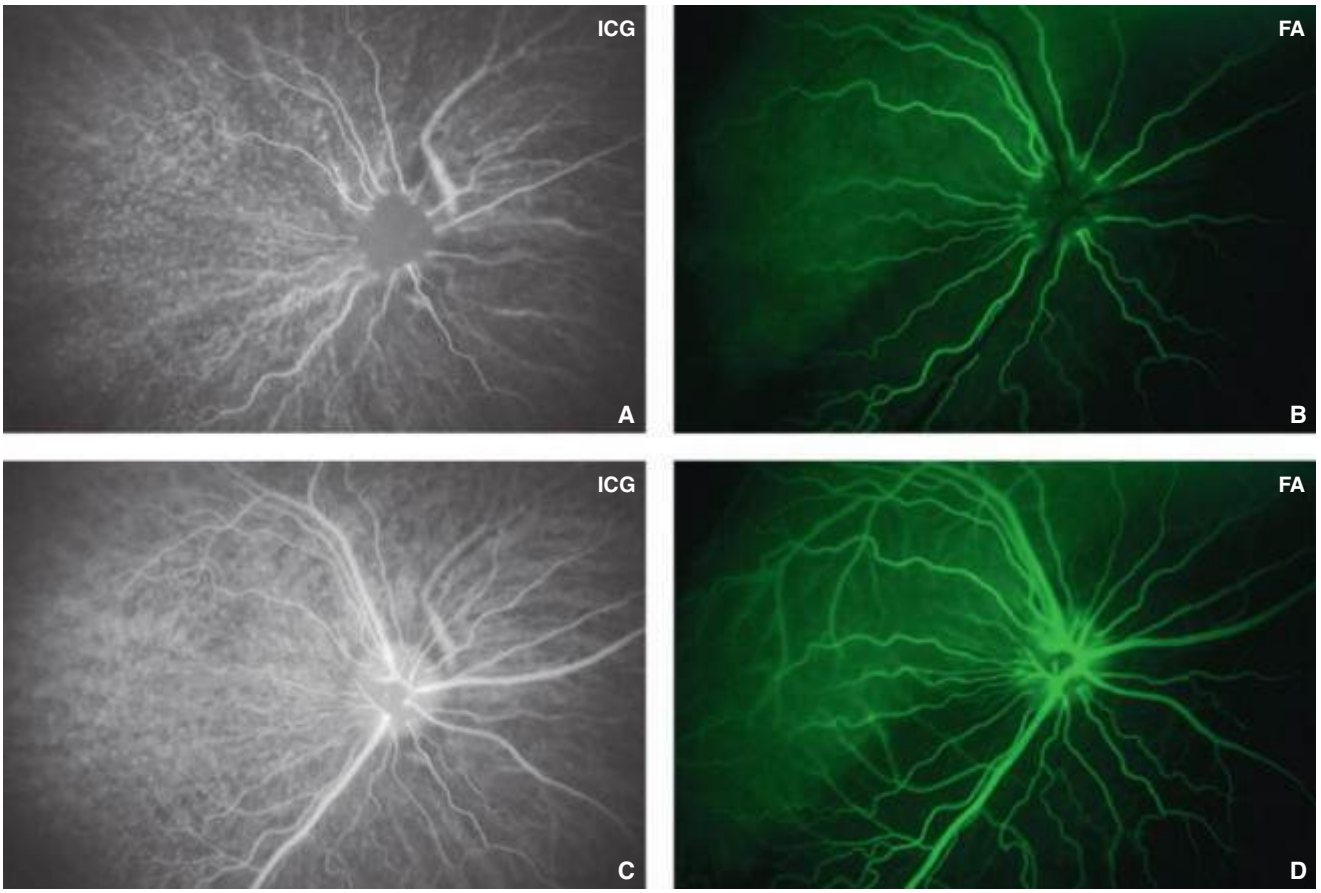


Figure 25.2 Simultaneous indocyanine green angiography (ICG) and fluorescein angiography (FA) of a normal dog fundus. Phases of angiography shown are arterial (**A, B**) and venous (**C, D**). Note the difference in visibility of the choroidal vasculature using ICG. (Courtesy of Dr. Chris Pirie.)

response is a summation of electrical potentials that result from light-induced changes in the movement of ions, mainly sodium and potassium, within the extracellular space. Thus, the ERG is an objective, functional test of the retina and is critically dependent on the function of the photoreceptors. It has a characteristic waveform that varies depending on the type of stimulus used. The intensity, duration, frequency, and wavelength of the light stimulus as well as the interval between stimuli, size of the retinal area illuminated, pupil size, and (very important) state of retinal light adaptation are variables that account for alterations in the ERG response. Other variables affecting the ERG are depth of anesthesia or other drugs in use, type of recording electrodes, age and breed of the dog, stage of retinal development, and clarity of the ocular media.

The ERG is recorded by using a recording corneal electrode, a reference electrode placed at a standardized location temporal to the lateral canthus (Mentzer et al., 2005) and a ground electrode. The signal is amplified, filtered, and displayed on a computer screen. In addition to evaluating the overall appearance of the ERG waveform, the a-, b-, and in some types of recordings c-waves are evaluated for the implicit time and amplitude of their peaks. Other responses, such as oscillatory potentials, can be extracted, and specific protocols have been developed to assess rod- and cone-mediated responses in the dark- and light-adapted retina (Fig. 25.3). For more information about clinical ERG, see Chapter 10, Part 4.

In clinical veterinary ophthalmology, the flash ERG is used in two broad applications (Acland, 1988; Aguirre, 1975; Narfström, 2006; Narfström et al., 1995). The first is to test whether a standard stimulus elicits an ERG response. This is useful in assessing retinal activity when the fundus is obscured (e.g., before cataract surgery) and in the differential diagnosis of retinal disease when ophthalmoscopic lesions are absent (e.g., suspect sudden acquired retinal degeneration syndrome, SARDS). The second is to specifically test rod and cone function in conjunction with research into retinal disease processes and in the early diagnosis of hereditary retinal degenerations and dystrophies. This second application applies knowledge of retinal physiology and basic electrophysiology, and requires more sophisticated

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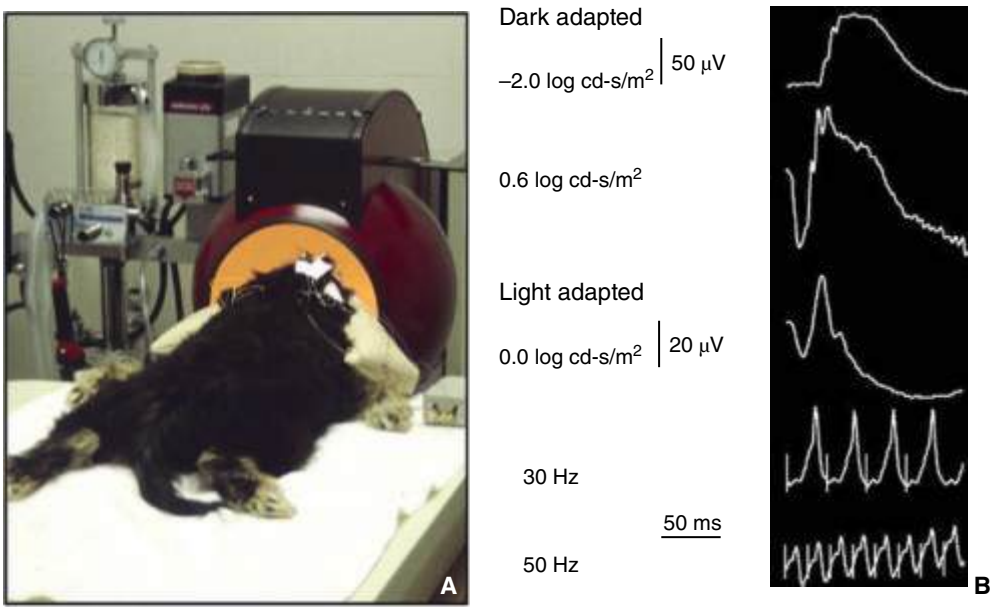


Figure 25.3 Bilateral electroretinography in progress using a protocol for evaluation of rod and cone function and Ganzfeld (full-field) stimulation **(A)**. The dog is under general anesthesia (propofol/isoflurane) in order to obtain maximally stable recordings. Details of the procedure are shown on the right **(B)**, which starts with dark adaptation, whereafter the eye is stimulated by low- and high-intensity white light. Light adaptation follows (using 37 cd/m^2), then recordings are obtained using single-flash and flicker stimulation with white light as indicated.

equipment and standardized procedures. Standardized guidelines for clinical evaluation of the canine retina have been developed (Ekesten et al., 2013), similar to that described in humans (McCulloch et al., 2015).

Pattern Electroretinography

The pattern ERG (PERG) measures a retinal response to a phase-reversing pattern stimulus that is focused onto the retina and maintains a constant overall mean luminance. The response is an electrical potential thought to derive from the retinal ganglion cells and the neighboring inner retinal structures (Arden et al., 1982).

The main characteristics of a pattern stimulus include overall screen brightness (i.e., mean luminance), brightness contrast of neighboring bars or checks (i.e., percent contrast), rate of pattern reversal (i.e., temporal frequency), and bar or check size (i.e., spatial frequency). In a description of PERG measurements, it is necessary to monitor one or more of these variables for the specific disease being studied (Bach et al., 2013). Moreover, for measurements to be reliable, the refractive error of the patient must be corrected during the testing so that the stimulus is focused on the retina, although in recently developed systems, SLO imaging and PERG stimuli can be combined to aid with focus of the image on the retina.

The PERG has been shown to be abnormal in human patients with established glaucoma, and a significant decrease in PERG amplitudes has also been found in early cases of glaucoma in humans (Bach et al., 1992). Further investigations have been performed also in dogs with suspected and early glaucoma (Bach et al., 1992; Graham et al., 1996; Hamor et al., 2000; Ofri et al., 1993).

In addition, PERG amplitudes correlate with visual field indices. Canine visual acuity was studied using evoked retinal and cortical field potentials by pattern stimulation, and canine acuity was 0.2–0.4 times that reported for primates (Odom et al., 1983). Differences in retinal anatomy, such as maximum density of ganglion cells, total number of ganglion cells, and total number of optic nerve fibers, may account for this variation between species. Another study using PERG estimated the mean acuity of the central 15 degrees of the canine retina to be 6.9 minutes of arc per phase, and the mean acuity of the toroidal 15 degrees of retina around this central area to be 11.8 minutes of arc per phase (Ofri et al., 1993). Other methods to estimate canine visual acuity include behavioral testing, assessment of the optokinetic response, and measurement of visually evoked cortical potentials (Lind et al., 2017; Miller and Murphy, 1995).

Visually Evoked Potentials

The visually evoked cortical potential (VEP), or visually evoked response, is an electrical signal generated at the occipital cortex in response to visual stimulation. These responses are of small amplitude (1–40 μV) and are extremely sensitive to stimulus changes. Therefore, computer averaging

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is necessary for their recording, and correct placement of electrodes is an important factor in achieving correct and reproducible results. The VEP reflects the electrical activity of the central retina, because this area has a much larger cortical representation than the peripheral regions. The VEP is a test not only of central visual function but also of the optic nerve and the higher visual tracts and visual cortex. It may be useful in patients with normal ophthalmic examination results and a normal ERG.

The VEP is typically recorded in response to flash or pattern stimuli. In flash VEP, which is used most often clinically in the dog (Sims et al., 1989), luminance, stimulus rate, and color of the flash can be varied. In pattern VEP, the field size, pattern size, contrast, retinal location, and rate of pattern presentation can be varied. The latter type of stimuli is either phase-reversed or flashed on and off. Important factors affecting the VEP are pupil diameter, age, and refractive error.

Latency (or time to peak) is the most useful clinical parameter to be evaluated in VEP, but waveform morphology and amplitude of the responses are often also used for specific evaluation. The VEP latency provides a sensitive means of detecting subclinical lesions in the canine visual pathways and of monitoring developmental changes in both neonatal and young animals (Ofri, 1993; Sjöström, 1985). Combined SLO imaging and VEP recording can be performed in more advanced ERG systems, allowing testing of specific regions of the retina (Cohen et al., 1994).

Focal and Multifocal Electroretinography

Regional functional testing procedures have been developed for ERG recordings in order to obtain precise topographical mapping of disease (Hood & Zhang, 2000; Seeliger et al., 2000; Sutter and Tran, 1992). This technique allows for simultaneous measurements of ERG activity from many different retinal locations, utilizing SLO for laser stimulation and direct visualization of the procedure, with an additional stimulus in the optical pathway of the SLO by means of a wavelength-sensitive mirror. Multifocal ERGs could be used to evaluate regional outcome from retinal therapy. For example, they were used to show regional functional rescue following subretinal injection of gene therapy in RPE65-deficient dogs (Le Meur et al., 2007; Mayser et al., 2003).

The Normal Ocular Fundus

The canine ocular fundus has enormous variation in normal ophthalmoscopic appearance (Fig. 25.4**).** Certain features of the fundus relate to macroscopic properties (e.g., iris color, coat color). The appearance of the normal canine fundus also varies according to age, with obvious color changes usually occurring during the first 3–4 months of life. The eyes of one individual are often symmetric, though marked differences may be seen in some dogs (e.g., in some breeds, such as Collies or Siberian Huskies, one eye may have a blue iris with an accompanying subalbinotic atapetal fundus and the other eye with a brown iris may have a fundus with a tapetum and pigmented nontapetal fundus). Familiarity with normal variation in fundus appearance is important to ensure accurate diagnosis of pathologic conditions. In most dogs, as in many domestic mammals, the fundus can be subdivided into a tapetal and a nontapetal zone.

Tapetal Fundus

The combination of the tapetum lucidum in the anterior choroid and an absence of pigment in the overlying RPE is the anatomic basis for the appearance of the tapetal fundus. The tapetal fundus forms an almost triangular area, with a horizontal base, in the superior half of the fundus. The area is usually brightly colored and reflective. The size of the tapetum varies extensively; usually, it is large, and may surround the ONH in sight hounds and large breeds. It is often poorly developed in toy breeds and only occupies a small area, typically temporal and superior to the ONH. The retinal blood vessels transverse the tapetal fundus, and the vessels are more easily viewed in the tapetal zone than in the nontapetal area.

In dogs with a merle coat color, the tapetum may be absent. A combination of an absent tapetum lucidum and lack of pigment in the pigment epithelium will cause the fundus to have a red/brown appearance because of the partial exposure of underlying choroidal vessels. Occasionally, the tapetum may be absent in other dog breeds; in this case, the entire fundus resembles the nontapetal area.

The tapetum varies widely in color, from orange/yellow to blue/green, with combinations possible. There is no apparent association of tapetal color and breed or coat color. The tapetal fundus is usually described to be bright and reflective in the normal dog, but it should not have an intense, metallic glare. In some dogs, the tapetal fundus is scattered with small foci of tapetal cells, surrounded by red/brown pigment similar to the nontapetal fundus. The border of the tapetum may be sharply demarcated or indistinct. The tapetal fundus has a light or dark blue color in young pups up to the age of 5–7 weeks. After this age, the adult coloration starts to develop.

Among breeds in which pale blue or heterochromic irides occur, a subalbinotic fundus may be found. The appearance of the fundus ranges from a small segment of albinism or subalbinism situated randomly in the tapetal or nontapetal fundus to almost complete absence of pigmentation in the fundus. The subalbinotic areas are identified by the visible, reddish, brick-colored choroidal vessels against the white scleral background. The tapetum is occasionally absent in subalbinotic fundi.

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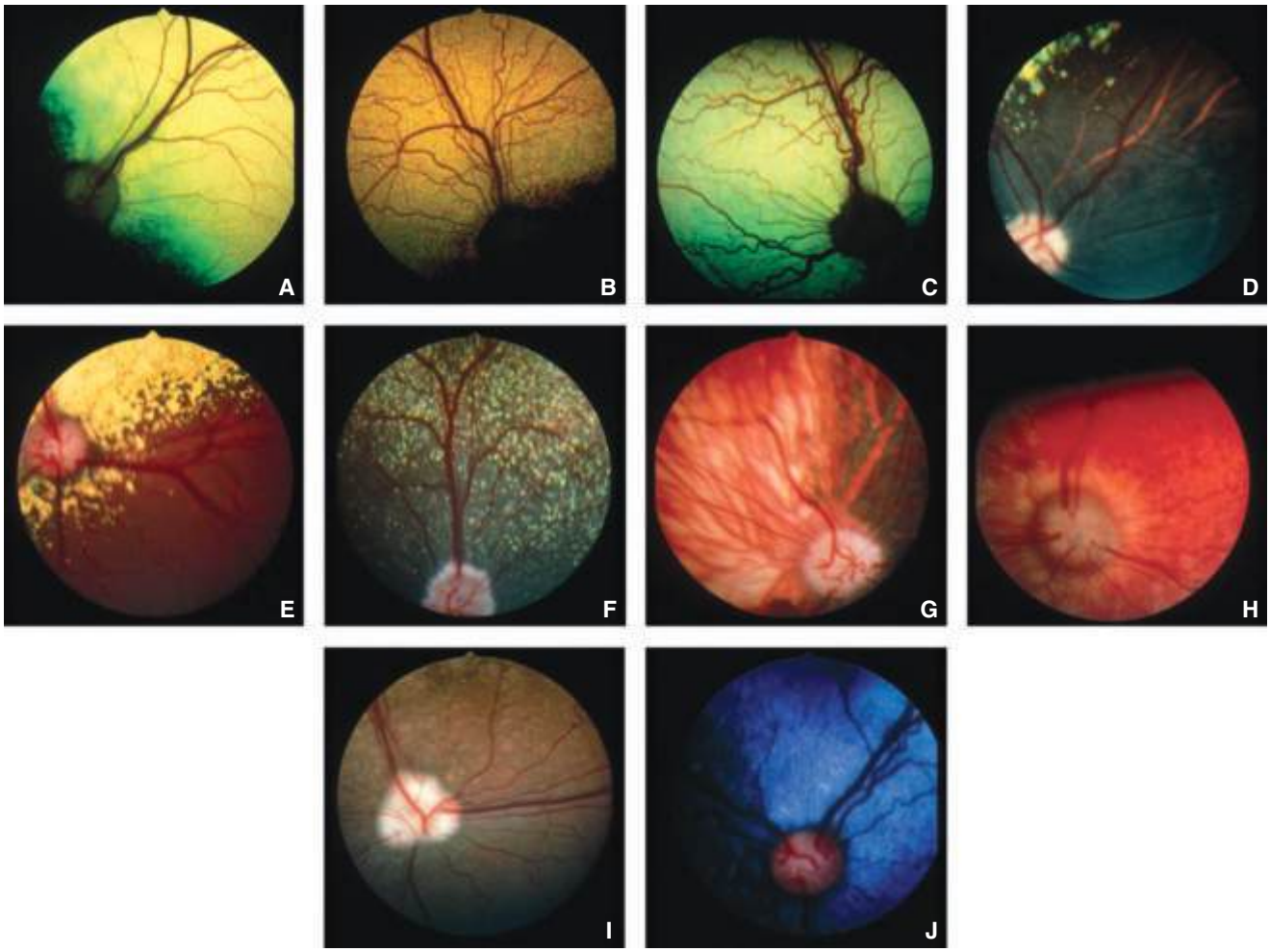


Figure 25.4 Normal appearance of the fundus in different canine breeds. **A**. A 4-year-old Beagle with a large, mostly yellow tapetal area and a relatively large, round disc at the border of the tapetal and nontapetal areas. **B**. A 1-year-old Briard with a yellow to orange tapetal fundus and a disc at the border of the tapetal and nontapetal fundus. **C**. A 3-year-old Irish Wolfhound in which the circular disc is enclosed in the yellow to green tapetal fundus and the vessels are slightly tortuous. **D**. A 6-year-old Toy Poodle in which the tapetal fundus is extremely small and the disc is located in the nontapetal fundus. Some large choroidal vessels are visible (light red) underlying the retinal vessels (dark red). **E**. A 2-year-old Clumber Spaniel with a rather lightly colored nontapetal fundus, with a reddish coloration in the area caused by the underlying choroid. The border of the tapetal and nontapetal fundus is uneven, with some scattering of tapetal cells. **F**. A 6-year-old Cavalier King Charles Spaniel with sparse tapetal cells within the tapetal fundus. The uneven borders of the optic disc are caused by pronounced myelination. **G.** A submelanotic right eye in a 1-year-old Papillon. The regular striation of the choroidal vessels is seen against the white sclera, and there are no tapetal cells. The nontapetal fundus is pigmented. The fellow eye had an orange-yellow "normal" tapetal and a pigmented nontapetal fundus. **H**. A 2-year-old blue merle Collie with an amelanotic fundus. There is a lack of tapetal cells and of visible pigmentation. **I.** A 4-year-old liver-colored Labrador Retriever with a light brownish coloration of the entire fundus. No tapetal cells are visible. **J**. A 7-week-old Collie pup with an immature, blue-colored fundus.

Pathologic conditions that lead to a decrease in retinal thickness (e.g., progressive retinal atrophy, PRA) will reduce the number of cell layers overlying the tapetum. In these cases, the tapetal reflectivity will be increased (i.e., tapetal hyperreflectivity), and in late stages of the retinal atrophy the tapetal fundus will have a metallic glare. In contrast, if the tissue overlying the tapetum thickens, it absorbs more light than normal and the tapetum will have a gray or brown coloration and appear hyporeflective (i.e., less light than normal will be reflected).

Nontapetal Fundus

The nontapetal fundus comprises the largest area of the ocular fundus in the dog. The junction between the tapetal and nontapetal fundus varies from a distinct line of demarcation to a gradual transition with scattered foci of tapetal cells. Isolated islets of tapetal fundus are commonly seen in the nontapetal region and patches of nontapetal pigment may be seen within the tapetal fundus in the normal dog.

The nontapetal fundus has a nonreflective, usually dark brown to black color. Sometimes, the nontapetal fundus

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adjacent to the tapetal fundus may appear paler compared with the darker, more inferior region. In dogs with a brown, chocolate, or liver coat color associated with a paler brown iris, the nontapetal fundus is less heavily pigmented and will appear paler brown or reddish brown. When reduced pigmentation allows the choroidal vessels to be seen, they result in a striped or tigroid appearance. In dogs with a subalbinotic fundus, parts of the nontapetal fundus will be nonpigmented, allowing visualization of the choroidal vessels overlying the white sclera. Absence of pigment in the entire nontapetal region is relatively common (e.g., in blue merle Collies).

Optic Nerve Head

The canine ONH, or the optic disc or papilla, also exhibits a wide range of normal variation in ophthalmoscopic appearance. It is located in the center of the fundus, sometimes within the nontapetal fundus and sometimes in the tapetal region in dogs with a more extensive tapetum. The ONH varies in size between individuals and dogs of different breeds, although breed does not appear to determine its shape or size (Fig. 25.5). The extent of myelinization affects the size of the ONH. Therefore, in young dogs, where the myelinization is incomplete, the ONH is smaller than that in the adult dog. Surrounding the ONH there may be an encircling zone of pigmentation, or focal retinal thinning, represented as an area of tapetal hyperreflectivity, known as conus (Fig. 25.6).

The shape of the ONH may be round, oval, triangular, or polygonal, and sometimes the disk edge may be indented. The edge may be sharply demarcated to a zone of diffuse transition at which the medullated nerve fibers extend into the surrounding fundus, especially along the retinal blood vessels. The anterior surface of the ONH is elevated compared with the surrounding retina in the adult dog, whereas this topographic difference can be difficult to detect in very young dogs with poorly myelinated nerves. The anterior surface is typically not flat, and an obvious, central prominence of medullated nerve fibers can be seen in some dogs, particularly Golden Retrievers and German Shepherds. In the center of the ONH a small, round, gray depression is commonly present, known as the physiologic pit; this represents the origin of the hyaloid vasculature.

The color of the ONH varies from pinkish white to deep pink, depending on the extent of the vasculature. The usually incompletely exposed venous circle is seated on the ONH, and the course of the vessels from this circle to the superficial venules of the fundus can help to determine the topography of the ONH.

Retinal Vasculature

The vascular architecture of the canine fundus is classified as holangiotic. The vasculature consists of arterioles and venules located within or vitread to the nerve fiber layer of the retina. The diameter of the vessels decreases with increasing distance from the ONH, but otherwise no differences should be observed with location.

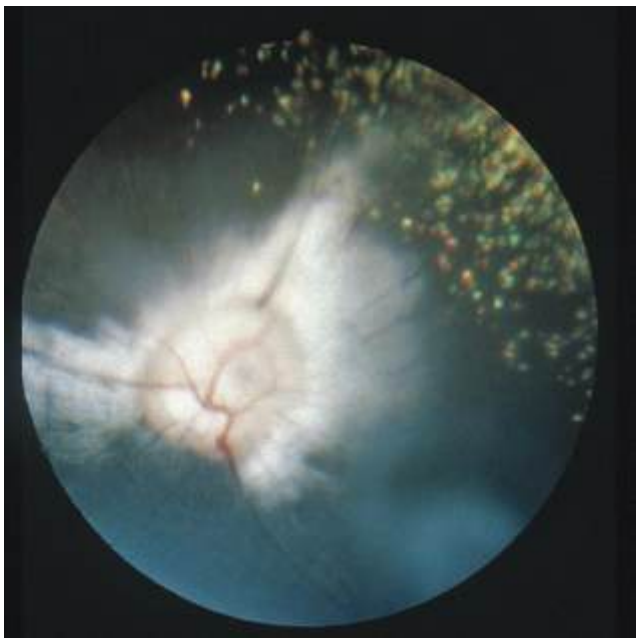


Figure 25.5 Extensive myelination of the optic nerve head in a 7-year-old Miniature Poodle. The dog also has progressive rod-cone degeneration.

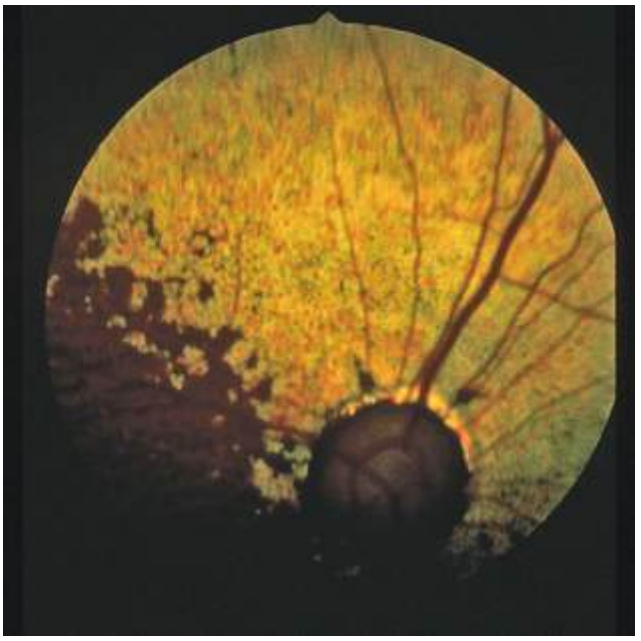


Figure 25.6 There is a distinct reflective zone or "conus" at the border of the optic nerve head in a 5-year-old Miniature Poodle.

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The arterioles (usually 15–20 in number) radiate away from their origin close to the periphery of the ONH. They appear slightly lighter in color compared with the vessels transporting venous blood and they may be more tortuous than the venules. The main veins (usually 3 or 4 in number) are obviously larger and darker red in color than the arterioles. They end in the venous circle on the ONH but may, in part, be covered by the ONH tissue. Several smaller venules coalesce with the major veins, thereby building a branching tree of vessels over the optic fundus. The area centralis is an indistinctly bordered area slightly superior and about two ONH diameters temporal to the ONH, which is devoid of blood vessels but encircled by fine branches (Mowat et al., 2008).

In a dog with a poorly pigmented or subalbinotic fundus, the choroidal blood vessels are readily visible. They are brick-colored and radiate out from the ONH in a regular pattern. Wider sinusoidal veins separated by narrower arterioles can be seen. The edges of the choroidal vessels usually appear less distinct than the retinal vessels.

Development of the Canine Fundus

The fundus undergoes marked changes in appearance during development. Examination of puppies less than 2 weeks of age is precluded by fusion of the eyelids until this point, and a relative lack of clarity of the ocular media, particularly the cornea. At eyelid opening, the fundus is gray in color; the ONH is small and round due to immature myelination. The retinal blood vessels are easily identifiable and appear relatively large in size. The developing tapetum causes the dorsal fundus to initially appear paler at 3–4 weeks of age, then takes on a blue to lilac coloration, intensifying with age. After 7–8 weeks of age, the tapetum is more granular in appearance, becoming more brightly colored. A mature tapetum is present by approximately 3–4 months of age (Fig. 25.7). Speed of development varies between individuals, even within the same litter.

Retinal differentiation and maturation (mainly of the photoreceptors) in dogs are complete by 7–8 weeks of age. At the end of this period, the retina, as monitored by ERG and both light and electron microscopy, is adult-like (Acland & Aguirre, 1987; Aguirre et al., 1972; Gum et al., 1984; Parry, 1953).

Developmental Anomalies

Congenital abnormalities of the eye can either be hereditary or nonhereditary.

Collie Eye Anomaly

Collie eye anomaly (CEA) is a congenital ocular syndrome involving defects of the posterior vascular and fibrous tunics of the eye. The pathogenesis of the defect is considered to be an abnormal mesodermal differentiation, which results in defects, mainly of the sclera, choroid, optic disc, retina, and retinal vasculature. The severity of the disease varies from no apparent visual deficit to total blindness. CEA is bilateral and has no sex predisposition. There is no difference in frequency related to coat color, type of coat, or presence of the merling gene (Rubin, 1989). The cardinal sign is a geographically defined region of choroidal hypoplasia temporal to the optic disc, which may be accompanied by obvious retinal or scleral defects or by optic disc or adjacent colobomas. Other anomalies can include retinal detachment and intraocular hemorrhage. CEA affects primarily the Collie breeds among others: Rough and Smooth Collie, Shetland Sheepdog, Australian Shepherd, Border Collie, Nova Scotia Duck Tolling Retriever, Longhaired Whippet, Boykin Spaniel, and Lancaster Heeler (Bedford, 1998; Genetics Committee of the American College of Veterinary Ophthalmologists, 2015; Parker et al., 2007). More recently it has been described in the Japanese Hokkaido Inu (Mizukami et al., 2012). Prevalence of CEA was historically reported to be high in certain Collie breeds: in 1969 the incidence of CEA in the Rough and Smooth Collie was between 75% and 97% in the United States (Donovan et al., 1969; Roberts, 1969), but due to selective breeding practices, prevalence decreased within a few years to 59% (Yakely, 1972). Later studies have shown a frequency of 64% among Collies in England (Bedford, 1982a), greater than 50% in Sweden (Wikström, 1986), and 41% in Norway (Bjerkas, 1991). High prevalence has also been reported in Shetland Sheepdogs (Bedford, 1982a) and Lancashire Heelers (Bedford, 1998), although prevalence



Figure 25.7 Maturation of the canine fundus. **A**. 5 weeks of age. **B**. 9 weeks of age. **C**. 12 weeks of age.

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may vary by country. CEA is reportedly rare in Border Collies, who comprise less than 1% of screened individuals in Norway (Grosås et al., 2017). Data obtained (S. Pearce-Kelling, personal communication, 2018) from a DNA testing laboratory based in the USA (OptiGen, Ithaca, NY, USA) show that the most commonly homozygous affected breeds in 2017 were the Collie (25%) followed by the Shetland Sheepdog (9%). According to these data, the percentage of submitted samples that were homozygous affected did not change considerably between 2013 and 2017, but the percentage of homozygous normal dogs in the Collie breed increased from 32% in 2013 to 41% in 2017, possibly indicating that selective breeding practices are impacting the number of carrier animals. Considering the high allele frequency in many breeds, gene testing and selective breeding practices will have to continue for many more generations before the disease is eliminated.

A simple autosomal recessive mode of inheritance was originally postulated (Yakely et al., 1968) through a test breeding scheme. This inheritance pattern was further supported by the results of pedigree analysis and test matings (Bedford, 1982a). Further genetic studies established that the primary CEA phenotype, choroidal hypoplasia, segregated as an autosomal recessive trait with nearly 100% penetrance, with partial penetrance in some dogs heterozygous for the mutant allele (Lowe et al., 2003). The CEA locus was mapped to a 3.9 cM region of canine chromosome 37 and subsequently an intronic deletion in the DNA repair gene, nonhomologous end-joining factor 1 (*NHEJ1*), was identified (Parker et al., 2007). Part of the deleted region, although not a coding region, is very well conserved across species and may have a regulatory role, perhaps in NHEJ1 expression (Parker et al., 2007), although studies exploring the biochemical pathway causing retinal degeneration with NHEJ1 disruption are lacking. Subsequent studies have examined *NHEJ1* mutant allele frequency, and have shown correlation between genotype and phenotype in Japanese Hokkaido Inu dogs (Mizukami et al., 2012), Norwegian Border Collies (Grosås et al., 2017), and Danish Shetland Sheepdogs (Fredholm et al., 2016). However, genotype/phenotype discordance has been described in Danish Rough Collies (Fredholm et al., 2016), limiting the utility of the mutation test in this population. In addition, CEA-like disease combined with anterior segment changes in Soft-coated Wheaten terriers (van der Woerdt et al., 1995) is not associated with the *NHEJ1* deletion, suggesting that other gene defects may cause a similar condition (Parker et al., 2007), or that the deletion is merely a marker for a causative mutation. Some investigators have suggested that a different gene mutation may cause optic nerve coloboma, perhaps inherited in a dominant manner (Donovan et al., 1969), and others have postulated a polygenic inheritance (Wallin-Hakanson et al., 2000a, 2000b). Further evidence supporting multiple gene involvement in aspects of CEA was provided in a recent study of Nova Scotia Duck Tolling Retrievers, in which optic nerve coloboma did not segregate with the described *NHEJ1* deletion (Brown et al., 2018). Due to the discrepancy in genotype/phenotype correlation in certain breeds, it is recommended that both ophthalmic screening and genetic testing are utilized to diagnose CEA in dogs.

Clinical Findings

Clinical findings in CEA include a high degree of pleomorphism. In a single litter there may be variation in the severity of the changes, and there may be variation between the eyes of an affected individual. Choroidal hypoplasia is considered the diagnostic lesion for CEA and is always bilateral, although the extent of the lesion may vary between eyes. The four main defects included in the CEA syndrome are:

- Choroidal hypoplasia
- Posterior polar colobomas
- Partial or complete retinal detachments
- Intraocular hyphema.

The latter two are often regarded as complications of large colobomas. Other changes also included in this syndrome by some authors are excessive tortuosity of the retinal vasculature and retinal folds in young pups (Barrie et al., 1981). The CEA syndrome is most accurately diagnosed ophthalmoscopically in pups at 6–7 weeks of age, prior to any additional pigmentation that can mask the lesions.

Choroidal Hypoplasia

Choroidal hypoplasia is a bilateral, but often asymmetric, defect. The area involved is usually temporal or superotemporal to the optic disc, generally at the junction of the tapetal and nontapetal fundi, and can be from one to several disc diameters in size. Within this area, the choroidal vessels exhibit abnormalities in both form and distribution, being fewer, wider, and abnormal in their arrangement (Fig. 25.8). Thus, there is often a loss in this area of the normal radial pattern of vasculature relative to the optic disc. The choroidal tissue can be visualized, because there is an associated lack of pigment in the overlying RPE in the nontapetal fundus and a focal absence of tapetal tissue in the tapetal fundus. The white scleral tissue is visualized through the abnormal choroid, giving the defect a whitish appearance. The diagnosis of choroidal hypoplasia can be difficult in eyes with albinotic or subalbinotic fundi in dogs with merle coats, especially if there is a patchy absence of pigment that coincides with the specific area where choroidal hypoplasia occurs. In such cases, specific assessment of the choroidal vasculature in the temporal region of the optic disc must be performed. This is, however, often a difficult and highly subjective evaluation.

Mild defects with choroidal hypoplasia observed at 5–7 weeks of age can become masked by the development of more pigment in the RPE as the dog grows older. Such cases are

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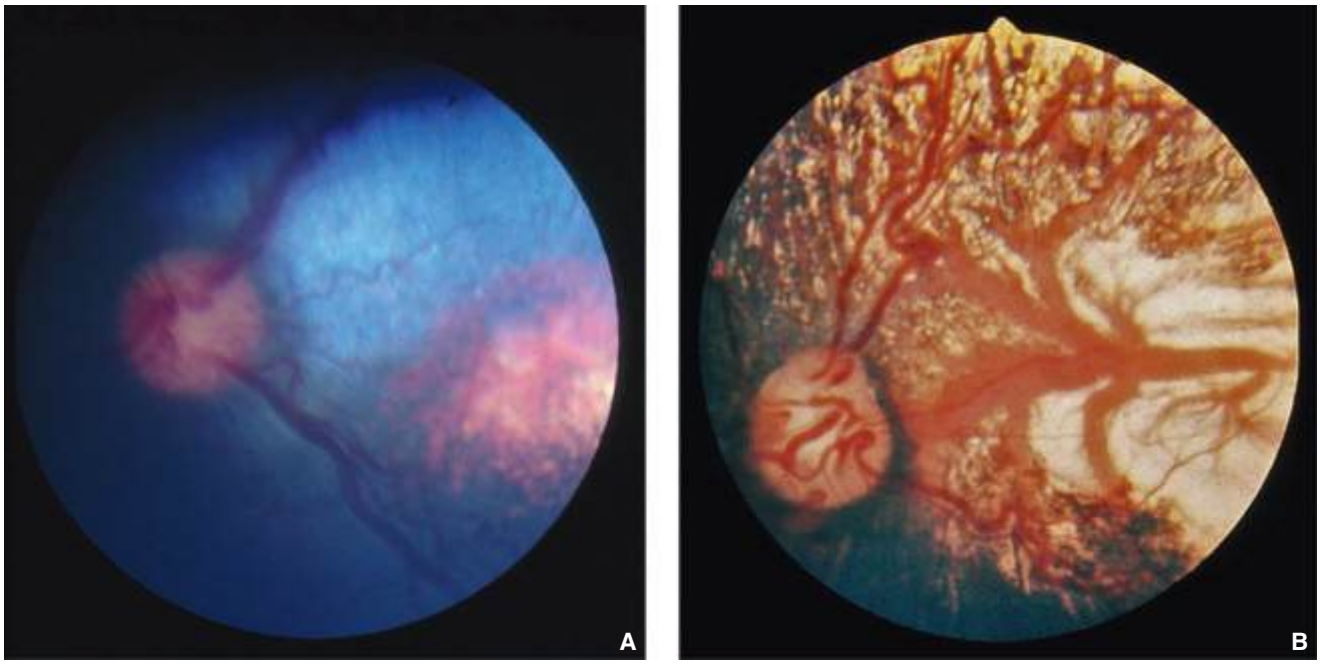


Figure 25.8 **A**. Choroidal hypoplasia temporal to the optic disc in a 6-week-old puppy, an optimal age to detect this lesion. (Courtesy of Michigan State University Comparative Ophthalmology Service.) **B**. A large area of temporal choroidal hypoplasia is visible in this 2-year-old Shetland Sheepdog. (Courtesy of Dr. Lennart Garmer.)

often referred to as "go-normals," and this phenomenon happens frequently. In one study (Bjerkas, 1991), 22 puppies were diagnosed with mild choroidal hypoplasia before 3 months of age, and 15 of these had ophthalmoscopically normal fundi at reexamination several months later. Another study (Buening & Erhardt, 2002) showed that the frequency of CEA was dependent on age, and this was hypothesized to be due to a go-normal rate of 53% in Shelties and 63% in Collies.

Posterior Polar Colobomas

Colobomatous defects involving the ONH (i.e., papillary colobomas) or the adjacent area (i.e., peripapillary colobomas) are common in dogs with CEA (Fig. 25.9). They are most often situated inferior to or toward the nasal or temporal borders of the optic disc and are caused by ectasia of the cribriform plate or the peripapillary sclera. The papillary lesions are frequently seen as a gray or pink indentation, and they vary in size, from shallow depressions to more extensive excavations or "holes" up to 30 D in depth (Bedford, 1982a). Large colobomas may distort the area of the disc severely (Fig. 25.10). Colobomas are identified by the color of the lesion and the way the retinal vasculature changes course or disappears at the rim of the defect. Small colobomas, however, especially if they are shallow and located centrally in the ONH, may be confused with the normal physiologic pit.

In a large survey by Bedford in 1982, 34% of 2000 Rough Collies with choroidal hypoplasia had posterior polar colobomas that were mostly unilateral and sometimes bilateral (Bedford, 1982a). Another 24 dogs had unilateral or bilateral colobomas in the absence of choroidal hypoplasia, in which the diagnosis of CEA could not be confirmed. Several, or even most, of these dogs could be go-normals, but some could also be affected by primary colobomatous defects not associated with CEA, as was recently suggested to be the case in the Nova Scotia Duck Tolling Retriever, in which only 4 of 7 dogs diagnosed with optic nerve coloboma had clinical evidence of choroidal hypoplasia and only 3 of 7 were homozygous for the described *NHEJ1* deletion (Brown et al., 2018).

Retinal Detachment

Large ONH colobomas predispose to retinal detachment (Fig. 25.11), occurring more commonly unilaterally than bilaterally. Early onset is most common, but they may also occur in adulthood, presumably due to vitreous degeneration and liquefaction predisposing to elevation and tearing of the retina. Early-onset large detachment may result in signs of amblyopia such as nystagmus or strabismus. Typically, retinal detachments arise adjacent to the ONH and may extend peripherally. Associated subretinal, intraretinal, or preretinal hemorrhages may also be observed. Small detachments may be treated with barrier retinopexy, although large detachments require vitreoretinal surgical reattachment.

Intraocular Hemorrhage

Hemorrhage as a consequence of CEA is rare, and predisposing factors are considered to be colobomatous defects and retinal detachments. In some cases, preretinal looping

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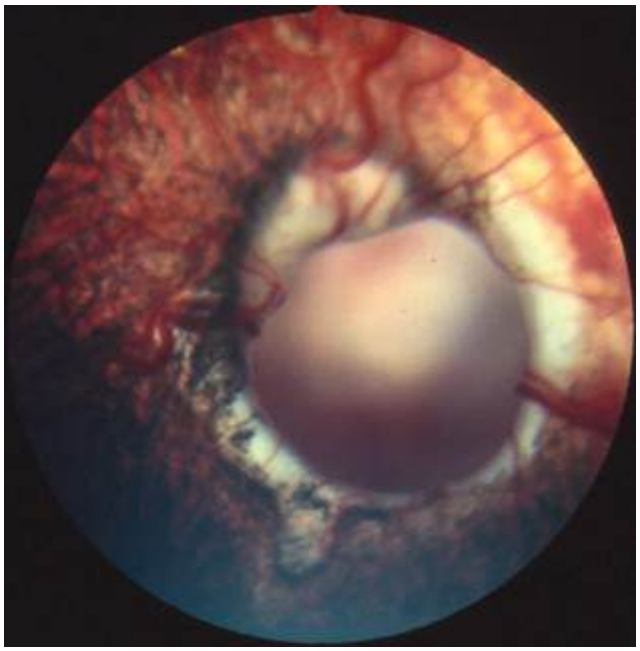


Figure 25.9 Typical coloboma in a Rough Collie with Collie eye anomaly. (Courtesy of Michigan State University Comparative Ophthalmology Service.)

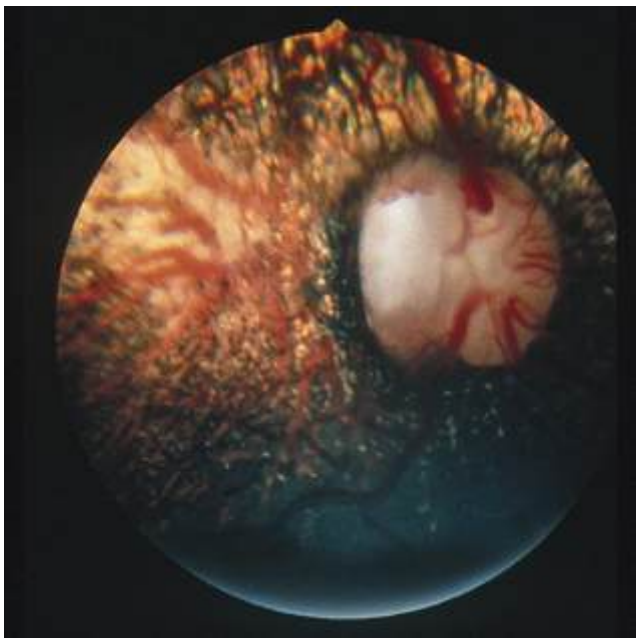


Figure 25.10 Coloboma in conjunction with a partially deformed disc and choroidal hypoplasia in a 2-year-old Collie.

of major vessels may be seen, particularly in association with large colobomatous defects (Bedford, 1982a). The fragility of the vessels may result in hemorrhage, which passes through the vitreous and into the aqueous fluid, resulting in hyphema (Barrie et al., 1981). Persistent hemorrhage may predispose to secondary glaucoma.

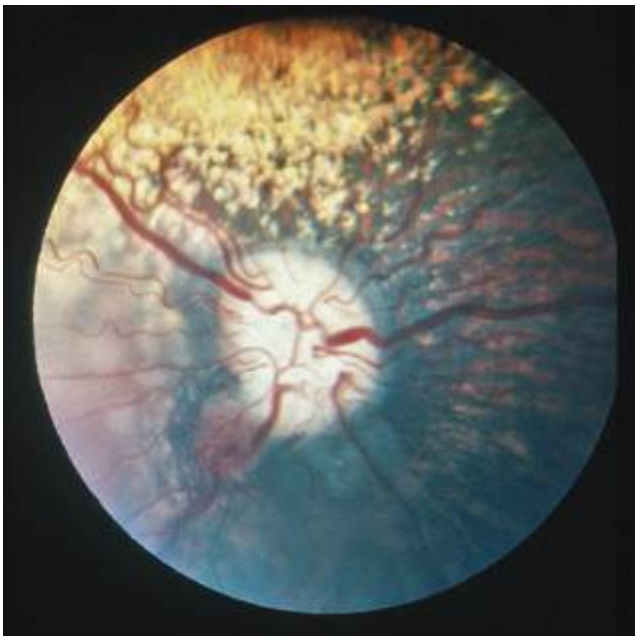


Figure 25.11 Retinal detachment is part of the Collie eye anomaly complex. Partial retinal detachments near the disc as well as vascular abnormalities in a young Collie.

Excessive tortuosity of retinal vessels is commonly present in eyes with CEA, but is commonly appreciated in normal eyes as well, and therefore is not considered a diagnostic feature of CEA.

Other Clinical Findings

Vermiform streaks or rosettes are folds in the neurosensory retina of the neonate, which arise because of the unequal growth of the sclera, the choroid, and the retinal layers. They are seen as linear or circular, grayish (in the tapetal area) or white (in the nontapetal area) configurations, usually in the central fundus and most commonly near the ONH (Fig. 25.12). These neuroretinal folds are seen in both normal and affected dogs and therefore are not diagnostic for CEA. Their frequency, however, may be greater in dogs affected with other congenital defects, such as CEA.

Microphthalmia has sometimes been claimed, though not proven, to be part of the CEA syndrome. It results from a selective breeding practice, favoring Collies with small eyes. This selection pressure might favor a high incidence of CEA in Collies compared with Border Collies, in which the frequency of CEA is low and the eyes are comparably larger (Barrie et al., 1981). Secondary glaucoma can be a sequel to retinal detachment or intraocular hemorrhage.

Histopathologic Findings

In dogs with choroidal hypoplasia, there is a marked thinning of the choroid in the area, with a decrease in melanocytes and hypoplasia or an absence of tapetal cells. In mild

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Figure 25.12 Multiple retinal folds in a 7-week-old Collie puppy with an otherwise normal fundus.

lesions, the RPE may show only a focal absence of pigment. It is only in severe cases of choroidal hypoplasia that the neural retina is also affected. The RPE then is often hypertrophied and hyperplastic, and the neural retina is thin, with cyst formation in inner layers and vacuolization of the ganglion cells. In some eyes, the outer nuclear layer is reduced in thickness, thus indicating a reduced number of photoreceptors in the area (Roberts et al., 1966a, 1966b).

Colobomas may originate embryologically from deformities in the primitive epithelial papilla or from defects in the fetal fissure. If localized in the optic disc, they represent a focal absence of tissue in the ONH. The retina overlying peripapillary colobomas is attenuated, and the outer nuclear layer may be absent. In extremely large colobomas, the RPE and choroid may be lacking, and the sclera is thin. Posterior ectatic areas may originate from orbital cysts, which result from a primary defect in the neuroectoderm/mesenchyme when the optic fissure is closing. There is protrusion of the inner retinal layers, because they develop more rapidly than the outer layers, through the fissure. The fissure cannot close in a normal way, and a cyst lined with retinal tissue develops. Retinal duplication in the region of the embryonic fissure may result from eversion of the inner retinal layer of the optic cup or from abnormal differentiation of the RPE. The most common defect, which has been observed after 28 days of gestation (Latshaw et al., 1969), is rosette-like structures near the optic disc in the region of the optic fissure. Such rosettes may result from abnormal differentiation of the RPE. Epithelial layers of cells and rosettes that prevent normal interaction of the inner and outer retinal layers and interfere with proper development and differentiation may cause the defect in the optic vesicle.

Problems in Diagnosis, Interpretation, and Control

The previously described lack of correlation between *NHEJ1* intronic deletion genotype and CEA phenotype in certain breeds necessitates careful breeding advice in an animal with visible choroidal hypoplasia or optic nerve coloboma, without the *NHEJ1* deletion. Until further work is completed, a combination of both genetic and ophthalmic examination testing is recommended in CEA-susceptible breeds. The high incidence of CEA in some breeds dictates that breeders should only attempt to reduce the disease and mutation incidence within the breed over several generations. Restricting breeding to dogs homozygous for the normal *NHEJ1* allele would limit the gene pool, possibly leading to loss of desirable features from the breed, and even leading to the emergence of a new hereditary disease that was present at low frequency within the breed.

Difficulties in trying to eliminate CEA by ophthalmoscopic screening have been partly due to certain problems in diagnosis. The go-normal phenomenon was a major issue, with affected animals being indistinguishable from unaffected animals by ophthalmoscopic examination, as described previously. Another problem of diagnosis is the differentiation between a small, centrally located coloboma in the optic disc and a normal physiologic pit. These two entities are sometimes very difficult to differentiate ophthalmoscopically, although OCT might be utilized to explore this in future studies. Another variation in the dog occurs in the degree of myelination of nerve fibers as they form the ONH. Cessation of myelin growth at the level of the scleral lamina cribrosa may give the impression of a uniformly recessed ONH, which could be diagnosed as a broad, shallow coloboma.

The location of colobomas at the ONH has been another problem because of differences in opinion between examiners. In CEA, colobomas are frequently seen at the nasal or temporal border of the ONH (i.e., “atypical” colobomas). The existence of a “typical” coloboma in the 6 o’clock position as the only finding in a Collie raises the question whether it is a go-normal dog with a typical coloboma and therefore should be considered as CEA affected, or whether the coloboma is unrelated to CEA.

Color-dilute animals can also cause problems in making an ophthalmoscopic diagnosis of CEA when only mild choroidal hypoplasia is present. In merles, it is important to closely evaluate the area temporal to the optic disc for changes due to choroidal hypoplasia. Inexperienced examiners may fail to recognize slight vascular changes temporal to the ONH and thus may incorrectly consider the animal to be normal. Others may erroneously classify a color-dilute animal as abnormal because there is a lack of pigment nasally to the optic disc. A lack of pigment temporally to the optic disc may, however, indicate choroidal hypoplasia.

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Merle Ocular Dysgenesis

The Australian Shepherd breed of dog and other breeds in which merling is common (e.g., Great Dane, Dachshund, Collie) are affected by multiple ocular anomalies (Gelatt & McGill, 1973; Gelatt & Veith, 1970). Affected dogs usually have a lot of white coat coloration (homozygous merle) and typically show microphthalmia to a varying extent. The defect is associated with microcornea of an irregular shape and, infrequently, with mineralization of the anterior corneal stroma. Affected dogs also commonly exhibit heterochromia iridis with dyscoria and corectopia with an oval pupil in which the long axis is vertical. The hypoplastic irides permit transillumination and respond poorly to mydriatics. Persistent pupillary membranes are reported to occur. False polycoria can occur in affected dogs. Often, the hypoplasia extends into the iridocorneal angle and posteriorly into the ciliary body. Cataracts, which are relatively common, can preclude examination of the posterior segment. Large equatorial staphylomas occur either as a single depression or several small excavations grouped together. The choroidal vasculature is greatly reduced or absent in the staphylomas, and the sclera is irregular and thin. Large staphylomas may extend from the ora ciliaris retinae to the ONH. Retinal and choroidal vasculature in the staphylomas may be markedly reduced or even absent (Fig. 25.13). Complete retinal detachment is reported, in addition to intraocular hemorrhage.

It has been shown that the posterior defects in affected Australian Shepherds are the result of a primary dysplasia of the outer layer of the optic cup, the future RPE (Cook et al., 1991). Failure of normal RPE development leads to failure of differentiation of the adjacent retina and periocular mesenchyme to form choroid and sclera. The neurosensory retina is usually normal, but the tapetum is either absent or only a few cells thick. The RPE contains few melanin granules as well, but the defect is not related to failure of melanization. In the staphylomas, the retina is reduced to thin glial membranes, and the sclera and choroid are markedly thin. The vitreous is often liquefied in affected dogs, and development of the secondary vitreous is usually absent (Cook et al., 1991). Failure of normal RPE development leads to failure of differentiation of the adjacent retina and periocular mesenchyme to form choroid and sclera. The neurosensory retina is usually normal, but the tapetum is either absent or only a few cells thick. The RPE contains few melanin granules as well, but the defect is not related to failure of melanization. In the staphylomas, the retina is reduced to thin glial membranes, and the sclera and choroid are markedly thin. The vitreous is often liquefied in affected dogs, and development of the secondary vitreous is usually absent.

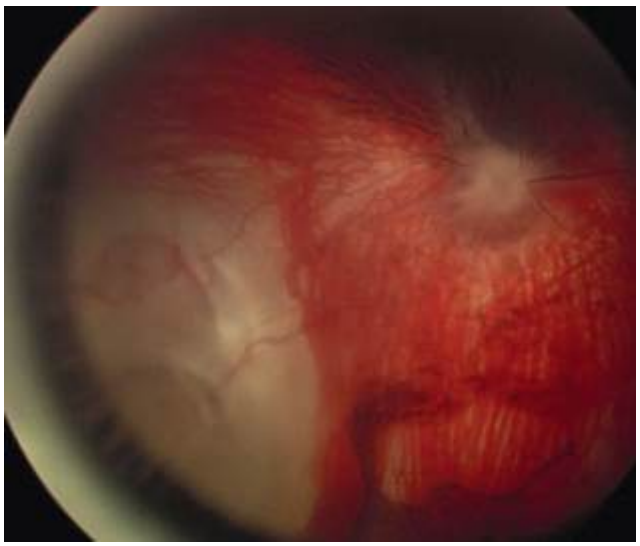


Figure 25.13 Merle ocular dysgenesis in an adult Collie dog. A large temporal scleral staphyloma is present, with profound choroidal dysplasia/hypoplasia overlying this area.

Although proposed to be inherited as an autosomal recessive trait with incomplete penetrance (Gelatt et al., 1981), the inheritance of merle ocular dysgenesis (MOD) has not been fully defined. The merle mutation (in the *SILV* gene) is inherited as a dominant trait with incomplete penetrance (Clark et al., 2006). The inheritance pattern of MOD may be similar to deafness in double merle-mutant dogs. In one study, 25% of double merle-mutant dogs were deaf, compared with 3.5% of single merle-mutant dogs, indicating that deafness is incompletely penetrant and potentially could be inherited in a dominant manner (Strain et al., 2009). A study in Border Collies has shown a high degree of correlation between heterochromia iridis and sensorineural deafness (De Risio et al., 2011).

Retinal Dysplasia

Retinal dysplasia has been defined as an anomalous differentiation of the retina accompanied by a proliferation of one or more of its constituent elements (Duke-Elder, 1963). It is a heterogenous group of conditions that present with a range of severity of lesions, from those that have no effect on vision to those that result in blindness. In some forms, retinal dysplasia lesions are present in an otherwise normal eye, while in others, they may accompany ocular malformations such as multiple ocular defects, including microphthalmos with persistent pupillary membrane or persistent hyperplastic primary vitreous. Syndromic forms of retinal dysplasia also occur where retinal lesions are accompanied by abnormalities such as skeletal dysplasia and dwarfism. Hereditary retinal dysplasia is recognized in many breeds of dogs, but dysplastic retinal lesions may also result from environmental factors including viral infection, vitamin A deficiency, X-ray irradiation, drugs, and intrauterine trauma.

Retinal dysplasia has been divided into three categories based on the severity of the retinal lesions:

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- The mildest form is called multifocal retinal dysplasia and does not have a detectable effect on vision.
- The second category is described as geographic retinal dysplasia, recognizing the larger map-like lesions that are present. This can lead to areas of retinal degeneration and in some instances retinal detachment, and therefore is expected to have a more profound effect on vision.
- The third is total retinal dysplasia or vitreoretinal dysplasia. This is the most severe form and is characterized by detachment of the retina. In some breeds this is a syndromic condition accompanied by skeletal abnormalities.

Mechanisms Underlying Lesion Development

The pathogenesis for spontaneous retinal dysplasia may vary. Silverstein and colleagues (Silverstein et al., 1971) proposed four different mechanisms:

- Hyperplastic extension of the neural retina into abnormal sites away from the RPE.
- Dysplastic processes within the neural retina that is detached from the RPE.
- Occurring in neuroretinal areas devoid of RPE (i.e., colobomas).
- Dysplastic processes in most or all of the neural retina, or only focal areas, without evidence of separation from the pigment epithelium.

The last mechanism could possibly involve defects in the pigment epithelium itself, because this structure has been shown to be important during retinal development (Silverstein et al., 1971; Vollmer & Layer, 1986).

Multifocal Retinal Dysplasia

With this form of retinal dysplasia, the lesions consist of what are described on ophthalmoscopic examination as retinal "folds." These are areas of reduced tapetal reflectivity, appearing as gray or green dots, linear or curvilinear streaks (or V- or Y-shaped streaks). They may occur anywhere in the tapetal region, but are most frequent in the central region of the fundus, around the dorsal retinal vessels (Fig. 25.14 and Fig. 25.15). Sometimes, the folds may appear elevated and distort the course of the overlying vessels. With some lesions tapetal, hyperreflectivity adjacent to the "fold" may develop. Retinal folds in the nontapetal fundus can also occur and appear as gray or white, linear or irregular streaks. This form of retinal dysplasia occurs in several different breeds of dog and in many instances is considered to be inherited (see Genetics Committee of the American College of Veterinary Ophthalmologists, 2015 for the reported incidence in different breeds of dog). Breeds reported in the literature include American Cocker Spaniel (Macmillan & Lipton, 1978), Beagle (Heywood & Wells, 1970), Golden Retriever (Crispin et al., 1999), Labrador Retriever (Nelson & Macmillan, 1983) and Rottweiler (Bedford, 1982b). The lesions can be detected in puppies at a few weeks of age. In some breeds, including the Rough Collie and Shetland Sheepdogs, retinal folds may disappear or become less apparent as the animals mature. When investigated by OCT or histology, the ophthalmoscopic "folds" may be seen to be true folds, where an otherwise normal retina is thrown into folds, or to actually be rosettes. Rosettes are where there is a localized duplication of retinal layers surrounding a lumen that results in an

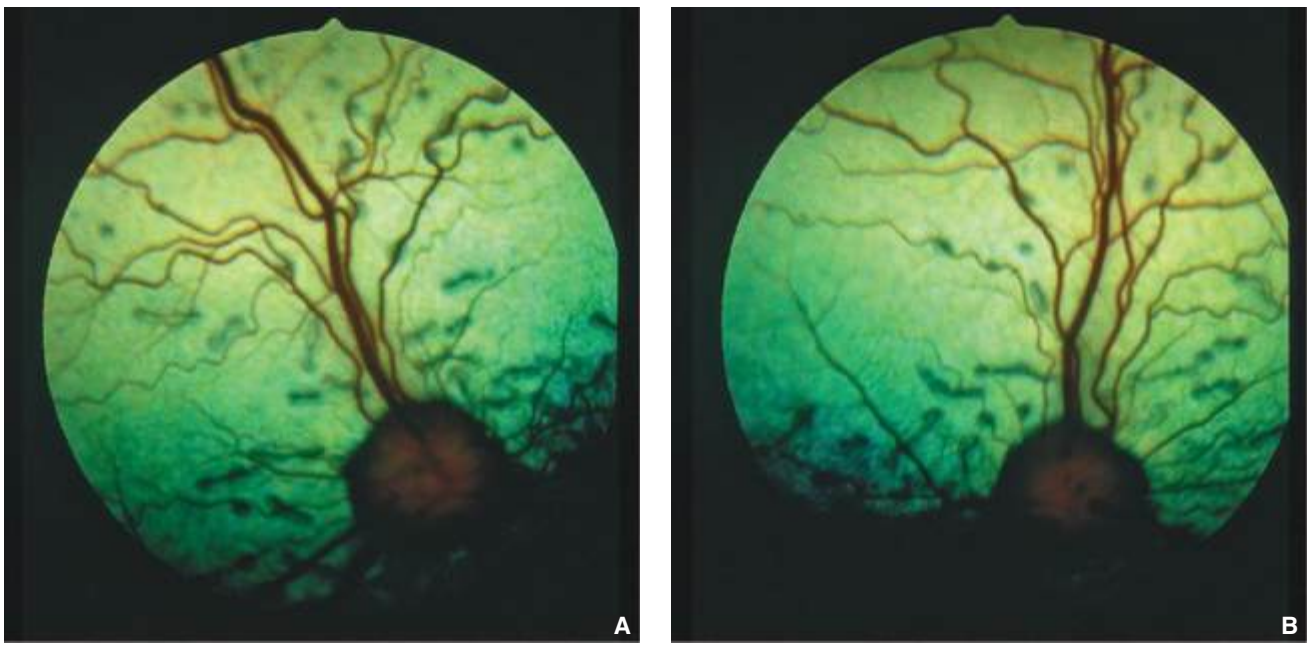


Figure 25.14 Bilateral multifocal retinal dysplasia in a 1-year-old Labrador Retriever. Several grayish, hyporeflective streaks and spots are seen in the tapetal fundus. **A**. Right eye. **B**. Left eye.

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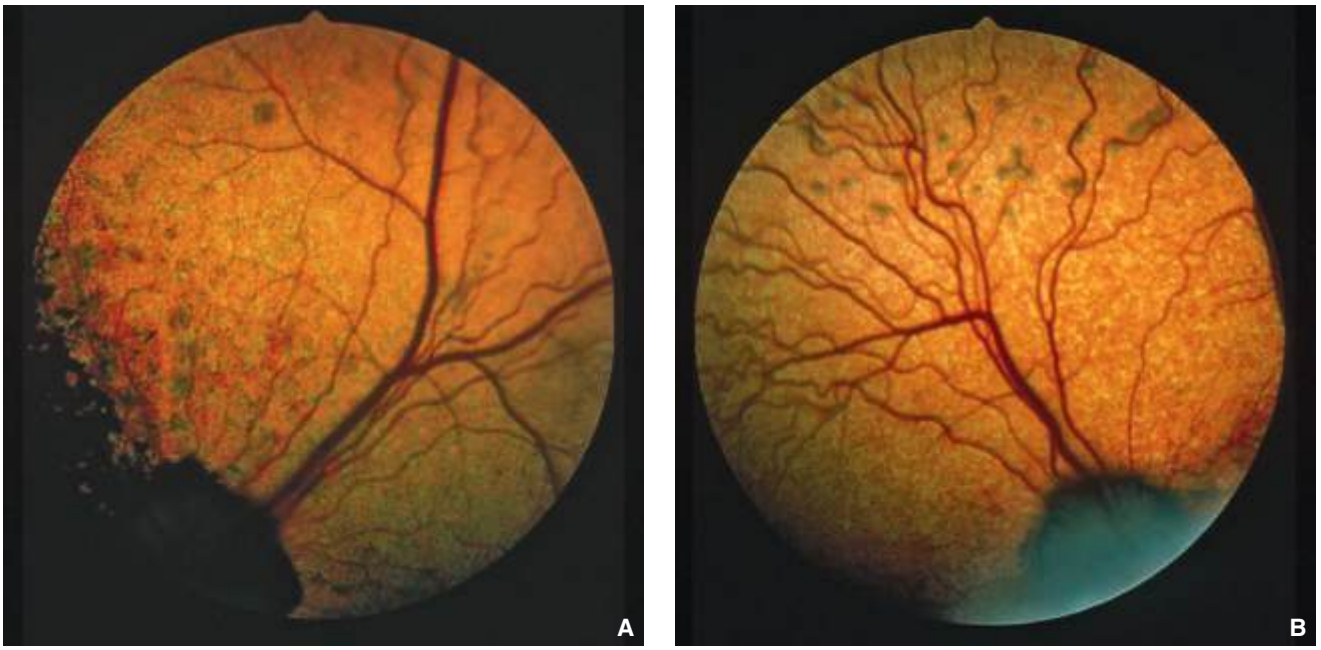


Figure 25.15 Focal and multifocal retinal dysplasia in a 6-year-old Springer Spaniel with no visual problems. **A**. Right eye, with a focal, small dysplastic lesion in the midperipheral tapetal fundus. **B**. Left eye, with multifocal lesions that are dot-, streak-, and Y-shaped in the tapetal fundus near the major blood vessels.

appearance on retinal sections reminiscent of a rosette. Commonly it is the outer nuclear layer that is duplicated, with photoreceptor inner and outer segments protruding into the lumen from the surrounding cell bodies (Fig 25.16). Studies in American Cocker Spaniels (Macmillan & Lipton, 1978) and Golden Retrievers (Long & Crispin, 1999) suggested, but did not prove, a recessive mode of inheritance. A genome-wide association study in American Cocker Spaniels reported an association of retinal dysplasia with a locus on canine chromosome 22 (Ahonen & Lohi, 2013).

A study of canine multifocal retinopathy type 3 (*cmr3*) in Lapponian Herders revealed a spectrum of retinal diseases within the breed, leading the authors to suggest that a mild manifestation of *cmr3* may manifest as multifocal retinal dysplasia (Zangerl et al., 2010), but this remains to be proven. With the exception of this possibility, the gene mutations underlying inherited multifocal retinal dysplasia are still to be identified.

Geographic Retinal Dysplasia

In geographic retinal dysplasia (Fig. 25.17), the lesion consists of an irregular or horseshoe-shaped area, typically among the blood vessels dorsal to the ONH. The lesion may have areas of both retinal thinning and retinal thickening and elevation. Usually, there is a demarcation zone between the lesion and adjacent normal retina that may appear gray. Frequently, there are hyperreflective parts, often in streaks, indicative of focal neuroretinal degeneration. With time, the focal or streak-like areas with pigmentation may increase, which indicates RPE hypertrophy or hyperplasia in the dysplastic area. The central part of the geographic dysplasia may stay slightly elevated (i.e., the neuroretina is partially detached). This form of retinal dysplasia has been described in several breeds of dog and may differ in appearance between breeds.

The formation of lesions during retinal development has been studied in detail in the English Springer Spaniel. In this breed, the condition is inherited in an autosomal recessive manner (Schmidt et al., 1979). Lesions are typically dorsal to the ONH and in young animals may appear as retinal folds accompanied by larger regions of tapetal hyporeflectivity due to retinal thickening. With progression these areas may thin, resulting in areas of retinal atrophy with central dark pigmentation (Fig. 25.18) (Lavach et al., 1978). Focal areas of retinal detachment may occur and in some dogs total retinal detachment develops (Lavach et al., 1978; O'Toole et al., 1983). Changes were detected by 45–50 days of gestation and consisted of retinal folds and disorganization of neuroblasts within the retina and subretinal space and the formation of mutilayered rosettes (Whiteley, 1991). There was focal loss of cell junctions forming the external limiting membrane, with an early decrease in the number of gap junctions (Whiteley, 1991; Whiteley & Young, 1986). Further studies have shown differences in intramembranous particle density and filipin binding to sterols in affected dogs compared with age-matched controls, as well as changes that may relate to the formation of retinal folds and disorganized dysplastic retinal proliferation (Whiteley et al., 1991). Retinal blood vessels

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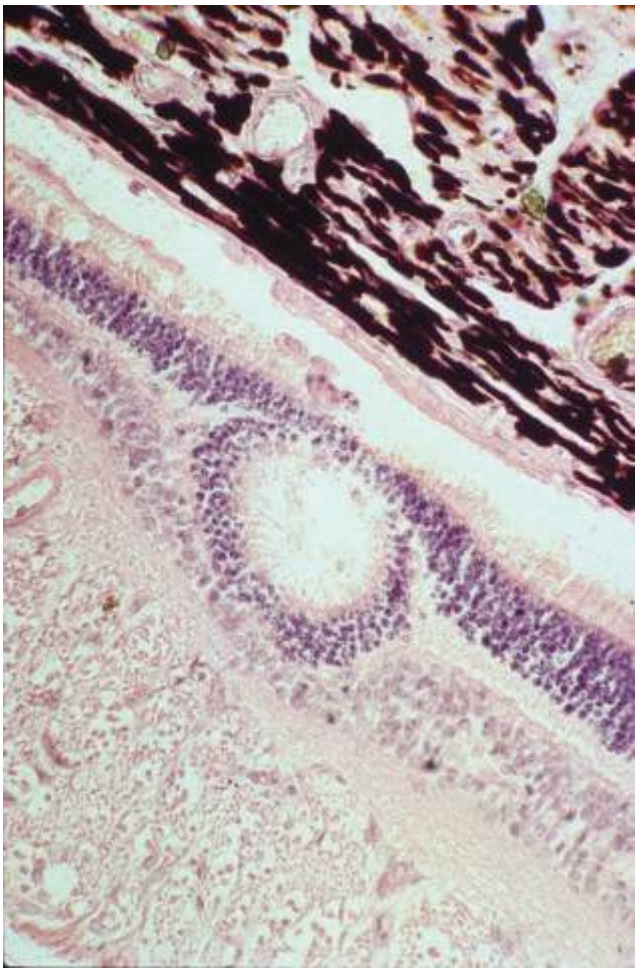


Figure 25.16 A retinal fold was observed upon routine ophthalmoscopy in the central fundus of a 7-week-old Cavalier King Charles Spaniel with no visual problems. Histology showed a one-layered rosette.

were found to extend into the dysplastic lesions in some instances and small areas of subretinal hemorrhage were present in affected embryos (Whiteley, 1991) and neonates (O'Toole et al., 1983). Histology of affected English Springer Spaniels from 1 day to 4 years of age showed that neonates had complex folds associated with subretinal capillaries and focal lack of the outer limiting membrane. There was focal or complete retinal detachment in some adolescent dogs and areas of retinal atrophy in adults, with some areas of RPE loss and even focal loss of the tapetum (O'Toole et al., 1983).

Geographic retinal dysplasia occurs in other breeds, including Cavalier King Charles Spaniel (personal observations; see Fig 25.17), and in one report the German Shepherd, Golden Retriever, and Labrador Retriever, and crosses between these three breeds (Holle et al., 1999). In these breeds the clinical presentation is somewhat different to that in the English Springer Spaniel. The lesions are most commonly circular or horse-shoe shaped and often within the

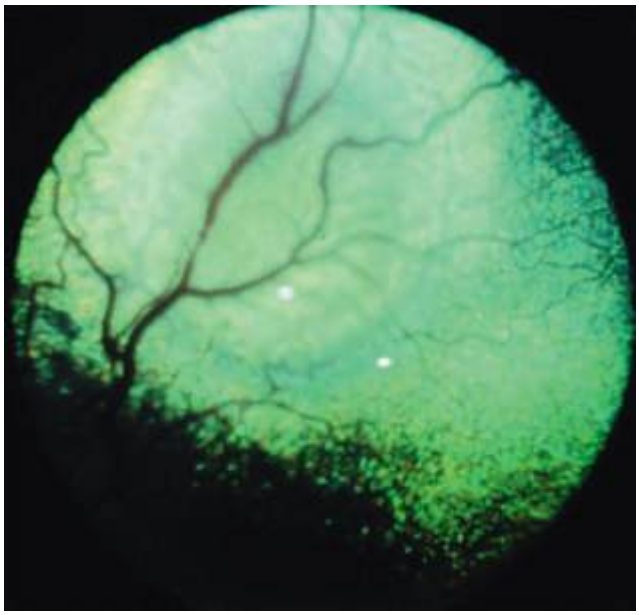


Figure 25.17 Geographic retinal dysplasia in a young Cavalier King Charles Spaniel. The lesion was among the dorsal retinal vasculature. The other eye had a similar lesion.

tapetal fundus dorsal to the ONH, although they can also occur in the nontapetal fundus. They frequently appear raised or thickened, resulting in a tapetal color change, and can be ringed by retinal folds. The dogs reported by Holle et al. (1999) were Seeing Eye dogs and typically had unilateral lesions, and in most instances these were not detected at the initial eye examination at 5–6 weeks of age, but had developed by a subsequent examination at between 5 months and 19 months of age. OCT examination of similarly affected dogs by the same authors reported that the raised lesions consisted of regions of disorganized inner retina (Guzman et al., 2014; Iwabe et al., 2020). The fact that in these breeds the major lesions appeared to develop after normal retinal maturation and involved the inner retina layers (although they were often surrounded by more typical retinal folds) led the authors to suggest that a different term other than retinal dysplasia might be more applicable for this condition.

Complete or Total Retinal Dysplasia

The most severe form of retinal dysplasia is associated with retinal nonattachment or detachment and resultant blindness. In some breeds retinal detachment may occur as a progression of geographic retinal dysplasia, and in others it is a result of vitroretinal dysplasia. Some breeds affected will have other congenital ocular abnormalities such as microphthalmos, and in others it occurs as a syndromic condition. Total retinal dysplasia, often in conjunction with other severe ocular defects, has been described in the Akita (Laratta et al., 1985), Australian Shepherd dog (Gelatt et al., 1970, 1973), Bedlington Terrier (Rubin, 1968), Chow Chow

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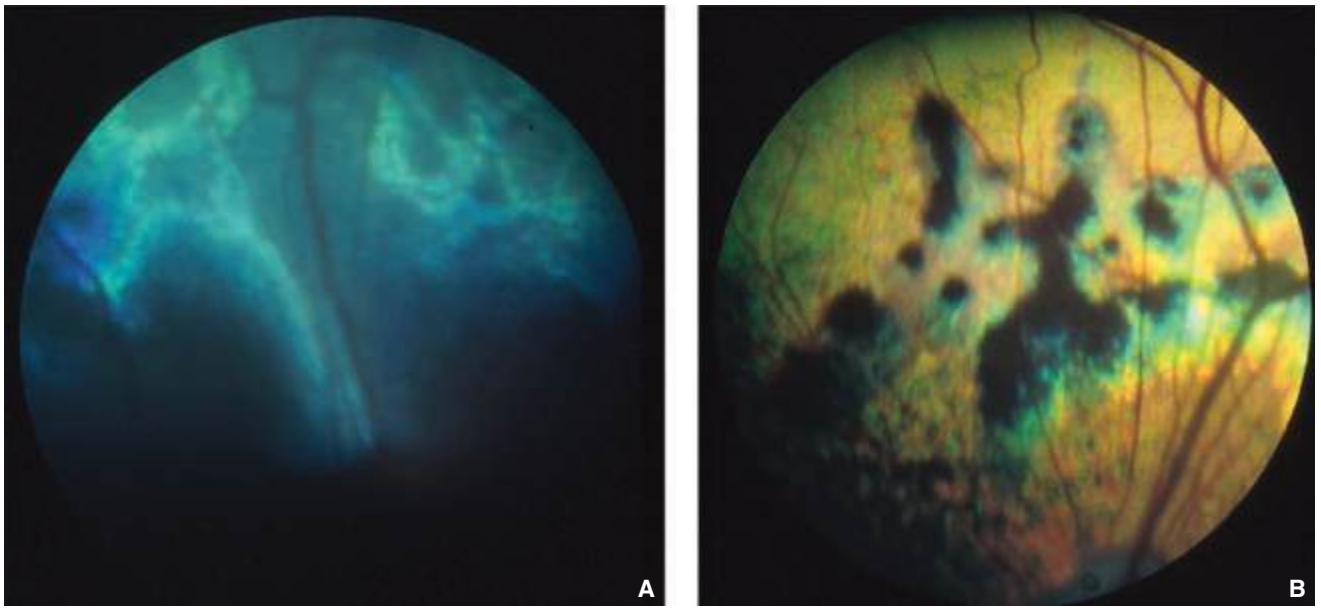


Figure 25.18 Geographic retinal dysplasia in English Springer Spaniels. **A**. The lesion in a puppy showing extensive thickening of the retina in the region dorsal to the optic nerve head. **B**. An adult Springer Spaniel showing areas of retinal thinning with pigmentation resulting from degeneration of geographic retinal dysplasia lesions.

(Collins et al., 1992), Doberman Pinscher (Bergsjö et al., 1984; Lewis et al., 1986; Peiffer & Fischer, 1983), Labrador Retriever (Barnett et al., 1970), Sealyham Terrier (Ashton et al., 1968), and Yorkshire Terrier (Stades, 1978).

In the Bedlington and Sealyham Terriers, the presenting signs may be esotropia, leukocoria, and blindness. Most affected dogs have infundibular (i.e., complete) retinal detachments. Parts of the retina may be attached to the posterior lens capsule, and there may be intraocular hemorrhage. In the Bedlington Terriers, the secondary vitreous is absent; therefore, the disease has been referred to as vitreoretinal dysplasia in this breed. Microphthalmia is not uncommon in conjunction with retinal dysplasia in Sealyham Terriers. In both breeds, an autosomal recessive trait for the defect has been postulated.

Canine Oculoskeletal Dysplasia: Dwarfism with Retinal Dysplasia

Labrador Retrievers (Carrig et al., 1977) and Samoyeds (Meyers et al., 1983) suffer from similar syndromic total retinal dysplasia where ocular lesions are accompanied by skeletal abnormalities (Fig. 25.19). The conditions in the two breeds were shown to be nonallelic and the locus names dwarfism associated with retinal dysplasia (*drd*) proposed, with the condition in Labradors being *drd1* and that in Samoyeds being *drd2* (Du et al., 2000). A genome-wide mapping study using microsatellites followed by investigation of positional candidate genes suggested by the similarity to Stickler syndrome in humans led to identification of the causal mutations (Du et al., 2000; Pellegrini et al., 2002). *Drd1* in the Labrador results from a 1 bp insertion in codon 4 within exon 1 of *COL9A3*, resulting in a frame shift and a premature stop codon at codon 49. *Drd2* in the Samoyed results from a deletion of 1267 bp, which removes part of the 5′ untranslated region, exon 1, and part of exon 2 in *COL9A2* (Goldstein et al., 2010a).

The condition is autosomal recessive, with dogs homozygous for the mutation having both complete retinal dysplasia and skeletal dysplasia (Goldstein et al., 2010a). Ocular changes include retinal detachment (Fig. 25.20), present in many dogs by 6 weeks of age but developing subsequent to that age in some dogs. Vitreal liquefaction and radial cortical equatorial cataracts were also present (Carrig et al., 1977; Goldstein et al., 2010a). In a study reported by Blair et al. (1985a) of dogs with skeletal and ocular abnormalities, 11 of the 20 eyes examined had rhegmatogenous retinal detachments. The detachments appeared to be associated with vitreal liquefaction and traction. Some eyes also had persistent hyaloid vasculature, and marked axial myopia was present in two animals that were refracted. The eyes without retinal detachments had marked tapetal hypoplasia and reduced pigmentation of the RPE, allowing visualization of choroidal vasculature (Blair et al., 1985a, 1985b). Skeletal abnormalities were detectable in affected dogs from an early age. Elbow and coxofemoral joints were particularly affected. There was retarded growth of the radius and ulna, with varus and valgus deformities of the forelimbs, widening of the diaphyseal and metaphyseal regions, curvature of the radius, and flattening of the physeal border of the distal radial and ulnar metaphyses (Carrig et al., 1990). Affected

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Figure 25.19 Oculoskeletal dysplasia in a Labrador Retriever. **A**. Note the angular limb deformities. **B**. Bilateral cataract formation is obvious. **C**. Ocular ultrasound reveals the presence of retinal detachment.

puppies were noted to have a characteristic doming of the cranium, with a more pronounced facial stop and moderate exotropic strabismus (Carrig et al., 1977; Goldstein et al., 2010a).

Studies of a breeding colony of Labrador Retrievers in which oculoskeletal dysplasia was segregating found that less severe ocular abnormalities, including vitreal strands and multifocal retinal dysplasia, occurred in some heterozygous animals, leading to the suggestion that the ocular phenotype was dominant with incomplete penetrance while the skeletal defect was autosomal recessive (Carrig et al., 1988). Identification of the causal gene mutation enabled this hypothesis to be examined in more detail. As part of the studies reported by Goldstein et al. (2010a), they investigated Labrador Retrievers with retinal folds and those heterozygous for the *COL9A3* mutation. Of 22 dogs with folds, only one was heterozygous for the mutation and of 88 phenotypically normal dogs, 7 were carriers and 2 of 13 obligate carriers had retinal folds, while 11 were ophthalmoscopically normal. Statistical analysis failed to show any correlation between the multifocal retinal dysplasia phenotype and carrier status for the *COL9A3* mutation. Association of the presence of multifocal retinal dysplasia or vitreal abnormalities in Samoyeds that were carriers for the *COL9A2* deletion was statistically significant, but this requires further study. A recent study reported that the retinal folds in heterozygous

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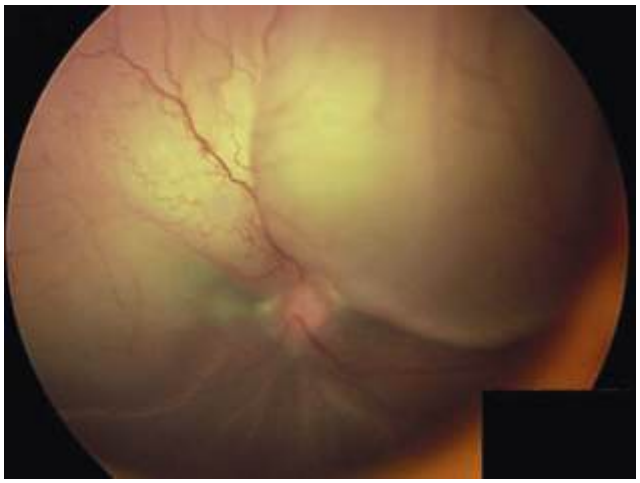


Figure 25.20 Total retinal dysplasia as part of oculoskeletal dysplasia in a Labrador Retriever puppy. There is a complete retinal detachment.

dogs had a specific perivascular distribution along the superior central vessels (Iwabe et al., 2020).

Retinal Dysplasia Associated with Short Stature

Retinal dysplasia ranging in severity from multifocal to total has been reported in American Pit Bull Terriers (Rodarte-Almeida et al., 2016). Segregation within a breeding colony suggested a possible autosomal-dominant mode of inheritance. The majority of affected dogs had geographic retinal dysplasia lesions and in some cases these progressed to retinal detachment. A few dogs only had multifocal retinal dysplasia lesions. The affected dogs had significantly shorter stature than unaffected controls, but radiographic examination of the limbs showed this was not a form of dwarfism. The dogs did not have the *drd1* or *drd2* gene mutations.

Inherited Retinal Dysplasia and Persistent Hyperplastic Primary Vitreous

A clinical syndrome of congenital retinal dysplasia and persistent primary vitreous has been described in the Miniature Schnauzer dog (Grahn et al., 2004). Test breeding suggested an autosomal recessive mode of inheritance. Of 24 dogs in the initial report, 13 had totally detached or nonattached retinas and 11 had marked dysplasia. One dog did not develop a retinal detachment until over 1 year of age. Those without total retinal detachment had dysplastic lesions extending nasal to temporal across the ONH, there could be detachment of those retinal regions, and the retina appeared noticeably thickened on ophthalmoscopy (Fig. 25.21). On histology, rosettes were identified in the nondetached regions. In those dogs without detachments, the retinal dysplasia lesions tended to become less apparent as they aged. Concurrently with the dysplastic retina, many dogs also had mild unilateral or bilateral persistent hyperplastic primary vitreous (PHPV). The PHPV changes were associated with small, white posterior lens capsule plaques, manifested as a central posterior lens capsule ring. This was usually accompanied by a white primary vitreous mass extending to Bergermeister's papilla on the ONH. Lenticonus or disrupted posterior lens capsules were not present, and the axial length of the globe was normal.

Histology showed that the external limiting membrane was incomplete in the abnormal retinal regions, as previously described in retinal dysplasia in the English Springer Spaniel (Whiteley & Young, 1986). A molecular study of affected dogs was performed to try to identify the abnormality underlying the condition, and appeared to show lower levels of mRNA coding for some mitochondrial proteins and some morphologic abnormalities in mitochondria from a variety of tissues from affected dogs compared to controls

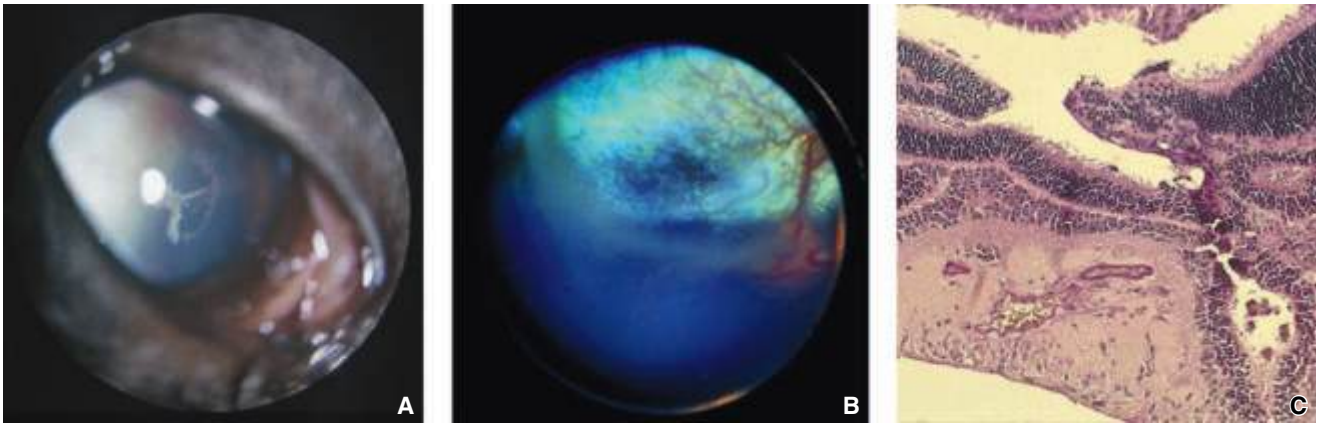


Figure 25.21 Retinal dysplasia and persistent hyperplastic primary vitreous in a young Miniature Schnauzer. **A**. There are posterior lenticular opacities, mainly manifested by a lens capsule ring, with some centrally located opacities. **B**. White primary vitreous strands are seen, and a pertinent hyaloid vessel extends to the Bergmeister's papilla. **C.** Histopathologic section of the posterior segment with severely dysplastic retina.

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(Appleyard et al., 2006). Further studies to screen one of the genes implicated by the first study, mitochondrial transcription factor A (*Tfam*), failed to identify any likely mutations in the coding region of the gene. Furthermore, electronic microscopy of mitochondria from lymphocytes from affected and control dogs did not have any significant morphologic differences, contradicting the findings from the first study (Bauer et al., 2011).

Induced Retinal Dysplasia

Infection with canine adenovirus has been shown to cause retinal dysplasia (Appel et al., 1973). Another infectious agent causing retinal dysplasia is canine herpesvirus. Experimental studies have demonstrated that severe ocular inflammation with subsequent retinal dysplasia and associated ocular anomalies can be induced in neonatal pups (Albert et al., 1976). Oral, nasal, and intraperitoneal inoculation at 1–4 days postnatal caused panuveitis and systemic signs of infection. Histopathologically, folds and rosettes were found in the retina, and there was a retardation of retinal cell maturation and retinal reorganization.

The immature mammalian retina is susceptible to radiation, which has been demonstrated in the dog. Irradiated newborn puppies exhibited retinal rosette formation (Shively et al., 1972). The rosettes were either few or numerous, and they involved both tapetal and nontapetal fundus. Morphologic studies showed lesions indicative of aberrant development after radiation-induced damage. The pathogenesis of the induced retinal dysplasia appeared to include necrosis of the neuroblastic or nuclear layers, disruption of the outer limiting membrane, ectopic mitosis and migration of photoreceptor cells to the subretinal space, and development of rosettes and tubules.

Gene augmentation therapy trials for the treatment of PRA in dogs has also been reported to induce changes typical of severe multifocal retinal dysplasia lesions (Beltran et al., 2011; Mowat et al., 2017b).

Canine Multifocal Retinopathy

Canine multifocal retinopathy (CMR) is characterized by the development of multifocal retinal bullae in young animals (Fig 25.22). The condition is recessively inherited and due to mutations in the canine *BEST1* gene. Currently, three different mutations have been identified, being responsible for *cmr1*, *cmr2*, and *cmr3*. CMR was first described in the Great Pyrenees dog (Grahn & Cullen, 2001; Grahn et al., 1998), followed by the Coton de Tulear, English and French Mastiff, Bullmastiff, and Lapponian Herder. Pedigree analysis and prospective matings in the Great Pyrenees dog showed that it had an autosomal recessive mode of inheritance (Grahn & Sandmeyer, 2006; Grahn et al., 2006, 2008). *Cmr1* has now been identified in at least 11 breeds of dog (Gornik et al., 2014; Hoffmann et al., 2012; www.ecvo.org/hereditary-eye-diseases/ecvo-manual.html), while *cmr2* has only been described in the Coton de Tulear and *cmr3* in the Lapponian Herder and Finnish Lapphund.

Mutations in the canine *BEST1* gene (*cBEST1*) were reported by Guziewicz and colleagues (Guziewicz et al., 2007). In Mastiffs and the Great Pyrenees with *cmr1*, a

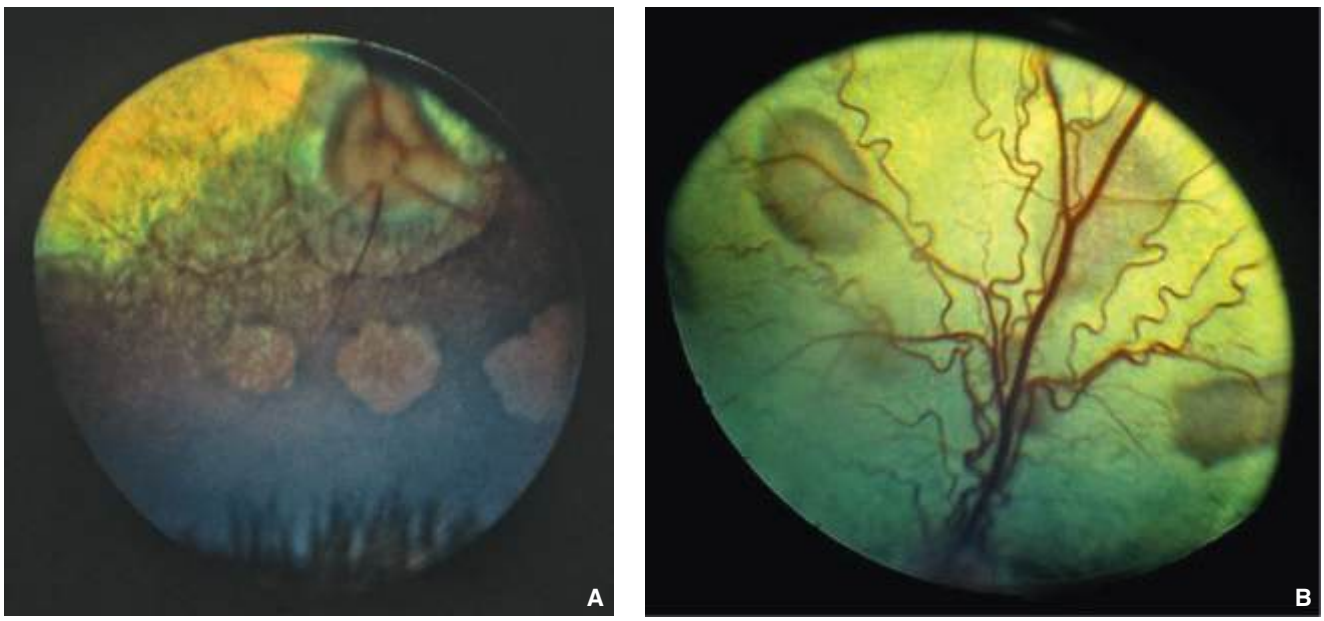


Figure 25.22 Canine multifocal retinopathy/retinal pigment epithelial dysplasia in a young Great Pyrenees dog. **A**. Note the serous retinal detachment around the optic nerve head and the multiple circular, tan fundic patches in the nontapetal fundus. **B**. In the midperipheral tapetal fundus, there are multiple grayish, slightly elevated circular lesions. (Courtesy of Dr. Bruce Grahn.)

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mutation was identified resulting in a stop codon at position 25 (c.73C>T; p.Arg25*) and a lack of the protein product bestrophin (Guziewicz et al., 2007). A missense mutation that changes a glutamine to aspartic acid at codon 161 in *cBEST1* was identified (c.482G>A; p.Gly161Asp) as the cause of *cmr2*. This latter mutation results in misfolding of the protein and a lack of trafficking of the misfolded protein from the endoplasmic reticulum to its normal position in the plasma membrane. Subsequently, the Lapponian Herder was shown to have CMR due to a different mutation (*cmr3*). In this breed, a 1 bp deletion (c.1388delC) and a predicted missense mutation (c.1466G>T; p.(Gly489Val)) were identified in all affected dogs. The deletion results in a frameshift that, when combined with the second downstream DNA variation, would be predicted to result in a premature stop codon at codon 489 (Zangerl et al., 2010). It was anticipated that this would not alter trafficking of the cBEST1 protein.

In dogs with *cmr1*, the retinal bullae are multifocal, with gray to tan colored subretinal fluid (Fig. 25.23). They vary in size from barely visible to some lesions that are larger than the ONH. They initially appear at approximately 11 weeks of age; usually they are sparse, but they develop bilaterally in the peripheral tapetal fundus, around the ONH, and occasionally under the major veins inferior to the ONH (see Fig. 25.22). The peripapillary lesions, observed as serous retinal detachments, develop within a few hours but remain the same size for years, while the peripheral lesions develop gradually and appear to increase slowly in size and number until the age of 20 weeks. Fluorescein angiography appeared normal at 7 weeks of age, but later, at the time of visible serous detachments, there was blocked choroidal fluorescence and sub-RPE pooling of fluorescein (Grahn & Cullen, 2001). With age the focal areas may degenerate, although a generalized retinal degeneration is not usually seen (Grahn et al., 1998). Coton du Tulear dogs with *cmr2* can show a reduced ERG, suggesting a more extensive retinal degeneration (Grahn et al., 2008). A study of *cmr3*-affected Lapponian Herders showed that the lesions developed between 9 months and 2 years of age and that some could disappear over time. Similarity in appearance to some multifocal retinal dysplasia lesions was noted and the suggestion made that there may be some overlap in the conditions, with perhaps some carriers for the *cmr3* mutation developing a multifocal retinal dysplasia phenotype (Zangerl et al., 2010). Further studies are needed to investigate this possibility.

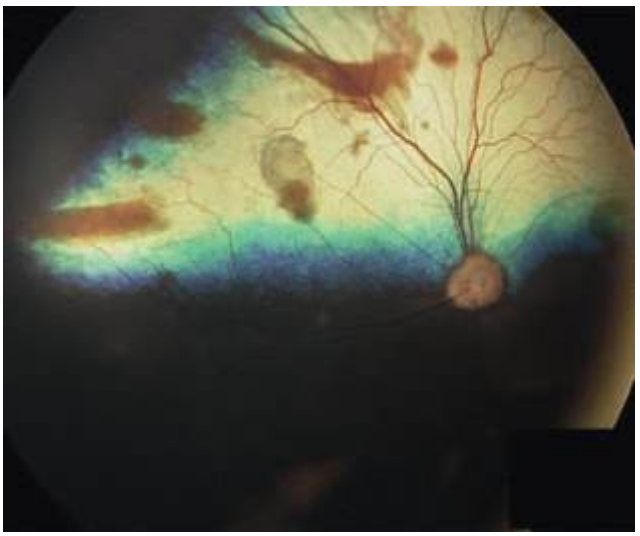


Figure 25.23 Canine multifocal retinopathy. An 8-year-old Mastiff with multiple bullae with tan-colored subretinal fluid.

Mutations in *BEST1* in humans can result in a variety of different phenotypes, the commonest of which is Best vitelliform macular dystrophy. The spectrum of retinal phenotypes in humans is known as the bestrophinopathies, named for the protein that is encoded by the *BEST1* gene, bestrophin (Johnson et al., 2017). Bestrophin is present in the RPE, where it is positioned in the basolateral portion of the cell membrane. It acts as an anion channel and is important for regulation of intracellular calcium. Lack of normal bestrophin function interferes with the ability of the RPE to properly metabolize photoreceptor outer segments, which is one of the important roles of the RPE. Detailed studies in affected dogs show that there is a buildup of subretinal autofluorescent material and RPE hypertrophy (Beltran et al., 2014). Furthermore, the important relationship between microvilli of the RPE and photoreceptors is disrupted. This was particularly apparent for the shorter cone outer segments, which require longer RPE microvilli. The interphotoreceptor matrix was disrupted, leading to altered outer segment morphology (Guziewicz et al., 2017). Within the areas of multifocal serous retinal detachments, photoreceptor outer segments degenerate. The RPE cells in the detachment areas were also more severely affected, being hyperplastic, hypertrophied, and showing increased pigmentation. Some of the cells in these lesions contained several small and large clear vacuoles, generally located in the basal portion of the affected cells. Bruch's membrane, under the basal part of the affected RPE cells, demonstrated areas with oval-shaped holes (Grahn & Cullen, 2001).

Inherited Retinal Degenerations

Inherited retinal degenerations represent a wide range of different conditions. They most commonly result from mutations of genes expressed in the photoreceptors or RPE. The commonest category is the group of conditions called the progressive retinal atrophies, which result typically from mutations in genes expressed in the photoreceptors (either rods or both rods and cones). Mutations in RPE genes result in a different set of phenotypes that do not always fit in the PRA category. Mutations that are of cone-expressed genes

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lead to cone dysfunction or degeneration, but do not cause a loss of rod photoreceptors so funduscopic changes are not apparent.

Progressive Retinal Atrophy

The term PRA is used to refer to a group of inherited retinal conditions with similar clinical signs. PRA should be reserved to describe those inherited retinal degenerations in which there is a bilateral progressive retinal thinning (atrophy) leading to vision loss. For most forms the photoreceptor loss is rod led, but some have involvement of cones prior to or at the same time as rods and are described as cone-rod dystrophies. The rod-led forms are characterized by an initial night blindness and most forms eventually lead to total blindness. Fundus changes include tapetal hyperreflectivity (as a result of retinal thinning), superficial retinal blood vasculature attenuation, and ONH atrophy. The clinical signs are discussed in more detail below.

The majority of conditions that fit into this description have proven to be due to mutations in genes expressed in retinal photoreceptors. These can be genes expressed only in rods, or in both rods and cones. Regardless of whether the mutant gene is expressed in cones or not, when rod photoreceptors (which make up about 95% of the total number of photoreceptors) die, cones will inevitably also die, leading to eventual blindness. There are other inherited retinal dystrophies that cause vision loss that do not fit into the category of PRA. These will be considered separately and include conditions due to mutations in genes expressed in the RPE, such as retinal dystrophy in Briards due to a mutation in the *RPE65* gene, and Swedish Vallhund retinopathy, which is associated with a putative mutation in the *MERTK* gene. Cone-only dystrophies that result in day blindness are now generally referred to as achromatopisias and are not associated with loss of rods or loss of rod function. The achromatopsias do not show thinning of the retina as seen with PRA and will be considered separately.

Clinical Signs of Progressive Retinal Atrophy

Clinical signs of PRA are similar between the different types of PRA, with a few exceptions that are considered later under the specific forms of PRA. The age at onset, and rate of progression of the condition, can vary considerably between the different forms and in some instances between animals with the same genetic form.

PRA is bilateral, and the generally slow and progressive vision loss in most forms starts as a loss of night vision and almost always progresses to blindness. Unilateral PRA is sometimes reported, which is conceivably possible in chimeric animals, but would be very rare and other reasons for a unilateral generalized retinal degeneration should be explored. Dogs often present with a history of difficulty in seeing at nighttime and may be reluctant to go out at night. With progression, daytime vision is also impaired, and with reducing cone-mediated vision they may only see well enough to negotiate unfamiliar objects under quite bright lighting conditions. However, the effect on vision is not always noticed by owners in the early stages and the ability of a dog with slowly failing vision to cope in familiar surroundings should not be underestimated. For this reason, dogs may first be presented with relatively advanced stages of PRA, perhaps the vision loss becoming apparent to the owners when the dog goes to unfamiliar surroundings or objects in the dog's environment are moved.

Funduscopic signs of PRA classically include altered reflectivity of the tapetal fundus, superficial retinal blood vessel attenuation, and pigmentary changes in the nontapetal fundus and the ONH. The altered appearance due to changes in retinal thickness because of PRA (or other conditions) can be readily detected in the tapetal fundus, where thinning of the retina results in increased reflection of the examining light from the underlying tapetum (Fig. 25.24). Retinal thinning cannot be detected so readily in the nontapetal fundus, nor in dogs with a lack of tapetum (Fig. 25.25). With at least some forms of PRA, an initial change in tapetal reflectivity resulting in hyporeflectivity, or a slightly dull appearance, may be an early change that is detectable on serial fundus photographs of animals known to have PRA (Fig. 25.26). The authors have found that this ophthalmoscopic appearance appears to coincide with a histologic distortion of photoreceptor outer segments that may scatter light passing through them, giving a slightly dull appearance to the tapetal fundus. Serial fundus photography is also helpful in allowing detection of very early attenuation of smaller retinal arterioles in early-stage PRA. Client-owned dogs presenting for fundus examination in these very early disease stages prior to retinal thinning would probably be considered to have fundus appearances that fall under the range of normal variation. However, once retinal thinning develops due to photoreceptor death, fundus changes are easier to detect.

The effect of retinal thinning due to PRA on tapetal reflectivity initially may be most obvious in the tapetal periphery. Hyperreflectivity of the tapetal peripheral fundus appears as a grayish discoloration on indirect ophthalmoscopy rather than a brighter reflection. The grayish discoloration is because the increased light reflection from the peripheral tapetum is not reflected directly back to the observer, whereas light striking the central tapetal fundus is reflected directly back to the observer, meaning that when there is retinal thinning a brighter reflection (hyperreflectivity) is seen. With progression, hyperreflectivity of the more central tapetal fundus becomes more obvious, developing an appearance described as a sheen and likened by some to the appearance seen on the reflection of light from fish scales. A slight vascular attenuation of retinal vessels, particularly arterioles, in the midperipheral and peripheral tapetal fundus may be

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Figure 25.24 Moderately advanced cases of bilateral retinal degeneration (progressive retinal atrophy) in two different canine breeds. Note the generalized change in reflectivity or hyperreflectivity and vascular attenuation in both cases. **A**. A 3-year-old Irish Wolfhound. **B**. A 4-year-old Dachshund.

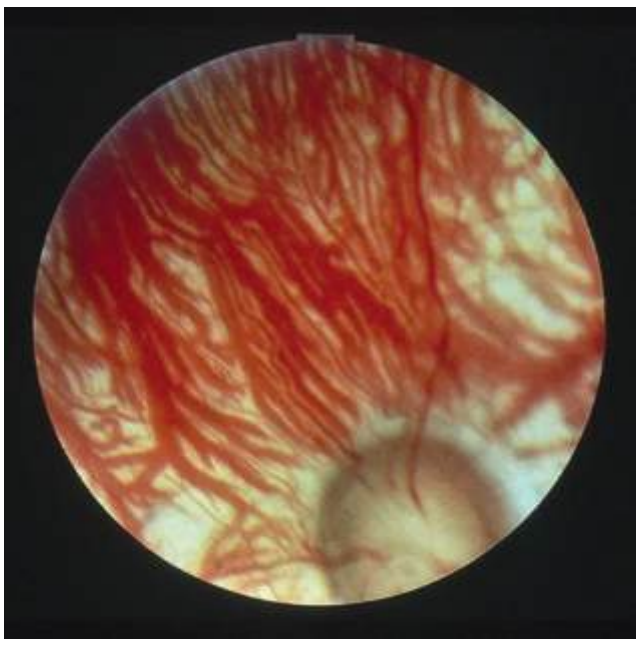


Figure 25.25 Retinal degeneration found in a young, blue merle Collie. Note the amelanotic fundus and lack of tapetum, which makes diagnosis difficult. Also note the severely attenuated retinal vessels, which indicate generalized retinal atrophy. (Courtesy of Dr. Dan Wolf.)

observed at this early stage as well. With progression of the disease, the hyperreflectivity becomes more pronounced and the color of the tapetum may appear to change. It is common to see radial lines of increased tapetal reflectivity in the peripheral tapetal area. The lines correspond with the pattern of the underlying choroidal vessels that slightly change the orientation of the overlying tapetum, thus slightly altering the direction in which light is reflected. In some animals, the visual streak may appear to have a different reflectivity to the adjacent central tapetal fundus, resulting in a discolored streak dorsal to the disk extending horizontally both medially and laterally (Fig 25.27). Concurrent with the increase in tapetal hyperreflectivity, the vascular attenuation becomes more pronounced. With advanced retinal degeneration, only the faint contours of blood vessels may remain (ghost vessels; Fig. 25.28 and Fig. 25.29). In the nontapetal fundus some waves of depigmentation or patchy pigmentation may be seen at moderately advanced and advanced stages (see Fig. 25.29B). With advanced disease the ONH atrophies, resulting in a dull appearance and a less prominent surface due to demyelination and axon loss.

Concurrent with loss of retinal function, PLRs become progressively more sluggish, and the resting pupil becomes more mydriatic than expected for the lighting conditions. Chromatic pupillometry shows a loss of pupillary constriction to red light as photoreceptors die, but the blue light stimulation of melanopsin-expressing ganglion cells will result in a pupillary constriction, until complete retinal degeneration develops that also involves retinal ganglion cells.

Secondary cataract is common in the more advanced stages of PRA (Fig. 25.30). The initial changes tend to occur in the posterior cortex of the lens and include vacuolation

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Figure 25.26 Fundus photographs showing progressive fundus changes in a Papillon with progressive retinal atrophy. **A**. 6 months of age. **B**. 12 months of age. **C**. 24 months of age. Note the progressive retinal vasculature attenuation and initial tapetal hyporeflectivity, which is apparent prior to development of generalized tapetal hyperreflectivity.

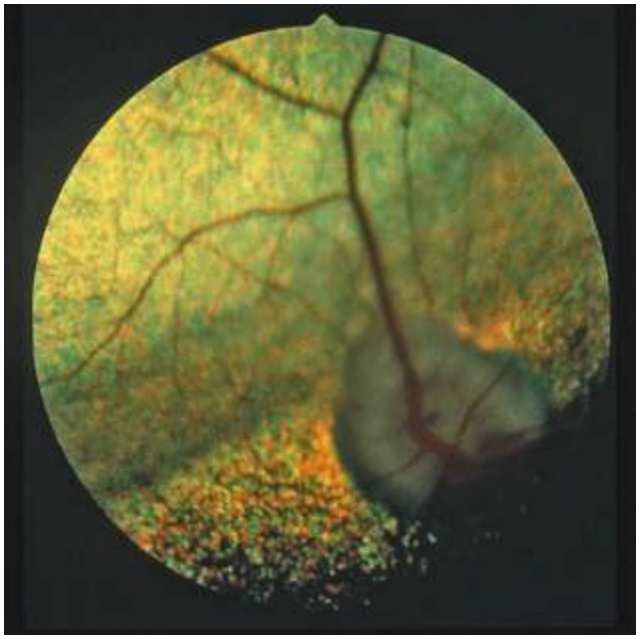


Figure 25.27 Moderately advanced progressive rod-cone degeneration seen in a 7-year-old English Cocker Spaniel. Note the hyporeflective streak slightly above the optic disc and on its sides, as well as the hyperreflectivity in other parts of the tapetal fundus.

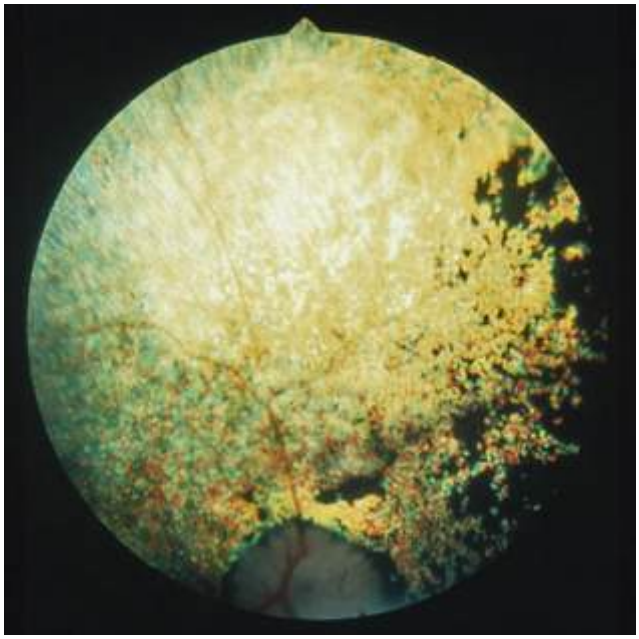


Figure 25.28 An advanced case of progressive retinal atrophy in a 7-year-old Tibetan Spaniel. Note the generalized hyperreflectivity and ghost vessels in the fundus.

and opacification. Often, irregular radiations are seen emanating from the posterior pole of the lens and extending to involve the equatorial cortex and, later, the entire lens. Mature cataracts, especially in certain breeds such as Miniature and Toy Poodles and American Cocker Spaniels, make the evaluation of retinal function using ERG of utmost importance before cataract surgery is performed, in order to rule out concurrent retinal degeneration.

Diagnosis

A diagnosis of PRA can often be made on a consideration of the history of vision change and the ophthalmoscopic examination. However, the clinician should be cautious because there can be noninherited causes of a retinal degeneration that might mimic the appearance of PRA (an animal with this phenomenon is described as being a "phenocopy"). If there is a history of PRA in related dogs, or this is a breed with a known PRA problem, that can increase confidence that the retinal degeneration is a result of PRA. For some breeds, a DNA-based test is available and can unequivocally show that an animal has a gene mutation known to cause PRA. However, as discussed in Chapter 11, there may be more than one form of PRA in a breed, and this can include forms for which the causal gene mutation has not been identified and for which therefore there is no DNA test. Electroretinography can be useful in certain circumstances; for example, prior to detectable funduscopic changes there can be photoreceptor functional changes that can be

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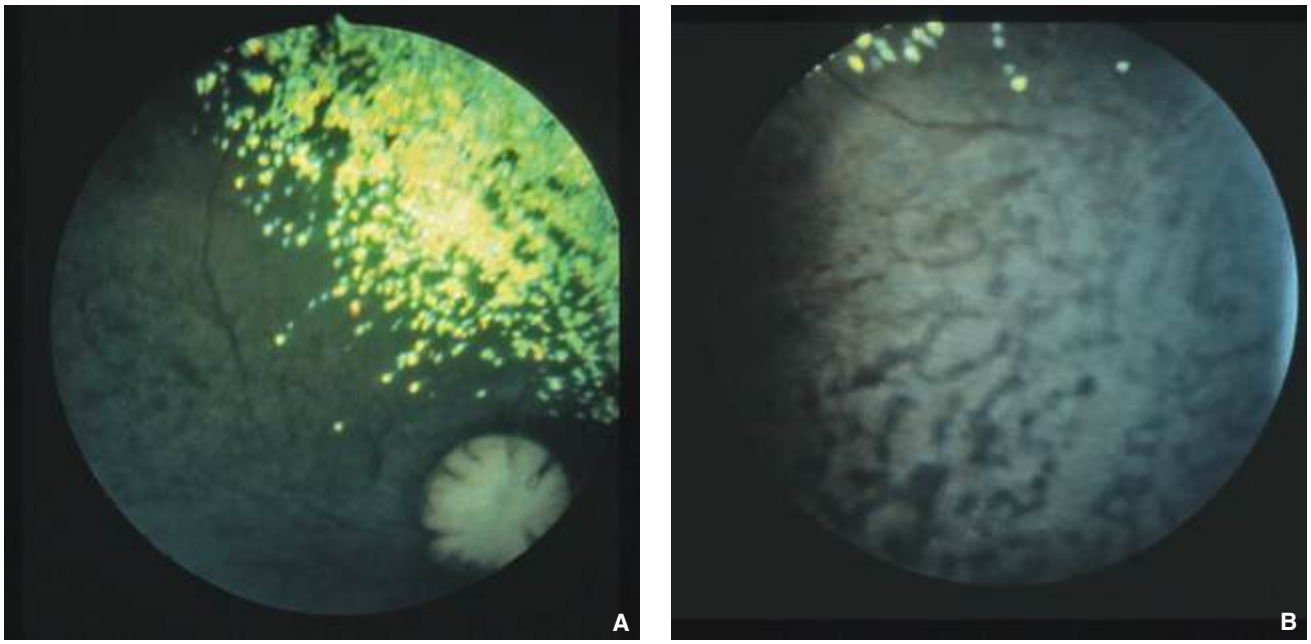


Figure 25.29 An advanced case of retinal degeneration (progressive retinal atrophy) in a 5-year-old Tibetan Terrier. **A**. The tapetal fundus is hyperreflective, and only ghost vessels are visible. **B**. The nontapetal fundus is depigmented and hyperpigmented in striae and patches.



Figure 25.30 Secondary cataract observed in a 7-year-old Miniature Poodle with progressive retinal atrophy.

detected. Several forms of PRA are due to genes involved in rod phototransduction and there are therefore reduced or absent rod-mediated ERG responses. A careful ERG study at an early age can detect the lack of rod responses. In forms of PRA where there is relatively normal function of photoreceptors prior to their death, reduction of ERG amplitudes may not be a significant feature until sufficient photoreceptors have been lost. Chromatic pupillometry has also become established as an additional method to assess retinal function, with the presence of normal pupillary constriction to red light exposure being an indicator of photoreceptor function. Vision testing can be helpful too in investigating suspected PRA. Careful assessment of vision in controlled lighting conditions is most effective. It should be remembered that in the early stages of many forms of PRA there can be fairly normal cone vision. It is therefore important that the lighting levels are reduced below those that allow for cone vision, so that rod-only function can be assessed. Obstacle courses can be relatively easily created, but techniques using purpose-built equipment such as a four-choice vision testing device can be valuable, particularly in a research setting (Annear et al., 2013; Gearhart et al., 2008).

Classification of Progressive Retinal Atrophy

PRA has been further categorized in several different ways. Initially, the age of onset of clinical signs was used to divide the PRAs into early-onset and late-onset forms. As studies revealed the details of early histopathologic changes in different forms of PRA, subdivisions based on these changes were introduced. These included terms such as *rod dysplasia*, *rod-cone dysplasia* (later further divided into Types 1, 1a, 1b, 2, and 3), *early retinal degeneration*, and *progressive rod-cone degeneration*. In the dysplasias, the photoreceptors fail to mature fully: development is halted prior to maturation and is followed by degeneration. In progressive rod-cone degeneration the photoreceptors reach maturity, but then are progressively lost. Further categorization was added when cones were found to be affected more severely or prior to rods. This led to the use of terms such as cone-rod dystrophy, reflecting the terms used in human medicine and indicating the early and more severe cone involvement. However, the ophthalmoscopic signs of cone-rod dystrophy are similar

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to those of the rod-led photoreceptor degenerations, so these conditions fall under the bucket term of PRA.

As more forms of PRA are studied, an expanding number of descriptive names have been used, such as PRA Type 1 (Winkler et al., 2013), GR_PRA1 in Golden Retrievers (Downs et al., 2011), and late-onset PRA (also called rod-cone *degeneration* Type 4). The use of the term rod-cone degeneration Type 4 is slightly misleading, however, because PRAs categorized as rod-cone *degeneration* Types 1–3 do not exist, although there are rod-cone *dysplasia* Types 1–3 that have the same initials. In some instances, the initial name was subsequently found to be inaccurate. For example, PRA in the American Staffordshire Terrier was described as a cone-rod dystrophy (cone-rod dystrophy 1) based on ERG analysis (Kijas et al., 2004). When the causal mutation was finally identified, it was in a gene expressed in rods and not cones and already associated with *rcd* (*PDE6b*) (Goldstein et al., 2013b), meaning that the cone-rod dystrophy classification was most likely inaccurate. Indeed, early retinal histology (11 weeks of age) showed more severe changes in rod inner segments than cone inner segments and a sparsity of outer segments (Goldstein et al., 2013b), suggesting that rod-cone dysplasia may have been a better descriptive name for this condition.

Categorization by mode of inheritance is also used, with most forms being inherited in an autosomal recessive manner, but both autosomal-dominant and X-linked forms also occur. More recently, the gene mutations underlying an expanding number of forms of PRA have been identified, and perhaps it is now time to move toward using the name of the mutated gene to categorize each form of PRA. This would move away from the growing number of sometimes illogical and confusing names based on pathologic changes. Table 25.1 lists forms of PRA with published causal gene mutations categorized by the known function of the gene.

Specific Forms of Progressive Retinal Atrophy

Several different forms of PRA have been studied in detail, often with the help of specific breeding colonies, allowing for detailed functional, biochemical, and histologic assessment.

*Rod Phosphodiesterase Genes: **PDE6A** (**rcd3**), **PDE6B** (**rcd1**, **rcd1a**, and **rcd1b**)*

The rod phosphodiesterase complex consists of two active subunits (alpha and beta) that are required for hydrolysis of cyclic guanosine-3,5′-monophosphate (cGMP) in the rod outer segment, reducing cGMP levels in response to light stimulation. The level of cGMP controls the opening or closure of cGMP-gated channels, thus depolarizing or hyperpolarizing the cell depending on whether the rod has been stimulated by light or not. The Irish Setter with *rcd1* was shown to have a mutation in the beta subunit, *PDE6B* (Clements et al., 1993; Suber et al., 1993). This form of PRA had been studied in detail from the 1940s in England and the 1970s in the United States, and was the first form of PRA for which the causal gene mutation was identified. Lack of functional PDE6B leads to a failure in rod phototransduction and an accumulation of cGMP in the rod outer segments, which occurs as the outer segments start to develop (Aguirre et al., 1978). The high levels of cGMP lead to opening of an abnormally large number of cGMP-gated channels, resulting in an influx of cations into the outer segment. This is damaging to the cell, resulting in halting the outer segment maturation (Aguirre & Rubin, 1975b). Cone outer segments are also stunted, although they do not express *PDE6B*. This form of PRA was therefore classified as a rod-cone dysplasia (*rcd*).

When other forms of nonallelic PRA were identified with similar histologic changes, this form of PRA in the Irish Setter became known as *rcd1*. Subsequently, dogs with two different mutations in *PDE6B* have been identified: the Sloughi and the American Staffordshire Terrier (Dekomien et al., 2000; Goldstein et al., 2013b). The condition in the Sloughi with a *PDE6B* mutation became known as *rcd1a*, although histologic studies have not been reported. PRA in the American Staffordshire Terrier had already been described as being a cone-rod dystrophy (*crd1*; Kijas et al., 2004), which is usually a term that describes a condition where cone function is reduced prior to rod function. Since the identification of the causal mutation in *PDE6B*, the condition in the American Staffordshire Terrier is now also referred to as *rcd1b*. Interestingly, the *PDE6B* mutation in the American Staffordshire Terrier results in a slower loss of photoreceptors than seen with *rcd1* in the Irish Setter. Dogs that were double heterozygotes for the two mutations had the more severe phenotype, mimicking that of the *rcd1* dog (Goldstein et al., 2013b).

PRA in the Cardigan Welsh Corgi was shown to be caused by a mutation in the alpha subunit of the rod phosphodiesterase, *PDE6A* (Petersen-Jones et al., 1999). Characterization of this form of PRA showed it to be very similar to *rcd1* in the Irish Setter (Tuntivanich et al., 2009) and it was named *rcd3* (the name *rcd2* having already been used to characterize a nonallelic form of PRA in the Collie with similar changes to *rcd1*).

Dogs affected with either *PDE6A* (*rcd3*) or *PDE6B* (*rcd1*) mutations have a very similar phenotype. ERGs in affected puppies showed that rod function did not develop (Fig. 25.31) and the absence of rod-mediated nighttime vision can usually be demonstrated at the earliest age such vision testing can be performed. In the Cardigan Welsh Corgi with *rcd3*, cone ERGs were shown to have a significantly reduced a-wave from a very early age, most likely because cone outer segments were shorter than normal. Fig. 25.32 shows the early and severe changes in photoreceptors in this condition. There was a progressive loss of rod photoreceptors, leading to severe thinning of the outer nuclear layer until a single

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Table 25.1 Genes known to be involved in canine progressive retinal atrophy (PRA).

Gene	Function	Breeds	Condition	Mutation	Inheritance	References
Genes Encoding Proteins Involved in Phototransduction						
CNGA1: cGMP-gated channel alpha subunit	Subunit of channel in rod outer segment that closes as a result of phototransduction	Shetland Sheepdog	PRA	4 bp deletion in exon 9 c.1752_1755delAACT Results in frame shift and premature stop codon	AR	Wiik et al. (2015)
CNGB1: cGMP-gated channel beta subunit	Subunit of channel in rod outer segment that closes as a result of phototransduction	Papillon, Phalene	PRA Type 1	A 1 bp insertion combined with a 6 bp deletion in exon 26 c.2387delA;2389_2390insAGCTAC Results in a frame shift and premature stop codon	AR	Ahonen et al. (2013); Winkler et al. (2013)
PDE6A: phosphodiesterase 6A	Subunit of the phosphodiesterase in rod outer segment that hydrolyzes cGMP as part of phototransduction	Cardigan Welsh Corgi, Chinese Crested	*Rcd3*: Rod-cone dysplasia Type 3	A 1 bp deletion in exon 15: c.1940delA Results in a frame shift and premature stop codon	AR	Petersen-Jones et al. (1999)
PDE6B: phosphodiesterase 6B	Subunit of the phosphodiesterase in rod outer segment that hydrolyzes cGMP as part of phototransduction	Irish and Red Setters	*Rcd1*: Rod-cone dysplasia Type 1	A guanine to adenine transition in exon 21 changing codon 807 to a stop codon c.2420G>A	AR	(Suber et al., 1993, Clements et al., 1993)
		Sloughi	*Rcd1a*: Rod-cone dysplasia Type 1a	An 8 bp insertion in exon 21 resulting in conversion of codon 816 to a stop codon c.2448-2449insTGAAGTCC	AR	Dekomien et al. (2000)
		American Staffordshire Terrier	*Crd1*: Rod-cone dystrophy 1	An in-frame deletion of 3 bp in exon 21 removing an arginine at codon 802 C.2404-2406del	AR	Goldstein et al. (2013b)
Rhodopsin	Rod opsin – combined with 11-*cis*-retinal as the visual pigment in rods Captures photons of light to initiate phototransduction	Bull Mastiff, Old English Mastiff	Dominant PRA	A cytosine to guanine transversion at codon 4. c.11C>G that changes a threonine to an arginine p.The4Arg	AD	Kijas et al. (2002)
S-antigen	Involved in deactivation of phototransduction by binding to phosphorylated activated rhodopsin			c.1216T>C alters the stop codon resulting in the addition of 25 amino acids (p.*405Rext*25)	AR	Goldstein et al. (2013a)
Genes Encoding Cilia and Cilia-Related Proteins for Trafficking of Molecules between Rod Inner and Outer Segments						
BBS4: Bardet–Biedel Syndrome Type 4		Hungarian Puli	PRA	An adenine to thymine transversion in exon 2 c.58A>T changing a lysine at codon 20 to a stop codon p.Lys20*	AR	Chew et al. (2017)

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C2orf71: Chromosome 2 open reading frame 71	Australian Cattle Dog English Setter Gordon Setter Irish Setter Llewellyn Setter Polish Lowland Sheepdog Small Munsterlander Standard Poodles Tibetan Terrier	Late-onset PRA *Rcd4*: Rod-cone degeneration type 4	A duplication of cytosine in exon 1 converting a run of 6 cytosines to 7 cytosines c.3149_3150dupC This results in a frameshift and premature stop codon	AR	Downs et al. (2013); Svensson et al. (2016)
CCDC66: Coiled coil domain containing 66	Schapendoes	PRA	A duplication of an adenine in exon 6 converting a run of 6 adenines to 7 adenines c.521_522dupA Results in a frame shift and premature stop codon	AR	Dekomien et al. (2010); Lippmann et al. (2007)
FAM161A: Family with sequence similarity 161, member A	Tibetan Spaniel Tibetan Terrier	*PRA3*: Progressive retinal atrophy 3	Insertion of a SINE element in intron 4 close to the splice site with exon 5 c.1758-15_1758-16Ins238 This causes skipping of exon 5	AR	Downs & Mellersh (2014)
IQCB1: IQ motif-containing protein B1 (also known as *NPHP5*)	American Pit Bull Terrier	*Crd2*: Cone-rod dystrophy 2	Caused by a duplication of a cytosine changing 2 cytosines to 3 cytosines c.953dupC	AR	Downs et al. (2016); Goldstein et al. (2013b)
NPHP4: Nephrocystin-4	Miniature Wirehaired Dachshund Standard Wirehaired Dachshund Shorthaired Dachshund	*Crd*: Cone-rod dystrophy	Caused by an 180 bp deletion removing part of exon 5 and intron 5 c.462_508+133del Leads to skipping of exon 5 and a premature stop codon in exon 6	AR	Wiik et al. (2008)
RPGR: Retinitis pigmentosa GTPase regulator	Siberian Husky Samoyed	*XLRA1*	Caused by a 5 bp deletion in ORF15 c.1028_1032del Results in an immediate stop codon	X-linked	Zhang et al. (2002)
	Crossbred	*XLPRA2*	Caused by a 2 bp deletion in ORF 15 c.1084_1085 The frame shift results in 34 altered codons before a top codon	X-linked	
RPGRIP1: Retinitis pigmentosa GTPase regulator interacting protein 1. Plus *MAP9*: Aster-Associated protein	Chihuahua English Springer Spaniel Miniature Long-haired Dachshund Miniature Smooth-Haired Dachshund Miniature Wire-Haired Dachshund	*Crd*: Cone-rod dystrophy	The inheritance is complex with variants in RPGRIP1 and MAP9 and possibly other loci contributing Variant in RPGRIP1 is a 44 bp insertion in exon 2 c.208_209Ins 44 There is a 22 kb deletion involving *MAP9* starting in intron 10 and extending to a downstream partial *MAP9* psuedogene	Complex	Forman et al. (2016); Mellersh et al. (2006)

(Continued)

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Table 25.1 (Continued)

Gene	Function	Breeds	Condition	Mutation	Inheritance	References
TTC8: Tetratricopeptide repeat domain 8		Golden Retriever Labrador Retriever	*GR_PRA2*: Golden Retriever PRA Type 2	A 1 bp deletion in exon 8 c.669delA Causes a frameshift and premature stop codon	AR	Downs et al. (2014)
Genes Encoding Proteins with Other Functions						
Gene	Function	Breeds	Condition	Mutation	Inheritance	References
ADAM9: A disintegrin and metalloproteinase domain 9	Keep outer segments of photoreceptors and RPE in close contact – adhesion protein	Glen of Imaal Terrier	*Crd3*: Cone-rod dystrophy 3	A genomic deletion of >20 kb removing exons 15 and 16 and resulting in a frame shift and premature stop codon in exon 17	AR	Goldstein et al. (2010c); Kropatsch et al. (2010)
NECAP1: NECAP endocytosis-associated protein 1	Involved in clarithin-mediated endocytosis that is involved in formation of vesicles for protein trafficking	Giant Schnauzers	*PRA*	A missense mutation: c.544G>A; p.Gly182Arg	AR	Hitti et al. (2019)
PPT1: palmitoyl-protein thioesterase	Maintenance of synaptic function	Miniature Schnauzer	*PRA*	Complex structural variant	AR	Murgiano et al. (2019)
PRCD: Progressive rod-cone degeneration	Positioned anchored to cytosolic surface of photoreceptor disc membranes binds to rhodopsin	Over 30 different breeds – commonest form of PRA	*PRCD*: Progressive rod-cone degeneration	A guanine to alanine transition at codon 2 c.5G>A This changes a cysteine to a tyrosine p.Cys2Tyr	AR	Zangerl et al. (2006a)
RD3: Retinal degeneration 3	Involved in trafficking of guanylate cyclases to outer segments and possible inhibition of their action prior to reaching outer segments	Rough Collie Smooth Collie	*Rcd2*: Rod-cone dysplasia Type 2	A 22 bp insertion in exon 4 c.489_490Ins22 causes a frame shift that is predicted to extend the normal amino acid coding beyond the normal stop codon	AR	Kukekova et al. (2009)
SLC4A3: Solute carrier family 4, member 3	Cl-/HCO3- exchange in Müller and horizontal cells Helps to maintain acid balance by removing photoreceptor-generated CO_2 waste	Golden Retriever	*GR_PRA1*: Golden Retriever PRA Type 1	A 1 bp insertion of a cytosine in exon 16 c.2601_2602 InsC This leads to a frame shift and a predicted stop codon in exon 18	AR	Downs et al. (2011)
STK38L: Serine/threonine kinase 38 like	A kinase involved in control of cell cycle	Norwegian Elkhound	*Erd*: Early retinal degeneration	A SINE insertion in exon 4 c.233_234ins233 that leads to skipping of exon 4	AR	Goldstein et al. (2010b)

AD, autosomal dominant; AR, autosomal recessive.

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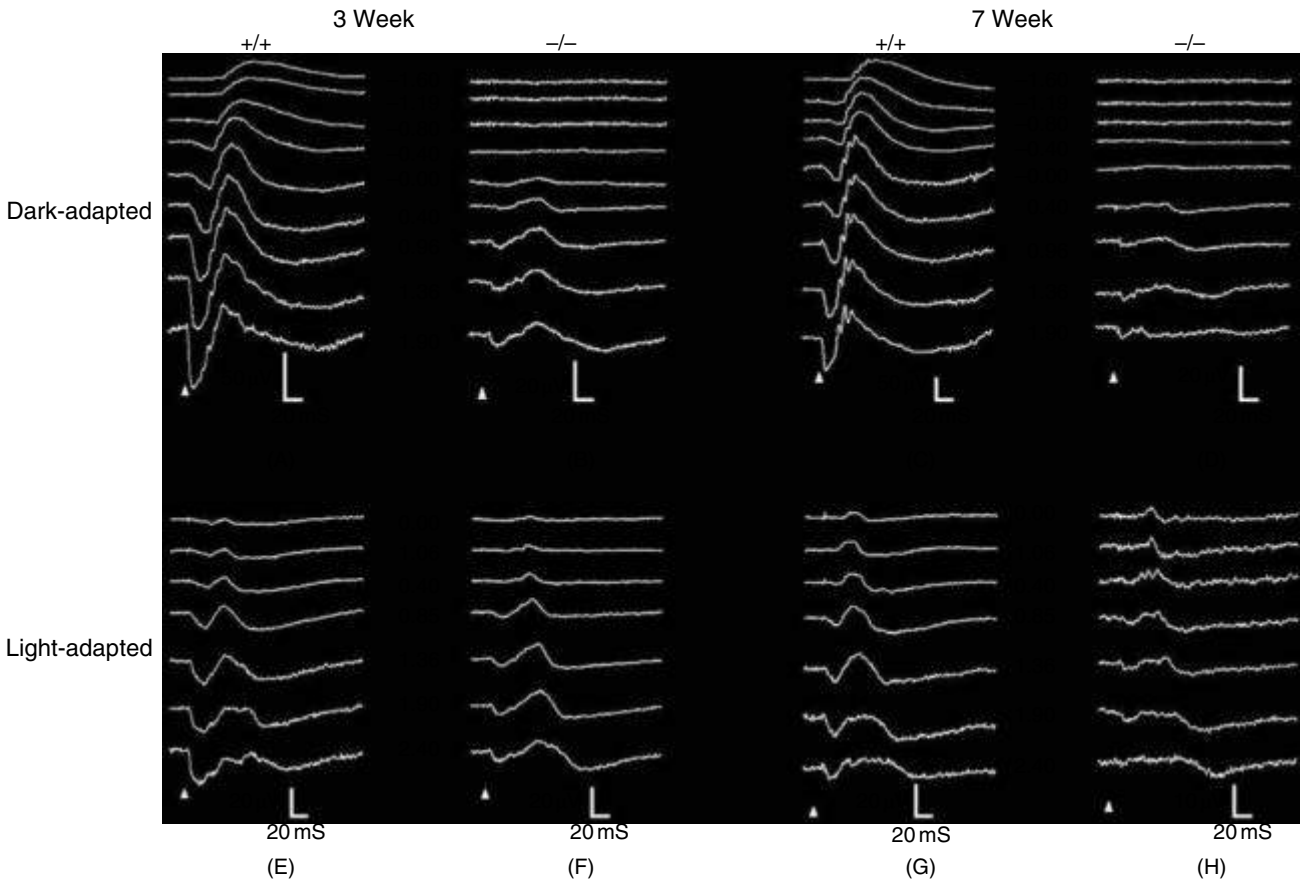


Figure 25.31 Representative dark-adapted (**A**–**D**) and light-adapted (to a background light of 30 cd/m^2; **E**–**H**) electroretinography intensity series responses from a normal control dog (indicated by the symbol +/+; **A**, **C**, **E**, **G**) compared to a PDE6A-mutant/*rcd3* dog (indicated by the symbol 2/2) at 3 weeks (**A**, **B**, **E**, **F**) and 7 weeks (**C**, **D**, **G**, **H**) of age. Arrowheads indicate the onset of flash. The flash intensity is indicated in log candela seconds/m^2. Note the difference in scales between the tracings. The vertical scale bar indicates amplitude in microvolts and the horizontal bars time in milliseconds. The *rcd3* puppies do not develop normal rod-mediated responses, and there is a rapid loss of the small amplitude response that is recordable. Much of this response is likely to represent cone responses. The light-adapted (cone) responses are also reduced from an early age. The cone a-wave is reduced at 3 weeks, and both a- and b-waves at 7 weeks. (Adapted with permission from Petersen-Jones, S.M., Tuntivanich, N., Montiani-Ferreira, F., & Wali Khan, N. (2006) ERGs of dog and chicken. In: *Principles and Practices of Clinical Electrophysiology of Vision* (eds. Heckenlively, J.R. & Arden, G.B.), Chapter 82. Boston, MA: MIT Press.)

layer of cone nuclei remained. As rods die, cone death follows, but more slowly. Eventually, all remaining cones are lost and the animals are completely blind. This can occur as early as 1 year of age, although some dogs retain some cone-mediated vision for several more years. At the later stages the cone ERG is extinguished, with residual vision being provided by a small number of surviving cones that may remain for up to a few years.

DNA-based tests are commercially available for detection of affected and carrier animals as well as those homozygous for the wild-type allele. The use of these tests gives the opportunity to eradicate these conditions from the affected breeds. Successful experimental gene therapy has been reported in both *PDE6A*- and *PDE6B*-mutant dogs (Petit et al., 2012; Pichard et al., 2016; Mowat et al., 2017b; Occelli et al., 2017). For these studies, an adeno-associated viral vector carrying a normal copy of the gene was introduced into the subretinal space of young puppies. Successful treatment resulted in rod function and preservation. The treated rods had apparently normal length of outer segments. The preservation of a population of functional rods in the treated retinal region allowed for survival of the cones in that region. Some possible toxicity from the therapy was reported in one study, resulting in areas of rescue but also areas of retinal change, including rosette formation and degeneration (Mowat et al., 2017b).

Rod cGMP-Gated Channel Genes: ***CNGA1, CNGB1***

Rod phototransduction results in a reduction of cGMP levels in the outer segment and closure of cGMP-gated channels. This leads to hyperpolarization of the photoreceptor and signaling to the second-order neurons. The rod cGMP channel

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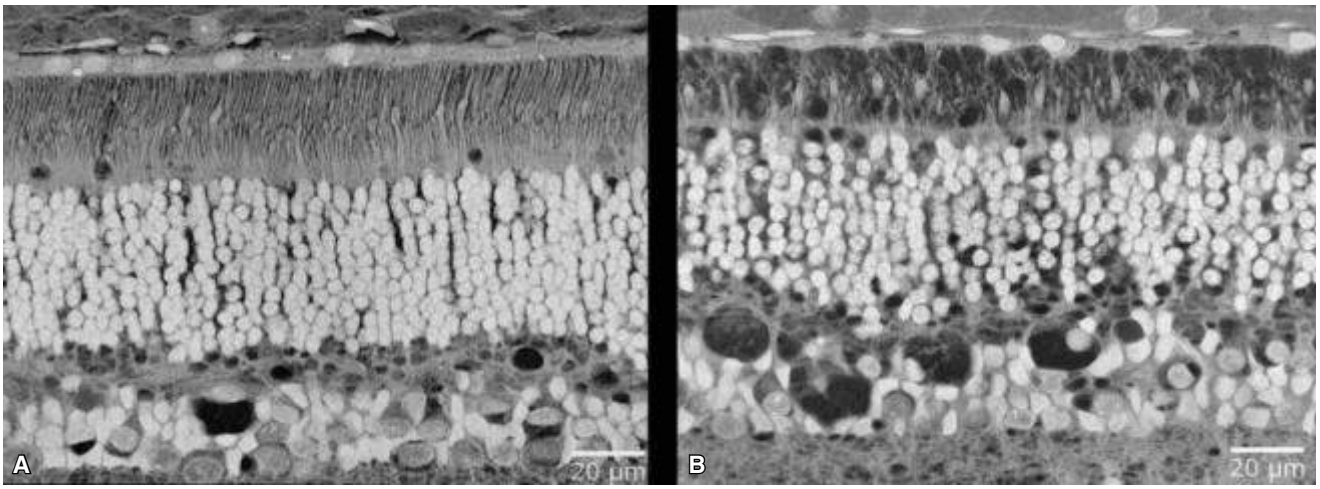


Figure 25.32 Light microscopy of the central retina from a normal 7-week-old dog (**A**) and an *rcd3*-mutant dog at the same age (**B**). Note the ordered arrangement of photoreceptor inner and outer segments in the normal dog. The *rcd3* dog has a reduction in numbers of outer and inner segments, with the remaining outer segments being shortened and distorted. The loss of rod inner and outer segments makes the residual cone inner and outer segments appear more prominent. The cone inner segments also appear swollen. There is also a loss of photoreceptor nuclei in the outer nuclear layer, with a reduction in the number of rows of nuclei as well as a reduction in the number of nuclei per unit area.

consists of a combination of three alpha subunits (CNGA1) and one beta subunit (CNGB1). Autosomal recessive PRA caused by mutations in both subunits has been identified.

One form of PRA in the Papillon accounting for 70% of cases was shown to be due to a mutation in the beta subunit, *CNGB1* (Winkler et al., 2013). The same mutation also causes PRA in the Phalene (which in some countries is considered to be a separate breed from the Papillon; Ahonen et al., 2013). The name *PRA Type 1* was used to reflect the presence of other forms of PRA in the breed for which the causal mutation(s) remain to be identified. *CNGB1*-mutant dogs have very severely reduced rod function, resulting in blindness at low lighting levels, but have a relatively slow rate of rod death (Fig 25.33). Ophthalmoscopic signs of PRA may not be readily detected until the dogs are at least several months of age. Earliest signs were a dull appearance to the tapetum and subtle blood vessel attenuation (see Fig 25.26). Actual tapetal hyperreflectivity takes longer to become appreciable. The reduced tapetum and dark tapetal coloration that are common in the breed can also make ophthalmoscopic detection of early retinal thinning difficult. Furthermore, being a small-breed dog they tend to have rather small superficial retinal vasculature that can make differentiation between early vascular attenuation and normal individual variation more challenging. Successful gene therapy in *CNGB1*-mutant dogs has been reported, restoring rod function and halting retinal degeneration (Petersen-Jones et al., 2018).

Autosomal recessive PRA in the Shetland Sheepdog was found to be caused by a mutation of the alpha subunit of the rod cGMP-gated channel (*CNGA1*; Wiik et al., 2015). Details of the phenotype have not been reported.

Rhodopsin-Dominant Progressive Retinal Atrophy

Rhodopsin is the molecule in the rod outer segment that is responsible for triggering the phototransduction cascade following its activation by a photon of light. A mutation in rhodopsin was identified as the cause of dominantly inherited PRA in the Bull Mastiff and Old English Mastiff (Kijas et al., 2003). Currently this is the only dominantly inherited form of PRA identified in dogs. The mutation is a missense mutation and the altered protein that results has a deleterious effect on the rod photoreceptor, leading to rod cell death. It appears that the mutant protein is transported normally to the rod outer segment and that the mutation is not associated with the unfolded protein response (this is a response that can occur when mutations alter the folding of a protein, interfering with its trafficking; Marsili et al., 2015). The mechanism leading to cell death may be by a gain of function. Acute damage to photoreceptors is induced by light exposure at levels that are not harmful to normal animals. This was shown to be dose dependent and photoreceptor loss could continue for several weeks following the light exposure (Cideciyan et al., 2005a; Gu et al., 2007; Iwabe et al., 2016; Sudharsan et al., 2017). This sensitivity to light exposure means that fundus examinations and photography can cause retinal damage. Therefore, it is very important that Mastiffs with suspected PRA should only be exposed to minimum examination lights. Without exacerbation from fundus photography or other additional light exposure, the affected dogs present with an atypical appearance for PRA due to a more rapid degeneration of the central retina, most likely associated with higher environmental light exposure to this region. Young adult dogs with degeneration of the central retina will have apparently normal-appearing

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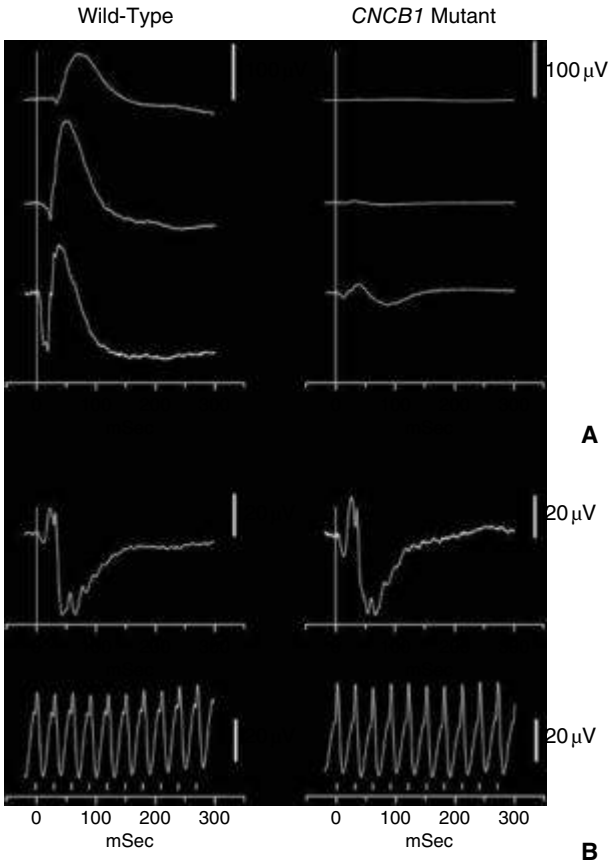


Figure 25.33 Representative electroretinographic (ERG) tracings from a normal control Papillon and a progressive retinal atrophy–affected Papillon, both 10 weeks of age. **A**. Dark-adapted ERG recordings at −2.4, −1.2, and 0.4 log cdS/m^2. **B**. Light-adapted flash and flicker (33 Hz) ERG tracings. Background white light of 30 cd/m^2 and flash intensity of 0.4 log cdS/m^2. The vertical bars on the flicker ERG indicates the flash timing. (Reproduced with permission from Winkler, P.A., Ekenstedt, K.J., Occelli, L.M., et al. (2013) A large animal model for CNGB1 autosomal recessive retinitis pigmentosa. *PLoS One*, **8**, e72229.)

peripheral regions. ERG studies showed that in puppies ERG amplitudes were normal, but became severely reduced by 12–18 months of age. More detailed investigation of rod function showed delayed recovery from exposure to brighter flashes of light (Kijas et al., 2002). Studies to develop a therapy for this form of PRA that can be translatable to humans with rhodopsin mutations with a similar gain-of-function mechanism are underway (Beltran et al., 2017b; Iwabe et al., 2014).

*S-antigen (**SAG**)*

S-antigen plays an important role in turning off the phototransduction cascade. A mutation in the S-antigen gene was identified in Basenjis with PRA (Goldstein et al., 2013a). Early stages of retinal thinning could be seen at about 5 years of age, with vascular attenuation detected at 6–7 years of age. A particular feature noted in affected Basenjis was that the fundus changes had an irregular or patchy appearance (Goldstein et al., 2013a).

Progressive Retinal Atrophy Due to Mutations in Cilia-Related Genes

The photoreceptor is a nonmotile, sensory-ciliated cell. Trafficking of proteins between the inner segment and the outer segment of the photoreceptor is very closely controlled and occurs via the connecting cilium. A large number of proteins are involved in control of transport along the connecting cilium. Mutations in proteins involved with this process are a common cause for photoreceptor dystrophies. Cilia play an important role in many cells, and in humans serious syndromic conditions occur in which retinal degeneration due to mutations in cilia genes are one part of the syndrome. Depending on the gene, other parts of the body affected vary, but can include brain and kidney. The term "ciliopathies" is used to describe the syndrome resulting from mutations in the cilia-related genes. Mutations in several cilia-related genes are recognized in dogs with PRA. In some instances these have been further characterized as cone-rod dystrophies, in which cones are involved early in the disease process and possibly preceding rod involvement. The forms of canine PRA currently known to be associated with mutations in cilia-related genes are listed in Table 25.1. One of the genes, *RPGR*, is on the X chromosome and is responsible for X-linked PRA. The remaining genes cause an autosomal recessive phenotype. Those in which further studies have been performed to characterize the condition will be considered further.

BBS4

PRA in the Hungarian Puli was shown to be associated with a nonsense mutation in *BBS4* (Chew et al., 2017). It is of interest that in humans *BBS4* mutations are associated with a syndromic condition, Bardet–Biedel Syndrome, which is characterized by obesity, retinal dystrophy, polydactyly, and hypogonadism. While these other features were not apparent in the PRA-affected Hungarian Pulis, one intact male was found to have abnormal spermatozoa.

C2orf71

A mutation in *C2orf71* was first identified as a cause of PRA in Gordon and Irish Setters (Downs et al., 2013). The same mutation was identified in other breeds with PRA (Svensson et al., 2016) and currently DNA-based testing is offered for 12 different breeds (www.ecvo.org/hereditary-eye-diseases/ecvo-manual.html). This makes this form of PRA numerically the second most important behind PRCD (see below). The form of PRA was given the name late-onset PRA or *Rcd4* (rod-cone degeneration Type 4). Studies in the Polska Owczarek Nizinny showed that the rod ERG could be reduced as early as 1.2 years of age and that early

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ophthalmoscopic changes were present at about 4.5 years of age. This appears to be a rod-led retinal degeneration (Svensson et al., 2016).

CCDC66

Schapendoes with PRA were shown to have a mutation in *CCDC66* (Dekomien et al., 2010; Lippmann et al., 2007). The onset of detectable clinical signs was reported to be between 2 and 5 years of age, with degeneration occurring over a 2-year period. Histology from a 5- and a 6-year-old affected dog was reported. The 5-year-old had complete loss of the photoreceptor layer, whereas in the 6-year-old the central retina still had two or three rows of photoreceptor nuclei. Immunostaining showed the absence of CCDC66 in the affected retinas.

FAM161A

PRA in Tibetan Terriers and Spaniels has been shown to be due to a mutation in *FAM161A* (Downs & Mellersh, 2014). PRA was first described in Tibetan Terriers in Sweden and later in England (Barnett & Curtis, 1978; Garmer et al., 1974). A breeding colony allowed for more detailed investigation (Millichamp et al., 1988). Affected dogs were night blind well before 1 year of age and rapid progression to blindness was reported. The scotopic ERG b-wave was reduced by 10 months of age and after 30 months the ERG was extinguished. Light microscopy revealed no major abnormalities at 10 weeks, but ultrastructurally some outer segments were severely disorganized and disoriented, with vesicle profiles occurring in the interphotoreceptor space. By 8 months there was considerable retinal thinning, and by 24 months the outer nuclear layer was reduced to only three or four rows of photoreceptor nuclei.

In the Tibetan Spaniel, PRA was reported in England, Sweden, Norway, and the United States. Ophthalmoscopic signs were detected between 3 and 5 years of age. Early detection by fundoscopy can be difficult due to variation in tapetal distribution and size. Affected dogs lose vision rather quickly, and they are severely visually impaired within a year following development of the initial ophthalmoscopic signs. Funduscopic examination reveals the classic findings for late-onset PRA, including hyperreflectivity of the peripheral tapetal fundus and severe attenuation of retinal vessels (see Fig. 25.28 and Fig. 25.29). The retinal atrophic changes spread inward, toward the ONH (Bjerkas & Narfström, 1994).

IQCB1/*NPHP5*

A mutation in *IQCB1* (NPHP5) was identified in American Pit Bull Terriers (Goldstein et al., 2013b) that had a form of PRA classified as a cone-rod dystrophy and named cone-rod dystrophy 2 (*crd2*; Kijas et al., 2004). ERGs from affected puppies at weaning showed severe dysfunction in both rods and cones. Funduscopy could detect retinal thinning between 3 and 6 months of age and the dogs were blind at 12 months, with an extinguished ERG and advanced generalized retinal degeneration (Kijas et al., 2004). A histologic study showed that as early as 3 weeks of age there appeared to be reduced inner segments and no outer segments (which are present in normal puppies of this age). By 12 weeks of age the outer nuclear layer was reduced to 5–7 rows (normally about 10–11) and by 20 months of age there were no inner or outer segments and the outer nuclear layer was reduced to only 1–2 rows (Goldstein et al., 2013b).

NPHP4

PRA in Miniature Wirehaired, Standard Wirehaired, and Shorthaired Dachshunds was found to be due to a mutation in *NPHP4* (Wiik et al., 2008). Initial studies in a colony of Shorthaired Dachshunds with PRA showed they had an early-onset, recessively inherited cone-rod dystrophy (Ropstad et al., 2007a). Approximately 60% of young affected dogs showed severe miosis in the light. By 5 weeks of age there was severely reduced or nonrecordable cone-derived ERG responses (Ropstad et al., 2007b), while rod responses were either normal or only slightly reduced. Funduscopic changes were not apparent until about 3 years of age. Then, signs of a generalized retinal degeneration appeared, with marked changes in the nontapetal fundus, with severe mottling (Fig. 25.34) and, within another year, pigmented ridges and spots. An unusual pigment migration into the neural retina has been detected at a comparably early stage of the disease by light and electron microscopy (Ropstad et al., 2008).

RPGR (X-linked Progressive Retinal Atrophy)

Three forms of X-linked PRA have been identified due to mutations in the *RPGR* gene (Kropatsch et al., 2016; Zhang et al., 2002). The first form was identified in Siberian Huskies. PRA in the breed was first described by Rubin (1989) and was subsequently shown to be X-linked (Acland et al., 1994). The causal mutation was in the open reading frame-15 (ORF15) region of *RPGR* and was also demonstrated to cause PRA in the Samoyed (Zhang et al., 2002). With the identification of a second form of X-linked PRA, the first form became known as *xlpra1*. Affected dogs were initially night blind and had early funduscopic signs at 2–4 years of age. Dark-adapted ERG b-wave amplitudes were decreased between 6 and 12 months of age and progressively declined and showed an increased response threshold (i.e., stronger flashes of light were required to induce a recordable ERG than for control dogs). Histologic changes were not apparent before 11 months of age. In the earliest stages, rod outer segments showed mild disorganization and ultrastructural fragmentation of individual discs could be seen. This was followed by a progressive rod degeneration. Initial

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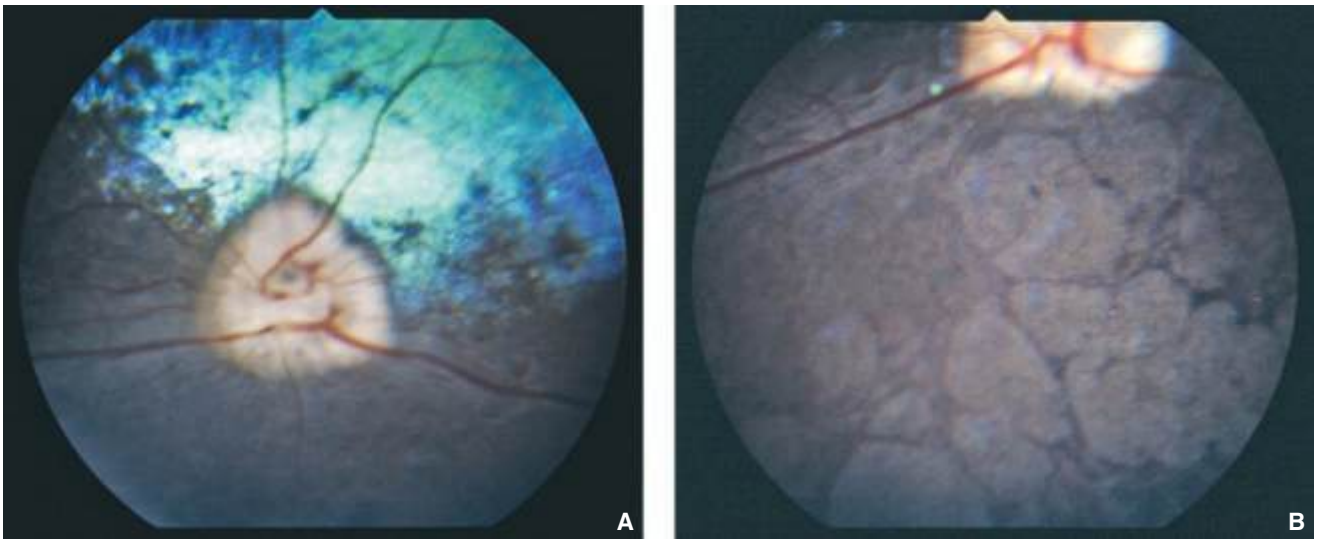


Figure 25.34 Early cone-rod dystrophy seen in a 1-year-old Wire-Haired Dachshund. **A**. In the tapetal fundus, hyperreflectivity is seen and vessels are moderately attenuated. **B**. In the nontapetal fundus, marked mottling is visualized. (Courtesy of Dr. Ernst-Otto Ropstad.)

changes in cones included a broadening of cone inner segments as rod outer segments were lost. Then, with further loss of rods, cone degeneration became apparent (Zeiss et al., 1999). The retinal changes started peripherally and spread centrally, such that in younger dogs (11–18 months of age) different stages of degeneration were apparent across the retina. Females homozygous for the mutation had a similar phenotype to the hemizygous males. There was considerable variation in degree of disease severity between individual male affected dogs that might suggest the influence of modifying loci. However, a study of potential modifying loci failed to show association of variants in the genes tested with disease severity (Appelbaum et al., 2016).

Retinal histology of heterozygous (carrier) females at 20 and 24 weeks of age appeared normal. Foci of local loss of outer segments and a decrease in rod density and outer nuclear layer thickness were detected in a 1.4-year-old carrier and became more severe with age. These foci had remaining cones noticeable as a line of wider cone inner segments. The scattered foci of rod loss is consistent with random X chromosome inactivation (Beltran et al., 2009; Zeiss et al., 1999; i.e., the portions of the retina where the X chromosome expressing the mutant allele was active degenerated, while those with the X chromosome expressing the normal allele did not). The degenerated regions seemed to be larger and progressed earlier in the peripheral retina.

The second form of X-linked PRA (*xlpra2*) was identified in a line of crossbred dogs (Zhang et al., 2002), having originated in the Miniature Schnauzer (Murgiano et al., 2019), and was also due to a mutation in ORF 15 of *RPGR*. *Xlpra2* is a more severe disease than *Xlpra1*, characterized by abnormal photoreceptor maturation and progressive degeneration. ERGs at 10 weeks of age showed decreased rod and cone responses. By 1 year of age rod responses were not detectable, while cone responses remained (Zhang et al., 2002). At an early age (3.9 weeks) there was early photoreceptor outer segment disruption, mislocalization of rod and cone opsins, and the numbers of pyknotic nuclei were increased in the outer nuclear layer, indicative of photoreceptor death. By 7.9 weeks of age there were severe outer segment disintegration and thinning of the outer nuclear layer. This continued, and by 26 weeks of age the outer nuclear layer thickness was less than 50% of normal and there was evidence of remodeling of the inner retina.

Xlpra2 female carriers show earlier retinal changes than *xlpra1* female carriers. In young carriers there were foci showing mislocalization of rod opsin and cone opsins, a sign of the disease process, and presumably reflecting regions in which the X chromosome with the mutant *RPGR* was active. With progression, it appeared that there was some redistribution of the normal photoreceptors across the retina, such that the foci of photoreceptor loss became less apparent and the retina appeared more uniform, although the outer nuclear layer was thinner than in control eyes. There seemed to be progression such that older carrier females showed complete atrophy of the peripheral retina, but maintained retinal morphology in the central retina, although with a thinner outer nuclear layer than normal (Beltran et al., 2009).

Gene therapy in *xlpra1* and *xlpra2* as a model for human X-linked retinitis pigmentosa due to *RPGR* mutations had shown success in rescuing photoreceptor function (as shown by ERG and vision testing) and slowing degeneration at different disease stages (Beltran et al., 2012, 2015, 2017a).

X-linked PRA has also been reported in Weimaraners with a large deletion mutation in *RPGR* (Kropatsch et al., 2016).

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RPGRIP1/MAP9

PRA in a colony of Miniature Longhaired Dachshunds was initially characterized (Curtis & Barnett, 1993) and shown to be a cone-rod dystrophy (Turney et al., 2007). The affected dogs had reduced cone ERG responses from 6 weeks of age, while at that age rod responses were considered normal. Ophthalmoscopic changes were apparent from 6 months of age and histologic changes as early as 10.5 weeks. Genetic mapping studies using the colony led to the identification of an insertion in *RPGRIP1* that segregated perfectly with the phenotype (Mellersh et al., 2006). However, further studies in pet dogs revealed that not all dogs homozygous for the insertion developed an early-onset cone-rod dystrophy (Busse et al., 2011; Kuznetsova et al., 2012; Miyadera et al., 2009). Furthermore, the same or a similar insert was found in *RPGRIP1* in other dog breeds where it did not always appear to segregate with disease. Interestingly, homozygosity for the *RPGRIP1* insert did seem to be associated with reduced cone ERGs, even if retinal degeneration did not develop. A second locus that was associated with whether dogs homozygous for the *RPGRIP1* insertion developed early- or late-onset retinal degeneration was mapped to the opposite end of the same chromosome (Miyadera et al., 2012). This locus was investigated and eventually shown to harbor a deletion involving *MAP9* (Forman et al., 2016). It seemed that this was a modifying locus. However, the deletion involving *MAP9* does not appear to completely explain the phenotypic variations seen.

A recent study showed that there is an absence of cone ERGs in some dogs homozygous for the *RPGRIP1* insertion regardless of *MAP9* genotype. These dogs had some discoloration of the tapetal fundus and some atrophic changes on OCT evaluation and altered cone morphology. Despite the ERG changes, the speed with which these dogs could negotiate an obstacle course was comparable to litter mates with normal cone ERGs. The conclusion of the study was that this form of cone-rod dystrophy is a multigenic disease in which mutations in neither *RPGRIP1* nor *MAP9* alone lead to the early progressive phenotype, and other loci may be involved in the cone-specific functional and morphologic defects (Das et al., 2017). Further studies will hopefully explain the molecular changes underlying these various phenotypes.

Genetic tests are offered to detect the presence of the *RPGRIP1* insert. However, they should be interpreted with care, particularly in some breeds where there is not good evidence to prove that the insert is responsible for PRA. The English Springer Spaniel is one such breed, where the incidence of dogs homozygous for the *RPGRIP1* insert is reported to be much greater than the incidence of PRA (Kuznetsova et al., 2012) and where ERG analysis of some homozygous dogs revealed no abnormalities (Narfström et al., 2012).

Progressive Retinal Atrophy Due to Mutations in Genes with Miscellaneous Functions

ADAM9

ADAM9 is involved in the normal close interaction between microvilli from the RPE cells and the distal tips of the photoreceptor outer segments. PRA in the Glen of Imaal Terrier was shown to be a cone-rod dystrophy (*crd3*) and was due to a mutation in *ADAM9* (Goldstein et al., 2010c; Kropatsch et al., 2010). Dogs homozygous for the mutation have ophthalmoscopic changes from 3–5 years of age, although one affected dog was reported to only show fundus pigmentary disturbances without obvious retinal thinning at 10 years of age. The initial funduscopic signs in the majority of affected dogs was a subtle generalized indication of retinal thinning. However, in a subset of dogs an isolated hyperreflective lesion in the area centralis was detected 2–4 years prior to development of generalized retinal thinning. The ERG was initially normal, but by 15 months of age there was reduced 30 Hz (cone-isolating) flicker responses, followed by a deterioration of both other cone and rod responses. Morphologically, at 4.7 weeks of age the rod and cone inner and outer segments did not show the usual tight and parallel arrangement. There was an apparent gap between the RPE layer and the tips of the photoreceptor outer segments. Electron microscopy showed that the RPE microvilli were not enveloping the outer segments. Instead, they formed a flattened tangled mat between the RPE and outer segments. This altered morphology may reflect the known involvement of *ADAM9* in the interaction between RPE and photoreceptors. By 5 years of age the outer nuclear layer was reduced to only a few rows of what were reported to appear to be predominantly rod nuclei (Goldstein et al., 2010c).

NECAP1

NECAP endocytosis-associated protein 1 (NECAP1) is involved in clarithin-mediated endocytosis that is involved in the formation of vesicles for protein trafficking. A missense variant (c.544G>A; p.Gly182Arg) was identified in Giant Schnauzers with autosomal recessive PRA. The proband was diagnosed with PRA at 4 years of age. A screening of other breeds identified heterozygotes for the mutation in various Spitz breeds and the Miniature Longhaired Dachshund (Hitti et al., 2019).

PRCD

The function of the PRCD protein was unknown, but recent studies have suggested that it plays a role in rod outer segment discs, where it is anchored to the cytosolic surface and binds to rhodopsin (Spencer et al., 2016). Progressive rod-cone degeneration (PRCD) is numerically the most important form of PRA, both because of the number of breeds affected but also because of the relatively high incidence in some of those breeds. The mutation arose prior to the dividing of dogs into breeds and is widely spread across the modern-day dog

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population. At the time of writing, over 50 breeds (including "designer breeds") are listed as having PRCD-PRA.

The characterization of the condition and the identification of the gene and causal mutation was a major effort spread over many decades. Identifying the underlying DNA mutation was made more difficult by the fact that the gene had not been previously recognized as a gene. The PRCD locus was initially mapped to canine chromosome 9 (Acland et al., 1998), then the confidence interval was further narrowed by using breeds that had been shown by test mating to have allelic disease (Goldstein et al., 2006). The newly identified gene was itself given the name *PRCD* after the condition in the dog. Coincidently, screening of human retinitis pigmentosa patients for mutations in the human *PRCD* gene identified one patient with a *PRCD* mutation, and that patient had the exact same mutation that causes PRCD in dogs (Zangerl et al., 2006b). The mutated protein that results from the PRCD mutation in dogs was investigated in a mouse model and this suggested that the mutation results in the protein not reaching the outer segments (Spencer et al., 2016). Although PRCD interacts with rhodopsin, the protein levels and mRNA levels for rhodopsin are normal in early disease stages, but then as disease advances they become rapidly reduced, which occurs prior to rod cell loss (Huang et al., 1994; Parkes et al., 1982).

While PRCD has been studied in several breeds of dog, the greatest depth of work has been in the Miniature Poodle and English Cocker Spaniel. Clinical signs are typical for PRA, with night blindness being the first owner-reported change. In Miniature Poodles, this was typically noted in affected dogs between 3 and 5 years of age. This progresses to complete blindness at between 5 and 7 years of age. The onset and progression do vary considerably between and within breeds. Funduscopic changes typically start at the peripheral tapetal fundus with an initial grayish discoloration, reflecting the onset of retinal thinning in this region. Blood vessel attenuation develops and with progression a more generalized tapetal hyperreflectivity becomes apparent (Fig. 25.35). Secondary cataract usually develops as the condition progresses and may obscure visualization of the fundus (see Fig 25.30). It is not uncommon for owners to assume that vision loss is due to the cataracts.

The condition is characterized by normal development and maturation of photoreceptors structurally and functionally, as assessed by ERG (Aguirre et al., 1982; Sandberg et al., 1986). This is followed by progressive photoreceptor degeneration and loss. As the photoreceptors degenerate, the rod-mediated ERG amplitudes become reduced compared to controls. A secondary loss of cones occurs and the cone ERG responses progressively deteriorate until they are extinguished. (Aguirre et al., 1982, Sandberg et al., 1986). This is followed by progressive photoreceptor degeneration and loss. As the photoreceptors deteriorate, the rod-mediated ERG amplitudes become reduced compared to controls. A secondary loss of cones occurs and the cone ERG responses progressively deteriorate until they are extinguished.

The histologic changes have been described in detail and divided into three phases, which are further subdivided into stages from 0 to 8 (Aguirre & Acland, 1988; Aguirre & O'Brien, 1986; Aguirre et al., 1982). In Phase 1 only photoreceptor outer segment changes are apparent. Phase 2 is characterized by degeneration of outer segments, inner segments, and photoreceptor nuclei. Phagocytic cells are frequently present in the interphotoreceptor spaces at this disease phase. Finally, Phase 3 is late atrophy with development of inner retinal changes, and with the most advanced disease stage complete retinal atrophy has occurred and only a glial scar remains. The earliest morphologic change reported was on electron microscopy in Miniature Poodles at 14.5 weeks of age. Abnormal vesicular profiles were present adjacent to the outer segment cell membrane and within apical villi of RPE. At this stage some rod outer segments also showed disorganization of discs (Aguirre et al., 1982). Vesicular profiles were not a common feature in English Cocker Spaniels with PRCD (Aguirre & Acland, 1988). The rate of turnover of outer segment discs, as investigated by autoradiography, was slowed in affected Miniature Poodles and the disorganization of outer segment discs became more extensive with age (Aguirre et al., 1982; Aguirre & O'Brien, 1986). These studies showed that the stage of disease varied spatially across the retina, with the inferior retina being most rapidly affected followed by the superior and then temporal retina.

PRCD in American Cocker Spaniels and Labrador Retrievers was also studied, contributing to our knowledge of the phenotype of this condition (Aguirre and Acland, 1988; Kommonen & Karhunen, 1990; Kommonen et al., 1994; see Fig. 25.27, Fig. 25.36, Fig. 25.37, Fig. 25.38, Fig. 25.39, Fig. 25.40). The availability of a DNA-based test for this common form of PRA is expected to dramatically reduce the incidence over the next several years.

PPT1

Palmitoyl-protein thioesterase (PPT1) plays a role as a hydrolase in lysosomes, but may also be involved in the maintenance of synaptic function. Murgiano et al. (2019) identified a complex structural variant in Miniature Schnauzers with PRA. They proposed the name PRAPPT1. There was evidence of incomplete penetrance. It is of interest that the PPT1 mutations in humans are associated with a form of neuronal ceroid lipofuscinosis, but in the dog the phenotype was restricted to PRA only.

RD3

RD3 is required for the transport of guanylate cyclases and guanylate cyclase activating protein 1 to the photoreceptor outer segments, and possibly acts to inhibit guanylate cyclase activity in the inner segment prior to it being trafficked to the

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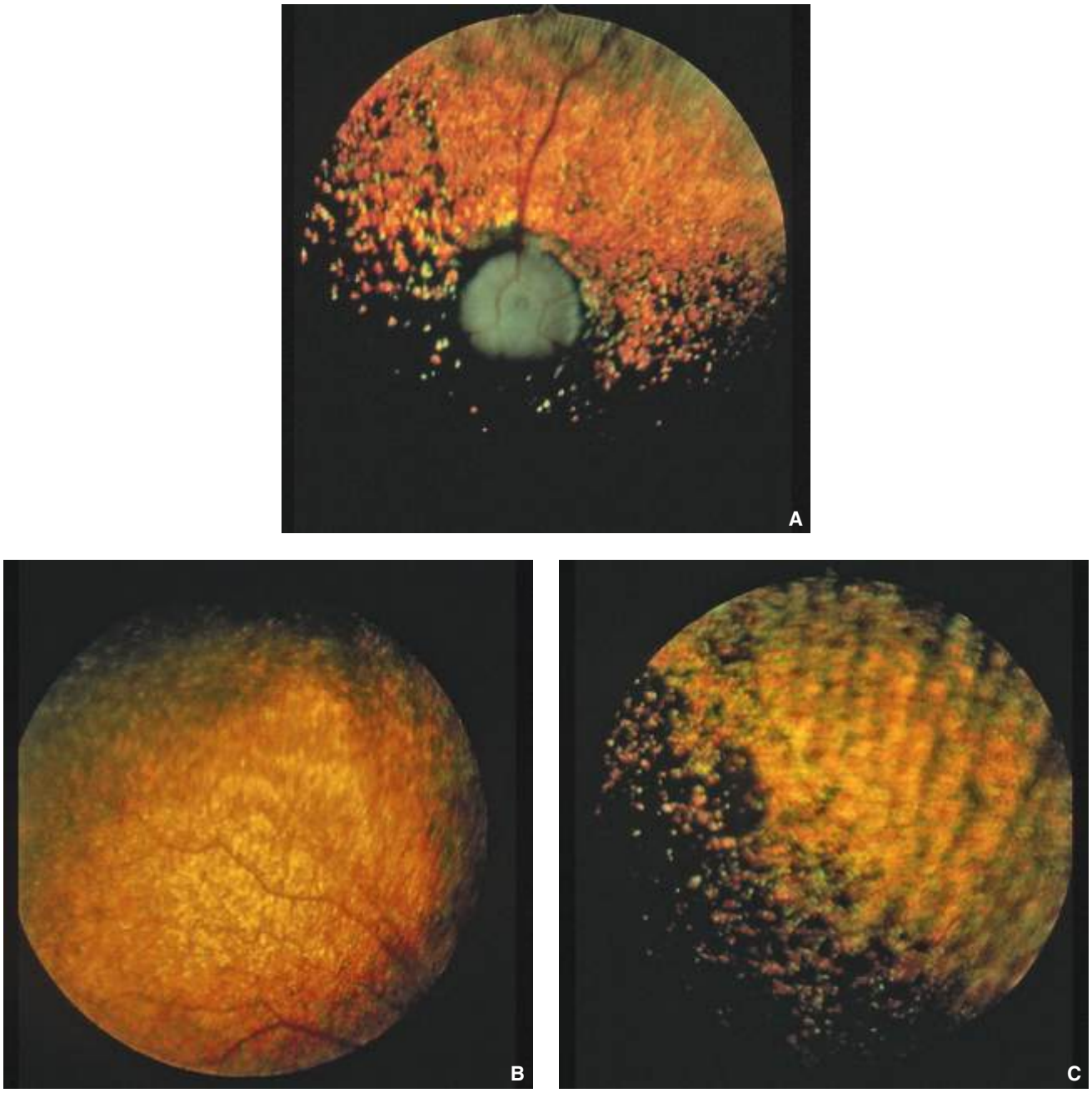


Figure 25.35 Advanced progressive rod-cone degeneration observed in a 7-year-old Miniature Poodle. **A**. Central part of fundus, with severe vascular attenuation and a grayish tapetal discoloration. **B**. Midperipheral fundus, with hyperreflectivity and discoloration in the peripheral part. **C**. Periphery of the tapetal fundus, with a marked striation. The contours of the choroidal vascular pattern are observed underlying the atrophic neural retina.

outer segment (Azadi et al., 2010; Peshenko et al., 2011, 2016; Zulliger et al., 2015). Functional and morphologic studies of PRA in Collies revealed that the maturation of photoreceptors became halted, as had been seen previously in rod-cone dysplasia in Irish Setters (*rcd1*), and therefore the condition in Collies was named *rcd2* (Acland et al., 1989). The causal mutation was identified in *RD3* (Kukekova et al., 2009).

Affected Collies are night blind, which is detectable by 6 weeks of age (Wolf et al., 1978), and are usually blind before 1 year of age. At 3.5–4 months of age, on fundoscopy there is a granularity of the central tapetal fundus, which spreads out to involve the more peripheral fundus. Generalized tapetal hyperreflectivity develops, as well as other signs of classic PRA (Fig. 25.41). The ERG was abnormal from day 16

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Figure 25.36 A 5-year-old American Cocker Spaniel with progressive rod-cone degeneration. Note the generalized vascular attenuation and both hypo- and hyperreflectivity of the tapetal fundus.

and shows an absence of rod responses and also abnormal cone function. Ultrastructural studies showed a delay in rod outer segment appearance and when outer segment material was present it was abnormal and disorganized. There was a rapid loss of the outer nuclear layer, which had thinned to just two to three rows by 6 weeks of age (Santos-Anderson et al., 1980). Abnormal elevation in cGMP levels was detected in the affected dog retina, although this was not proceeded by reduced phosphodiesterase activity, unlike in the *rcd1* Irish Setter (Woodford et al., 1982). With the discovery that the condition results from a mutation in *RD3*, it seems feasible that the elevated cGMP might be associated with a lack of inhibition of guanylate cyclase activity within the inner segments (Molday et al., 2014).

SLC4A3

A mutation in *SLC4A3* was associated with PRA in Golden Retrievers (Downs et al., 2011). The mutation was reported to account for 60% of PRA in the breed in Sweden and 76% in the UK. It accounted for a lower proportion of PRA cases in France and Finland and was not identified in PRA-affected Golden Retrievers from the United States. The average age at ophthalmoscopic diagnosis of PRA was 7 years of age.

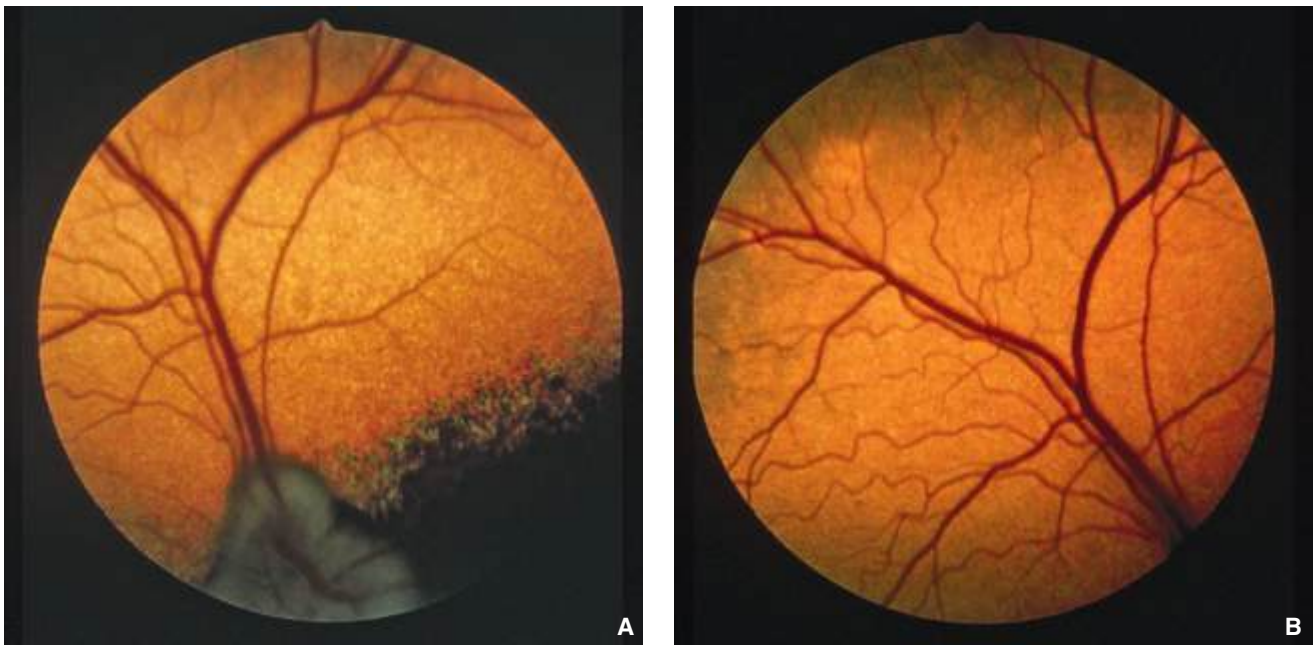


Figure 25.37 A 7-year-old American Cocker Spaniel not affected by progressive rod-cone degeneration (PRCD). The fundus vasculature is normal in both the central (**A**) and peripheral (**B**) parts. In the peripheral tapetal fundus, there is a bilateral, slightly grayish discoloration, probably resulting from a thin tapetal area in this region. These ophthalmoscopic signs can, however, be confused with those found in early PRCD. Often, an electroretinogram must be performed to differentiate the conditions.

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Figure 25.38 A generalized change in tapetal reflectivity, though the retinal vasculature still appears normal, in a 4-year-old Labrador Retriever with early progressive rod-cone degeneration. The dog had visual problems at night and a nonrecordable scotopic electroretinogram.

STK38L

A form of PRA in the Norwegian Elkhound was given the name early retinal degeneration, *erd*. This has been shown to be due to a mutation in the *STK38L* gene (Goldstein et al., 2010b).

Affected dogs were night blind by 6 weeks of age and blind by 12–18 months. The tapetal fundus had a granular appearance and was slightly discolored at 6 months of age. By 13.5 months there was tapetal hyperreflectivity and marked retinal blood vessel attenuation. The ERGs of the younger affected puppies failed to develop a normal b-wave and had an a-wave–dominated waveform. There was some increase in amplitudes from 30–52 days of age, but they remained a-wave dominated. Subsequently both a- and b-wave ERG amplitudes decreased, but there was a more rapid decrease in the b-wave, which accentuated the overall a-wave dominance of the remaining waveform. Both rod and cone flicker responses were abnormal as well, with a switch from positive to negative with age. Rod function was lost before cone function, with the latter not being lost until approximately 1 year of age (Acland & Aguirre, 1987).

Morphologic changes in *erd*-affected dogs have been reported and show some rather unique features compared to other forms of inherited retinal degenerations (Acland & Aguirre, 1987; Berta et al., 2011). Photoreceptors started to differentiate normally, but rods showed variation in outer

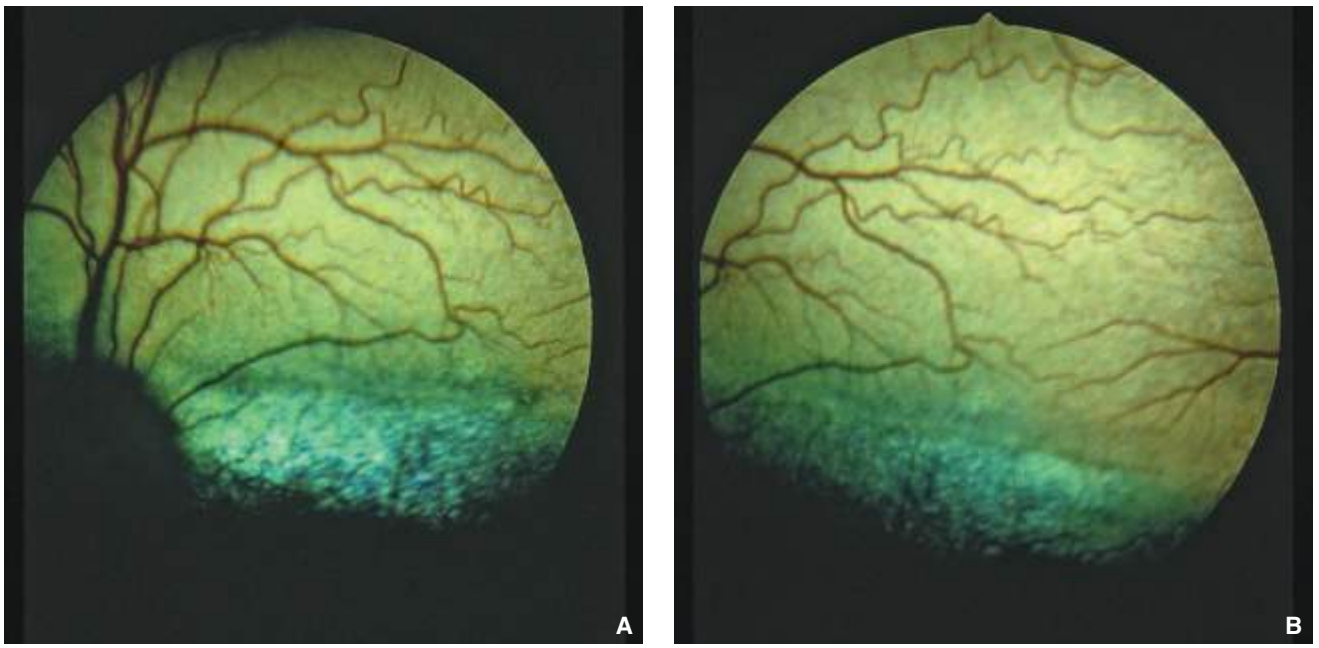


Figure 25.39 Bilateral funduscopic changes in a 4-year-old Labrador Retriever with early progressive rod-cone degeneration. Most of the tapetal fundus is hyporeflective, and there is a horizontal zone on either side of the disc, with grayish discoloration as well as hyperreflectivity. **A**. Central fundus. **B**. Midperipheral fundus.

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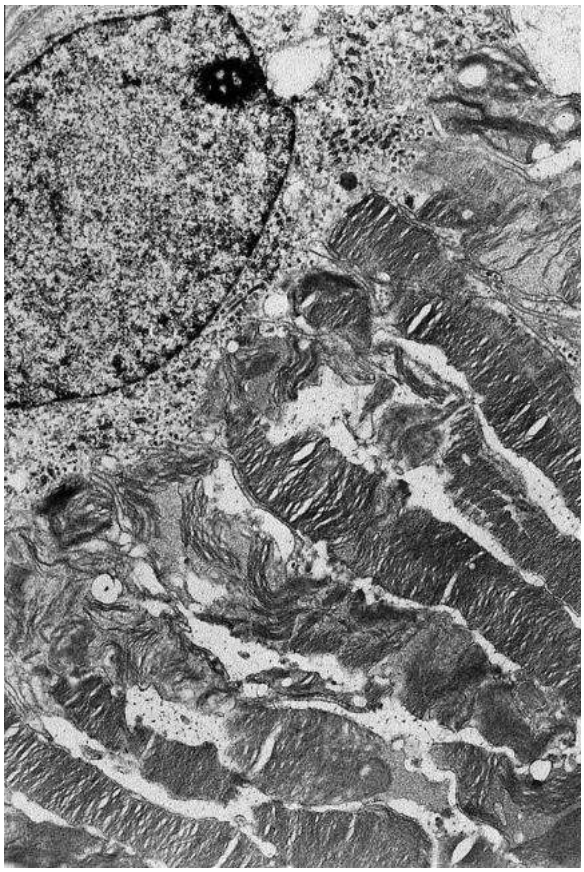


Figure 25.40 Ultrastructure of the outer retina in a 4-month-old Labrador Retriever with hereditary retinal degeneration (progressive rod-cone degeneration). Degenerative changes are seen in specific rod outer segments, whereas the retinal pigment epithelium appears normal. (Original magnification 14,000×.) (Courtesy of Dr. Bertel Kommonen.)

segment lengths and the inner segments also varied with some being abnormally long. Opsin mislocalization and neurite sprouting from rods also occurred. Cone outer segments appeared to be normal in early disease stages. Early death of photoreceptors occurred, but then there was a phase of photoreceptor proliferation (this is well past the stage of the normal proliferation of photoreceptor progenitor cells). After proliferation, both S and M/L cones remained, but there was a new population of "hybrid" photoreceptors that had both rod (rhodopsin) and cone (S-cone opsin) proteins and were probably the product of the proliferation. Therefore, despite the death of many photoreceptors, the thickness of the outer nuclear layer was initially maintained, most likely due to the newly produced hybrid photoreceptors (Berta et al., 2011).

With progression of the disease, there was a marked reduction of both size and number of rod and cone inner and outer segments. By 20 weeks of age, the outer nuclear layer was severely diminished. There was dysgenesis of both rod and cone synaptic terminals. Rod spherules were reduced in

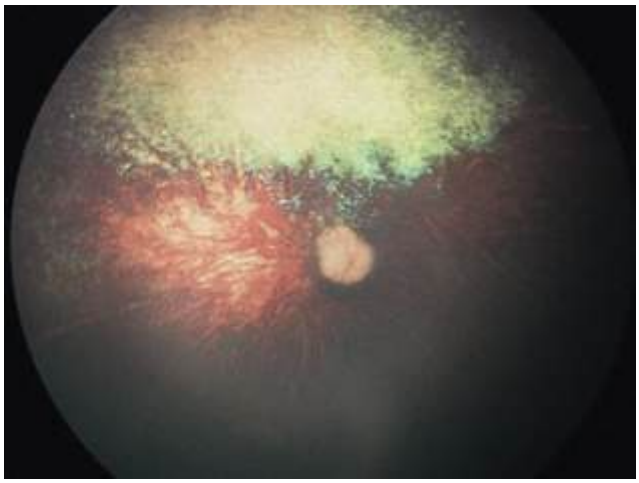


Figure 25.41 Right eye of a Collie with both progressive retinal atrophy and Collie eye anomaly. Note the choroidal hypoplasia lesion and the marked attenuation of retinal vasculature. The tapetal fundus is hyperreflective.

number and appeared immature. Cone synaptic terminals appeared to start developing normally initially, but then failed to mature with age. At 20 weeks, cone pedicles had degenerated and had vacuolated cytoplasm (Acland & Aguirre, 1987). These early changes in synaptic terminals may explain the ERG phenotype, suggesting that the lack of a b-wave (the b-wave being primarily the result of ON bipolar cell response) could be due to interference with the communication between photoreceptors and bipolar cells.

Photoreceptor degeneration progressed and by 4 years of age only a few neuronal cells with morphology reminiscent of photoreceptors remained. The phenotype of affected dogs suggests that *STK38L* plays a role in control of cell division and morphogenesis in photoreceptors.

Other Forms of Progressive Retinal Atrophy for Which a DNA-Based Test is Available

DNA-based tests are currently available from some testing laboratories for additional forms of PRA for which a peer-reviewed manuscript presenting the DNA changes and supporting evidence that they are causing the phenotypes have not been published.

Miniature Schnauzer

Two tests are available for PRA in Miniature Schnauzers called Type-A and Type-B through www.optigen.com. Type-A was reported to be rare and Type-B associated with 55% of PRA cases in the breed. Apparently, dogs homozygous for the Type-B DNA variant have an 86% chance of developing PRA, with 14% having no clinical signs at 7 years of age. A missense variant reported in the phosducin gene (Zhang et al., 1998) was interpreted by some as the cause of PRA in the breed. Further studies showed a lack of associa-

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tion of the variant with PRA in Miniature Schnauzers in South Korea (Jeong et al., 2008). It had been reported on the OptiGen website (www.optigen.com) that this was in fact a polymorphism and not the cause of PRA. Unfortunately, some DNA testing laboratories are still offering identification of this polymorphism as a test for PRA in the breed, which it is not. Some clarification was provided by Murgiano et al. (2019), who describe the mutation in PPT1 that has been described above. They also explain that PRA-type A was an X-linked condition due to a mutation in RPGR and was what was described as Xlpra2 (see above).

Original studies of PRA in Miniature Schnauzers in the 1980s and 1990s were of a form given the term *photoreceptor dysplasia* (*pd*; Parshall et al., 1991). It is not reported whether the dogs with *pd* had the Type-A or Type-B DNA variant, or represented a third form of PRA in the breed. There were early morphologic changes suggesting developmental retardation (observed on histology from 24 days of age). The rod photoreceptors had abnormal outer segments that were shortened and disorganized. Rod inner segments were variably altered, being either long and slender or diminutive. Cone inner segments appeared normal, but the cone outer segments were short. Affected dogs were night blind and had markedly depressed dark-adapted ERG responses. Despite this early onset, funduscopic changes were not apparent until between 2 and 5 years of age (Fig. 25.42). At 5 years of age, only a single row of photoreceptor nuclei remained in the central retina and there was complete degeneration in the periphery.

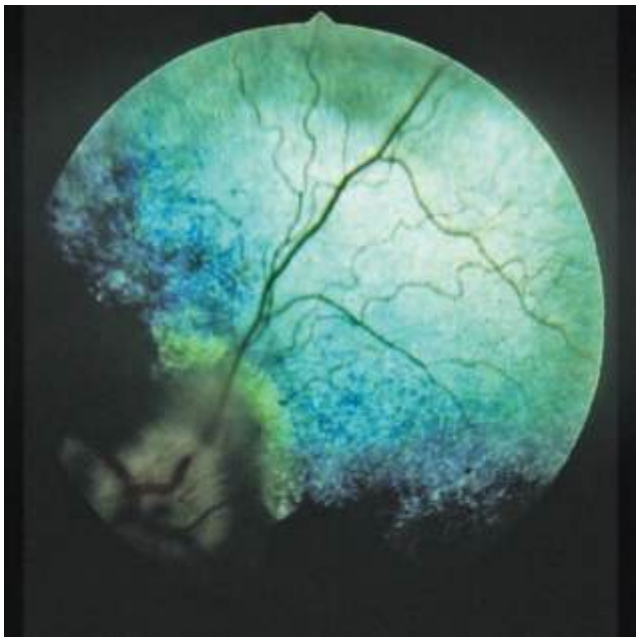


Figure 25.42 Retinal degeneration observed in a 4-year-old Miniature Schnauzer. Note the hyperreflectivity, mainly in the midperipheral fundus, as well as the grayish discoloration in the periphery. There is also a generalized vascular attenuation. This dog was visually impaired only in low lighting conditions.

Other Breeds

Genetic tests have been offered for PRA in Italian Greyhounds (www.optigen.com) and Lhasa Apsos (www.ahtdnatesting.co.uk). Italian Greyhounds with PRA are reported to first show funduscopic changes at 5–8 years of age (Goldstein et al., 2011). Goldstein (2014) mapped Italian Greyhound PRA (IG-PRA) to canine chromosome 11 and found that there was downregulation of a collagen gene, *COL27A1*, and a microRNA, mir455, in dogs heterozygous for the risk allele (retinal samples from homozygotes prior to retinal degeneration were not available) and suggested that low levels of mir455 might cause IG-PRA.

Forms of Progressive Retinal Atrophy without a Molecular Diagnosis

With PRA having been reported in upward of 100 breeds of dog, there are several forms awaiting more detailed investigation. Below are descriptions of some forms that have been investigated in more detail, but for which the causal DNA mutation has not been identified.

Rod Dysplasia in Norwegian Elkhounds

A recessively inherited photoreceptor dystrophy was described in the Norwegian Elkhound many years ago (Aguirre & Rubin, 1971a, 1971c). Subsequently, the mutant strain was lost (Acland & Aguirre, 1987; Aguirre, 1978). The disease was first described as "photoreceptor abiotrophy," because it was initially believed that normal photoreceptor development preceded photoreceptor degeneration (Cogan & Kuwabara, 1965). Later studies, however, showed developmental abnormalities, specifically of rods.

Clinically affected dogs became night blind at 6 months of age, and were totally blind at between 3 and 5 years of age. The initial funduscopic changes were a brownish granular appearance of the central tapetal fundus. More severe ophthalmoscopic changes (i.e., vascular attenuation and hyperreflectivity of the tapetal fundus) were not observed until approximately 2 years of age. At this time, there was also patchy loss of pigment in the nontapetal fundus.

The ERG showed major alterations by 6 weeks of age. Rod responses were absent, whereas cone responses were initially normal, but subsequently became abnormal. The photopic b-wave was nonrecordable at approximately 3 years of age (Aguirre & Rubin, 1971b). Morphologically, changes in the rod photoreceptors were observed at 12 weeks of age. The rod inner segments were short and the outer segments disorganized. At 1 year of age, the rod inner segments were also disorganized, and pyknotic photoreceptor cell nuclei were seen. These changes were followed by degeneration of the cones. The retina was completely atrophic at approximately 6 years of age (Aguirre, 1978).

In rod dysplasia of Norwegian Elkhounds, there were no abnormalities in cyclic nucleotide (cGMP) metabolism, thus distinguishing the disorder from *rcd1* in Irish Setters (Acland

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et al., 1980). Also, matings between the two breeds failed to produce affected progeny, showing that the two conditions were nonallelic.

Progressive Retinal Atrophy in Akitas

Recessive PRA with a variable age at onset and variable initial funduscopic changes has been described in Akitas (O'Toole & Roberts, 1984; Paulsen et al., 1988). Night blindness occurs between 1 and 3 years of age, with complete blindness developing between 3 and 5 years of age. Ophthalmoscopically, two patterns of initial funduscopic changes were described. The most common was development of a hyperreflective horizontal band in the central tapetal fundus, starting in the area centralis region and then extending horizontally following the visual streak. The other pattern was characterized by changes of fundus appearance indicative of retinal thinning in the peripheral tapetal fundus. With progression of both patterns, a generalized hyperreflectivity of the entire tapetal fundus, vascular attenuation, and atrophy of the ONH developed.

Early ERG findings included significant reductions in scotopic b-wave amplitudes. Dark adaptation curves were abnormal, and there appeared to be both rod and cone dysfunction. Because there was marked variation in ERG changes, a definite diagnosis by ERG could not be made until 1.5–2 years of age.

X-linked Progressive Retinal Atrophy in the Border Collie

An apparent X-linked PRA has been described in the Border Collie. It was shown not to be due to either of the *xlpra1* or *xlpra2* mutations. By 3–4 years of age night blindness had progressed to total blindness (Vilboux et al., 2008).

Progressive Retinal Atrophy in Whippets

A somewhat unusual form of PRA in Whippets has been reported (Somma et al., 2017). Prior to retinal degeneration the ERG had a characteristic lack of b-wave, but with an apparently normal a-wave. The ERG b-wave originates primarily from activity of ON bipolar cells. A lack of ERG b-wave is characteristic of a lack of ON bipolar cell responses to photoreceptor stimulation. Nystagmus was seen in young affected dogs, but was not apparent in adults. Small retinal bullae (small foci of separation between photoreceptors and RPE) were detected in the early stages, but these became less apparent as retinal degeneration developed. The affected dogs developed a loss of photoreceptor layers as detected by spectral domain OCT, the outer nuclear layer being markedly thinned by 18 months of age.

Treatment for Progressive Retinal Atrophy

There is currently no treatment for PRA. Gene augmentation therapy has shown promise in some forms in the early stages while there are still remaining photoreceptors that can be rescued. These studies have been undertaken to help develop therapies for human patients with analogous conditions such as retinitis pigmentosa. Dietary supplements have been investigated and some are being recommended, although clinical trials with dogs with PRA have not been reported. Docosahexanoic acid supplementation failed to alter the course of PRCD (Aguirre et al., 1997). Antioxidant supplements have been shown to increase ERG amplitudes in normal Beagles (Wang et al., 2016), but studies in dogs with inherited retinal degenerations have not been reported.

Other Retinal Dystrophies

RPE65 Retinopathy

A specific retinopathy due to a mutation in *RPE65* in Briards has been studied in detail. It was first described as a congenital stationary night blindness and that term continues to be used today (Narfström et al., 1989). However, the name does not fit well for several reasons. Firstly, the condition is not stationary; secondly, affected dogs also have reduced vision in mesopic conditions; and thirdly, it is quite different from the group of conditions in humans that make up the congenital stationary night blindness. *RPE65* mutations in humans most commonly cause Leber congenital amaurosis. The causal mutation in *RPE65* was identified in affected Briards originating in Sweden (Veske et al., 1999) and the same mutation was subsequently shown to be present in Briards in the United States (Aguirre et al., 1998). *RPE65* is expressed in the RPE, where it plays a necessary role in the visual cycle as a retinoid isomerase (Jin et al., 2005; Moiseyev et al., 2005). Lack of functional RPE65 prevents the formation of 11-*cis*-retinal, which is the retinal that combines with opsins in the photoreceptors to form light-sensitive visual pigments. There is very reduced sensitivity of photoreceptors and therefore only visual function under relatively bright lighting conditions. The phenotype of affected dogs has been described and very successful gene augmentation studies performed with colonies of affected dogs. These led to clinical trials in human patients with Leber congenital amaurosis due to *RPE65* mutations, and now a gene therapy treatment has been approved in the United States by the Food and Drug Administration.

Studies from Narfström and colleagues initially described the phenotype in affected Briard dogs (Ekesten & Narfström, 1992; Narfström et al., 1989, 1994; Nilsson et al., 1992; Wrigstad et al., 1992, 1994). Affected puppies had night blindness and some degree of vision loss in mesopic and photopic conditions, a rapid nystagmus, and reduced PLRs. The fundus initially appeared normal. However, there are some differences in phenotype between different *RPE65* dog colonies. In one colony, created by crossing affected Briards with Beagles, an early degeneration of the area centralis was noted, starting in affected puppies (Mowat et al., 2017a).

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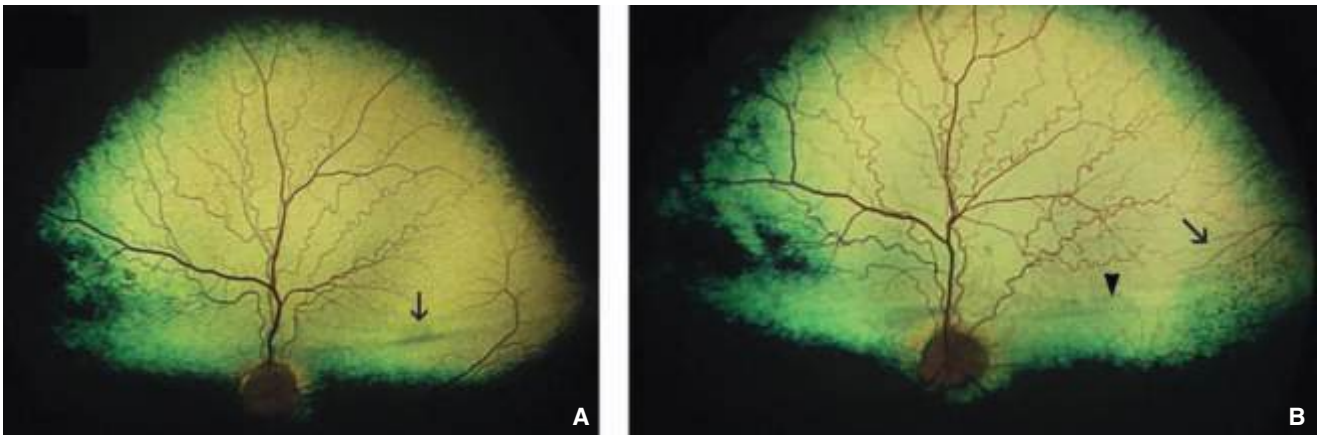


Figure 25.43 Ophthalmoscopic lesions in *RPE65*-mutant dogs. **A**. *RPE65*$^{-/-}$ dog at 2 years of age. There is a focal area of thinning in the area centralis resulting in tapetal hyperreflectivity (arrow). There is also a change in tapetal reflectivity along the visual streak. **B**. Fundus changes in a 4-year-old *RPE65*$^{-/-}$ dog. The arrowhead indicates tapetal hyperreflectivity in the area centralis. The arrow points to a series of grayish lesions in the lateral portion of the tapetal fundus.

This resulted in loss of photoreceptors in this region and retinal thinning, showing as a focal area of tapetal hyperreflectivity (Fig. 25.43). This was not reported in other colonies, suggesting that it may occur in some lines and not others due to effects such as differing background genetics. From 3 years of age onward, some dogs start to develop small grayish spots in the tapetal fundus (see Fig 25.43B), and in older dogs slight retinal blood vessel attenuation could be appreciated. On histologic examination, apart from changes in the area centralis in some dogs, the most striking feature is the accumulation of inclusion bodies in the RPE cells (Fig. 25.44). These increase in both number and size with age. With progression, abnormalities are apparent in photoreceptor outer segments, and a slow loss of photoreceptors occurs.

The ERG of affected dogs shows very reduced sensitivity, with grossly elevated dark-adapted response threshold and reduced amplitudes. The light-adapted ERG is also abnormal, with cone flicker responses being extremely reduced or even not recordable. However, single-flash light-adapted responses can be quite large, and this may be because in the affected dog they may have contributions from the rod system which is so desensitized in the absence of 11-*cis*-retinal that it may not be suppressed by the background light used in the protocols for recording light-adapted ERGs. In normal dogs this background light exposure suppresses the rod-mediated responses, allowing recording of cone-only responses. There was a similar finding in *Rpe65-/-* mice (Seeliger et al., 2001).

A ground-breaking gene therapy study was performed in *RPE65*-mutant dogs using an adeno-associated viral vector to deliver a functional copy of the *RPE65* gene (Acland et al., 2001). Adding to these results, at least another three groups became involved in gene therapy trials in *RPE65*-mutant dogs. These contributed important information to human clinical trials like safety and efficacy of therapy, optimization of the gene therapy construct, duration of rescue, ability to treat the second eye, and so on (Annear et al., 2011; Le Meur et al., 2007; Narfström et al., 2003). For more details of the results of gene therapy in the dog model, the reader is referred to review articles (Petersen-Jones et al., 2012).

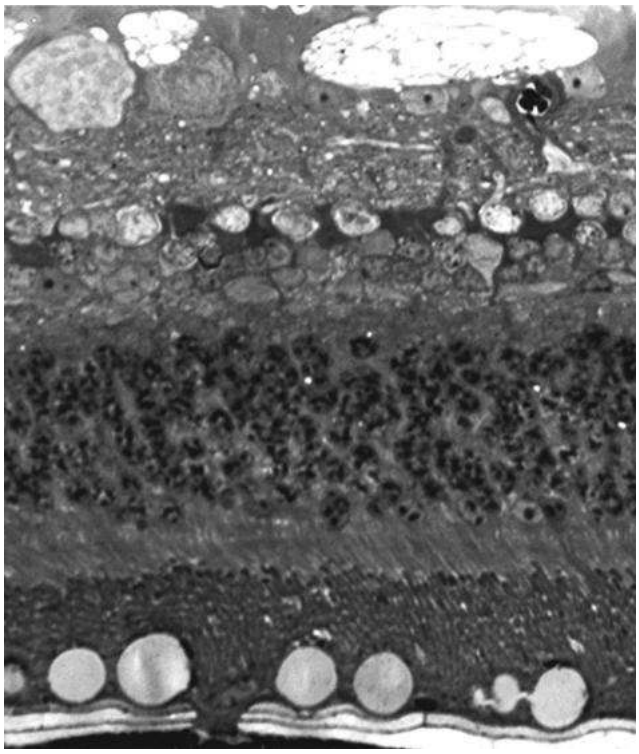


Figure 25.44 Electron microscopy showing vacuolation in the retinal pigment epithelium. This is due to the accumulation of lipid vesicles, which is a characteristic of the condition.

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Swedish Vallhund Retinopathy

A recently recognized, unique retinopathy of Swedish Vallhunds has been described with a prevalence of 34.9% in the breed (Cooper et al., 2014). Three disease stages have been described:

- *Stage 1*. Multifocal red or brown tapetal discoloration. There is no vision loss. The mean age that this was seen was 4.3 years of age, with a wide range from 1.9 months to 17.8 years.
- *Stage 2*. Multifocal retinal thinning, starting in periphery. Some night vision deficits are apparent and ERG amplitudes are reduced.
- *Stage 3*. More generalized retinal thinning. There is night blindness and severe daytime vision problems, and a severe reduction in ERG amplitudes. Dogs with this stage of disease were between 9.2 and 15.4 years of age.

On histologic assessment, there were small islands of relatively normal retina surrounded by completely degenerate regions in which there was accumulation of autofluorescent material in the RPE.

A molecular study showed that affected retina had increased levels of mRNA for *MERTK* (Ahonen et al., 2014) and an intronic LINE insertion in the gene was identified (Everson et al., 2017). Although highly associated with the phenotype, there was some discordance, with some affected dogs not having the insertion and some dogs with the insertion not showing a phenotype. The reason for this discordance needs further investigation. *MERTK* is important for the phagocytosis of photoreceptors by the RPE, a process that is needed for the maintenance of normal retinal health. The mechanism by which possible overexpression of *MERTK* leads to retinal disease also needs further study.

ABCA4 Dog

Recently a mutation causing a late-onset retinopathy in Labrador Retrievers was found to be due to a 1 bp deletion that introduced a frameshift and premature stop codon (c.4176insC, p.Phe1393LeufsTer3) in ATP binding cassette subfamily A member 4 (ABCA4; Makelainen et al., 2019). ABCA4 is an ATP-dependent flippase expressed in the photoreceptor disc membrane and is necessary in the visual cycle for its transport of N-retinylidene-phosphatidylethanolamine and phosphatidylethanolamine out of the lumen into the cytoplasm (Quazi et al., 2012).

The affected Labradors were diagnosed at 10 years of age and had impaired vision under daylight and dimlight conditions. The pupils were dilated and PLRs reduced. The menace response was present, but the dazzle reflex was abnormal. Fundus changes included a grayish hyporeflectivity to the visual streak and mild vascular attenuation. Retinal sections from an affected dog showed absence of ABCA4 on immunohistochemistry, thinning of the outer nuclear layer with loss of both rods and cones, and accumulation of lipofuscin in the RPE cells.

Achromatopsia

Achromatopsia in dogs has previously been known as day blindness, hemeralopia, or cone degeneration. Two different mutations involving *CNGB3* have been identified in different breeds of dog (Sidjanin et al., 2002) causing recessive achromatopsia, and more recently two different mutations have also been identified in *CNGA3* (Tanaka et al., 2015). CNGA3 and CNGB3 are the two subunits that make up the cGMP-gated channel in the outer segment cell membrane of cone photoreceptors. This channel is closed as the result of cone phototransduction as levels of cGMP are decreased.

The condition was originally identified and characterized in the Alaskan Malamute (Aguirre & Rubin, 1974, 1975a; Rubin, 1971a, 1971b; Rubin et al., 1967). Affected puppies were diagnosed with day blindness and photophobia between 8 and 12 weeks of age. Vision under dim lighting conditions remained normal. Cone ERG responses of reduced amplitude can be detected in young affected puppies during retinal maturation, but these are rapidly lost and cannot be recorded from adult affected dogs (Komáromy et al., 2013). Rod ERG responses remain normal.

The *CNGB3* mutation in the Alaskan Husky is a deletion of 404,820 bp that removes the entire coding region of the *CNGB3* gene. The same mutation is also found in the Siberian Husky, Alaskan Sled Dog, and Miniature Australian Shepherd (Sidjanin et al., 2002; Yeh et al., 2013). The sharing of the same mutation across breeds suggests a common shared ancestor. There are reports of day-blind Alaskan Malamutes that do not have the genomic deletion that removes *CNGB3*, suggesting that there could be genetic heterogeneity (Seddon et al., 2006; Yeh et al., 2013). A second *CNGB3* mutation was identified in German Shorthaired Pointers with achromatopsia (Sidjanin et al., 2002). The mutation was a missense mutation changing a very well conserved aspartic acid to asparagine (p.Asp262Asn). The phenotype was very similar to that resulting from the genomic mutation of *CNGB3*.

The achromatopsia dogs studied had a very gradual loss of cones. The earliest reported ultrastructural change was a lamellar disorganization of cone outer segments seen in some cones from 7 weeks of age. There was also accumulation of bundles of filaments in some cone inner segments (Aguirre & Rubin, 1974). Cone degeneration was slow and the more recent studies have reported that even in older animals some intact cones with shortened outer segments remain (Komáromy et al., 2013). Displacement of some cone nuclei to the inner segment and then extrusion into the subretinal space adjacent to the RPE was noted (Aguirre & Rubin, 1974; Gropp et al., 1996).

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Gene augmentation therapy with adeno-associated viral vectors delivering a normal version of *CNGB3* has been successful in restoring cone function in younger dogs (Komáromy et al., 2010). The therapy was not successful in older dogs, despite the fact that they still had cones present. However, it was found that pretreatment with ciliary neurotrophic factor (CNTF) followed by gene therapy could restore cone function to older dogs (Komáromy et al., 2013). CNTF causes photoreceptors to lose their outer segments. It appeared that the regrowth of new cone outer segments made them amenable to the gene augmentation therapy.

CNGA3 mutations were identified in both German Shepherd Dogs and Labrador Retrievers with day blindness (Tanaka et al., 2015). The affected dogs had lost photopic function by 8–10 weeks of age. The mutation in the German Shepherd Dog was a missense mutation (c.C1270T; p.Arg424Trp) that changes a very well-conserved amino acid. The Labrador Retrievers had a 3 bp deletion (c.1931_1933delTGG) that removes a well-conserved valine (Val644del).

Day blindness has been reported in other breeds including the Miniature Poodle (Rubin, 1989) and as single case reports in a Rhodesian Ridgeback cross, a Chihuahua, and an Australian Cattle Dog (Hurn et al., 2003). A condition in related Gordon Setters in which there is day blindness and a lack of cone ERG responses has been described (Good et al., 2016). The fundus appeared normal ophthalmoscopically. These changes were suggestive of achromatopsia. However, both affected and most unaffected related dogs had low rod-mediated ERG responses compared to other breeds of dog, although it was not clear whether this was part of the condition or was really a form of cone-rod dystrophy. Longer-term follow-up of the affected dogs has not been reported.

Congenital Stationary Night Blindness

Recently, a recessively inherited congenital stationary night blindness (CSNB) was reported in Beagles (Kondo et al., 2015). The phenotype was very similar to that of some forms of human CSNB. The affected dogs were night blind and had a normal-appearing fundus. The ERG showed a lack of dark-adapted b-wave, but an a-wave of normal amplitude. Light-adapted ERG b-wave amplitude was reduced in response to stronger stimuli and long flash responses showed a reduced ON-response but a normal OFF-response. Loss of b-wave suggests a lack of function in ON bipolar cells. This can occur due to mutations of genes expressed in the ON bipolar cells or in the photoreceptor presynaptic terminals (Pardue & Peachey, 2014; Zeitz et al., 2015). There was no progression of the ERG changes over a 5-year period. The retinal layer thicknesses of affected dogs were comparable to controls and ultrastructural studies showed normally appearing synapses between rods and second-order neurons. Immunohistochemistry showed altered levels of PKCalpha, Goalpha, and RGS11, which are involved in signaling in ON bipolar cells. It was suggested that these changes were likely secondary downstream effects rather than being the primary cause of the defect. The causal mutation was subsequently identified in the leucine-rich repeat, immunoglobulin-like and transmembrane domains-containing protein 3 (LRIT3) gene (c.762_763delG, p.Lys246AsnfsTer5). LRIT3 is involved in photoreceptor to bipolar cell synaptic transmission (Das et al., 2019).

Early Retinopathy in the Bernese Mountain Dog

In the Bernese Mountain dog, a familial retinopathy has been described (Chaudieu & Molon-Noblot, 2004; Krahenmann, 1974) and was given the term "early retinopathy," although clinical signs were not apparent until about 1 year of age. On fundoscopy, a horizontal zone of tapetal hyperreflectivity developed parallel to the tapetal/nontapetal junction, which is the region of the visual streak. Some dogs also showed peripapillary hyperreflectivity. The ERG b-wave was reported to be decreased. The clinical changes only progressed slowly.

Retinal Pigment Epithelial Dystrophy

This condition was originally described in the UK in the 1950s, often occurring in working breeds of dog (Barnett, 1965b; Parry, 1954b). Parry initially used the term central progressive atrophy with pigment epithelial dystrophy. The term central PRA (CPRA) came into common usage and is still used in the UK, although retinal pigment epithelial dystrophy (RPED) is now used more commonly. Initially described as a hereditary problem, there is now strong evidence that, at least in some breeds of dog, environmental (dietary) factors may play a major role in development of the retinal lesions.

The funduscopic changes start with the appearance of irregular light brown foci or spots in the tapetal fundus. In the Briard these were reported to appear first at the lateral corner of the tapetal fundus (Bedford, 1984). Over time, these foci increase in size and become distributed throughout the tapetal zone. At this stage there are also atrophic changes, such as hyperreflectivity around the pigment foci that indicate atrophy of the overlying neural retina. The nontapetal fundus shows similar foci, with hyperpigmentation and depigmented areas in between. With progression of the disease, pigmented lesions coalesce into widely spaced, irregular patches, interspersed with hyperreflective areas in the tapetal fundus (Fig. 25.45). End-stage atrophy includes a more generalized hyperreflectivity, with sparse amounts of pigmented foci or striae (or both), with the latter findings not always being obvious to the examiner.

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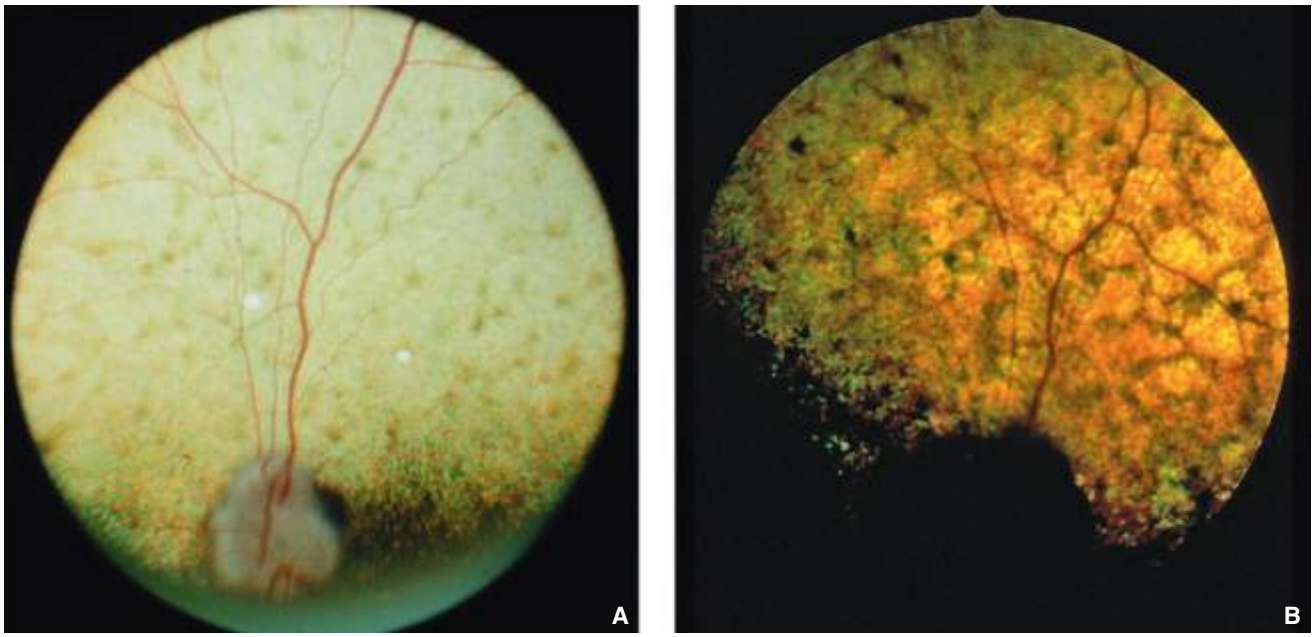


Figure 25.45 Advanced retinal pigment epithelial dystrophy with typical ophthalmoscopic changes. **A**. A 4-year-old English Cocker Spaniel with multiple light brown spots across the tapetal fundus. This dog had low circulating vitamin E levels. **B**. A 5-year-old English Cocker Spaniel with darkly pigmented spots surrounded by hyperreflective zones and severely attenuated retinal vessels.

The effect of RPED on vision becomes apparent when there are moderately advanced retinal lesions. Initially, affected dogs may have problems seeing stationary objects in brighter light, but can still see moving and distant objects. Vision tends to be better at low light levels. Not all affected dogs become blind and there is a very variable age at onset and rate of progression. Secondary cataracts may develop in the advanced stages.

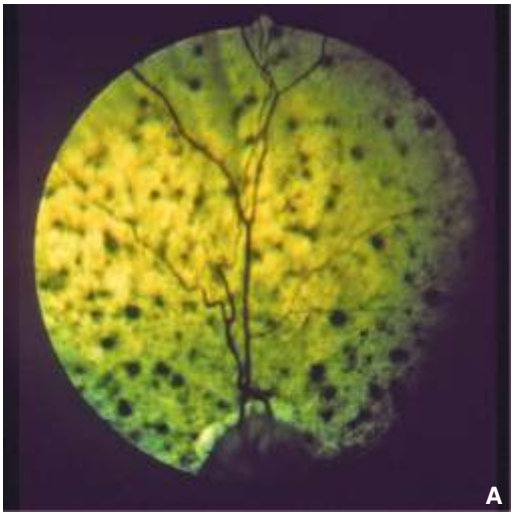
RPED has been recognized in many breeds in several different countries, but it appears to have been most prevalent in the UK. Breeds that have been reported to be affected included Labrador and Golden Retrievers, Border Collies, Rough and Smooth Collies, Shetland Sheepdogs, English Cocker Spaniels, English Springer Spaniels, Chesapeake Bay Retrievers, Briards, and others (Barnett, 1965a, 1969, 1979; Bedford, 1984). In Briards an unusually high frequency of the disorder was reported, with 30% and 40% of examined Briards in the UK being affected (Bedford, 1984; Lightfoot et al., 1996). However, the condition seemed to disappear from the breed, coinciding with many owners improving the diet of their dogs or adding additional supplements, after hearing of a possible association with low dietary antioxidant levels. Recent reports from the Briard health committee in the UK indicate that a diagnosis of RPED has not been made at eye-screening sessions for several years. These findings suggest that at least in some breeds, poor diets low in antioxidants may play a role in the development of the condition.

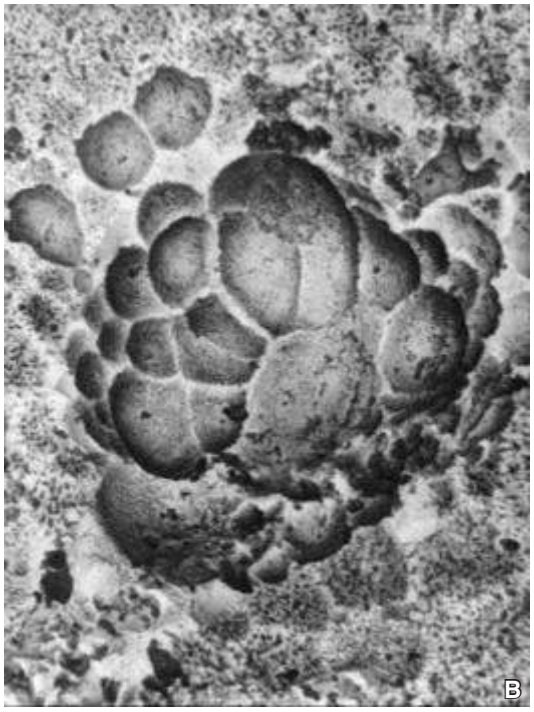
Morphologic studies showed that early in the disease the RPE cells become hypertrophied and accumulate a light brown granular material in the cytoplasm. This is an autofluorescent lipopigment (Aguirre & Laties, 1976; Lightfoot et al., 1996; Fig. 25.46**)**. With progression of the disease, more RPE cells become hypertrophied, and at the end stage hypertrophic pigment epithelial cells form multicellular nests. Photoreceptors adjacent to the hypertrophied RPE initially have shortened outer segments and go on to degenerate. In late disease stages photoreceptor loss is widespread.

Association of Retinal Pigment Epithelial Dystrophy with Vitamin E Deficiency

Retinal lesions in dogs with dietary deficiencies in vitamin E result in retinal changes that appear identical to those of RPED. Effects of dietary deficiency of vitamin E are considered later in this chapter. However, a breed-related condition consisting of RPED and neurologic dysfunction associated with low circulatory levels of vitamin E has been described in English Cocker Spaniels (McLellan et al., 2002, 2003). The affected dogs had very low plasma levels of vitamin E and developed funduscopic lesions typical for RPED (McLellan et al., 2002). Of 15 affected English Cocker Spaniels, 11 had neurologic dysfunction such as ataxia, proprioceptive deficits, abnormal spinal reflexes, and muscle weakness (McLellan et al., 2003). Treatment with high levels of dietary vitamin E supplementation appeared to improve the neurologic signs. It is recommended that English Cocker Spaniels diagnosed with vitamin E deficiency should be supplemented with 600–900 IU twice daily oral tocopherol (McLellan & Bedford, 2012).

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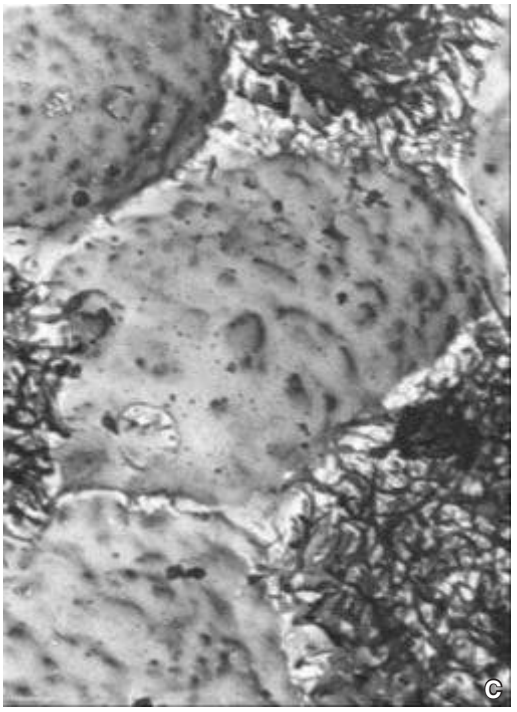


Figure 25.46 Retinal pigment epithelial dystrophy **(**RPED) in a 5-year-old German Shepherd. **A**. Note the generalized pigmented spots, generalized hyperreflectivity, and severe vascular attenuation at this advanced stage of RPED. **B**. Scanning electron micrograph of the retinal pigment epithelium (RPE) in the same dog. Nests of hypertrophied RPE cells are seen bulging up toward the photoreceptor cells that have been peeled away. (Original magnification 480×.) **C**. Scanning electron micrograph of abnormal RPE cells that have lost their apical microvilli. (Original magnification 3000×.) (Courtesy of Dr. Claudio Peruccio.)

Pigmentary Chorioretinopathy in the Chinese Crested Dog

A novel retinopathy has been described in the Chinese Crested Dog from northern Europe and the United States (Narfström et al., 2011). Affected dogs developed funduscopic changes from 3 to 4 years of age. The lesions were darkly pigmented, with a light center (donut-like), and started in the peripheral fundus. They were easier to detect in the tapetal fundus, but were also prevalent in the nontapetal fundus. As the condition progressed the lesions increased in number and also involved the central fundus. The first ERG changes were reductions in a- and b-wave amplitudes. Morphologic studies showed that in early disease stages the RPE cells appeared hypertrophied and bulged into the subretinal space. Atrophy of photoreceptors developed, perhaps secondary to the RPE changes. Dystrophic changes in the choriocapillaris were also observed in

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conjunction with the RPE lesions. In older affected dogs (6–8 years of age), areas of geographic atrophy were found, mainly in the midperipheral and peripheral fundus. The mode of inheritance for the defect has not been established.

Lysosomal Storage Diseases

Some lysosomal storage disease result in retinal changes and are considered here. They include neuronal ceroid lipofuscinosis, mucopolysaccharidosis, and gangliosidosis.

Neuronal Ceroid Lipofuscinosis

The neuronal ceroid lipofuscinoses (NCL) are a group of recessively inherited progressive neurodegenerative diseases that occur in human patients and other species, including dogs (Goebel, 1992a). Katz and colleagues in a recent review suggested that only those conditions in dogs that are caused by one of the known human NCL genes should be automatically classified as NCL (Katz et al., 2017). They also stated that for a canine disorder to be considered as a potential form of NCL, it should show a progression of neurologic signs and include at least four of the following: loss of vision, behavioral changes including changes in personality (e.g., becoming aggressive) and loss of learned behaviors, tremors, cerebellar ataxia, cognitive and motor decline, sleep disturbance, and seizures.

The NCL genes include those that code for known soluble lysosomal enzymes, and others for proteins where the function is not fully understood (Williams & Mole, 2012).

So far, 12 mutations in 8 genes are reported in dogs (see Katz et al., 2017 for a review), which represent 8 of the 13 known human forms of NCL. The breeds include Dachshund and Cane Corso (different mutations in *PPT1*), Dachshund (*TPP1*), Border Collie and Australian Cattle Dog (same mutation in *CLN5*), Golden Retriever (*CLN5*), Australian Shepherd (*CLN6*), Chinese Crested Dog and Chihuahua (same mutation in *MFSD8*), English Setter, Australian Shepherd and Alpenländische Dachsbracke (different mutations in *CLN8*), American Bulldog (*CTSD*), and Tibetan Terrier (*ATP13A2*). An additional 14 breeds are reported with NCL-like conditions for which the causal gene mutation has not been identified (Katz et al., 2017).

There is variation in the onset and rate of progression of the different forms of NCL in dogs. Vision loss is a common feature, but in several forms this has a central origin. The retina as well as the brain of affected dogs have accumulation of autofluorescent cytoplasmic inclusion bodies. Ganglion cells, bipolar cells, and RPE may be affected. The rapid demise of the affected animals in some forms probably means they do not live long enough to develop retinal degeneration (Goebel, 1992b; Jolly et al., 1994; Taylor & Farrow, 1992). However, retinal dysfunction and degeneration are reported in some forms and are outlined below.

In a study of Tibetan Terriers with NCL, Riis and colleagues reported that affected puppies were night blind (the only neurologic sign for the first 5–6 years of life) and had a negative-shaped ERG waveform with a lack of b-wave. With progression, the negativity of the ERG decreased to reveal an underlying b-wave, which then gradually declined with age suggesting a slow photoreceptor loss (Riis et al., 1992). Katz and Narfström reported on a group of 7- to 10-year-old affected Tibetan Terriers, finding them to have moderately or severely depressed rod responses, but only slightly reduced cone-mediated responses (Katz et al., 2005). There was photoreceptor cell loss and disrupted outer segment morphology late in the disease.

NCL-affected English Setter dogs usually develop clinical signs at approximately 1 year of age. These include progressive cortical blindness, ataxia, muscle weakness, and dementia. The disease is ultimately fatal in 2- to 3-year-old dogs. ERG responses were normal in young dogs despite the presence of neurologic changes, but became abnormal with disease progression (Aguirre et al., 1986; Berson & Watson, 1980). In advanced cases, the c-wave of the ERG, which is recordable by using a direct current (DC) ERG recording technique (rather than the more commonly used alternating current (AC) ERG recording), was replaced by a negative component, and the standing potential of the eye was reduced (Nilsson et al., 1983). These changes are suggestive of a dysfunction of the RPE.

In the Polish Owczarek Nizinny, visual dysfunction and funduscopic alterations occur relatively early (Fig. 25.47), often between 1 and 2 years of age, while neurologic changes become apparent in middle-aged dogs (Wrigstad et al., 1995). Fundoscopy reported for two affected dogs revealed gray to brown spots across the tapetal fundus, tapetal hyperreflectivity, and blood vessel attenuation. On histology there was photoreceptor loss as well as the characteristic intracytoplasmic inclusions (Fig. 25.48). The scotopic ERG responses were absent and the cone flicker responses reduced, but recordable, in a 2-year-old affected dog (Wrigstad et al., 1995). Similar to the changes reported in affected English Setters, using DC-ERG recording the c-wave was found to be replaced by a slow negative potential, suggesting a dysfunction of the RPE.

A case report of two affected Miniature Schnauzers described that they both developed progressive blindness over a 3-month period when they were 3 and 4 years of age. This was accompanied by the onset of neurologic signs (Smith et al., 1996). They were reported to have severe retinal atrophy (Jolly et al., 1997).

A study of Dachshunds with a mutation in *TTP1* showed that they appeared to have normal visual behavior and retinal function at 3 months of age, but by 7 months they had reduced vision, reduced PLRs, and their ERG amplitudes were declining. There was a grayish discoloration and mottling in the tapetal fundus and vascular attenuation (Katz

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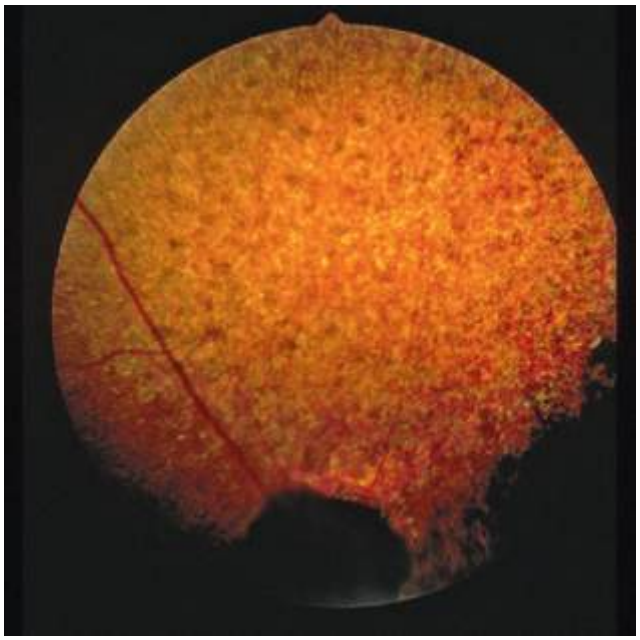


Figure 25.47 Marked funduscopic changes are seen in this 16-month-old Polish Owczarek Nizinny dog, which was affected with neuronal ceroid lipofuscinosis and behavioral problems and was virtually blind.

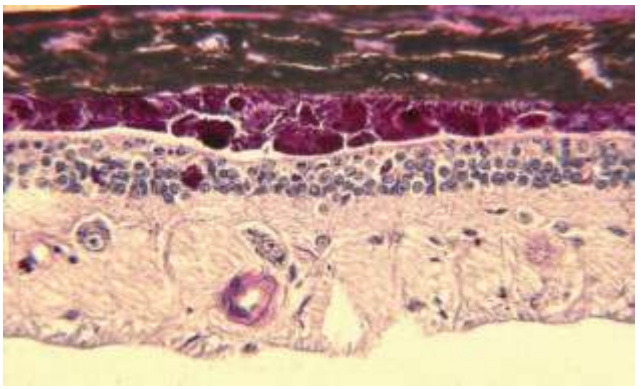


Figure 25.48 Light microscopy and periodic acid–Schiff (PAS) staining of the retina of a 24-month-old Polish Owczarek Nizinny affected with neuronal ceroid lipofuscinosis. Note the marked staining in the retinal pigment epithelium (RPE) and some staining in the inner retina. RPE cells were distended and filled with PAS-positive material, and in some areas there were multiple layers of RPE cells.

et al., 2008). Autofluorescent material accumulated in most layers of the retina. It was subsequently reported that 65% of affected Dachshunds also develop a multifocal retinopathy consisting of multiple small bullae (retinal detachments) across the fundus (Whiting et al., 2015).

Morphologically, retinal changes vary between affected breeds. Ganglion cells and RPE cells are most often affected. An accumulation of periodic acid–Schiff (PAS)–positive material may be seen in the RPE and in neuronal cells of the inner retina. Ultrastructurally, intracellular inclusions with a granular appearance, known as granular osmeophilic dense deposits, may be seen in neuronal cells of brain and retina. These cells may also contain membranous fingerprint-like material or curvilinear profiles (resembling ceroid) enclosed by a membrane, especially in RPE and ganglion cells. In the brain, the size and the morphologic appearances of the storage bodies differ among brain regions, but are comparable to those found in the retina.

Therapy for Neuronal Ceroid Lipofuscinosis

Therapeutic trials are underway to treat some forms of NCL. Experimental treatment in Dachshunds with a mutation in *TTP1* consisted of either repeated infusion of recombinant TTP1 protein into the cerebrospinal fluid (Katz et al., 2014; Vuillemenot et al., 2015) or delivery of a normal copy of *TTP1* via a gene therapy vector (Katz et al., 2015). These treatments significantly slowed down the progression of neurologic disease, but did not delay retinal degeneration or loss of retinal function, although the gene therapy approach did slow loss of retinal ganglion cells (Whiting et al., 2016). Therefore, to try to slow or prevent retinal degeneration, intravitreal implantation of autologous bone marrow–derived stem cells transduced to express normal *TTP1* was performed. This *ex vivo* gene therapy approach significantly slowed the progression of retinal changes (Tracy et al., 2016).

Mucopolysaccharide Storage Diseases

In both humans and animals, mucopolysaccharide storage diseases (MPS) are caused by the inherited deficiency of lysosomal enzymes, and they represent generalized, multisystemic abnormalities, of which ocular lesions are but one component. The lysosomal enzymes participate in the degradation of glycosaminoglycans. Morphologic studies have shown accumulation of intracellular inclusions in secondary lysosomes in the enzyme-deficient RPE. In the dog, MPS VI and VII have been described (Haskins et al., 1991; Ponder et al., 2002; Ray et al., 1998; Stramm et al., 1990). In MPS VII, single cytoplasmic inclusions are initially present in the RPE during the early postnatal period. Their number and size increase during the period of photoreceptor differentiation. The pigment epithelial cells enlarge, and the whole monolayer becomes hypertrophied. Despite the pigment epithelial histopathology, the neuroretinal structures and functions were preserved, and photoreceptor degeneration was not reported (Aguirre et al., 1986).

Gangliosidosis

Shiba Inus were identified with a mutation in *HEXB* causing a form of gangliosidosis (GM2) with neurologic changes

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associated with vision loss (Kolicheski et al., 2017). Autofluorescent intracellular inclusion bodies were found in ganglion cells and to a lesser extent cells of the inner nuclear layer of the retina.

Inflammation and Infections Affecting the Ocular Fundus

Inflammatory lesions of the ocular fundus are not uncommon in the dog. Retinal involvement, however, is usually secondary to disease processes extending from the choroid or sometimes the vitreous, whereas primary retinal inflammation (i.e., retinitis) is uncommon. The terms chorioretinitis (i.e., starting in the choroid) and retinochoroiditis (i.e., initially involving the retina) indicate the primary site and direction of spread when both the choroid and retina are involved. There may also be concurrent involvement of the anterior uvea (see Chapter 21), as in panuveitis (inflammation of the entire uveal tract), endophthalmitis (inflammation of the internal structures of the eye), and panophthalmitis (inflammation of the entire eyeball). The inflammatory process may accompany a systemic disease; a full physical examination is an essential part of the work-up, and further investigations such as chest radiographs and abdominal ultrasound should be considered. In addition to routine laboratory investigations such as a complete blood count, serum chemistry, urinalysis, and infectious disease testing may be indicated. In certain instances, aspirates (e.g., from lymph nodes, aqueous humor, vitreous, subretinal fluid) may be obtained and subjected to a variety of tests, including cytology, culture, and polymerase chain reaction (PCR) amplification. Diagnostic testing should be fully utilized in an attempt to identify the etiology of the inflammation, particularly as the use of anti-inflammatory or immunosuppressive medications, although desired in idiopathic or immune-mediated inflammation, may be contraindicated in certain infectious diseases.

Chorioretinitis

Chorioretinitis may have various causes, including several infectious diseases, neoplasia, foreign bodies, and trauma. Infectious agents may be restricted to the eye or related to a systemic infection. In many instances, the exact cause of the inflammatory process cannot be identified. The appearance of the lesions in the fundus may give some guidance as to the etiology, but this is seldom specific. Sampling from the choroid and retina presents certain difficulties and can be associated with undesired complications. Vitreous paracentesis to obtain material for cytology and culture can be informative, but is usually reserved for patients presenting with severe posterior-segment inflammatory disease.

Ophthalmoscopically visible signs of chorioretinitis vary depending on the stage and severity of the disease process (Albert, 1970; Rubin, 1974). Lesions may be unilateral or bilateral, are usually irregular in shape, and are rarely symmetric. Certain noninflammatory conditions, such as geographic retinal dysplasia, may give rise to lesions resembling chronic chorioretinitis.

Acute chorioretinitis may be identified in the nontapetal fundus as perivascular cuffing, appearing as gray/white perivascular opacities. Retinal edema or cellular infiltrate in the tapetal fundus appear as grayish hyporeflective lesions and in the nontapetal area may appear grayish to white in color. Hemorrhage may accompany severe inflammation, and the appearance of hemorrhage depends on location. Small, discrete, round hemorrhages are seen if the blood is enclosed within the retinal layers. Bleeding within the nerve fiber layer results in a flame-shaped appearance, whereas a subretinal hemorrhage causes an indistinctly bordered, diffuse, dull red area. Bleeding from the superficial retinal vessels can cause a separation of the vitreous from the retina, which in turn causes the hemorrhage to assume a keelboat shape, thus reflecting the force of gravity. Hemorrhages may be a common feature of certain infectious chorioretinitis cases, such as those caused by rickettsial infections. Accumulation of exudate between the photoreceptors and pigment epithelium causes a detachment of the neurosensory retina. The detached area of retina is elevated compared with the surrounding retina and appears gray or yellow/white, with a relatively distinct border. The cellularity of the subretinal fluid influences the appearance of the detached area. If the fluid has a low cellularity, the color of the tapetum will be seen through the detached retina in the tapetal area, but a high cellularity, or the presence of red blood cells, will make the detached area appear dull or red, respectively. Granulomatous lesions may be seen in some forms of chorioretinitis, particularly those caused by fungal infections.

In chronic chorioretinitis, macrophage invasion removes debris and pigment, fibrovascular proliferation, which may contribute to retinal tears or folds, retinal degeneration, and chorioretinal scar formation. The RPE contributes significantly to the progress of healing; it can become hypertrophic or hyperplastic or even migrate into the lesions. The RPE cells overlying the tapetum are normally nonpigmented, but may produce pigment as a result of inflammation. Ophthalmoscopic signs of an inactive, chronic inflammatory process are quite different from those of an acute inflammation. Atrophy of the neural retina in the tapetal fundus is seen as irregular, hyperreflective areas with a distinct border (Fig. 25.49 and Fig. 25.50). A well-demarcated zone in the center of the lesions may be heavily pigmented if the RPE is affected. The color of the tapetum may be altered in the affected area or the tapetum may even be destroyed, exposing choroidal vessels and sclera. Chronic inflammatory lesions in the nontapetal fundus appear as distinctly

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Figure 25.49 An inactive peripapillary chorioretinitis lesion. There is retinal thinning in the tapetal fundus, resulting in an area of tapetal hyperreflectivity with a pigmented center due to pigment proliferation in the retinal pigment epithelium. There is damage to the full thickness of the retina that has resulted in a sector atrophy of the adjacent optic nerve head. This damage is caused by loss of the ganglion cell axons feeding into that sector of the optic nerve head because of destruction of the nerve fiber layer in the region of postinflammatory scarring.

bordered, depigmented areas with exposure of choroidal vessels and sclera. Sometimes, areas of pigment clumping will also be apparent (Fig. 25.51). The retinal vasculature may also be altered during the chronic stages of inflammation. Vessels crossing the inflammatory lesions may be attenuated or sometimes tortuous. Pigment may outline the vessels within affected areas. When visible, choroidal vessels may also appear atrophied or even destroyed (Fig. 25.52).

Chorioretinitis can have secondary inflammatory consequences to the RPE, causing release of pigment, although this is often obscured by other lesions. Extension of inflammation into the vitreous may cause vitritis, manifesting as haze, consolidated inflammatory precipitates, and syneresis. The ONH may also be secondarily involved, with swelling and hemorrhage in acute stages, and atrophy in chronic stages.

Choroiditis

Choroiditis, strictly confined to the choroid without involvement of the anterior uvea or retina, appears to be an uncommon condition. Ophthalmoscopically, nongranulomatous choroiditis in the tapetal fundus can cause loss of tapetal reflectivity or changes in tapetal color. In the nontapetal fundus, areas of increased redness can be observed. Subretinal

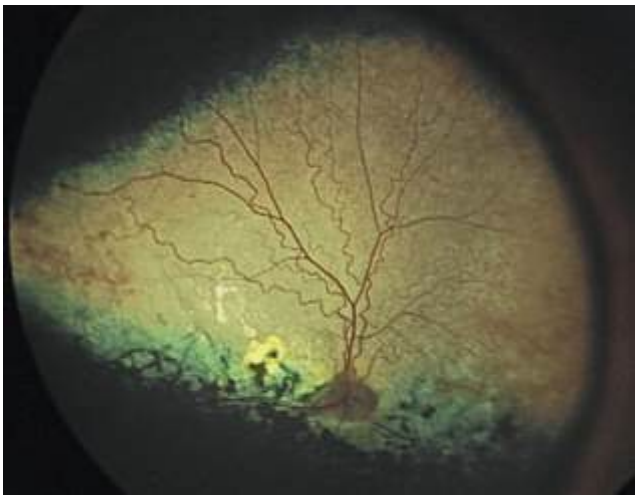


Figure 25.50 Inactive chorioretinitis lesions as an incidental finding in a 2.5-year-old Irish Wolfhound. There are multiple small, hyperreflective lesions in the tapetal fundus near the ventral tapetal–nontapetal border. Lesions to the left of the optic nerve head have a pigmented center due to retinal pigment epithelial proliferation. The more peripheral lesions, although hyperreflective, look dull in the photograph because the camera light is reflected off at an angle and not directly back to the camera. (Courtesy of Michigan State University Comparative Ophthalmology Service.)

accumulation of fluid can cause elevation of the overlying retina. Retinal blood vessels should not show signs of active inflammation (e.g., perivascular infiltrates) when only the choroid is inflamed. Complete destruction of the tapetum lucidum, thereby allowing the choroidal vessels to be readily viewed in the affected area, can occur during the chronic stages of severe choroiditis. In less severe cases, increased pigmentation can obscure the tapetum if the RPE is involved in the transition from active to inactive inflammation. Reddish foci, however, can often be detected in the tapetal area, which enables the examiner to distinguish between a postchoroiditis status and a congenital absence of tapetal tissue.

Viral Diseases

Viral diseases can sometimes cause detectable signs in the ocular fundus. Several systemic viral diseases can affect the tissues of the eye, and the fundus is considered to be most susceptible to viruses preferentially affecting the central nervous system (CNS).

Canine Distemper

Canine distemper virus, a morbillivirus, is the most frequent viral cause of posterior segment disease in the dog. Multiple, irregular areas of retinochoroiditis, with or without inflammation of the optic nerve, are typical findings, but there are

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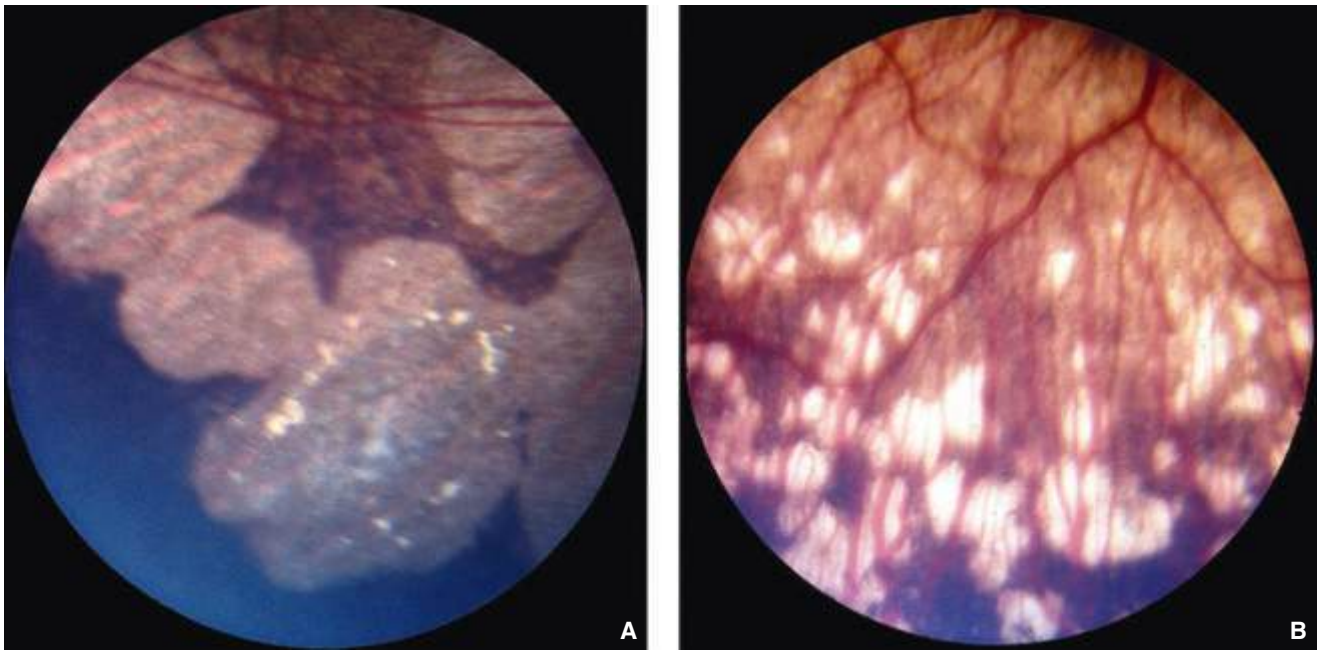


Figure 25.51 Inactive chorioretinitis lesions in the nontapetal fundus. **A**. There are irregular patches of loss of retinal pigment epithelial pigment, revealing choroidal vasculature. Some white-colored retinal surface deposits are also present. **B**. This dog had multiple small areas of depigmentation and choroidal damage, revealing the white of the underlying sclera.

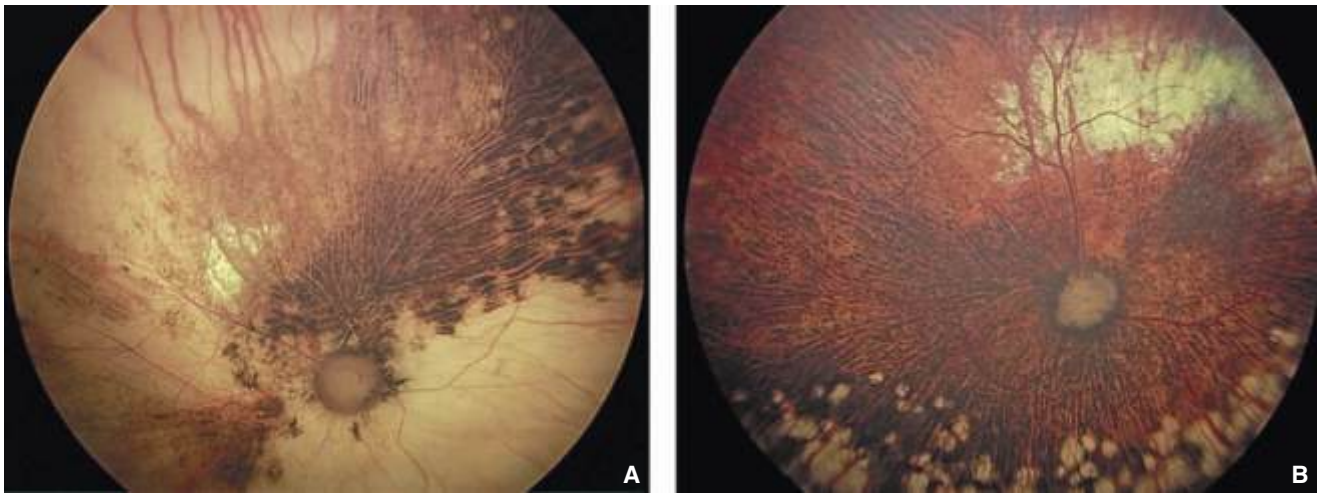


Figure 25.52 Right **(A)** and left (**B**) eyes of an 8-year-old Bulldog with a chronic, presumed immune-mediated chorioretinitis. There are extensive changes with tapetal destruction and extensive depigmentation, and the right eye has attenuation of the retinal vasculature and evidence of optic nerve head atrophy. Azathioprine was needed to control the inflammation. An extensive laboratory work-up had failed to ascertain the etiology. (Courtesy of Michigan State University Comparative Ophthalmology Service.)

no ophthalmoscopic findings pathognomonic for canine distemper. The signs of posterior segment disease do not necessarily correlate with the usually more obvious, external ocular signs (e.g., mucopurulent conjunctivitis).

During the acute stages, the ophthalmoscopic picture is characterized by active retinochoroiditis, and the appearance of multifocal inflammatory lesions corresponds with the previous, general description of active inflammation in the retina and choroid. The appearance of the lesions changes during the transition from acute to chronic retinochoroiditis (as discussed in the section on chorioretinitis). Visual impairment usually is not detectable in patients with retinochoroiditis unless there is involvement of the optic nerve. In severely affected eyes, however, the inflamed areas can coalesce and produce complete destruction of the retina, thereby causing blindness.

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Optic neuritis may accompany the retinochoroiditis. Signs of active inflammation of the ONH may be visible ophthalmoscopically, and a hyperreflective, peripapillary crescent or, in more severe cases, optic atrophy with demyelination can be found in dogs with chronic distemper. Optic neuritis is likely to cause an obvious impairment of vision.

The histopathologic changes, which reflect primary localization of the virus in the retina, have been described (Jubb et al., 1957; Parry, 1954a). Parry subdivided the primary retinochoroidal lesions into four types:

1) Peracute generalized retinopathy
2) Chronic generalized retinopathy
3) Dystrophy or swelling of the RPE, with or without damage to the retina
4) Sporadic foci of advanced retinal degeneration, focal retinal atrophy, and sclerosis.

The nontapetal fundus has been considered to be more involved during the acute phase, and eosinophilic inclusion bodies in glial cells may be found during these stages (Jubb et al., 1957). Ganglion cells exhibit the most severe degeneration, but photoreceptors, RPE, and the choroid can also degenerate. Depending on the severity of the disease, disorganization of the retinal layers may occur. Hypertrophy and proliferation of the RPE are common in dogs with distemper retinochoroiditis.

The presence of virus in the retina may result from primary localization concurrent with the infection of other organs or from secondary extension from the brain (Jubb et al., 1957). Active retinitis without detectable involvement of the brain or optic nerve is seen when the canine distemper virus is primarily located to the retina. Ganglion cell and optic nerve degeneration in dogs with optic neuritis but without other inflammatory changes in the retina are suggestive of a retrograde degenerative process.

Canine Herpesvirus

Experimental inoculation of newborn puppies with canine herpesvirus results in bilateral retinochoroiditis and optic neuritis that peaks at days 5–7 after infection, slightly delayed compared with the onset of systemic inflammation (Albert et al., 1976). Histopathologically, acute lesions consist of predominantly mononuclear cell inflammation with retardation of retinal development, photoreceptor cell necrosis with folds and rosettes consistent with retinal dysplasia, and patchy depigmentation, migration, and necrosis of RPE cells. In chronic cases, panretinal cell atrophy and dysplasia are evident with atrophy, proliferation, and migration of RPE cells.

Mokola Virus

Focal, inflammatory, nonspecific lesions were observed in the retina of a dog experimentally infected with Mokola virus, which is a rabies serogroup virus (Percy et al., 1973). Histopathologically, focal degeneration of ganglion cells and perivascular cuffing were observed.

Infectious Rhinotonsillitis

A contagious viral infection, infectious rhinotonsillitis, in which the ophthalmoscopic and systemic findings cannot be distinguished from those of canine distemper, has been described (Darraspen & Lescure, 1962; Fontaine, 1962). The signs of posterior segment disease include nonpathognomonic focal chorioretinitis and optic neuritis.

Bacterial Diseases

Tick-Borne Pathogens

Tick-borne infections may affect the posterior segment of the eye as part of the systemic disease. The posterior segment lesions are not pathognomonic, but hemorrhage is a common feature. The frequency of posterior segment involvement varies.

Canine Anaplasmosis/Ehrlichiosis

Ehrlichiosis and anaplamosis are tick-borne rickettsial infections reported worldwide. *Ehrlichia canis*, *E. chaffeensis*, *E. risticii* (now reclassified as *Neorickettsia risticii*), *E. ewingii*, *E. phagocytophilia* (formerly *E. equi* and now reclassified as *Anaplamsa phagocytophilia*), and *E. platys* (now reclassified as *Anaplasma platys*) are potential canine pathogens (see Stiles, 2000 for a review) transmitted by ticks such as *Rhipicephalus sanguineus*, but *Ixodes* spp. can also act as a vector for *Ehrlichia* spp. (Neer et al., 2002). *E. canis* is the main species associated with uveitis (Komnenou et al., 2007), although there is a case report of uveitis associated with *A. platys* infection (Glaze & Gaunt, 1986). In a study of experimental infections with *Ehrlichia canis*, *E. ewingii*, *E. chaffeensis*, or human granulocytic ehrlichia (HGE), only dogs infected with *E. canis* developed ocular inflammation (Panciera et al., 2001). Granulocytic erhlichial species (*A. phagocytophilia*, and the as yet unidentified *Ehrlichia* species responsible for HGE) replicate and spread in neutrophils and eosinophils. *A. phagocytophilia* is spread by *Ixodes pacificus* and is commonest along the west coast of the United States. It is reported to have been associated with chorioretinitis and retinal detachment (Stiles, 2000). Species-specific PCR testing has shown that individual dogs may be infected with more than one rickettsial species at one time (Breitschwerdt et al., 1998). Furthermore, ehrlichiosis and anaplasmosis may be complicated by other diseases transmitted through the same vector, for example with *Bartonella spp*. (Breitschwerdt et al., 1998), *Rickettsia* spp., or *Babesia* spp.

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Canine ehrlichiosis is an acute, febrile disease with an associated pancytopenia, especially thrombocytopenia, which can lead to serosal and mucosal hemorrhages. Severe hemorrhage or secondary bacterial infections may lead to death. Ophthalmoscopically, signs of retinal inflammation, retinal hemorrhage, and hyphema can be observed (Ellett et al., 1974; Swan & Dubielzig, 1986). Authors of one study reported retinal vasculature engorgement and tortuosity in 15.6% of 64 dogs, retinal hemorrhages in 7.8%, and findings corresponding to chronic chorioretinitis in 12.5% (Thirunavukkarasu et al., 1994). The experimental study reported by Panciera and colleagues showed that in experimental *E. canis* infection, ocular inflammation was monocytic in nature, predominantly affected the ciliary body, and was less pronounced in the choroid, iris, and retina (Panciera et al., 2001). In a retrospective study of 46 dogs in Spain with ocular signs and a positive antibody titer to *E. canis*, exudative retinal detachment was the most common ocular change. Other ocular changes seen were exudative anterior uveitis, optic neuritis, and intraocular hemorrhage (Leiva et al., 2005).

The causative agent can be demonstrated on Giemsa-stained smears, where it appears as blue cytoplasmic inclusions, mainly in monocytes and lymphocytes. Diagnostic tests (e.g., serology: indirect fluorescent antibody test showing a rising titer in the active phase of the infection, in combination with PCR or Western blot for the pathogen) are used to confirm infection and to detect chronically infected carriers, in which the organism rarely can be demonstrated in blood cells. Note that in chronic infections the organism may be sequestered in reticuloendothelial cells, and therefore a PCR performed on a blood sample may be negative. PCR should therefore not be used in isolation, but should be combined with serology (Neer et al., 2002). Systemic tetracyclines, such as doxycycline have been recommended as the treatment of choice (Cohn, 2003; Neer et al., 2002). These drugs may be combined with systemic anti-inflammatories (Cohn, 2003) to control the ocular inflammation and immune-mediated inflammation resulting from ehrlichial infection.

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever (RMSF) is an acute infectious disease caused by the bacteria *Rickettsia rickettsii*, which is transmitted by ticks of the genus *Dermacentor*. Widespread vasculitis accompanied by hemorrhage results from damage to the vascular endothelium. The ocular lesions resemble those in canine ehrlichiosis, although hyphema has been considered to be less common. Anterior uveitis, chorioretinitis, and retinal hemorrhage, however, have been described in dogs infected with *R. rickettsia* (Davidson et al., 1990; Rutgers et al., 1985).

Davidson and colleagues (Davidson et al., 1990) observed multifocal retinal vasculitis, which corresponded to areas of altered vascular permeability, within 1–2 days after the onset of fever and rickettsemia. Furthermore, the retinal vascular permeability was demonstrated to be abnormal by fluorescein angiography, even during the third week after onset, which was past the period of clinical and clinicopathologic recovery. Development of retinal vasculitis was associated with thrombocytopenia, increased circulating fibrinogen level, and prolonged activated partial thromboplastin time.

The diagnosis may be confirmed serologically with the indirect fluorescent antibody or enzyme-linked immunosorbent assay (ELISA) methods. A PCR-based assay is also available (Breitschwerdt et al., 1999). Systemic treatment with doxycycline is the treatment of choice, although enrofloxacin or trova-floxacin is also efficacious (Breitschwerdt et al., 1991, 1999). A study of experimentally induced RMSF concluded that concurrent use of prednisolone at anti-inflammatory or immunosuppressive doses with doxycycline did not have any clinically relevant detrimental effects, with the caveat that the experimental infection resulted in a mild to moderate disease. Therefore, extrapolation to severe, naturally occurring disease could not be made (Breitschwerdt et al., 1997).

Bartonella

Bartonella species are small, Gram-negative bacteria, which have been identified in a wide range of mammalian species. Infections in dogs are associated with endocarditis, myocarditis, and granulomatous disease (Breitschwerdt et al., 2004). There is a single case report of a dog seropositive for *Bartonella vinsonii (berkhoffii)* that presented with fever, anterior uveitis, and chorioretinitis lesions, although the authors could not conclusively prove that the ocular lesions were caused by the *B. vinsonii (berkhoffi)* infection (Michau et al., 2003). Serology, culture, and PCR-based diagnostic tests are available. There is limited information regarding treatment. However, prolonged medication is recommended, and azithromycin, doxycycline, and enrofloxacin have been used (Guptill, 2003).

Borreliosis

There is limited evidence that *Borrelia burgorferi* (Lyme borreliosis) results in ocular manifestation in dogs. However, occasional reports of chorioretinitis or retinal vascular disease have been described in dogs seropositive for *Borrelia* (for a review, see Dziezyc, 2000).

Other Bacterial Causes of Chorioretinitis

In addition to the bacterial organisms transmitted by ticks, other organisms, such as *Leptospira* spp. and *Brucella* spp., have been suggested as a cause of uveitis in dogs. As reviewed by Dziezyc (2000), there is limited evidence that leptospirosis is a significant cause of uveitis in dogs. Brucellosis is similarly not a commonly cited cause of uveitis in dogs, although it has been demonstrated in experimental studies and case

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reports (Gordon et al., 1985; Gwin et al., 1980a; Saegusa et al., 1977).

Systemic Mycoses

Posterior segment disease may be seen in a number of systemic mycoses in the dog (see Krohne, 2000 for a review). The frequency of ocular involvement, however, varies considerably. The infection may spread hematogenously, directly from the anterior parts of the eye, or by infiltration along the optic nerve and meninges.

Acremoniasis

Systemic disease accompanied by anterior uveitis, focal chorioretinitis, and secondary retinal detachment has been described in a case of infection with *Acremonium* sp., which is a saprophytic fungus found in soil (Simpson et al., 1993). The dog exhibited ataxia, progressive head tilt, anorexia, lethargy, and weight loss. It was treated with antibiotics and antifungal drugs (initially ketoconazole and later itraconazole), but was finally euthanized because of poor general condition. Histopathologic examination revealed chronic pyogranulomatous, necrotizing inflammation, and granulomatous inflammation affecting several organs, including the retina. The clinical and histopathologic findings are similar to those seen in disseminated aspergillosis, which is a fungus belonging to the same group (i.e., nondematiaceous hyphomycetes) as *Acremonium* sp.

Aspergillosis

A multifocal infection with *Aspergillus fumigatus*, a fungus composed of septate hyphae, was diagnosed in a dog presenting with severe neurologic and ophthalmic signs (Gelatt et al., 1991). The causative organism was demonstrated by cytology and culture from vitreous paracentesis. PAS-positive, slender septate hyphae were observed on the lens capsules, in the vitreous, in the ganglion and nerve fiber layers of the retina, and in the choroid and optic nerve. The infection had caused an inflammatory reaction resulting in panuveitis and inflammation of the iridocorneal angles and ciliary clefts; partial syneresis; infiltration of the vitreous body with inflammatory cells, blood, and debris; and partial retinal detachment and optic neuritis. Identification from smears alone may be difficult, because conidial heads may be absent and other fungi also show septate hyphae when invading tissue, therefore culture is recommended as well as cytology in suspected cases.

Blastomycosis

Blastomycosis is the most frequently reported ocular disease of mycotic origin (Bloom et al., 1996; Brooks et al., 1991; Buyukmihci & Moore, 1987; Simon & Helper, 1970; Trevino, 1966). Blastomycosis is commonly reported in areas close to waterways, such as the regions of the Mississippi, Wisconsin, and Ohio River systems and the Great Lakes region in North America and southern Canada, whereas it is not reported in other parts of the world (e.g., northern Europe).

Blastomyces dermatitidis is a dimorphic soil fungus; infection occurs when its conidia are inhaled and incubated in the lungs. The fungus then assumes the yeast phase and may spread hematogenously or lymphogenously to, for example, the eyes and the CNS. Ocular disease, including anterior uveitis, hyalitis, retinitis and chorioretinitis, optic neuritis, and their sequelae (e.g., secondary glaucoma, retinal detachment), is reported to occur in 30%–52% of cases (Fig. 25.53) (Arceneaux et al., 1998; Brooks et al., 1991; Legendre et al.,

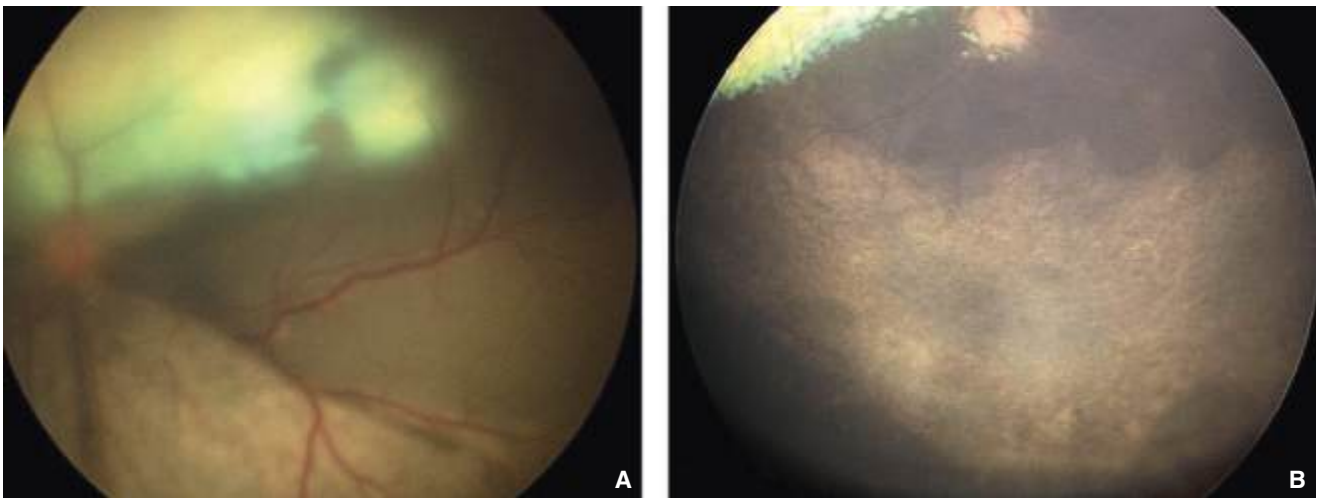


Figure 25.53 Blastomycosis in a 2-year-old West Highland White Terrier. The dog initially developed respiratory signs and then presented with sudden vision loss. **A**. At initial presentation, there was retinal detachment and the appearance of subretinal granulomas. **B**. After 3 months of itraconazole treatment, the retina has reattached, but shows evidence of the previous inflammation with depigmentation in the nontapetal fundus. (Courtesy of Michigan State University Comparative Ophthalmology Service.)

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1981). Extraocular blastomycosis can cause exophthalmos and strabismus. Patients may show respiratory illness, although even without respiratory signs, thoracic radiographs may show multiple noncalcified nodules in the lungs and hilar lymphadenopathy, suggestive of blastomycosis. However, these changes are not pathognomonic.

Cytologic identification of the organism is an optimal method of diagnosis, either via sampling of draining skin lesions, lymph node aspirates, or, in cases with severe ocular changes, vitreous paracentesis. It is less common for aqueous paracentesis to be diagnostic. Histopathologic examination reveals widespread granulomatous inflammation and destruction of ocular tissue. Small granulomas are often present in the retina, and the fungus may be identified in subretinal exudates. In smears and histopathologic sections, *B. dermatitidis* is identified as a PAS-positive, round, budding yeast with thick walls. Serologic testing is available but may not be reliable (see Kerl, 2003 for a review). An enzyme immunoassay urine antigen test for *B. dermatitidis* is available and has been shown to be more sensitive than antibody testing (Spector et al., 2008).

Systemic antifungal therapy can be instituted with fluconazole, itraconazole, amphotericin B, ketoconazole, or a combination of amphotericin B and ketoconazole (Bloom et al., 1996; Brooks et al., 1991; Mazepa et al., 2011). The dose of potentially nephrotoxic amphotericin B can be lowered without compromising efficacy when used concomitantly with oral ketoconazole; improvement was seen in 40% of eyes after combined amphotericin B and ketoconazole therapy (Bloom et al., 1996). Vision was retained in two dogs with optic neuritis during this therapeutic regime, whereas eyes with severe endophthalmitis did not respond to the combination of antimycotics. The most commonly used treatment is itraconazole or fluconazole, and systemic remission is achieved in 75%–90% of cases using either medication, although fluconazole has a more protracted course and itraconazole is more costly (Mazepa et al., 2011). Orally administered itraconazole, 5 mg/kg twice daily in dogs with ocular blastomycosis, was reported to give a positive result in 42% of affected eyes (Brooks et al., 1991). Eyes with signs of posterior segment disease other than optic neuritis displayed a tendency to respond to itraconazole therapy more frequently than other ocular forms of blastomycosis. However, in a survey of 36 dogs blind as a result of blastomycotic endophthalmitis, a comparison of the prevalence of organisms and histologic changes in eyes that were either untreated or undergoing treatment with itraconazole showed there was no significant difference between treated and untreated eyes (Hendrix et al., 2004). Additional treatment of ocular disease (e.g., intraocular inflammation, glaucoma) is indicated. Though not proven beyond doubt, it does not appear to be necessary to routinely enucleate globes that are blind from blastomycosis to prevent recurrence (Bloom et al., 1996). Addition of systemic steroids to the treatment regimen does not appear to negatively affect prognosis (Finn et al., 2007).

Histoplasmosis

Infection with *Histoplasma capsulatum*, a dimorphic fungus, occurs mainly by inhaling spores of the mycelial form (Turner et al., 1972), but infection via the gastrointestinal tract is possible. The subsequent course of infection is usually subclinical, indicating that animals may be resistant or develop latent infections. Immunosuppression has been proposed to contribute to systemic dissemination (Berry, 1969).

Ocular involvement in *Histoplasma* infections has been reported infrequently (Bergstrom et al., 2017; Gwin et al., 1980b; Huss et al., 1994). Multifocal inflammatory lesions, retinitis, chorioretinitis, and retinal detachment have been reported. Granulomatous uveitis has been reported in 50% of experimentally infected dogs (Salfelder et al., 1963), with *H. capsulatum* demonstrated in the uvea, sclera, orbital tissues, extraocular muscles, and lacrimal gland. Diagnosis can be definitively made by cytology or histopathology. Cytology specimens may be obtained from rectal mucosal scrapings; lymph node or dermal nodule aspiration; aspiration from bone marrow, spleen, or liver; and endotracheal washes (Kerl, 2003). Serology is unreliable, although a urine immunoassay, similar to that offered for blastomycosis diagnosis, has been shown to be both sensitive and specific (Cunningham et al., 2015).

Literature on the treatment of histoplasmosis is sparse. Long-term success was not achieved in one dog by systemic treatment with ketoconazole and amphotericin B (Huss et al., 1994). Currently, itraconazole appears to be the drug of choice (Bromel & Sykes, 2005; Kerl, 2003).

Cryptococcosis

Cryptococcus neoformans is a saprophytic organism that only exists in a yeast form, not in a mycelial form, unlike other fungi causing mycotic diseases. *C. neoformans* may cause focal or disseminated infections in the dog. Infection usually manifests clinically with signs caused by involvement of the CNS (e.g., ataxia, circling, head tilt). Ocular cryptococcosis has only been reported in cases of disseminated infection, and the organism may spread by direct extension from granulomatous meningitis and optic neuritis, or hematogenously from more remote locations (Bistner et al., 1971; Carlton et al., 1976; Gelatt et al., 1973; Jergens et al., 1986; Kurtz & Finco, 1970; Lipton, 1973; Walde & Burtscher, 1980). Ocular signs without systemic signs are rare in canine cryptococcosis, but have been reported (Wolfer et al., 1996).

Ophthalmic findings have been reported to occur in 45% of cases (Trivedi et al., 2011) and include focal or multifocal subretinal granulomas (Fig. 25.54). Granulomas overlying the tapetum will appear discolored, whereas those in the nontapetal fundus will appear lighter in color than the surrounding choroidal and RPE pigment; inflammatory

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changes may be observed involving the ONH. Vitreal hemorrhage or inflammation may obscure a view of the fundus and complete retinal detachment may occur. In chronic cases, several small, pigmented nodules (i.e., cryptococcal granulomas) can be scattered throughout the tapetal fundus.

Vitreous paracentesis for cytology and culture can be diagnostic. *C. neoformans* appears as a round to ovoid organism approximately 20 µm in diameter. The cryptococcal elements are surrounded by a thick, polysaccharide capsule that distinguishes them from *Blastomyces*. Testing for cryptococcal antigen via a latex agglutination test is the most commonly



Figure 25.54 Fundus lesions in dogs with cryptococcosis. **A**. There is a chronic chorioretinitis lesion one disc diameter from the disc close to the tapetal–nontapetal junction. A zone of slight hyperreflectivity surrounds a central area of pigment proliferation. Among the dorsal vasculature, there is an active chorioretinitis lesion with cellular infiltrate, resulting in a tapetal color change. To the left of that region is a small, chronic lesion with a pigmented center. **B**. This dog had multiple subretinal granulomatous lesions scattered across the fundus. These show as small gray lesions that result in slight elevation of the surrounding overlying retina. **C**. This dog has extensive subretinal granulomas with a resulting retinal detachment. Numerous small retinal hemorrhages are also visible. **D**. In this dog the cryptococcal infection has resulted in extensive retinal degeneration (thinning), showing as tapetal hyperreflectivity. There are also small areas of pigment proliferation and tapetal color change. (A and C courtesy of Michigan State University Comparative Ophthalmology Service.)

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utilized diagnostic, reported to have high sensitivity in dogs (Trivedi et al., 2011). CSF sampling may also be recommended if clinical suspicion is high, but serum antigen testing is negative.

Histopathologic changes are usually confined to the posterior segment. In the choroid and retina, there are large, multifocal accumulations of macrophages and plasma cells, neutrophils and lymphocytes, and abundant cryptococci. Both the size and location of the inflammatory lesions vary considerably. Cryptococci may be present in the choroid as well as in the proteinaceous subretinal exudates in cases of retinal detachment.

CNS involvement is a negative prognostic indicator. Most commonly adopted treatments are fluconazole or itraconazole, although other azole antifungals, amphotericin B, or flucytosine have been described (Bentley et al., 2018; Faggi et al., 1993; Malik et al., 1996; Mason et al., 1989; Noxon et al., 1986). Antifungal sensitivity may vary by geographic location and molecular type (Singer et al., 2014).

Coccidioidomycosis

Valley fever, or coccidioidomycosis, is caused by the dimorphic, saprophytic soil fungus *Coccidioides immitis*. The disease is endemic in the semi-arid, low-altitude areas of the southwestern United States (i.e., the lower Sonoran life zone), but it may occur elsewhere through the mobility of the canine population.

Coccidioidomycosis is mainly caused by the inhalation of spores, whereas transmission from animal to animal is rare (apparently because the endospores are too fragile). *C. immitis* mainly causes respiratory disease characterized by granuloma formation in the pulmonary and thoracic lymph nodes. It is usually an insidious and chronic disease. Disseminated coccidioidomycosis is most likely to occur in immunocompromised or immunosuppressed dogs.

Signs of ocular disease may be the only apparent clinical manifestation in some patients (Angell et al., 1987; Armstrong & Dibartola, 1983; Cello, 1960; Shively & Whiteman, 1970). Ocular coccidioidomycosis can be uni- or bilateral. In one study, no evidence of systemic disease was present in 15 of 35 patients (43%) and anterior segment changes such as iritis and granulomatous uveitis were the most frequent presenting signs (Angell et al., 1987), although on histopathologic investigation these appeared to have extended from the posterior segment, as chorioretinitis and retinal detachment were detected. Systemic signs included weight loss, lethargy, lameness, and respiratory disease.

Histopathologically, the disease is essentially a granulomatous panuveitis, with granulomas appearing most frequently in the ciliary cleft, iris root, ciliary body, choroid, and retina. Various stages of retinal degeneration and exudative retinal detachment may be present. Presence of respiratory disease and geographic location can increase clinical suspicion. The diagnosis should be confirmed by culture or serology. Aqueous or vitreous paracentesis may yield mononuclear inflammatory cells and fungal elements. *C. immitis* is a spherical organism (diameter 20–100 µm) containing endospores (diameter 2–5 µm). Serologic diagnosis can be useful in the diagnosis of coccidioidomycosis (see Kerl, 2003 for a review), but is of limited sensitivity (Shubitz & Dial, 2005). Although antigen detection via PCR has been described, the transient presence of coccidiodes in the circulation may render this test on serum relatively insensitive (Johnson et al., 2004). A recently described enzyme immunoassay to detect antibodies may provide a more sensitive diagnostic test (Chow et al., 2017).

Treatment has been described with ketoconazole (Angell et al., 1987), although the necessity for long-term treatment increases the risk of ketoconazole-associated cataract formation (Da Costa et al., 1996). More recently, itraconazole and fluconazole have been used to treat canine coccidiomycosis (for a review, see Bentley et al., 2018). Because of the risk of relapse, treatment duration is usually protracted. Enucleation may be indicated if the eye appears to be the only site of active infection; otherwise, the ocular lesions are treated symptomatically.

Geotrichosis

Geotrichum candidum is a fungus that can cause disseminated infections in the dog (Rhyan et al., 1990). Uveitis with choroidal granulomas and subsequent exudative retinal detachment has been reported in geotrichosis with ocular involvement (Lincoln & Adcock, 1968).

Pseudallescheriasis

Severe bilateral exudative chorioretinitis and retinal detachment in combination with systemic signs, including intermittent fever, lethargy, and lameness, have been described in a dog with disseminated pseudallescheriasis (Baszler et al., 1988). Histopathology revealed granulomatous to pyogranulomatous inflammation in all affected organs, and hyphae invading blood vessels and thrombosis were frequently observed. Irregularly branched septate hyphae, often with thick-walled terminal or intercalated vesicles, were demonstrated. The immunofluorescence test was positive for *Pseudallescheria boydii*. A second case report of disseminated *P. boydii* also isolated organisms from the eye (Elad et al., 2010).

Candidiasis

Candida albicans has been reported as a cause of unilateral endophthalmitis in a dog that had a history of bloody diarrhea and a positive titer to *Candida* (Linek, 2004). A retinal detachment was identified on ocular ultrasound; the eye developed secondary glaucoma and was removed. The causal agent was identified on histopathology. A second case of bilateral endophthalmitis was described in an immunosuppressed dog with candiduria (Enders et al., 2017).

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Algal Disease

Plant material is rarely associated with posterior segment disease. The most frequent lesions caused by plant material are seen in the external ocular structures or in the anterior segment after corneal penetration.

Protothecosis

The achlorophyllic alga Prototheca is a saprophyte widely spread in the environment. Two species, *Prototheca wickerhamii* and P. *zopfii*, are reportedly capable of causing systemic disease in the dog (see Hollingsworth, 2000 for a thorough review). It is thought that the organisms are ingested and localized to the colon, then are spread further both hematogenously and lymphogenously. The alga usually causes a slowly disseminating disease affecting the brain, eyes, heart, intestines, kidney, and liver. An acute dissemination has been reported in dogs with colitis.

Prototheca occasionally reaches the eye hematogenously, and ocular disease (e.g., blindness) may be the presenting sign in some patients (Blogg & Sykes, 1995; Buyukmihci et al., 1975; Carlton & Austin, 1973; Hosaka & Hosaka, 2004; Merideth et al., 1984; Shank et al., 2015). In one report, there was a history of systemic illness in 6 of 14 cases with confirmed ocular protothecosis (Shank et al., 2015). The alga causes anterior uveitis, granulomatous chorioretinitis, or panuveitis, which may progress to chronic endophthalmitis (Fig. 25.55) (Buyukmihci et al., 1975; Carlton & Austin, 1973; Font & Hook, 1984). The retina is often detached secondary to the posterior segment inflammation (Shank et al., 2015) and blindness is reported in approximately 50% of cases (Migaki et al., 1982).

Vitreous paracentesis or tissue sampling can be used to obtain material so that the organism can be demonstrated and identified by culture. Histopathologically, Prototheca organisms, which resemble fungal organisms, are usually found bilaterally in the choroid and subretinal exudates. It is a unicellular, ovoid organism with a refractile cellulose wall surrounding a nucleus and granular cytoplasm. One study reported that *Prototheca* organisms could be identified in urine sediment in 4 out of 8 cases and on urine culture in 5 out of 7 cases, suggesting that urine cytology and culture may aid in the diagnosis of protothecosis in dogs (Pressler et al., 2005).

Treatment with systemic antifungals can be attempted, although the long-term prognosis for survival is grave (Cook et al., 1984; Moore et al., 1985; Stenner et al., 2007). Survival for more than 5 years with treatment has been documented after enucleation (Shank et al., 2015); long-term therapy with itraconazole in combination with amphotericin B has allowed remission in a small number of reported cases (Stenner et al., 2007).

Protozoal Diseases

Posterior segment diseases caused by protozoans are infrequently reported in the dog.

Toxoplasmosis

Infections with the protozoon *Toxoplasma gondii* have been observed in several species and in most areas of the world. The parasite has an enteroepithelial cycle occurring in domestic cats and some other members of the family *Felidae*;

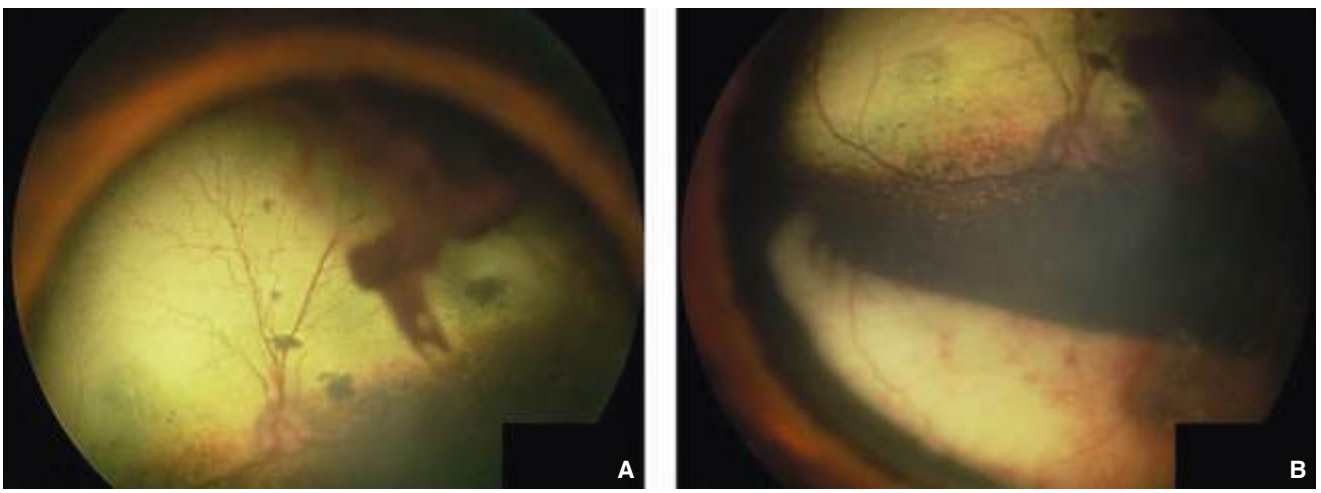


Figure 25.55 Prototheca chorioretinitis. **A**. The right eye of a 6-year-old dog showing vitreal hemorrhage and chorioretinal scars. **B**. The nontapetal fundus in the same eye had significant subretinal granulomatous infitrate. (Courtesy of Michigan State University Comparative Ophthalmology Service.)

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nonfeline species serve only as intermediates. In felines, ingestion of intermediate hosts containing tissue cyst bradyzoites results in the enteroepithelial production of oocysts, released in their unsporulated form in feces. Oocysts sporulate in the environment within 1–5 days. Ingestion of sporulated oocysts or tissue cysts by dogs can result in an extraintestinal cycle that can lead to hematogenous lymphogenous dissemination to other organs. The lungs and liver are frequently involved, but other organs, such as the lymph nodes and muscles, may show disease as well. Subacute or chronic infections may affect the brain, and common signs of toxoplasmosis in the dog include pneumonia, hepatitis, and encephalitis (Frenkel et al., 1970; Jones, 1973; Turner, 1978). Concurrent, active infections with canine distemper virus and toxoplasmosis have, for uncertain reasons, been frequently recorded.

T. gondii is recognized as a cause of ocular disease in several species. The most common findings are iridocyclitis and retinochoroiditis, but lesions may occur in most ocular structures. Histopathologically, there are perivascular accumulations of inflammatory cells, hyalinization of vessel walls, and infiltration of inflammatory cells into the retina. Retinal detachment may be seen in severely affected dogs. Retinal elevations without detachment can result from the accumulation of exudate within the choroid. One study reported that in 37 dogs with toxoplasmosis, 27 had retinal lesions and 18 had choroidal lesions (Piper et al., 1970).

Diagnosis of toxoplasmosis is described in detail elsewhere in this text (see Chapter 7). Measurement of serum *Toxoplasma* immunoglobulin (Ig) G and IgM antibodies as a single or paired examination is recommended, although healthy animals may have high titers. PCR and antibody testing from ocular samples may aid in diagnosis.

Treatment for toxoplasmosis is recommended for at least 4 weeks, and various treatments have been reported in dogs, including clindamycin and trimethoprim-sulfonamide (Dubey et al., 2009). Complete clearance of the parasite is unlikely, so clinical recurrence is possible, particularly with immunosuppression. Dogs will remain seropositive, so repeat antibody titers are of little diagnostic utility.

Neosporosis

The domestic dog and coyote are definitive hosts of *Neospora caninum* in a similar manner to felid species are definitive hosts for *Toxoplasma*. Coinfection with *Toxoplasma* is possible. Purebred dogs may be at increased risk. In infected carnivores, tachyzoites are found within macrophages, inflammatory cells, spinal fluid, and neural and other cells (Dubey et al., 2009). Transplacental infection has been documented (Dubey et al., 1990), although the oral route is thought to be most common. Ocular involvement causes local retinitis (primarily of the inner retinal layers), retinochoroiditis (in severe cases), choroiditis, and mild anterior uveitis. *N. caninum* tissue cysts and tachyzoites (i.e., proliferative organisms) were associated with the retinal lesions in some dogs. Mortality was reported to be high, particularly in young dogs. Serum immunofluorescence and ELISA antibody titers are available, and an IgG agglutination test has been reported to be sensitive and specific (Dubey et al., 2009). Tissue cysts have thicker capsules than those formed by *Toxoplasma*, and can be differentiated using immunohistochemical methods. PCR antigen testing has been reported.

Treatment is most effective in the early stages of disease. Treatment of *N. caninum* using currently available drugs is only partially effective, even using clindamycin, and treatment is ineffective in destroying tissue cysts (Dubey et al., 2007).

Leishmaniasis

Dogs are the principal reservoir host of *Leishmania infantum*, a flagellate protozoan naturally transmitted by sand flies (*Phlebotomus* spp.). Leishmaniasis is endemic in Mediterranean Europe, parts of East Africa, India, and Central and South America.

Ocular involvement is common in infected dogs, concurrent with systemic disease; ophthalmic manifestations alone have not been reported. The most common clinical findings are keratoconjunctivitis, blepharitis, and anterior uveitis (Ciaramella et al., 1997; Pena et al., 2000; Pietro et al., 2016). The posterior segment can be involved, presumably from extension from the anterior segment. A study reported fundus abnormalities in 9.4% of shelter dogs diagnosed with leishmaniasis, and 12.5% of client-owned dogs. Another study reported 1 dog with bilateral retinal detachment out of 60 examined cases (Pena et al., 2008), and histopathologically 5.8% of eyes had choroidal infiltration with macrophages, lymphocytes, and plasma cells, with 3.3% of eyes containing the parasite. Serologic diagnosis by ELISA, cytologic evidence of intracellular parasites, and antigen PCR are all used in the diagnosis of *Leishmania* (Travi et al., 2018).

Therapy with a combination of meglumine antimonite (4–6 weeks) and allopurinol (6–12 months) has been described; these medications will not clear infection, but do maintain remission (Travi et al., 2018). Response of ocular abnormalities to antiprotozoal treatment occurred in 48% of cases in one report, although fundus lesions were not described specifically (Pietro et al., 2016).

Parasitic Diseases

A hematogenous invasion of the eye by a migrating nematode larva, or ocular larva migrans, is a rare condition in the dog.

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Toxocara Chorioretinitis

Toxocara canis, an ascarid nematode, is a common and important intestinal parasite in the dog, and dogs are a reservoir for zoonotic infection (Woodhall et al., 2012). Toxocara ocular larval migrans is reported infrequently in dogs (Johnson et al., 1989; Rubin & Saunders, 1965). However, multifocal fundus lesions, some of which were histologically proven to be associated with *toxocara* invasion, were present in 39% of working sheepdogs in New Zealand (Hughes et al., 1987).

Parasitic granulomas are visible ophthalmoscopically as multifocal, well-delineated areas of subacute to chronic inflammatory lesions in the fundus, which are characterized by tapetal hyperreflectivity, depigmented areas in the nontapetal fundus, and vessel attenuation (Hughes et al., 1987; Johnson et al., 1989). End-stage chorioretinopathy appears similar to generalized retinal atrophy and can be difficult to differentiate from PRA. Vision is then severely impaired or affected animals become blind unilaterally or bilaterally. These findings are similar to those of diffuse subacute neuroretinitis in humans (which may be unilateral or bilateral), which is a condition attributed to damage secondary to nematode migration in the subretinal space (Audo et al., 2006). A direct toxic effect of worm byproducts on the retina was proposed as well as secondary inflammatory and autoimmune processes.

Histopathologically, well-organized granulomas extending from the choroid to the subretinal space, and eventually with a focally detached retina, are typical findings. Granulomas may also be found in the optic nerve. Parts of the larvae may be seen within the granuloma, and eosinophils may be present around its periphery. Because of the focal nature of the granulomas, they can be easily missed at routine sectioning.

Treatment against the parasite in the retina normally is not indicated, because viable larvae are unlikely to be present within ophthalmoscopically detectable granulomas. The public health and hygiene aspects of migrating *T. canis* larvae, however, should be considered.

Angiostrongylosis

Angiostrongylus vasorum is enzootic in parts of Europe and Africa, but it may appear elsewhere (e.g., in imported dogs). Wild foxes act as a reservoir for domestic dogs. Canids are infected by ingestion of gastropod intermediate hosts (snails and slugs). It is a nematode usually found in the pulmonary arteries and right side of the heart in both dogs and wild carnivores. The parasite can occasionally, however, affect the eyes, and in some cases the nematode has been free-floating in the anterior chamber (i.e., ocular larva migrans; King et al., 1994; Rosenlund et al., 1991). *Angiostrongylus* is also capable of causing posterior segment disease, with subsequent impairment of vision (Perry et al., 1991).

Ocular signs include granulomatous uveitis or panuveitis, subretinal hemorrhage, and chorioretinitis. Patent angiostrongylosis can be diagnosed on the basis of larvae in the feces or tracheal mucus. The pulmonary nodules associated with the disease may be seen on thoracic radiographs. The authors of one study reported successful treatment consisting of surgical removal of the organism from the anterior chamber combined with systemic therapy using levamisole (Rosenlund et al., 1991).

Ophthalmomyiasis

In humans, migration of fly larvae from the order *Diptera* beneath the retina (i.e., ophthalmomyiasis interna posterior) results in subretinal tracks, retinal hemorrhage, pigmentary disturbances, and other signs. A similar condition has been reported in a dog with a 48-hour history of unilateral blepharospasm and miosis, in which migration of a larva within the tissues of the posterior segment was monitored (Gwin et al., 1984). The larva could not be identified, but resembled those of *Diptera*.

Specific Retinopathies

Breed-Related Multifocal Chorioretinitis

A breed-related chorioretinitis has been reported in different breeds of dog, including Beagles (Weisse et al., 1981), Borzois (Acland et al., 2004; Scagliotti & Macmillan, 1977; Storey et al., 2005), and Border Collies. Ophthalmoscopic examination of 2887 research-quality Beagles revealed chorioretinitis without clinically apparent signs in 2.3% of the dogs (Weisse et al., 1981). Multifocal serous retinal detachments, mainly in the lower quadrants of the fundus and not associated with the retinal vessels, were observed during the acute phase. After 8 days, multifocal depigmented areas could be seen ophthalmoscopically in the nontapetal fundus, whereas small detachments healed without visible lesions. Histopathologically, focal accumulation of serous fluid between the RPE and photoreceptors, without other inflammatory changes in the retina and choroid, were observed. In large areas of detachment, however, total loss of the outer nuclear layer and focal rarefaction of the tapetum lucidum were present. Tests for canine distemper virus were negative, and the lesions either healed or became inactive within 4–8 days without treatment.

In another study of this condition in Beagles, fluorescein angiograms showed leakage of fluorescein into the subretinal space on the first day, whereas no leakage could be seen at day 7 (Von Landenberg et al., 1990). The retinal vessels appeared to be patent during the entire course of the disease. Results of virologic examination were negative, but a filiform, microaerobically growing bacteria was isolated from

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the ocular specimens. The bacteria, however, was not identified.

A multifocal chorioretinitis was identified in 25 (20 males and 5 females) of 180 Borzois examined in one study (Scagliotti & Macmillan, 1977), and in 12 (7 male and 5 female) of 103 Borzois in a second study (Storey et al., 2005). The lesions were often detected at the inferior-temporal tapetal border and initially appeared as multiple focal areas of retinal edema with loss of choriocapillaris and tapetum (Fig. 25.56). They occurred unilaterally or bilaterally. Within days, the tapetal defect was obscured by pigment proliferation. The chronic lesions appeared as well-circumscribed hyperreflective lesions with pigment proliferation and clumping within the borders of the lesions. Fluorescein angiography revealed the presence of lesions in the nontapetal fundus (Chaudieu, 1995; Storey et al., 2005) that ophthalmoscopically appeared as mild pigmentary changes (Storey et al., 2005). The lesions could be up to twice the diameter of the optic disc (Storey et al., 2005). Although one group suggested the condition might be a manifestation of PRA (Scagliotti & Macmillan, 1977), others found that it was most probably unlikely. Pedigree analysis and a test mating failed to prove the condition to be inherited (Storey et al., 2005).

Another group also described the condition in Borzoi dogs and an apparently similar disease entity in Border Collies (Acland et al., 2004). They found that the initiating lesion was microhemorrhage from the subretinal vasculature.

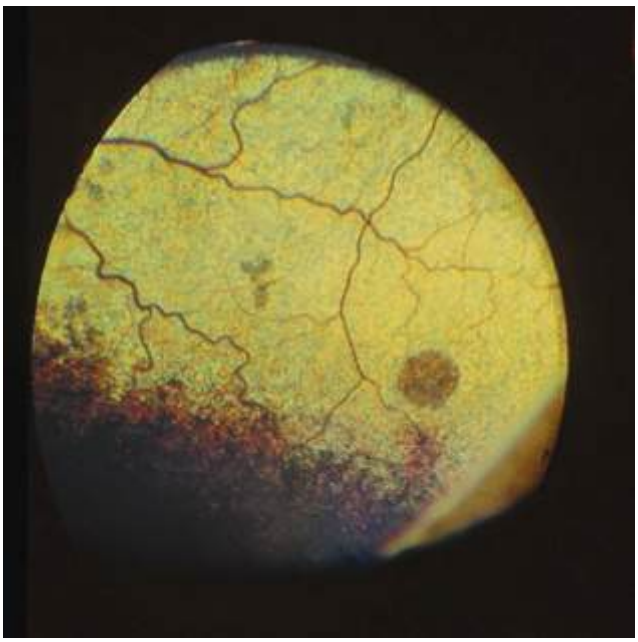


Figure 25.56 Left fundus of a 13-month-old male Borzoi dog with Borzoi chorioretinopathy. Note the circular area of pigmentation and the perivascular foci of chorioretinal degeneration. (Courtesy of Dr. Bruce Grahn.)

A higher incidence in males was also noted in this study, as was the progressive nature of the condition in some individual dogs. They also noted that left eyes were affected more frequently than right eyes and found no evidence of heritability. Another group published a report on further studies in the Border Collie, in which uni- or bilateral chronic chorioretinitis-like lesions were found to develop initially, at the age between 6 months and 9 years, which progressed into generalized retinal degeneration in most cases (Vilboux et al., 2008). ERG showed normal responses if lesions were unilateral and focal or more diffusely spread. Segregation analysis suggested an X-linked mode of transmission for the defect; however, *Xlpra1* and *Xlpra2* were excluded through genetic testing.

Uveodermatologic/Vogt-Koyanagi-Harada Syndrome

Uveodermatologic syndrome (UVD), or Vogt-Koyanagi-Harada (VKH) syndrome of humans, encompasses a variety of clinical signs, including uveitis, chorioretinitis, skin depigmentation (i.e., vitiligo), loss of hair pigment (i.e., poliosis), and auditory and meningeal abnormalities. In humans, there is a strong association with human leukocyte antigen alleles and it is more common in races with high levels of skin pigmentation. Infection with cytomegalovirus is cited as a possible autoimmune trigger, followed by acute uveitis and choroiditis; convalescent stages are associated with skin, hair, and uveal depigmentation. Recurrence has been described in some patients.

A very similar disease has been reported in dogs of Arctic breeds, most commonly Akitas (Asakura, 1977; Furlong et al., 1989; Kern et al., 1985; Murphy et al., 1991; Romatowski, 1985). Cases may present with a history of sudden blindness or with chronic uveitis leading to secondary glaucoma (see Chapter 21). Dermatologic changes include vitiligo and poliosis affecting the periocular skin, lips, and muzzle most frequently, and often occur later than ocular signs. Polymyositis has been described in one reported case (Baiker et al., 2011). Preliminary immunologic study in two cases revealed that the ocular lesions were consistent with a B-cell and macrophage response (Th2 immunity), while the skin lesions were mediated by T cells and macrophages (Th 1 immunity; Carter et al., 2005). The precise cause of the disease is unknown. The histopathology is consistent with antimelanocyte autoimmunity, however, and the breed incidence suggests the involvement of genetic factors. A similar disease was induced experimentally in two Akitas by immunizing them to tyrosine-related protein 1 (Yamaki et al., 2005), although similar studies in other breeds of dog have not been reported. A relationship between circulating antiretinal antibodies and clinical signs has been found, which could be indicative of a breakdown in the blood–retina barrier and exposure to retina-specific antigens and a secondary

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production of the antiretinal antibodies (Murphy et al., 1991). A study of canine leucocyte antigen (DLA) complex class II alleles in Akitas with and without uveodermatologic syndrome showed that DLA-DQA1*00201 was associated with a significantly higher relative risk (risk ratio 15.99) for uveodermatologic syndrome than other DLA class II antigens (Angles et al., 2005). However, the presence of DLA-DQA1*00201 is not a useful clinical predictor for the condition, because in the study 19 of 26 affected Akitas did not carry the allele.

Sudden Acquired Retinal Degeneration Syndrome

SARDS is a retinal disorder of unknown cause that results in sudden and permanent blindness in affected adult, middle-aged dogs (Acland et al., 1984; Curtis, 1988; Mattson et al., 1992; Miller et al., 1998; Riis, 1990; van der Woerdt et al., 1991). A comprehensive review of SARDS literature was published in 2016 by Komáromy et al. (2016), which concluded that SARDS is a leading cause of incurable vision loss in dogs. Many studies report a predilection for female dogs, ranging from 60% to 90% of diagnosed cases, the majority of which are spayed (Carter et al., 2009; Montgomery et al., 2008; van der Woerdt et al., 1991), although other studies have not found a significant female predisposition. (Heller et al., 2017; Keller et al., 2006). A recent study of 495 dogs (Heller et al., 2017) identified a predilection for small-breed dogs, with mixed-breed dogs the most commonly affected (21.8% of cases), followed by Dachshunds (13.7%), Chinese Pugs (8.9%), and Miniature Schnauzers (7.9%); many other breeds were represented to a lesser extent.

Clinical signs are characterized by a sudden decline in vision, usually within days or weeks, although owners may describe a more protracted period of unusual behavior (lethargy, inattentiveness) that may reflect mild vision changes over a more protracted period prior to acute vision changes (Young et al., 2018). Associated systemic clinical signs in this syndrome include weight gain, polyphagia, polyuria, polydipsia, skin/haircoat changes, hearing deterioration, decline in sense of smell, and change in behavior (van der Woerdt et al., 1995; Young et al., 2018). These changes may in some cases precede the onset of vision loss (van der Woerdt et al., 1991, 1995).

There are often initial laboratory blood work changes such as elevated serum alkaline phosphatase, serum alanine aminotransferase and serum cholesterol, increased total white cell count and neutrophil count, and reduced urine specific gravity (Carter et al., 2009; Gilmour et al., 2006; van der Woerdt et al., 1991; Young et al., 2018). Van der Woerdt and colleagues found that 17 of 25 cases tested had abnormal serum biochemistry (van der Woerdt et al., 1991). A proportion of affected dogs will test positive for hyperadrenocorticism, ranging from 10% (Young et al., 2018) to 60% of cases (van der Woerdt et al., 1991). However, further investigations often do not support the initial suggestion of hyperadrenocorticism (Mattson et al., 1992). Nevertheless, it is the authors' experience that clinical signs rarely improve in response to hyperadrenocorticism treatment and it is not recommended that treatment for hyperadrenocorticism is initiated based on a low-positive diagnostic test. Further consultation with an internal medicine specialist might be indicated for further evaluation of systemic health concerns. Hypothyroidism and diabetes mellitus are reported as potential comorbidities (Stuckey et al., 2013).

On ophthalmic examination, conjunctival hyperemia was reported in 8 of 10 cases in one study (Young et al., 2018), and 29% of cases in another study. Aqueous tear production has been reported to be normal (Young et al., 2018). There is a bilateral, symmetric reduction in vision (menace response, cotton ball test, maze test). Pupils may be moderately dilated; pupil responses to bright white light are generally intact, although response may be diminished. Pupil response to blue light is robust, confirming appropriate inner retinal (presumed melanopsin photopigment) activity and optic nerve function (Grozdanic et al., 2007). Red light pupil response, mediated afferently by the photoreceptors, is absent or severely diminished, reflecting outer retinal disease. On fundus examination, the degree of fundus change does not reflect the extent of vision loss (Fig. 25.57), with changes ranging from no observable abnormalities to mild vascular attenuation, mild generalized tapetal hyperreflectivity, focal areas of tapetal hyperreflectivity, or, in the nontapetal fundus, focal hypopigmented lesions. Swelling of the ONH is not commonly associated with SARDS, and may indicate optic nerve or central causes of vision loss (Montgomery et al., 2008). After a period of weeks to months, the retina will appear similar to end-stage degeneration seen in PRA. The main diagnostic technique to distinguish between SARDS and central causes of sudden-onset vision loss is ERG. In SARDS the ERG has been traditionally reported as nonrecordable, although a recent study identified a long-latency negative waveform in the dark-adapted retina, most identifiable at bright light luminances (3–10 cds. m^2), increasing in amplitude with increasing stimulus strength (Young et al., 2018; see Fig. 25.57B). This waveform is most consistent with a scotopic threshold response, a rod photoreceptor-derived response generated in the inner retina, typically seen in a normal retina at below rod b-wave threshold. This may represent residual retinal function in SARDS cases. In contrast, dogs with optic nerve or central causes for vision deficits typically have identifiable a- and b-waves, and apparently normal ERGs.

Histologically, abnormalities initially involve the photoreceptor cell layer (O'Toole et al., 1992; Riis, 1990; see Fig. 25.57C and Fig. 25.58). There is a rapid loss of photoreceptor outer segments (both rod and cone). Photoreceptor cells die by apoptosis (Miller et al., 1998), which is followed

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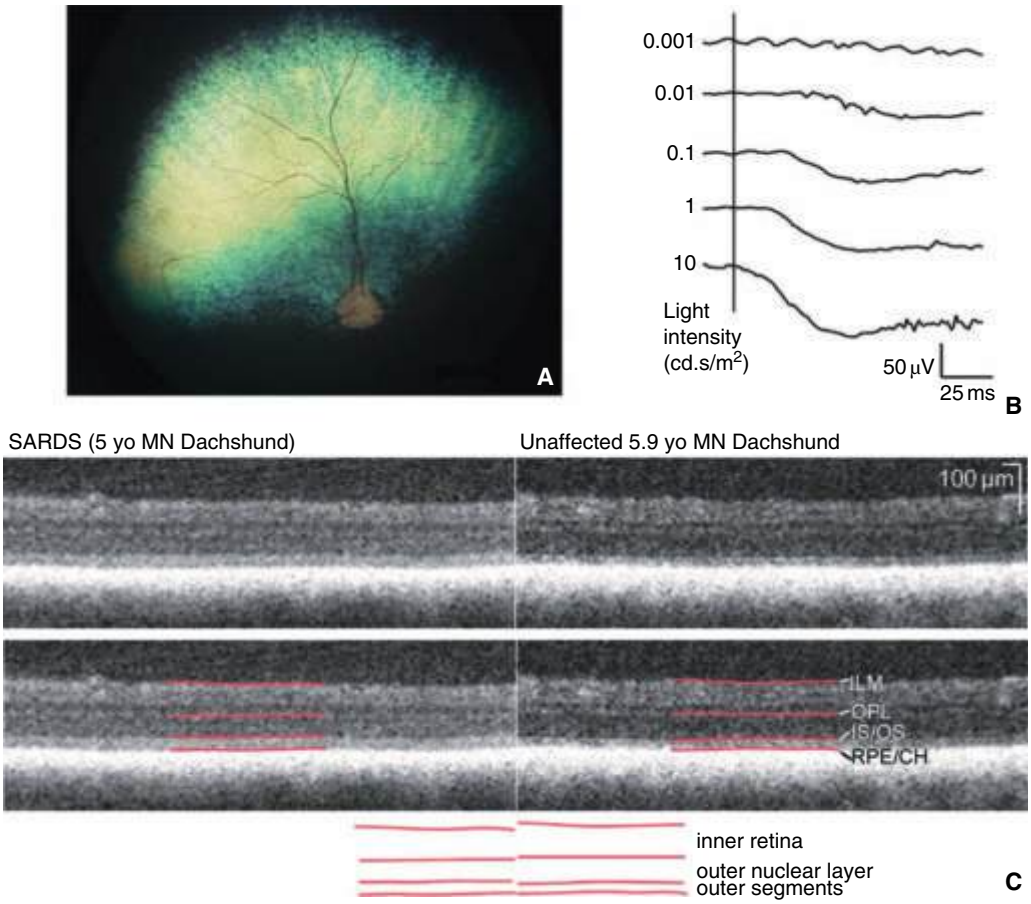


Figure 25.57 **A**. Normal fundoscopic appearance of a 5-year-old Dachshund that had become acutely blind 2 weeks previously. **B**. Typical electroretinographic findings from early sudden acquired retinal degeneration syndrome (SARDS) patients in the author's experience include a negative waveform with long implicit time, which increases in amplitude with increasing light intensity. This waveform is typical for a scotopic threshold response. **C**. Optical coherence tomography imaging of the dorsal retina of SARDS and age- and breed-matched control dogs shows that even in the relatively early stages of disease, retinal thinning is present, particularly affecting the outer nuclear layer (between OPL and IS/OS). ILM, internal limiting membrane; IS/OS, boundary between photoreceptor inner and outer segments; OPL, outer plexiform layer; RPE/CHOR, interface between retinal pigment epithelium and choroid. (Courtesy of North Carolina State University Ophthalmology Service.)

by a slow degeneration of the other retinal layers, leading eventually to the appearance of an end-stage retinal degeneration. Different regions of the retina are equally affected. The underlying etiology of SARDS is not understood. A similarity to human autoimmune retinopathy (AIR) has been proposed (Komáromy et al., 2016). AIR in humans can be associated with cancer (paraneoplastic AIR) or not associated with cancer (nonparaneoplastic AIR; Grewal et al., 2014). In dogs with SARDS, no evidence of systemic neoplasia has been identified (Bellhorn et al., 1988; Gilmour et al., 2006). Studies exploring the presence of circulating antiretinal antibodies in dogs with SARDS have been contradictory. Two studies have shown the presence of antiretinal antibodies in cases with SARDS (Bellhorn et al., 1988; Braus et al., 2008), while other studies demonstrated that affected dogs had no higher incidence of antiretinal antibodies than normal dogs (Gilmour et al., 2004; Keller et al., 2006). Further studies are needed to definitively confirm the underlying etiology of SARDS.

There is a paucity of evidence on the effects of treatment in SARDS patients. There is one peer-reviewed publication describing the efficacy of treatment with the immunosuppressive mycophenolate mofetil for SARDS (Young et al., 2018), which did not identify any benefit of 6 weeks of oral treatment on systemic health or vision. Other treatments anecdotally used in SARDS patients include intravenous or intravitreal human Ig, immunosuppressive doses of corticosteroids, or combination immunosuppressive medications. However, controlled prospective studies exploring the efficacy and side effects of these treatments have not yet been reported. Prognosis for vision is grave long term in SARDS patients. Many of the associated clinical signs such as polyuria are anecdotally reported to subside over time, although one study demonstrated a persistence of clinical

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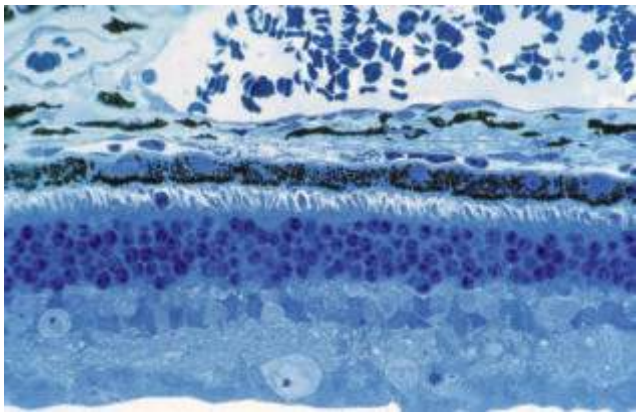


Figure 25.58 Light micrograph of a 5-year-old Dachshund affected by sudden acquired retinal degeneration syndrome. Note the degeneration of the photoreceptor outer segments and the abnormally short inner segments. Also there is a reduction in the number of photoreceptor cell nuclei in the outer nuclear layer.

signs and an increase in polyphagia one year after diagnosis (Stuckey et al., 2013). One-year survival in this study of 100 dogs was 83% and quality of life was reported by owners to remain good.

Retinal Toxicities

Systemic Toxicities

Drug- and Chemical-Induced Retinotoxicity

Some compounds can directly cause retinal damage by damaging neuroretinal or RPE cells, or indirectly cause such damage by inflammatory reactions that lead to focal or more generalized cell death. Assessment of retinal integrity is an essential component in ocular drug safety evaluations. Usually, ophthalmoscopy and biomicroscopy of treated animals and histopathology of retinal tissues are used in routine toxicologic studies. These methods are adequate to detect gross retinal degenerative changes; however, they fail to detect minor pathology of the retina, such changes involving subtle though generalized structural alterations without degeneration (Aguirre, 1990). Minor morphologic changes may be elucidated using improved methods of tissue fixation and both light and electron microscopy. Functional evaluation can be accomplished using electrophysiologic testing, such as ERG or VEP (or both). To determine target-tissue specificity and examine mechanisms of compound-associated retinal damage, *in vitro* methods (e.g., tissue culture) can be used. Preliminary extended protocols for ocular toxicity testing have already been proposed in some areas of toxicology (Hamernik, 1994; Rosolen et al., 2005).

Drug-induced retinopathies are usually characterized by bilateral symmetry. There is usually a relationship between the duration of the administration of a toxic compound, the dosage, and the onset of clinical signs. Some well-known and representative drug-related retinotoxic compounds are discussed here. For examples, see Fig. 25.59.

Drugs

Vasodilating Drugs

Some experimental vasodilating drugs have been reported to cause a tapetal color change in the region overlying the long posterior ciliary arteries, thought to be due to a slight distortion of the choroid overlying the vessels altering the direction of light reflected off the tapetum (see Fig. 25.59C; Rubin, 1974).

Digoxin Digoxin is a cardiac glycoside used to treat congestive heart failure in small animals. It has been shown to cause cone dysfunction in many species including dogs, which is reversible on discontinuation of the drug (Maehara et al., 2005).

Azalide Azalide is a macrolide antibiotic drug that can cause tapetal color changes if administered in high doses (e.g., 100-fold the recommended clinical dose; Fortner et al., 1993). Ophthalmoscopically, there is a dull white appearance of the tapetal fundus. Microscopic examination of ocular tissue shows tapetal cells that are swollen and vacuolated as well as retinal cells (primarily ganglion cells) that contain lysosomal lamellar bodies. No other effects have been found, either in the eye or systemically.

Ethambutol The antibiotic ethambutol is used in the treatment of tuberculosis, and causes discoloration of the tapetal fundus (see Fig. 25.59D–F); this discoloration is reversible (Kaiser, 1963; Vogel & Kaiser, 1963). There is no effect on vision, and the ERG and VEP remain normal (Sato, 1985). Morphologically, affected tapetal cells have swollen and disoriented, intracellular rod–like bodies, which appear to interfere with the diffraction and reflection of light. In humans, ethambutol produces a decrease in visual acuity and loss of ability to perceive the color green (Rubin, 1974).

Closantel Intoxication with closantel, which is an antihelmintic used in domestic ruminants, has been described in a dog (Entee et al., 1995). Eye examination revealed bilateral mydriasis with absent pupillary reflexes. Funduscopically, the optic discs were swollen, and several small papillary and peripapillary hemorrhages were seen. The tapetal fundus was diffusely hyperreflective. Retinal vasculature appeared to be normal. Over time, there was progression of the lesions, which resulted in generalized retinal and optic disc atrophy. Blindness was irreversible.

Rafoxanide The large animal antihelmintic rafoxanide causes a rapidly progressing optic nerve edema that can

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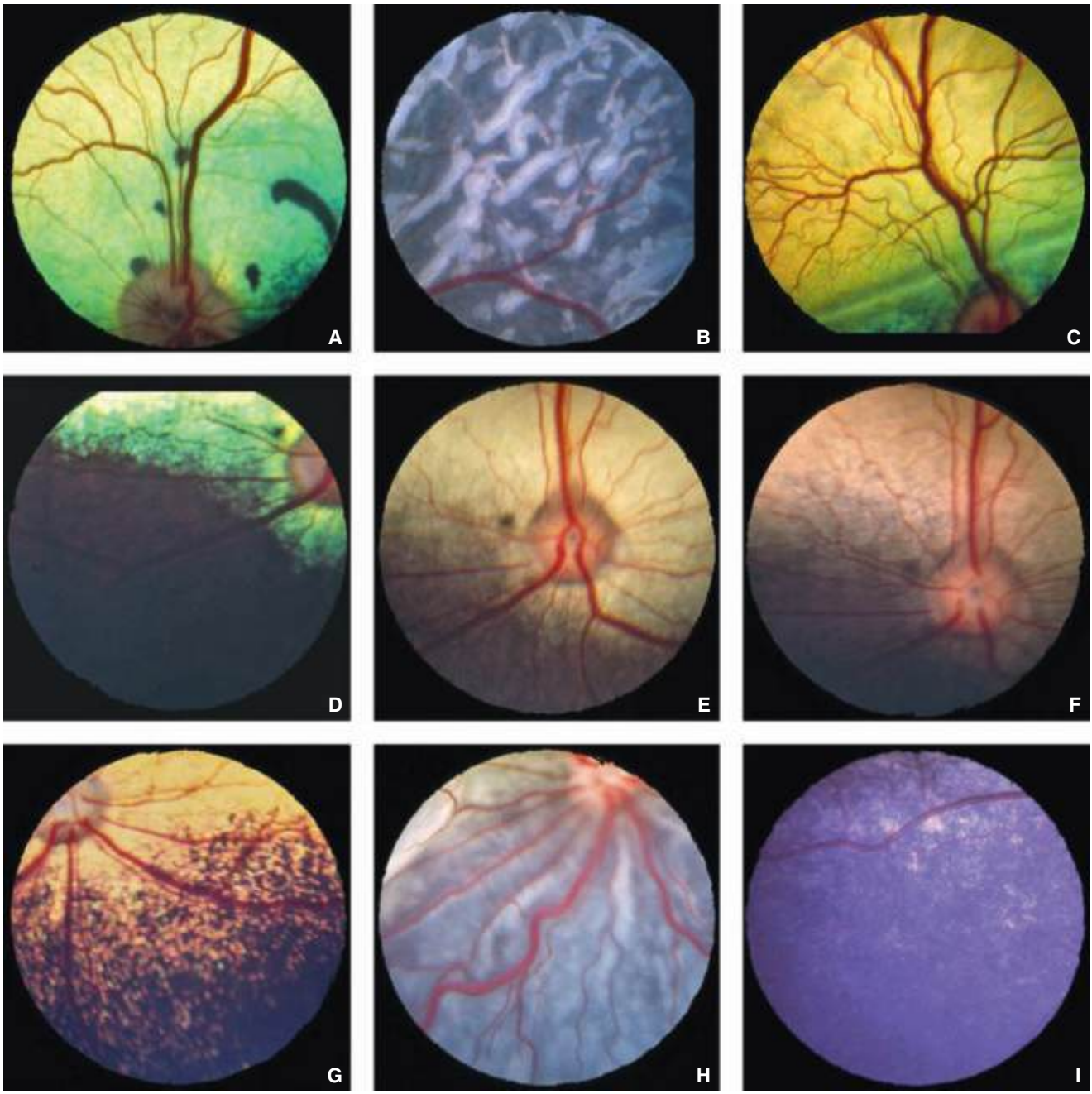


Figure 25.59 Drug-induced retinal effects and toxicities have been described for the dog fundus. **A**, **B**. Toxic neuroretinitis is shown in a 6-month-old dog with initial intestinal problems, then clinically blind, 3 days after rummaging in a trash heap. The tapetal fundus (**A**) shows comma-shaped pigmentary changes. In the nontapetal fundus (**B**), there are multiple areas with retinal edema. **C**. Some experimental vasodilating agents produce transient color changes in the dog retina, generally in the zone corresponding to the distribution of the long posterior ciliary arteries. The color changes observed are related to localized distortion of the retinal and choroidal curvature by the widely dilated larger vessels. **D**, **E**, **F**. Fundus of a 1-year-old Beagle treated with ethambutol. The tapetal junctional area is shown prior to treatment (**D**). There is progressive discoloration of the tapetal retina after oral administration of ethambutol, 800 mg/kg body weight, after 9 and 23 days (**E**, **F**), respectively. **G**, **H**. Diphenylthiocarbazone (dithizone) toxicity is shown in a German Shepherd. The normal fundus of the dog is shown prior to treatment (**G**), and the same area after intravenous administration of 20 mg/kg body weight of dithizone (**H**). Note that only 24 hours after treatment, the retina is detached in some areas and thrown into multiple folds in others. **I**. Chloroquine toxicity is shown in a dog, most easily observed in the nontapetal fundus as scattered gray-white specks. Histologically these lesions correspond to membranous cytoplasmic bodies, mainly in ganglion cells. (Reproduced with permission from Rubin, L.F. (1974) *Atlas of Veterinary Ophthalmoscopy*. Philadelphia, PA: Lea & Febiger, © Lionel F. Rubin.)

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result in blindness (Brown et al., 1971). Histopathologically, there is vacuolation and edema of the optic nerve, chiasm, and white matter of the brain and spinal cord.

Ivermectin Intoxication with the antiparasitic ivermectin causing blindness in dogs has been reported in the peer-reviewed literature (Epstein & Hollingsworth, 2013; Kenny et al., 2008). One dog ingested large animal ivermectin, presumed to be present in horse feces; the other was prescribed oral ivermectin to treat demodecosis that had been used for approximately 8 weeks prior to vision loss. Both dogs tested negative for the multidrug sensitivity mutation in the gene *MDR1*. Both dogs had reduced ERG amplitudes, and evidence of retinal edema and folds (Fig. 25.60). ERG amplitudes increased and vision subjectively improved in both dogs after discontinuation of the drug, with evidence of mild chorioretinal scarring in the regions of prior edema.

Thiram Thiram (tetramethylthiuram disulfide) is a general-purpose pesticide. Toxicity studies in dogs showed that thiram caused ocular lesions including fundus changes, as well as more generalized changes such as liver failure and kidney damage (Maita et al., 1991).

Quinine The antimalarial drug quinine and some of the cinchona derivatives cause rapid vasoconstriction of retinal arterioles and pallor of the optic disc within a few hours of administration in dogs. Later, a partial or complete destruction of ganglion cells with subsequent optic atrophy is found (Rubin, 1974).

Chloroquine The antimalarial drug chloroquine has an affinity for melanin and ocular tissues containing melanin. In the dog, the earliest changes may be seen in the nontapetal fundus as scattered, gray-white specks (see Fig. 25.59I). Histopathologically, membranous cytoplasmic bodies are seen in ganglion cells at ultrastructural analysis (Rubin, 1974).

Chemicals

Diphenylthiocarbazone

Administration of the metal-chelating chemical diphenylthiocarbazone (dithizone) causes funduscopic alterations within 24 hours of intravenous injection (see Fig. 25.59G, H). Funduscopic changes include a dark red color and diffuse retinal edema. Pigmentary aberrations follow, thus giving the fundus a mottled appearance. Minimum doses may cause reversible changes, but also bullous retinal detachment, thereby causing blindness. High doses cause irreversible damage with retinal degeneration (Rubin, 1974).

Hydroxypyridinethione The metal-chelating chemical hydroxypyridinethione has been shown to cause blindness in dogs as a sequel to tapetal necrosis, edema, and retinal detachment (Delahunt et al., 1962).

Retinopathy Induced by Light and Oxygen

There is a well-established association between high light intensity and retinotoxicity. Phototoxicity in the rat model has been extensively studied (Penn et al., 1992). Illumination of the canine fundus with light from an indirect ophthalmoscope for 20 minutes may be sufficient to cause

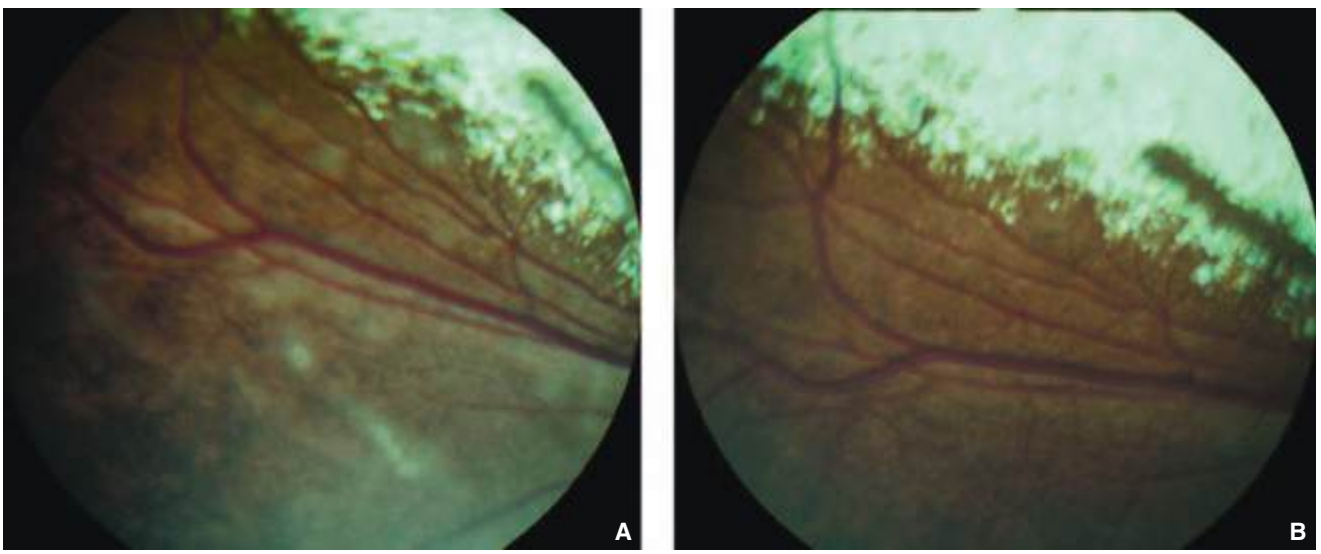


Figure 25.60 Ivermectin toxicosis in the canine retina. **A**. Areas of presumed retinal edema are most visible at the junction of the tapetal and nontapetal fundus, adjacent to retinal blood vessels. **B**. After 9 months, retinal changes are no longer visible. Reproduced with permission from Epstein, S.E. & Hollingsworth, S.R. (2013) Ivermectin-induced blindness treated with intravenous lipid therapy in a dog. *Journal of Veterinary Emergency Critical Care*, **23**(1), 58–62.

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ophthalmoscopically visible changes, and has been shown to exacerbate degeneration in dogs with dominant PRA due to a rhodopsin mutation (see earlier discussion; Cideciyan et al., 2005a; Iwabe et al., 2016; Sudharsan et al., 2017). Prolonged exposure in normal dogs results in areas of increased granularity in the tapetal fundus, which is followed by retinal pigmentation and increased tapetal reflectivity. The nontapetal fundus, however, appears relatively unaffected, possibly because of the protective effect of pigmentation. Histopathologic changes in mild light toxicity include vesiculation and shortening of photoreceptor outer segments and vesiculation of the RPE. More advanced cases have photoreceptor degeneration and atrophy of the RPE (Buyukmihci, 1981). The risk of phototoxic retinopathy should be considered during intraocular surgery because it is possible for light from the operating microscope to cause a focal area of retinal damage. This is seen as a circular area of degeneration, typically in the central retina.

Exposure to high oxygen tensions produces selective damage to the visual cells in the dog (Rubin, 1974). Oxygen administration has been strongly linked with human retinopathy of prematurity, and there is evidence that light exposure may play a contributing role in its pathogenesis (Glass, 1990). Oxidative processes and generation of free radicals have also been suggested to be important in the development of the disease (Penn et al., 1992). The dog has been established as an experimental model for human retinopathy of prematurity (McLeod et al., 1996, 1998). Neonatal dogs exposed to 95%–100% oxygen for 4 days develop a peak of revascularization of the posterior segment between 3 and 10 days following return to room air (McLeod et al., 1996). Lesions include dilated and tortuous retinal vessels, pigmentary changes, incomplete vascularization of the peripheral retina, vitreal hemorrhage, and persistence of intravitreal neovascularization with retinal folds due to traction bands (McLeod et al., 1998).

The combination of light and oxygen can interact to produce oxygen-free radicals in a process known as photosensitization (Sadda et al., 1994). Experimental studies in newborn Beagles showed both clinical and histopathologic abnormalities in eyes exposed to light in the presence of rose Bengal, which is a photosensitizing agent. A spectrum of retinal lesions was identified, including vitreous hemorrhage, fibrovascular and fibrocellular proliferation with retinal traction, complete and partial retinal detachment, and retinal dysplasia.

Retinopathy Induced by Radiation

Radiation-induced ocular injury secondary to treatment of nasal cancer occurs in both humans and animals. In a clinical and histopathologic study (Ching et al., 1990), immediate changes such as blepharitis and keratoconjunctivitis were found. At 3–6 months posttreatment (i.e., 36.0–67.5 Gy in fractionated doses given over 4 weeks using a 6 mV linear accelerator), however, a degenerative angiopathy of retinal vessels appeared, with multifocal retinal hemorrhage and mild, diffuse retinal degeneration, first affecting the outer retinal layers but then progressing to involve the inner retina. At 1–2 years following treatment, there was a moderate retinal degeneration, with swelling and loss of ganglion cells and, subsequently, optic nerve axonal degeneration. Even tapetal and choroidal atrophy was observed. Thus, structures of the canine eye are sufficiently sensitive that even relatively low total doses of radiation cause significant long-term injury.

A study of the ocular effects of intravenous radium in Beagles showed that the radium was retained within the tapetum and induced varying degrees of tapetal degeneration. However, the major changes involved the anterior uvea and consisted of the development of melanotic plaques and melanomas (Taylor et al., 2000). Experimental *in utero* exposure to radiation resulted in bilateral focal retinal dysplasia and in some instances a slowly progressive retinal degeneration, with the portion of the retina most severely affected being that which was differentiating at the time of radiation exposure (Schweitzer et al., 1987).

Retinopathies of Nutritional Causes

Vitamin A Deficiency

Systemic vitamin A deficiency is characterized by night blindness in several species (Dowling & Wald, 1958; Hayes, 1974). Specific objective studies using psychophysical testing and fundus reflectometry in humans with vitamin A deficiency, both before and after supplementation, showed that subjects initially had no measurable rod function and delayed cone adaptation. After oral supplementation with vitamin A, visual function was restored to normal (Kemp et al., 1988). In the dog, systemic diseases causing impaired fat absorption could result in vitamin A deficiency, but this clinical situation is extremely rare.

Vitamin E Deficiency

Vitamin E is an antioxidant with an important function in maintaining cell membrane stability by preventing lipid peroxidation. A deficiency in vitamin E may result in pathologic changes in the muscle, CNS, reproductive tract, and retina (Hayes et al., 1970; see Fig 25.45A and Fig. 25.61). Experimental studies that produced vitamin E deficiency have been performed in the dog by Riis and colleagues (Riis et al., 1981). After weaning, dogs were fed a diet deficient in vitamin E. Ophthalmoscopic signs of disease developed early (within 3 months) and were described as a mottled tapetal fundus appearance, particularly centrally, with numerous, discrete yellow-brown foci. Over time, the central

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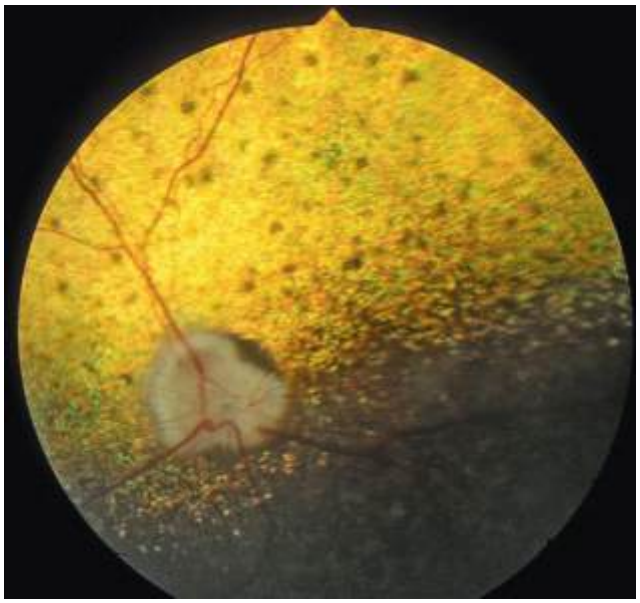


Figure 25.61 Vitamin E deficiency. The fundus of an English Cocker Spaniel with very low circulating alpha-tocopherol levels. The presenting complaint was mild visual impairment. Multiple pigmented lesions typical of vitamin E deficiency and also central progressive retinal atrophy/retinal pigment epithelial dystrophy were present across the entire tapetal fundi of both eyes.

fundus became hyperreflective and there was attenuation of the retinal vessels. The ERG was nonrecordable at 4 months of age. ERG changes at the early stages were partially reversible with vitamin E supplementation.

Histopathologically, an accumulation of autofluorescent pigment within the RPE cells was observed and, at later stages, within migrating, presumably macrophage cells in the retinal layers. Photoreceptor damage occurred in areas overlying affected regions of the pigment epithelium. After 6 months of deficiency, there was complete atrophy of the photoreceptor layer. The obvious similarities between vitamin E deficiency and hereditary CPRA/RPED suggest some common etiologic factor, and recent reports have substantiated this suggestion. Davidson and colleagues (Davidson et al., 1998) described retinopathy from vitamin E deficiency in a group of 16 Walker Hounds and in 2 Beagles. These dogs were kept in a common pen and fed a diet consisting of meat scraps, poultry carcasses, and offal. A spectrum of funduscopic changes, which varied in severity with increasing age, was found. Results of clinical as well as laboratory investigations showed that the retinopathy resembled CPRA/RPED. McLellan and colleagues measured alpha-tocopherol levels (the predominant vitamin E homologue in the retina and RPE) in 15 dogs (including 11 English Cocker Spaniels) with clinical signs of CPRA/RPED and 28 clinically normal dogs. All 11 CPRA/RPED-affected English Cocker Spaniels had very low plasma alpha-tocopherol levels and very low ratios of plasma alpha-tocopherol to cholesterol and triglycerides compared to normal controls (McLellan et al., 2002). The results from the four CPRA/RPED-affected dogs of other breeds were not conclusive. A subsequent study showed that after oral vitamin E supplementation, CPRA-affected English Cocker Spaniels absorbed vitamin E, but had lower plasma levels than normal dogs (McLellan & Bedford, 2012), indicating that dietary insufficiency alone is not responsible for CPRA/RPED in English Cocker Spaniels, and that a hereditary abnormality in vitamin E metabolism could contribute. Studies in English Cocker Spaniels have shown that dietary supplementation with vitamin E can halt the progression of neurologic changes (ataxia, proprioceptive deficits, abnormal spinal reflexes, and muscle weakness) and resulted in an improvement of the neurologic signs and in exercise tolerance. It did not, however, appear to alter the ocular changes that had already developed (McLellan et al., 2003). It is recommended that English Cocker Spaniels diagnosed with vitamin E deficiency should be supplemented with 600–900 IU twice daily oral tocopherol (McLellan & Bedford, 2012).

Nutritional Supplementation

Results of several studies show that dietary supplementation in dogs with omega-3 fatty acids, from a natural source, such as salmon oil, with a high level of docosahexanoic acid (DHA), increases plasma and red blood cell levels of fatty acids, improves the ratio of omega-6 to omega-3, and positively benefits cognitive development, visual acuity, and ERG amplitudes (Filburn & Griffin, 2005; Zicker et al., 2012). DHA acts to maintain photoreceptor outer segment disc morphology (Shindou et al., 2017). A recent meta-analysis of previously published studies did not find any benefit on progression of human inherited retinopathy with supplementation with DHA (Brito-Garcia et al., 2017).

Supplementation with vitamins A and E has been studied in groups of human patients with retinitis pigmentosa (RP), a disease complex comparable to PRA (Berson et al., 1993). The results support a beneficial effect of 15,000 IU/day of vitamin A on the rate of ERG decline, particularly if supplemented early in disease, although other measures of visual function (visual fields and acuity) remained unchanged by supplementation. The same study found an adverse effect of 400 IU/day of vitamin E on the rate of ERG decline in RP. It is worth noting that in some retinopathies vitamin A supplementation is to be avoided. For example, in Stargardt's disease, which is characterized by lipofuscin accumulation, studies in experimental animals suggest that a reduction in vitamin A levels may slow down lipofuscin accumulation (Radu et al., 2005).

The carotenoids lutein and zeaxanthin are more commonly referred to as macular pigments in humans, and contribute to protection from ultraviolet light damage and

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oxidative damage in the retina (Stringham & Hammond, 2005). The addition of lutein to vitamin A supplementation had a beneficial effect in human RP patients, slowing midperipheral visual field loss (Berson et al., 2010).

Zinc has the potential to aid in oxidative injury to the retina by competitive displacement of iron and prevention of its redox cycling (Grahn et al., 2001). However, there are conflicting studies regarding the benefit of zinc supplementation in humans and further studies are needed.

Although commercially available to pet owners for canine use, the benefit of antioxidant supplements on canine retinal health have not yet been established. Further large, well-controlled studies will be necessary to definitively determine their effect on canine retinal degeneration.

Vascular Disease Processes

The retinal vasculature is well suited to direct, noninvasive examination. Systemic disease as well as local ocular pathology can produce observable changes in both retinal and choroidal vessels (Lane et al., 1993). Except for blood constituent analysis, blood flow and blood pressure measurements, and coagulation studies, specific methods of examination include ophthalmoscopy and fluorescein angiography. Furthermore, in the research environment, specific histopathologic studies may be performed, as well as studies of the ocular circulation and the sequelae of vascular disease processes by using radioactively marked microspheres (Alm & Bill, 1972; Hillerdal et al., 1987). A short description of funduscopic lesions associated with systemic hypertension, hyperviscosity, and hyperlipidemia is given here; for a more comprehensive discussion on these disorders, see Chapter 36, Part 1.

Systemic Hypertension

Dogs with experimentally induced hypertension exhibit retinal hemorrhage, retinal detachment, and arteriolar changes (Fig. 25.62; Preiswerk & Breitenfeld, 1984). In cases of spontaneous systemic hypertension, visual disturbance is often the initial presentation. The most common ocular findings in clinical cases are posterior segment hemorrhage (retinal, preretinal, and vitreal), retinal detachment, tortuous retinal vessels, subretinal edema, and hyphema (Bovee et al., 1989; Gwin et al., 1978; Leblanc et al., 2011; Littman et al., 1988; Paulsen et al., 1989; Sansom & Bodey, 1997). In one study, the presence of ≥ 1 type of ocular lesion had moderate sensitivity and specificity of 62% and 61%, respectively, for identification of hypertension (Leblanc et al., 2011).

Hyperviscosity Syndromes

In dogs with hyperviscosity syndromes, for example with multiple myelomas or polycythemia, distended and tortuous retinal blood vessels are seen in conjunction with sacculation of venules, retinal hemorrhage, and in severe cases retinal edema, retinal detachment, and papilledema (Fig 25.63; Brightman et al., 1980; Gray et al., 2003; Hendrix et al., 1998; Lane et al., 1993; Macewen et al., 1977; Martin, 1982). In a single case report of a dog with polycythemia vera, the ocular presentation was of a unilateral anterior uveitis and active chorioretinitis (Gray et al., 2003).



Figure 25.62 Hypertensive retinopathy. Right fundus of dog with hyperadrenocorticism and systemic hypertension. A large dorsal bullous retinal detachment is present, with subretinal hemorrhage pooling at the inferior edge of the detachment. Peripapillary and nasal retinal hemorrhages are also present. (Courtesy of North Carolina State University Ophthalmology Service.)

Hyperlipidemia

Hyperlipidemia may impart a milky pink coloration to retinal vessels, which is most easily observed in the nontapetal fundus (Brightman et al., 1980; Martin, 1982).

Diabetic Retinopathy

Though diabetic retinopathy occurs in the dog, the extent and severity of the retinal lesions are milder compared with those that can develop in diabetic humans. In the dog, the ocular lesions include anomalies of the retinal vasculature and cataract formation, as they do in humans. Whereas the vascular changes in humans are of major importance in the disease and contribute to blindness, they are much less severe and of minor clinical importance in the dog with spontaneously occurring diabetes (Fig. 25.64). Cataract formation, on the other hand, is an early and common finding in the dog.

In humans, the initial retinal vascular change is the formation of microaneurysms, caused by sacculation of a small

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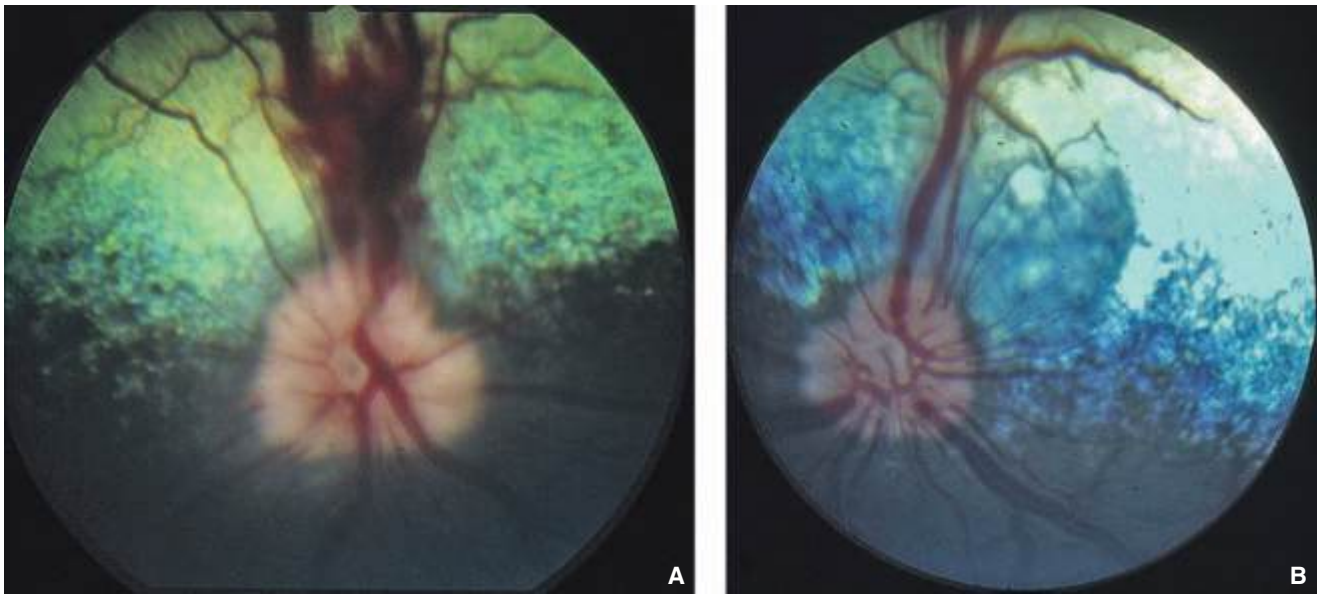


Figure 25.63 Hyperviscosity syndrome. **A**. Hyperviscosity due to polycythemia has resulted in retinal vasculature dilation and a preretinal hemorrhage. **B**. Hyperviscosity due to multiple myeloma has resulted in retinal vascular dilation and a focal area of retinal detachment dorsal to the optic nerve head. This reattached after the condition was treated.

area of the capillary wall. Rupture of these aneurysms results in ophthalmoscopically visible focal hemorrhages, and there may be accompanying edema and vascular tortuosity. These are the so-called background changes in diabetic retinopathy. Proliferative changes, including preretinal and vitreal neovascularization, often with connective tissue formation in the vitreous, may also develop. The accompanying vitreal hemorrhage and nonrhegmatogenous retinal detachments that may follow will often cause blindness. In dogs with diabetes, background retinopathy can occur, but not the proliferative changes that develop in humans. A retrospective study of 52 spontaneously diabetic dogs and 174 nondiabetic dogs that had undergone cataract surgery found retinal hemorrhages or microaneurysms in 21% of the diabetic dogs and in only 1 (0.6%) of the 174 nondiabetics. The mean time from the onset of diabetes to the diagnosis of diabetic retinopathy was 1.4 years (range 0.5–3.2 years; Landry et al., 2004). In a similar study, prevalence of retinopathy in spontaneously diabetic dogs was found to be 20% over a 2-year follow-up time (Herring et al., 2014), although cataract formation may preclude identification of diabetic retinal changes. Diabetes can also be induced for research purposes in dogs, for example by administration of alloxan or galactose (Engerman & Kern, 1987; Frank, 1995; Kador et al., 1995; Kern & Engerman, 1995; Takahashi et al., 1992).

Histopathologic changes in both spontaneous and induced diabetic retinopathy include thickening of the vascular basement membrane, pericyte loss, microaneurysm formation, and capillary closure. There is also a loss of smooth muscle cells in the retinal arterioles (most obvious in the central retina) that accompanies the loss of pericytes (Gardiner et al., 1994). Regional differences in the distribution of vascular lesions within the same retina also are evident (Kern & Engerman, 1995). Thus, microaneurysms and acellular capillaries are more prevalent in the superior temporal retina than in the inferior nasal quadrant, whereas the distribution of pericyte ghosts (i.e., a pocket in the basement membrane

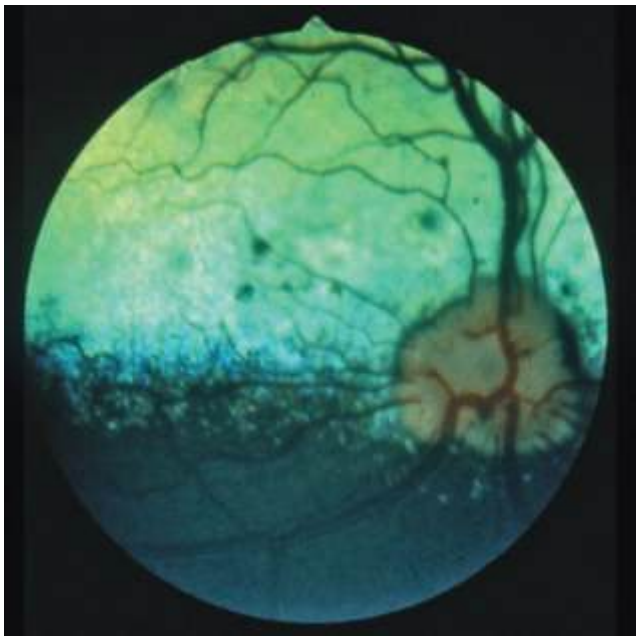


Figure 25.64 Diabetic retinopathy in a middle-aged dog. There are several small retinal hemorrhages in the central tapetal fundus. (Courtesy of Dr. Lennart Garmer.)

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at the site from which a pericyte has disappeared) in the same eye was not significantly different between quadrants. These findings show that local factors within the eye are important in the response of the retinal microvasculature to the disease process.

Retinopathies with Immunologic Diseases

Immune-Mediated Thrombocytopenia

Immune-mediated thrombocytopenia is a clinical disease characterized by anemia, hemorrhage, and low platelet counts. The presenting sign is often petechiation and ecchymosis of the gingiva or conjunctiva, and both hyphema and retinal hemorrhage are common findings (Shelah-Goraly et al., 2009). Treatment consists of controlling the hemorrhage; blood transfusion may be necessary in severe cases. Treatment of the immune-mediated disease process is important to control the disease in the long term. Current internal medicine texts should be consulted for more information.

Immune-Mediated Hemolytic Anemia

Immune-mediated hemolytic anemia affects both humans and dogs. Presenting clinical signs are acute to chronic anemia, and ophthalmoscopically, the retinal vessels are light red and difficult to follow because of the blood disorder (Curtis et al., 1991). Retinal hemorrhage has not been shown to be associated with canine anemia (Shelah-Goraly et al., 2009). Treatment of the immune-mediated disease process is important to control the disease in the long term. Current internal medicine texts should be consulted for more information.

Systemic Lupus Erythematosus

Systemic lupus erythematosus is a multisystem disorder with immunologic abnormalities related to autoantibodies in both the blood and the lesions of the body. There is a genetic predisposition for the disease. Ocular lesions include hemorrhages and serous retinal detachments.

Cancer-Associated Retinopathy

Cancer-associated retinopathy (CAR) is a form of AIR described in humans in which cancer patients develop antibodies that cross-react with retinal antigens, and the resulting immunologic attack on the retina causes retinal cell death and vision loss (for a review see Shildkrot et al., 2011). Several tumor types may lead to this condition, but melanomas are the most commonly described. The vision loss may be apparent before the tumor is detected. There is little information on the occurrence of CAR in dogs, although no evidence of cancer has been identified in dogs with SARDS (Gilmour et al., 2006).

Secondary Retinal Degeneration

Glaucoma

Glaucomatous retinal damage is well documented in dogs. In acute stages, the retina may appear normal ophthalmoscopically or show areas of edema with optic nerve swelling. When there is severe retinal damage, retinal degeneration becomes apparent surprisingly rapidly; sometimes this may appear as more severe zones of retinal thinning radiating out from the ONH. Cupping and atrophy of the ONH also develop (see Chapter 20 and Chapter 27). Histopathologic studies of eyes removed because of primary narrow-angle glaucoma show that essentially all retinal layers are affected and that the progression of retinal changes occurs rapidly. Within 1 day of the onset of glaucoma, necrosis of retinal ganglion cells has developed and is followed by the induction of apoptosis of cells in the ganglion cell layer as well as the inner and outer nuclear layers (Whiteman et al., 2002). There is release of taurine and glutamate from photoreceptors, possibly secondary to ischemic damage (Madl et al., 2005). Glutamate release may induce excitotoxicity, thus inducing apoptosis in additional retinal neurons. Glutamate accumulates in Müller cells in glaucoma-affected dogs (Madl et al., 2005), and an increased level of glutamate in the vitreous has also been reported (Brooks et al., 1997). Interestingly, there is a notable sparing effect over the tapetal area, with the retina in this area being less severely affected than in the nontapetal areas (Brooks et al., 1997; Madl et al., 2005; Smedes & Dubielzig, 1994; Whiteman et al., 2002). The reason for the tapetal sparing effect is not known. Other changes include partial or panretinal necrosis, hypertrophy of the RPE, disorganization of retinal layers, and severe retinal atrophy. Changes in the retina of dogs with glaucoma-associated retinopathy that have less severe intraocular pressure (IOP) increases than typically seen in narrow-angle glaucoma are likely to be more slowly progressive.

The effects of raised IOP on retinal function can be detected by ERG. A study of the flash ERG with raised IOP showed a decay of b-wave amplitude, whereas the a-wave amplitude was less affected (Howard & Sawyer, 1975). This indicates a more pronounced effect of glaucoma on the bipolar cells, which are the origin of Granit's PII, an ERG component corresponding to the b-wave, as compared to the photoreceptors, the major generators of PIII, which cause the increasing negativity of the a-wave. In a study of short-term induced IOP rise in dogs, Hamor and colleagues found that the pattern ERG was more sensitive to IOP rises than

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the flash ERG (Hamor et al., 2000). This finding would be expected, because the pattern ERG response originates predominantly from the inner retina (Sieving & Steinberg, 1987), Grozdanic and colleagues also recently reported the sensitivity of pattern ERG over flash ERG in dogs with angle-closure glaucoma (Grozdanic et al., 2010).

Retinal Detachment

Various pathologic conditions of the eye can cause focal, multifocal, or total retinal detachment. The neuroretina is separated from the underlying RPE, which implies a disruption of the intimate and essential (but structurally weak) association between the outer segments of the photoreceptors and the RPE. This loss of structural integrity is associated with a loss of function and secondary retinal degeneration in the affected area. Thus, a focal retinal detachment will not usually result in clinically detectable impairment of vision, whereas detachment of the entire retina is a blinding condition. PLRs are retained even with complete detachment, due to the activity of melanopsin in the retinal ganglion cell layer driving light response. Detachments involving large areas of the retina may result in tearing of the peripheral retina as the multilayered neurosensory retina becomes thinner at the periphery, to continue as the nonpigmented ciliary body epithelium at the ora ciliaris retinae. The complete tearing of the peripheral retina is often termed disinsertion, or dialysis (Fig. 25.65).

Ophthalmoscopy reveals an anterior displacement of the retinal surface and the retinal blood vessels. Large volumes of subretinal fluid can cause segments of the retina to balloon anteriorly, even extending to the posterior surface of the lens in extreme cases. When there is anterior displacement of the detached retina, it can often be readily viewed directly through the pupil with a focal light source. If there is a total detachment with dialysis, the retina will hang in folds from the ONH, where it remains attached due to the ganglion cell axons converging from the retina to form the optic nerve. The retina resembles a grayish-colored curtain hanging in the vitreous, and the tapetum will appear extremely hyperreflective and devoid of retinal blood vessels. Retinal tears and holes will also result in exposure of underlying tapetum and focal hyperreflectivity. The presence of retinal tears of holes is important in making decisions about management (see Chapter 26), so a detached retina should be examined carefully for the presence of tears or holes. Scleral depression may be required to view the complete periphery to the ora ciliaris retinae. Other ophthalmic consequences of retinal detachments include iris neovascularization, hyphema, and cataracts.

Retinal detachments can occur as a consequence of retinal dysplasia, as described previously; nondevelopmental etiologies can be subdivided according to the causative mechanism into rhegmatogenous, traction, and exudative detachments. A rhegmatogenous detachment is one associated with a tear or hole in the neuroretina; the retinal defect allows vitreous and fluid to dissect the neuroretina from the RPE, thus exacerbating the lesion. A force from the vitreous body pulling the neuroretina anteriorly (e.g., from an organizing hemorrhage in the vitreous body) can result in traction detachment (Fig. 25.66). Fluid and cell deposition (e.g., in chorioretinitis or hypertension) in the subretinal space elevates the retina and causes an exudative detachment.

Rhegmatogenous retinal detachment can occur commonly in dogs, associated with retinal disorders causing retinal tears such as CEA, lenticular disease, retinal dysplasia,

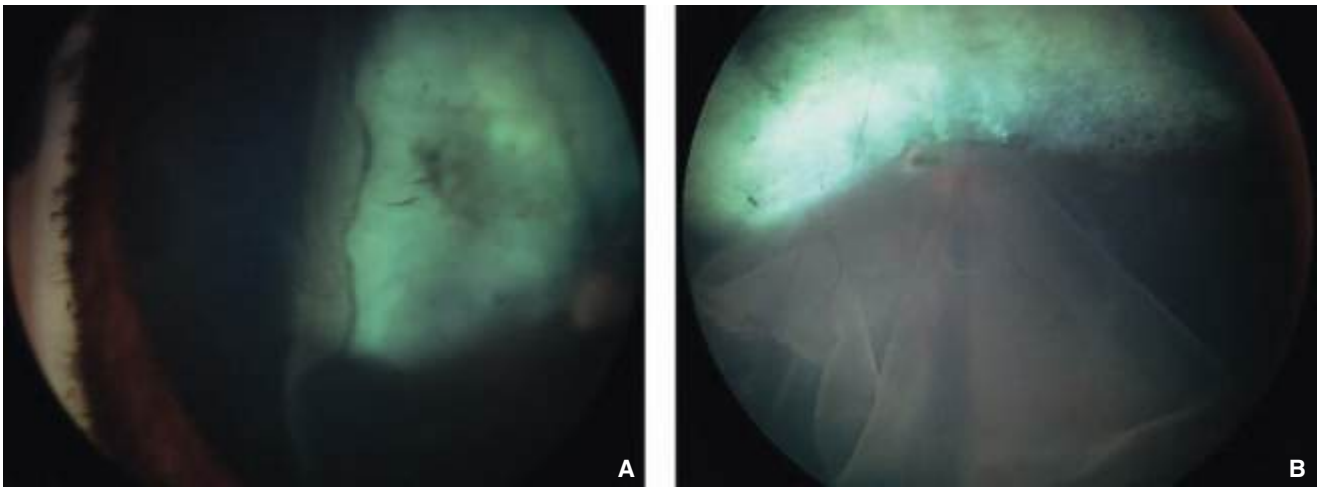


Figure 25.65 Progression of retinal dialysis in a 5-year-old Boston Terrier. **A**. At initial presentation, partial detachment was diagnosed with approximately three clock hours of dialysis dorsotemporally. **B**. 1 month later, total retinal disinsertion was evident with a "bridal veil" detachment, characterized by the retina hanging from the optic nerve head obscuring the view of the optic nerve head. (Courtesy of North Carolina State University Ophthalmology Service.)

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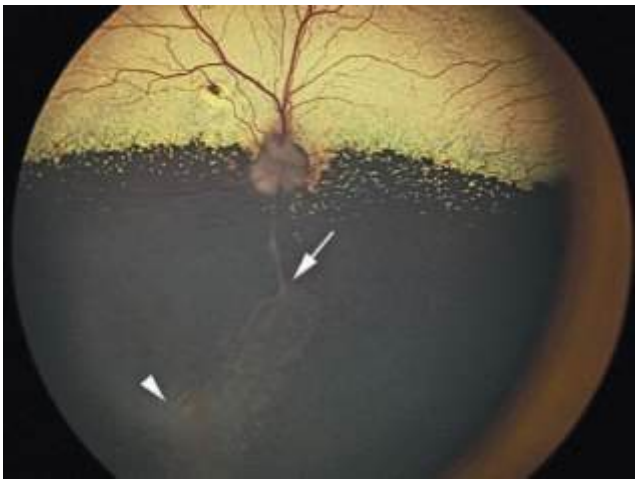


Figure 25.66 Retinal traction band. An inflammatory chorioretinitis lesion is associated with a band running anteriorly in the vitreous. The band appears as a gray-colored structure; the arrow shows its attachment to the retina. The chorioretinitis lesion associated with the traction band can be seen as an area of depigmentation in the nontapetal fundus. There is slightly raised, gray subretinal granuloma shown by the arrowhead. An inactive chorioretinitis lesion is present in the tapetal fundus. (Courtesy of Michigan State University Comparative Ophthalmology Service.)

and glaucoma (Hendrix et al., 1993). One study reported that in 23 of 46 dogs (62 eyes) with retinal detachment, the detachments were associated with lenticular disease (Hendrix et al., 1993). In 23% of the eyes, the detachment occurred after extracapsular cataract extraction. Retinal detachments secondary to cataract surgery are generally believed to be rhegmatogenous, although the cause of these neuroretinal tears is difficult to determine. Other causes of retinal detachment identified in the described study included panuveitis, infectious disease (including bacterial, rickettsial, and mycotic infections), systemic hypertension, trauma, and congenital ocular disease. Retinal tears were seen in 26% of the eyes and traction bands in 5%. Rhegmatogenous detachments in Labrador Retrievers with oculoskeletal dysplasia have been investigated as a model for rhegmatogenous retinal detachments in humans (Blair et al., 1985a, 1985b). The cause of retinal tears leading to detachment in this animal model appears to be traction on the retina from the vitreous. Formation of fibrocellular membranes on the surface of the totally detached retina, to which the RPE, nonpigmented ciliary epithelium, macrophages, and glial cells contribute, occurs later in the disease. A proliferative vitreoretinopathy of this type is an important cause of failed retinal detachment surgery in humans.

Exudative retinal detachment for which an etiology is not established despite laboratory work-up has been well recognized for many years (Gwin et al., 1980c). It has been termed steroid-responsive retinal detachment (Fig. 25.67) (Andrew et al., 1997); the affected dogs typically present with a history of an acute-onset loss of vision. The detachments are commonly bilateral and nonrhegmatogenous, and in some cases vitreal hemorrhage may develop (see Fig. 25.67). Andrew

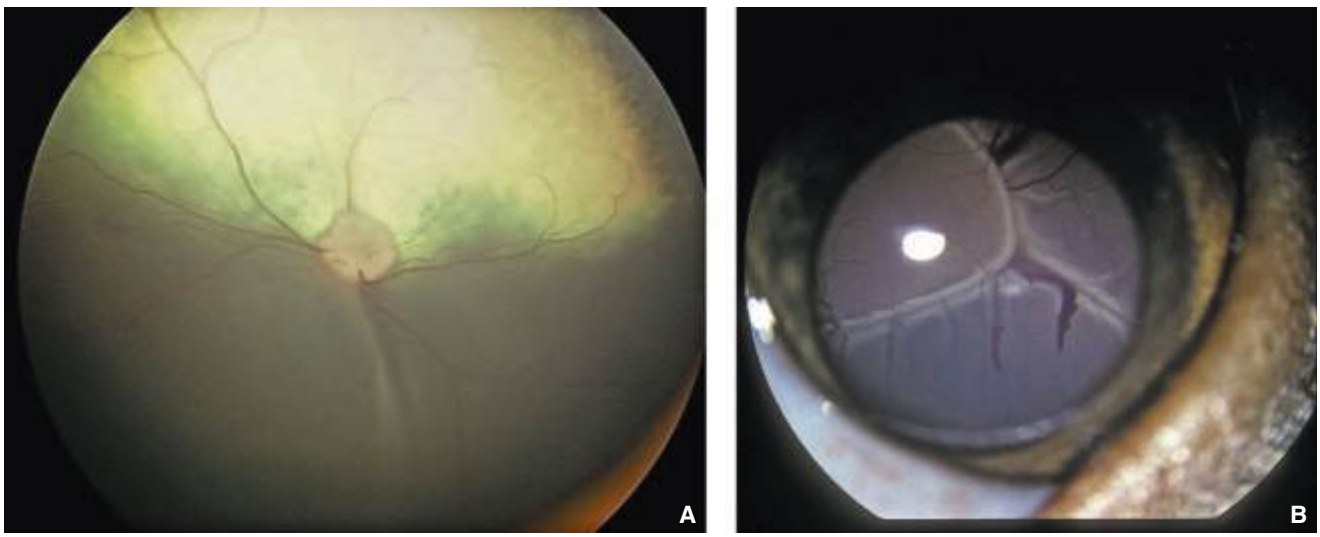


Figure 25.67 Steroid-responsive retinal detachment. In both cases, the condition was bilateral and the dogs presented with a sudden-onset vision loss. Physical examination, blood work, and serology failed to find an underlying etiology. Both dogs were treated with systemic steroids and regained vision. **A**. On ophthalmoscopic examination, the retina can be seen ballooning forward in the vitreous as a semilucent gray membrane with superficial vessels. It remains attached at the optic nerve head and is thrown into a fold ventral to the optic nerve head. The tapetum is seen through the detached retina in the dorsal fundus. **B**. Complete bullous retinal detachment. The retina can be viewed directly through the pupil as a gray membrane with superficial vessels that is thrown into folds and is adjacent to the posterior surface of the lens. Preretinal hemorrhages are present. (Courtesy of Michigan State University Comparative Ophthalmology Service.)

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and colleagues recorded a series of 22 cases in which German Shepherd crosses (6/22), German Shepherds (3/22), and Labrador crosses (2/22) were overrepresented. Vitreal hemorrhage was shown to be associated with an increased time to reattachment; the mean time to reattachment was 18.2 days (range 4–51) for the eyes with no hemorrhage and 63.5 days (range 14–144) for eyes with vitreal hemorrhage (Andrew et al., 1997).

Treatment of the retinal detachments depends on the presence of a detectable underlying disease and both the cause and the extent of the detached area. Even extensive detachments may be reattached with return of vision provided that treatment is commenced early (Fig. 25.68). When a steroid-responsive exudative detachment is suspected, systemic steroids should be started as soon as possible, after ruling out potential infectious and systemic causes for which systemic corticosteroids might be contraindicated. Failure to reattach leads to retinal degeneration and loss of visual capacity in the affected area. Further treatment options are discussed in Chapter 26.

Peripheral Cystoid Retinal Degeneration

This is a common incidental finding in older dogs. The peripheral retina adjacent to the ora ciliaris retinae undergoes a cystic change, leading to the appearance of multiple cystic structures that protrude into the vitreous (Fig. 25.69) (Bellhorn & Haring, 1974). These protrusions can be quite large in some dogs. Their peripheral nature means that they are unlikely to have any effect on vision.

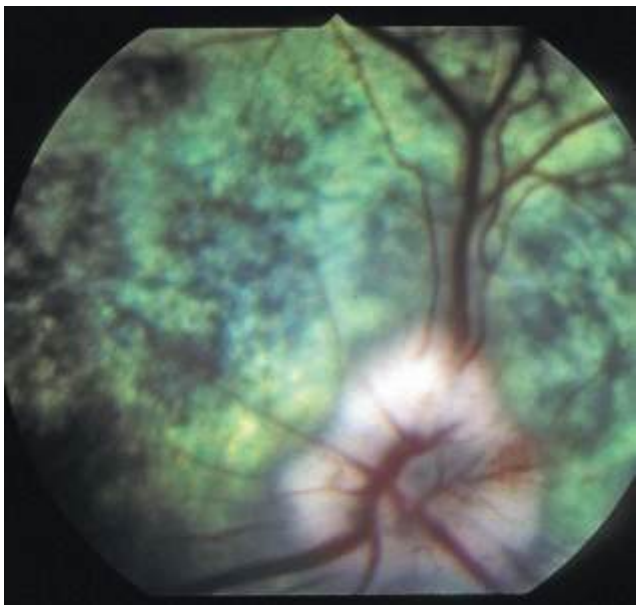


Figure 25.68 This eye had previously had a complete bullous retinal detachment. It had been steroid responsive and reattached. There are pigmentary changes that have resulted from the chorioretinitis that induced the detachment. There is a resolving hemorrhage on the optic nerve head.

Retinoschisis

Retinoschisis is a splitting of retinal layers that occurs in humans as either an X-linked hereditary disorder (Sieving et al., 1993) or an acquired condition. The splitting of retinal layers can progress to retinal detachment, and the inherited form can impair vision. A histological diagnosis of secondary retinoschisis was reported in an 8-month-old English Springer Spaniel with retinal detachment and glaucoma (Schuh, 1995).

Proliferative and Neoplastic Conditions

Granulomatous Meningoencephalitis (Reticulosis)

Granulomatous meningoencephalitis (GME) is a subform of meningitis of unknown etiology, and is an idiopathic, nonsuppurative, inflammatory disease of the CNS that can affect the eye. The disseminated form of GME has been previously described as inflammatory or granulomatous reticulosis, whereas the focal form was previously described as neoplastic reticulosis. GME is characterized by the proliferation of

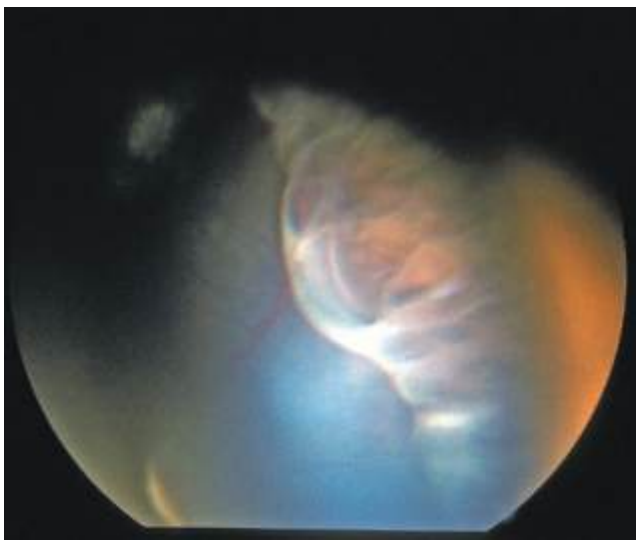


Figure 25.69 Peripheral cystoid retinal degeneration in a dog. The peripheral retina has a number of cystic protrusions into the vitreous running circumferentially at the peripheral edge of the neurosensory retina.

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reticuloendothelial elements and lymphoplastic infiltrates of the CNS vessels. The cellular reaction of the intracranial vasculature apparently may be shared by the blood vessels of the posterior segment of the eye and the anterior uvea. Sporadic cases of canine ocular involvement have been reported from different parts of the world (Fischer & Lice, 1971; Garmer et al., 1981; Rubin, 1974; Smith, 1995).

Perivascular infiltration of mainly histiocyte-like epithelioid cells and mononuclear cells (lymphocytes and plasma cells) has been described as a classic change (Kitagawa et al., 2009). The disease affects blood vessels in the CNS, posterior segments of the eyes, and uveal tract. Silver-stained sections have shown a whorled pattern of reticulin fibrils around the vessels (Garmer et al., 1981; Smith, 1995).

Ocular signs may develop before CNS abnormalities. The disease is usually bilateral, but the extent of involvement varies. Papillitis and peripapillary edema and inflammatory infiltrate have been reported to be associated with blindness, and cases can also have retinal hemorrhage or dilation of the retinal vasculature present. Various secondary ocular disease processes such as uveitis, retinal detachment, and secondary glaucoma may occur, depending on the localization of the inflammatory lesions. It is recommended to perform imaging of the brain and a cerebrospinal fluid tap on cases of papillitis to evaluate the extent of disease beyond the eyes.

Vision may be improved in dogs presenting with papillitis through treatment with immunosuppressive medications (Garmer et al., 1981; Smith, 1995). The prognosis for vision, however, and even for long-term survival, is considered to be poor.

Ocular Melanosis

Ocular melanosis in Cairn Terriers manifests as a proliferation of melanocytes predominantly involving the anterior uvea and sclera, which frequently leads to a secondary glaucoma. However, the characteristic plump, pigment-laden cells are commonly present histologically within the retina and choroid of dogs with advanced disease. Close monitoring of affected dogs reveals that there is a slowly progressive posterior segment pigmentation that leads to a reduction in tapetal area due to the pigmented cells encroaching over the tapetal area (Fig. 25.70) (Petersen-Jones et al., 2007).

Primary Tumors

Primary tumors of the retina, choroid, and optic disc are very rare in the dog.

Astrocytoma

Tumors of astrocytic origin are rarely reported in the dog (Caswell et al., 1999; Dubielzig, 1993; Meyerholz & Haynes, 2004; Naranjo et al., 2008). Immunohistochemistry aids in the possible identification of astrocytomas because of their positive staining for glial fibrillary acid protein.

Neurectodermal Tumors

Primary intraocular neuroepithelial tumors are divided into two groups: neoplasms derived from mature neuroepithelium; and neoplasms derived from primitive neuroectoderm.

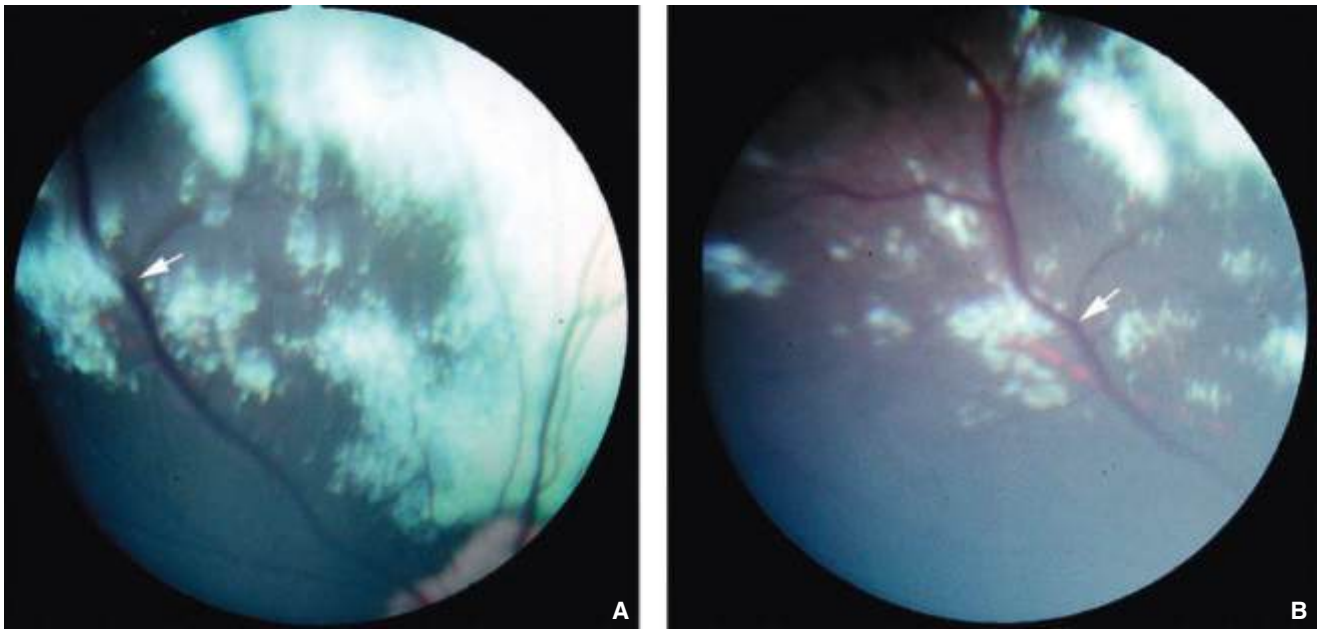


Figure 25.70 Cairn Terrier with ocular melanosis. Fundus photographs taken 19 months apart show progression of pigmentation that is obscuring or replacing the tapetum (A was taken first; B was taken 19 months later). The white arrows indicates the same position on the photographs and are to help orientation. (Reproduced with permission from Petersen-Jones, S.M., Forcier, J.Q., & Mentzer, A.E. (2007) Ocular melanosis in the Cairn Terrier: Clinical description and investigation of mode of inheritance. *Veterinary Ophthalmology*, **10**(Suppl. 1), 63–69.)

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Neoplasms from mature neuroepithelium include adenomas and adenocarcinomas, which develop from the ciliary epithelium. Tumors derived from primitive neuroectoderm are thought to originate from germinal neuroepithelium of the neural tube and can form in the retina or ciliary body. Examples of neuroectodermal tumors are medulloepitheliomas and retinoblastomas (Langloss et al., 1976).

Medulloepitheliomas occur in the ciliary body or retina of dogs (Dubielzig, 1993); the age range has been described as between 5.5 months and 11 years (Langloss et al., 1976; Regan et al., 2013). Clinical signs include corneal vascularization and opacity, a discrete mass filling the anterior chamber, hyphema, and secondary glaucoma. Bilateral tumors have not been described. Medulloepitheliomas are considered to be benign tumors, but local tissue destruction can be seen (Dubielzig, 1993). Langloss and colleagues reported that all affected eyes were enucleated and that there was no evidence of recurrence (Langloss et al., 1976).

Histopathologically, medulloepitheliomas are neoplasms of poorly differentiated neuroectodermal tissue arranged in clusters and columns (pseudorosettes). The cells are large and pleomorphic, and the mitotic rate is high. Medulloepitheliomas contain sheets and tubular structures formed by neuroblastic cells resembling primitive retina, with a basement membrane (i.e., internal limiting membrane) along one surface and a series of terminal bars (i.e., external limiting membrane) on the opposite surface. Structures not normally derived from medullary epithelium, such as neuronal cells, hyaline cartilage, and skeletal muscle fibers, can be scattered throughout the tumor, in the teratoid form of the tumor. A mixed tumor containing mature ganglion cells and glial cells in a 5.5-month-old mixed-breed dog was initially classified as a ganglioglioma (Saunders et al., 1969). Later, however, the specimen was reclassified as a medulloepithelioma (Langloss et al., 1976).

Retinoblastoma has been described to occur in eyes of young dogs. One study, describing retinoblastoma in four canine eyes, had an age range of 10 months to 2 years, significantly younger than medulloepithelioma cases (Regan et al., 2013). Retinoblastoma is characterized by the presence of true rosettes in three forms: cuboidal cells with a basally located nucleus surrounding a clear central lumen (Flexner–Wintersteiner rosette); spindloid cells surrounding an indistinct lumen containing eosinophilic fibrilar material (Homer–Wright rosette); and rosettes with a poorly defined lumen (fleurette). Histopathologic descriptions of canine retinoblastoma have demonstrated the presence of Flexner–Wintersteiner rosettes (Regan et al., 2013; Syed et al., 1997) and both Homer–Wright rosettes and fleurettes (Regan et al., 2013). A single case of a retinal tumor that had characteristics of both medulloepithelioma and retinoblastoma has been described (Jensen et al., 2003).

Choroidal Melanomas

In the dog, intraocular primary melanomas typically arise in the anterior uvea, and the choroid is usually involved through extension from the anterior uvea. Melanomas with their origin in the choroid are less frequently detected (Aguirre et al., 1984; Collinson & Peiffer, 1993; Dubielzig et al., 1985; Morgan & Patton, 1993; Ryan & Diters, 1984; Schoster et al., 1993; Steinmetz et al., 2012; Weisse et al., 1985). Choroidal melanomas occur as darkly pigmented masses arising from the choroid underlying the tapetum lucidum, most typically adjacent to or near the optic disc (Fig. 25.71 and Fig. 25.72). The tapetal cells may be absent or obscured in the area of tumor development. To date, most reported primary melanomas of the choroid have tended to be clearly demarcated, raised, subretinal masses, with some showing similarities to a uveal nevus in humans.

Histopathologically, large, round, plump cells predominate. Plump or thin spindle cells may also be found, as well as small epithelioid-type cells. The tumors are generally considered to be benign because of the lack of mitotic figures, vascular invasion, and nuclear anaplasia. Extension of the tumor into the optic nerve and retrobulbar tissue, however, has been reported (Collinson & Peiffer, 1993; Schoster et al., 1993; Steinmetz et al., 2012).

Obvious clinical signs are reported to be rare, but infiltration beneath the retina can lead to retinal detachment and hemorrhage. Secondary glaucoma may result from obstruction or closure of the iridocorneal angle by preiridal fibrovascular membranes.



Figure 25.71 A pigmented choroidal neoplasm in an 8-year-old Golden Retreiver.

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Secondary Tumors

Tumors may involve the posterior segment by extension from a primary focus in the anterior segment, optic nerve, or extraocular tissues, or by metastasis from a remote site. Clinical signs usually develop late in the disease. Signs may include intraocular hemorrhage, uveitis, glaucoma, and blindness. With metastatic tumors, systemic signs may be present and the ocular findings incidental.

Tumors located outside the eye may cause signs suggestive of posterior segment disease, such as retinal detachment and blindness. Cases have been reported in which tumors affected the optic nerve, optic tract, or visual cortex, thereby causing visual impairment, or in which serum hyperviscosity secondary to plasma cell myelomas, is followed by retinal detachment (Davidson et al., 1991; Hare, 1993; Sansom & Dunn, 1993).

Metastatic Tumors

Metastatic neoplasms in the choroid and retina are often incidental findings, and their ophthalmoscopic appearance and clinical course vary. Several tumors and sites of origin have been reported, including mammary gland adenocarcinomas, thyroid adenocarcinoma, renal adenocarcinoma, malignant melanoma, hemangiosarcoma, rhabdomyosarcoma, neurogenic sarcoma, and pheochromocytomas (Barron et al., 1963; Bellhorn, 1972; Cello & Hutcherson, 1962; Crow et al., 1995; Fidler & Brodey, 1967; Krohne et al., 1994; Ladds et al., 1970; Nyska et al., 1992; Szymanski, 1972). Tumors that metastasize to the anterior uvea may also extend to involve the retina and choroid.

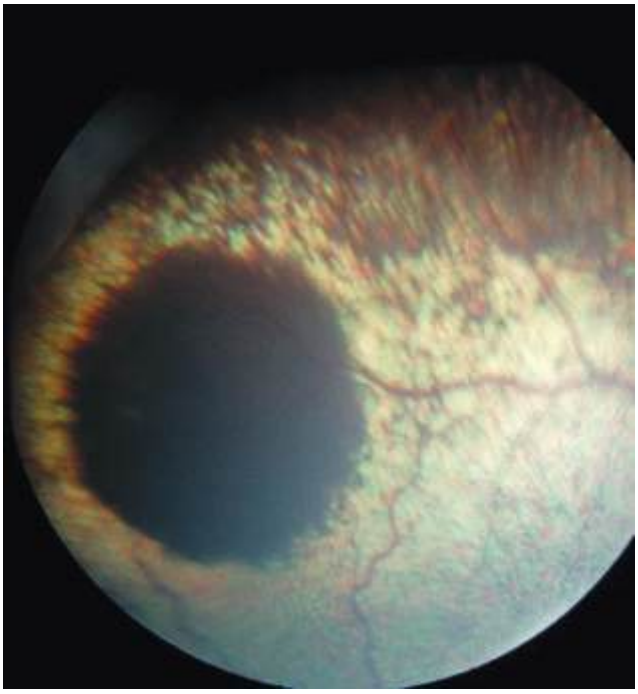


Figure 25.72 Pigmented raised choroidal lesion in the peripheral tapetal fundus of an elderly Shetland Sheepdog. This was a very slow-growing lesion and most likely represents a choroidal melanoma.

Lymphomas

Malignant lymphoma, usually affecting both eyes, seems to be the most common secondary intraocular tumor. Ocular involvement has been reported to be the second most consistent presenting sign (after lymphadenopathy) in dogs affected with multicentric lymphoma (Krohne et al., 1994). Involvement of the choroid and the retina is noticed infrequently, but signs from the posterior segment may sometimes be masked by the more frequently observed changes in the anterior segment (Cello & Hutcherson, 1962; Peiffer et al., 1976; Saunders & Barron, 1964; Whitford, 1965).

Ophthalmic signs depend on whether the anterior or posterior segment (or both) is involved. Krohne and colleagues (Krohne et al., 1994) detected posterior uveitis in 3% of dogs with multicentric lymphomas, panuveitis in 5%, and retinal hemorrhages in 9% (Fig. 25.73). Flame-shaped retinal hemorrhages are considered to be the earliest ophthalmoscopic sign. In more advanced stages, alterations in tapetal color occur, and papilledema may be present. Generally, systemic involvement precedes or accompanies intraocular disease, although dogs with intravascular lymphoma may present initially with only ocular changes (Cullen et al., 2000; Kilrain et al., 1994).

Microscopic changes vary with the tissue affected. Tumor cells in the choroid, especially in the tapetal fundus, contribute to the color changes. There can be extensive invasion of tumor cells in the retina and the optic disc as well.

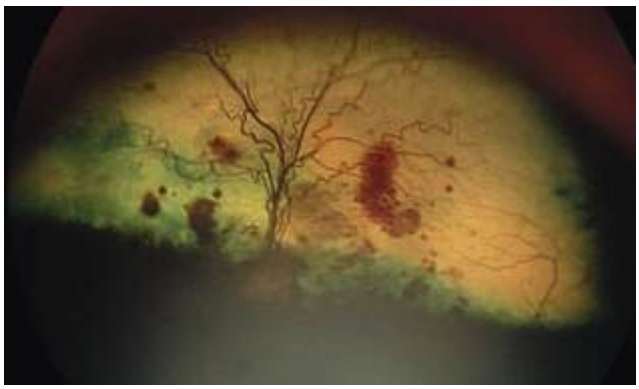


Figure 25.73 Multiple retinal hemorrhages in a 10-year-old dog under treatment for a B-cell lymphoma. (Courtesy of Michigan State University Comparative Ophthalmology Service.)

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Malignant angioendotheliomatosis (i.e., malignant intravascular lymphoma) is a proliferation of neoplastic lymphocytes from the vascular bed. Dogs with this condition may present with only ocular changes, and the systemic nature of the condition may only become apparent later. Affected dogs may present with ocular changes including bilateral subretinal hemorrhages and retinal detachments (Cullen et al., 2000; Saunders & Barron, 1964) and only show systemic signs later in the disease. Histopathologic examination reveals multifocal, intravascular proliferation of large, pleomorphic mononuclear cells within the lumen of blood vessels of affected organs.

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Surgery of the Canine Posterior Segment

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Since the last edition of this text, there have been no radical changes in the way in which vitreoretinal surgeons perform the repair of retinal detachment (RD) in the canine species. However, there has been steady improvement in technique, instrumentation, and numbers of surgeons performing this surgery. This updated chapter will summarize what is happening in canine vitreoretinal surgery, both for the adept and for those wishing to pursue this discipline.

For the most part, 20-gauge surgery has gone out of favor with veterinary vitreoretinal surgeons and has been supplanted by 23-gauge sutureless pars plana vitrectomy. Although two authors (JCW, ARH) experimented with 25-gauge surgery many years ago, the expense and delicacy of the instrumentation ensured the prominence of 23-gauge surgery in our field. Numerous innovations in the vitrectomy machines now employed by veterinarians have led to substantial refinements in our techniques, with a resultant increase in success rates. The interest in our discipline by industry is increasing and will hopefully lead to further investment in the unique equipment that is sometimes required for this type of surgery in the canine patient.

We have left some of the older techniques from past chapters in this current edition, as it is important to remember where we came from. However, many techniques such as scleral buckles, pneumatic retinopexy, cryoretinopexy, and transscleral laser retinopexy are no longer part of our lexicon. Anyone interested in reviewing these procedures should refer to the previous editions of this textbook. This chapter will focus instead on 23-gauge surgery and its refinement in veterinary medicine over the past few years.

We have also updated the sections on retinal implants for humans with retinal degeneration and will review the latest work in gene therapy. New additions include a section on potential new vitreous substitutes that are being developed for use in humans and may one day be used in canines, and a section on subretinal injection.

Anatomic Considerations

Knowledge of the anatomy of the posterior segment is crucial to understanding proper surgical technique. Thus, the specific segments involved with vitreoretinal surgery are briefly discussed here.

Vitreous

The vitreous body is the most important intraocular tissue in the pathogenesis of RD. It is the gel that fills the vitreous cavity and is in contact with the retina, ciliary body, lens zonules, and posterior surface of the lens. Physically, it is composed of salts, proteins, and hyaluronic acid contained in a network of insoluble protein fibrils (Balaza, 1994; Eisner, 1995). These collagen fibrils are arranged randomly within the gel. They are most dense along the posterior lens capsule (hyaloideocapsular ligament), a circumferential area attached to the pars plana and peripheral retina (vitreous base), and along the vitreoretinal interface, especially around the margins of the optic nerve. The vitreous is attached to the retina via collagen fibrillar insertions into the internal limiting membrane, which is formed by the fused terminations of Müller cells (Balaza, 1994; Eisner, 1995). The fibrillar network of the vitreous is attached or anchored in a basal lamina (basement membrane), which is tightly attached to the cell membrane of Müller fibers (Balaza, 1973). In the canine, the vitreous has been described as being of the "nuclear type," in which the central vitreous is dense and the peripheral cortex is semifluid (Eisner & Bachmann, 1974; Tolentino

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et al., 1965). This is the opposite of that in humans, in which the center is more fluid and the cortex is denser.

The vitreoretinal interface formed by the outer surface of the vitreous cortex and the internal limiting membrane of the retina contribute to the pathogeneses of rhegmatogenous retinal detachment (RRD). Normal vitreous exerts traction where it adheres to the retina; whenever the eye moves, the vitreous follows this movement, with a delay resulting from inertia. The result is sudden traction wherever the vitreous adheres to the retina (Machemer, 1984). In normal eyes this is not usually a problem, as the vitreous has both liquid and gel components. The liquid vitreous, which generally represents a small amount of the total vitreous in the dog, can create intraocular turbulence during both ocular and head movements. With rotational movements of the eye, liquid vitreous flows more easily and rapidly than normal vitreous. This liquid vitreous moves over the surface of the retina counter to the direction of the eye movements (Fig. 26.1; Machemer, 1984). If a retinal tear, preexisting hole, or atrophic area in the retina is present, this liquid vitreous may cause enough turbulence to increase the tear or induce a tear in the area of retinal atrophy (Machemer, 1984).

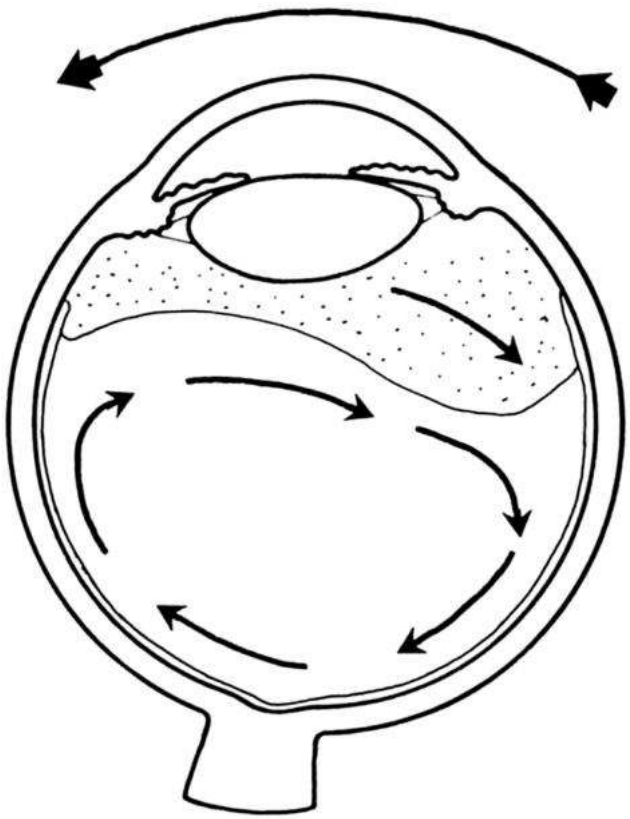


Figure 26.1 Eye movements result in countercurrents of the vitreous and intraocular fluids, especially when the vitreous is liquefied. (Reproduced with permission from Machemer, R. (1984) The importance of fluid absorption, traction, intraocular currents, and chorioretinal scars in the therapy of rhegmatogenous retinal detachments. *American Journal of Ophthalmology*, **98**, 681–693.)

Abnormal vitreous is necessary to the pathogenesis of spontaneous RRD in humans and is also responsible for RRD in several breeds of dogs. Liquid vitreous, fibrillary changes, RD, and vitreoretinal traction have been described in the Labrador Retriever with oculoskeletal abnormalities (Blair et al., 1985a). We have seen several breeds with abnormal liquid vitreous, notably the Shih Tzu, Boston Terrier, Poodle, Jack Russell Terrier, Italian Greyhound, and Yorkshire Terrier. If this clinical abnormality is present in a dog that violently shakes its head while playing with toys, the vitreous will likely tear the retina where it is most adherent to the retina or the vitreous base. The highest incidence of clinical spontaneous giant retinal tears is in dogs that demonstrate aggressive head shaking (Fig. 26.2; Vainisi & Wolfer, 2004).

Vitreous degeneration is also common in eyes with hypermature cataracts (Dietrich, 1996; van der Woerdt et al., 1993). It appears to be associated with the lens-induced uveitis (LIU) that accompanies the hypermature cataract. This type of uveitis can result in vitreous traction. These vitreous changes along with the inflammatory changes in the retina, such as obliteration of peripheral retinal vessels, thinning of the retina, formation of retinal cysts, pigment proliferation in the choroid, and retinal and choroidal atrophy, create circumstances that predispose to RRD (Banker & Freeman, 2001).

Proliferative vitreoretinopathy (PVR) is an important pathologic change seen with RRD and is probably the largest single factor resulting in the failure of human retinal reattachment surgery (Lewis & Aaberg, 1991). The basic pathologic process in eyes with PVR is the growth and contraction of cellular membranes on the posterior vitreous surface and within the vitreous base, both in contact with the retinal surface (Lagua & Machemer, 1975; Machemer & Lagua, 1975; Rice & Wilkinson, 1997). A full-thickness retinal break and release of retinal pigment cells

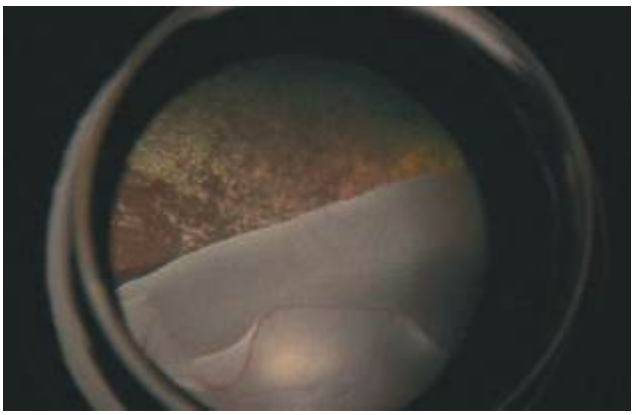


Figure 26.2 Giant retinal tear in a dog intraoperatively.

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into the vitreous base are probably necessary for the development of clinically significant PVR. Laboratory animal experiments and clinicopathologic correlations have shown pigment epithelial cells, glial cells, macrophages, and fibroblasts in these epiretinal and subretinal membranes (Lagua & Machemer, 1975; Machemer & Lagua, 1975; Vidaurri-Leal & Glaser, 1984). The basic process is one of rapid cellular migration and proliferation that forms cellular membranes. These membranes then contract, causing traction on adjacent collagen fibrils of the vitreous and on the retina itself that distorts the underlying and adjacent tissues (Glaser et al., 1987). The cellular proliferation and contraction account in part for the clinical picture and include distortion, detachment, marked folding, and immobilization of the entire retina (Fig. 26.3; Rice & Wilkinson, 1997).

PVR occasionally occurs in the dog. It is rarely seen with spontaneous RRD. It has been reported in the Labrador Retriever with RRD associated with oculoskeletal dysplasia (Blair et al., 1985a). Surgical repair in these patients requires a relaxing anterior retinectomy. We have also seen canine PVR associated with lens surgery and, most notably, trauma (Fig. 26.4). PVR can be seen in dogs with RD secondary to full-thickness retinal holes after transscleral laser retinopexy (Fig. 26.5).

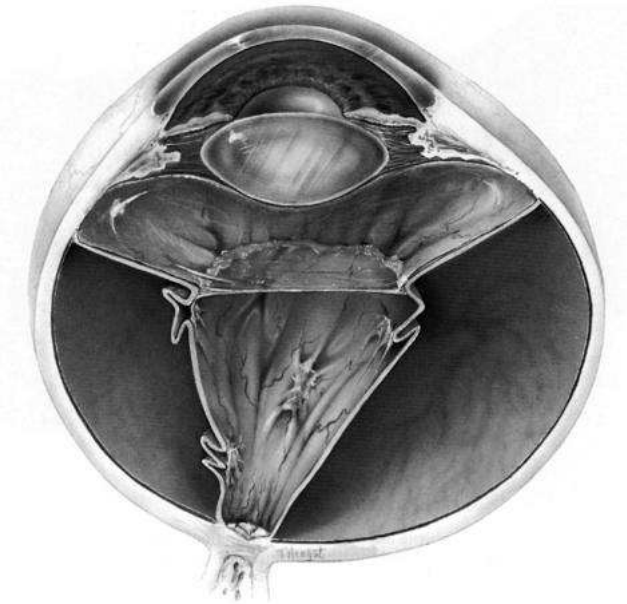


Figure 26.3 Proliferative vitreoretinopathy causing total fixed retinal detachment. Cellular proliferation and contracture on the posterior vitreous surface and inner retina result in marked transvitreal traction, high elevation of the retina, and fixed folds of retinal tissue. (Reproduced with permission from Rice, T.A. & Wilkinson, C.P. (eds.) (1997). *Michels Retinal Detachment*, 2nd ed. St. Louis, MO: Mosby.)

Pars Plana

To prevent damage to the lens and retina during vitreocentesis or vitreoretinal surgery, the surgeon must have knowledge of the pars plana. Studies on canine cadaver eyes have identified proper penetration sites for the four quadrants of the eye (P.S. Smith et al., 1997). Ideally, the surgeon wants to penetrate the center of the pars plana. In globes measuring approximately 22.2 ± 1 mm, the recommendation is a distance of 6–7 mm from the limbus in the superotemporal and

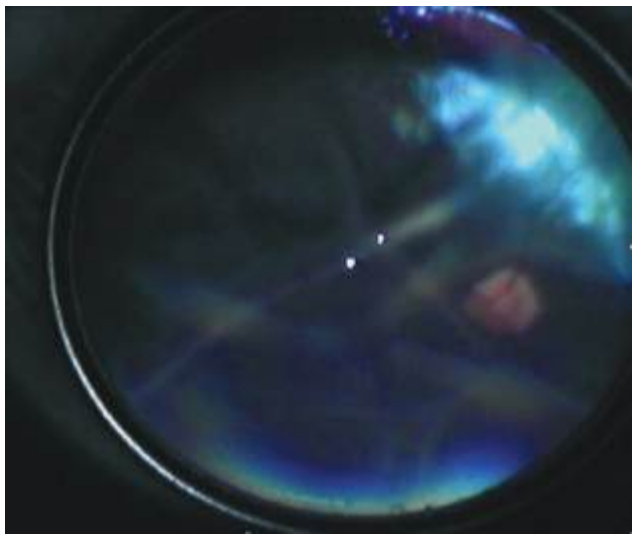


Figure 26.4 Tractional retinal detachment in a dog after ocular trauma.

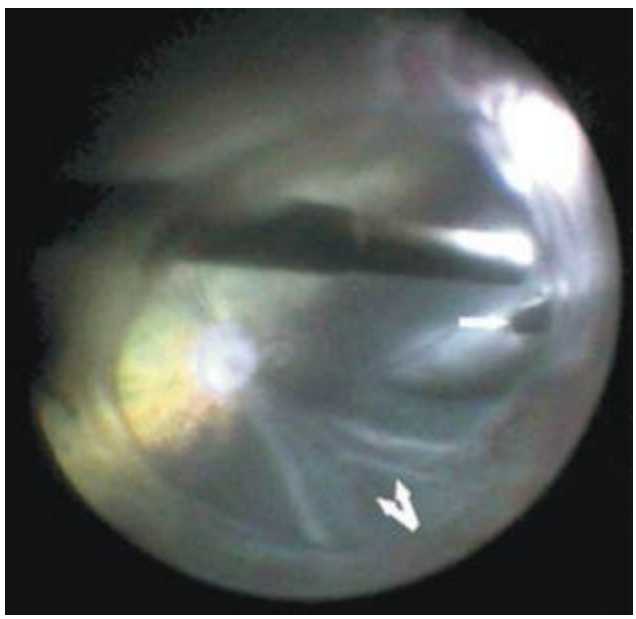


Figure 26.5 Proliferative vitreoretinopathy (double arrow) resulting in retinal detachment in the dog secondary to a full-thickness retinal hole (arrow) caused by transscleral laser retinopexy.

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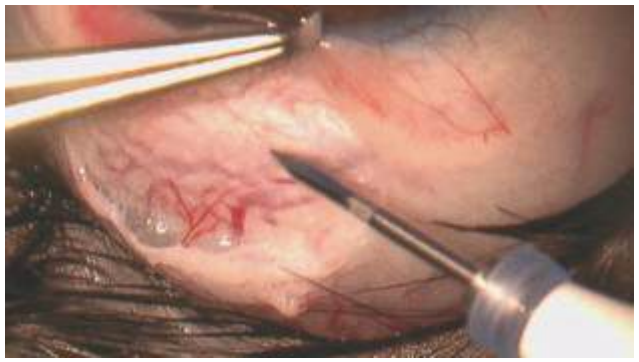


Figure 26.6 Intraoperative photograph of wide intrascleral venous plexus in the dog. The trocar points to the anterior margin of the venous plexus (circle of Hovius).

inferotemporal quadrants, 5 mm for the superonasal quadrant, and 4 mm for the inferonasal quadrant (P.J. Smith et al., 1997).

We have found that, working superiorly, 5–6 mm from the limbus is adequate in most breeds of dogs. The insertion of the extraocular muscles may be used as an anatomic landmark to guide sclerotomy placement. Penetration at 7 mm has resulted in subretinal placement of ports in a few cases. In certain breeds, such as the Siberian Husky, the pars plana tends to be extremely narrow nasally; thus, placement of ports at even 5 mm may end up damaging the retina. In performing postmortem examinations on Siberian Husky eyes, one of the authors (SJV) has found that some dogs had almost no apparent pars plana nasally. Because of the type of inherited cataract seen in this breed of dog and the frequent secondary LIU, it has not been unusual to see RRD following cataract surgery. Surgical ports in the Siberian Husky occasionally need to be placed superiorly and temporally.

Intrascleral Plexus

The vascular intrascleral plexus (circle of Hovius) is a network of veins that receives aqueous drainage (Fig. 26.6). This venous network, which is 4–5 mm wide, is situated 3–4 mm from the limbus, precisely in the area where surgical sclerotomies are placed. Judicious cautery is needed to avoid serious bleeding before penetrating the eye. It is not uncommon to induce additional bleeding during insertion of instruments through sclerotomies or during closure, necessitating additional cautery. In addition, the patient's blood pressure may influence the bleeding tendencies; therefore, close monitoring may be needed.

Types of Retinal Detachment

RD is the separation of the neurosensory retina from the underlying retinal pigment epithelium (RPE). RD can be either rhegmatogenous or nonrhegmatogenous (non-RRD). In RRD, fluid from the vitreous cavity enters the subretinal space through a break in the retina. RRD can be either primary or secondary. Primary RRDs are spontaneous and are not the result of trauma, inflammation, surgery, or other specific ocular disorder. Primary RRDs are preceded by alteration or degeneration of the vitreous, which predisposes the retina to detachment. The most common type of primary RRD is retinal dialysis or giant retinal tear, seen frequently in the Shih Tzu. In this breed, the retinal dialysis or giant retinal tear is thought to occur after vigorous head shaking and is predisposed to by vitreal syneresis or liquefaction. A retinal dialysis is distinguished from a giant retinal tear. When a retinal dialysis occurs, the neurosensory retina tears away from the pigmented ciliary epithelium at the ora ciliaris retinae. A giant retinal tear involves 90 degrees or more of the retinal circumference, with attached vitreous gel to an anterior flap of retina. These tears usually progress from a dorsal RD to a complete RD, resulting in a retina that hangs over the optic nerve (see Fig. 26.2). Another form of primary RRD occurs in instances of optic nerve coloboma where there is a separation of the retinal layers at the junction of coloboma and normal retina, which allows fluid from the vitreous space to enter the subretinal space. This phenomenon has been documented in the Collie eye anomaly (CEA; Vainisi et al., 1989). Other types of primary RRDs include atrophic retinal holes or tears. Secondary RRDs are the result of trauma, glaucoma, lens surgery, aggressive laser retinopexy, or surgery involving the ciliary body or ora ciliaris retinae, the most prominent of these being cataract surgery (Hendrix et al., 1993). Additionally, one of the authors (ARH) has noted an increased incidence of RD following cryoprobe-assisted lensectomy when intact zonules are present. This can lead to choroidal and RDs from ciliary body disruption or avulsion.

Non-RRDs are classified as serous or tractional. A serous non-RRD occurs without a break in the retinal tissue and results from fluid accumulation in the subretinal space between the photoreceptors and the RPE. Serous non-RRDs are further specified as either inflammatory or exudative, although this distinction is clouded by the fact that permeability factors that lead to exudation below the retina may possess proinflammatory influences (Adamis & Shima, 2005). Tractional non-RRD occurs when there is a pulling force (band or membrane) in the vitreous that forces the retina to separate from the RPE.

Factors Responsible for Retinal Detachment

Although the exact mechanism of RD in the dog is unknown, it is assumed that, as in humans, canine RD can be ulti-

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mately attributed to retinal tear formation, exudation, or traction (Green, 1985; Kanski & Gregor, 1994).

Postoperative Phacoemulsification

Cataract surgery is one of the most common causes of RD in the dog (Gelatt et al., 2003; Hendrix et al., 1993; Schmidt & Vainisi, 2004; Vainisi & Wolfer, 2004). The exact incidence of RD after cataract surgery is unknown. However, in one study, the second most common histopathologic finding in eyes enucleated or eviscerated because of complications following cataract surgery was RD, present in 64% of the eyes studied (D.L. Moore et al., 2003). In this study, 24% of all eyes had a retinal tear. The underlying cause of the RD was generally not histopathologically evident in most cases (D.L. Moore et al., 2003). Interestingly, the incidence of the RD being noted on the clinical examination before enucleation was very low compared with the incidence of RD in these eyes in general, suggesting that RD after cataract surgery may be higher than is generally thought. Another retrospective clinical study found an incidence of RD after phacoemulsification of 1–2% for all time periods (Sigle & Nasisse, 2006). Another recent study demonstrated the incidence of RD following cataract surgery as 7.7% and 8.9% for the Boston Terrier and Shih Tzu, respectively (Foote et al., 2017).

Patients that experience an alteration of the vitreous during cataract surgery (e.g., posterior capsular tear or vitreal hemorrhage) are at even greater risk of RD. Eyes that have previously had LIU are at greater risk of postoperative RD than eyes that have not. This finding is likely related to liquefaction or alteration of the vitreous base and/or cystoid change in the peripheral retina resulting from the iridocyclitis. Microcystoid or cystoid peripheral retinal degeneration may cause weakening of the attachment of the retina at the ora ciliaris retinae. This weakened attachment, combined with dynamic contraction of the vitreous base, could predispose to a retinal tear with potential for complete detachment. This phenomenon most often results in a dorsotemporal giant retinal tear or dialysis (Fig. 26.7). In humans with retinal tears related to posterior vitreous detachment, the break is most often superior (Peyman & Schulman, 1994a). Breeds with rapidly progressive cataract formation, such as the Bichon Frise, Maltese, Siberian Husky, and American Cocker Spaniel, are more prone to LIU as immune tolerance to lens proteins is overcome. These breeds may be the most susceptible to RD due to LIU. Lens surgery in humans is generally recognized as increasing the risk of RD. Thus, in dogs that undergo any form of lens surgery, be it phacoemulsification or intracapsular lensectomy for lens luxation, there is a potential for vitreoretinal disease. Risk factors for pseudophakic RD in humans include age; presence of RD in the fellow, or contralateral, eye; increased axial length (myopia); lattice retinal degeneration; vitreous loss; and capsular integrity (Grand, 2003; Lois & Wong, 2003; Ramos et al., 2002;

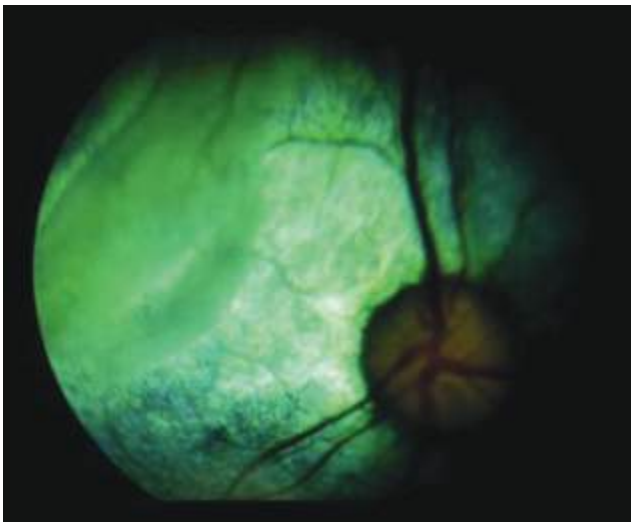


Figure 26.7 Early peripheral retinal tear in a dog.

Ripandelli et al., 2003). Although it is readily accepted that cataract surgery and LIU contribute to the incidence of RD in dogs, no definitive study has been performed to elucidate the exact cause of the retinal tears in these cases. Patients should be discouraged from violent head shaking with toys in the postoperative period, especially in those predisposed breeds or dogs with vitreous consolidation.

Cataracts and Lens-Induced Uveitis

The exact mechanism by which LIU predisposes the canine eye to RD is unknown. In two studies looking at complications of cataract surgery, LIU was responsible for a lower success rate, with RD being one of the reasons for failure (Davidson et al., 1991; Klein et al., 2011; van der Woerdt et al., 1992). Possible sequelae of LIU that could predispose to RD include vitreous degeneration, obliteration of retinal vessels with associated retinal thinning, retinal cyst formation, or globe enlargement due to transient bouts of glaucoma (Banker & Freeman, 2001). Preliminary evaluation of eyes with LIU using ultrasound biomicroscopy shows cystic degeneration in the peripheral retina near the ora ciliaris retinae (JCW, unpublished results). Canine vitreoretinal surgeons very commonly perform simultaneous cataract surgery, intraocular lens (IOL) placement, and retinal reattachment surgery with a high success rate. The authors believe this surgery is best performed in one anesthetic episode, instead of a staged approach. There are several advantages of a combined surgery beyond one anesthetic episode for the patient. The retina is attached sooner, improving the prognosis; capsular scarring is not present; and there is less inflammation and bleeding during a primary surgical procedure versus a secondary surgery when the blood–ocular barrier is compromised.

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Retinal Abnormalities

Retinal factors that predispose to detachment include genetic vitreoretinal dysplasias (Labrador Retriever and English Springer Spaniel), peripheral retinal thinning and microcystoid degeneration, atrophic retinal holes, and PVR. Vitreoretinal dysplasia results in areas of abnormally thin retina and holes, which, combined with liquefaction of the vitreous, can lead to RD (Blair et al., 1985a, 1985b). Also, many dogs will concomitantly have abnormally developed vitreous with firmer retinal attachments.

Peripheral retinal thinning with microcystoid degeneration or retinoschisis, or both, allows for a potential weakening of the retina and/or the ora ciliaris, potentially resulting in a retinal tear and subsequent detachment. Retinoschisis (Fig. 26.8) characterized by microcavitations of the retina has been observed by one of the authors (ARH) in geriatric Italian Greyhounds and Poodles. Significant retinal vascular tortuosity and increased vessel caliber are seen in dogs with oculoskeletal dysplasia. Atrophic retinal holes can occur spontaneously or because of trauma or other inflammation. Liquefaction of vitreous or vitreal traction on the edge of the hole can elevate the retina from the RPE and lead to detachment. PVR results when a full-thickness hole in the retina allows RPE cells to migrate into the vitreous space and form sheets or bands on the surface of the inner limiting membrane of the retina (see Fig. 26.5). Metaplasia of the RPE cells allows fibrous contraction to occur, lifting the retina into a detached state, and is characterized by retinal folding and rigidity (Kanski & Gregor, 1994, pp. 49–64). Treatment of RD with PVR has a lower success rate because of reformation of PVR bands. The authors of the chapter have used intravitreal vascular endothelial growth factor (VEGF) inhibitors preoperatively to address contractile membranes and to improve surgical outcome, as found by Chen and Park (2006).

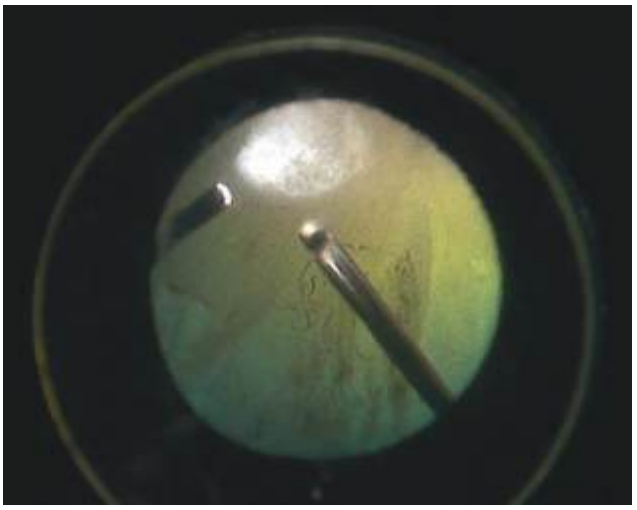


Figure 26.8 Intraoperative view of retinoschisis in a dog.

Vitreous

As previously mentioned, the vitreous plays a major role in retinal attachment, and thus any changes in the status of the vitreous can lead to RD. Posterior vitreous detachment is a well-recognized predisposing factor for RD in humans (Sebag, 1989). Vitreal diseases are poorly understood in the dog; however, it is well recognized that vitreous liquefaction predisposes to RD, especially in certain breeds, such as the Shih Tzu. Vitreous degeneration is reported in nearly 130 breeds by the Orthopedic Foundation for Animals (2017).

Trauma

Trauma is a common cause of RD in the dog. Penetrating trauma, including bite wounds, can result in infection, phacoclastic uveitis, or cyclodialysis, all of which can easily result in RD. Blunt trauma can result in a retinal tear, retinal dialysis, or both, with subsequent RD (Peyman & Schulman, 1994b). In cases of trauma with vitreal hemorrhage, the hemorrhage may be removed, either by treatment with intravitreal tissue plasminogen activator (tPA) or by vitrectomy, to prevent tractional RD. Early surgical intervention is important in cases of trauma prior to the onset of endophthalmitis, scleral or retinal necrosis, globe atrophy, or PVR in dogs.

Iatrogenic Causes

Several forms of iatrogenic RD exist, usually related to either endoscopic laser or cryoablation of the ciliary body for the treatment of glaucoma. It is also possible, if the surgeon is too aggressive, to cause RD during prophylactic laser of the peripheral retina. These detachments can be effusive in nature or, in the worst instances, can be related to full-thickness retinal holes and PVR. Inaccurate placement of needles for intravitreal injections or during retrobulbar injections can result in RD as well. In these examples, the retina can be pierced or the drug may be injected subretinally. One of the authors (ARH) has also seen RDs secondary to third eyelid gland tacking procedures, with inadvertent piercing of the retina during globe anchoring.

Tractional Retinal Detachment

Tractional RDs occur most commonly after membrane formation subsequent to a bleed into the vitreous cavity, or after the development of PVR secondary to a full-thickness retinal hole. Tractional detachments occasionally are seen with anomalous development of retinal vasculature associated with persistent hyaloid remnants. In canine cataract surgery, collectively we have noted complications that led to RD in the dog. Most common are posterior lens capsular rents with vitreous presentation, residual lens fibers leading to cortical

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regrowth, dropped nuclear lens fragments, or displaced IOLs. For those cases with cortical regrowth and RD, the patient history is often consistent. Patients have an uneventful recovery from cataract surgery and then present with severe LIU obscuring binocular indirect ophthalmoscopy. Aggressive therapy with anti-inflammatory medications is initiated, and when the inflammation is finally controlled, the ophthalmologist then sees an RD. Because of this, it is recommended to perform ultrasonography in patients that have significant postoperative inflammation that hinders the view of the retina. The cortical regrowth in these cases leads to tractional membranes and RD. Thorough removal of traction bands and lens material at the time of vitrectomy prevents recurrence of the RD and will allow for visualization during vitrectomy. The authors have also encountered cases of RD following endoscopic cyclophotocoagulation. The cause is most likely related to traction from movement of the endoscope within the vitreous, bleeding, retinal holes, and postinflammatory changes near the ora ciliaris retinae. The most common cause of tractional RDs in humans is diabetic retinopathy, and this type of RD is a result of preretinal fibrovascular proliferation (Regillo & Benson, 1999).

Effusion

Effusive RD occurs when fluid accumulates in the potential subretinal space, elevating the retina away from the RPE. Effusive RD can be caused by immune-mediated, neoplastic, or infectious disease. In all instances, the effusion results from a breakdown in the blood–ocular barrier, at the level of either the RPE or the retinal vasculature. Infectious causes include bacterial, fungal, viral, or rickettsial disease (Vainisi & Wolfer, 2004). Systemic hypertension in cats can also cause effusive RD because RPE necrosis occurs, breaking down the blood–ocular barrier. This breakdown leads to leakage of fluid, proteins, and fibrin from the choroid through the RPE and into the subretinal space (Crispin & Mould, 2001). One author (ARH) is studying the effects of panretinal photocoagulation to halt recurrence of immune-mediated retinal detachments (unpublished results).

Persistent Hyperplastic Primary Vitreous

Persistent hyperplastic primary vitreous (PHPV) has been reported sporadically in a variety of breeds of dogs and as an inherited condition in the Doberman Pinscher (Stades, 1983) and the Staffordshire Bull Terrier (Leon et al., 1986). It is a complicated disease of the lens-vitreous-hyaloid system that results in a wide spectrum of disease, which can include RD (Boevé & Stades, 1999). If severe, PHPV can result in RD or retinal nonattachment. Not uncommonly, PHPV is a cause of leukokoria, often with cataract development. Surgery to restore vision can result in hemorrhage from the patent hyaloid vasculature, which in time can result in vitreous traction and RD (Bayón et al., 2001; Gemensky-Metzler & Wilkie, 2004). In humans, PHPV is often associated with severe optic nerve and retinal malformations (Goldberg & Mafee, 1983). The diagnosis and treatment of PHPV are discussed in Chapter 24.

Endophthalmitis

Endophthalmitis is an inflammatory response to ocular infection: bacterial, viral, fungal, or parasitic. The most common cause of endophthalmitis in the veterinary population is cataract surgery. Bacterial and fungal contamination of the anterior chamber is common during cataract surgery (Ledbetter et al., 2004); nevertheless, endophthalmitis is rare. Any form of intraocular surgery, such as lens luxation surgery, glaucoma filtering procedures, intravitreal injection, or vitrectomy, can result in endophthalmitis. Trauma, especially cat scratch wounds or foreign body penetrations, can result in endophthalmitis. Endophthalmitis, if untreated, results in massive neutrophil migration and cellular proliferation with destruction of intraocular tissues. RD is a common complication of endophthalmitis. Treatment consists of appropriate topical, systemic, and intravitreal antibiotic and anti-inflammatory therapy. If the endophthalmitis is severe, complete vitrectomy may be a more appropriate therapy than antibiotics alone (Endophthalmitis Vitrectomy Study Group, 1995). One author (ARH) has used the 27-gauge diagnostic vitrectomy system (Dutch Ophthalmic USA, Exeter, NH, USA) for the treatment of endophthalmitis in dogs.

Collie Eye Anomaly

The CEA syndrome encompasses several manifestations, including chorioretinal hypoplasia, optic nerve colobomas, RD, intraocular hemorrhage, and scleral staphyloma (Barnett, 1979; Roberts et al., 1966). This ocular anomaly occurs in the Rough and Smooth Collie (Sargan, 2001), Shetland Sheepdog (Barnett & Stades, 1979), Australian Shepherd (Rubin et al., 1991), and Border Collie (Bedford, 1982). Choroidal hypoplasia, the primary CEA phenotype, is inherited as an autosomal recessive trait with almost 100% penetrance (Lowe et al., 2003). As it relates to RD, the phenotype of interest in dogs with CEA is optic nerve coloboma. A defect has been shown to exist in the optic nerve coloboma or pit that directly communicates with the subretinal space and can allow fluid from liquefied vitreous to create an RD (Brown et al., 1979). The first successful treatment of serous RD in Collies involved transscleral diathermy of the affected area. Subretinal fluid was drained via the first or second diathermy puncture (Rubin, 1974). Serous RD due to optic nerve coloboma in the CEA syndrome is presently successfully treated, if detected

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before total RD, with transpupillary laser retinopexy (Fig. 26.9; Vainisi et al., 1989). Xenon arc, argon, neodymium:yttrium-aluminum-garnet (Nd:YAG), or diode lasers may be used, although the diode laser will be less effective in poorly pigmented fundi. Intraocular hemorrhage seen with CEA usually is due to tearing of retinal vessels associated with RRD. The CEA may also cause RD due to vitreous hemorrhage from abnormal vessels in the coloboma or from PHPV (Tolentino et al., 1965). Unfortunately, Collies seen at very young ages that have complete RDs associated with colobomas or scleral ectasia have not been acceptable candidates for reattachment surgery.

Lens Luxation

Lens luxation predisposes the eye to RD. Lens instability causes a disruption in the anterior hyaloid face, causing disturbance of the vitreous and enabling the process of RD. Traction on the peripheral retina as the lens and vitreous move during luxation can cause tearing of weak areas of retina that can lead to detachment. The incidence of RD in humans ranges between 0.75% and 1.65% after phacoemulsification, 0.55%–1.65% after extracapsular cataract extraction, and 0.4%–3.6% after intracapsular cataract extraction (Ramos et al., 2002). This implies that removal of the entire lens with subsequent disruption of the anterior hyaloid face, as in the case of lens luxation, increases the risk of RD. In a study by Hendrix et al. (1993), 15% of 46 dogs studied with RD presented with lens luxation or had been treated surgically for anterior lens luxation. Nasisse and Davidson (1999) reported that RD occurred less frequently if lens removal was accomplished early in the course of the disease. Stuhr et al. (2009) reported a 5% incidence of retinal detachments following intracapsular lensectomy with sulcus IOL fixation. Adjunctive transpupillary retinopexy is believed to decrease the incidence of RD following lensectomy procedures. Endoscopic retinopexy could be used to try to prevent RD after lens luxation.

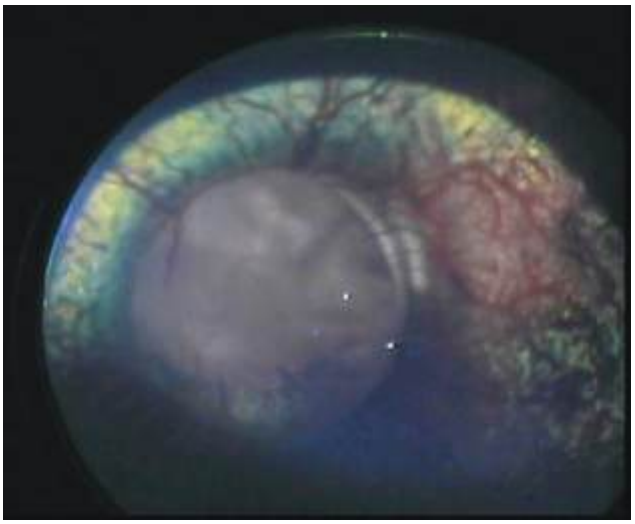


Figure 26.9 Collie eye anomaly with retinal detachment.

Dropped Nuclear Fragments

In humans, three-port pars plana vitrectomy (PPV) is indicated if large (> 25% of the nucleus) lens fragments are dropped through the posterior lens capsule during extracapsular cataract extractions; otherwise, serious sequelae, primarily intractable uveitis with retinal damage and/or RD, are likely to occur. Retained lens fragments after cataract surgery cause secondary complications directly related to the volume of the retained intraocular material and the degree of manipulation used in attempting to remove the fragments (Wood, 1994). Efforts to manually retrieve or to flush such fragments forward with fluid from anterior segment incisions likely will create inflammation that leads to vitreoretinal traction or tears, both of which can result in RRD.

If lens fragments fall posteriorly into the vitreous, the surgeon should remove any lens material that can be easily obtained from the anterior segment and perform an anterior vitrectomy. Manipulation of lens material in the vitreous should be avoided or minimized, because this will increase the inflammation and significantly increase the occurrence of RD (Wood, 1994). If the lens nucleus is rock hard (i.e., would not fragment with low power during PPV), retrieval can be performed using techniques to bring the lens forward, such as impaling with a needle or grasping with forceps, but again, these techniques carry a greater risk of creating retinal tears. A higher-concentration viscoelastic substance placed posteriorly may levitate a single lens fragment, but visibility can be challenging and may risk posterior segment trauma. Perfluorocarbon liquids (PFCLs) may facilitate the return of dropped lens fragments to the anterior chamber, but once injected, all fluorocarbon must be removed because of the potential retinotoxicity. Such removal is difficult to perform from the anterior segment.

A small fragment of lens material may be managed by close observation, with frequent topical and sub-Tenon's injections of steroids, cycloplegic agents, and systemic anti-inflammatory medications. If inflammation or intraocular pressure (IOP) is not easily controlled in such cases, vitrectomy is indicated. If dropped fragments are greater than 25% of the nucleus, it is best to perform posterior vitrectomy in the same operation, after closure of the anterior incisions. Surgery is performed via a three-port pars plana procedure, and the posterior vitrectomy is followed by phacofragmentation. During removal of lens fragments from the vitreous, it is best to remove as much vitreous as possible before attempting to draw up (aspirate), because inadvertent traction on the retina can result in RD (Eller & Berger, 2001). Low power (5%–10%) should be used to prevent the lens fragments from

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being blown onto the retina, and a second instrument can facilitate the direction of fragments to the phacofragmatome tip (Wood, 1994). Whether lens fragments are retrieved immediately after their posterior displacement or in a separate vitreoretinal procedure, scleral depression at the conclusion of the procedure should be performed while still in the operating room. Thus, if retinal tears are identified, immediate intervention (e.g., laser retinopexy) can be performed. If no tears are identified, close postoperative evaluation of the peripheral retina should always be part of any follow-up examination, again to detect retinal tears or RDs at an early stage.

In humans, RD is a common complication in eyes that require PPV for retained lens fragments (J.K. Moore et al., 2003), and visual acuity can also be affected by cystoid macular edema (Scott et al., 2003; Yang et al., 2002). Rapidity of intervention may enhance long-term results, indicating the need for immediate removal of the fragments or timely referral for PPV (Lai et al., 2004).

Posterior luxation of IOLs, either intraoperatively or as a postoperative complication, should be treated using PPV procedures. IOLs may be tolerated for long periods in the vitreous without removal, but if inflammation, vitreal hemorrhage, retinal edema, or RD develops, surgical intervention is indicated. During retrieval, perfluorocarbons may be used to float the IOL anteriorly for haptic fixation (Stuhr et al., 2009) or removal. Caution must be used, however, because all perfluorocarbon requires removal.

Prophylactic Retinopexy

Although there has been an increasing awareness that prophylactic treatment of normal fellow eyes in cases of spontaneous RD may be beneficial (Wolfensberger, 2000), it remains a controversial issue. In humans, the natural history of fellow eyes on nontraumatic giant retinal tears is characterized by a high combined incidence of retinal breaks and RDs in up to 60% of cases (Freeman, 2001). The results of a large human study on high-risk eyes have shown the benefit of prophylactic treatment. Retinal breaks developed in 27% of untreated eyes compared with 4% of treated fellow eyes (Freeman & Castillijos, 1981). In a study of 302 eyes with RRD, 205 fellow eyes were treated with argon laser (360 degrees, four radial rows) and followed up for 46 months. The incidence of bilateral RD was 2.4% in treated eyes compared with 11% in untreated eyes (Madelain & Turut, 1990).

In another study of 760 eyes with RRD, 350 fellow eyes had predisposing lesions and were given prophylactic treatment; RRD developed in 1.2% of treated eyes compared with 13.4% in the untreated group (Avitable et al., 2004). Despite numerous studies supporting prophylactic treatment for predisposed fellow eyes, the American Academy of Ophthalmology Preferred Practice Pattern does not strongly suggest prophylactic treatment of fellow eyes other than for symptomatic flap tears (Wilkinson, 2000). Although there may still be controversy in humans regarding prophylactic treatment, very few studies have been performed in the veterinary field. One such study compared treatment versus no treatment in the Bichon Frise with cataracts associated with LIU (Schmidt & Vainisi, 2004). Although the study consisted of only 57 dogs, it was statistically significant that prophylactic treatment is beneficial. Of the 39 dogs that received prior laser photocoagulation retinopexy before surgery, RRD developed in 5 dogs (12%). In 18 dogs that did not receive treatment, 10 dogs (55%) experienced RRD.

Several studies reveal the risk factors as well as the breeds associated with RRD (Boydell, 1991; Curtis et al., 1991; Gelatt et al., 2003; Hendrix et al., 1991, 1993). Risk factors include cataract surgery, spontaneous cataract resorption, LIU associated with the previous two factors, lens luxation, vitreous degeneration, retinal dysplasia, and CEA. Because of the frequency of RD after cataract surgery when LIU previously has occurred, laser retinopexy is recommended. A study of 46 eyes with RDs attributed 50% of the cases to lenticular disease or cataract extraction (Gelatt et al., 2003). More than 75% of the cataracts were hypermature and presumably had LIU. It is important to obtain ultrasonograms in eyes before performing retinopexy to be sure the retina has not already detached (Fig. 26.10). Because RDs occur frequently with luxated lenses or luxated lens surgery, we recommend retinopexy before surgery if possible or shortly afterward. In dogs with vitreous degeneration, especially certain breeds (Shih Tzu, Boston Terrier, Jack Russell Terrier, Italian Greyhound, Yorkshire Terrier, Maltese, and Poodle), there is a risk of developing giant retinal tears at the peripheral aspect of the retina, especially if the dog violently shakes its head while playing with toys. For some animals with geographic areas of retinal dysplasia, where the retina is extremely thin and there is associated vitreous degeneration, prophylactic retinopexy in the form of a contiguous barrier is advised. Labrador Retrievers affected with the oculoskeletal syndrome usually have larger globes, retinal dysplasia, cataracts, and vitreous degeneration and frequently experience RRD at an early age. We find it beneficial to perform retinopexy in these eyes as soon as possible, before the cataract worsens or the retina detaches. The reader should remember that perhaps the most important recommendation for prophylactic retinopexy should be the condition of the vitreous. Let the vitreous be your guide. One can consider the vitreous body as the silent protagonist in the drama of RD.

Procedure for Retinopexy

Retinopexy can be performed with cryotherapy (Fig. 26.11) or with either a red or green laser. Laser surgery is best performed in a transpupillary fashion with the indirect oph-

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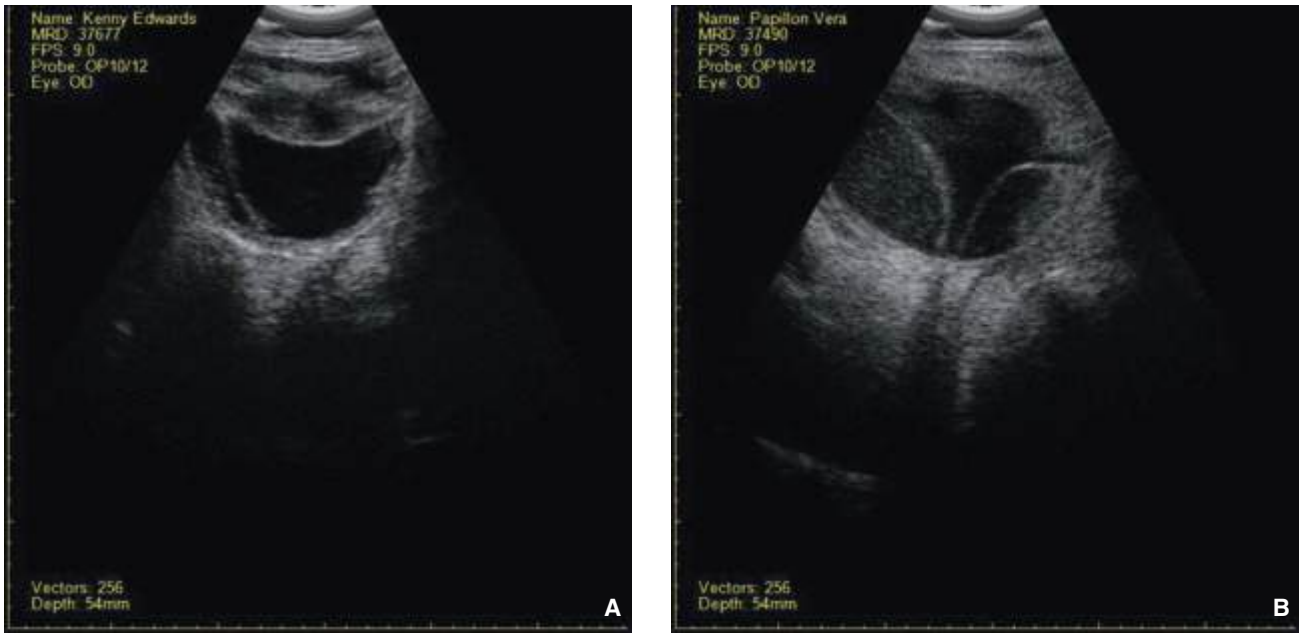


Figure 26.10 Sonograms of canine eyes with retinal detachment. **A**. Partial retinal detachment. **B**. Complete detachment.

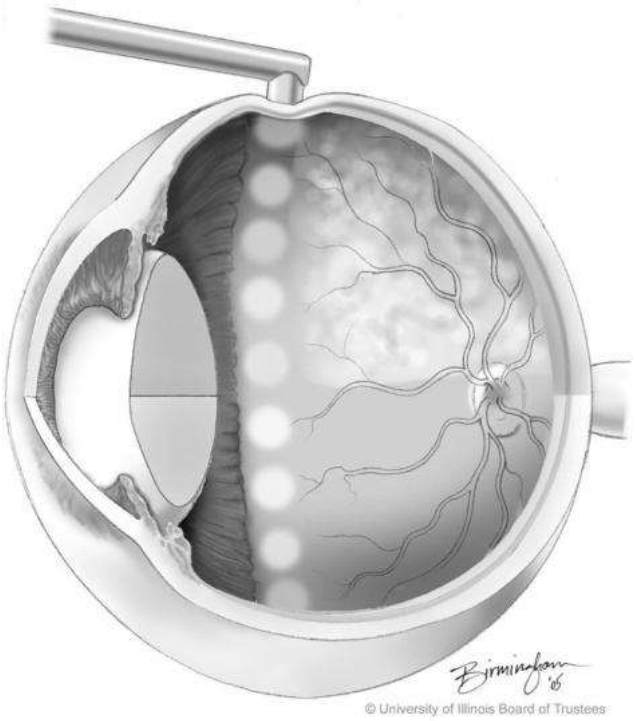


Figure 26.11 Cryopexy applications to the canine eye. (Copyright 2005, University of Illinois Board of Trustees. Used with permission.)

thalmoscope when possible, or transsclerally when observation of the retina is not possible (Mehta et al., 2000). It is important not to give excessive treatment because it can result in vitreous contraction or retinal holes and induce a giant retinal tear (Mehta et al., 2000).

Laser retinopexy is most easily delivered with the indirect ophthalmoscope unless there is a cataract or the vitreous media is too hazy to allow a focused beam. A double row of noncontiguous burns on the peripheral retina for 360 degrees is advised (Fig. 26.12; Chignell & Wong, 1999). This is best achieved with the patient in dorsal recumbency and using scleral depression. It is recommended that the least amount of energy and time be used to produce a small lesion, which is close to the diameter of the laser spot. Successful and efficient retinopexy is best achieved by a well-focused and defined spot size on the retinal surface. Hazy edges to the spot will lead to an unnecessary increase of energy dialed from the laser console, and greater risk of retinal hole formation. Prior to increasing energy on the laser console, other parameters can be adjusted to achieve the desired effect when the spot is not clearly defined. These include adjusting the table height or the surgeon's distance from the retina, changing the angle of incidence, or adjusting the mirror on the headset. Excessive energy and collateral thermal damage can cause rupture of Bruch's membrane, choroidal hemorrhage, or a retinal hole. If the retina is not flat against the choroid, it is possible to create a hole (see Fig. 26.5). The diode laser set at 250 mW of power for a 1000 msec duration works well for most cases. The settings for a green laser will be lower. Again, power and time setting will vary depending on the type of laser used, clarity of ocular media, degree of tissue pigmentation, and angle of incidence of the laser beam. Thinning of

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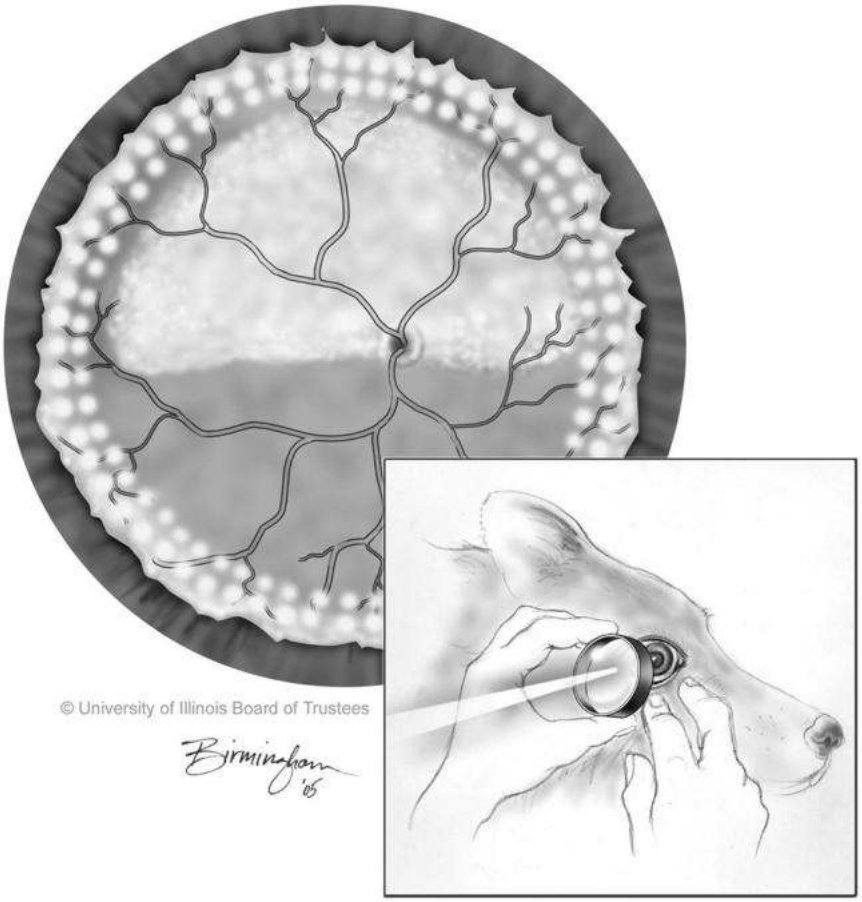


Figure 26.12 Indirect laser retinopexy in the canine eye. (Copyright 2005, University of Illinois Board of Trustees. Used with permission.)

the peripheral retina can predispose to formation of a retinal hole during laser retinopexy.

The diode laser is preferable in eyes with media opacities, because infrared light has the advantage of both transmission through lens opacities and vitreous hemorrhage (Isola et al., 2001). As diode laser energy can produce variable tissue effects, there may be some difficulty in obtaining reproducible burns because of change in melanin density of the RPE and choroid. This is especially true in animals with a tapetum lucidum; therefore, laser settings must be adjusted to effect. This 250 mW setting is higher than that recommended by others (Pizzirani et al., 2003).

Transpupillary retinopexy can be performed at the time of pseudophakic cataract surgery, particularly in those breeds predisposed to RD or where ultrasonography or ophthalmoscopic findings show liquefied or degenerative vitreous. Figure 26.13 is an example of the type of degenerative vitreous that warrants transpupillary retinopexy, regardless of the breed. Those dogs with consolidations of vitreous, often in the form of corkscrews or tendrils, are more likely to develop RD, in our observations. A widely dilated pupil will enable the laser beam to be directed peripheral to the IOL and achieve a thorough and effective retinopexy. The surgeon may also consider transpupillary retinopexy prior to IOL placement for enhanced visualization. This would require redraping and closing the corneal wound twice, but likely translates to higher precision and success (preferred by ARH).

Surgical Procedures for Treatment of Retinal Detachment

Pneumatic Retinopexy

Pneumatic retinopexy (PR) was first described in human patients in the mid-1980s (Dominguez, 1985; Hilton & Grizzard, 1986); however, the technique using air for somewhat similar surgery had been described a half-century earlier (Rosengren, 1938). PR involves the transscleral injection of gas into the vitreous cavity, combined with cryosurgery or laser retinopexy, followed by positioning of the gas tamponade over the retinal break until a chorioretinal adhesion occurs. The technique was introduced as an alternative surgery to scleral buckling (rarely used in canine retinal surgery)

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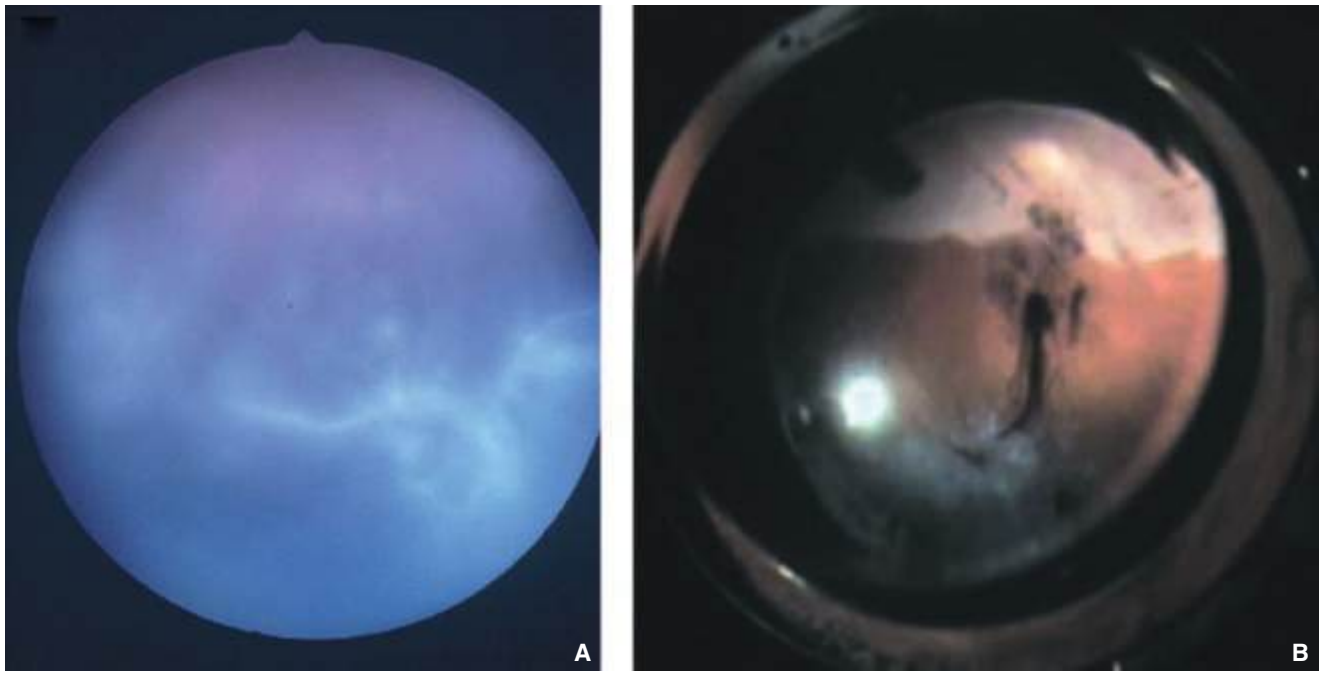


Figure 26.13 Degenerative vitreous characterized by corkscrews, tendrils, and pigment. **A**. Clinical photograph. **B**. Intraoperative view through silicone lens.

for retinal tears no larger than one clock hour located in the superior half of the peripheral retina. As more expertise was acquired, reports have been published of PR for treatment of retinal tears in more than one quadrant, inferior tears, and giant retinal tears (Chang et al., 2003; Irvine & Lokey, 1994; McAllister et al., 1987; Melgen & Michels, 1994; Parver & Lincoff, 1978; P.J. Smith et al., 1997; Tornambe, 1988, 1992; Tornambe et al., 1988).

The surgery is relatively easy and can be done as a single- or two-step procedure. It is usually an outpatient surgery; however, close observation is required for changes in IOP, retinal perfusion, or acceleration of the detachment. The patient must keep his or her head in the desired position for 10–15 hours a day for several days until the chorioretinal scar forms. This can be difficult to achieve in the dog and would require sedatives or tranquilizers.

The most common gases used for PR are sulfur hexafluoride (SF_6) or octofluoropropane (C_3F_8). The gases are nontoxic to the retina and have different expansile properties as well as length of duration in the eye. Furthermore, SF_6 will double in volume within 36 hours and remain in the eye for 10–14 days, and C_3F_8 will quadruple its volume within 72 hours and can persist for 4–6 weeks. The expansion of the gases is not due to expansion per se but due to invasion of gases, notably nitrogen and oxygen from surrounding tissues. The time of most rapid expansion is during the first 6 hours after injection. If either gas is diluted with air (20% with SF_6, 16% with C_3F_8), it will not expand but will probably persist in the eye longer than the pure concentration. In humans, usually 0.3–0.4 mL of SF_6 or C_3F_8 is injected. An injection of 0.3 mL of C_3F_8 in people will expand to 1.2 mL and cover approximately four clock hours (Tornambe, 1988). We have injected both SF_6 and C_3F_8 in dogs: usually 0.5 mL unless it is diluted; then 2–3 mL is used.

Reports of PR surgery in the dog are scant. One case report in which PR was performed was a postcataract RRD with associated glaucoma. The retina detached again 6 days postoperatively (P.J. Smith et al., 1997). Because most RRDs seen in dogs are giant tears and because most pet owners must travel long distances to reach a veterinary vitreoretinal specialist, the tendency has been to do the surgery that offers the best chance of success. Thus, PR has never been given the clinical trial it should have. Hopefully, this will change with earlier recognition of superior peripheral retinal tears of less than one clock hour.

Demarcation and Barrier Retinopexy

Demarcation retinopexy is an attempt to halt an RD in progress. In humans, it has been helpful in stopping temporal rhegmatogenous detachments before the RD extends to the macula (Vrabec & Baumal, 2000). This "salvage retinopexy" in the dog can be used for vertical dialysis, either nasal or temporal, moving toward the optic disc (Vainisi, 2002). However, it should not be viewed as a definitive surgery, but only as a stopgap measure to slow a detachment before referral for PPV. If one or two rows of laser burns are made along the leading edge of the RD (Fig. 26.14), it is sometimes

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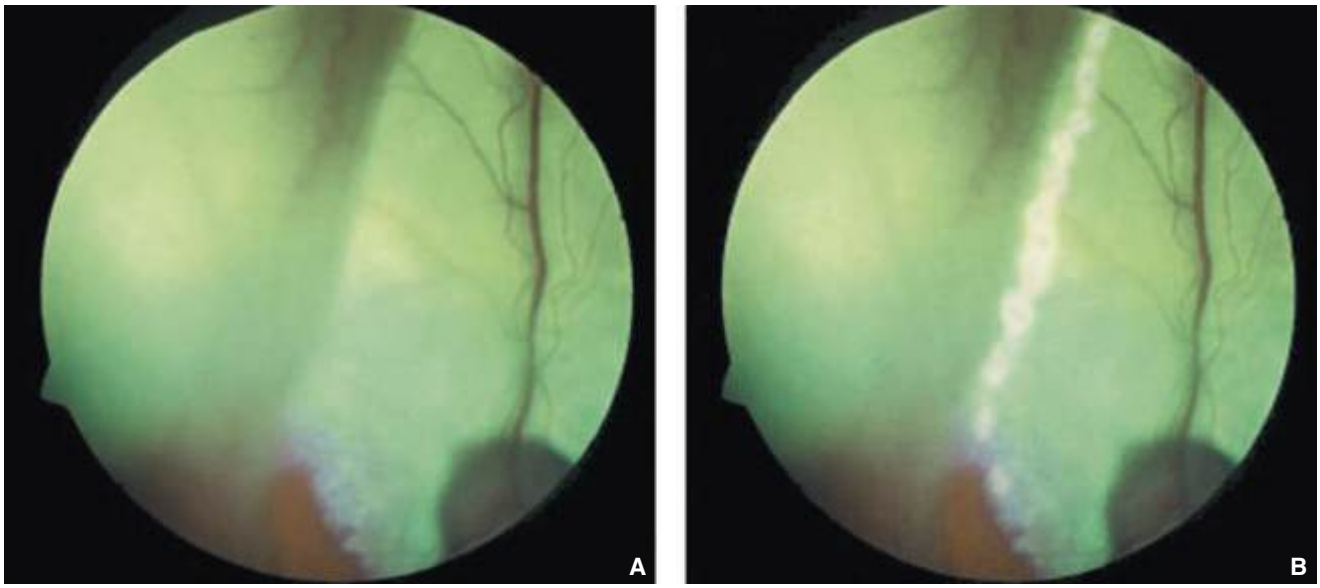


Figure 26.14 **A**. Vertical retinal detachment in a dog. **B**. After demarcation laser retinopexy in the same eye. (Reproduced with permission from Vainisi, S.J. & Wolfer, J.C. (2004) Canine retinal surgery. *Veterinary Ophthalmology*, **7**, 291–306.)

possible to stop the detachment. Surgeons should avoid aggressive laser treatment at the leading edge of the tear, and avoid a coalescing burn effect. Inadvertent laser treatment of an area of low-height retinal separation will incite thermal damage and accelerate the detachment. Barrier retinopexy has often been helpful on inferior and horizontal RDs, but not superior detachments, because gravitational forces usually overcome the adhesions. It is effective in treating serous RDs resulting from optic nerve pits or colobomas in the Collie. In one study, a row of xenon photocoagulation burns adjacent to the optic disc, when choroidal pigment was present, or around the serous detachment resulted in reattachment in all of 23 dogs (Vainisi et al., 1989).

Barrier retinopexy is generally indicated for small tears and retinal holes (Fig. 26.15) or for thin areas of retina associated with geographic retinal dysplasia. Although it is rare for older patients with retinal dysplasia but a stable sighted eye to progress to an RD, it is possible, and concerned owners should be given the option of prophylactic barrier retinopexy around an area of significant geographic dysplasia. A noncontiguous row of photocoagulation treatment is placed around the affected areas. However, barrier retinopexy is most often used in patients that have undergone cataract surgery, with the subsequent development of a retinal tear and detachment. There are several reasons why a surgeon might opt for barrier retinopexy rather than perform PPV or refer the patient to a center that performs this procedure. First, owners may have difficulty in affording further surgery, and barrier retinopexy is much less expensive than PPV. Second, some pet owners simply may not be able to travel to a surgeon who performs PPV. Third, some canine eyes with a pseudophakic detachment are in a state of

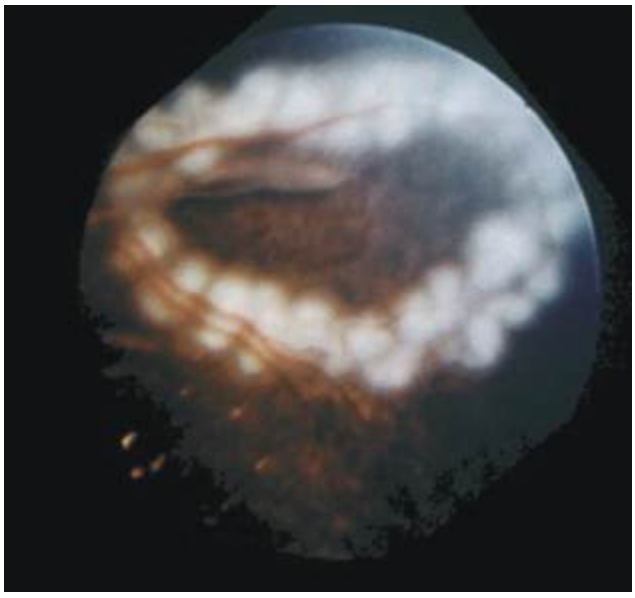


Figure 26.15 Postoperative barrier retinopexy of a retinal hole.

increased lability regarding their blood–ocular barrier. This makes the ocular vasculature prone to bleeding and to the leakage of protein into the ocular humor, thus impairing visualization during PPV. These eyes, however, can be improved before PPV with an intravitreal injection of an anti-VEGF medication. This injection should be performed 24–48 hours before PPV. Nevertheless, the success rate of barrier retinopexy is not as high as for PPV, and patients should be referred to a retinal center if possible. As a general rule, retinal detachments that are observed through an

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undilated pupil are best addressed with vitrectomy and perfluoro-octane (PFO – silicone oil) exchange.

Demarcation retinopexy has also been performed using diode endolaser in a series of 14 cases of partial RD detected on ultrasound images prior to cataract surgery (Webb et al., 2008). After phacoemulsification, a posterior capsulotomy was performed to gain access to the retina. Other approaches included limbal with peripheral capsulotomy and pars plana sclerotomy. A curved or straight endolaser probe was used to create a double row of retinal burns, with an average energy of 0.3 W (Webb et al., 2008). The benefit to endolaser barrier retinopexy is the size of the burns, which is greater than with conventional transpupillary laser retinopexy. In theory, the larger surface area of the burns should improve their holding power, although, to our knowledge, data are lacking in this area. Additionally, a larger burn is potentially more damaging. The disadvantage of endoscopic barrier retinopexy is the need for the disruption of the posterior lens capsule in pseudophakic or aphakic patients, which allows communication between the anterior and posterior segments, and the disruption of the vitreal matrix due to the introduction of a large-bore endoscopic probe. Endoscopic retinopexy, as with conventional barrier retinopexy, works best on temporal or medial tears where the leading edge of the detachment is approaching the optic nerve in a vertical orientation. Superior tears will still result in subretinal fluid that is being forced downward by gravity and will break through the retinal burns. Ventral tears can be addressed with endoscopic retinopexy.

The major disadvantage, however, of all barrier techniques is that abnormal vitreous is left behind and can foil the plans of the most skilled surgeon. Thus, PPV to remove all vitreous, and subsequent replacement with silicone oil, is the preferred technique whenever possible.

Vitrectomy for Giant Retinal Tears

As mentioned earlier, most RRDs seen in the canine are giant retinal tears or giant dialyses (which detach at the ora with no anterior flap of retina). These are circumferential breaks of 90 degrees (three clock hours) or more. In a series of more than 500 surgical cases with giant retinal tears, the tears were 270 or more degrees in approximately 75% of cases (Vainisi & Wolfer, 2004). These RDs are too far advanced to benefit from demarcation or PR and thus require vitrectomy.

Criteria for Vitrectomy

The duration of the RD is important in predicting any anticipated return of vision. In humans, determining the duration of the detachment is not a problem, but in animals, the timeline of events is often unknown. Astute owners will notice acute vision loss in their pet. In most spontaneous RDs in dogs, one retina has been detached long term, and only when the fellow retina detaches is the owner aware of a visual problem. The fellow retina might also be partly detached for weeks or even months before completely detaching and producing obvious vision problems.

In humans, if a return of 20/20 visual acuity is to be achieved, the retina must be reattached within 7–9 days. Studies on nonhuman primates have shown considerable retinal degeneration after 1 week of RRD. Surgical reattachment, however, results in prompt reversal of the disorganized retina (Kroll & Machemer, 1969a, 1969b).

In the dog, in a previously published series on giant retinal tear repair (Vainisi & Packo, 1995) and in our series of surgical treatment of giant tears (Vainisi & Wolfer, 2004), it was observed that if the retina is reattached within 4 weeks, there is a reasonable chance of return of some functional vision. Giant RDs that have remained partly attached for months appear to recover useful vision after being reattached. Obviously, the sooner the repair, the better the odds of good vision. Dogs whose retina has been detached for less than 1 week are more likely to have vision within days of surgery, compared with those dogs with a more chronic detachment, which may take 3 weeks or more postoperatively for sight to be restored. Histopathologic findings of an eye with a 360-degree RRD of approximately 2 weeks' duration in a dog that died shortly after reattachment surgery showed loss of photoreceptors on the superior retina, with preservation of the inferior photoreceptors (Fig. 26.16). This is typical of most spontaneous RRDs in the dog: the superior retina detaches first, then the inferior retina. These surgical cases generally require 2–3 weeks before owners report a return of vision. A positive pupillary light response is a good sign; however, it can be misleading, because it is not uncommon in certain cases to see a good pupillary light response in retinas that have been detached for several months. Electroretinograms (ERGs) have not been reliable indicators in determining cases suitable for surgery. We have operated on numerous cases in which the ERG been extinguished and the patient still recovered useful vision. However, a recordable ERG, even if attenuated, is associated with return of vision and a favorable prognostic indicator (Hoffman et al., 2017). Studies in nonhuman primates with RRD revealed an abolished ERG within 1 week. After reattachment of the retina, the ERG activity gradually returned within 1 week and continued to improve (Hamasaki et al., 1969).

The visual prognosis is also based on careful inspection of the retinal health, conformation, and number of holes or tears preoperatively. Radial tears that extend to the optic nerve head can carry a lower success rate because of interruption of visual signals and a greater anatomic instability of the retina, even with laser retinopexy and silicone oil tamponade (Fig. 26.17). The presence of retinal atrophy with scrolled peripheral edges will also lower the success rate

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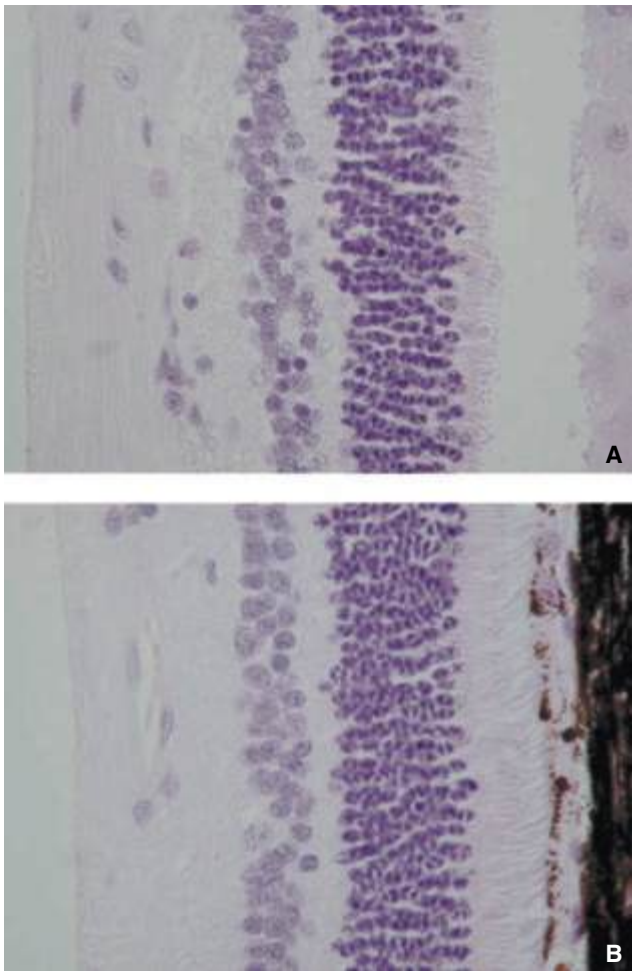


Figure 26.16 Histopathologic study of a canine eye immediately after surgery to repair a 360-degree retinal detachment. **A**. Superior aspect of retina. **B**. Inferior portion of retina. (Reproduced with permission from Vainisi, S.J. & Wolfer, J.C. (2004) Canine retinal surgery. *Veterinary Ophthalmology*, **7**, 291–306.)

even when a pupillary light reflex and dazzle are present preoperatively (Fig. 26.18). Additionally, the retinal conformation in a tight funnel or scroll may be difficult to separate or lie flat against the eye wall intraoperatively. Figure 26.19 shows a tightly scrolled RD in a Shih Tzu. Despite this conformation, this young Shih Tzu regained sight, with a likely advantage of a young age of 4 years.

Fortunately, PVR is not commonly seen in most cases of canine RRD. It has been reported in the Labrador Retriever with oculoskeletal dysplasia (Blair et al., 1985a). We have encountered it in the Italian Greyhound in long-standing detachments. PVR can also be seen in cases of ocular trauma in which the posterior segment has been penetrated. If PVR is present, the prognosis for surgical success is reduced. Reproliferation of contractile membranes is common in dogs and humans and may ultimately lead to redetachment of the retina. Any signs of inflammation or elevated IOP must be treated. Operating on an inflamed globe is almost certain to result in failure or serious complications. Although gonioscopy is controversial for predicting glaucoma, we suggest it be performed, as it may be helpful in planning postoperative care. Corneal scars, synechiae, and capsular opacities can all interfere with proper visualization. Dense capsular opacities or residual cortical lens material should be removed. Aphakic eyes in which silicone oil is used occasionally have a problem maintaining the silicone oil in the vitreous cavity. In cases in which vitreous opacities prevent a full view of the retina, it is important to examine the vitreous–retina interface using brightness (B)-scan ultrasonography. The patient's general health should be carefully evaluated prior to surgery. Preoperative complete blood cell count, chemistry profile, urine analysis, blood pressure, and coagulation panel (where indicated) are considered minimum investigations for baseline data.

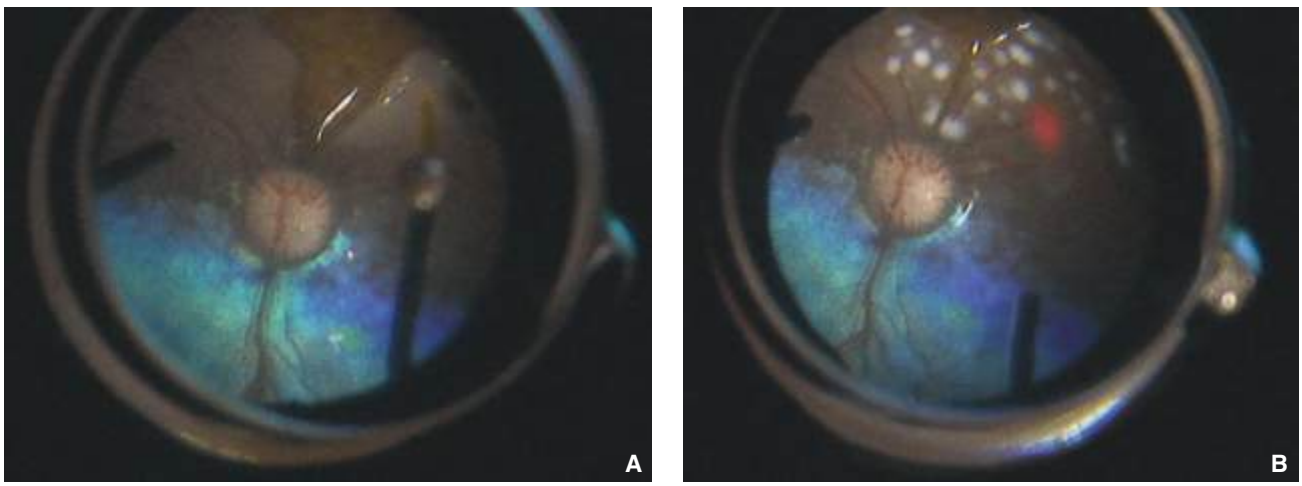


Figure 26.17 Retinal radial tears. **A**. Before laser treatment. **B**. After laser treatment..

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Figure 26.18 Intraoperative view of a chronic giant retinal tear.

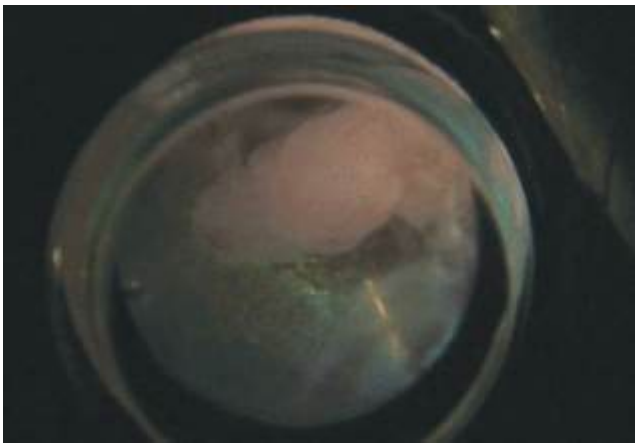


Figure 26.19 Intraoperative view of a tightly scrolled retinal detachment in a Shih Tzu.

Surgical Equipment

An operating microscope with coaxial illumination and X–Y functions is needed. A beam splitter will give the assistant a coaxial view. Several different lens viewing systems work satisfactorily in the dog. The Machemer irrigating lens as well as sew-on ring sets can be used on the dog; however, these lenses are made for the human cornea, which is considerably smaller than the canine cornea. These lenses generally have only approximately a 30-degree field of view; thus, prism lenses need to be used to view the peripheral retina. Self-retaining silicone lenses, both wide-angle and prism type, work well in the dog (Fig. 26.20). We have successfully used all three types of lenses on dogs.

Wide-angle systems, either contact or noncontact, work very well on dogs but are more expensive. The wide-angle lenses give a panoramic view, between 90 and 130 degrees. These systems are based on principles of binocular indirect ophthalmoscopy and thus require an inverter to be mounted on the microscope. The SDI-BIOM™ (Oculus Surgical, Port St. Lucie, FL, USA) is an excellent wide-angle, noncontact system (Fig. 26.21A). An alternative to the SDI-BIOM system is the Eibos™ (Möller-Wedel, Wedel, Germany). The Eibos is a noncontact, wide-angle viewing system, similar to the SDI-BIOM, which uses mirrors to invert the indirect image and therefore does not require a microscope-mounted inverter (Fig. 26.21B). This system is less expensive than the SDI-BIOM. The Volk wide-angle system™ (Volk Optical, Mentor, OH, USA), which requires an inverter, is inexpensive and works well on animals. It is a contact system with a large lens, thus requiring an assistant to help secure the lens in position (Fig. 26.21C). Volk also has a noncontact system (Merlin) with detachable condensing lenses to switch between 80- and 120-degree viewing (Fig. 26.21D). The Zeiss Resight fundus viewing system™ (Carl Zeiss Meditec, Jena, Germany; Fig. 26.22) also works well for the canine patient.

New instrumentation and devices improve the safety and speed of vitreoretinal surgery. With the constant updating of equipment, many prior models become available at a lower cost. Illuminating sources, electrocautery, air infusion units, ultrasonic fragmentation, and silicone oil pumps are built into these units (Fig. 26.23). Most present-day vitrectomy probes (20, 23, and 25 gauge) are small, pneumatic, and disposable; however, some are electric with only the tip disposable. New vitrectomy probes have a guillotine-type cutter on the side of a blunt tube. Most cutters operate at 1500–5000 cuts per minute, but some currently attain speeds of 16,000 cuts per minute. With the faster cutters and using less vacuum pressure, there is a lower risk of drawing the retina into the tip, causing iatrogenic tears. The newest technology includes integrated lasers, intraocular tonography at the infusion port, ability to titrate the duty cycle, and halogen and mercury light sources (Fig. 26.24). This technology offers 23-, 25-, or 27-gauge probes (Fig. 26.25). These units are expensive, but will become more affordable as demonstrator models become available. Although 20-gauge vitrectors were originally the mainstay for veterinary vitreoretinal surgeons, 23-gauge and 25-gauge vitrectors are now more popular and will be discussed later in this chapter. Diagnostic vitreous sampling can be performed with a 27-gauge vitrectomy system, which has recently become available (Dutch Ophthalmic USA).

Light Sources

Halogen and metal halide light sources have been used extensively for vitreoretinal work. More recently, xenon and hexon illumination has been introduced as a brighter and

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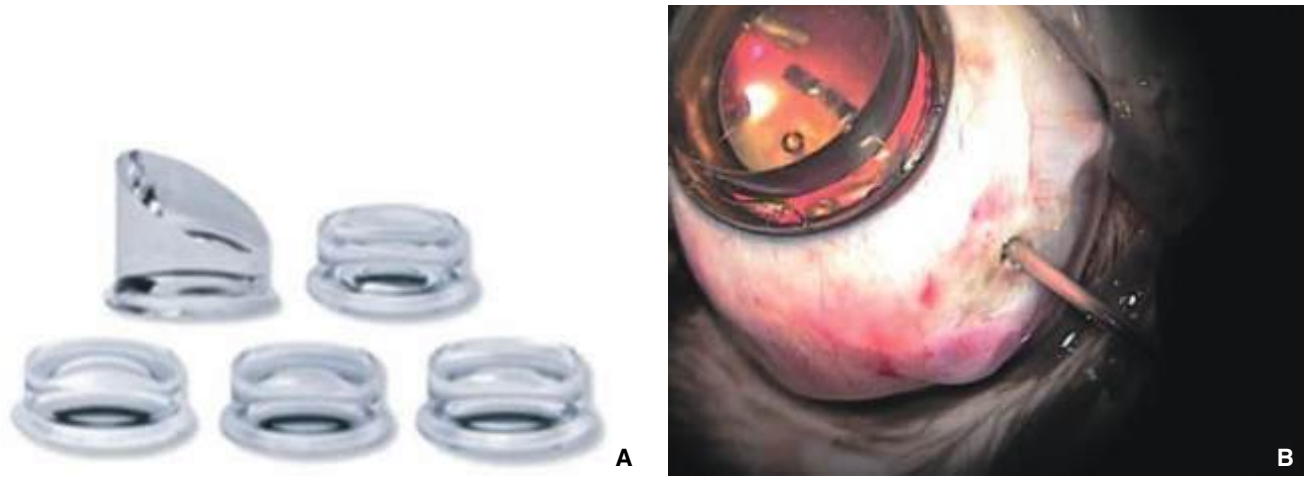


Figure 26.20 **A**. Self-retaining silicone lens set (Dutch Ophthalmic USA, Exeter, NH, USA). **B**. Endolaser retinopexy viewed through a self-retaining silicone lens.

more powerful source to improve visualization, particularly for smaller-gauge vitrectomy (23 and 25 gauge). The newer vitrectomy units (see Fig. 26.23, Fig. 26.24) have built-in xenon, mercury vapor, or light-emitting diode (LED) light sources. Xenon is a "whiter" light source. Mercury vapor light decreases the risk of phototoxicity for prolonged procedures. Additionally, optional integrated color filters or tints can be employed, depending on safety parameters or surgeon's preference. Some surgeons are better able to visualize the vitreous using a yellow filter, and better able to visualize traction bands using a green filter.

Laser Technology

Newer vitrectomy systems are equipped with integrated laser systems. Veterinary vitreoretinal surgeons can also have a separate diode or argon laser console. One surgeon (ARH) employs the argon laser for vitreoretinal work in breeds with less retinal pigment or with subalbinism. Several options of laser probes are available. These include a tapered probe for ease of entry, an adjustable curvature to the probe tip manually operated at the handpiece, a combined laser and aspiration probe, and white light illumination surrounding the laser spot for better visualization. Micropulse technology (Iridex IQ810, Iridex, Mountain View, CA, USA) is available to replace continuous-wave energy. This minimizes thermal damage to the adjacent retina, while still creating chorioretinal adhesion.

Other equipment and accessories necessary for vitreoretinal surgery include microvitreoretinal blades, gauge-specific trocars and cannulae, high-viscosity infusion tubing (4 or 6 mm cannula), scleral plugs and plug holder, electrocautery sets, endocautery, vitreous scissors and forceps, silicone soft-tipped cannula, or dual-bore coaxial cannula (Fig. 26.26), Charles flute needle and handle, PFCLs, and silicone oil (1000–5000 centistokes). If not integrated into the vitrectomy machine, adjustable illumination, air, and cautery systems will be needed.

There is a wide variety of vitreoretinal surgery accessories depending on the surgeon's preferences and best surgical approach for the case. Options include an illuminated infusion cannula, adjustable curvature to the light pipe, illuminated vitrector, and an irrigating light pipe.

Most canine vitreoretinal surgeons now place valved (Fig. 26.27) or nonvalved cannulas (Fig. 26.27C, D) for ease of entry and exit, and to minimize surgical trauma. Valved cannulas control for hypotony, which can lead to choroidal hemorrhage, particularly in the dog.

It is best to place all instrument consoles (vitrectomy machine, laser, etc.) on an instrument table near the foot of the patient (Fig. 26.28) so that all lines can be draped in a sterile fashion over the patient and be easily accessible to the surgeon. Another instrument table with surgical instruments and supplies is located alongside the surgeon and assistant. Surgical preparedness and operating room support staff are essential to the time efficiency and success of the surgery.

The latest in vitreoretinal surgery offers three-dimensional heads-up vitrectomy, which improves ergonomics and depth of field and allows a wider field of view. None of the authors has transitioned to this yet.

Vitreous Substitutes

Canine postoperative mobility (i.e., head shaking and inability to keep the eye in a fixed orientation) increases the need for a long-term vitreous substitute that can, either alone or in combination, close both superior and inferior retinal breaks. In addition, because of the complicated and large nature of RRD in the dog, both intraoperative and postoperative use of vitreous substitutes is highly beneficial for successful vitreoretinal surgery in this species.

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A



C



B



D

Figure 26.21 Wide-angle viewing systems. **A**. SDI-BIOM (Oculus Surgical, Port St. Lucie, FL, USA). **B**. Eibos (Möller-Wedel, Wedel, Germany). **C**. Volk ROLS (Reinverter Operating Lens System) with Volk Mini Quad contact lens at right (Volk Optical, Mentor, OH, USA). **D**. Volk Merlin noncontact system and associated lenses (inset).

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Figure 26.22 Zeiss Resight 500 fundus viewing system (Carl Zeiss Meditec, Jena, Germany).

Perfluorocarbons

Previous experience with PFCLs as artificial blood replacements suggests these compounds are biologically inert (Koester & Lutz, 1980; Meyer et al., 1992). These properties have led to investigations of their use as vitreal substitutes. PFCLs have unique physical properties that facilitate complex vitreoretinal surgery, including low viscosity, transparency, immiscibility with water, biologic inertness (and thus nontoxicity), and a specific gravity (1.73–2.03 g/cm^3) higher than that of saline (Doi & Refojo, 1994; Millsap et al., 1992). Because PFCLs are clear, with refractive indices similar to that of water, minimal optical aberrations occur when working through the liquid, and conventional vitrectomy contact lenses may be used. An interface can be visualized between the PFCL and saline, and visualization of this interface facilitates complete removal of the PFCL from the eye, thus reducing the incidence of residual droplets. The PFCLs currently in use are PFO, perfluorotributylamine, perfluorodecalin, and perfluoroperhydrophenanthrene.

The characteristics of PFCLs make them a useful surgical tool for intraoperative or short-term retinal tamponade. They can flatten a detached retina intraoperatively as well as float posteriorly displaced lens fragments or IOL implants. Use of PFCLs to help flatten and unroll complicated RRD with a giant retinal tear is well established (Augustin et al., 1995; Bryan et al., 1994; Eller & Berger, 2001; Han et al., 1994; Millsap et al., 1992). Because they are heavier than saline, they can be used to tamponade inferior retinal tears. Long-term tamponade with PFCLs would be particularly useful, especially with inferior tears, but such use is limited by toxic effects on the retina (Augustin et al., 1995; Moreira et al., 1992). One vitreous substitute, perfluorohydrophenanthrene, has been left in rabbit eyes for up to 6 weeks, in monkey eyes for 22 weeks, and in human eyes for 4 weeks, with minimal toxic effects (Millsap et al., 1992).



Figure 26.23 Eva vitrectomy system (Dutch Ophthalmic USA, Exeter, NH, USA).

The specific gravity of PFCLs is almost twice that of water, thereby providing a tamponade force far greater than that of silicone oil. This characteristic makes it possible for PFCLs to flatten the retina intraoperatively, by displacing subretinal fluid anteriorly through the peripheral breaks and into the vitreous cavity. The interfacial tension of PFCLs tends to remain as one cohesive bubble. The low viscosity of PFCLs (0.8–8.0 centistokes at 258C versus 1000–5000 centistokes at 258C for silicone oil) allows for easy introduction and removal with small-gauge instruments.

Silicone Oil

Silicone oil is a polymer of several different molecular-weight polydimethylsiloxane chains. Its viscosity is related to the length of the polymer chain or chains, and thus its molecular weight (Hutton et al., 1994). Silicone oil is available in different viscosities, of 1000, 1300, or 5000 centistokes.

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Figure 26.24 **A**. Constellation vision system (Alcon Laboratories, Fort Worth, TX, USA). **B**. Stellaris PC Vision Enhancement system (Bausch & Lomb, Rochester, NY, USA).

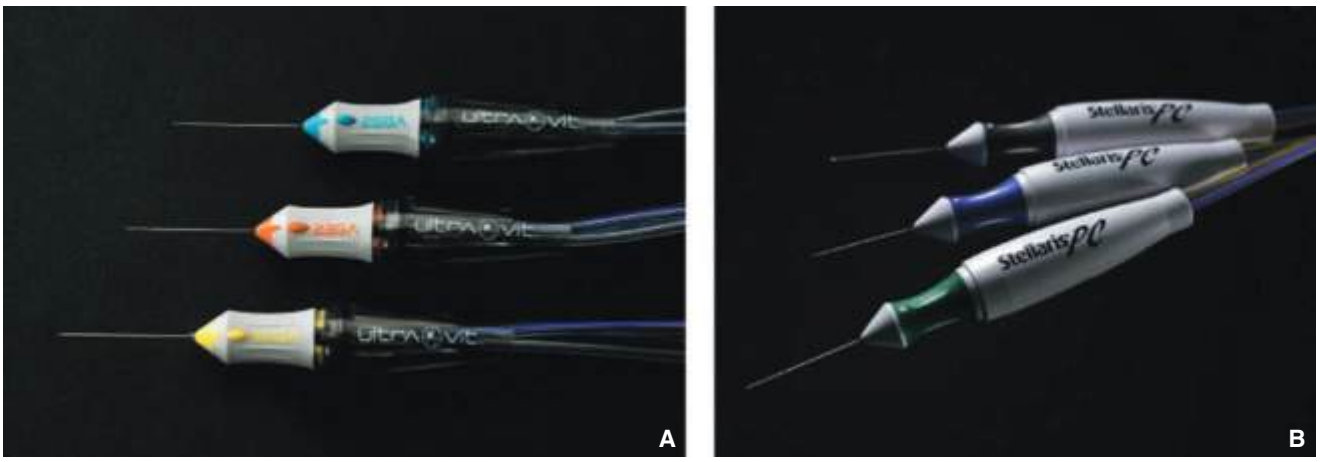


Figure 26.25 Vitrectomy probes. **A**. Alcon Constellation vitrectomy probes (Alcon Laboratories, Fort Worth, TX, USA). **B**. Bausch and Lomb vitrectomy probes (from bottom, 23-, 25-, and 20-gauge; Bausch & Lomb, Rochester, NY, USA).

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The 5000-centistoke silicone oil has been used in most reported canine cases. However, one of the authors (JCW) uses 1300-centistoke oil exclusively, seeing no increased propensity for this oil to present in the anterior chamber and finding a much faster and smoother transition from PFO to silicone oil. Intraocular silicone oil is used to provide long-term tamponade of the retina. Silicone oil has a specific gravity of 0.971 (less than that of water) and forms a buoyant sphere within the vitreous cavity, exerting a tamponade effect. The interfacial tension of silicone oil with water helps maintain an oil sphere. These properties result in a silicone oil bubble that floats toward the superior vitreous cavity. Failure to completely fill the vitreous cavity prevents proper tamponade of the inferior retinal surface, possibly leading to RD and/or retinal slippage.



Figure 26.26 Dual-bore coaxial cannula. Balanced salt solution travels through the outer lumen of the cannula and out through a small opening on the outside of the eye near the yellow connector.

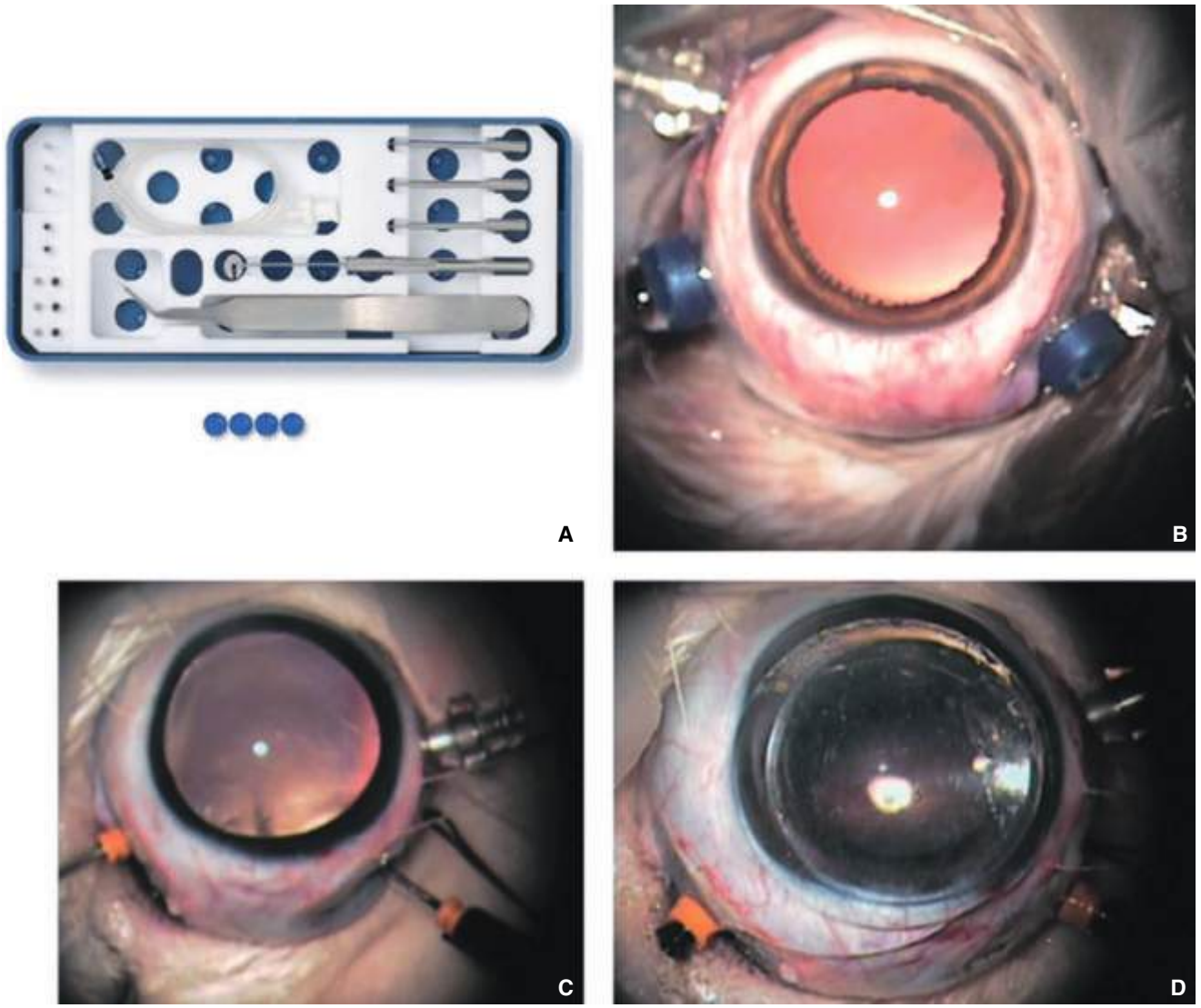


Figure 26.27 Cannula systems. **A**. 23-gauge valved cannula system (Dutch Ophthalmic USA, Exeter, NH, USA). **B**. 23-gauge valved cannulas placed in the canine eye (Dutch Ophthalmic USA). **C**. Trocar placement of 23-gauge cannulas (Alcon Laboratories, Fort Worth, TX, USA). **D**. Canine eye prepared for vitrectomy with 23-gauge cannulas and closure valves (Alcon Laboratories) and a self-retaining silicone lens (Dutch Ophthalmic USA).

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Figure 26.28 Aerial view of operating room setup during canine vitreoretinal surgery.

The major indication for silicone oil in domestic species is giant retinal tears and RRD associated with PVR. In humans, conventional surgery is performed before considering silicone oil tamponade. This usually entails vitrectomy, membrane peeling, C_3F_8 gas tamponade, scleral buckling, or some combination (Cox et al., 1986; Hutton & Fuller, 1994; McCuen et al., 1985). Silicone oil usually is necessary in the dog, however, because this species represents a similar situation to uncooperative human patients. In the dog, use of silicone oil is a first choice, both because of the complexity and large nature of RRDs and because of the dog's inability to stay immobile and maintain a designated head position for 18 hours a day. When silicone oil is used, it is important that all retinal traction be released and the retina be completely reattached before injection.

In humans, when silicone oil is used in aphakic and pseudophakic eyes, inferior peripheral iridectomy is required to help prevent glaucoma; alternatively, an inferior-sector iridectomy or sphincterotomy extending the inferior aspect of the pupil margin may be used. Without iridectomy or creation of a flow route under the oil bubble, the silicone oil may block the pupil, thus resulting in aqueous misdirection or malignant glaucoma. This aqueous misdirection also leads to forward migration of the silicone oil and secondary keratopathy, which is seen clinically as corneal edema. Inferior peripheral iridectomy allows the aqueous to flow into the anterior chamber, avoiding this complication (Silicone Study Group, 1992a). In the dog, pupillary block in pseudophakes and aphakes from silicone oil has not been a problem. However, if necessary, an inferior sphincterotomy would be a safer procedure than an inferior iridectomy. This can be done with the vitrector probe at the time of surgery.

Several complications have been documented with the use of silicone oil as a permanent tamponade in humans (Nakamura et al., 1990), rabbits (Chan & Okun, 1986), nonhuman primates (Lin et al., 2005), and dogs (Vainisi & Packo, 1995; Vainisi & Wolfer, 2004). These complications include silicone oil emulsification (Nakamura et al., 1990; Valone & McCarthy, 1994), anterior chamber migration (Vainisi & Packo, 1995; Vainisi & Wolfer, 2004), keratopathy (Choi et al., 1993; Sternberg et al., 1985; Valone & McCarthy, 1994), glaucoma (Chan & Okun, 1986), cataract formation (Vainisi & Wolfer, 2004), inner retinal toxicity (Falkner et al., 2001; Minckler, 2001; Nazemi et al., 2001), and subconjunctival migration from sclerotomy sites (Vainisi & Wolfer, 2004). In one series using silicone oil for repair of canine RRD, some degree of lens opacity developed in all dogs in the year after surgery (Vainisi & Packo, 1995). Keratopathy and glaucoma are more frequent in aphakic and, to a lesser extent, pseudophakic eyes, which potentially allows easier access of oil to the anterior chamber. Emulsification has been reported to occur more readily with the less viscous (1000-centistoke) oils, oils having lower interfacial tension against water, and oils containing impurities (Nakamura et al., 1990); however, a comparison of RD repair using 1000- versus 5000-centistoke silicone oil found no different in emulsification between the two viscosities (Scott et al., 2005). Keratopathy results from endothelial damage caused by direct contact with the oil, which in part may result from nutritional deprivation (i.e., lack of exposure to aqueous humor; Sternberg et al., 1985). Large oil bubbles as well as less obvious droplets may contribute to keratopathy. No significant corneal abnormalities have been seen in dogs with very small anterior chamber oil bubbles. However, moderate persistent stromal edema has been observed in dogs with large oil bubbles in the anterior chamber. Because corneal endothelial damage results from oil contact, all oil in the anterior chamber should be removed in almost all cases.

If necessary to remove silicone oil from the anterior chamber, it is best to wait at least 3 weeks to allow chorioretinal scars to form. Figure 26.29A, C shows the clinical appearance of silicone oil in the anterior chamber. Figure 26.29B shows a near complete oil fill, which can make it more difficult to discern the oil meniscus (noted laterally). The pupil should be made miotic before surgery. This procedure should be done under the operating microscope. The dog is placed in dorsal recumbency, and bridle sutures can be used to

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Figure 26.29 Silicone oil in canine anterior chamber. **A**. Single small bubble. **B**. Nearly complete silicone oil fill. **C**. Multiple bubbles in the anterior chamber. (Courtesy of Eric Storey.)

control globe rotation intraoperatively. The silicone oil bubble will ideally float superiorly. If there is already considerable corneal edema or scarring superiorly, place the dog in dorsal recumbency so silicone bubbles will float away from the scarred area. Using a 27-gauge needle, inject a viscoelastic into the inferior anterior chamber, slightly elevating the IOP. At the same time, make a 2–3 mm stab incision at the dorsal limbus above the oil bubble (Fig. 26.30A) and continue injecting the viscoelastic until the oil bubble has been removed (Fig. 26.30B). Do not allow the eye to become hypotonic, because hyphema or retinal slippage may occur. One suture should adequately close the incision. Antiglaucoma therapy should be given postoperatively as needed, and intraocular pressure should be monitored closely. A video of silicone oil removal can be viewed at https://www.youtube.com/watch?v=AvVsI2ELm4o.

In a new technique developed by Eric Storey (2017) and presented at the 2017 Veterinary Vitreous Society Meeting, the silicone oil removal is accomplished with one stab incision using a 20-gauge needle. After the stab incision in the cornea, a fluid line is placed into the anterior chamber, and the influx of balanced salt solution (BSS) will cause egress of silicone oil from the stab incision. Once the oil is removed, the incision is closed with one suture.

In humans, silicone oil is generally removed 2–6 months postoperatively. Removal of silicone oil in humans helps avoid cataract formation and PVR, and helps correct anisometropia. The rate of retinal slippage or redetachment after complete oil removal varies from 3% to 33% (Silicone Study Group, 1992a, 1992b). There is, however, a gradual increase of RD over time in eyes with silicone oil retention compared with those in which the oil is removed (Hutton & Fuller, 1994). A follow-up study on silicone oil in humans revealed a significant likelihood of improved visual acuity in eyes in which the oil was removed, along with a slight increase in recurrent RRD (Hutton et al., 1994). The visual acuity retained in human eyes that receive vitrectomy and oil, with or without removal, is often no better than 5/200 (Hutton et al., 1994; McCuen et al., 1985; Silicone Study Group, 1992a). This poor vision probably relates to the severe retinal disease and history of repeated operations rather than to a direct relationship to the use of

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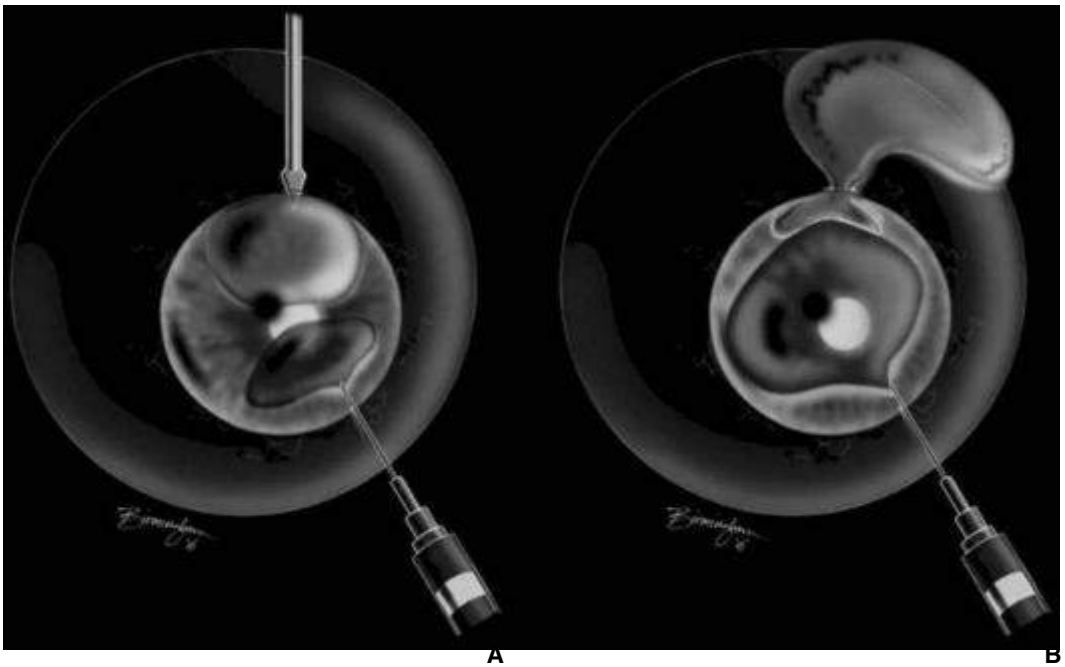


Figure 26.30 Removal of silicone oil from the anterior chamber. **A**. Injection of a viscoelastic agent inferiorly while a stab incision is made at the dorsal cornea. **B**. Continued injection of viscoelastic until silicone is completely removed. (Copyright 2005, University of Illinois Board of Trustees. Used with permission.)

silicone oil. We do not routinely remove silicone oil except in cases in which it continually escapes into the anterior chamber. In rabbits and monkeys, the retinal toxicity caused by silicone oil is controversial, but with time, the inner retinal layers are damaged (Doi & Refojo, 1994, 1995). Long-term pressure of the viscous oil bubble on the retina may contribute to this retinal degeneration. We have had a number of eyes that have regained vision after surgery only to lose it in 2–3 years without any obvious reason. By the same token, we have had many canine eyes that have had silicone for 10–12 years and still maintain good vision. At this time, we believe that silicone oil should remain in the eye long term to act as a vitreous substitute. Thus, until studies become available to show the benefit of silicone oil removal in dogs, we believe it should be left in place. In fact, in patients that lose silicone oil for any reason or that do not have a complete silicone oil fill, RD may recur, as shown in Fig. 26.31.

The refractive index of silicone oil and vitreous differs (1.405 D and 1.336 D, respectively) and leads to refractive changes postoperatively. Hoffman et al. (2012) compared refractive errors with lens status (phakic, pseudophakic, or aphakic) and with the type of silicone oil viscosity in 63 eyes. Hyperopia was observed in all dogs that received silicone oil tamponade, regardless of lens status. Aphakic eyes undergo a myopic shift when filled with silicone oil. Pseudophakic eyes are more hyperopic than phakic eyes when filled with silicone oil (Hoffman et al., 2012).

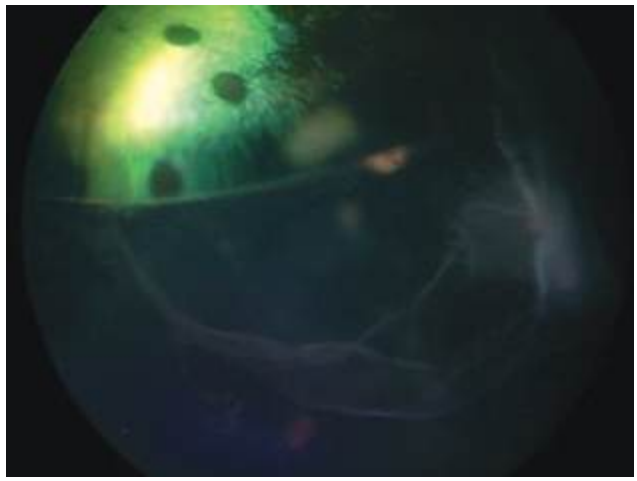


Figure 26.31 Incomplete silicone oil fill in a Brussels Griffon. Note redetachment of the retina.

New Vitreous Substitutes

New vitreous substitutes are being developed to replace gases and oils in human vitreoretinal surgery (Donati et al., 2014; Gao et al., 2008; Hayashi et al., 2017; Kashiwagi et al., 2011; Schramm et al., 2012; Sommer et al., 2007; Su et al., 2015; Wirostko et al., 2014). These heavy liquids slowly resorb over 2–3 months. Current technologies such as gases and silicone oil have some limitations in humans and may be replaced by "hydrogels." Gases prevent a patient from

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airplane travel and silicone oil requires a second surgery for removal (due to emulsification, hypertropia, and/or retinopathy). As such, researchers are investigating novel technologies to address these limitations. Hydrogels are transparent, biocompatible, and similar to the native vitreous (Alovisi et al., 2017). One example of a hydrogel that may be used as a vitreous substitute was developed by Uesugi and colleagues (2017). This self-assembling peptide gel has shown biocompatibility in animal models. Hydrogels have a potential role as a vitreous substitute in veterinary posterior segment surgery.

Vitreoretinal Surgical (23-Gauge) Technique

The patient is prepared as for cataract surgery, in dorsal recumbency with the head deviated medially. Sufficient globe exposure for a three-port vitrectomy can be difficult in many canine patients; therefore an attempt should be made to proptose the globe. In the brachiocephalic breeds and in most mesocephalic breeds, the globe can be proptosed quite easily. Some brachiocephalic breeds are so exophthalmic that minimal eyelid pressure on the side of the globe will easily proptose it; however, in most cases a temporal canthotomy is necessary. At the canthotomy 4-0 silk sutures are placed, to be tied after the proptosis to secure the globe in position. The surgeon grasps the globe with a fixation forceps while the assistant, using two muscle hooks, presses against the lids, gently proptosing the globe. Care must be taken that the canthal sutures are not so tight as to cause venous stasis, but tight enough that the globe does not fall back into the orbit. If there is considerable venous congestion after proptosis, it is best to abort the proptosis. A rubber dental dam can be fitted over the prolapsed globe to ensure sterility. A transparent incise drape can also be used over the patient and table for better anesthetic monitoring. In cases in which the globe cannot be proptosed, a liberal canthotomy should be performed along with placement of a large speculum. It is helpful in these cases to place 4-0 silk sutures around the horizontal rectus muscles and attach them to adjacent tissue to partially elevate the globe.

A three-port vitrectomy is the routine approach to the vitreous cavity. The ports will penetrate the pars plana and thus will be placed 5–7 mm from the limbus. All ports may be placed superiorly (see Fig. 26.20B); however, one breed exception is the Siberian Husky. In this breed, the nasal pars plana is frequently very narrow (1 mm); thus, the ports may need to be placed temporally. To avoid the larger draining veins and allow for more room between working ports, the infusion cannula can be placed inferotemporally and is preferred by two authors (JCW and ARH).

The conjunctiva is incised 6 mm posterior to the limbus, reflected anteriorly, to expose the sclera, intrascleral venous plexus, and the anterior ciliary vein. One author (JCW) performs a 180-degree peritomy right at the limbus and reflects the conjunctiva posteriorly. Relaxing incisions may be necessary at the 3 and 9 o'clock positions. Closure of the peritomy is accomplished with two simple, interrupted sutures at the 3 and 9 o'clock positions.

With the conjunctiva reflected, a 4-0 silk suture is placed around the horizontal rectus muscles. These sutures help control the eye and are important for repeated proptosis of the globe in case it should fall back into the orbit. As mentioned previously, these sutures can also be used to elevate globes that cannot be proptosed. An alternative to dissection and isolation of rectus muscles is a suture placed at the 3 and 9 o'clock limbal positions using 6-0 polyglactin 910 (Vicryl®, Ethicon US, Somerville, NJ, USA) and a spatulated needle.

The intrascleral plexus (circle of Hovius), which is 3–4 mm from the limbus and 4–5 mm wide, is where the ports are made to penetrate the pars plana (see Fig. 26.6). Therefore, adequate cautery of these vessels is very important to prevent bleeding into the eye. Once blood enters the eye, it can adhere to the retinal surface and be challenging to remove; consequently, this will lengthen surgical time and complication rate. Therefore, meticulous cautery and limiting bleeding in the canine patient are critical. One author (ARH) performs conjunctivectomy and cautery only within the anticipated working ports and infusion site. Most ports are 5–6 mm from the limbus; however, the surgeon should refer to the article by Smith and colleagues (1997b) regarding pars plana distance from the limbus in different canine breeds. If the port for the infusion tubing (4 or 6 mm) is placed superiorly, it is positioned between the nasal and temporal ports. If it is placed temporally, it is placed 5–6 mm from the limbus on either side of the anterior ciliary vein.

After adequate cautery of the venous plexus, a horizontal mattress suture of polyester fiber (or 6-0 polyglactin) is preplaced for the infusion port. Alternatively, a sutureless infusion can be placed, which is preferred by the authors (Fig. 26.32A). The advantages of a sutureless infusion are speed, less need for cautery, and less bleeding. The disadvantages are it is possibly less reliable and outside the field of view (thus not monitored closely). This can lead to potentially serious complications of hypotension and therefore intraocular bleeding. One author (ARH) prefers to make an S shape in the tubing and then secure it to the drape (Fig. 26.32B). A 20-gauge microvitreoretinal blade is passed between the sutures and directed toward the center of the vitreous cavity, avoiding the crystalline lens. The flow is turned on for the infusion tubing to release any air, then shut off, and the tip secured in the port. An alternative to the horizontal mattress suture is a figure-of-eight pattern tied with a slip knot. This allows rapid closure of the infusion port at the end of the surgery. It is important that the tip (cannula) is inserted through the pars plana in cases where the retina is not detached, before the infusion of BSS is turned on, to ensure it is not under the choroid or retina. If the globe is indented with the cannula, the tip should be visualized by

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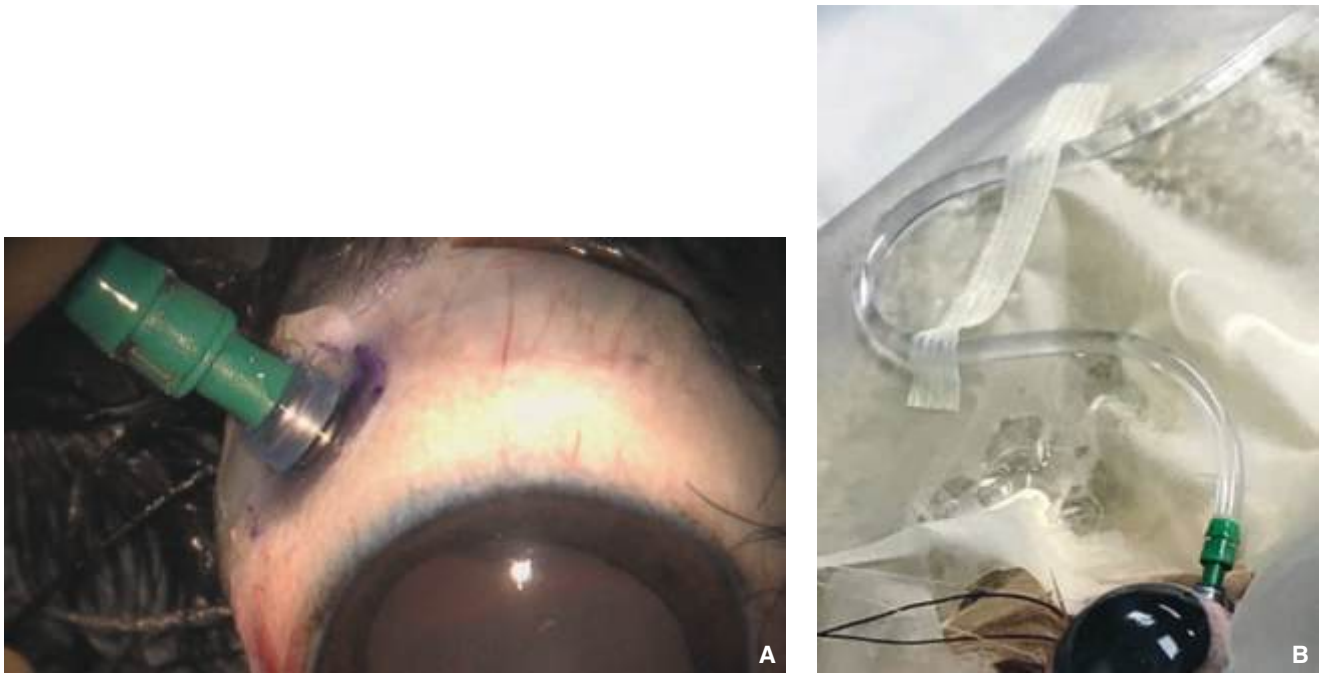


Figure 26.32 Sutureless infusion. **A**. Against globe. **B**. Sterile draping and tubing.

the surgeon. The two other ports are made nasal and temporal to the infusion port approximately 160 degrees from each other. Narrower working distances decrease surgeon comfort and instrument range. The ports are closed with plugs until the surgeon is ready to insert the light pipe and the vitrectomy probe, except where valved cannulas are used and fluid loss is less of a concern. Using the nondominant hand, the surgeon inserts the light pipe into the globe. Instruments should always be directed posteriorly to avoid touching the lens. If a wide-angle viewing system (contact or noncontact) is used, inversion and focusing are now performed. The vitrectomy probe can now be inserted and vitrectomy started.

If a cataract is present, it can be removed by the referring veterinarian prior to reattachment surgery, or it can be removed by the retinal surgeon as a dual procedure. For simultaneous cataract removal and PPV, routine phacoemulsification can be performed before the eye is proptosed or via the pars plana approach with the phacofragmatome. The lens equator can be penetrated with the tip of the fragmatome needle, which is then placed in the center of the lens nucleus. With the use of high vacuum pressure and low phacofragmentation power, first the nucleus is removed, then the cortex. If during phacofragmentation of the nucleus "lens milk" appears, especially in hard lenses, the phacofragmentation needle is probably plugged and must be removed from the eye and backflushed to clean the needle. If lens fragments accidentally fall posteriorly, they can be removed after the vitrectomy. The fragments can be attached to the phacofragmentation tip using only vacuum suction and then emulsified away from the retina. As mentioned previously, fragmentation should be done with low power (5%–10%) to prevent blowing fragments into the retina. Fluorocarbon liquids are also helpful in floating lens fragments for easier removal. Most canine vitreoretinal surgeons routinely perform cataract surgery with an anterior approach and IOL placement, and then proceed with three-port PPV.

RDs present commonly in canine patients that have undergone prior cataract surgery. When cortical regrowth or lens capsular opacities are present that prevent proper viewing, they must be removed. Soft cortical regrowth can be removed with the vitrector, but will be more difficult with small-gauge instrumentation. Dense capsular opacification often requires removal with end-gripping forceps (Fig. 26.33A) and scissors (Fig. 26.33B, C) designed to fit through variable-sized cannulas such as those made by Alcon Grieshaber (Schaffhausen, Switzerland). Care must be taken not to disrupt the capsular integrity to the extent of causing IOL instability. Small foreign bodies can also be removed with end-gripping forceps (Fig. 26.33D).

The eye can be easily manipulated with the two instruments. It is best to keep the light pipe just inside the globe at the edge of the pupil and directed posteriorly to optimally illuminate the vitreous cavity. Removal of the vitreous occurs in small pieces (Fig. 26.34). It is desirable to keep the vacuum pressure low (below 150 mmHg), and when closer to the retinal surface the vacuum pressure should be lowered further (to 80 mmHg). By increasing the cut rate and decreasing the vacuum pressure, there is less tendency to draw the retina into the tip. The cutting port on the vitrectomy probe should always face away from the retina. Vitrectomy probes

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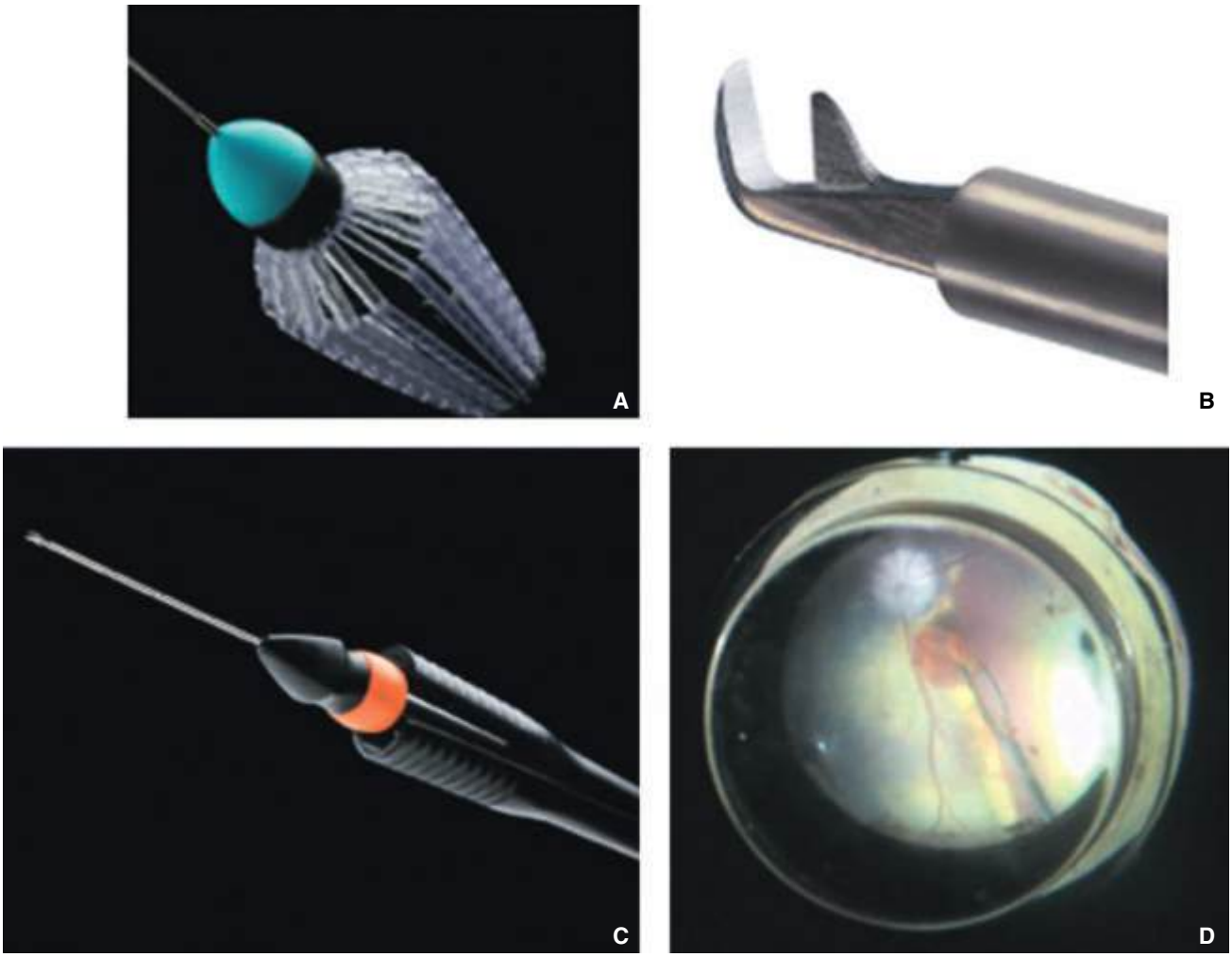


Figure 26.33 Surgical equipment. **A.** 25-gauge end-gripping forceps (Alcon Laboratories, Fort Worth, TX, USA). **B**. Tip design of vertical scissors (Alcon Laboratories). **C**. 23-gauge intraocular scissors (Alcon Laboratories). **D**. Removal of intraocular foreign body using 23-gauge end-gripping forceps.

have recently been engineered with the port opening 0.15 mm closer to the tip, enabling the surgeon to work closer to the retina. The duty cycle (time when the port is open) should be adjusted depending on whether the surgeon is performing the core vitrectomy or shaving the vitreous base or close to the retina. When cutting close to the retina, the surgeon may find it necessary to keep the tip of the light pipe close to the vitrectomy probe to help prevent aspirating the retina into the cutter.

Approximating the vitrectomy probe and light pipe may help outline very clear, indiscernible vitreous. If it is difficult to identify clear vitreous, an injection of triamcinolone (0.1 mL plus 0.3 mL BSS) into the vitreous cavity will become suspended within the vitreous matrix, making identification easier. In most cases of giant retinal tears in dogs, there will be numerous blood clots mixed with the vitreous. It is more difficult to remove the peripheral vitreous (base) than the posterior vitreous, especially in the phakic animal. In these animals, it is best to cut the vitreous base and any torn retina on the same side as the port for the vitrectomy probe. This area can be illuminated indirectly, to avoid touching the lens (Fig. 26.35); then the procedure is reversed for the opposite side. On a proptosed globe, the surgeon can indent the sclera opposite the cutting port with his or her finger to bring the vitreous base in view. However, with this maneuver, care must be taken not to touch the large canine lens. A wide-angle viewing system is very helpful in removing the vitreous base; however, scleral depression may still be required. For more chronic RDs, the peripheral retina may be fibrotic and scroll inward. It is necessary to perform a peripheral retinectomy of the devitalized, fibrotic retina, because it will not be amenable to flattening with PFCLs (Fig. 26.36).

Once the vitreous has been removed, the retina can be gently manipulated using the tip of the light pipe and the vitrectomy probe. Occasionally, a 360-degree RD will be rotated at the optic disc and require gentle rotation before

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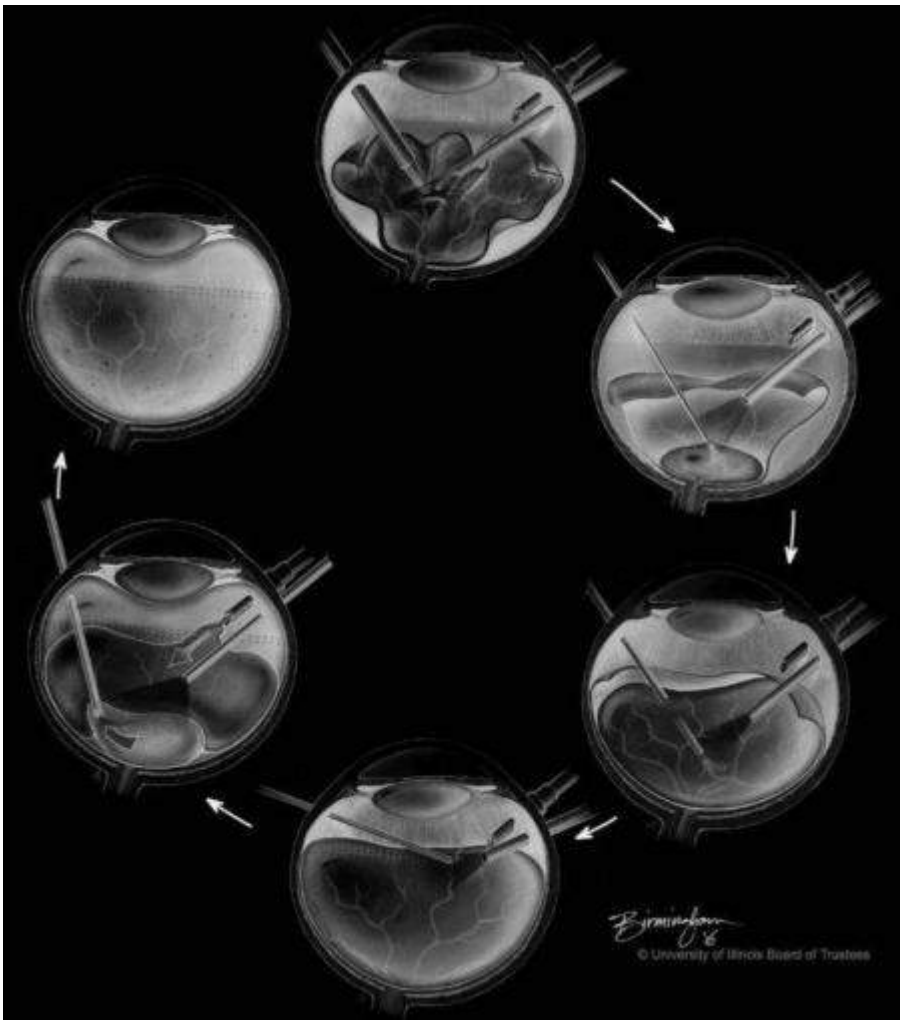


Figure 26.34 Procedure for surgical reattachment of 360-degree retinal detachment. **A**. Vitreous and any traction bands are removed. **B**. Perfluorocarbon liquid (PFCL) is injected slowly via a soft-tipped silicone needle over the optic nerve. **C**. Vitreous cavity is filled to completely flatten the retina back to a normal position. **D**. Laser application near ora serrata, also randomly, and around any holes or tears. **E**. Silicone oil infusion with passive removal of PFCL. **F**. Complete silicone oil fill. (Copyright 2005, University of Illinois Board of Trustees. Used with permission.)

attempting to flatten with PFCLs. As the retina is manipulated, one often will uncover retinal holes or radial tears (those that extend from the optic nerve and tear peripherally). For small tears or dialyses (less than 90 degrees), the retinal configuration will be released as long as a complete vitrectomy has been performed. As previously mentioned, more than 75% of canine retinal surgeries involve tears over 270 degrees; therefore, PFCL will be needed to flatten and hold the retina in position.

The PFCL is injected slowly via a soft-tipped silicone needle over the optic nerve in the surgeon's dominant hand (Fig. 26.37A; see Fig. 26.34B, C). It is important to maintain the PFCL in a large bubble, especially if retinal holes or radial tears are present, in order to prevent subretinal migration. It also is important to inject the PFCL under any retinal flap in contact with internal limiting membrane. It may be necessary to rotate the eye so the PFCL stays under the flap. This same rotational procedure is needed too when large retinal holes are present, to keep PFCL from entering the holes. If PFCL migrates under the retina (sometimes occurring in multiple bubbles), it must be removed via a flute needle.

After PFCL injection, the retina should slowly begin to unravel and flatten against the eye wall. If there is resistance to the injection of PFCL, it is probably because of an incomplete vitrectomy procedure. At this stage, the vitrectomy probe is reinserted, and residual vitreous is removed. Valved cannulas can also cause greater resistance when PFO is injected, and a coaxial dual-bore cannula can be employed (see Fig. 26.26). As shown in Fig. 26.26, the BSS will travel

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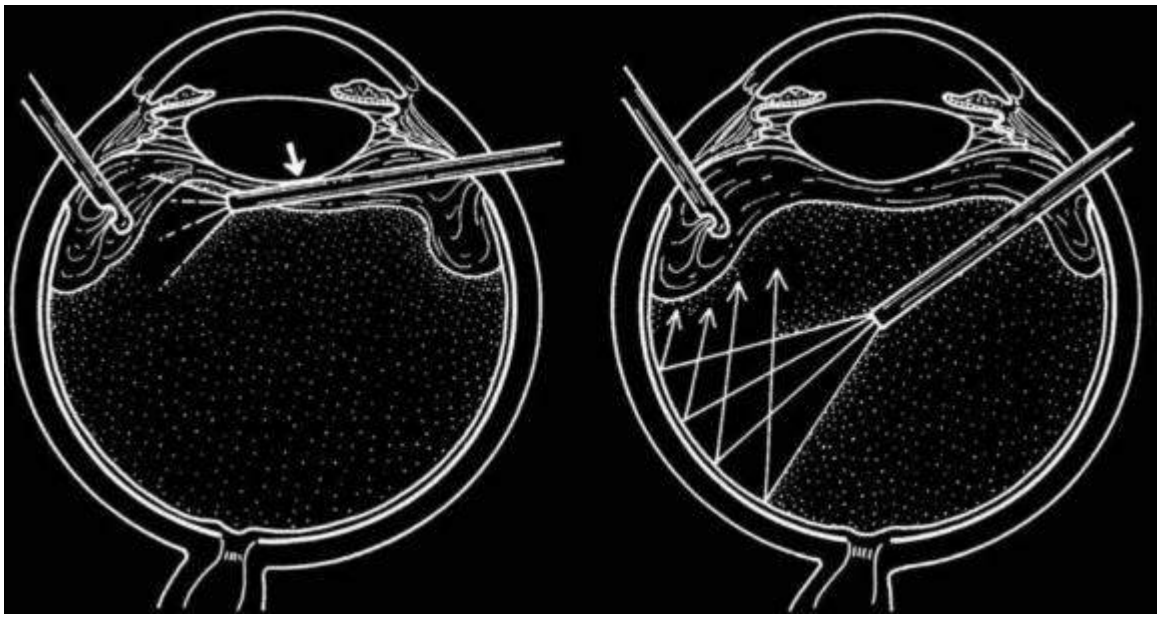


Figure 26.35 **A**. Lens touch with endoilluminator while vitreous is illuminated on the opposite side of the eye. **B**. Indirect illumination of vitreous avoids lens touch. (Reproduced with permission from Abrams, G.V. & Werner, J.C. (2001) Posterior segment vitrectomy. In: *Manual of Retinal Surgery* (ed. Packer, E.J.), 2nd ed., pp. 69–104. Woburn, MA: Butterworth-Heinemann.)

through the outer lumen of the cannula and out through a small opening on the outside of the eye near the yellow connector. As the retina flattens, it is not uncommon to have folds still present. These can be gently flattened using the soft silicone-tipped needle (Fig. 26.37B). If, during the PFCL infusion, membranes are noted that prevent the retina from flattening, PFCL infusion is stopped, and the membranes are removed. Occasionally, a relaxing retinotomy is necessary to enable flattening of the retina (see Fig. 26.36). This can be done with the vitrectomy probe, and endocautery should be performed to avoid bleeding, but usually this area of retina has poor viability. Endocautery can be performed with unipolar diathermy along the path of the intended retinotomy. PFCL is often useful in this manner of membrane removal when it is difficult to stabilize the retina. As the retina is flattened, any fluid under the retina will be forced out anteriorly.

The eye is now ready for endolaser photocoagulation. Either diode or argon lasers work well for laser retinopexy. Power and time should be set at the lowest settings needed to produce a burn. Settings will vary depending on the amount of pigment present, the angle of incidence required, and the precision of the focused laser light. Two rows of noncontiguous burns near the ora ciliaris retinae for 360 degrees are applied (see Fig. 26.35D). Laser should be applied around all holes (Fig. 26.38) and tears as well as minimal scatter in all four quadrants. In subalbinotic animals, it may be necessary

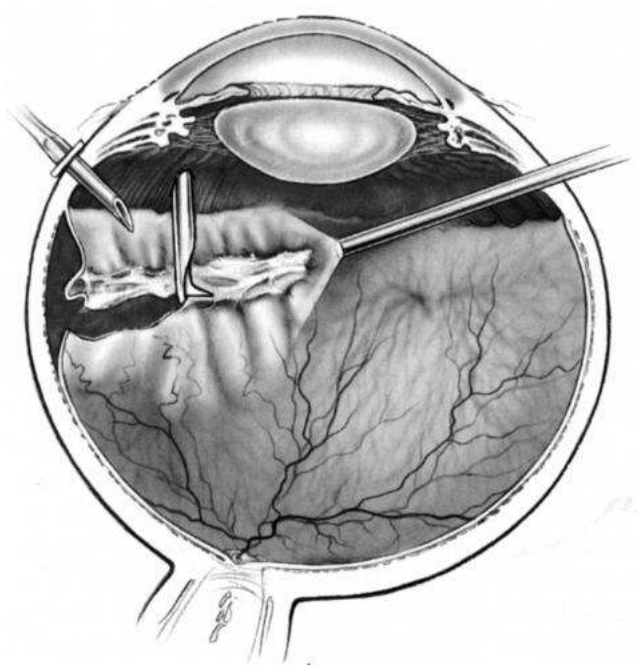


Figure 26.36 Relaxing retinotomy. When vitreoretinal traction cannot be relieved, a retinotomy can be performed to help mobilize the retina and facilitate reattachment. (Reproduced with permission from Chang, S. & Lopez, J.M. (1999) Vitreous surgery. In: *Vitreoretinal Disease: The Essentials* (eds. Regillo, C.D., Brown, G.C., & Flynn, H.W.). New York: Thieme Medical Publishers.)

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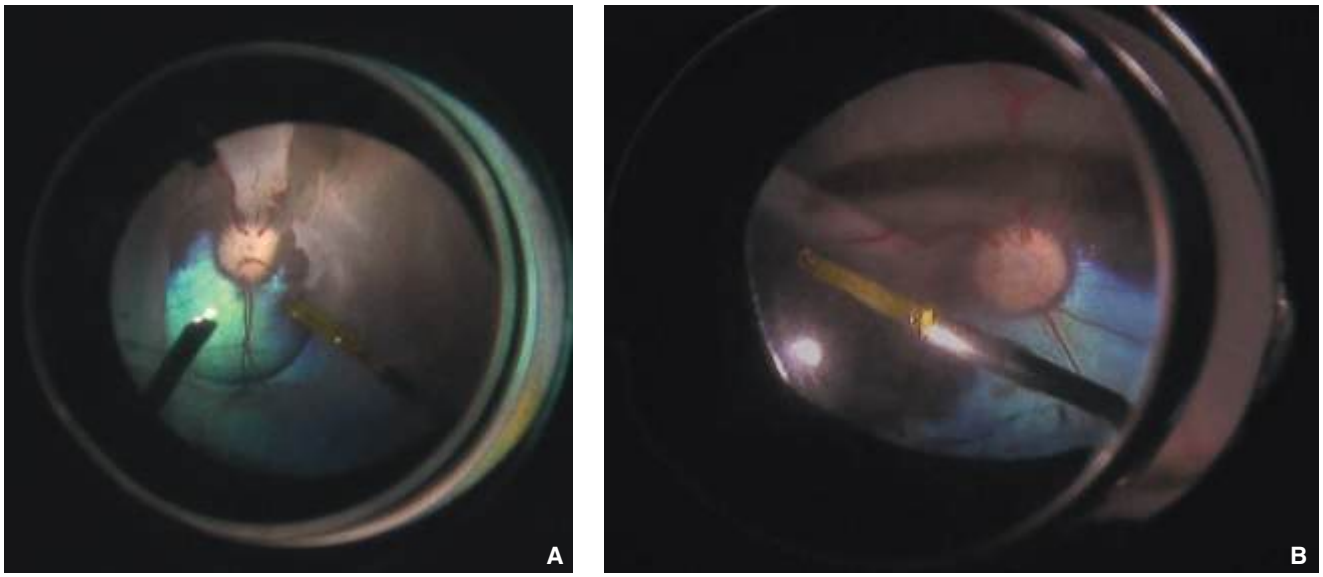


Figure 26.37 Canine retinal surgery using perfluorocarbon liquid (PFCL). **A**. Early injection of PFCL. **B**. Flattening a retinal fold under PFCL, with a soft-tipped silicone sleeve.

to apply cryosurgery transsclerally or to use an argon laser. The final step is to replace the PFCL with silicone oil (see Fig. 26.34E) or with air. PFCLs are very toxic to the retina and therefore must be removed. For smaller tears, a PFCL–air exchange followed by an air–gas exchange can be done. An expandable gas – either C_3F_8 or SF_6 at nonexpandable concentrations (16% or 20%, respectively) – can be used.

For larger tears, silicone oil has been more helpful in preventing retinal slippage than has air. When the PFCL is exchanged with air, the edge of a giant tear can slip (slide posteriorly), creating a retinal fold. This slippage is produced by fluid collection behind the anterior retina that may not be fully attached by the PFCL. As more air goes in the eye, it forces the fluid more posteriorly, causing more slippage and folds (Abrams & Werner, 2001). In a reported series of retinal surgeries in the canine for giant retinal tears, stainless-steel tacks were placed throughout the retina, choroid, and sclera near the peripheral retina in an attempt to prevent retinal slippage (Vainisi & Packo, 1995). Tacks have been used historically in human vitreoretinal surgery. In most cases, some or all of the tacks dislodged into the anterior chamber and had to be surgically removed by one of the authors (SJV). We prefer a direct PFCL–silicone oil exchange for all large tears. Silicone oil (5000 centistokes) is injected through the infusion cannula using an automated infusion pump. This PFCL–silicone oil exchange is a critical maneuver in the dog, because any hypotony during this transfer can result in expulsive choroidal or retinal hemorrhages. The infusion tube is temporarily clamped, and the intravenous line of BSS is exchanged for the silicone oil syringe. The infusion line is opened, and the silicone oil injection is started (see Fig. 26.34E). Figure 26.39 is an intraoperative photograph of early automated silicone oil infusion. The Charles flute needle and handle are placed just above the optic disc and will passively evacuate the PFCL. Again, in the dog, it is important to avoid hypotony during this exchange. The PFCL removal should be a passive process while the silicone oil is actively filling at a steady rate. The interface between the silicone oil and PFCL will become obvious as the PFCL becomes a smaller sphere over the posterior pole. After the silicone oil fill, it is important to examine the eye carefully to be sure all drops of PFCL have been removed (Fig. 26.34F).

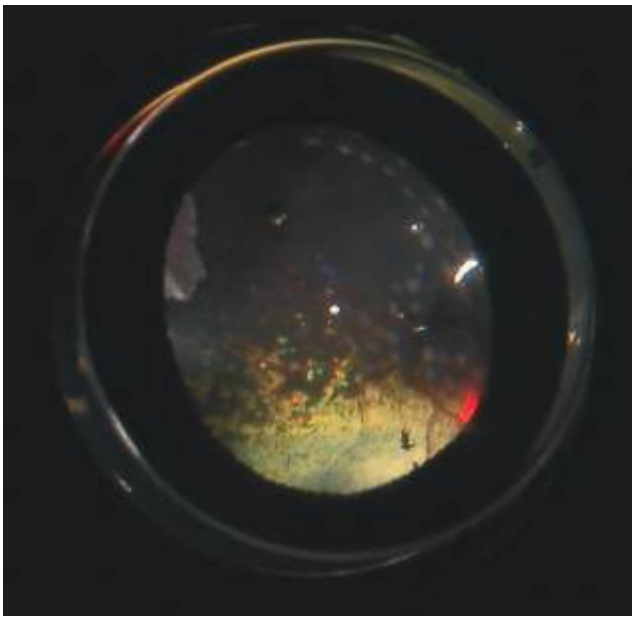


Figure 26.38 Endolaser retinopexy of a peripheral retinal hole.

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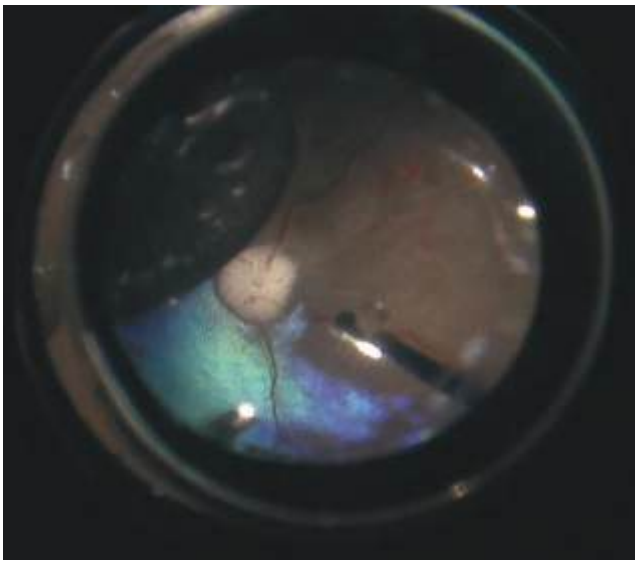


Figure 26.39 Intraoperative view of early silicone oil automated infusion.

The nasal and temporal ports are closed first with 7-0 polyglactin sutures using a three-throw pattern; then the infusion port is closed with either a similar pattern or the figure-of-eight pattern previously discussed. The conjunctiva is closed with 7-0 polyglactin sutures, and the globe reposited. After the canthotomy is closed, a subconjunctival antibiotic is given and a temporary tarsorrhaphy is placed. The tarsorrhaphy can be removed 1 week postoperatively. Corneal coverage is particularly necessary in brachiocephalic breeds with shallow orbits, as corneal erosions secondary to exposure are not uncommon.

Transconjunctival Sutureless Vitrectomy

Pars plana vitrectomy using sutureless incisions has been reported in the literature over the past 15 years (Chen, 1996; Fujii et al., 2002a, 2002b; Hilton et al., 2002; Jackson, 2000; Josephberg, 2003; Kwok et al., 1999; Milibak & Suveges, 1998; Rahman et al., 2000). Fujii et al. (2002a, 2002b) reported the use of a 25-gauge transconjunctival sutureless vitrectomy (TSV) system. Purported advantages of the sutureless, narrow-gauge system include less trauma to the eye, reduced postoperative inflammation, less astigmatism, greater patient comfort, and possibly a faster recovery (Ibarra et al., 2005). Sutureless vitrectomy may, however, present theoretical risks of postoperative vitreous incarceration, hypotony, endophthalmitis, or retinal traction (Lam et al., 2003; Meyer et al., 2003). Newer techniques such as beveled incisions with linear trocars result in smaller incisions and have helped reduce the chances of wound leakage and bacterial entry. If it is obvious that a wound is leaking or may leak, then a partial-thickness suture should be placed through the conjunctiva and sclera.

The 23-Gauge Pars Plana Vitrectomy for Repair of Retinal Detachment

One of the authors (JCW) prefers the 23-gauge TSV technique in the canine, described here. Not only has 23-gauge surgery made a huge difference in the ability to repair RD in the canine species, it also has allowed vitreoretinal surgeons to work on an eye without first proptosing it from the orbit. The original idea behind globe proptosis was to allow adequate room and exposure for an extensive peritomy and construction of the two 20-gauge working ports and the infusion line, which had to be sutured into place. With the advent of 23-gauge trocars, a peritomy is no longer required, and adequate exposure can be achieved, if necessary, by performing a lateral canthotomy and with use of an eyelid speculum. This approach allows surgery to be performed in all canine patients, whereas in the past, only dogs whose eyes could be proposed were adequate surgical candidates.

Cases that undergo 23-gauge surgery heal faster with less discomfort to the patient.

Because no peritomy is performed, the conjunctiva remains in an almost pristine form, which could be important if other surgeries such as a glaucoma filtering valve are necessary later for any reason. The smaller-gauge surgery improves fluid dynamics in the eye and increases safety during work close to the retina. Although 23-gauge vitrectomy may be slightly slower than 20-gauge vitrectomy, most dogs have a rather liquified vitreous, regardless of whether their detachment is primary or secondary; hence, vitrectomy is accomplished in an expedient fashion in almost all cases. By their nature, 23-gauge instruments are more flexible and do warp more easily than 20-gauge instruments.

First introduced by Claus Eckardt (2005), the 23-gauge transconjunctival vitrectomy technique is now the standard in both humans and dogs. The valved trocars maintain a closed system in the posterior segment, which reduces flow of BSS and lessens the chance of a decrease in IOP that could result in a choroidal hemorrhage or introduction of proteins into the aqueous or vitreous humor. Safety is one of the major advantages to this system. Time reduction in the operating room is another benefit. Additionally, 23-gauge surgery has allowed vitreoretinal treatment of cats, whose eyes, of course, cannot be proptosed. Although RD is rare in the cat, vitrectomy may be useful in the treatment of aqueous misdirection syndrome as well as idiopathic uveitis.

The only instance in which 20-gauge vitrectomy is routinely performed is if a pars plana phacofragmentation is required. If cataract and RD are present, the lens must first be removed to allow visualization of the posterior segment. The lens can adequately be removed from an anterior approach; however, the author (JCW) finds it more expedient to remove the lens via a pars plana approach. The author still uses a 20-gauge phacofragmatome to accomplish this, requiring a small peritomy and creation of a 20-gauge sclerostomy via a microvitreoretinal blade. Another method is to

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perform the phacofragmentation with a 23-gauge phacofragmatome using the 23-gauge working port.

Surgical Technique

The patient is placed in dorsal recumbency, and the head is positioned with a restraint pillow. The eye has already had the lateral canthus clipped and has been aseptically prepared. It is advisable to employ neuroparalysis and ventilation, to bring the eye central. The author (JCW) uses topical tropicamide ophthalmic solution (Mydriacyl®, Alcon, Fort Worth, TX, USA) to dilate the pupil before induction of general anesthesia. A generous lateral canthotomy is performed, and a Castroviejo eyelid speculum is used to open the lids as far as possible. Ophthalmic calipers (again of the Castroviejo variety) are used to measure 5–6 mm posterior to the limbus, and the infusion line port is placed. One can place this port at either the 12 o'clock position or in the ventrolateral region. The latter area keeps the infusion line in a safer spot so that it cannot be accidentally interfered with during the surgical procedure. The 23-gauge trocar is inserted such that the blade is placed into the sclera, parallel to the limbus. The trocar is then rotated perpendicular to the limbus and directed at a 45-degree angle toward the optic nerve. It is introduced through the sclera and into the vitreous cavity with gentle twisting motions of the surgeon's hand until the base of the valve is flush with the conjunctival surface. The valve is then gently grasped with valve forceps or Colibri forceps, and the stylet is removed from the port. It is very important at this stage for the surgeon to view the posterior segment through the pupil, to ensure that the port is indeed in the vitreous cavity and not subretinal. A light pipe can be employed for increased illumination to aid in visualization. Once the surgeon is satisfied that the port is not subretinal, the infusion line can be placed into the port and the fluid line turned to the on position. The two working ports are now placed at 10 and 2 o'clock, as per the instructions for the infusion port.

Next, the viewing system is deployed and the microscope light is extinguished.

With his or her nondominant hand, the surgeon introduces the light pipe into the eye. The optic nerve head and retinal vessels are brought into focus. The surgeon should now zoom down and microadjust the focus, which will allow perfect focus at any magnification throughout the surgical procedure. After backing off the zoom, the surgeon focuses midvitreous. With the surgeon's dominant hand, the vitrector is introduced into the eye. The tip of the light pipe is held close to the tip of the vitrector to highlight the vitreous strands, and vitrectomy is commenced. In dogs with RD, vitrectomy is usually accomplished quickly, because the entire vitreous is often liquified, leaving only large strands and clumps of congealed collagen, pigmented cells, and old blood. Some patients will have clumps of vitreous so large that a 23-gauge vitrector may have difficulty removing them. In this instance, one may need to decrease the cut rate of the vitrector and increase aspiration.

If the entire vitreous is filled with blood, great care must be taken to go very slowly until one can see retinal vessels and know for certain where the retina is. Removing large vitreous hemorrhages can result in repeated bleeding. If this occurs, one should immediately increase the IOP, either by changing the IOP setting on the vitrectomy machine or by raising the BSS bottle on older machines. If this is not sufficient to stop the hemorrhage, PFO may be introduced into the eye to flatten the retina and tamponade the bleeding vessel.

Once all vitreous material has been removed from the posterior segment, which may be aided by the introduction of sterile nonpreserved triamcinolone to highlight remaining vitreous, one is ready to assess the state of the retina. Often veterinary ophthalmologists are faced with the worst kinds of RDs, because dogs are not presented for ophthalmic inspection with the same alacrity as humans. Thus, the retina may actually be twisted at its insertion at the optic nerve head. The retina must be rotated back to its normal orientation by a gentle twisting motion in the opposite direction. One of the authors (JCW) usually uses a light pipe in the left hand and a soft-tipped infusion needle in the right hand to gently slide and rotate the retina in small increments back to a normal position. Once the retina is untwisted, there may still be small folds in the retinal tissue, and these can be smoothed once again by using the soft-tipped cannula.

Because many of our patients have RD due to vitreous liquefaction and retinal tearing secondary to head-shaking behaviors, large radial tears may be present, especially in the inferior retina. The surgeon should try to align these torn edges as close together as possible. Because of contraction of the retinal tissue, exact repositioning may be impossible. Once the retina is repositioned as normally as possible, one should inspect the far periphery for adherent vitreous. This should be removed with the vitrector using as high a cut rate as possible and very low vacuum pressure. As time passes, adherent vitreous strands may have formed a fibrous membrane at the peripheral edge of the retina that constricts the funnel of the detached retina, thus preventing it from being able to fully flatten. This problem becomes apparent during final flattening of the retina with PFO, whereby the surgeon notes that the retina flattens to a certain point and not further, and PFO spills over the retinal edge and into the subretinal space. If this occurs, small retinotomies will need to be performed at the edge of the retina to release tension and allow complete flattening once the PFO has been removed from the subretinal space. Occasionally, fibrous tissue will be present on the retinal surface, extending inward from the periphery toward the optic nerve, and may create an area of retina that will not flatten at all. If this is the case, one may need to do a rather extensive retinectomy to remove this area

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of retina. The author usually uses the vitrector, striving to avoid large blood vessels. If bleeding occurs, simply increase the IOP as described previously and wait, or apply more PFO. It may be possible to peel this fibrous tissue, or PVR, from the retina, thus releasing the tension. However, specialized instruments are required such as microvitrectomy forceps and/or scissors. While these instruments are expensive and require practice, they can be very effective. It is recommended that bimanual instrumentation be used because, at this point, the detached retina may still be free floating. Use of only one instrument would make it difficult to apply much force to the intended tissue. With one instrument to stabilize the retina in the nondominant port and an active instrument in the dominant port, the surgeon will have no light. Therefore, one should insert a chandelier-type light (25-gauge Tornambe torpedo light, Oculus Surgical, Port St. Lucie, FL, USA) through the pars plana 5–6 mm posterior to the limbus and well away from the other ports. These chandelier lights plug into the illumination ports on the vitrectomy machine.

Once the surgeon has the retinal tissue free and unencumbered, definitive repositioning is performed using PFO. The active infusion on the vitrectomy machine is turned off, or in older machines the infusion line is clamped. The infusion cannula, which is attached to the PFO syringe by a short infusion line, is introduced through the dominant working port, leaving the light pipe in the nondominant port. The infusion cannula tip is placed directly over the optic nerve head, and PFO is gently introduced by the surgeon's assistant, who is holding the PFO syringe. Aggressive introduction of PFO can jet from the tip of the cannula and damage the optic nerve, or can actually tear a hole in the retina. Patience is needed while one is flattening a retina using PFO.

Since the PFO accumulates as a single bubble over the optic nerve, it will (because it is heavier than water) flatten the retina against the RPE and displace the fluid from under the retina to an epiretinal position. This fluid will now build up in the eye, greatly increasing IOP as the trocars are valved and do not allow reflux of fluid out of the eye until a certain pressure is reached. This can sometimes make it difficult to inject the PFO near the end of the flattening procedure. To overcome this, one must use a dual-bore cannula, which allows the BSS to egress up one bore while the PFO is ingressing through the other. This tiny instrument will make for a smooth transition from a posterior segment filled with BSS to one filled with PFO.

With the retina flattened and the eye filled with PFO, one may begin laser retinopexy. The author (JCW) uses a straight 23-gauge endolaser probe attached to a 810 nm diode laser. The laser is introduced in the dominant trocar after removal of the dual-bore cannula. Laser retinopexy for treatment of giant retinal tears, the most common detachment we see in dogs, has traditionally been done at the most peripheral retina in a double-row interlocking fashion. Turning the laser to repeat mode helps speed this procedure. Lasering the approximately 30 degrees directly beneath the dominant trocar is difficult with a straight laser, and the surgeon is instructed to switch the laser and light pipe so that the laser is now in the nondominant port and can more easily treat the non-laser-treated area. Alternatively, one may purchase a straight laser that will curve its tip once inside the eye, via a trigger on the laser handle piece. The author, however, has abandoned the peripheral double-row laser technique and now uses a shotgun pattern in the entire retina, avoiding the area centralis and horizontal streak. With either technique, one must also be sure to laser the edges of any radial tears to seal them against sliding or other movements.

Next, the surgeon removes the PFO and introduces silicone oil into the posterior segment. It is advisable for the surgeon to set up the silicone infusion set before beginning vitrectomy. If one uses a three-way stopcock, placed between the infusion line and tubing set, then one can have the silicone oil syringe connected ahead of time, making for a smooth transition to oil, simply by turning the stopcock. It is advisable to have a viscous fluid pump on the vitrectomy machine to push the silicone oil into the eye. If not, an assistant directly pushes the silicone oil from the syringe; however, this is more difficult and somewhat tedious. There is a range of silicone oil viscosities, from 1000 centistokes to 5700 centistokes. Each has its pros and cons. The author obtains a much smoother transition from PFO to oil if he uses 1000–1300-centistoke silicone oil; however, it is possible that this lower-viscosity oil may be more prone to moving into the anterior chamber than the 5000-centistoke oil. In veterinary medicine, the protocol for retinal reattachment surgery was developed at a time when active infusion was not a part of our armamentarium, and any sudden drop in IOP could result in choroidal hemorrhage. Thus, air–fluid exchange was abandoned in favor of direct PFO–silicone oil exchange. However, with the advent of active infusion technology, air–fluid exchange is possible (Dr. Chris Dixon, personal communication). Thus, as the surgeon is injecting silicone oil, which will spill into the eye from the infusion port, PFO is passively removed via a fluted needle. The tip of the flute needle is placed within the bubble of PFO just above the optic nerve head. Silicone oil will continue into the eye and spread slowly across the back of the lens until a complete meniscus is formed with PFO below and silicone oil above. As the oil continues to ingress, the surgeon must watch carefully for this meniscus. It may be difficult to see at first, and the novice surgeon is instructed to watch for a line slowly moving down the flute needle. Eventually this line is revealed as the top of the remaining bubble of PFO.

By continuing to slowly inject silicone oil via the foot pedal, the surgeon will see the bubble growing smaller. Egress of PFO can be controlled in two ways: by releasing the

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foot pedal or by closing the tip of one's finger over the flute hole on the handpiece. Do not rush this procedure and keep the tip of the flute needle within the bubble of PFO. Eventually, there will be just a tiny bubble of PFO left, and one last push on the foot pedal will inject enough silicone oil to run this up the flute needle. It is advisable at this point to do a full inspection of the posterior segment to ensure that all PFO has been removed. Retained PFO is toxic to the ocular tissues and can result in endophthalmitis and irreversible blindness.

Once the eye is stable, the retinal photoreceptors are in contact with the RPE, and the vitreous cavity is filled with silicone oil, all instruments are removed from the working ports, as is the chandelier light if one was used. Removal of the working ports can be done with specialized trocar forceps, or more commonly with Colibri forceps. The cannulae are designed to be self-retaining during surgical manipulations so they sometimes do not remove easily. If so, grasp the trocar with a forceps and, with the nondominant hand, grasp the conjunctiva 180 degrees from the trocar to stabilize the globe. Once both working trocars are removed, the surgeon should assess IOP using either a Tono-Pen™ applanation tonometer (Reichert Technologies, Buffalo, NY, USA) or a Terry-Barraquer™ tonometer (Ocular, Bedford, MS, USA). Silicone oil may be added or subtracted using the corresponding functions on the vitrectomy machine; that is, viscous fluid injection or viscous fluid aspiration.

Once satisfied with the IOP, the surgeon can remove the infusion line trocar. As each trocar is removed, bleeding may occur. These trocars have been placed directly through the scleral venus plexus. Avoid the temptation to apply pressure to the sclerostomies if bleeding occurs. Applying direct pressure will disrupt the architecture of the self-sealing sclerostomies created by the specially designed trocars, which may lead to leakage of silicone oil postoperatively. Also, direct pressure can force the blood to flow into the back of the eye, rather than harmlessly into a subconjunctival position, from which it will be resorbed in days to weeks. Some surgeons prefer to place sutures to close the scleral wound; however, the author (JCW) believes that this is unnecessary. The final step is to close the lateral canthotomy.

The 25-gauge TSV system has replaced the 20-gauge TSV surgery for all but the most complicated retinal surgeries for many MD vitreoretinal surgeons. In dogs, the 25-gauge TSV system lends itself well to the treatment of vitreal diseases such as nonclearing vitreous hemorrhage, vitreal degeneration, and chronic endophthalmitis.

Feline Retinal Reattachment Surgery

According to one author (ARH), feline retinal reattachment surgery is best suited for detachments of a congenital nature or secondary to lensectomy procedures. There are challenging adaptations to this surgery that deviate significantly from canine retinal reattachment surgery. Anatomic considerations include a deep orbital without an option to proptose, and very poor medial exposure. The intrascleral venous plexus in the cat is wider than that of the dog, and the pars plana is further posterior to the limbus (7 mm). To gain access to the posterior segment, cats are placed in a dorsal oblique recumbency, lying perpendicularly to the length of the surgery table so that the lateral canthus is at 12 o'clock. A wide lateral canthotomy is needed to gain exposure, with the infusion cannula placed between the working ports. Extra care must be taken not to disrupt the larger feline lens with instrumentation. The vitreous volume tends to be greater in the cat, so more silicone oil is needed. Successful retinal reattachment surgery can be achieved in cats with an understanding of the ocular anatomy and necessary surgical modifications. These modifications were also used to successfully place subretinal photovoltaic implants in cats (McCreery et al., 2020).

Endoscopic Pars Plana Vitrectomy with Perfluorocarbon Liquid/Silicone Oil Exchange

Endoscopic surgery is finding new purpose in the hands of the canine vitreoretinal surgeon. The endoscopic visualization lends a view of the posterior segment not possible with standard vitrectomy. The view can be described as "inside-out" as opposed to "outside-in." One author (ARH) has likened standard vitrectomy to snorkeling with a face mask, and endoscopic vitrectomy to scuba diving.

Endoscopic vitrectomy can be used in the setting of anterior segment–based media opacities, which would diminish the surgeon's view and restrict the ability to reattach the retina. Conditions that lend themselves to the endoscopic approach, because of a diminished view, are significant anterior or posterior synechia, a pupil that will not dilate with mydriatics, endophthalmitis, corectopia, corneal melanosis, postoperative corneal grafts, or corneal mineralization.

The sclerotomy for the standard endoscope port requires a 19-gauge microvitreoretinal stab incision. The probe moves three-dimensionally inside the eye and replaces the nondominant hand where the light pipe is typically held for standard vitrectomy. The straight endoscopic probe is recommended for vitrectomy work, as it is more intuitive to use. When using the endoscope, lighting levels are adjusted depending on the work performed. Higher illumination is needed when the endoprobe is retracted. Low illumination eliminates whiteout on the video monitor and is ideal for closer work. Other variables beyond the X–Y–Z position for using a camera in the eye that contribute to the learning curve are the presence of torsion and vector distance. Once mastered, the surgeon can proceed with vitreous removal,

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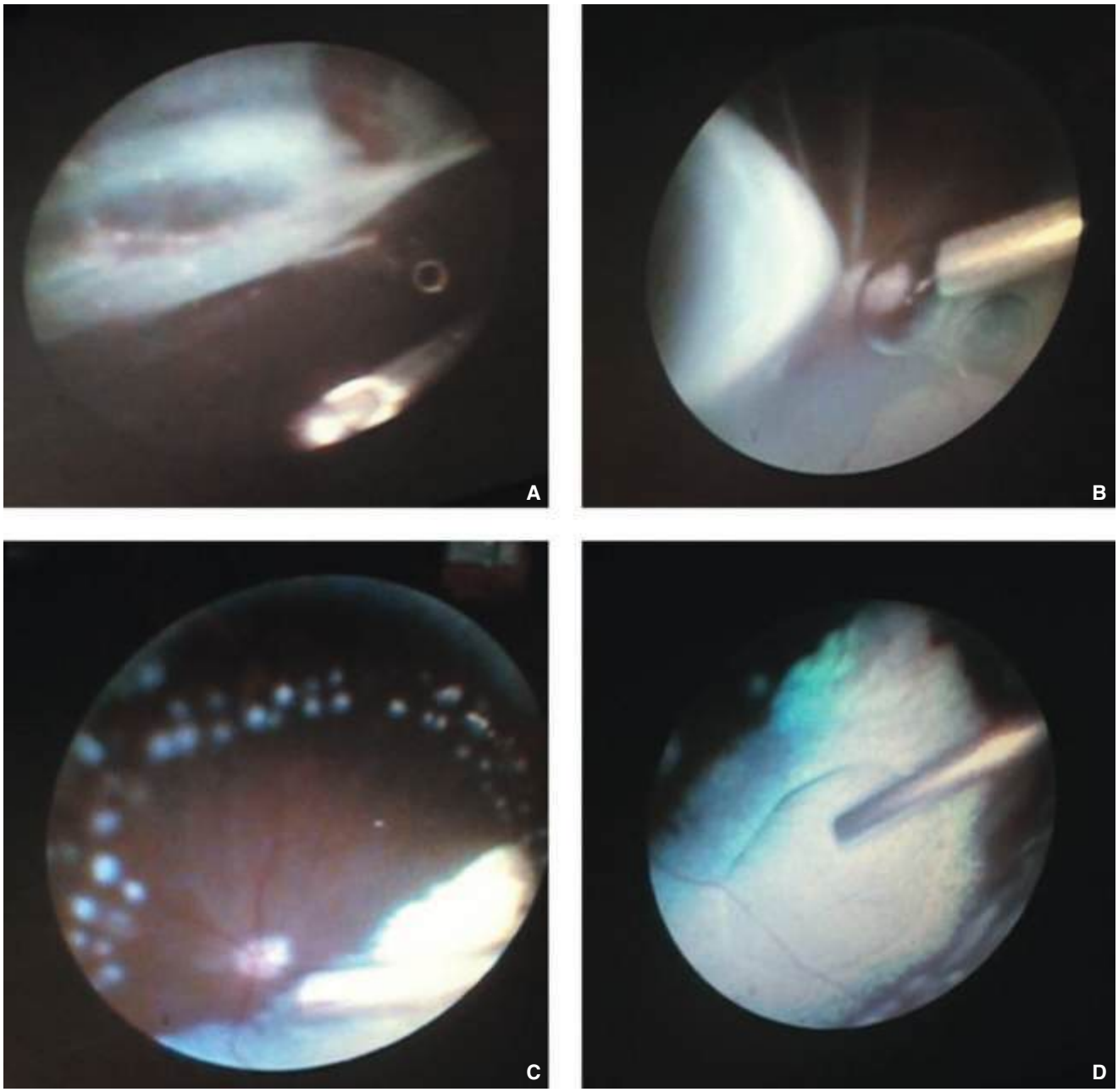


Figure 26.40 Endoscopic vitrectomy and retinal reattachment in a dog, viewed from a monitor. **A**. Vitreous removal. **B**. Perfluorocarbon liquid (PFCL) injection. **C**. Endolaser treatment. **D**. Silicone oil fill and PFCL removal.

PFCL injection, endolaser, and silicone oil fill with excellent viewing potential (Fig. 26.40). One author (ARH) prefers 20-, 23-, or 25-gauge endolaser in the dominant hand for the retinopexy stage of surgery, as the laser from the endoscope creates excessive chorioretinal damage from the larger spot size.

Endocyclophotocoagulation via the Pars Plana

One author (ARH) prefers to perform endocyclophotocoagulation surgery for treatment of glaucoma via the pars plana in pseudophakic patients, using a 23-gauge system. A sutureless infusion is placed with three-valved ports. Vitrectomy is used to remove anterior traction or membranes, and the endoscope can be directed through any of the three ports for excellent visibility and ciliary body coverage. This technique also preserves the anterior segment and does not require a viscoelastic to inflate the ciliary sulcus. The 23-gauge endoscope also allows for a simultaneous retinopexy without the large burns that result from the larger, 19-gauge probe.

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Success of Retinal Detachment Repair

Experimental Rhegmatogenous Retinal Detachment

Experiments on RDs in the rabbit, nonhuman primates, and the cat provide some information on the retina's ability to recover from detachment, which influences the functional success of vitreoretinal surgery. Studies in the rabbit showed that retinal degeneration occurs more rapidly if the retina is more elevated (i.e., bullous detachments) and when subretinal fluid is hemorrhagic or exudative (inflammatory) compared with serous (Erickson et al., 1983; Glatt & Machemer, 1982). Presumably, this relates to the limits of the diffusion of oxygen and nutrients from the RPE and lamina choriocapillaris through a subretinal space that is wider or is filled with exudates or red blood cells. Possibly most important to visual recovery is the duration of detachment (Erickson et al., 1983) and recovery of acuity (Guerin et al., 1989), with longer durations producing a progressive decline in final acuity. Results of experimental studies in animals support this latter finding.

In most species studied, the primary changes occurring in the first week after RD are marked outer segment degeneration, cystoid edema in the inner retinal layers, RPE dedifferentiation (i.e., truncation or loss of microvilli and disappearance of melanin), and hypertrophy of RPE cells (Anderson et al., 1983; Erickson et al., 1983; Guerin et al., 1989; Kroll & Machemer, 1969a, 1969b; Machemer & Norton, 1968). The owl monkey is a rod-dominant species with an area centralis but no fovea, which is somewhat similar to the situation in the dog and cat. After RRD in the owl monkey, most photoreceptor outer segments appear disorganized and degenerate within 1 week. Phagocytic cells move into the subretinal space to phagocytize the material, and by 4 weeks, cystic spaces are seen in the inner and middle retinal layers (Kroll et al., 1968).

Subsequent investigators using this monkey model studied the retina's ability to recover after being detached for 4 weeks; they found that after surgical reattachment, prompt and progressive reversal of the atrophic and disorganized outer segments occurred, and that cystoid retinal spaces disappeared (Kroll & Machemer, 1969a). Marked loss of photoreceptor nuclei in the outer nuclear layer was not reported. In a Rhesus monkey model (a foveate species), similar changes were observed (Kroll & Machember, 1969b). After 1 day of reattachment, outer segment material was regenerating, and by 1 month after RRD, the outer segment–RPE interface was often indistinguishable from control retinas. In other studies on macular detachment in Rhesus monkeys, good recovery followed RD that was relatively shallow and of short duration (1 week; Guerin et al., 1989).

Studies in owl monkeys with RRD revealed that the ERG amplitude was abolished by 1 week after total RRD, but with partial RRD some response could be elicited (Kroll & Machember, 1969a). Retinas reattached after 4 weeks had a small ERG, which appeared as early as 17 hours, but more typically approximately 1 week after reattachment. The b-wave amplitude and threshold progressively improved over the subsequent 12-week follow-up. The authors did not comment on whether values returned to normal, but examination of their data suggests that good recovery of b-wave amplitude occurred. All these findings in the owl monkey suggest that a fair prognosis may be given in the dog for a successfully reattached retina with an RD duration of 4 weeks or less.

In the cat, retinas were surgically detached for 30 minutes to 14 months (Erickson et al., 1983). Results indicate that the longer the duration and the greater the height of RDs, the greater the occurrence of cell death. By 1 hour after detachment, outer segment disorganization and early hypertrophic changes in the RPE were evident. By 2 weeks, most synaptic terminals were necrotic or in the process of retracting. After 4 weeks, the photoreceptor nuclei had decreased to approximately 40% that of control areas. At 50 days, synaptic contact between the photoreceptors and second-order neurons was essentially absent. Müller cells proliferated and hypertrophied to fill the spaces left after loss of nuclei in the outer nuclear layer. Müller cells also protruded into the subretinal space, forming layers of cell bodies between the RPE and retina. By 14 months, the retina appeared as an astroglial scar (composed of Müller cells), with no identifiable retinal cells being evident (Erickson et al., 1983).

Clinical Rhegmatogenous Retinal Detachment

Successful reattachment of the retina does not necessarily imply visual success. In the earlier section "Criteria for Vitrectomy," we mention that many of our patients, if their retinas are reattached within 4 weeks, have a reasonable chance of achieving some functional vision. We are referring to blind animals with giant tears, which are often 360 degrees. Four weeks is the time used arbitrarily, as we have no way of definitely knowing how long a dog's retina has been detaching. Dogs can navigate well with limited vision. It is not uncommon for a veterinary ophthalmologist to encounter an owner who is unaware that his or her pet is blind, since the dog can adjust to its environment. Many of our retinal cases have likely been detaching for weeks or months before the retina finally breaks loose and the animal experiences a sudden loss of vision.

Obviously, those animals whose retinas completely detach earlier than later should recover better vision after reattachment surgery. Human patients who receive the same type of vitreoretinal surgery we perform in dogs are usually complicated cases. They are frequently second or third surgeries with PVR, proliferative diabetic retinopathy, giant tears, or

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trauma. The vision before surgery is usually very poor, often hand motion or worse. Although the anatomic success is good in humans – well over 90% reattachment – the visual success is considerably lower, with only a very small percentage achieving 20/50 visual acuity (Ferrone et al., 1994; Fiderman & Schubert, 1988; Lichter, 1988). On the other hand, our canine cases are usually first-time retinal surgeries. In those animals with RRDs secondary to vitreous degeneration (50% of cases), if operated on early (within 4 weeks), the surgeries are anatomically successful 90%–95% of the time, with a visual success rate of 85% (Fig. 26.41). For more complicated cases, such as those secondary to vitreoretinal dysplasia, occasionally seen with PVR, or those secondary to cataract surgery or trauma, the anatomic success rate is closer to 80%, with a 70% visual success rate. The extent of globe trauma from bite wounds or blunt force varies considerably in dogs. It is not uncommon for us to see choroidal detachments with RD following trauma. For those cases, anatomic success is 50%, with a visual success rate less than that. In some cases, choroidal drainage may be necessary, which is approached via a scleral microincisional cutdown. In a reported series of more than 500 cases of canine RRD, a reattachment rate of 90% was achieved, with vision in 76% of animals (Vainisi & Wolfer, 2004). In two other large series of retinal reattachment surgery, retinal reattachment rates of 95% and 99% were achieved, and vision returned in 73% and 90% of cases, respectively (Nadelstein, 2010; Steele et al., 2012). Onset of vision can occur as early as 24 hours or as long as several weeks after surgery. Most cases regain vision within 10–14 days. Again, the sooner the reattachment is done, the better the chance of good vision. Because animals can adapt to their environment, we can only speculate that the range of visual success is anywhere from 20/100 to light perception. It has been reported that normal vision in the dog is approximately 20/65 (Miller & Murphy, 1997). Although some dogs appear to see normally postsurgically and both their fundus findings and ERG studies appear normal, it would be presumptuous for us to claim 20/65 visual acuity. The goal is for dogs to have functional vision, characterized by the ability to return to normal activity and have an improved quality of life. If they have their former personality restored and are able to recognize their owners, then we should be able to call the procedure a success.

Retinal Prosthesis

Retinitis pigmentosa, and its variants, is one of the most common and, as yet, untreatable forms of blindness. The canine and feline species also are commonly afflicted with heritable degenerations of the retina. Many gene defects have been discovered in the inherited retinal degenerations and are a common and devastating condition in both humans and canines that results in premature degeneration of the retina and loss of photoreceptors. In dogs, treatment of individual cases is not yet possible, and most of the effort to reduce the effect of these diseases has centered on genetic eye testing programs and selective breeding. Recently, gene therapy has been successful in reversing retinal degeneration in one heritable form in the dog (Aguirre, 2004; Ford

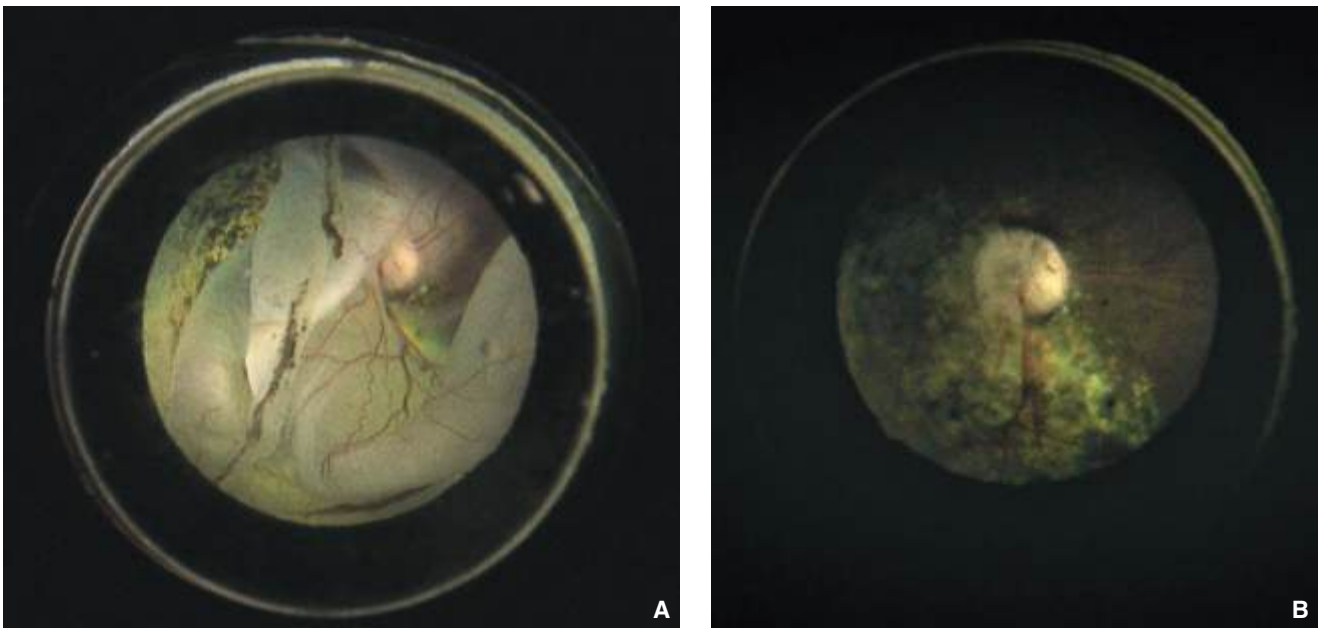


Figure 26.41 Retinal detachment surgery on a giant retinal tear. **A**. Before surgery. **B**. After retinal detachment surgery.

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et al., 2003; Narfström et al., 2003). Nevertheless, retinal degeneration remains a devastating disease that can have a huge emotional impact on humans and their pets alike.

Recent technological advances have made the concept of a retinal prosthesis possible. The first indication that the inner retina possibly could be stimulated even if the photoreceptors were damaged came about with the discovery of the electrical-evoked response (Potts et al., 1968). Stimulation of the retina with electric current produced the sensation of light (phosphenes) and elicited perception of light in patients with retinitis pigmentosa. Work was then done to document cortical visual activation by microelectrical stimulation of the retina (Humayun et al., 1995). This research has ushered in vast amounts of research into determining the best materials and the best anatomic placement of an artificial photoreceptor array. Much of this initial work has been animal based, using rats (Eckhorn et al., 2001), rabbits (Humayun et al., 1994; Nadig, 1999; Walter & Heimann, 2000), sheep (Kerdraon et al., 2002), dogs (Majji et al., 1999), cats (Hesse et al., 2000; Schanze et al., 2002), and miniature pigs (Laube et al., 2003). It would be only fair, then, that this technology should someday benefit pets with retinal degeneration. In this spirit, we give a short overview of the fascinating advances that have been made in restoring vision to those with retinal degeneration.

The first report of the retinal prosthesis concept was by Humayun et al. (1994). They concluded that multifocal electrical stimulation of the retina might be possible to provide some vision to those with outer retinal degeneration. As well as the basic research done in animals to look at various anatomic and physiologic questions surrounding the use of a retinal prosthesis, early research was done in human volunteers that determined that light sensation could be achieved with electrical stimulation of the retina (Humayun et al., 1996). This technique has been improved, and testing has been done with permanently implanted microelectrode arrays (Humayun et al., 2003). At this time, there are basically two designs being studied: subretinal and epiretinal prosthetics (Margalit et al., 2002). With the epiretinal prosthesis, images are taken with a camera and transmitted to an encoder, and the retina is then electrically stimulated by the epiretinal prosthesis. The epiretinal implant varies with the type of camera components and their location, either intraocular or extraocular (Loewenstein et al., 2004). With the subretinal implant, the microphotodiode array, driven by incident light, directly stimulates the outer retinal surface (Chow et al., 2004). When light is absorbed by the microphotodiode, it is converted to electricity. Each photodiode acts like an artificial photoreceptor receiving ambient light and converting it to an electrical response (Chow & Chow, 1997; Zrenner et al., 1997). The electrical response may then act to stimulate adjacent nerve cells, such as bipolar cells, and the impulse is forwarded via the optic nerve to the brain. Animal experiments with both types of implants have shown that local activation of the visual cortex can be achieved with stimulation currents and charge transfers that are in a biocompatible range. Initial trials in human subjects have shown that visual precepts can be achieved. It is hoped with this clinical approach that ambulatory vision can be restored to otherwise untreatable degenerative diseases of the retina (Walter, 2004).

Despite intense competition and research, a working, long-lasting retinal implant does not seem to be on the immediate horizon. However, much of the recent research highlights how close this technology is to becoming reality. Because of its simplicity, if a functional subretinal implant ever becomes a reality, it would be the most practical prosthetic device for canine application. Our better understanding of how phosphene production in the retina by electrical stimulation translates into cortical activity is certainly encouraging (Eger et al., 2005; Schanze et al., 2003). Ongoing research will evaluate safety and biocompatibility issues with retinal implants (Volker et al., 2004). Various other approaches are being examined and include a visual cortex prosthesis, suprachoroidal prosthesis, and direct optic nerve stimulation (Chowdhury, 2004; Fujikado, 2004; Xiaoyun et al., 2005).

Retinal implants, in their basic design, can deliver electrical impulses to the inner retinal layers either via a microphotodiode array or via a microelectrode array. The former uses ambient light that enters the eye, while the latter uses a camera (usually mounted on glasses) and processing unit system. Photodiode arrays have the obvious advantage of not requiring a camera system, while the microelectrode implants can generate larger impulses and can use various computer-based algorithms to enhance certain aspects of artificial vision.

Some work has actually been done in the canine species. Both a suprachoroidal retinal implant (Morimoto et al., 2011) and a subretinal implant (Matsuo et al., 2017) have been tested in dogs.

Today, the only retinal implant that is commercially available is the Argus II implant (Fig. 26.42; Weiland & Humayan, 2014). This epiretinal implant comes with a hefty cost, and results vary from patient to patient. Although the progress in retinal implants is slow, it continues unabated.

If the reader is interested in the most up-to-date information regarding retinal prosthetics, they are encouraged to consult the proceedings of the Eye and the Chip meeting held in Detroit, Michigan.

Subretinal Injection

Direct targeting of photoreceptors and the RPE with therapeutic agents, such as viral gene therapy vectors or cells,

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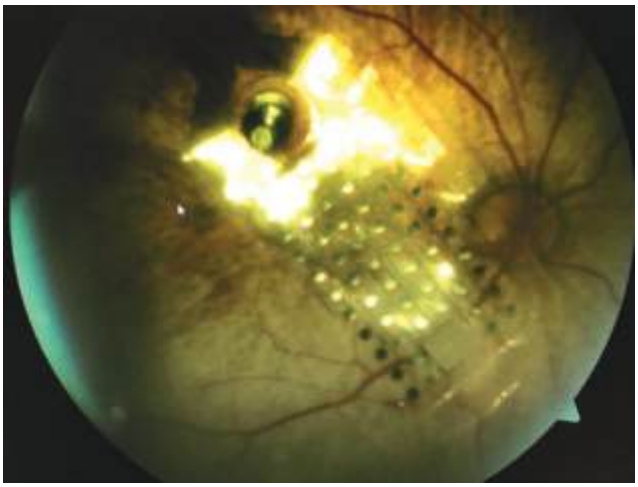


Figure 26.42 Argus II retinal implant (Second Sight Medical Products, Sylmar, CA, USA) in a human with retinitis pigmentosa.

generally requires subretinal injection. In dogs, this technique has been used most commonly in the laboratory for the successful gene therapy of inherited retinopathies with adeno-associated virus (AAV; see Chapter 25 for details). Preparation of the eye, pars plana approach, and choice of lens system for visualization of the ocular fundus are comparable to other posterior segment surgeries described in this chapter. Other technical aspects, including the use of anti-inflammatory drugs, mydriatics, neuromuscular blockage, conjunctival stay sutures, and light sources, are based on the surgeon's preference and type of reagent to be administered. With some genetic mutations the retina becomes more light sensitive, so exposure to light must be minimized to avoid acceleration of retinal degeneration (Komáromy et al., 2008). Comparable to protocols for human patients, vitrectomy can also be considered in dogs to allow better control of subretinal bleb location and size. In general, reasonable bleb sizes can be achieved in dogs without vitrectomy. Depending on the volume to be injected, removal of fluid by aqueous paracentesis may be necessary to avoid IOP spikes and to facilitate bleb formation.

Choice of injector and cannula depend on the surgeon's preference and the reagent to be injected. Factors to consider include commercial availability and dead space within the device, because some reagents are costly to manufacture. Standard subretinal injection cannulas and small-gauge (e.g., 27–30-gauge) anterior chamber cannulas are well suited to the procedure, but because they are blunt tipped, the placement of a pars plana port is needed to enter the vitreal chamber (Komáromy et al., 2006). Although smaller-gauge cannulas are preferable to minimize the retinotomy size, there may be limitations given by the type of reagent to be injected. For example, cells may be damaged by the shearing forces inside a thin cannula. The combination of a sharp

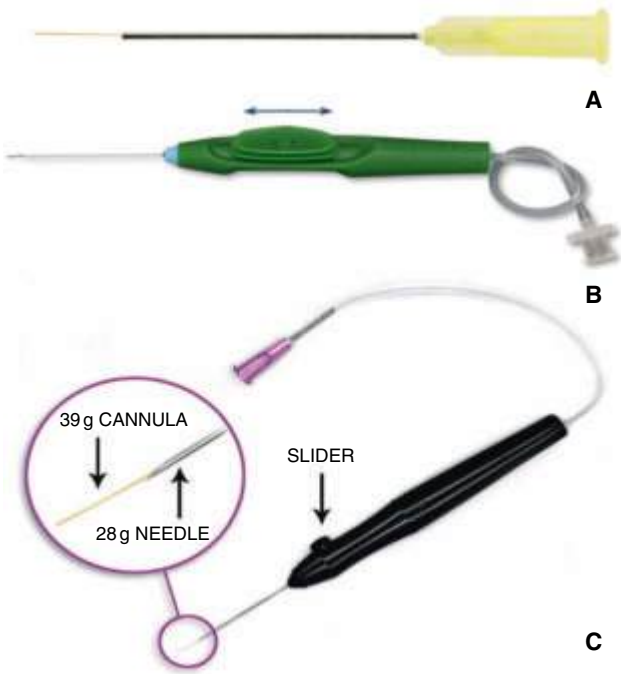


Figure 26.43 Examples of subretinal injection devices. **A**. The Retinal Hydrodissection Cannula (Storz Ophthalmic Instruments, Bausch & Lomb, Heidelberg, Germany) consists of a 39-gauge flexible tubing extending from a 20-gauge metal cannula. **B**. The 20–25G FlexTip™ cannulas (MedOne Surgical, Sarasota, FL, USA) use soft silicone tubing that can be extended with a slider. The syringe containing the reagent is attached to thicker tubing at the opposite end of the handpiece. **C**. A slider on the RetinaJect™ subretinal cannula (Surmodics, Eden Prairie, MN, USA) moves the 39-gauge polyimide cannula within the 28-gauge needle. The syringe with reagent is connected to the needle hub at the end of the thin, flexible silicone tubing. The RetinaJect is no longer commercially available.

needle with an extendable, blunt-tipped cannula is ideal for fast, minimally invasive subretinal injection without a pars plana port (Fig. 26.43). The syringe containing the reagent can be attached either directly to the injection cannula or via a tubing system. The direct connection minimizes dead space, but there is a chance that the cannula may shift on the retinal surface while the syringe plunger is being pushed during the injection. This risk is avoided by attaching the syringe via a tubing system and having an assistant push the plunger. Unfortunately, some tubing systems add a lot of dead space, resulting in a loss of reagent that may be cost prohibitive.

In general, subretinal injections are technically not difficult, because the subretinal space between the photoreceptors and the RPE is a natural space that easily separates. The disease status of the retina may also play a role. Although microdetachments with BEST1 mutations (canine multifocal retinopathy) facilitate the formation of a subretinal bleb, it

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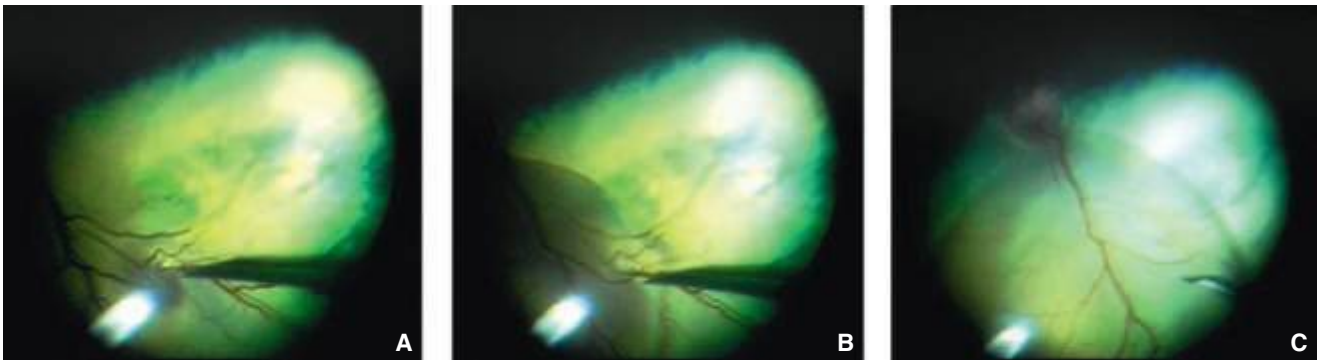


Figure 26.44 Subretinal injection. **A**. The blunt-tipped 39-gauge cannula of the RetinaJect subretinal cannula (formerly made by Surmodics, Eden Prairie, MN, USA) is gently pushed against the retinal surface to loosen the neuroretina and occlude the cannula tip. **B**. The fluid exiting the cannula creates the retinotomy, followed by the formation of a subretinal bleb. **C**. The completed subretinal bleb is shown superior to the optic nerve head. (Courtesy of Simon Petersen-Jones.)

may be more difficult to detach a thinned, degenerated retina without causing additional damage (Guziewicz et al., 2018).

After entry into the vitreal chamber, the retinal surface is carefully approached with the blunt-tipped cannula in a 30–45-degree angle. The cannula tip is gently pushed against the retinal surface to completely occlude the opening (Fig. 26.44A). During this process, the retina may slightly fold over the cannula tip. The injection of the reagent can occur manually or via a special pump. The retinotomy is created by the reagent exiting the cannula tip; this is followed by the formation of a subretinal bleb (Fig. 26.44B). Typically, the bleb rises in the direction of the fluid exiting the cannula tip. The bleb size is determined by the volume injected. As a rule of thumb, a volume of 150 µL covers an estimated 20%–25% of the retinal surface in an adult-sized globe. For most reagents, only the retina covered by the bleb is being treated. In most therapeutic trials, the goal is to cover the cone-rich area centralis and surrounding retina (Fig. 26.45). Without the use of vitrectomy, a critical size will be reached at which the bleb does not get bigger with more injected volume, but rather the reagent will begin to leak around the cannula into the vitreous. On occasion, the retinotomy site may tear a little as the retina rises around the stably positioned cannula tip. Optimal contact and angle of the cannula with the retina are critical. If the cannula opening is not completely occluded, the reagent will leak into the vitreous and no bleb is formed. On the other hand, if the cannula is pushed too hard and at a steep angle, both the neuroretina and RPE may be penetrated, resulting in a sub-RPE injection. The latter can be recognized by an immediate pink discoloration of the injected tapetal area, which will turn black over several days.

On completion of the injection, the cannula is carefully removed from the globe. The need for scleral and conjunctival closure depends on the type of approach chosen. In most instances, the subretinal bleb will flatten and the retina will reattach within 24–48 hours after injection of the AAV gene therapy vector.

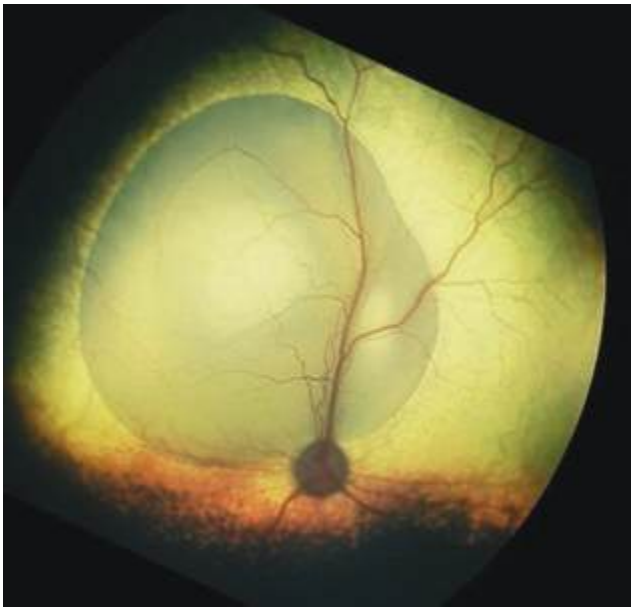


Figure 26.45 Subretinal bleb in a canine eye immediately after successful injection. The bleb covers the area centralis and the supratemporal central retina in this right eye.

Even if performed with the greatest care, a subretinal injection represents a traumatic event in which the photoreceptors are forcefully separated from the RPE. Most retinas handle the process quite well, with minimal or no detectable long-term damage (Komáromy et al., 2006; Nork et al., 2012); however, degenerated retinas may be injured more easily by a subretinal injection. The development of novel, capsid-mutated AAV gene therapy vectors that can reach the outer retina after intravitreal administration is of high priority so that subretinal injections would no longer be needed (Boyd et al., 2016). Subretinal injections will remain the state of the art for reaching the outer retina until a therapeutic effect can be achieved by intravitreal gene therapy vector administration.

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Diseases of the Canine Optic Nerve

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Introduction

Degenerative, traumatic, and inflammatory optic nerve diseases are common in dogs and may be either primary, arising in and principally involving the optic nerve itself, or may represent a secondary effect of pathology elsewhere in the eye, as in glaucoma, or an extension of local disease from the globe, orbit, or central nervous system. The optic nerve may also be involved in more generalized, systemic disease processes (addressed in Chapter 37). Anatomy and physiology of the optic nerve and central visual pathways are described in detail in Chapters 2 and 4, in Volume 1 of this text. Further review in this chapter relates morphology and function to normal and pathological features that may be observed on clinical examination of the canine optic nerve, and provides context to facilitate understanding of underlying pathophysiology and manifestations of optic nerve disease in dogs.

Structure and Function of the Optic Nerve

The optic nerve is a white matter tract of the brain, rather than a true cranial nerve, and is principally composed of the axons of retinal ganglion cells (RGCs) (Brooks et al., 1999a). The RGC axons project from somas in the ganglion cell layer of the inner retina, coursing intraocularly, approximately centripetally, within the retinal nerve fiber layer (RNFL) towards the optic nerve head (ONH), where they make a sharp turn to exit the eye as the optic nerve (Brooks et al., 1999a). In afoveate animals, such as the dog, optic nerve axons from ganglion cells in the superior retina are located in the superior half of the ONH, and axons from the inferior retina lie in the inferior half of the ONH, with a similar pattern noted for axons in the nasal and temporal quadrants (Jonas & Naumann, 1993).

Anatomically, the optic nerve is considered to extend from an anterior limit at the ONH to a posterior limit at which axons reach the optic chiasm. However, the RGC axons actually pass through the chiasm without synapsing and continue within the optic tracts, with the majority of canine RGC axons ultimately projecting to the lateral geniculate nucleus (LGN) where they synapse with central neurons that in turn project within the optic radiations from the LGN to the visual cortex. A minority of RGC axons, including those of intrinsically photosensitive, melanopsin-containing RGCs, project to the superior colliculus, the hypothalamus, the pretectal nucleus, or other midbrain centers, where they play a role in regulation of circadian rhythms, pupillary light reflex, and coordination of eye and head movements (Evans, 1993; Martins & Brooks, 2013). The nasal and temporal halves of the retina of carnivores are divided by an imaginary vertical line called the vertical meridian that passes through the cone-rich *area centralis* (Cooper & Pettigrew, 1979). RGC axons nasal to the vertical meridian cross at the optic chiasm to the contralateral LGN and visual cortex, whereas axons from the temporal retina remain uncrossed and project to the ipsilateral LGN and visual cortex.

The optic nerve is not simply a cable that links the eye to the brain. Its anatomic and physiologic complexity provides a basis for regional, interindividual, and interspecies differences in susceptibility to various disease processes. In particular, the sheer length of the RGC axons within the optic nerve poses significant metabolic challenges (see later). Furthermore, the concentration of all RGC axons from an eye into a single nerve, with a one to one ratio of RGC somas to axons, means that the optic nerve represents an extremely vulnerable segment of the visual pathway (Arey et al., 1942). This vulnerability is compounded by limited functional redundancy in the normal canine optic nerve compared with other neurons in the visual system, because of its comparatively small total population of axons which, at 115,000–167,000, is

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equivalent to only about 10% of the total axon population of the human optic nerve (Albrecht May, 2008; Arey & Gore, 1942; Arey et al., 1942; Bruesch & Arey,1942; Peichl, 1992).

The optic nerve can be subdivided into four anatomic regions: a short *intraocular* segment; a retrobulbar, *orbital* segment, which constitutes the longest region of the optic nerve; a relatively fixed, *intracanalicular* segment within the optic canal, and a short *intracranial* segment that merges with the optic chiasm (Jonas & Naumann, 1993).

Intraocular Optic Nerve

The anterior-most part of the optic nerve, the ONH, which is also referred to as the optic disc or optic papilla, is the only part of the optic nerve that can be visualized on ophthalmoscopy. In humans, the ONH is surrounded by the white, peripapillary scleral border tissue of Elschnig (Fig. 27.1) (Jonas & Naumann, 1993), but pigmentation and/or myelin obscure the view of the ring of Elschnig in most dogs. Bergmeister's papilla is formed by glial cells covering the site of the hyaloid artery at the ONH and may be observed ophthalmoscopically in some dogs. The inner limiting membrane of the retina covers the anterior surface of the ONH, where it is referred to as the inner limiting membrane of Elschnig, or the thicker central meniscus of Kuhnt (Jonas & Naumann, 1993). Although not readily appreciated with an ophthalmoscope, these features may be observed on optical coherence tomography images of some ONHs.

There are no RGC somas in the optic nerve itself, just their axons. In the ONH, glia, including astrocytes, microglia, and oligodendrocytes, represent a significant cellular component with astrocytes predominating (Hernandez et al., 2008). Astrocytes in the ONH provide physical and metabolic support to the RGC axons, and astrocyte cell processes both isolate and nourish RGC axons within bundles, and integrate individual axons with other neural, vascular, and connective tissue elements of the ONH. In contrast to many other species, including humans, in which myelination commences in a myelination transition zone immediately posterior to the lamina cribrosa (LC) of the ONH, the axons of the canine optic nerve are typically myelinated anterior to the LC (Brooks et al., 1999a). Variability in the extent of intraocular myelination of RGC axons within the prelaminar tissue and RNFL is responsible for pronounced interindividual

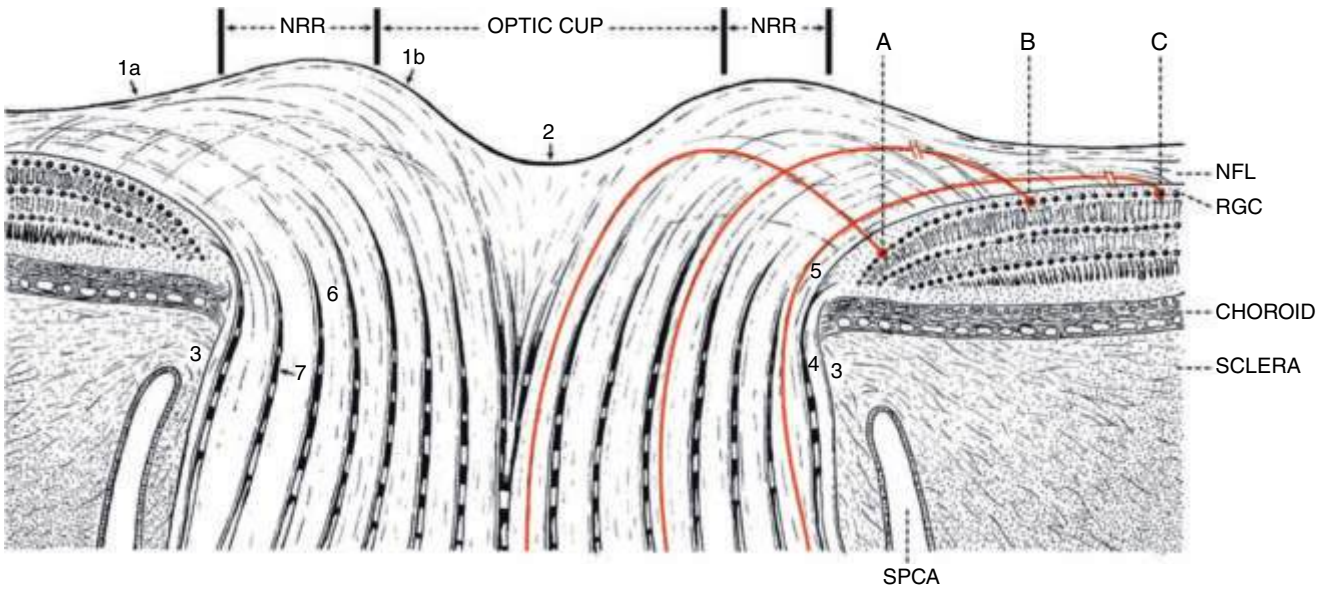


Figure 27.1 A sagittal section through the canine optic nerve head and lamina cribrosa region of the canine optic nerve. Müller cell processes forming the retinal inner limiting membrane (1a) are in continuity with astrocyte processes that form the internal limiting membrane of Elschnig (1b) on the surface of the optic disc. Elschnig's membrane becomes thickened in the center of the disc in some species to form the central meniscus of Kuhnt (2). The scleral border tissue of Elschnig (3) lies between the choroidal stroma and a collection of astrocytes surrounding the optic nerve bundles known as the border tissue of Jacoby (4). The border tissue of Jacoby is continuous anteriorly with astrocytes of the intermediate tissue of Kuhnt (5) at the termination of the retina. Axons are segregated by astrocytes anterior to the lamina into bundles (6) prior to reaching the lamina cribrosa (7). The optic cup, neuroretinal rim, nerve fiber layer (NFL), retinal ganglion cell (RGC) layer, choroid, sclera, and short posterior ciliary arteries (SPCA) are illustrated. Retinal ganglion cells with cell bodies located near the optic disc (A), midperipheral retina (B), and peripheral retina (C) send their axons (RED) to the central, middle, and peripheral regions of the optic disc and nerve, respectively. (*Source*: Reproduced with permission from Martins & Brooks (2013) Diseases of the canine optic nerve. In: *Veterinary Ophthalmology* (eds Gelatt, K.N., Gilger, B.C. & Kern, T.J.), pp. 1432–1473. Oxford: John Wiley and Sons.; Fig. 26.1A [previously modified from Brooks, et al., (1999) Comparative RGC and optic nerve morphology. *Veterinary Ophthalmology*, **2**, 3–12].)

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variation in ONH ophthalmoscopic appearance in dogs (as described in a later section of this chapter).

At the ONH, bundles of RGC nerve fibers and associated astrocyte processes pass through spaces between the interleaved collagenous beams of the LC (Fig. 27.1 and Fig. 27.2). The LC further subdivides the ONH into *prelaminar, laminar* and *retrolaminar regions* (Fig. 27.3). The canine LC consists of 10–15 layers, forming about 250 pores ranging in diameter from 12 to 50 µm (Fig. 27.4). Nerve fiber bundles generally follow a direct channel through aligned sets of laminar pores in adjacent laminar plates, though not all pores in the LC are perfectly aligned and some plates branch and coalesce (Fig. 27.2 and Fig. 27.4) (Martins & Brooks, 2013). In contrast to humans, there are no regional differences in pore size of the dog LC (Brooks et al., 1989a; Fukuchi et al., 1987). The canine central laminar thickness is ~500 µm, which is only slightly thinner than, and comparable to, that of humans (Balaratnasingam et al., 2009). The extracellular matrix (ECM) of the LC in young dogs consists primarily of collagen types I, III, and VI (Martins & Brooks, 2013), and differs from that of sclera which contains primarily fibrillar collagen type I (Hernandez et al.,1987).

Anatomic and biomechanical features of this region are considered to play a significant role in susceptibility to axonal damage in glaucoma (see later, and Chapter 20 for further discussion of the ONH in glaucoma). The LC has a backward curve in it, like a hammock suspended across the neural canal within the sclera. Another useful analogy considers the LC as a trampoline attached to the surrounding sclera via strong anchoring structures of the laminar insertion zone, which consist of specialized collagen, elastin, and laminin, and which function like the coiled springs that anchor a trampoline bed to its rigid steel frame, or in the case of the LC, to the dense, circumferentially oriented collagen of the peripapillary sclera. This structural organization is considered important in supporting the ONH structures that are subjected to continuously fluctuating IOP-related stress (i.e., force per cross-sectional unit area) and hoop stresses around the scleral neural canal, and strains (local tissue deformation under those stresses) (Burgoyne, 2011), even under normal physiological conditions. These complex and dynamic stresses and strains are intensified in glaucoma and can negatively impact the patency of ONH capillaries (see later) and alter the biology of optic nerve axons, astrocytes, and other glial cells, including microglia, oligodendrocytes, and precursors, which reside in the optic nerve.

Aging and disease result in a loss of resiliency, compliance, and elasticity in the human LC, associated with changes in ECM, most notably collagen (Hernandez et al., 1989; Liu et al., 2018). Age-dependent and disease-dependent alterations in structural and biomechanical properties of the posterior sclera have been identified in both normal dogs and dogs with open angle glaucoma caused by *ADAMTS10* mutation (Boote et al., 2016; Palko et al., 2013, 2016). Combined with age-related changes, genetically determined differences in ECM properties of the LC region of the ONH could conceivably underlie some of the differences in glaucoma susceptibility that are recognized clinically between canine breeds. Interindividual ONH connective tissue variability arises from both anatomical and microarchitectural factors. Anatomical factors include the size and shape of the

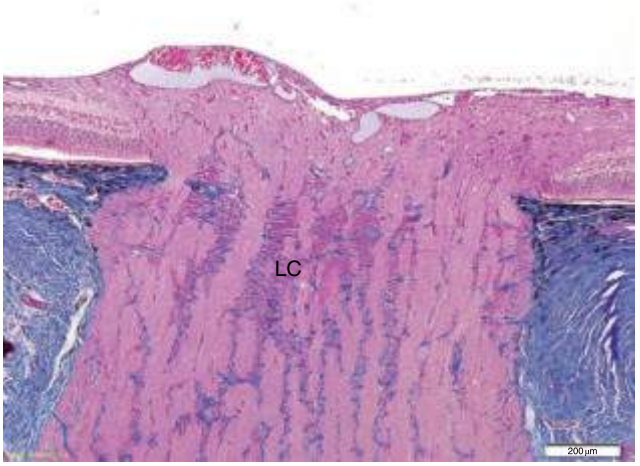


Figure 27.2 Masson's trichrome stained sagittal section of a normal canine optic nerve head. Collagen is stained blue with this stain, which readily identifies both scleral collagen and the collagen of the horizontally oriented beams of the lamina cribrosa region (LC) (Bar = 200 µm). (*Source*: Courtesy of Dr. Leandro B.C Teixeira and the Comparative Ocular Pathology Laboratory of Wisconsin, with permission.)

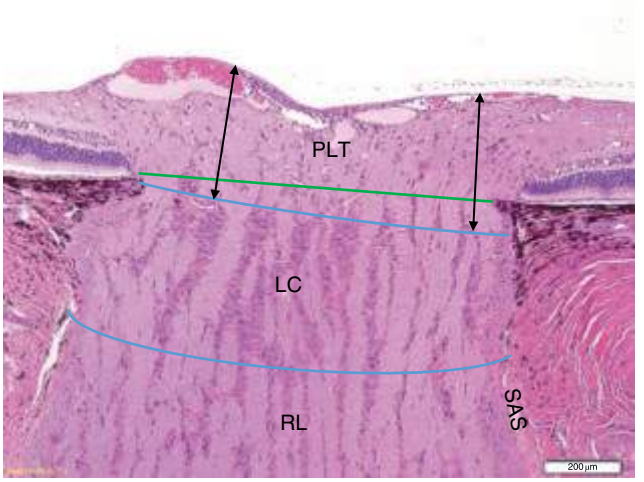


Figure 27.3 Photomicrograph of a sagittal section of the same, normal canine optic nerve head shown in Fig. 27.2 illustrates the prelaminar tissue (PLT) thickness (black arrows), with lamina cribrosa (LC) region delineated with blue lines, and optic nerve diameter at the internal neural canal (Bruch's membrane opening) depicted by a green line. The retrolaminar (RL) tissue is also shown, as is the proximity of the subarachnoid space (SAS) (Scale bar = 200 µm). (*Source*: Courtesy of Dr. Leandro B.C Teixeira and the Comparative Ocular Pathology Laboratory of Wisconsin, with permission.)

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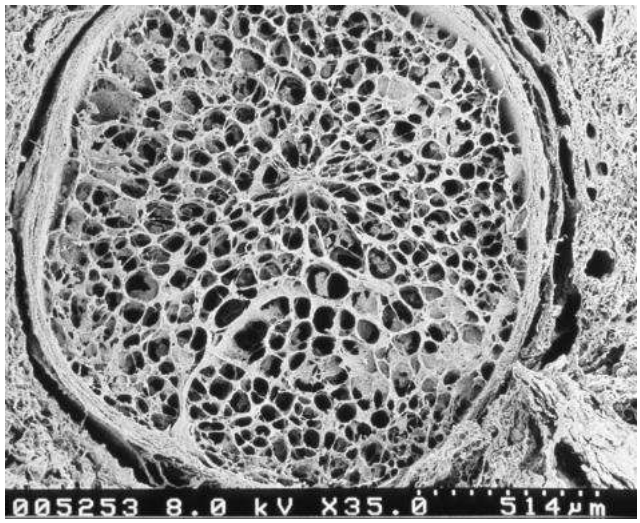


Figure 27.4 Scanning electron micrograph of a trypsin digest transverse cross-section of a normal canine optic nerve at the level of the scleral lamina cribrosa. A series of collagenous beams and plates create pores through which axons pass. In contrast to the human lamina cribrosa, there are no significant regional differences in pore size density in the canine lamina cribrosa. (Original magnification, 35×). (*Source*: Reproduced with permission from Martins & Brooks (2013) Diseases of the canine optic nerve. In: *Veterinary Ophthalmology* (eds Gelatt, K.N., Gilger, B.C. & Kern, T.J.), pp. 1432–1473. Oxford: John Wiley and Sons.)

scleral (neural) canal; the thickness of both the LC and the adjacent, peripapillary sclera, and LC beam and pore dimensions. Microarchitectural features of fibrillar and nonfibrillar ECM components, which ultimately depend on resident fibroblasts and astrocytes for their maintenance and turnover, determine local material properties of the ONH and LC tissues. This combination of ONH anatomy and material properties defines the overall structural stiffness of ONH connective tissues, which in turn dictate the strains (deformations) experienced by the ONH tissues in response to loads from intraocular pressure (IOP) and retrolaminar tissue pressure (RLTP) (Fig. 27.5) (Palko et al., 2013, 2016; Stowell et al., 2017).

Strength, resiliency, and compliance are particularly important features of this region of the optic nerve because the LC region represents a transition zone between high and low hydrostatic tissue pressures across a pressure gradient formed between the IOP and RLTP, respectively (Balaratnasingam et al., 2009; Brooks et al., 1999b; Burgoyne, 2011; Morgan et al., 1995). The optic nerve vasculature and optic nerve axons of the normal dog are subjected to a substantial drop in tissue pressure across the LC. Factors that influence this translaminar pressure gradient (TLPG), which is calculated by subtracting RLTP from IOP, can have a profound impact on both vascular perfusion of the ONH, choroid and retina, and on axoplasmic flow within the optic

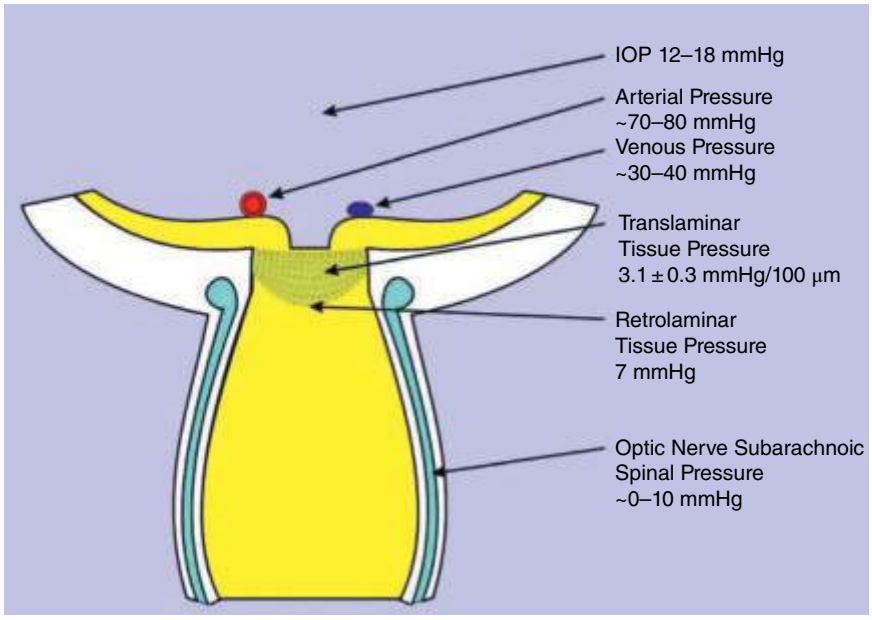


Figure 27.5 Diagrammatic representation of complex pressure relationships in tissues of the canine posterior segment and optic nerve. Opposing forces of intraocular pressure (IOP) and blood pressure impact ocular perfusion pressure. IOP is the major determinant of the translaminar pressure gradient under conditions of normal cerebrospinal fluid pressure. Arrrows depict approximate direction of forces. (*Source*: Adapted with permission from an original image courtesy of K.N. Gelatt previously published in Martins & Brooks (2013) Diseases of the canine optic nerve. In: *Veterinary Ophthalmology* (eds Gelatt, K.N., Gilger, B.C. & Kern, T.J.), pp. 1432–1473. Oxford: John Wiley and Sons.)

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nerve itself (Fig. 27.5) (Morgan et al., 1995). The TLPG in the dog is reported as 3.1 ± 0.3 mmHg/100 µm tissue (Morgan et al., 1995), which is very similar to that reported for humans (Balaratnasingam et al., 2009). Although IOP is the major determinant of the TLPG, continuity between the optic nerve subarachnoid space and the intracranial lateral ventricles in the dog means that at CSF pressure (CSFp) greater than zero, increases in CSFp can exert a substantial influence on RLTP and the TLPG (Fig. 27.5), and can negatively impact axoplasmic flow (Morgan et al., 1995, 1998, 2002). However, swelling of the ONH resulting from high CSFp ("papilledema", discussed later in this chapter) is not commonly recognized clinically in dogs, compared with humans. Blood flow within vessels in the superficial and laminar layers of the optic nerve is more likely to be directly impacted by IOP, whereas vessels in the retrolaminar region are less subject to the influences of IOP. Adequate vascular perfusion of ocular tissues is critical to meet high metabolic needs of the energy dependent processes of the ONH and retina. Ocular perfusion pressure drives this circulation and is influenced by systemic arterial blood pressure, local venous pressures, and, to a great extent, by the opposing effects of IOP (Hayreh, 2001) (Fig. 27.5).

The rich ONH vasculature is associated with a high rate of blood flow necessary to meet the high metabolic demands of this region and is responsible for the pink hue of the normal healthy canine ONH. The primary blood supply to the eye of dogs is provided by the large external ophthalmic artery, which arises from the maxillary artery and is thus extracranial in origin. In contrast, the human ONH receives its blood supply from the internal ophthalmic artery, which is intracranial in origin. The internal ophthalmic artery in dogs is a small artery that arises from the anterior cerebral artery at the level of the optic chiasm, passes through the optic canal on the dorsal surface of the optic nerve, and courses rostrally to anastomose with the external ophthalmic artery about midway between the optic canal and the posterior pole of the globe (Evans, 1993; Martins & Brooks, 2013). Neural innervation to the internal ophthalmic artery may play some role in the regulation of blood flow to the optic nerve (Martins & Brooks, 2013). Two long posterior ciliary arteries, one medial and one lateral, and 9–14 short posterior ciliary arteries (SPCA) arise from the anastomoses of the external and internal ophthalmic arteries in dogs. The SPCA surround the canine ONH and supply the LC, choroid, retina, and ONH (Fig. 27.6) (Brooks et al., 1989b; Fick & Dubielzig, 2016). Vascular supply to the LC is from the SPCA, cilioretinal arteries, and longitudinal pial vessels (Brooks et al., 1989). The retrolaminar optic nerve also receives a centripetal vascular supply from the pial vessels (Hayreh, 1995). There is compelling evidence that optic nerve blood flow is tightly regulated through a number of different mechanisms, across a broad physiologic range of perfusion pressures (Hayreh, 2001). In contrast to the primate ONH that has a central retinal artery and vein, blood flow within the vasculature of the canine anterior optic nerve is more abundant and varied (Brooks et al., 1989b; Hayreh, 1995; de Schaepdrijver et al., 1996). Thus, the canine optic nerve and retina may be relatively protected from adverse effects of venous occlusion compared with the optic nerve and retina of humans. However, the location of the canine short posterior ciliary arteries, immediately adjacent to and effectively within the neural canal of the canine ONH, where they are relatively unsupported by scleral tissue, may render them *more* susceptible to compression and occlusion during episodes of pronounced IOP elevation (Fig. 27.6) (Fick & Dubielzig, 2016).

The extensive, nonfenestrated capillary beds of the surface, prelaminar, laminar, and retrolaminar optic nerve regions are confluent (Hayreh, 1995). Capillaries with a continuous basement membrane are surrounded by astrocytes in the ONH laminar tissue. However, there is no cell layer with tight junctions separating the choriocapillaris from the ONH such that a potential defect exists in the blood–ocular barrier at the level of the ONH. Substances may thus enter the ECM of the optic nerve and LC from the choroid, but are prevented from entering the subretinal space by the tight cell junctions adjoining glial cells in the intermediate tissue of Kuhnt (Jonas & Naumann, 1993). This is recognized as fluorescence of the ONH during fluorescein angiography (see later).

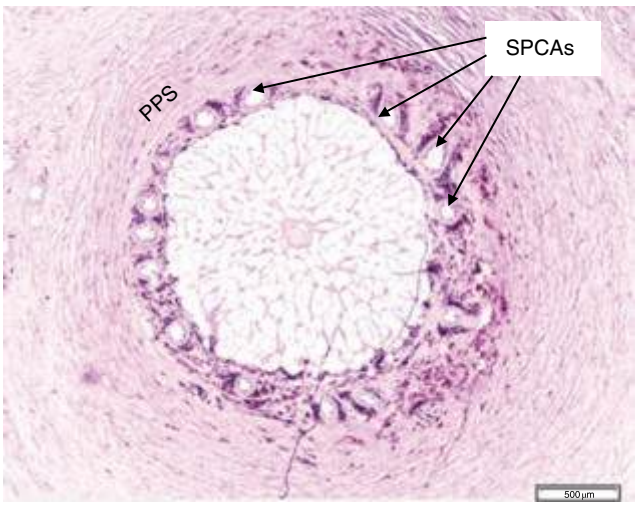


Figure 27.6 Histologic cross-section through a normal canine optic nerve head at the level of the lamina cribrosa. Numerous short posterior ciliary arteries (SPCAs, some indicated by arrows) encircle the nerve and are in such close proximity to the neural canal that they are virtually contiguous with the nerve in this species. In this location, the canine SPCAs may be more susceptible to collapse and occlusion during episodes of elevated intraocular pressure than those of other species, such as the cat, in which SPCAs are located within the dense, circumferentially oriented peripapillary scleral collagen (PPS). The canine optic nerve head, choroid, and retina are thus susceptible to ischemia in response to acute IOP elevation (Bar = 500 µm). (*Source*: Courtesy of Dr. Richard R. Dubielzig, Comparative Ocular Pathology Laboratory of Wisconsin, with permission.)

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Intraorbital Optic Nerve

The intraorbital, or retrobulbar, optic nerve begins posterior to the LC and consists of optic nerve axons, oligodendrocytes, and astrocytes. The orbital optic nerve is longer than the direct distance between the globe and optic canal, providing an S-shaped curve that allows for globe movement (Evans, 1993). The normal dog has fewer total numbers of optic nerve axons than humans (Jonas et al., 1990), but has a larger mean fiber diameter of individual axons (~1.5 µm versus ~1 µm) compared with humans and monkeys (Brooks et al., 1995; Jonas et al., 1990; Sanchez et al., 1986). The diameter of the canine intraorbital optic nerve (1825.8 ± 59.7 µm) is larger than that of the optic nerve at the level of the LC (~1592 µm), but considerably smaller than that of the human optic nerve (2590 ± 80.6 µm) (Balaratnasingam et al., 2009). As it exits the globe, the canine optic nerve shows an approximately 1.4-fold increase in diameter at the outer scleral canal, in contrast to the nearly 2-fold increase in diameter of the human optic nerve. The greater increase in diameter in humans can be explained by commencement of myelination in the retrolaminar region of the human optic nerve (Balaratnasingam et al., 2009), compared with dogs, in which axons are myelinated in the ONH. Axons in the RNFL are unmyelinated in order to keep the retina sufficiently transparent for light to reach the photoreceptors. Developmentally, myelination of the optic nerve begins near the optic chiasm and progresses toward the LC (Jonas & Naumann, 1993). As described above, the adult canine ONH is characterized by the presence of prelaminar myelination of axons, extending anterior to the LC. However, as with tapetal development and retinal maturation, myelination of the canine anterior optic nerve is a postnatal process. This accounts for the relatively small, dark, and round ophthalmoscopic appearance of the ONH in young puppies.

Although myelination of the ONH varies according to species, all axons are myelinated posterior to the LC in mammals in order to conserve energy and speed neural conduction. The primary cell type in the retrobulbar, intraorbital optic nerve posterior to the LC is the oligodendrocyte (Jonas & Naumann, 1993). Myelin is derived from multiple wrappings of the plasma membranes of an oligodendrocyte around each optic nerve axon (Jonas & Naumann, 1993). The cell type responsible for myelination of optic nerve axons is in sharp contrast to other cranial nerves which, with the exception of the olfactory nerve, derive their myelin sheaths from Schwann cells, the latter typical of the peripheral nervous system. The myelin sheath of optic nerve axons is interrupted to form nodes of Ranvier at the termination of the boundary of one oligodendrocyte and the beginning of another. Nodes of Ranvier are important in the saltatory conduction of optic nerve impulses (Jonas & Naumann, 1993). Thus, slowed conduction is an important feature of optic nerve diseases associated with hypo- or demyelination. Myelin is an insulating material, and is associated with reduced neuronal energy and metabolic demands. For this reason, metabolic demands may be greater in unmyelinated regions of the optic nerve (Hollander et al., 1995). Greater rates of blood flow and greater concentrations of mitochondria, astrocyte processes and capillaries in the ONH may represent adaptations to cope with greater metabolic demands of the ONH, particularly in the LC and prelaminar regions of the ONH which are unmyelinated in other species (Balaratnasingam et al., 2014; Bristow et al., 2002).

Inside their myelin sheath, optic nerve axons have a thin, collapsible outer cell membrane, and a gel-like axoplasm within which transmitter molecules, neurotrophins, proteins, microtubules, and organelles such as mitochondria are transported substantial distances (Nickells, 1996). This axoplasmic flow occurs along an intra-axonal pressure gradient and is susceptible to interruption in disease, including glaucoma (Brooks et al., 1999b; Calkins & Horner, 2012). Axonal transport is orthograde from the RGC somata toward the intracranial synapse and retrograde from the brain toward the RGC somata. The orthograde and retrograde axoplasmic flow between RGC somata and their synapses in the brain extends over considerable distances. Although the absolute length of RGC axons in the optic nerve is likely to be influenced by highly variable orbital and calvarial morphology in dogs, it has been proposed that a human RGC soma the size of an apple would have an axon about a half-mile long (Jonas & Naumann, 1993)! This analogy hints at the profound challenge imposed on the RGC by the length of its axon, and in turn, its susceptibility to injury under certain disease conditions, particularly those that contribute to ischemia. Axoplasmic flow or transport requires considerable metabolic energy produced locally by mitochondria within each axon segment along the pathway and is therefore subject to ischemic episodes and other processes that impair energy generation and mitochondrial function. There is some evidence that unmyelinated segments of axons are more susceptible to axoplasmic flow interruption (Hollander et al., 1995), thus it might be anticipated that myelination in the ONH of dogs could be protective, particularly under conditions of high IOP. However, in addition to challenges presented by their length, RGC axons are also subjected to a precipitous change in tissue pressure, as described previously, as they exit the globe (Brooks et al., 1999b), that renders them susceptible to collapse. Axoplasmic flow in dogs with primary glaucoma may be more precarious (Samuelson et al., 1983) and therefore more sensitive to elevations in IOP than in normal dogs (Williams et al., 1983).

Meningeal sheaths invest the intraorbital optic nerve (Fig. 27.7) and pial septa derived from the meninges are accompanied by blood vessels that extend between axonal bundles. Arteriolar and capillary blood vessels pierce the dura mater, cross the trabeculae of the arachnoid, and

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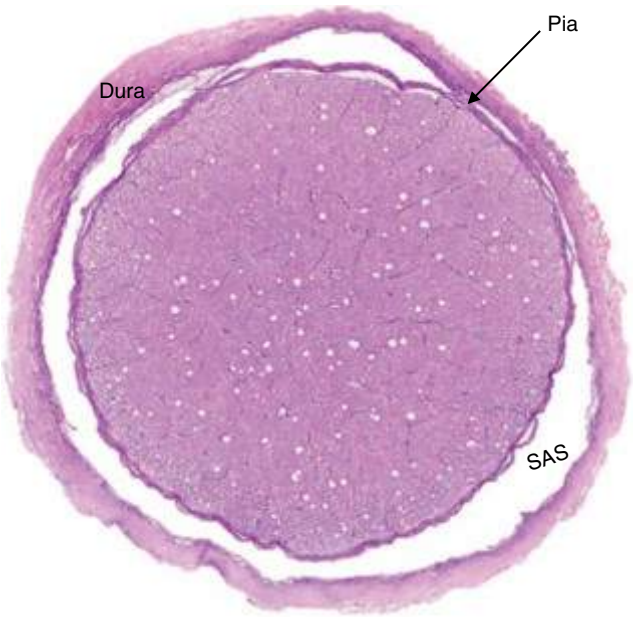


Figure 27.7 Transverse histologic section through the normal canine retrobulbar/orbital optic nerve. The nerve is surrounded by meninges, including the outermost dura mater, arachnoid that delineates the subarachnoid space (SAS) filled with CSF, and innermost pia mater that sends fine projections into the substance of the optic nerve. Vacuoles in the substance of the nerve represent an artifact of fixation and processing. (*Source*: Courtesy of Dr. Leandro B.C Teixeira and the Comparative Ocular Pathology Laboratory of Wisconsin, with permission.)

branch to enter the pia mater. The dural sheath of the intraorbital optic nerve merges with the sclera anteriorly and is continuous posteriorly at the orbital apex with the periosteum of the optic canal (Jonas & Naumann, 1993).

Intracanalicular Optic Nerve

This short, relatively fixed segment of the optic nerve begins at the orbital apex, where it is surrounded by the origins of the superior, medial, and inferior recti muscles. The optic nerve enters the bony optic canal within the sphenoid bone complex. Within the optic canal, the dura of the optic nerve and the periosteum of the canal are fused, but the subarachnoid space of the intraorbital optic nerve contains cerebrospinal fluid (CSF) and communicates with the intracranial subarachnoid space (see previously).

Intracranial Optic Nerve and Optic Chiasm

On exiting the bony optic canal there is only a very short, intracranial portion of the optic nerve prior to axons reaching the optic chiasm. The optic chiasm is the site of decussation of optic nerve axons, whereby RGC axons from the nasal retina cross the midline to reach the contralateral side of the brain, whereas axons arising from RGCs in the temporal retina remain ipsilateral. The percentage of axons crossing the midline at the optic chiasm varies between individuals but represents about 75% in the dog (compared with about 65% decussation in the cat, 50% in humans, and 100% in most birds and fish) (Martins & Brooks, 2013; Prince et al., 1960). The optic chiasm in the dog is located at the rostroventral surface of the brain stem, demarcates the rostral level of the diencephalon, and is intimately associated with, and located in close proximity to, the third ventricle, hypothalamus, and pituitary gland (Evans, 1993; Martins & Brooks, 2013). These anatomic relationships explain the spectrum of ocular, neurological, and systemic clinical signs that may be associated with neuropathology and systemic diseases affecting this region, as outlined in Chapter 36 and Chapter 37, Part 1 of this text.

Clinical Examination of the Optic Nerve

Neuro-Ophthalmic Examination

In addition to a thorough general physical examination, a thorough neuro-ophthalmic examination should be conducted in the unsedated subject, and prior to instillation of mydriatics or other pupilloactive drugs, as outlined in Chapters 10 and 36. Briefly, vision in dogs is typically assessed by the animal's demeanor, ability to navigate a maze and track moving objects, as well as menace response and, when practical, visual placing reflexes. Direct and consensual pupillary light reflexes (PLRs) should be carefully assessed with a bright light source under dim light conditions. Animals with unilateral optic nerve or retinal disease will have afferent PLR deficits, notably, they are likely to exhibit absent or diminished direct PLR, and absent or diminished consensual PLR from the stimulated to the contralateral eye. Testing by means of a swinging flashlight or cover/uncover test will yield a positive Marcus Gunn sign. Animals judged to have normal PLRs are more likely to have blindness caused by CNS disease rather than by optic nerve disease. The dazzle reflex is a subcortical response which shows relative functional integrity of the retina and optic nerve but does not determine integrity of the central visual pathways and visual cortex and may also be impacted by efferent defects, e.g., in facial nerve function.

Pupillometry

The PLR provides valuable information about the functional integrity of the afferent retinal and central visual pathways, including the optic nerves, as well as the efferent pathways. Although PLR assessment in a clinical setting is most often qualitative, quantitative measurement of response amplitude and latency may be achieved by pupillometry. However, usefulness of diagnostic tests involving the PLR may be

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limited in subjects with efferent PLR defects, whether neurological or structural, e.g., associated with iris atrophy.

Though a significant component of the PLR arises from photoreceptor activity, intrinsically photoreceptive retinal ganglion cells, which contain the photopigment melanopsin, are also responsible for initiating a significant component of the PLR. By leveraging the peak spectral sensitivity of melanopsin (~480 nm) it is possible to use differences in response to blue and red light stimuli to help distinguish between photoreceptor and inner retinal, optic nerve, and CNS diseases that impact vision. Chromatic pupillometry quantifies responses to luminance matched, bright and dim, red and blue stimuli. A simple chromatic PLR testing system has been developed for assessment of the canine visual pathway (Grozdanic et al., 2007, 2013), and applicability of this approach has been independently validated in research and clinical settings (Terakado et al., 2013; Whiting et al., 2013; Yeh et al., 2017). Characteristics and magnitude of the PLR can be particularly helpful in distinguishing optic nerve disease from retinal causes of blindness. For example, in sudden acquired retinal degeneration syndrome (SARDS), sustained PLR responses generated by intrinsically photoreceptive retinal ganglion cells are retained to blue stimuli because of preservation of the inner retina and optic nerve, in contrast to optic nerve diseases in which this response will be significantly attenuated or lost. Thus, pupillometry can be useful in determining the most appropriate diagnostic tests to pursue in subjects with acute onset blindness: either electroretinogram (ERG) if SARDS is suspected, or diagnostic imaging and CSF analysis when optic nerve pathology is suspected.

Ophthalmoscopy

As described for ophthalmoscopic examination of the fundus as a whole, detailed ONH examination is best accomplished with the pupil dilated. Both the widest and the smallest width illumination beams should be used. The widest beam will provide a highly magnified field of view that encompasses a region just slightly larger than the canine ONH. By sweeping the small beam (preferably just one-third to one-half of the optic disc diameter) back and forth, vertically and horizontally across the surface of the ONH, shadows are produced that provide additional depth cues to enhance the observer's ability to appreciate three-dimensional alterations in the ONH contour (Jonas, et al., 1999). This technique is especially valuable in identifying pits and colobomas in the ONH, and in determining the location of the neuroretinal rim (Fig. 27.8).

The color of the ONH, which in the normal canine eye represents a composite of white myelin and the red/pink hue from ONH vasculature, should be noted. The course of the blood vessels over the ONH and adjacent retina is carefully evaluated. It is important to record any changes in retinal vessel caliber and number, as well as any kinking or changes in course of retinal vessels (Jonas et al., 1999; Martins & Brooks, 2013). To the extent to which they are visible, the cup depth and features such as pores in the LC are

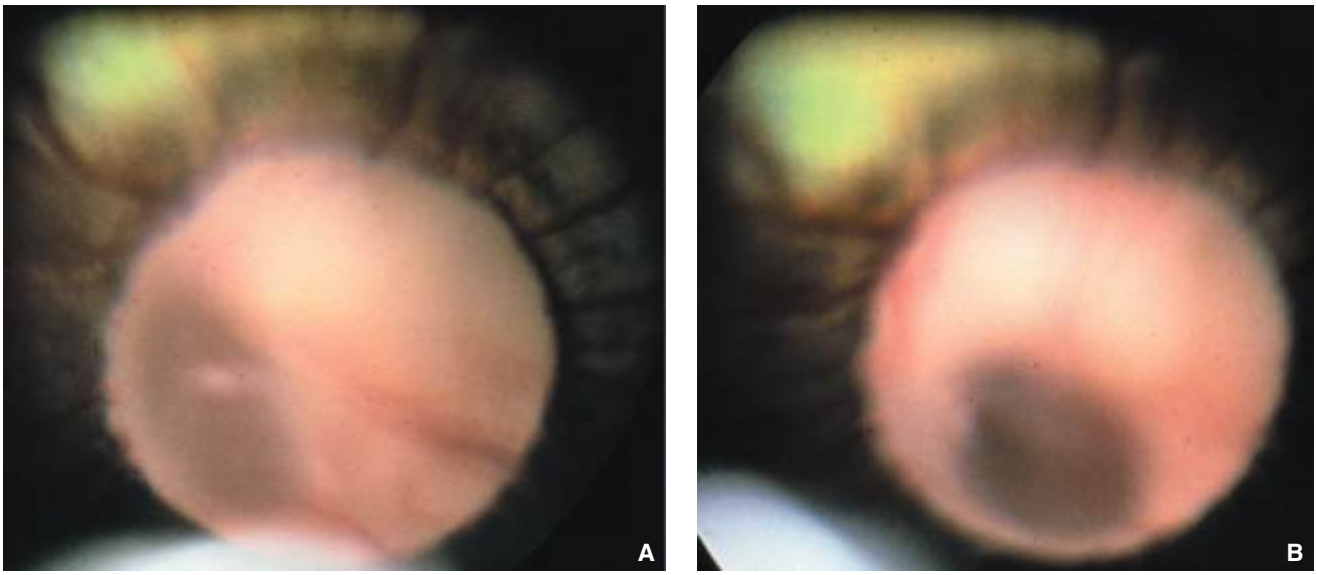


Figure 27.8 **A.** Dramatic optic disc cupping in a Chow Chow with glaucoma. The dark gray region on the left, within the optic nerve head, represents a shadow cast by the cup wall. **B.** Changes in viewing angle and direction of illumination beam can enhance depth cues and aid in detection of cupping, pits, and colobomas in the optic nerve head. (*Source*: Reproduced with permission from Martins & Brooks (2013) Diseases of the canine optic nerve. In: *Veterinary Ophthalmology* (eds Gelatt, K.N., Gilger, B.C. & Kern, T.J.), pp. 1432–1473. Oxford: John Wiley and Sons.)

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evaluated, though these are often obscured by myelin in the normal canine ONH. Switching from the optic disc rim to the bottom of the physiologic cup requires the addition of negative Diopter lenses to change and maintain focus (Murphy & Howland, 1987). It should be borne in mind that axial magnification of the canine fundus is markedly greater than lateral magnification with direct ophthalmoscopy. Although height or depth of lesions can be estimated from published values predicting diopter equivalents in millimetres (Fig. 27.9), with each 1D change in focus equivalent to an estimated 0.275 mm (Murphy & Howland, 1987), these estimates rely on assumptions in theoretical models and have not been validated in the living canine eye.

Binocular indirect ophthalmoscopy provides stereopsis and allows evaluation of the optic disc even through hazy ocular media. Slit lamp indirect systems provide greater magnification than headset systems. Use of a +78D or +90D indirect lens in conjunction with a table-mounted slit lamp biomicroscope is typically used to evaluate the human ONH, because this technique provides a highly magnified view of the ONH. This technique is much more challenging to perform than conventional indirect ophthalmoscopy, particularly in uncooperative subjects, and is seldom utilized in veterinary patients. Use of a binocular indirect ophthalmoscope headset during a complete eye examination provides a less favorable view of the ONH than slit lamp examination and for this reason is not generally used in human patients, e.g., to evaluate glaucomatous excavation of the ONH. In particular, use of 20–30D lenses is not recommended for evaluation of the ONH in humans. Although these lenses are helpful for providing an overview of the fundus, neither stereopsis nor magnification are considered sufficient to enable full appreciation of the extent of ONH excavation or elevation in people (Jonas et al., 1999). Use of a 14D indirect ophthalmoscopy lens may be considered a reasonable compromise for evaluation of the ONH in canine patients, although predicted lateral magnification (2.6×) and axial magnification (9.03×) are considerably less than with direct ophthalmoscopy (Murphy & Howland, 1987). These values represent estimates from theoretical models that incorporate a number of assumptions (including viewing distance and emmetropia) that may not hold true in a clinical setting.

Direct ophthalmoscopic examination with red-free (i.e., green) light allows RNFL visualization, because the red-free light does not penetrate beyond the NFL but is reflected back from the innermost retinal layers as light, silvery streaks of reflection from axon bundles. Thus, areas of RNFL attenuation, caused by glaucoma or by other retinal and optic nerve disease, appear dark in red-free light because of absorption of incident light by the retinal pigment epithelium in the absence of these reflective structures (Quigley & Addicks, 1982; Quigley et al., 1982). These RNFL defects are easier to see in the thickest portions of the RNFL, close to the ONH and retinal vasculature (Quigley & Addicks, 1982), and in dogs visualization of the RNFL is more readily accomplished in the pigmented, non-tapetal region of the peripapillary fundus (Fig. 27.10).

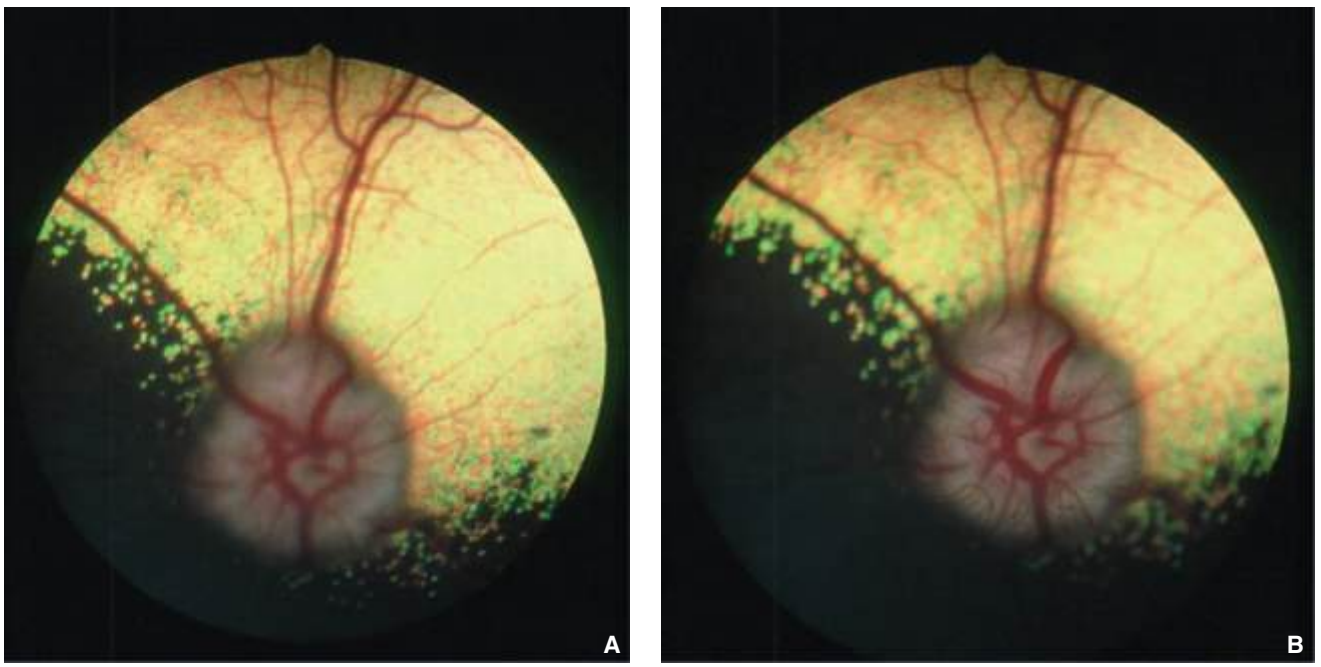


Figure 27.9 Extent of pathological swelling and elevation of the optic nerve head surface can be appreciated by noting dioptric correction needed to focus on the vasculature of the optic nerve head surface (**B**), relative to focus on the vasculature of the surrounding retina (**A**). (*Source*: Courtesy of Dr. C. Heinrich, with permission.)

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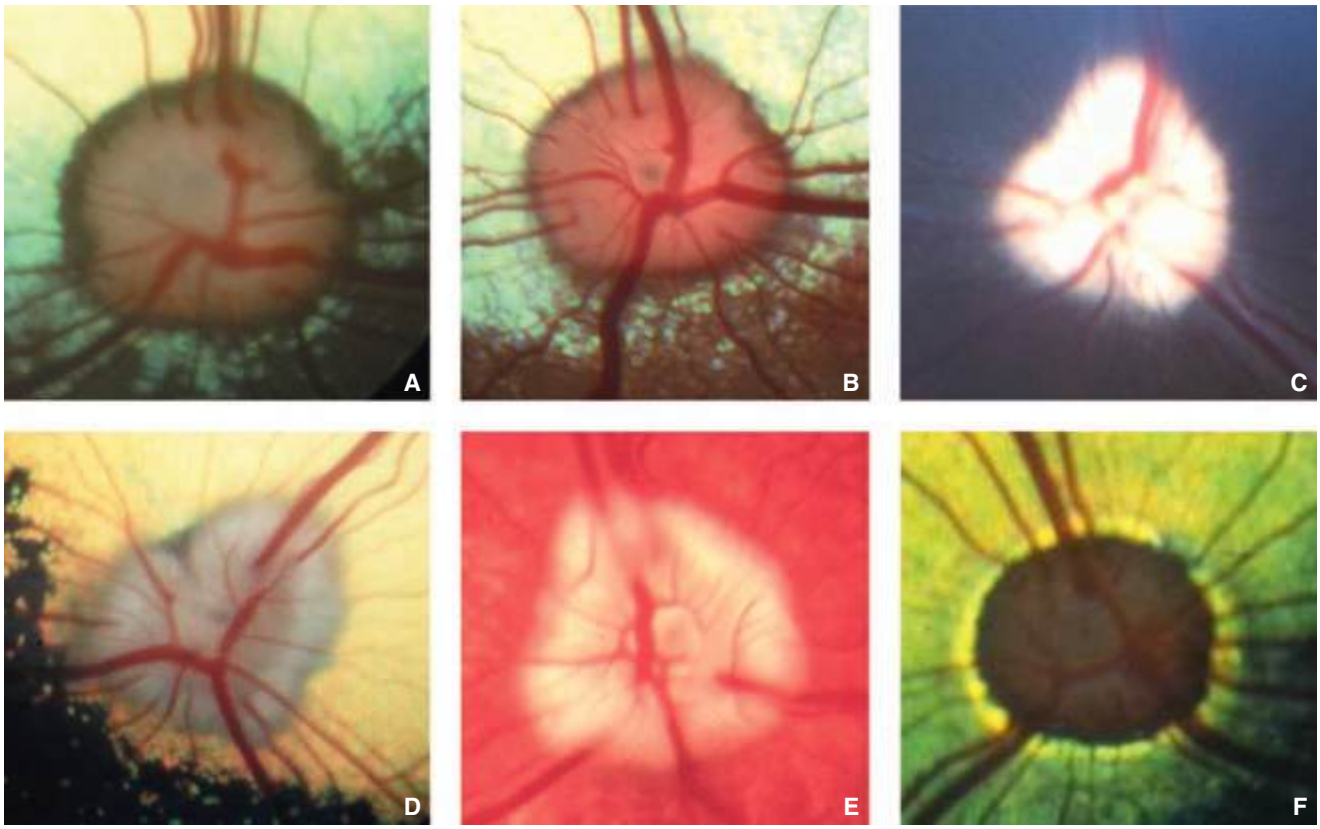


Figure 27.10 The canine optic disc exhibits dramatic variation in appearance between individuals but is generally approximately circular and white to pale pink in appearance (**A**, **B**) because of the combination of myelination of retinal ganglion cell axonal fibers as they reach the optic nerve head (ONH), anterior to the lamina cribrosa, and the ONH vasculature. A small grey spot at the center of the disc is the normal "physiologic pit" (**B**). Particularly in eyes that have dark pigmentation surrounding the ONH, and within the non-tapetal fundus, (**C**) fine, faint, glistening streaks may be seen radiating from the disc, following the course of major vessels, that represent axon bundles in the nerve fiber layer. These fibers may be myelinated to a variable extent within the retinal nerve fiber layer extending from the ONH and raised above the surrounding plane of the adjacent retina, termed pseudopapilledema (**D**, **E**). The border between superior, tapetal and inferior, non-tapetal regions of the fundus often extends just inferior to the optic disc (**A**, **B**, **D**, **F**). Usually three to five major venules converge at the disc, deviating slightly at its margins. These vessels may anastomose on the optic disc surface to a variable degree, forming a near complete or partial venous circle. About 12–20 smaller retinal arterioles emerge at the ONH and some follow the course of the retinal veins. The optic disc may be surrounded by a ring of pigment (**A**, **B**), or by a thinner region of neuroretinal tissue that appears as a "halo" of hyperreflectivity, often referred to as "conus" (**F**).

Clinical Appearance of the Canine Optic Nerve Head

A thorough clinical examination of the canine ONH should evaluate the following features: color, size, caliber, and course of visible vasculature; relative extent of the optic cup and neuroretinal rim; presence of an identifiable physiologic pit, as well as the sharpness of delineation of the boundaries of these features and their plane of focus. The appearance of the vasculature and RNFL reflection in the peripapillary retina should also be evaluated with red-free light.

The anterior-most portion of the ONH that is viewed by an ophthalmoscope, also referred to as the optic disc or papilla, is delineated by the termination of Bruch's membrane and choroid, at the scleral canal (also referred to as the neural canal), and consists of the neuroretinal rim and the optic cup (Fig. 27.11) (Jonas et al., 1988). The optic cup is defined on the basis of contour, where the axons make a 90-degree turn to exit the eye, and is considered an important feature in the clinical evaluation of the human ONH. In contrast to humans, however, the boundaries of the true optic cup may be difficult to identify in dogs, particularly in those with extensively myelinated nerve fibers, in which only the central physiologic pit may be appreciable as a small dark spot (Fig. 27.10). In humans, larger-sized optic discs tend to have larger cups, which is an important reason for relating the width of the optic cup to overall size of the disc and neuroretinal rim width (Jonas et al., 1988).

Optic Disc Cupping and the "Cup to Disc" Ratio

Enlargement of the ONH cup, or "cupping", is an ophthalmoscopically visible abnormality associated with advanced glaucoma in humans (Jonas & Naumann, 1993) and dogs (Brooks et al., 1989a) (see Chapter 20 of this text, in which

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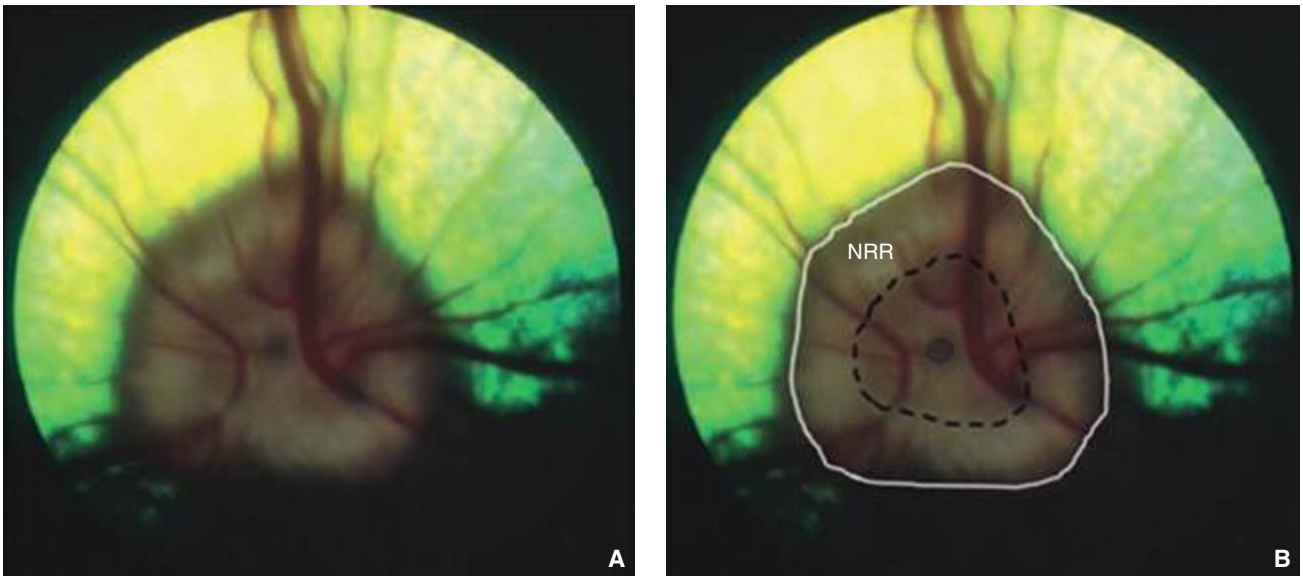


Figure 27.11 **A.** The optic nerve head (ONH) of the dog is often irregular in shape because of the myelination of nerve fibers anterior to the lamina cribrosa. Retinal arterioles and venules anastomose on the ONH surface, and combined with white myelin, lend an overall pink hue to the ONH. **B.** The margins of the optic cup (dashed black lines) and physiologic pit (central small black circle) can be seen, as can the neuroretinal rim (NRR), although determination of its outer boundary, at the ONH margin (white line), is often subjective because of myelin extending into the nerve fiber layer of the retina in many dogs.

ONH features in glaucoma are described in greater detail). In humans and nonhuman primates, optic nerve "cupping" results from a combination of: axonal loss; laminar plate compression and remodeling; posterior displacement and rotation of the scleral insertion zone of the LC; outward bowing of the LC, and a widening of the scleral canal delineated by Bruch's membrane. The associated enlargement of the ONH cup with these laminar and axonal changes is specific to glaucoma, and distinct from changes observed in other optic neuropathies (Burgoyne, 2015). Unfortunately, although similar structural changes are thought to occur in canine glaucoma, myelination of the canine ONH often obscures clinical ophthalmoscopic detection of early increases in optic cup size in dogs with early glaucoma.

The ratio of the cup to disc diameter or area is used to evaluate progression of glaucomatous optic nerve damage in humans. Enlargement of the cup to disc ratio indicates optic nerve axonal loss and is associated with deterioration in visual fields (Quigley et al., 1982). The normal average cup to disc ratio for humans is 0.32 (Jonas et al., 1994), and for normal Beagles and normal Whippets, ratios are reportedly 0.31 and 0.29, respectively (Martins & Brooks, 2013). The cup to disc ratio increases in advanced canine glaucoma as the demyelination of optic nerve axons proceeds in association with RGC death and axonal degeneration. As in human subjects (Reis et al., 2012), advances and application of confocal laser scanning ophthalmoscopy (cLSO) (Fig. 27.12) and optical coherence tomography (OCT) (Fig. 27.13 and Fig. 27.14) may provide a means to improve accuracy in delineation of ONH topography and quantification of the nerve fiber layer thickness and disc area in dogs (Bemis et al., 2017), and ultimately neuroretinal rim width and optic cup width and depth in dogs. The latter, OCT-derived parameters are currently unreliable, and are difficult to delineate and measure manually in dogs, due to pronounced interindividual variability in extent of ONH myelination (Graham et al., 2020). Given properties such as viscoelasticity and compliance of ONH tissues, IOP should be controlled if quantitative measurements are to be acquired for the ONH, and careful attention paid to scan alignment and centration (McLellan & Rasmussen 2012). Because advanced imaging technologies including cLSO, OCT, and OCT angiography (see later) are increasingly available in human and veterinary clinical and research settings, multimodal imaging strategies will enhance our abilities to detect morphologic changes in the ONH throughout the course of disease. The Heidelberg Retinal Tomograph cLSO system provided the first *in vivo* evidence to support movement of the ONH and LC in dogs with glaucoma in a research setting. However, this cLSO system relies on comparison with a normal database, which is lacking for the dog, and with rapid developments in the OCT field, is being superseded by OCT in human patients.

Angiography

Fluorescein and indocyanine green angiography are described in detail elsewhere in this text (Chapter 25) and allow simultaneous, sequential visualization of blood flow

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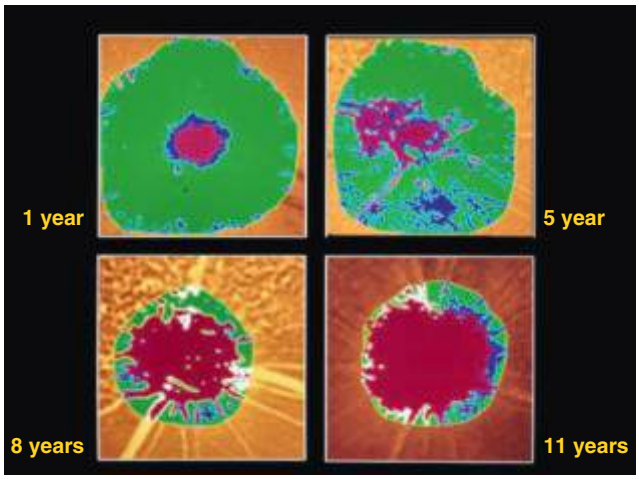


Figure 27.12 Confocal scanning laser ophthalmoscopic pseudocolor images of the optic nerve head in Beagles with chronic open-angle glaucoma illustrates the increases in cup area and depth and reduction of neuroretinal rim width as the disease progresses. In these images, red represents optic nerve head cupping and posterior displacement of the lamina cribrosa, whereas green depicts the neuroretinal rim, which appears elevated relative to the adjacent retinal surface in many dogs because of the presence of myelin. (*Source*: Reproduced with permission from Martins & Brooks (2013) Diseases of the canine optic nerve. In: *Veterinary Ophthalmology* (eds Gelatt, K.N., Gilger, B.C. & Kern, T.J.), pp. 1432–1473. Oxford: John Wiley and Sons.)

through the retina, ONH, and choroid. Fluorescein angiography can show areas of slow filling, nonperfusion, and hemorrhage in diseased segments of the optic disc (Martins & Brooks, 2013). Shifts in the course of ONH arterioles occur as the ONH swells or is pushed forward, or as the optic cup deepens and widens with advancing glaucomatous damage. Unfortunately, fluorescein angiography is insensitive to the early phases of tissue loss in the neuroretinal rim in optic nerve degeneration and glaucomatous atrophy. Optic discs develop a persistent hyperfluorescence that is more pronounced in association with optic nerve inflammation through leakage of fluorescein dye into the ONH ECM from the choroid (Smith et al., 2017). Indocyanine green is an alternative dye for angiography of the retina, choroid, and optic nerve. In contrast to fluorescein, indocyanine green is highly protein bound and does not readily leak out of the vasculature and does not result in persistent hyperfluorescence of the ONH. Recently, advances in OCT angiography promise to supersede conventional fluorescence angiography, by providing exquisitely detailed images of integrity, course and perfusion defects in the microvasculature of the human ONH without need for intravenous injection of fluorescent dyes (Akil et al., 2017). Though promising, use of OCT angiography has not yet been described in canine eyes in a veterinary clinical or research setting.

Diagnostic Imaging in Optic Nerve Disease

Magnetic Resonance Imaging and Computed Tomography

Magnetic resonance imaging (MRI) is considered the cross-sectional imaging technique of choice in diagnostic investigation of humans with suspected prechiasmatic optic nerve disease (Menjot de Champfleur et al., 2013). MRI can be used to identify or exclude intraorbital or intracranial mass lesions in the differential diagnosis of canine optic nerve swelling, and to diagnose optic nerve tumors, and is invaluable in localizing pathology in subjects with suspected elevation in intracranial pressure, helping to differentiate causes of ONH swelling. The utility of MRI as a clinical diagnostic tool to aid in diagnosis and localization of lesions affecting the optic nerves and central visual pathways is now well established by studies of MRI findings in veterinary patients with suspected intracranial, optic nerve, and orbital diseases (Armour et al., 2011; Dennis, 2000; Grahn et al., 1993; Seruca et al., 2010; Smith et al., 2017). Findings in dogs with optic neuritis included hyperintensity of one or both optic nerves, or of the optic chiasm (Armour et al., 2011). In this series, 7/13 patients with suspected optic neuritis showed intracranial multifocal contrast enhancement (Armour et al., 2011), although specific etiologic diagnosis was not always confirmed. In another reported series of dogs with optic neuritis, presence of intracranial contrast-enhancing, hyperintense lesions distinguished meningoencephalomyelitis of unknown origin (MUO) from isolated optic neuritis (Smith et al., 2017). In another study, which examined MRI findings in dogs and cats with acute, postretinal blindness, lesions affecting the visual pathways were observed on MR images in six cases (Seruca et al., 2010). Neuroanatomic localization included lesions of the olfactory region with involvement of the optic chiasm, the pituitary fossa with involvement of the optic chiasm and optic tracts, and optic nerve lesions. Of the lesions detected, five were consistent with intracranial neoplasia (two meningiomas, one pituitary tumor, and two instances of nasal neoplasms with intracranial extension), and one was consistent with bilateral optic neuritis, subsequently confirmed by CSF analysis (Seruca et al., 2010). MRI can therefore be used to identify or exclude intraorbital or intracranial mass lesions in the differential diagnosis of optic nerve swelling, and to diagnose optic nerve tumors, and is invaluable in localizing pathology in subjects with suspected elevation in intracranial pressure, helping to differentiate causes of ONH swelling.

In combination with gadolinium contrast enhancement, and fat-suppression techniques, MRI can provide images of the optic nerves that incorporate highly detailed 3D spatial information and are generally superior to those of computed tomography (Boroffka et al., 2008; Parry & Volk, 2011).

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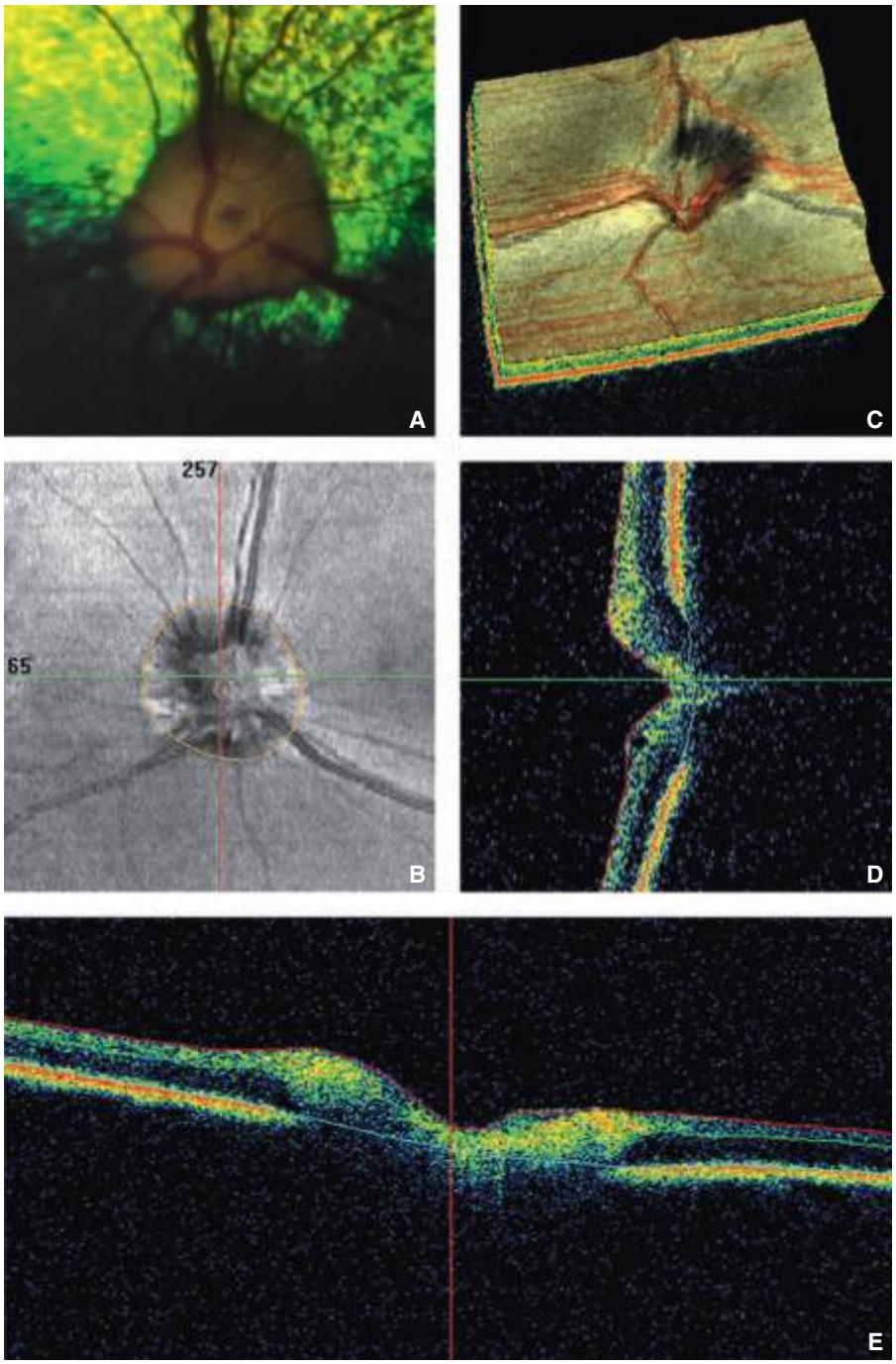


Figure 27.13 **A.** Fundus photograph of a normal canine optic disc, with corresponding *en face* infrared image, **B**. Optical coherence tomography scans of this optic nerve head shown as three dimensional cube scan (**C**) and line scans clearly (**D, E**), that clearly illustrate the raised contour of the neuroretinal rim and central, depressed optic cup (green and red lines on **C** indicate orientation of line scans depicted in **D** and **E**). (*Source*: Courtesy of Dr. C. Pirie, with permission.)

Because the canine optic nerve is sigmoid within the orbital region, and is also small in cross-section, relatively thin slice thicknesses (e.g., 1–2 mm) are required especially for adequate visualization of the optic canal and prechiasmatic portions of optic nerves (Boroffka et al., 2008). Ideally, high-field MR systems (1.5–3 Tesla), T1- and T2-weighted views, with and without gadolinium contrast enhancement should include axial, coronal, and sagittal sections; oblique views aligned with the long axis of the optic nerve (oblique sagittal) may also be of value.

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Figure 27.14 Optical coherence tomography scan of feline optic nerve head (ONH). In contrast to the typical heavily myelinated canine ONH, the feline ONH is depressed relative to the surrounding retinal surface and does not have highly reflective myelin within nerve fibers of the prelaminar ONH tissue surface, allowing visualization of exquisite detail of subsurface reflective structures in the ONH, including the lamina cribrosa (LC) that approaches "in vivo histology" (compare with photomicrographs in Fig. 27.2 and Fig. 27.3). Such detail may also be observed in less myelinated variants of the canine ONH.

The intraorbital and intracanalicular parts of the optic nerve are consistently visible, and differentiation between the optic nerve and optic nerve sheath complex is possible, even using low-field MR systems (Boroffka et al., 2008; Parry & Volk, 2011). The mean diameter optic nerve sheath complex in the dog, calculated in one MR study, was 3.7 mm, and diameter of the canine optic nerve itself was 1.7 mm (Boroffka et al., 2008). Because there is continuity between the intracranial subarachnoid space and the subarachnoid space of the optic nerve sheath, a shift in CSF in patients with increased intracranial pressure (ICP) leads to enlargement of the optic nerve sheath. Sensor placement for direct measurement of ICP in dogs is generally considered cost-prohibitive and highly invasive. It has been shown that MRI-derived measurements of the diameter of the optic nerve sheath, expressed as a ratio relative to body weight, may provide a surrogate measure of ICP in dogs (Scrivani et al., 2013). Although a limitation of that study was reliance on other MRI features suggestive of increased ICP to diagnose intracranial hypertension, rather than true ICP, results showed acceptable interobserver reliability (Scrivani et al., 2013).

Advanced, high field, and diffusion tensor-weighted MRI is increasingly utilized in both clinical and research settings in human subjects, and animal models with a range of neuroinflammatory and dysmyelinating disorders, including optic neuropathies associated with multiple sclerosis and glaucoma in people. These techniques provide a means to assess the nature, extent, and progression of pathology of white matter tracts of the CNS, including the optic nerves and optic tracts, noninvasively (Ogawa et al., 2014), and their application has been described in both dogs and cats in a research setting (Jacqmot et al., 2013; Li et al., 2018; McLellan et al., 2017; Middleton et al., 2018; Olivier et al., 2013).

Computed tomography (CT) provides detail superior to that of plain-film radiography for orbital bone, soft tissue, and foreign bodies (Dennis et al., 2014). Although less favorable for imaging soft tissue and neural structures than MR, CT provides information complementary to MRI that can be critical in the evaluation of patients with orbital trauma, including detection and localization of metallic foreign bodies and bone fragments. Additionally, three-dimensional reconstructions can prove invaluable in surgical planning (Fig. 27.15). Orbital CT scans with axial and coronal views also allow the integrity of the optic nerve and the presence of an optic nerve sheath hematoma, orbital hemorrhage, or orbital fracture to be assessed. CT is also valuable in the investigation of optic neuritis, orbital cellulitis, and in localizing optic nerve and orbital neoplasia, with the advantage of affording the opportunity for CT-guided biopsy. The presence of tumors within or impinging on the optic nerve may cause the optic nerve to appear to be diffusely enlarged, irregularly thickened, or fusiform. Calcification of optic nerve and orbital tumors may be noted and is a common feature of canine orbital meningioma (Fig. 27.16).

Ultrasonography

Real-time, *B-scan ultrasonography* enables visualization of the optic nerve and its dural sheath, aids in localization and differentiation of solid, soft-tissue masses from cystic orbital space occupying lesions, determination of the size and integrity of ocular and orbital structures in patients with known or suspected trauma, and can assist with localization of some orbital foreign bodies (see Chapter 10, Part 3). Although lacking the diagnostic specificity and sensitivity of MRI or CT in the investigation of suspected optic nerve disease, ultrasonography has the practical and economic advantage of seldom requiring general anesthesia in veterinary patients (Dennis et al., 2014).

In specialist applications, color-flow Doppler imaging combining conventional B-mode ultrasonography with Doppler flow analysis has been used to evaluate blood flow in the orbital vasculature of normal and glaucomatous dogs (Gelatt et al., 2003; Gelatt-Nicholson et al., 1999a, 1999b; Schmid & Murisier, 1996). Although, as discussed above, MRI may be used to identify signs consistent with increased ICP and intracranial hypertension, MRI is costly and time consuming for longitudinal monitoring of patients, and in dogs this would also require general anesthesia for immobilization. For this reason, ultrasonographic measurement of optic nerve sheath diameter has been widely used in human patients as a surrogate measure of ICP. Applicability and

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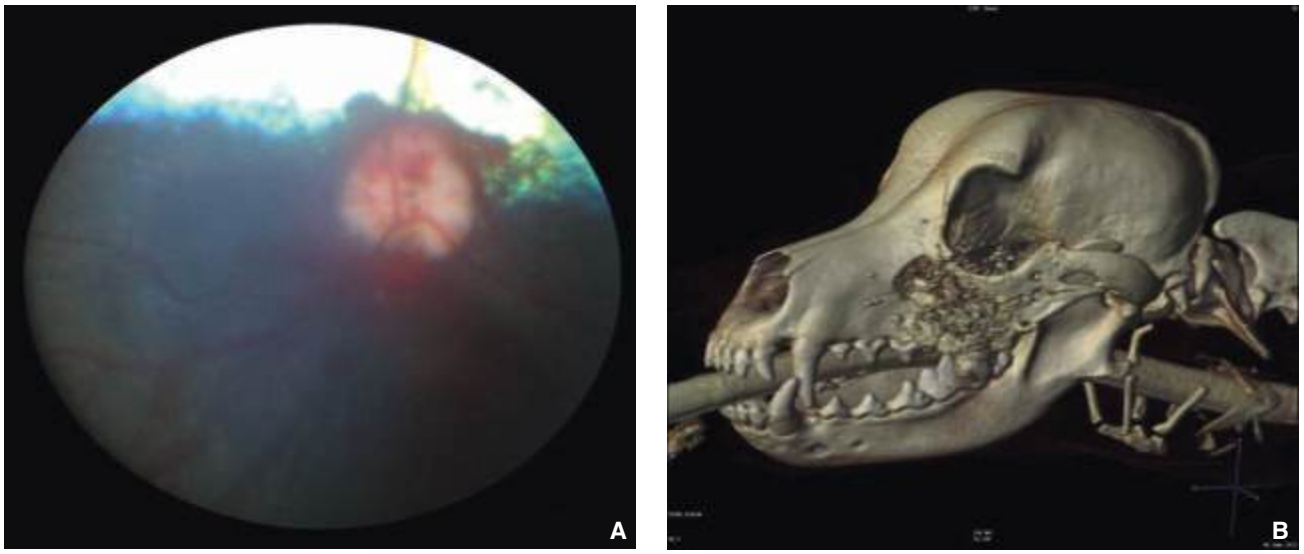


Figure 27.15 **A.** Fundus photograph of a young adult male Beagle that sustained a gunshot wound, with the entry wound on the contralateral maxillary region of the face. Swelling and congestion of the optic nerve head with extensive nerve fiber layer, peripapillary preretinal and multifocal intraretinal hemorrhages. The eye appeared outwardly normal but was blind, with complete afferent pupillary light reflex deficit. **B.** Three-dimensional reconstruction from computed tomography scans illustrates extent of traumatic disruption of the inferior orbit and maxilla, with multiple bone fragments present within the orbit. The optic canal appeared intact. Possible laceration and contusion of the orbital and intra-canalicular optic nerve were suspected, respectively.

reproducibility of ultrasound-derived optic nerve sheath diameter measurement has been evaluated in normal dogs, and shows promise as an applicable technique in an emergency and critical care setting (Ilie et al., 2015; Lee et al., 2003; Smith et al., 2018).

Electrophysiological Testing in Optic Nerve Disease

Electrophysiological tests, including recording of visual-evoked cortical potentials (VEPs), pattern electroretinograms, and the photopic negative responses of the full-field flash electroretinogram, provide non-invasive functional measures that reflect RGC axon and soma pathology (Maffei & Fiorentini,1982; Parisi et al., 2001; Viswanathan et al., 1999, 2000) (see also Chapter 10, Part 4). However, these tests are technically demanding, show high degrees of inter-individual variability and require significant expertise and specialized testing equipment. Consequently, they have not been widely adopted in clinical veterinary medicine, and their application in animals has largely been confined to a research setting. The most widely utilized electrophysiological test in the diagnosis of human optic nerve disease is the VEP

Visual-Evoked Potential

The VEP is an electrical signal generated in the occipital cortex in response to visual stimuli, and it is used to evaluate optic nerve function (American Clinical Neurophysiology Society, 2006; Odom et al., 2016). Thus, VEP can be used to help distinguish vision loss from retinal or optic nerve pathology, when combined with ERG. Complete optic nerve transection results in absence of the flash VEP, but with preservation of the flash ERG (Sims et al., 1989). Diseases such as optic neuritis or neuropathies that preferentially cause optic nerve demyelination or hypomyelination are associated with delayed latency of the VEP (You et al., 2011; Heidari et al., 2019). In contrast, diseases such as glaucoma that directly cause axonal degeneration and loss will tend to reduce VEP amplitudes as well as increasing their latencies.

Studies involving flash VEP (Kimotsuki et al., 2006; Sims et al., 1989) and pattern VEP recorded to checkerboard or grating patterned stimuli have been reported in dogs (Itoh et al., 2010; Ito et al., 2016; Ofri et al., 1993), but both techniques are considered technically demanding and require sedation or general anesthesia in veterinary patients. The pattern VEP responses exhibit less intra- and interindividual variability and are most sensitive to detection of optic nerve pathology in human patients, but they are particularly challenging to record reproducibly in dogs and require careful calibration of the source of the pattern stimulus presented to ensure consistency of luminance to avoid introducing artifact (Odom et al., 2016). Canine pattern VEP amplitudes are not only affected by the anesthesia and sedation that are necessary in veterinary subjects that cannot fixate on the stimulus (Ito et al., 2015), but are also affected by age (Kimotsuki et al., 2006), and refractive state (Ito et al., 2016). Thus,

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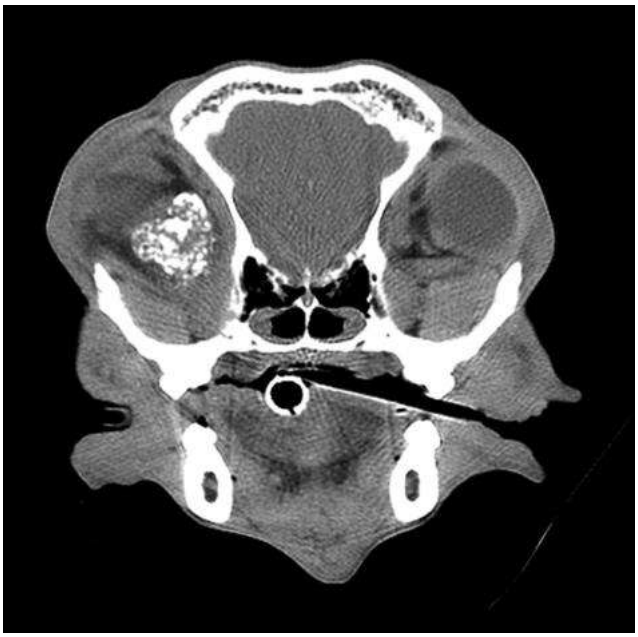


Figure 27.16 Computed tomography scan of a mineralized mass within the right orbit of a 9-year-old Boston Terrier that presented with exophthalmos, pronounced optic nerve swelling, and a dilated pupil with afferent pupillary light reflex deficit in the right eye. Histopathology after exenteration subsequently confirmed canine orbital meningioma, a tumor type that very frequently incorporates islands of chondroid and osseous metaplasia.

although the VEP is relatively sensitive to optic neuropathy and myelin disorders, VEP recording is not commonly performed in clinical veterinary practice because of a need for consistent sedation or anesthesia and lack of equipment, expertise and, importantly, a lack of species, breed, age, and gender-specific normative data for comparison. It is also important to consider that VEP relies not simply on integrity of the optic nerve, but also on integrity of the retina, the optic chiasm, optic tracts, and optic radiations/central visual cortex, limiting specificity of VEP in the detection of optic nerve disease.

Optic Nerve Disorders

Congenital Optic Neuropathies

Optic Nerve Hypoplasia/Micropapilla

The distinction between micropapilla and optic nerve hypoplasia is based on clinical appearance of small ONH dimensions, with either presence or absence of vision, respectively. Thus, a small optic disc in an eye with clinically normal PLRs and vision, is termed micropapilla, whereas if the number of axons is so low that PLR deficits and visual deficits are identifiable, the condition is termed optic nerve hypoplasia. Micropapilla and hypoplasia of the optic nerve may be unilateral or bilateral, and are associated with an abnormally small optic disc size identified by ophthalmoscopy. Optic nerves that are smaller than two standard deviations below the mean diameter are considered statistically abnormally small in humans (Jonas & Naumann, 1993). Using this same definition, ONHs less than about 1.7 mm in diameter could be considered abnormally small in the dog (Balaratnasingam et al., 2009). However, there is a relatively wide range in the number of RGC somas and optic nerve axons reported for normal dogs, and in puppies, myelination of the ONH is not complete until several weeks of age so that the ONH of young puppies appears small, round, and dark in color. The size of the ONH can vary with number of axons and, in general, larger ONHs incorporate more nerve fibers than smaller ONHs (Arey & Gore, 1942; Arey et al., 1942; Brooks et al., 1995; Jonas et al., 1992), but in dogs the true dimensions of the optic nerve are often obscured by myelination in the ONH. Although it has been shown that optic disc size is positively correlated with total optic nerve axon fiber count in human eyes, this association is relatively weak and similar studies have not been carried out in dogs (Jonas et al., 1992). Together with the confounding variability in the extent of intraretinal and prelaminar myelination of the ONH in normal dogs, accurate determination of true ONH dimensions is problematic in a clinical setting in this species, meaning that assessment of the relative size of the canine ONH is usually subjective.

On ophthalmoscopy, in both micropapilla and optic nerve hypoplasia, the ONH will appear small and often relatively gray because of lack of myelinated fibers visible on the disc surface (Fig. 27.17 and Fig. 27.18). This feature may be subtle or pronounced. The appearance of the retina and its vasculature may appear normal or vessels may be tortuous but typically normal in caliber, even though the observer may perceive retinal blood vessels to be larger than normal, relative to the small size of the ONH (Fig. 27.17). Visual deficits associated with optic nerve hypoplasia span a spectrum from reduced but near normal vision, which may not be appreciated by owners, particularly when unilateral, to total blindness in dogs with severe bilateral optic nerve hypoplasia. In contrast, whether unilateral or bilateral, micropapilla is generally considered an incidental finding in the absence of any appreciable clinical signs. In dogs with optic nerve hypoplasia, the afferent component of the PLR is abnormal and, in dogs with unilateral optic nerve hypoplasia, the efferent component of the consensual PLR from the unaffected to the affected eye is normal. Resting pupil size is likely to be normal in dogs with micropapilla and may be slightly larger than normal on the affected side in dogs with unilateral optic nerve hypoplasia. Both pupils may be widely dilated and unresponsive in dogs with bilateral optic nerve hypoplasia. Normal full-field flash ERG responses confirm intact photoreceptor and bipolar cell function (Ernest, 1976).

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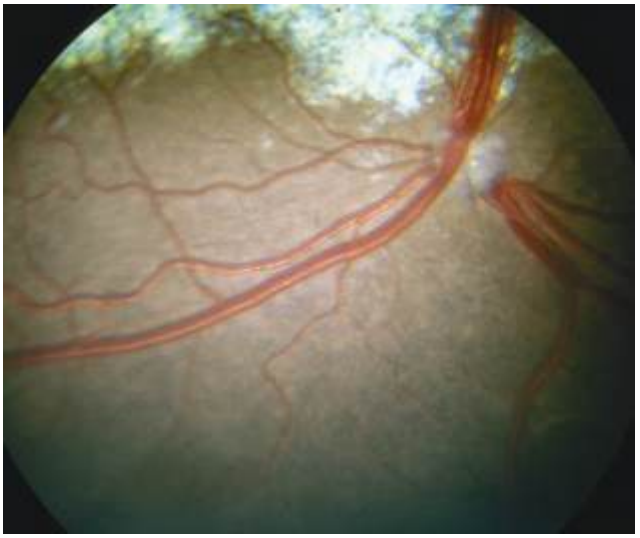


Figure 27.17 Extreme optic nerve hypoplasia in a dog. Retinal vessels are normal sized in this condition but appear more prominent relative to the small optic nerve head. (*Source*: Reproduced with permission from Martins & Brooks (2013) Diseases of the canine optic nerve. In: *Veterinary Ophthalmology* (eds Gelatt, K.N., Gilger, B.C. & Kern, T.J.), pp. 1432–1473. Oxford: John Wiley and Sons.)

In the dog, both micropapilla and optic nerve hypoplasia may occur sporadically in any breed, either in isolation or accompanying other ocular malformations (Fig. 27.19) (Garcia da Silva et al., 2008; Kern et al., 1981). Micropapilla, and less frequently, optic nerve hypoplasia, have been reported in Australian Shepherds, Beagles, Belgian Sheepdogs, Belgian Tervuren, Borzoi, Bullmastiffs, Collies, Dachshunds, Flat-Coated Retrievers, German Pinschers, German Shepherd dogs, Great Pyrenees, Gordon Setters, Irish Setters, Irish Wolfhounds, Labrador Retrievers, Miniature Pinschers, Schnauzers, Norfolk Terriers, Nova Scotia Duck Tolling Retriever, Old English Sheepdogs, Papillons, Poodles (miniature and toy), Pugs, Pulis, Shelties, Shih Tzus, Soft-Coated Wheaten Terriers, and Tibetan Spaniels (Ernest, 1976; Garcia da Silva et al., 2008; Grahn & Sandmeyer, 2009; Negishi et al., 2008; The Genetics Committee of the American College of Veterinary Ophthalmologists, 2018). Optic nerve hypoplasia and micropapilla are specifically considered inherited in the Miniature and Toy Poodle and Dachshund breeds. However, pedigree and candidate gene association studies in Miniature Poodles have not yet established the molecular genetic basis of optic nerve hypoplasia and micropapilla in this breed (Becker et al., 2020). Dogs with optic nerve hypoplasia should not be used for breeding.

Histopathologically, the hypoplastic optic nerve is composed of sparse neural elements and a moderate amount of connective and glial tissues. In these eyes, the RNFL and ganglion cell layers of the retina may be thinner than normal, and RGC somas will be sparse or absent (Ernest, 1976, Garcia da Silva et al., 2008; Negishi et al., 2008). Mild to moderate retinal disorganization may be observed, and in some affected eyes, the peripheral retina may be avascular, with vitreal extension of peripheral retinal blood vessels in some cases (Garcia da Silva et al., 2008). Two pathogenic mechanisms for optic nerve hypoplasia have been proposed that could both result in reduced numbers of optic nerve axons in these patients: either a failure of RGC development or excessive perinatal RGC death beyond that which occurs normally in the perinatal period after initial overproduction of RGCs during fetal development. The latter could

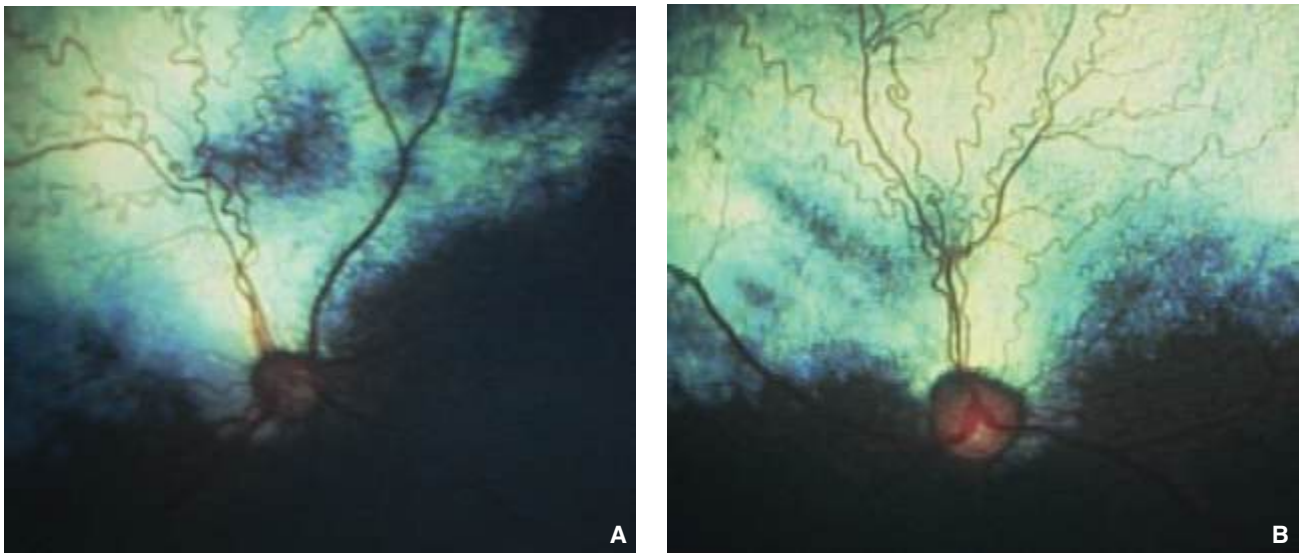


Figure 27.18 **A.** Unilateral optic nerve hypoplasia with (**B**) micropapilla in the contralateral eye of a one-year-old dog. (*Source*: Courtesy of Dr. F. Mowat and North Carolina State University College of Veterinary Medicine, with permission.)

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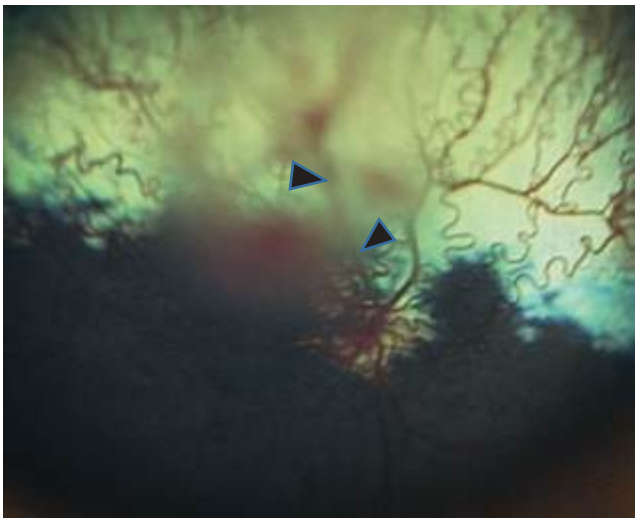


Figure 27.19 Extreme optic nerve hypoplasia in the blind eye of a 12-week-old puppy. A patent, persistent hyaloid artery is also seen extending from the posterior pole of the globe (where the optic nerve head should be located) into the vitreous in this dog (arrowheads). (*Source*: Courtesy of Dr. F. Mowat and North Carolina State University College of Veterinary Medicine, with permission.)

potentially be caused by failure of normal projection of RGC axons to meet their targets elsewhere in the central visual pathways (Martins & Brooks, 2013; Provis & Penfold, 1988).

Optic Nerve Aplasia

Optic nerve aplasia is very rare and involves a congenital complete absence of RGCs and their axons. Eyes with optic nerve aplasia show a complete lack of retinal vasculature (Fig. 27.20) (Dubielzig et al., 2010a; Garcia da Silva et al., 2008; Martins & Brooks, 2013). Optic nerve aplasia may be recognized in eyes with other abnormalities including microphthalmos, retinal disorganization, retinal detachment/non-attachment, anterior segment dysgenesis, and persistent hyaloid vasculature. In one histopathologic study, optic nerve aplasia was always unilateral (Garcia da Silva et al., 2008). However, optic nerve aplasia has also been observed bilaterally in a Beagle and a mixed-breed dog, and reported in the Irish Wolfhound (Martins & Brooks, 2013).

Achiasmatic Belgian Sheepdogs

Detailed neuropathologic reports have been published describing achiasmatic optic nerves with nystagmus in a small family of Belgian Sheepdogs (Groenendael). Congenital nystagmus is the most striking clinical feature. In affected dogs, all RGC axons projected directly to ipsilateral brain targets, with no chiasmal decussation. Although micropapilla appears to be relatively common in Belgian Shepherd breeds, no optic nerve hypoplasia or micropapilla was reported in achiasmatic dogs (Hogan & Williams, 1995).

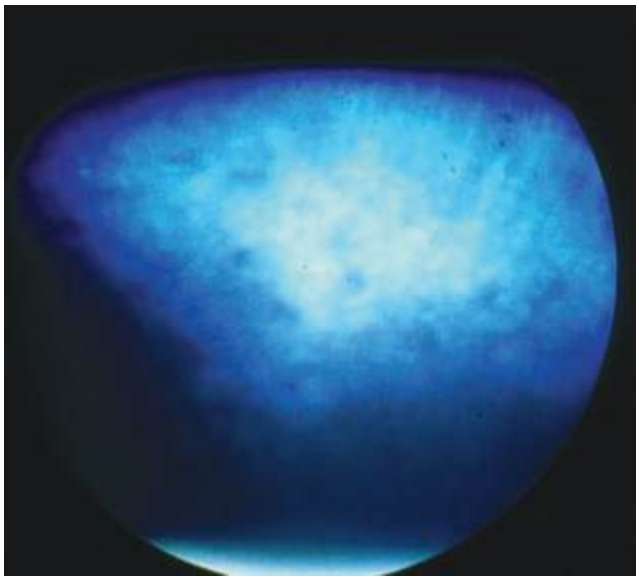


Figure 27.20 Fundus photograph illustrating complete absence of visible retinal vasculature or optic nerve head in a dog with optic nerve aplasia. (*Source*: Reproduced with permission from Martins & Brooks (2013) Diseases of the canine optic nerve. In: *Veterinary Ophthalmology* (eds Gelatt, K.N., Gilger, B.C. & Kern, T.J.), pp. 1432–1473. Oxford: John Wiley and Sons.)

Optic Nerve Coloboma

Optic nerve colobomas are congenital malformations of the ONH that result in outward distortion of the ONH caused by focal absence of normal tissue in the ONH and/or peripapillary sclera. They may appear as enlarged optic discs with a deep excavation and distorted margins, or as slightly enlarged, irregular discs containing deep pits within the borders of the nerve head. Coloboma of the ONH is most commonly recognized along with choroidal hypoplasia, as a component of the clinical syndrome "Collie Eye Anomaly" (described in detail in Chapter 25) in Collie breeds, including Australian Shepherds, Bearded and Border Collies, Rough and Smooth Collies and Shelties, as well as other breeds including Boykin Spaniels, Curly-Coated Retrievers, Hokkaido dogs, Lancashire Heelers, Nova Scotia Duck Tolling Retrievers, Silken Windhounds, and Whippets (Bedford, 1998; Mizukami et al., 2012; The Genetics Committee of the American College of Veterinary Ophthalmologists, 2018). However, ONH coloboma also occurs sporadically, either in isolation, or in association with other congenital ocular defects, such as persistent pupillary membranes and appears to be inherited in the Basenji, Dachshund and Old English Sheepdog (Barnett & Knight, 1969; The Genetics Committee of the American College of Veterinary Ophthalmologists 2018). Colobomas have also been reported in Australian Shepherds, Beagles, Bernese Mountain Dogs, American and English Cocker Spaniels, Flat-Coated Retrievers, German Shepherds, Golden

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Retrievers, Huskies, Irish Setters, Labrador Retrievers, Malamutes, Norfolk Terriers, Samoyeds, Tibetan Spaniels, and Whippets (The Genetics Committee of the American College of Veterinary Ophthalmologists 2018) and are sporadically identified in mixed breed dogs (Rampazzo et al., 2005).

On ophthalmoscopy, optic disc colobomas may be small and hard to differentiate from a prominent physiologic pit or deep physiologic cup, or they may be very large in diameter and up to 30D in depth (Fig. 27.21, Fig. 27.22 and Fig. 27.23). Colobomas located inferiorly in the optic nerve are considered to represent faulty closure or fusion (or both) of the fetal fissure of the ventral optic stalk and cup, whereas "atypical" peripapillary colobomas may originate from orbital cysts, or failure of normal differentiation of the outer layer of the optic cup (Cook, 1999). Thus, clinically, colobomas may be referred to as "typical" at the inferior, 6-o'clock position (in the location of the fetal fissure), or as "atypical" when located at the nasal or temporal disc margin (Briziarelli & Abrutyn, 1975). Colobomas of the optic disc in Collies are associated with ectasia of the LC, whereas colobomas of the peripapillary retina are best characterized as foci of ectatic sclera lined by attenuated retinal and choroidal tissues. Although small colobomas of the ONH are generally not associated with appreciable defects in vision in dogs, large colobomas communicate with the vitreous and subretinal space and their presence is a risk factor for retinal tears and detachment. For this reason, dogs with a diagnosis of ONH coloboma should not be bred.

A homozygous intronic deletion mutation in the *NHEJ1* gene is predictive for choroidal hypoplasia in dogs with Collie Eye Anomaly (Lowe et al., 2003; Parker et al., 2007). However, discordance between this gene mutation and colobomas has been reported in the Nova Scotia Duck Tolling Retriever (Brown et al., 2018), and it is apparent that it is not solely responsible for coloboma. Reports on outcomes of selective breeding practices in Rough Collies in Sweden, which permitted breeding of dogs with choroidal hypoplasia but not colobomas and resulted in substantial increase in prevalence of choroidal hypoplasia without concomitant increase in prevalence of coloboma, are supportive of this discordance (Wallin-Hakanson et al., 2000). In breeds affected by Collie Eye Anomaly, it has been suggested that colobomas result from a mutation or sequence change in a modifier (gene or genes) that requires that the homozygous intronic deletion in the *NHEJ1* gene is present. However, genotyping of Nova Scotia Duck Tolling Retrievers with colobomas identified dogs that were homozygous for the wild-type allele, as well as dogs that were either homozygous or heterozygous for the *NHEJ1* mutation (Brown et al., 2018). Research is ongoing to identify the locus associated with the presence of colobomas in dogs with Collie Eye Anomaly.

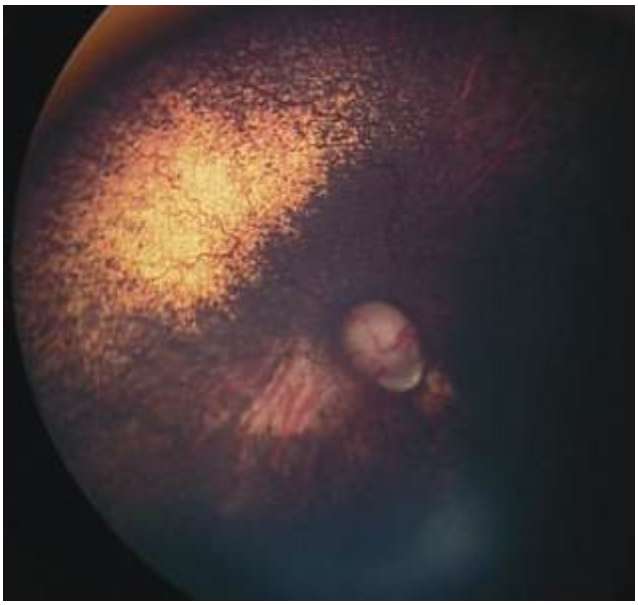


Figure 27.21 Fundus photograph of a young adult dog with Collie Eye Anomaly and a small "typical" coloboma involving the inferior margin of the optic disc. Choroidal hypoplasia is visible as a pale patch temporal to the optic disc. (*Source*: Courtesy of Dr. F. Mowat and North Carolina State University College of Veterinary Medicine, with permission.)

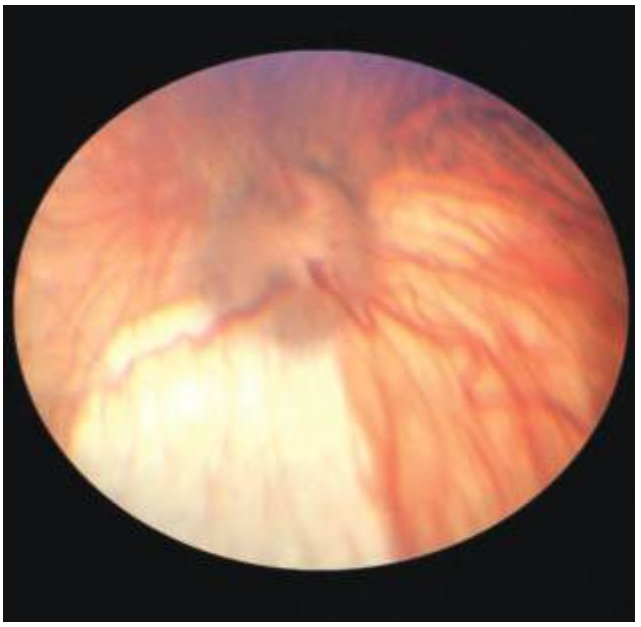


Figure 27.22 Optic nerve coloboma in an adult merle Rough Collie with Collie Eye Anomaly. There is no venous circle visible on the disc surface and dark shadows are seen at the margins of deeper pits in the uneven surface of this optic nerve head. A large area of choroidal hypoplasia/ectasia also involves the ocular fundus inferior to the optic nerve head.

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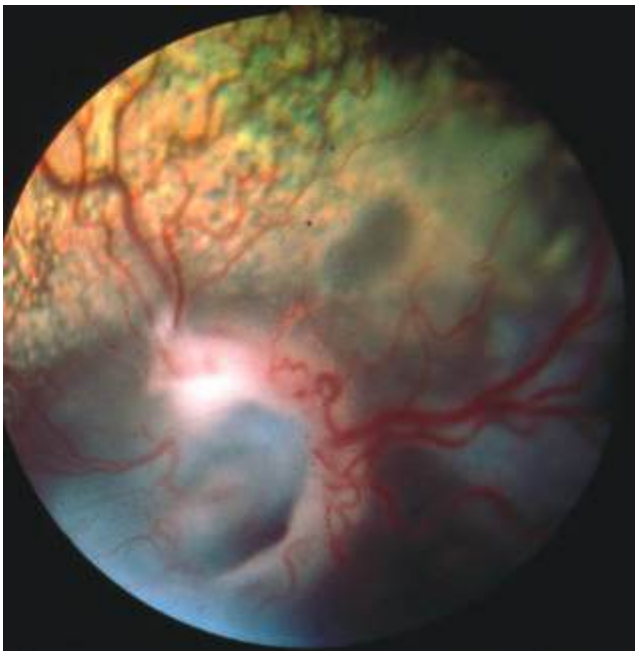


Figure 27.23 A large, irregularly oval optic nerve head with a pronounced dark optic nerve coloboma in a Collie. Pigmented and depigmented peripapillary laser burns are visible and there is elevation of the peripapillary retina. (*Source*: Reproduced with permission from Martins & Brooks (2013) Diseases of the canine optic nerve. In: *Veterinary Ophthalmology* (eds Gelatt, K.N., Gilger, B.C. & Kern, T.J.), pp. 1432–1473. Oxford: John Wiley and Sons.)

Acquired Optic Neuropathies

Disorders of the prechiasmatic visual pathways are a diagnostic challenge. Acquired optic nerve disorders may be caused by infection, inflammatory or neoplastic cellular infiltration, ischemia, trauma, or mechanical compression. These processes may arise within the nerve itself but more often reflect extension of local disease from the CNS or adjacent tissues, or involvement in a systemic disease process, underscoring the need for thorough ophthalmic, neurological and general clinical examination in affected dogs. If bilateral, optic neuropathies can lead to blindness, a presentation that is often acute in dogs. Other signs of optic nerve disease include ONH swelling, vascular congestion, or hemorrhage. These signs may, or may not, be accompanied by other signs of ocular, orbital, CNS and/or systemic disease. With chronic damage, end stage optic nerve degeneration may occur leading to loss or attenuation of vasculature (ONH pallor), demyelination (darkening), and loss of prelaminar neural tissue (resulting in enhanced visualization of LC structure and laminar pores). Optic disc cupping, with remodeling and posterior displacement of the LC, is a characteristic feature of glaucomatous optic neuropathy. In the dog, abrupt onset of vision loss with a relatively normal fundus appearance is highly suggestive of either SARDS or of retrobulbar optic neuritis. In contrast, slowly progressive loss of vision is more typical of, but not pathognomonic for, neoplastic compression or infiltration of the prechiasmatic optic nerve (Martins & Brooks, 2013).

Differential Diagnosis of the "Swollen Disc"

Pseudopapilledema

This elevation of the ONH surface by prelaminar myelination of nerve fibers in clinically healthy, normal dogs may resemble optic disc swelling caused by neoplasia, optic neuritis, or elevated ICP (i.e., noninflammatory papilledema), and may be a cause for alarm and misdirected diagnostic procedures in dogs, as well as in humans (Chiang et al., 2015). Pseudopapilledema in humans is typically associated with small and tilted optic discs. In the dog, pseudopapilledema is considered to simply result from extensive myelination of optic nerve axons anterior to the LC, which is not associated with pathology (Fig. 27.24). This raised appearance may involve the ONH focally or regionally, extend along retinal blood vessels, or involve most of the ONH, which can have an irregular, domed or "donut" appearance. Because the funduscopic appearance mimics papilledema or optic neuritis, there is a risk that some patients may receive misguided diagnostic workups or therapy (or both) for intracranial disease (Chiang et al., 2015). In humans, pseudopapilledema typically results from increased local density of nerve fibers in small, "crowded" optic discs that may be seen in small, hyperopic eyes, in tilted discs that are common in myopia, and from drusen deposits accumulating within the ONH (Chiang et al., 2015). A multimodal imaging approach, including cLSO autofluorescence imaging and OCT, has been proposed for differentiating pathological ONH swelling from pseudopapilledema in people (Chiang et al., 2015). However, imaging of the canine ONH by OCT is confounded in pseudopapilledema by pronounced reflectivity of the ONH surface in dogs with extreme myelination, as well as anterior position of the ONH surface, and limitations posed by limited focal length predetermined by the instrument or its software (Fig. 27.24). Autofluorescence imaging is less likely to be informative in dogs with pseudopapilledema than in humans, because age-related ONH autofluorescent drusen have not been recognized in dogs. Thus, distinction between pseudopapilledema and true papilledema in dogs remains subjective and somewhat dependent on observer experience and judgement. However, experience suggests that papilledema, without evidence of optic nerve dysfunction or other clinical signs suggestive of neurologic or systemic disease (see later), is very rarely encountered in dogs. In contrast, pseudopapilledema is very common in adult dogs, including, but not limited to, many of the Retriever breeds, Arctic breeds and German Shepherds (Martins & Brooks, 2013; Palmer et al., 1974).

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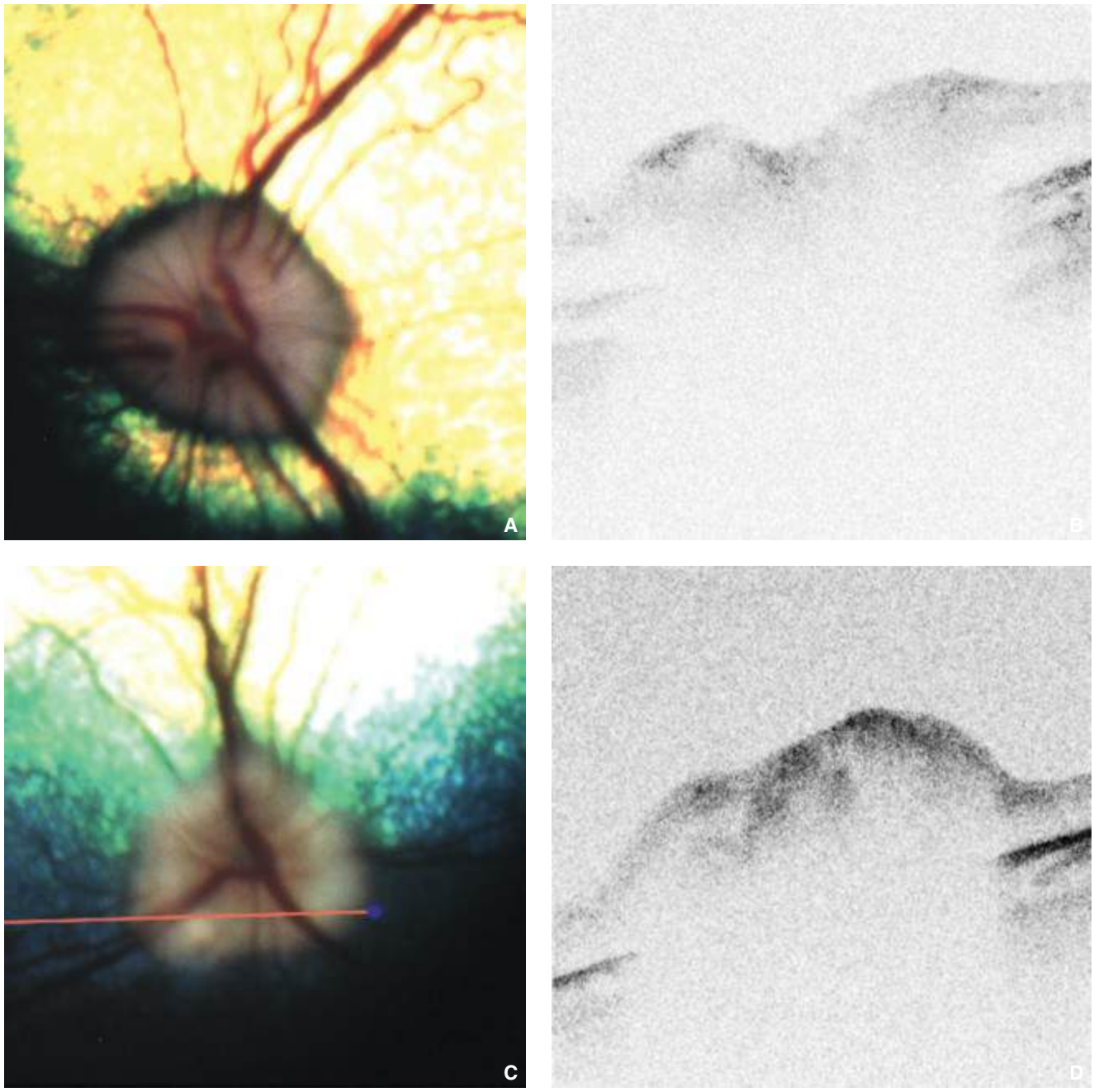


Figure 27.24 The surface of the normal canine optic nerve head (**A**) is often extensively myelinated and its surface appears relatively raised above that of the surrounding retina (**B**) shown here by optical coherence tomography imaging. In some normal dogs (**C**) more extreme myelination can be found and distinguishing this "pseudopapilledema" from pathologic swelling can be challenging. **D.** Optical coherence tomography illustrates that the extent to which the neuroretinal rim is raised above the surrounding retina in pseudopapilledema can be dramatic. **C**, **D.** Note, however, that the swelling is localized and a central depression with physiologic pit is still visible in this normal dog with pseudopapilledema.

Features that can help to distinguish pseudopapilledema from pathologic swelling of the ONH caused by increased intracranial pressure, inflammation, and/or infiltration are discussed in the sections below and are summarized in Table 27.1.

Papilledema

Papilledema, or noninflammatory swelling of the ONH, may be recognized in patients with increased intracranial pressure, and must be differentiated from the apparently "swollen disc" of pseudopapilledema (see previously), and from optic neuri-

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Table 27.1 Clinical features that may aid in differentiating pseudopapilledema from pathologic swelling of the optic nerve head in dogs.

Clinical feature	Pseudopapilledema	Pathologic swelling
Vision intact	+	±
Intact PLRs	+	±
Papillary/peripapillary hemorrhages in RNFL	–	±
ONH raised above plane of surrounding retina	+	+
Distinct physiologic pit in ONH	±	–
Margins of ONH ill-defined and blurred	–	+
Vitreous haze ± cell	–	±
Chorioretinitis (active/inactive)	–	±
Edema or elevation of surrounding, peripapillary retina	–	+
Signs of other neurologic or systemic disease	–	±

ONH, optic nerve head; PLRs, pupillary light reflexes; RNFL, retinal nerve fiber layer.

tis or other infiltrative optic nerve disease (see later). Edema of the ONH can accompany acute glaucoma, uveitis, or postoperative ocular hypotony after glaucoma surgery, and there are anecdotal reports of ONH edema in dogs with severe arterial hypertension. Axonal swelling caused by disruption of axoplasmic flow is thought to be primarily responsible for papilledema from elevated ICP as well as disc swelling caused by optic nerve compression by orbital tumors, ocular hypotony, and acute glaucoma (Tso et al., 1977a, 1977b).

Early in the course of disease, true papilledema may not affect vision, in contrast to optic neuritis, which is associated with loss of vision that is often acute and is accompanied by diminished or absent PLR. Primary (e.g., meningioma, glioma) and secondary optic nerve neoplasia (e.g., lymphoma) may cause a "swollen disc" (see later). Neoplastic infiltrates in the optic nerve and ONH may lead to elevation of the ONH and peripapillary retina, but this is generally associated with loss of vision. Orbital mass lesions characteristically produce exophthalmos, but when slowly progressive they may also present as very chronic, unilateral ONH edema secondary to local infiltration, compression, and/or changes in the local pressure gradients. In humans, lesions compressing the optic nerve are associated with insidiously advancing visual field loss, but very subtle visual field loss is likely to go unnoticed by most dog owners.

Papilledema of Raised Intracranial Pressure Papilledema associated with raised ICP is almost always bilateral and is not associated with visual deficits, at least in human patients diagnosed at earlier stages that precede optic nerve atrophy. The proposed pathogenesis of papilledema involves interruption of axoplasmic flow (Tso et al., 1977b), caused by compression of optic nerve fibers resulting from changes in the translaminar pressure gradient in the ONH, that in turn are caused by an increase in retrolaminar tissue pressure related to increased CSFp in the subarachnoid space of the intraorbital portion of the optic nerve (Morgan et al., 1998, 2002). Obstruction of axoplasmic flow caused by increased retrolaminar tissue pressure results in swelling of the axons in the prelaminar region of the ONH (Tso et al., 1977b), with venous obstruction and dilation and nerve fiber hypoxia considered secondary, contributory events. Though severe papilledema can be observed in people with acute intracranial hypertension, early and even well-developed papilledema may not be symptomatic. However, when papilledema persists for many weeks or months, axon loss, progressive vision loss, and optic nerve degeneration ultimately ensue. Although relatively common in human patients, reports of papilledema in dogs remain infrequent in the veterinary literature. It has been proposed that dogs seldom develop papilledema with increased CSFp compared with humans because, unlike humans, dogs do not have a central retinal artery whose flow could be affected by elevated CSFp. However, CSFp in the dog is transmitted directly to the retrolaminar tissue space (Morgan et al., 1995, 1998), and a rise in CSFp could theoretically still affect the vascular perfusion of the ONH through changes in this compartment. Papilledema in dogs may simply go unrecognized in many cases because papilledema has no associated PLR or vision deficits during its early stages. Additionally, variability in the extent of myelin anterior to the lamina cribrosa in the normal canine ONH is likely to confound diagnosis of papilledema in animals with pronounced myelination of prelaminar axons. Thus, the true incidence of papilledema associated with increased CSFp in dogs may be underestimated. In one veterinary report, papilledema was associated with brain tumors of various types in 10 of 21 dogs in the series. However, out of these 21 dogs, 15 were blind or had reduced vision, and/or had PLR deficits that, in many cases, could be ascribed to lesion location rather than caused by

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papilledema (Palmer et al., 1974). Most dogs in this series were bilaterally affected and increased ICP was suspected based on other clinical signs or pathologic findings at necropsy but was not directly confirmed.

Optic Nerve Swelling in Arterial Hypertension In addition to the clinical features of hypertensive chorioretinopathy, which are commonly identified in dogs and cats with hypertension (described in Chapters 25 and 37), target organ damage secondary to systemic arterial hypertension in humans can present as an optic neuropathy characterized by papilledema that can lead to optic nerve atrophy in chronic disease (Hayreh, 1989). In contrast, though anecdotal reports exist, papilledema does not appear to be a prominent feature in canine patients with hypertension in a clinical setting, potentially related to species differences in vascular supply to the canine versus the human ONH. However, this observed difference in prevalence could also reflect the challenges of diagnosing papilledema in this species (see previously), combined with a clinical picture that is dominated by retinal hemorrhage and detachment in dogs with hypertension (Leblanc et al., 2011; Sansom & Bodey, 1997). Hypertensive vasculopathy in dogs is also known to contribute to hemorrhage and ischemia in the central nervous system that can involve the visual pathways, including optic nerves and chiasm, resulting in blindness (Mari et al., 2018).

Inflammatory Optic Neuropathies

Optic neuritis represents a clinical syndrome rather than a single disease. Causes of optic neuritis in dogs are listed in Table 27.2, and include idiopathic, immune-mediated and infectious diseases, neoplasia and toxins, as well as extension of inflammatory diseases from adjacent paranasal sinuses, retina, brain and meninges, and orbit to involve the optic nerve (Nafe & Carter, 1981; Nell, 2008; Busse, et al., 2009; Smith et al., 2017). Optic nerve swelling associated with optic neuritis must be distinguished from papilledema and pseudopapilledema (see Table 27.1). When optic neuritis is suspected, extensive diagnostic testing is usually indicated, as outlined in the following sections, to exclude or confirm specific etiologic diagnoses.

Clinical Signs of Optic Neuritis

Inflammation of the canine optic nerve may be unilateral or, more frequently, bilateral though not necessarily symmetrical in presentation (Nafe & Carter, 1981; Nell, 2008; Smith et al., 2017). The disease often presents acutely in dogs, because of sudden blindness, and the pupils of the affected eyes are dilated with either absent pupillary light reflexes, or sluggish and incomplete pupillary light reflexes. This presentation in canine patients is in stark contrast to subtle defects in vision that are frequently reported by human patients at an earlier stage of disease. However, some particularly astute pet owners may notice more subtle visual deficits in their dogs, or may observe pupil dilation, anisocoria, or other neurologic signs. The retrobulbar, orbital, intracanalicular, and/or intracranial portions of the optic nerve may be affected without involvement of the intraocular portion of the ONH, particularly in granulomatous focal or multifocal disease. Thus, some patients with the focal, retrobulbar form of optic neuri-

Table 27.2 Causes of optic neuritis in dogs.

Immune-mediated/idiopathic
Mengioencephalomyelitis of unknown origin (MUO)
Isolated optic neuritis
Reactive histiocytic disease
Infectious
Protozoa
Toxoplasmosis
Ehrlichiosis
Rocky Mountain spotted fever (*Rickettsia rickettsii*)
Neosporosis
Leishmaniosis
Bacteria
Secondary – by direct extension, e.g., orbital abscess
Secondary – bacteremia, mycobacteria, brucellosis
Mycoses
Cryptococcosis
Blastomycosis
Histoplasmosis
Aspergillosis
Parasites
Ascarids, e.g., *Toxocara canis*
Filarioids, e.g., *Angiostrongylus vasorum*, Onchocerciasis
Neoplastic
Primary, e.g., orbital meningioma, optic nerve glioma
Secondary, direct invasion, e.g., by orbital or CNS neoplasia
Secondary, metastatic, e.g., lymphoma
Toxic
Ivermectin
Lead
Closantel
Traumatic
Proptosis
Blunt force
Penetrating trauma
Vascular accidents and ischemia
Hypertension
Acute angle closure glaucoma

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tis show no funduscopic abnormalities (Nafe & Carter, 1981). In patients with severe disease and focal, multifocal, or diffuse disease that involves the anterior portion of the optic nerve (papillitis), the ONH appears to be swollen and edematous, with blurring of its margins (Fig. 27.25, Fig. 27.26 and Fig. 27.27). The physiologic pit is frequently obscured (Nafe & Carter, 1981). The blood vessels on the surface of the ONH appear raised and congested, and hemorrhages may be present that typically have a flame-shaped appearance as they track centrifugally along nerve fiber bundles in the RNFL. Papillitis is often associated with vitreous cells and haze, and peripapillary retinal edema and neuroretinitis are also commonly seen in dogs with optic neuritis (Nafe & Carter, 1981; Nell, 2008; Smith et al., 2017). In more chronic cases, curvilinear pigmented, gray or white scars or folds may be observed throughout the fundus, most often within the peripapillary region (Fig. 27.26) (Smith et al., 2017). Ultimately, optic nerve degeneration may be observed, with darkening or pallor of the shrunken ONH (Fig. 27.27). Conventional flash electroretinograms are typically normal in subjects with optic neuritis (unless there is also clinical evidence of significant retinochoroiditis), but VEPs may exhibit latency delays and reduction in amplitude.

Causes of Optic Neuritis

Reported causes of optic neuritis in the dog are shown in Table 27.2 and include: viral infections such as Canine Distemper Virus and Tick-Borne Encephalitis Virus (Fischer & Jones, 1972; Jubb et al., 1957; Nell, 2008; Richards, et al., 2011; Stadtbäumer et al., 2004); bacterial infections, systemic mycoses, including blastomycosis (Bloom et al., 1996); cryptococcosis (Gelatt et al., 1973; Jergens et al., 1986); histoplasmosis (Meadows et al., 1992), and aspergillosis (Smith et al., 2017); protozoal infections such as toxoplasmosis, ehrlichiosis, leishmaniosis and Rocky Mountain spotted fever (Leiva et al., 2005; Pena et al., 2000, 2008; Piper et al., 1970; Smith et al., 2017); trauma (see later); vascular accidents (Mari et al., 2018); and toxins, e.g., closantel (McEntee et al., 1995), lead (Kowalczyk, 1976), or ivermectin (Kenny, et al., 2008; Smith et al., 2017). Extension of orbital abscesses/cellulitis and sphenoid bone osteomyelitis, as well as optic nerve involvement in systemic, CNS, and orbital neoplasia are other reported causes of optic neuritis in the dog (Busse et al., 2009; Nafe & Carter, 1981; Nell, 2008; Smith et al., 2017). In a retrospective study of 96 cases of canine optic neuritis, an etiologic diagnosis was not established in about 80% of patients. Neoplasia was diagnosed in just under 10% of cases and infectious disease was identified in under 6% of dogs, and extension of orbital inflammatory disease and exposure to toxins were infrequent causes of optic neuritis in that series. In this cohort of 96 dogs, 35 were diagnosed with MUO and 42 with isolated optic neuritis, both diagnoses presumed to be immune-mediated. In this series, female, small breed, middle aged dogs were more likely to be diagnosed with MUO than larger breed and male dogs (Smith et al., 2017).

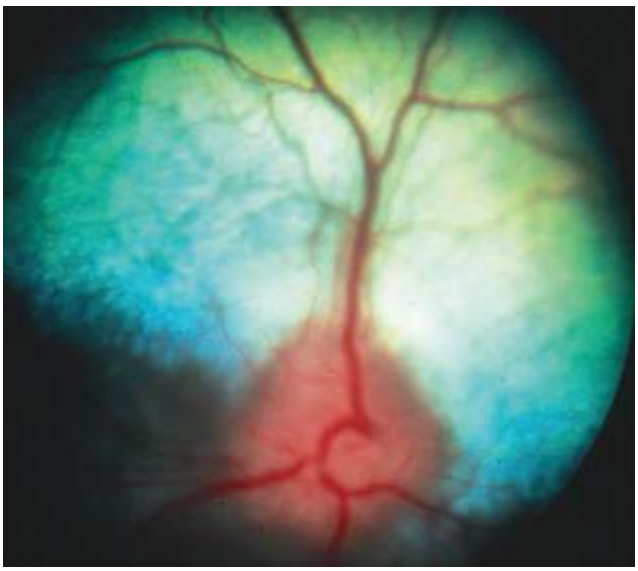


Figure 27.25 Optic neuritis may exhibit a swollen, raised, and hyperemic optic disc with indistinct margins. There is no apparent physiologic cup or pit and there is evidence of edema and possibly folding in the adjacent, peripapillary retina and/or choroid. (*Source*: Reproduced with permission from Martins & Brooks (2013) Diseases of the canine optic nerve. In: *Veterinary Ophthalmology* (eds Gelatt, K.N., Gilger, B.C. & Kern, T.J.), pp. 1432–1473. Oxford: John Wiley and Sons.)

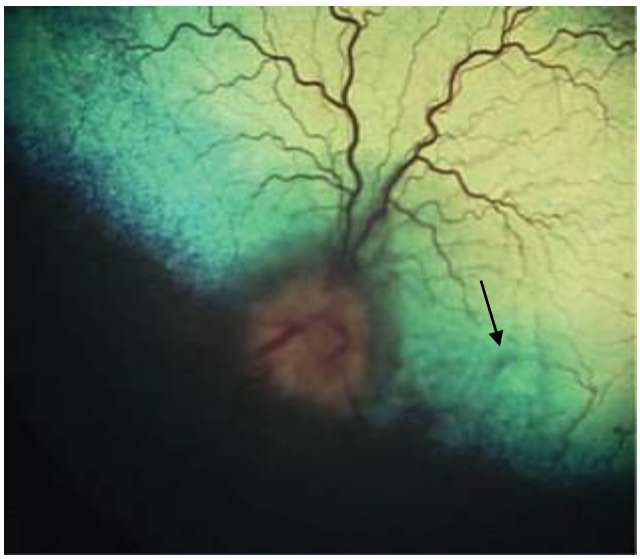


Figure 27.26 Swollen and congested optic disc in a 5-year-old dog with meningoencephalomyelitis of unknown origin. The margins of the disc are indistinct and there is pronounced peripapillary retinal edema with partial detachment. A curvilinear pigmented lesion within the tapetal fundus (arrow) has an appearance suggestive of a retinal or choroidal fold. Lesions such as these are a common finding in dogs with active or prior meningoencephalomyelitis. (*Source*: Courtesy of Dr. F. Mowat and North Carolina State University, with permission.)

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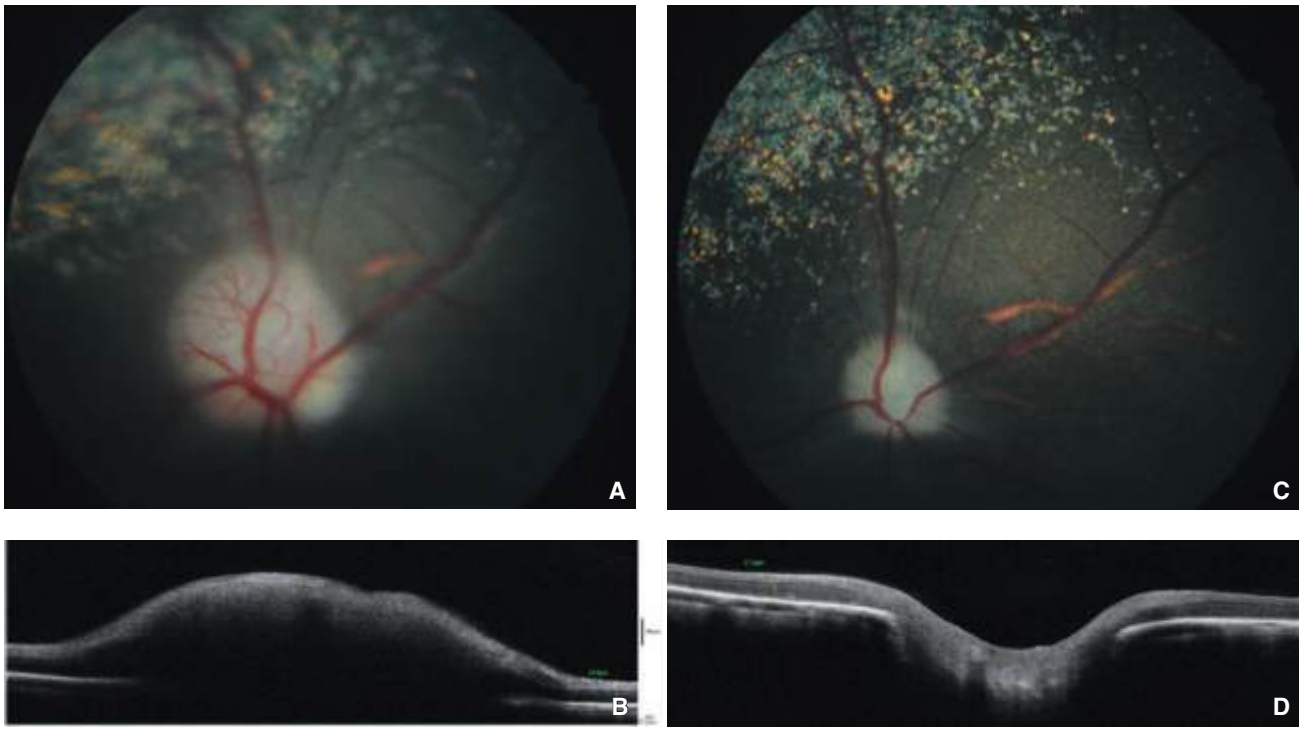


Figure 27.27 **A.** Fundus photograph illustrates the right optic nerve head (ONH) and peripapillary retina of a Maltese with optic neuritis that presented with a history of acute blindness seven days previously. The ONH is swollen, elevated, and congested with no obvious cup or physiologic pit. There is peripapillary retinal edema and the ONH margins appear blurred and indistinct. **B.** In the corresponding optical coherence tomography (OCT) image, the ONH surface is markedly elevated relative to the surrounding retinal surface and no cup or physiologic pit is apparent (bar = 250 μm). **C.** Three weeks later, after immunosuppressive therapy, vision has been restored and the ONH has distinct margins and the physiologic cup can now be seen, because ONH and peripapillary edema have resolved. However, disc pallor is suggestive of optic nerve degeneration. **D.** With resolution of inflammation, greater subsurface detail can be found on OCT, consistent with reduced edema but also suggestive of loss of prelaminar tissue from the neuroretinal rim. Recurrence of blindness was subsequently reported by the owner, about 4 months after initial presentation. (*Source*: Courtesy of Dr. S. Yoo, Yoolim Animal Eye Clinic, South Korea, with permission.)

Optic neuritis is ultimately ascribed to idiopathic, infiltrative, immune-mediated inflammatory disease in a majority of canine patients (Nafe & Carter, 1981; Nell, 2008; Pumphrey et al., 2013b; Smith et al., 2017). Diagnoses span a range of syndromes, from isolated optic neuritis through a range of diseases with variable CNS involvement that now generally fall under the umbrella term of MUO. This latter diagnosis may also be referred to as "meningoencephalomyelitis of unknown (a)etiology" (i.e., MUA or MUE, reflecting differences between UK and US spelling), but is referred to as MUO throughout this chapter to avoid confusion (Coates & Jeffery, 2014). The clinical diagnosis of MUO encompasses a spectrum of pathology that includes conditions that would previously be diagnosed clinically as granulomatous meningoencephalitis (GME) or, historically, as reticulosis (Cuddon & Smith-Maxie, 1984; Fischer & Liu, 1972; Fischer et al., 1971; Nafe & Carter, 1981; Ryan et al., 2001; Smith et al., 1977); as well as cases of necrotizing encephalitis. Both are inflammatory diseases of unknown etiology, with a predilection for small breed dogs. More severe, presenting signs of neurologic disease, such as seizures, altered mentation, central vestibular disease, and/or blindness in relatively younger dogs, mean that dogs with necrotizing encephalitis are more likely to be initially presented for neurologic rather than ophthalmic evaluation. In GME, pathology and corresponding clinical signs may be subdivided into three forms, based on anatomic localization, as either focal, multifocal/disseminated, or ocular (Coates & Jeffery, 2014; Maehara et al., 2009). In the focal and disseminated forms, other neurologic signs may predominate, including similar signs to those described for necrotizing encephalitis. In contrast to necrotizing encephalitis, GME most often affects middle-aged dogs between 3 and 7 years. Pugs, Maltese, Pekingese, French Bulldogs, and Chihuahuas are predisposed to both diseases, implying an underlying genetic, likely immunogenetic, susceptibility (Coates & Jeffery, 2014). Both GME and necrotizing encephalitis are now considered histologic diagnoses (Coates & Jeffery, 2014). Unfortunately, histologic diagnosis is only definitively confirmed postmortem in most cases, because brain biopsy is seldom pursued antemortem in dogs due to cost and

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patient risk. In GME, neuropathology consists of disseminated or focal perivascular whorls of mononuclear cells within the meninges, white matter, or spinal cord. Lesions at the more aggressive end of the histopathologic spectrum may represent forms of CNS lymphoma or malignant histiocytosis (Coates & Jeffery, 2014).

Diagnosis, Treatment, and Prognosis

Electroretinography and/or chromatic pupillometry (see earlier sections of this chapter) are indicated to distinguish SARDS from retrobulbar optic nerve disease in canine patients presenting with acute blindness and widely dilated pupils in which ophthalmoscopic findings are unremarkable. MRI (Fig. 27.28) followed by CSF analysis, including determination of protein concentration, cytology, and appropriate serologic/molecular diagnostic testing for potential infectious causes, are strongly recommended to establish an etiologic diagnosis whenever possible (see previously and Table 27.2). MR findings in inflammatory CNS diseases such as MUO include: solitary, diffuse, or multifocal lesions that are hyperintense relative to brain parenchyma on T2-weighted and on fluid-attenuated inversion recovery (FLAIR) sequences; variably hypointense to isointense on T1-weighted sequences, with variable degrees of contrast enhancement (Coates & Jeffery, 2014). Higher sensitivity to the detection of MUO has been reported for FLAIR sequences (Cherubini et al., 2006). However, normal neuroimaging findings do not exclude a diagnosis of CNS or isolated optic nerve inflammatory disease. In one study of dogs with inflammatory CSF findings, no conclusive findings were detected in 25% of affected dogs on brain imaging (Lamb et al., 2005). Diagnostic testing on CSF may have greater sensitivity and specificity for infectious diseases than serologic testing of blood samples, but the small fluid volume will often necessitate focused testing for the most likely causes based on other clinical signs, geographic area, and patient signalment and lifestyle. In patients with MUO, CSF protein concentration is usually, but variably, elevated, and mononuclear or mixed pleocytosis is often observed.

Infectious causes of optic neuritis should be managed with appropriate specific antimicrobial therapy if indicated. Additional supportive therapy, including anticonvulsive, colloidal fluid therapy or hyperosmotic therapy (if signs indicate elevated intracranial pressure) may be necessary in patients with other systemic signs or severe neurologic signs. Systemic corticosteroid therapy at anti-inflammatory doses (0.25–0.5 mg/kg/day) is recommended pending results of serologic tests in patients with no other evidence of systemic infectious disease. Patients with confirmed MUO or isolated optic neuritis are frequently managed by immunosuppressive doses of corticosteroids (e.g., 1–2 mg/kg prednisone, administered orally every 12 hours for 3–4 weeks before very slowly tapering every 3–4 weeks, over a period of several months, to reach a low, alternate day maintenance dose indefinitely) (Coates & Jeffery 2014). Alternative, second-line immunosuppressive and immunomodulatory regimens that have been proposed for the management of MUO include azathioprine; cytosine arabinoside in combination with oral prednisone (Nuhsbaum et al., 2002; Zarfoss et al., 2006), oral cyclosporine (Adamo & O'Brien, 2004), and adjunctive procarbazine (Coates et al., 2007). Detailed description of these therapies, which may extend remission and prolong survival, particularly in dogs severely affected by MUO, is not within the scope of this chapter and readers are referred to other sources for further detail (Coates & Jeffery, 2014). In as many as 25% of cases of canine optic neuritis, definitive clinical diagnosis proves elusive and systemic immunosuppressive doses of corticosteroids are often used empirically in these cases to target the presumed immune-mediated inflammation in the hope of restoring vision. In these cases, owners should be made aware of the risk for exacerbation of undiagnosed infectious disease.

Unfortunately, long-term visual outcome is generally poor, particularly because initiation of immunosuppressive therapy is often (appropriately) delayed while diagnostic test results for infectious diseases are pending. Although vision may be temporarily restored, the prognosis for long-term recovery and retention of vision in cases of optic neuritis is guarded to poor, even in those patients that regain vision, because recurrence is common and subsequent episodes of optic neuritis are often permanently blinding and result in irreversible optic nerve degeneration (see later) (Nafe & Carter, 1981; Nell, 2008; Smith et al., 2017). For this reason, discontinuation of therapy is not recommended and is rarely achieved. In a series of 96 dogs with optic neuritis, only about 30% of the affected dogs for whom adequate follow up was available regained or retained any vision, whereas about 70% remained blind (Smith et al., 2017).

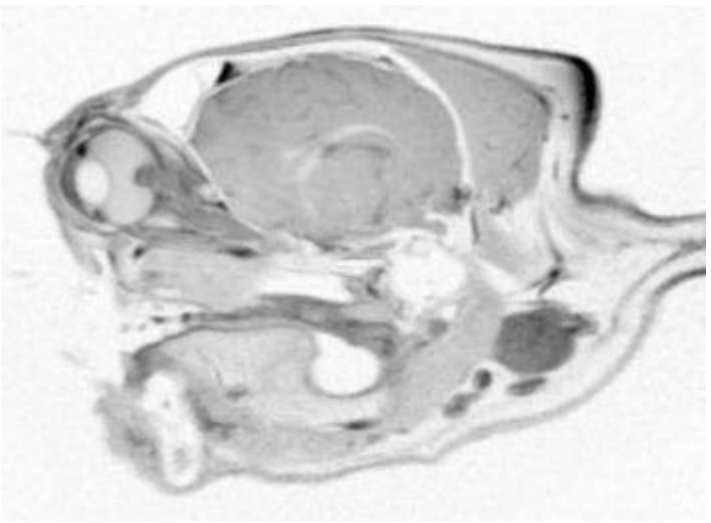
Extension of Inflammation from Adjacent Tissues

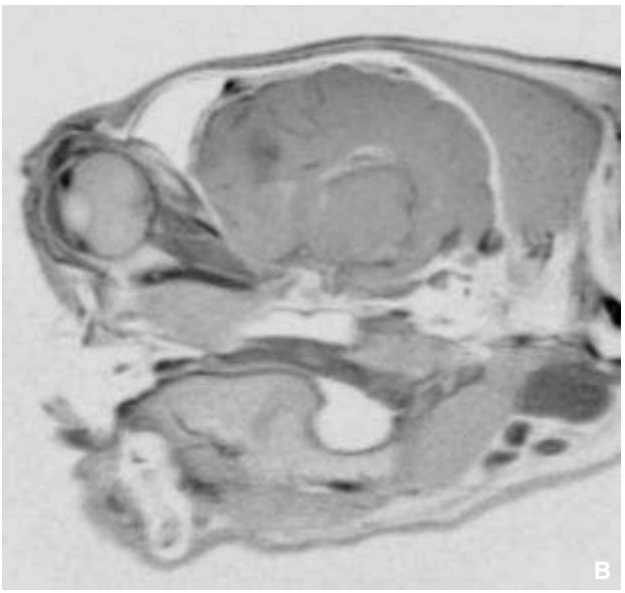
The optic nerve may be secondarily affected by various inflammatory or neoplastic lesions of adjacent tissues, including the uvea, retina, sclera, orbit, paranasal sinuses, and meninges. Vision defects may be caused by inflammation or by pressure on the optic nerve from cellular infiltration or compression by an encroaching mass (e.g., orbital or CNS neoplasia or calvarial hyperostosis) (Dubielzig et al., 2010b; Martins & Brooks, 2013).

Traumatic Optic Neuropathies

All portions of the optic nerve (i.e., intraocular, intraorbital, intracanalicular, intracranial) are susceptible to injury, and traumatic proptosis and orbital fractures are frequently encountered in the dog. In particular, proptosis is a common problem in brachycephalic breeds, in which the initiating traumatic event may be minor. Proptosis in mesaticephalic and dolichocephalic breeds is often associated with more serious head trauma, underscoring the need for thorough

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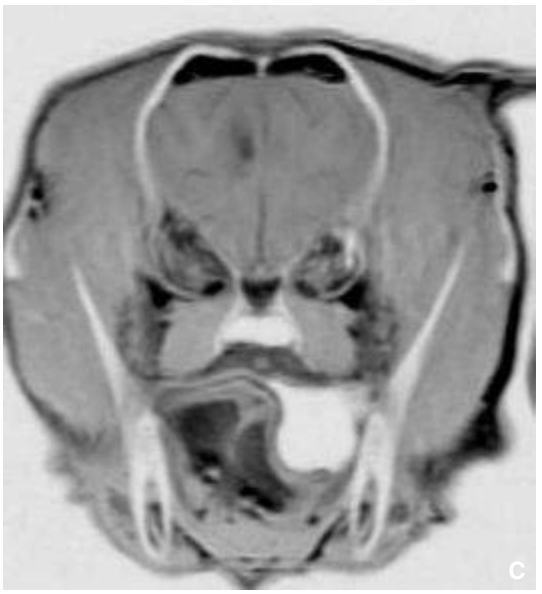


Figure 27.28 Magnetic resonance images of a Cavalier King Charles Spaniel-cross presenting with unilateral blindness, a swollen right optic nerve head, with afferent pupillary light reflexes deficit and pain on palpation of cervical and thoracic spine. **A**, **B.** Oblique sagittal T1-weighted, postcontrast images with fat suppression show that (**A**) the right optic nerve is swollen throughout its length and there is dramatic protrusion of the optic nerve head into the vitreous cavity. The uvea, optic nerve, and surrounding soft tissue all show pronounced contrast enhancement consistent with inflammation. **B.** In an adjacent slice to that shown in **A**, the extent of swelling of the proximal optic nerve is clearly illustrated (up to 4 mm in diameter) and an ill-defined area of cerebral parenchymal contrast enhancement is visible. **C.** Transverse postcontrast T1-weighted image of the brain at the level of the frontal lobes shows an ill-defined area of modest contrast enhancement in the dorsomedial part of the right frontal lobe, close to the falx. There is no associated mass effect. Diagnostic imaging features were consistent with multifocal central nervous system and right ocular inflammatory pathology. Cerebrospinal fluid was sampled by cisternal puncture and cytology identified severe, mixed pleocytosis with elevated protein content that, together with clinical presentation, signalment and magnetic resonance findings, supported a diagnosis of meningoencephalomyelitis of unknown origin (MUO). (*Source*: Courtesy of Dr. R. Dennis, Animal Health Trust, UK.)

general physical and neurological assessment in dogs with proptosis or other suspected optic nerve trauma (Gilger et al., 1995). Advanced cross-sectional imaging (CT or MR) may be indicated in patients with known or suspected severe blunt or penetrating head injuries. Diagnosis, prognostic features, and clinical management of canine globe proptosis are described in detail in Chapter 14 of this text.

Rapid deceleration of the anterior portion of the optic nerve relative to the more fixed, posterior, intracanalicular and intracranial portions of the canine optic nerve in traumatic globe proptosis can result in ONH avulsion, globe rupture, optic nerve laceration and atrophy, as well as ONH vascular compromise (Fritsche et al., 1996; Gilger et al., 1995) (Fig. 27.29). In avulsion injuries, vision is lost

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immediately and irreversibly, and an afferent PLR defect is evident. Vitreous and retinal hemorrhages may also be evident in traumatic optic neuropathy (Fig. 27.15). There is often very dramatic glial proliferation visible as gray tissue at the surface of and surrounding the ONH after optic nerve avulsion in dogs (Fig. 27.30). However, if damage to the nerve occurs posteriorly within the orbit, the optic disc may initially appear normal.

Penetrating foreign bodies, compression, and fractures may cause traumatic damage to the intraorbital and intracanalicular segments of the optic nerve (Fig. 27.15). However, traumatic damage may also be indirect, for example, resulting from a blow to the frontal region or anterior orbit, because these forces can be transmitted to the optic foramen, with subsequent traction, contusion, and shearing forces applied to the optic nerve axons and optic nerve vasculature (Anderson et al., 1982; Stunkel & Van Stavern, 2018). Hemorrhage after trauma may disrupt the optic nerve parenchyma or accumulate within the nerve sheaths (Fig. 27.31), and interference with vascular supply and tissue compression contribute to necrosis and to subsequent neurodegeneration (Dubielzig et al., 2010c).

A number of treatment options have been advocated for traumatic optic neuropathy in humans, including hyperosmotic therapy systemic corticosteroids, and surgical decompression of the orbit, optic nerve sheath, or canal. However, aggressive surgical intervention coupled with aggressive medical management is now controversial in human patients (Stunkel & Van Stavern, 2018). In dogs, management of traumatic optic neuropathy is typically confined to replacement of prolapsed globes, repair of displaced orbital fractures, or removal of bone fragments, and/or local and systemic anti-inflammatory therapy. High-dose corticosteroid therapy may reduce trauma-induced edema and secondary injury caused by inflammation (Stunkel & Van Stavern, 2018), but is not necessarily supported by current practices in the management of CNS trauma (Platt et al., 2016). Spontaneous visual recovery has been reported in humans and dogs with traumatic optic neuropathy, and anti-inflammatory therapy together with appropriate surgical intervention is recommended in the absence of optic nerve avulsion, other severe ocular trauma, or other negative prognostic indicators in dogs presenting with traumatic injury such as proptosis (see Chapter 14).

Optic Nerve Degeneration

Optic nerve degeneration is a nonspecific sequela to optic nerve compression (e.g., by local orbital and calvarial space-occupying lesions), inflammation, blunt and penetrating trauma, and ischemia, and is a common outcome in glaucoma in which there is characteristic optic disc cupping (see later). Optic nerve degeneration may also occur as a rare complication of local radiation therapy in dogs (Ching et al., 1990). As in human patients with radiation-induced optic neuropathy, this is a late onset complication and prognosis for restoration of vision is very poor. In people with radiation-induced optic neuropathy, the lesion is typically retrobulbar and so, at least initially, the ONH may appear normal on ophthalmoscopy (Danesh-Meyer, 2008).

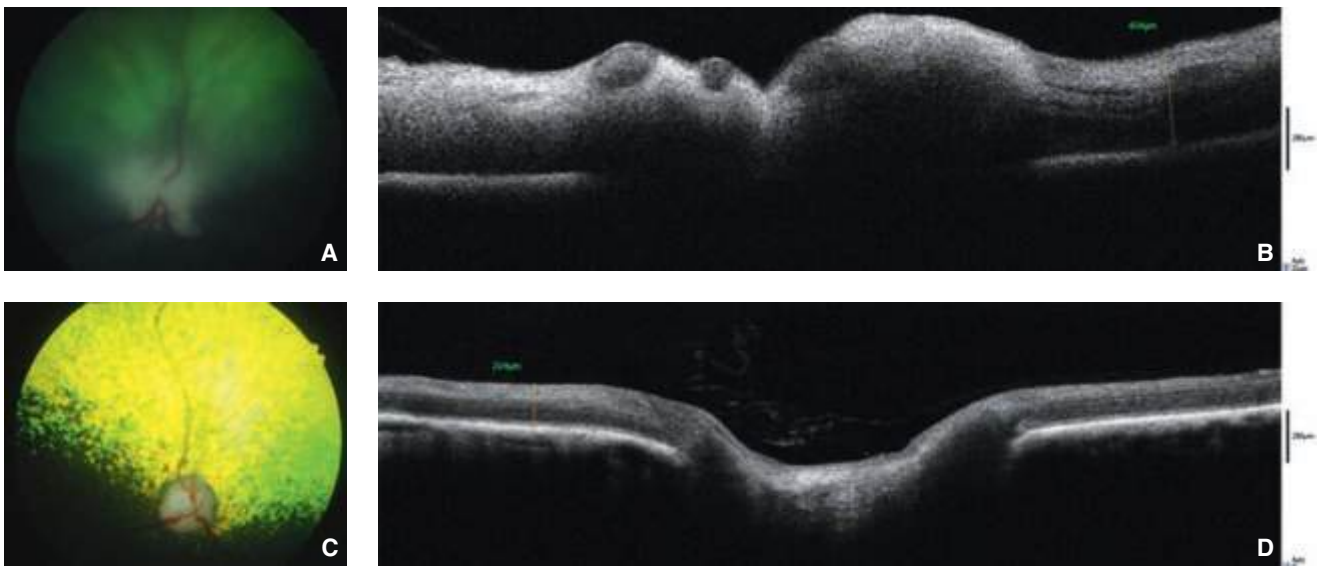


Figure 27.29 Fundus photographs (**A**, **C**) and corresponding optical coherence tomography images (**B**, **D**) of the right eye (top, **A**, **B**) and contralateral, left eye (bottom, **C**, **D**) of a 2-year-old Maltese which sustained a bite wound resulting in traumatic proptosis of the right eye one day previously. Despite prompt resolution of proptosis, there was pronounced, irregular swelling, anterior protrusion and blurring of the margins of the optic nerve head, with severe retinal edema, that signaled severe traumatic optic neuropathy. (*Source*: Courtesy of Dr. S. Yoo, Yoolim Animal Eye Clinic, South Korea, with permission.)

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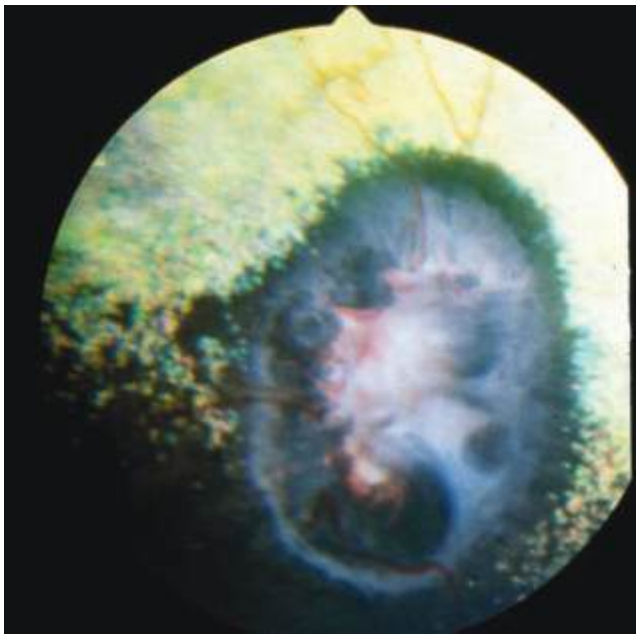


Figure 27.30 Complete optic nerve avulsion caused by traumatic proptosis in an American Cocker Spaniel. The pupil was fixed and dilated, but the eye appeared completely normal in external appearance. Glial tissue covers the site of the optic nerve head. (*Source*: Reproduced with permission from Martins & Brooks (2013) Diseases of the canine optic nerve. In: *Veterinary Ophthalmology* (eds Gelatt, K.N., Gilger, B.C. & Kern, T.J.), pp. 1432–1473. Oxford: John Wiley and Sons.)

The degenerate or atrophic ONH will typically appear shrunken with reduced vascular perfusion recognizable as optic disc pallor, and with loss of myelin recognizable as darkening of the optic disc which takes on a dark gray appearance. With loss of prelaminar nerve fiber tissue and myelin, pores in the LC may become visible (laminar dot sign) (Fig. 27.32). Presence of other ocular signs or history consistent with prior traumatic or inflammatory disease can help to distinguish acquired degeneration from hypoplasia of the optic nerve.

Optic Nerve Neoplasia

Primary neoplasms arising in the optic nerve are infrequently encountered in dogs (Dubielzig et al., 2010a), with optic nerve meningioma the most common of these tumors, followed by astrocytoma and, very rarely, medulloepithelioma. Dogs with optic nerve tumors may be presented for evaluation by diligent owners who notice differences in pupil size and reactivity. Affected dogs may also present with exophthalmos, which may be accompanied by a unilateral or, rarely, bilateral swelling of the ONH, and with signs that could be consistent with optic neuritis (Mauldin et al., 2000; Nafe & Carter, 1981; Paulsen et al., 1989; Smith et al., 2017; Spiess & Wilcock, 1987) (Fig. 27.33). Direct neoplastic infiltration or impingement neoplasms on the optic nerve or chiasm can reduce axoplasmic flow, ultimately leading to axonal degeneration.

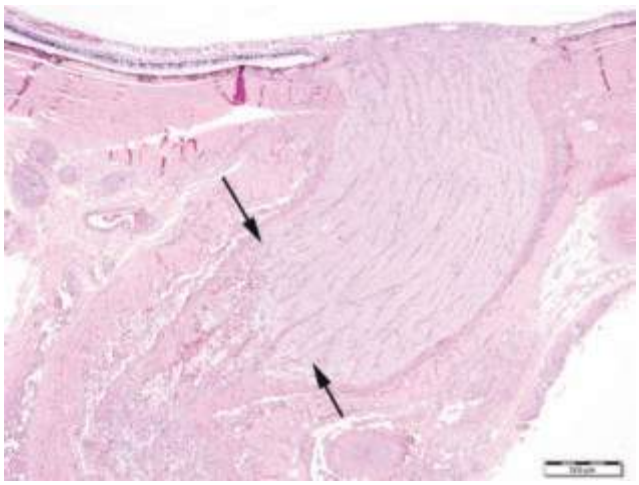


Figure 27.31 Photomicrograph illustrating extensive necrosis (arrowed) and hemorrhage within the orbital optic nerve of a brachycephalic dog after proptosis. (*Source*: Courtesy of Dr. Leandro B.C Teixeira and the Comparative Ocular Pathology Laboratory of Wisconsin.)

Optic Nerve Meningioma

Canine orbital meningioma is the most common primary tumor involving the canine optic nerve, but is relatively infrequently diagnosed, accounting for just ~1.5% of ocular neoplasms submitted to a busy mail-in ocular pathology service (Dubielzig et al., 2010a). These tumors present as slow-growing orbital space-occupying lesions filling the orbit and causing exophthalmos and they are typically, but not always, associated with ONH swelling and congestion (Fig. 27.33). Affected eyes are often blind with a dilated pupil and absent afferent pupillary light reflex, and indentation of the globe may be observed on ophthalmoscopy or on cross-sectional imaging. About 80%–90% of orbital meningiomas exhibit foci of osseous and chondroid metaplasia, and/or undifferentiated myxomatous tissue (Dubielzig et al., 2010a,b; Mauldin et al., 2000; Montoliu et al., 2006). This can prove to be a very helpful clinical diagnostic feature on advanced imaging (Fig. 27.16). Unilateral involvement is typical, although chiasmal and intracranial extension resulting in contralateral blindness has been reported (Barnett & Singleton, 1967; Mauldin et al., 2000; Regan et al., 2011).

Although slow growing, complete surgical excision of orbital meningiomas can prove difficult, particularly for those tumors that extend to the optic foramen. Recurrence is therefore quite common after resection, and may be associated with chiasmal and intracranial invasion. Chiasmal extension on recurrence may result in blindness in the remaining eye (Mauldin et al., 2000). Distant metastasis has been reported but is rare (Dugan et al., 1993; Perez et al., 2005).

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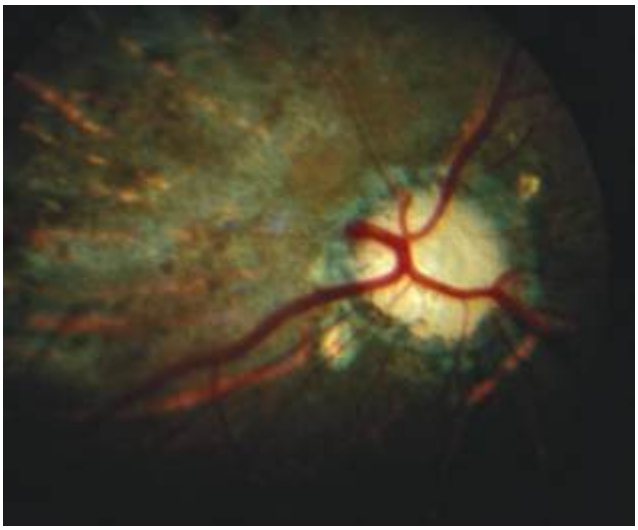


Figure 27.32 Optic neuritis associated with granulomatous meningoencephalitis resulted in optic atrophy. Note exposure of laminar pores (visible as irregular gray spots within the optic nerve head) by loss of overlying axons and myelin from the anterior, prelaminar region of the optic nerve head. (*Source*: Reproduced with permission from Martins & Brooks (2013) Diseases of the canine optic nerve. In: *Veterinary Ophthalmology* (eds Gelatt, K.N., Gilger, B.C. & Kern, T.J.), pp. 1432–1473. Oxford: John Wiley and Sons.)

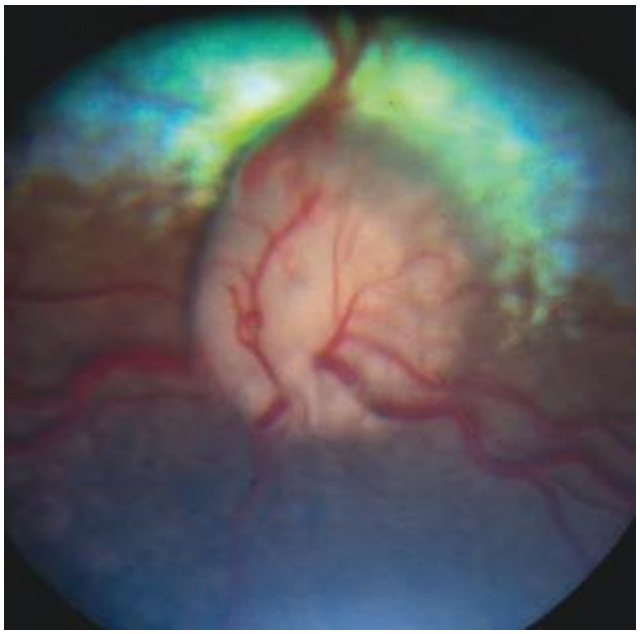


Figure 27.33 Swelling, pronounced anterior protrusion, and congestion of the optic nerve head caused by meningioma in a Labrador Retriever. (*Source*: Reproduced with permission from Martins & Brooks (2013) Diseases of the canine optic nerve. In: *Veterinary Ophthalmology* (eds Gelatt, K.N., Gilger, B.C. & Kern, T.J.), pp. 1432–1473. Oxford: John Wiley and Sons.)

Meningioma may also involve the optic nerve by extension of intracranial neoplasia. However, primary canine orbital meningiomas tend to have specific morphologic and cellular characteristics, differing from their intracranial counterparts in seldom forming the whorls of spindle cells that are frequently seen in intracranial meningioma (Dubielzig et al 2010a, 2010b; Langham et al., 1971; Montoliu et al., 2006). Primary orbital meningiomas are considered to arise from arachnoid cap cells of the meninges and consist of "meningotheliomatous" aggregates of large, polygonal cells with abundant cytoplasm. Orbital meningiomas form a very characteristic cone shape where they are tightly packed surrounding the optic nerve and infiltrate orbital fat in looser aggregates (Fig. 27.34). Although these cells have an epithelial-like appearance, which may even be mistaken for squamous cell carcinoma, meningiomas show positive immunolabeling for vimentin and are negative to cytokeratin (Dubielzig et al., 2010a, 2010b; Montoliu et al., 2006).

Optic Nerve Glioma

Gliomas, which are tumors of non-neuronal tissue arising within the CNS, are relatively infrequently diagnosed in the optic nerve, and accounted for under 0.4% of ocular neoplasia diagnosed by a busy mail-in ocular pathology service (Naranjo et al., 2008). Primary retinal and optic nerve gliomas, classified on the basis of their tissue of origin and positive immunolabeling with the astrocyte marker, glial fibrillary acidic protein are predominantly astrocytomas that may range from low to high grade in terms of their cytologic characteristics (Caswell et al., 1999; Dubielzig et al., 2010a; Naranjo et al., 2008). Other glioma types, including oligodendrogliomas and oligoastrocytomas (mixed cell tumors), are seldom identified in the canine optic nerve (Dubielzig et al., 2010a; Naranjo et al., 2008). These tumors often involve the ONH and should be considered in the differential diagnosis of unilateral optic nerve swelling. Bilateral ocular involvement is extremely rare with primary optic nerve gliomas but may be recognized in patients with chiasmal involvement. Although gliomas may occasionally present as an orbital space-occupying lesion associated with exophthalmos, this is a relatively unusual presentation for this tumor type (Barnett & Grimes, 1972; Martin et al., 2000; Naranjo et al., 2008; Spiess & Wilcock, 1987), compared with orbital meningiomas. Common intraocular complications of optic nerve gliomas include retinal detachment, pre-iridal fibrovascular membranes, intraocular hemorrhage, and secondary glaucoma, all of which may preclude or limit visualization of the fundus (Naranjo et al., 2008; Rozov et al., 2016) (Fig. 27.34). In those patients in which ophthalmoscopy is not possible, ocular ultrasonography findings may be suggestive of an ONH mass. However, canine ocular gliovascular syndrome (COGS) may have a very similar clinical presentation to optic nerve glioma, and intraocular hemorrhage, intravitreal membranes, and aggregates of glial cells within the vitreous in COGS may be echogenic and thus may

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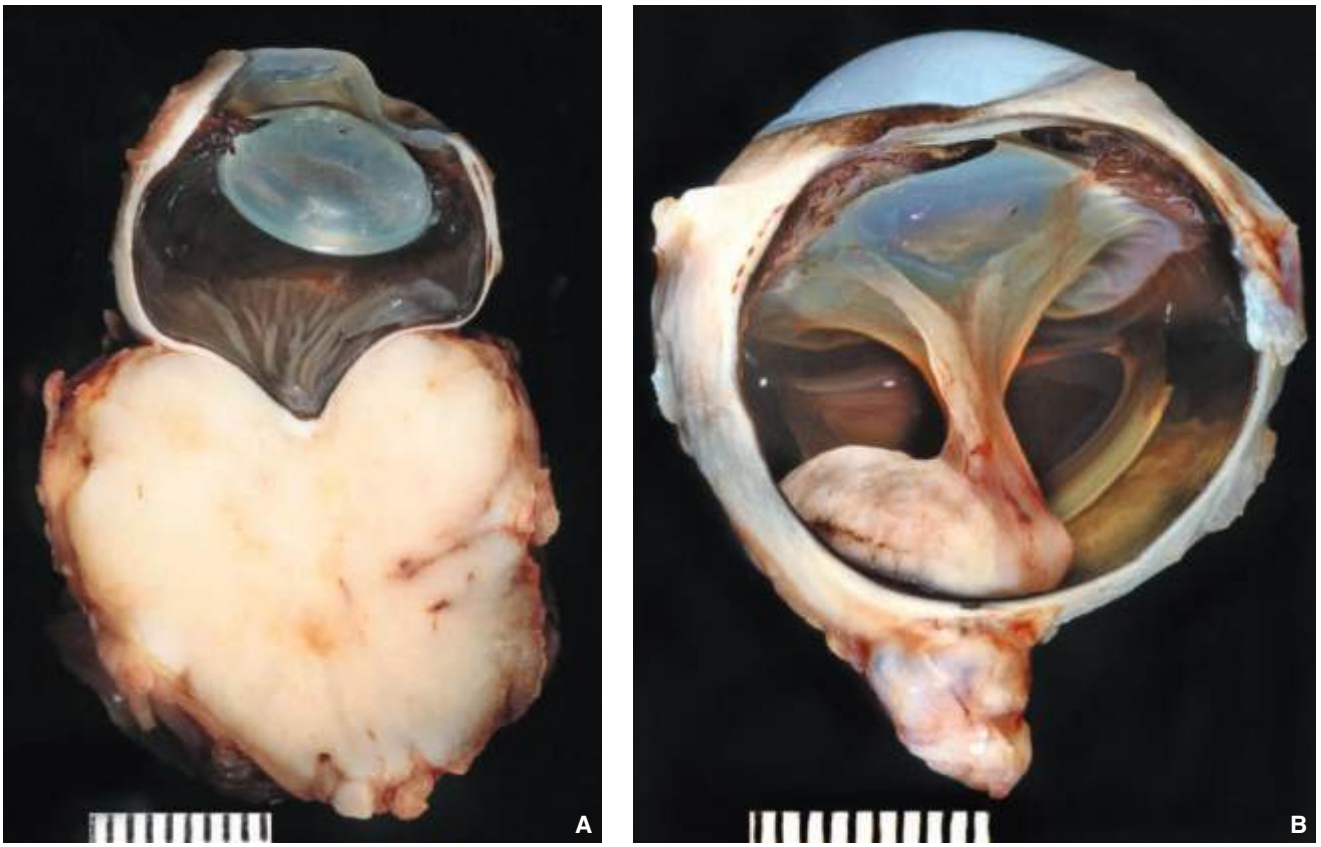


Figure 27.34 Gross pathology of canine primary optic nerve neoplasia. **A.** An orbital meningioma completely surrounds and compresses the optic nerve, fills the orbit, and indents the posterior globe. This orbital space-occupying lesion was associated with exophthalmos and blindness. **B.** A large optic nerve glioma is associated with dramatic anterior protrusion and enlargement of the optic nerve head as well as secondary retinal detachment and blindness (Scale divisions = 1 mm). (*Source*: Courtesy of Dr. Leandro B.C. Teixeira, Comparative Ocular Pathology Laboratory of Wisconsin.)

mimic an ONH mass on ocular ultrasonography in some patients (Gallhoefer et al., 2013; Treadwell et al., 2015). Because COGS is commonly associated with hemorrhage, retinal detachment, and neovascular glaucoma, it should be an important differential consideration when optic nerve glioma is suspected. Unlike optic nerve gliomas, which can affect middle-aged and older dogs of any breed, COGS has a strong breed predilection for the Labrador Retriever (Treadwell et al., 2015), and may be readily distinguished from optic nerve glioma in enucleated globes by its characteristic histopathologic features.

The metastatic potential of primary optic nerve gliomas appears to be low (Naranjo et al., 2008), with only one documented case of confirmed pulmonary metastasis in a dog with a large, anaplastic astrocytoma involving the orbital optic nerve (Martin et al., 2000). However, ascending invasion of the brain is possible, even for low grade gliomas, and is a particular concern when initial tumor excision is deemed incomplete at the time of initial excision by enucleation or exenteration, when 'dirty' margins are identified in the optic nerve stump (Naranjo et al., 2008; Spiess & Wilcock, 1987). Thus, when optic nerve gliomas are suspected, care should be taken to remove as much optic nerve as possible attached to the globe at the time of initial surgical excision to enhance the likelihood of obtaining clean margins, because this may enhance survival times in affected dogs.

Secondary Neoplasia Involving the Optic Nerve

Most neoplasms involving the optic nerve arise in other structures. Intraocular and intracranial tumors may both involve the optic nerve by extension; common orbital tumors that include squamous cell carcinoma, adenocarcinoma, fibrosarcoma and osteosarcoma, may affect the optic nerve by invasion and/or compression, and metastatic neoplasia may involve the optic nerve or chiasm (Hendrix & Gelatt, 2000; Nafe & Carter, 1981; Smith et al., 2017). Thorough ophthalmic and general clinical examination, together with appropriate cross-sectional imaging with guided biopsy, can determine the nature and extent of the primary disease in most cases.

Lymphoma is another neoplastic disease that can masquerade as optic neuritis when involving the optic nerve. Unlike most primary optic nerve neoplasms which involve

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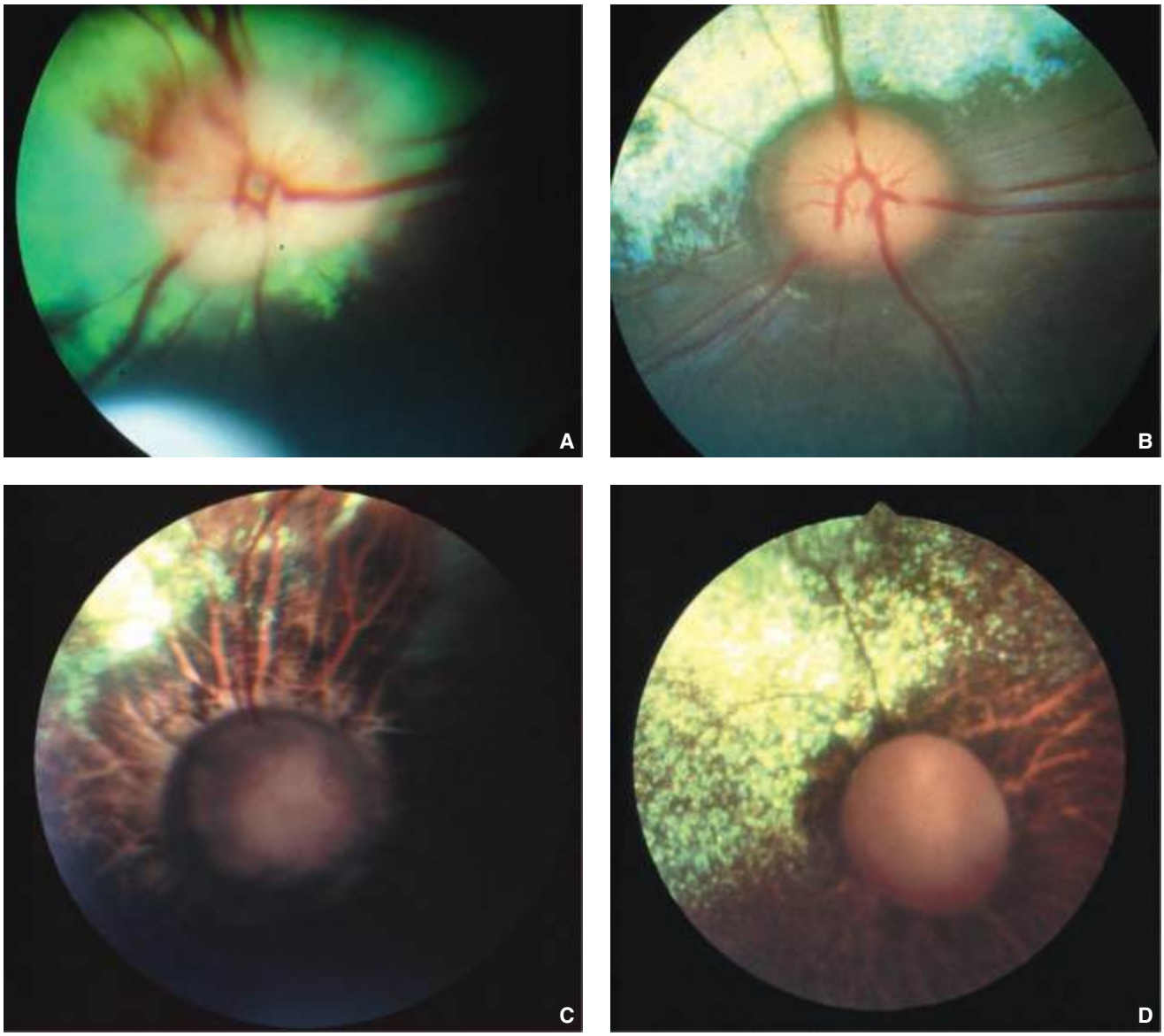


Figure 27.35 Canine glaucomatous optic neuropathy. **A.** Optic disc edema and nerve fiber layer hemorrhages in a dog with acute glaucoma. (*Source*: Courtesy of Dr. John Sapienza.) **B.** Early optic disc cupping in a dog with glaucoma. **C.** More advanced cupping of the optic disc in a dog with glaucoma. Note pallor of choroidal vasculature surrounding the optic nerve head, suggestive of compromise of the short posterior ciliary arteries and reduced choroidal blood flow with ischemia. **D.** Optic nerve cupping and degeneration in a canine eye that was blind as a result of chronic glaucoma. The optic nerve head is round and dark, and the optic cup occupies the entirety of the optic disc. (*Source*: Reproduced with permission from Martins & Brooks (2013) Diseases of the canine optic nerve. In: *Veterinary Ophthalmology* (eds Gelatt, K.N., Gilger, B.C. & Kern, T.J.), pp. 1432–1473. Oxford: John Wiley and Sons.)

just one optic nerve unless there is chiasmal involvement, optic nerve lymphoma can be bilateral in presentation, with acute blindness attributable to involvement of the optic chiasm and/or prechiasmatic optic nerves (Nagel et al., 2013; Smith et al., 2017). Unfortunately, antemortem differentiation between MUO and CNS primary or metastatic lymphoma can be very challenging in patients with clinical signs consistent with optic neuritis, and that may be accompanied by other focal or multifocal neurologic signs, particularly because clinical signs suggestive of multicentric lymphoma are often absent in patients with intracranial lymphoma. Although MRI features may be supportive of specific types of intracranial neoplasia, and MRI features suggestive of intracranial lymphoma have been described (Palus et al., 2012; Wisner et al., 2011), overlap exists between findings reported in MUO and CNS lymphoma. In some cases of optic nerve involvement in CNS lymphoma, definitive diagnosis is only made on histopathology at necropsy, because CSF cytology lacks diagnostic sensitivity and specificity for lymphoma, and stereotactic biopsy of CNS lesions that

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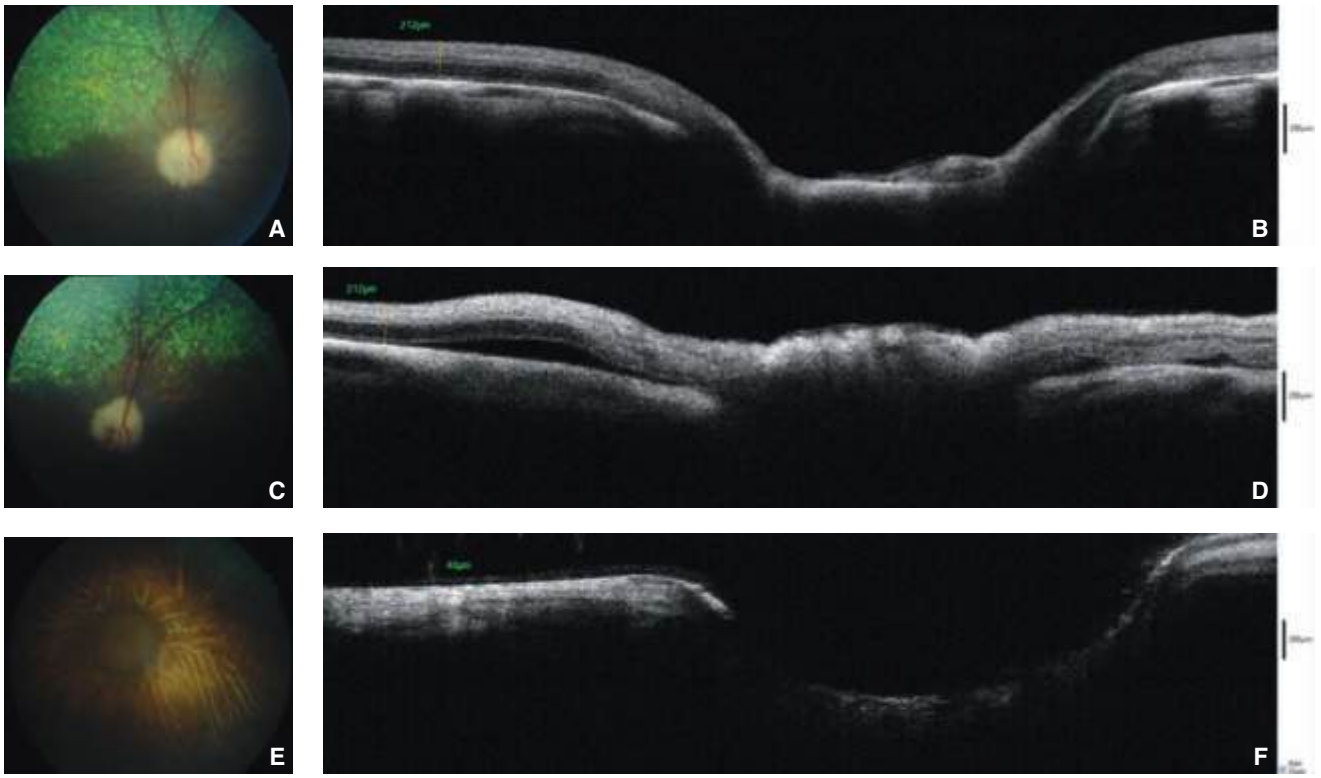


Figure 27.36 Spectral domain-optical coherence tomography imaging of the canine optic nerve head (ONH) at different stages of glaucoma. **A**, **B.** Fundus photograph and corresponding optical coherence tomography of a 13-year-old Shih Tzu with acute glaucoma. **A.** Intraocular pressure (IOP) was 71 mmHg at the time of presentation. **B.** The ONH was a cupped and depressed with little prelaminar tissue visible. **C**, **D.** Imaging the same eye after acute IOP reduction to 12 mmHg was associated with decompression of the viscoelastic prelaminar tissue, and increase in its thickness, with apparent, relative, forward movement of the ONH surface and peripapillary retinal edema and elevation. In contrast, in the buphthalmic eye of a 9-year-old Shih Tzu with chronic glaucoma (**E**, **F**) and IOP of 41 mmHg, the ONH is deeply cupped and atrophic and there is attenuation of retinal and choroidal blood vessels. **F.** Note increased width as well as depth of the cup and absence of prelaminar ONH tissue, which persists regardless of IOP in chronic glaucomatous optic nerve degeneration. (*Source*: Courtesy of Dr. S. Yoo, Yoolim Animal Eye Clinic, South Korea, with permission.)

would be necessary to reach a definitive histologic diagnosis antemortem is seldom performed in veterinary patients because of cost and patient risk. Pilot studies of serum immunosignature protein microarray assays in dogs yielded promising results, clearly distinguishing between dogs with confirmed diagnoses of intracranial neoplasia and those with MUO, and showing that immunosignatures of these two groups are also distinct from normal dogs (Lake et al., 2018). However, serum immunosignatures have not been specifically assessed for CNS lymphoma.

Optic Neuropathy in Glaucoma

The complex pathophysiology of glaucomatous optic neuropathy is addressed in greater detail in Chapter 20. In dogs with glaucoma, as in other species, characteristic optic nerve damage occurs after IOP-related insult to RGC axons in the ONH, which is considered a critical site for initial damage. Structural changes to the LC, with active remodeling of connective tissue ECM in response to IOP-induced mechanical deformation (Downs et al., 2011), vascular insufficiency in the ONH and retina, caused by compression of SPCAs and stretching and compression of ONH capillaries by IOP-mediated stresses and strains in the LC and peripapillary sclera, negatively impacting mitochondrial function and axon metabolism (Osborne, 2010), disruption of normal axoplasmic flow with resulting neurotrophin deprivation (Iwabe et al., 2007; Samuelson et al., 1983; Williams et al., 1983), and activation of glial cells that can intensify fibrosis and inflammation, are all recognized as potential contributors to loss of RGC axons in the optic nerve.

Cupping of the ONH often precedes pronounced visual field loss in human primary open angle glaucoma patients, but is hard to see in dogs with glaucoma because of ONH myelination. Indeed, unlike the typical presentation of insidious vision loss in glaucomatous human patients and cats, glaucoma in dogs is often acute and fulminant in clinical presentation. In addition to disruption of axoplasmic flow in the optic nerve, decreased vascular perfusion and hypoxia, with disturbance in vascular autoregulation, metabolism, and energy supply to these highly energy dependent tissues, is undoubtedly a major

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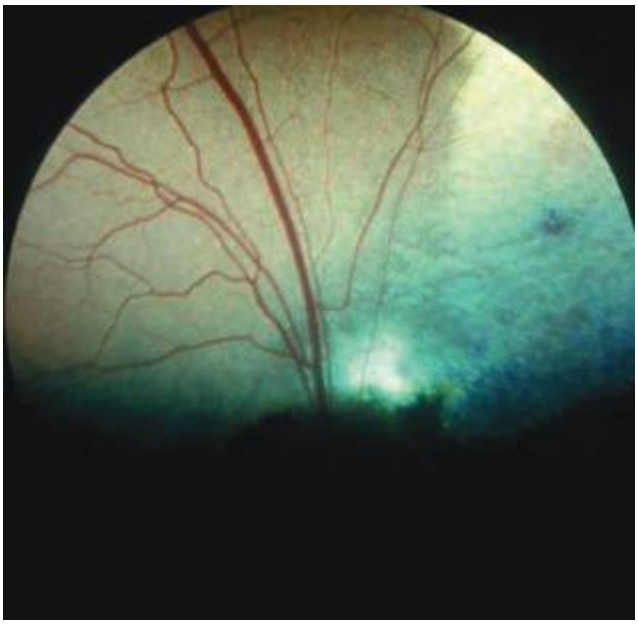


Figure 27.37 Wedge-shaped regions of tapetal hypo- and hyperreflectivity to the left of the photograph and hyperreflectivity to the right, indicative of sectoral retinal and choroidal necrosis in a Basset Hound with glaucoma. It is suggested that this common pattern of outer retinal and choroidal degeneration represents occlusion of short posterior ciliary arteries. (*Source*: Reproduced with permission from Martins & Brooks (2013) Diseases of the canine optic nerve. In: *Veterinary Ophthalmology* (eds Gelatt, K.N., Gilger, B.C. & Kern, T.J.), pp. 1432–1473. Oxford: John Wiley and Sons.)

contributor to axonal degeneration in dogs, particularly in dogs with acute angle closure glaucoma, in which ONH swelling at initial presentation often resembles the clinical appearance of optic neuritis (Fig. 27.35). The histologic observation of necrosis of RGCs and optic nerve tissue in dogs soon after onset of acute glaucoma, supports a role for hypoxia and ischemia in this disease (Scott et al., 2013).

As discussed earlier in this chapter, biomechanical stress on the ONH requires strong connective tissue to withstand even normal IOP (Stowell et al., 2017). A progressive posterior displacement of the surface of the ONH and progressive excavation of the prelaminar tissues, beneath the level of the anterior scleral canal, are clinical hallmarks of glaucomatous optic neuropathy in people (Burgoyne, 2015), and are observed in dogs with chronic glaucoma, typically once myelinated axons in the prelaminar tissue are compressed, and/or lost (Fig. 27.35 and Fig. 27.36). It is noteworthy that in young animals, the ocular tissues, including the peripapillary sclera and the LC, are more compliant than in adults. This reduces compressive forces on neural and vascular tissue so that young animals are often able to retain visual function that would be lost in adult animals after IOP spikes – even when buphthalmos and optic disc cupping are clinically apparent. Similarly, differences between breeds and individuals in ECM character and turnover within the ONH could have a profound influence on the susceptibility of ONH structures and resident cells to damage associated with fluctuations in IOP. However, as described previously, because of their location at the margin of the neural canal, the canine SPCAs are particularly susceptible to occlusion with high IOP. Disruption to the SPCA blood flow can affect peripapillary retina and choroid as well as the ONH itself, so ophthalmoscopic changes in dogs with glaucoma are often not confined to the ONH. Pigmentary changes and thinning of the neural retina may be observed in some human subjects with compressive lesions or glaucoma, and are very frequently identified in canine glaucoma patients, as radiating wedge-shaped zones of altered tapetal reflectivity and choroidal pigmentation (Fig. 27.37). Interrogation of hypothesized alterations in ONH blood supply may be facilitated by new *in vivo* imaging technologies including OCT angiography (Ghasemi Falavarjani et al., 2016).

Other mechanisms that may play contributory roles in glaucomatous optic neuropathy and subsequent blindness in dogs with glaucoma include glutamate excitotoxicity (Brooks et al., 1999b), generation of reactive oxygen species, and neuroinflammation (Soto & Howell, 2014). Neuroinflammation is increasingly recognized as playing an important role in glaucoma pathophysiology (Oikawa et al., 2020; Pumphrey et al., 2013a; Soto & Howell, 2014), and may have an immunogenetic component that could in turn be responsible for some of the differences observed between breeds in their susceptibility to blindness in glaucoma.

Because optic neuropathy in glaucoma is complex and multifactorial, with different mechanisms playing more or less important roles in individual patients, no single neuroprotective therapy is likely to prove highly effective in preserving vision. As our understanding of pathophysiologic mechanisms responsible for vision loss in glaucoma continues to improve, this will ultimately inform the development and validation of new neuroprotective strategies to preserve vision (Almasieh & Levin, 2017).

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Section IV

Special Ophthalmology

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28

Feline Ophthalmology

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No one really knows when cats were first domesticated. The earliest association between people and what we know as the domesticated cat occurred in Egypt around 2000 BC (Malek, 1993). The ancient Egyptians believed that cats were magical creatures, capable of bringing good luck to the people who housed them. From that auspicious beginning, cats have continued to enchant, becoming the most popular household pet in the United States and Europe, with populations numbering 94 million and 100 million, respectively. With that growth has come increasing interest in feline well-being, the evolution of veterinary practices devoted exclusively to their care, and a demand for increasingly sophisticated healthcare that includes management of their ocular disease.

A renowned veterinary ophthalmologist once proclaimed that feline ocular disease should be considered using a different side of the brain than that used for studying the ophthalmic problems of the dog. There is no denying the multitude of unique ocular disorders encountered in cats that simply have no canine counterpart. And even those ocular problems they share inevitably demonstrate a distinctive feline "flare." As the British poet Arthur Symons once stated, "it is in their eyes that their magic resides."

Diseases of the Eyelids

Kittens are born with their eyelids fused (physiologic ankyloblepharon), with opening generally predicted between 10 and 14 days of age (Manning, 2014; Mitchell & Oliver, 2015). Eyelid opening occurred between 3 and 12 days after birth, with a mean of 7.7 days, in a detailed study of 61 kittens from 22 litters. In the majority of kittens (40/61) both eyes opened on the same day, with separation usually beginning at the medial canthus (Blakemore & Cummings, 1975).

The eyelids serve to protect the globe and distribute the tear film across the cornea. To do so effectively, the lids should close completely when blinking, with smoothly curved margins closely apposed to the corneal surface. In the normal feline eye, the lid margins should just cover the upper and lower limbal arc of the cornea. Little conjunctiva is visible within the palpebral fissure, with the exception of a small portion of the third eyelid medially and a small area of bulbar conjunctiva laterally. The adult feline palpebral fissure measures approximately 28 mm in length (Stades et al., 1992). Brachycephalic breeds tend to have slightly longer eyelids, a factor that may explain their predilection for surface diseases such as sequestration (Stades et al., 1992). The eyelid margins are usually pigmented and devoid of hairs. The cat has no true eyelashes, but a row of thicker facial hairs serves as rudimentary lashes along the upper lid.

The eyelid is arranged in four basic layers, beginning with the outer skin, the orbicularis muscle, a region of loosely organized connective tissue referred to as the tarsus, and the innermost conjunctiva. Within the tarsus are muscles that elevate the upper lid, as well as 25–35 meibomian glands in each eyelid that open in a shallow groove along the eyelid margin, commonly referred to as the gray line. There is a generous blood supply to the eyelids that facilitates even delayed wound repair.

Blinking occurs with contraction of the orbicularis oculi muscle, innervated by a branch of the facial nerve. The upper eyelid is more mobile than the lower and is raised by the levator palpebrae superioris and Müller's muscle, innervated by the oculomotor nerve and by sympathetic fibers, respectively. Adult cats blink completely only once every 5 minutes (Barnett & Crispin, 1998).

Congenital Eyelid Abnormalities

Abnormalities of Eyelid Opening

On the rare occasion that the eyelids separate prematurely, a neonatal kitten's tear production may not be sufficient to

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prevent desiccation of the ocular surface. Frequent lubrication using a topical artificial tear or prophylactic antibacterial ointment is necessary to discourage secondary progressive ulceration until the lacrimal system matures. A partial temporary tarsorrhaphy might be considered in extreme cases of surface drying if the eyelids open within the first few postpartum days.

Eyelid opening is more likely to be delayed than early, a condition referred to as pathologic ankyloblepharon to differentiate it from the normal postpartum fusion. Delayed separation has been reported in Persian cats (Manning, 2014), with an anecdotal online reference to heritability in blue-eyed Persians (www.animalwised.com). If the lids remain fused beyond the usual 10–14 days of age with no evidence of eyelid swelling or discomfort, conservative therapy with warm compresses may encourage natural separation. If the eyelids are distended to any degree by trapped secretions, if the site is painful, or if any purulent exudate is evident, it is imperative to rule out neonatal conjunctivitis (aka ophthalmia neonatorum) and treat promptly. Primary infectious pathogens in kittens include feline herpesvirus (FHV) and *Chlamydia felis*, as well as secondary bacteria that include *Staphylococcus* spp. or Gram-negative bacteria of fecal origin. The eyelids should be gently pried apart with firm digital pressure over the medial canthus, or the closed tip of a small mosquito hemostat may be inserted at the medial canthus where a small gap often exists, sometimes identified by a drop of exudate. The hemostat is carefully opened to separate the lids, followed by liberal flushing of the ocular surface with sterile saline or dilute (1:50) povidone iodine solution until all exudate is removed. Sharp instruments are best avoided, since inadvertent damage to the lid margins or meibomian glands could predispose to chronic keratitis. Topical therapy is directed at the most likely bacteria, notably *Chlamydia felis*, applying tetracycline, erythromycin, or a fluroquinolone several times daily for 7–10 days until signs of infection resolve. Antiviral therapy is rarely used in this circumstance unless corneal ulceration fails to respond to conventional topical antibiotics. Even then, the ulcer's appearance should be carefully considered to distinguish between the superficial epithelial loss that characterizes FHV infection and the stromal involvement indicative of bacterial infection. Tear production and the blink reflex may be inadequate in these very young kittens, so consideration should also be given to supplemental lubrication. Failure to promptly address an infection beneath the fused eyelids can lead to permanent corneal scarring, symblepharon, and even corneal perforation (Fig. 28.1).



Figure 28.1 Ankyloblepharon and neonatal ophthalmia in a 2.5-week-old Domestic Shorthair kitten. Exudate is trapped beneath the left fused lids, but seeps from the partially opened right palpebral fissure.

Eyelid Agenesis

Eyelid agenesis or coloboma is the most common congenital eyelid abnormality in the cat (Narfström, 1999). Although this developmental defect occurs sporadically in any breed, agenesis has been reported in the Domestic Shorthair (DSH; Dziezyc & Millichamp, 1989; Martin et al., 1997), Burmese (Koch, 1979), and Persian (Bellhorn et al., 1971). Agenesis is reported along with other ocular anomalies in exotic feline species including the snow leopard (*Panthera uncia*; Barnett, 1981; Barnett & Lewis, 2002), the Texas cougar (*Felis concolor*; Cutler, 2002), and the cheetah (*Acinonyx jubatus*; Boucher et al., 2016). Embryologically, the defect may be linked to inadequate induction of the surface ectoderm by an abnormally oriented optic vesicle (Cook, 2007). In any affected cat, a thorough ocular examination should be performed to rule out concurrent colobomas of the iris, choroid, and optic nerve (Martin et al., 1997).

The effect of this developmental defect ranges from a small notch in the lid margin to complete absence of two-thirds or more of the upper eyelid and its conjunctival lining (Fig. 28.2). The temporal aspect of the superior lid is most commonly affected; medial canthal involvement is rare. Lesions are typically bilateral. Affected kittens are often born with the palpebral fissure partly or fully open (Manning, 2014). Mildly affected animals may be asymptomatic, but patients more often exhibit secondary corneal disease and discomfort resulting from corneal contact with adjacent facial hair, failure of the eyelid to close, or both. Ocular discharge, corneal

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Figure 28.2 Eyelid agenesis. The normal pink margin is missing in the temporal third of the upper eyelid, calling attention to this subtle example of agenesis.

vascularization, epithelial hyperplasia, and ulceration are common sequelae.

Treatment is dictated by the severity of the agenesis. Mild deformities may require only supplemental lubrication with a topical artificial tear ointment. Cryoepilation of misdirected hairs (Fig. 28.3) or correction of the trichiasis using a Hotz-Celsus or Stades (Stades, 1987) technique may suffice if the eyelid retains sufficient mobility and bulk to protect the cornea. Otherwise the choice of surgical technique is governed by the extent of the coloboma. Defects involving one-quarter to one-third of the lid margin may be closed directly by converting to a simple wedge, with a releasing incision at the lateral canthus to create an advancement flap if needed to minimize wound tension (Blogg, 1985). The majority of lesions are too large for primary apposition. The classical reparative technique utilizes a rotational pedicle of lower eyelid skin and orbicularis muscle, anchored at the lateral canthus, sutured into the upper defect, and lined by neighboring conjunctiva undermined and mobilized at the site (Cutler, 2002; Roberts & Bistner, 1968; Fig. 28.4). The most common complication relates to corneal irritation from the downward angle of hairs within the grafted skin, often requiring a second procedure such as cryoepilation to correct the trichiasis (Cheng et al., 2006). A modification of the rotational technique includes conjunctiva transposed from the anterior surface of the third eyelid to line the newly created upper eyelid (Dziezyc & Millichamp, 1989). A buccal mucosal island graft has also been used in conjunction with a single pedicle advancement flap from the dorsolateral forehead skin to recreate a rudimentary superior fornix (Welihozkiy et al., 2009). The likelihood of trichiasis can be reduced by harvesting a pedicle flap from the upper rather than lower eyelid, making an incision 10–12 mm above and parallel to the eyelid defect and rotating the graft downward from its attachment dorsotemporal to the coloboma (Hamilton et al., 1999). Sliding skin grafts (Bedford, 1980; Welihozkiy et al., 2009), Z-plasty skin flaps (Stiles, 2013), and semicircular skin grafts (Pellicane et al., 1994) can also be used for correction. In a notable departure from the classic technique, one group theorized that trichiasis is caused by conjunctival contracture at the graft site and advised against lining the skin pedicle with conjunctiva (Reed et al., 2018). The same study promoted the use of tissue adhesive to repair the donor and recipient wounds, citing benefits of reduced surgical time and less postoperative inflammation (Reed et al., 2018).

By altering the angle of dissection and including the commissure in a mucocutaneous subdermal plexus flap from the lip, Whittaker et al. (2010) successfully modified the lip-to-lid flap to reach the upper lid, repairing the agenesis and recreating the lateral canthus in 9 eyes of 5 cats. Traditionally used to repair extensive lower lid defects (Pavletic et al., 1982), this single-step modification reconstructs the upper



Figure 28.3 **A**. Eyelid agenesis. In more extensive eyelid defects, corneal health is compromised by secondary trichiasis and exposure. **B**. The same patient following cryoepilation of the misdirected cilia.

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Figure 28.4 Eyelid agenesis. Surgical reconstruction of the upper lid combines a myocutaneous pedicle graft from the lower eyelid with a rotational graft of third eyelid conjunctiva using Diezyc-Millichamp's modification of the Roberts-Bistner technique. (Reproduced with permission from Gelatt, K.N. & Plummer, C.E. (2017) *Color Atlas of Veterinary Ophthalmology*, 2nd ed. Ames, IA: Wiley.)



Figure 28.5 Eyelid agenesis. Restoration of the upper lid and lateral canthus immediately following a modified lip-to-lid procedure. (Reproduced with permission from Gelatt, K.N. & Plummer, C.E. (2017) *Color Atlas of Veterinary Ophthalmology*, 2nd ed. Ames, IA: Wiley.)

lid with skin, muscle, and mucus membrane, provides stable upper lid and lateral canthal margins, and avoids the problem of trichiasis (Gelatt & Plummer, 2017; Ruiz et al., 2013; Whittaker et al, 2010; Fig. 28.5). Alternative multistage techniques used for extensive defects include the Cutler-Beard or bucket handle technique, borrowing skin, orbicularis muscle, and conjunctiva from the lower eyelid (Doherty, 1973; Hamilton et al., 1999); a modification of the Mustardé cross-lid technique using the full-thickness lower eyelid to reconstruct the upper lid (Munger & Gourley, 1981), combined with a lip-to-lid transposition to repair the secondary lower lid defect (Beel, 2015; Esson, 2001); and a technique using injectable subdermal collagen to replace the eyelid stroma, combined with a modified Stades technique to remove misdirected hairs (Wolfer, 2002).

Structural Eyelid Abnormalities

Entropion

Inversion of the eyelid is less common in cats than in dogs, with a relative prevalence of 1:7 estimated in one study (Williams & Kim, 2009; Fig. 28.6). Primary entropion occurs most often in the Persian (Laus et al., 1999; Narfström, 1999; Roberts & Lipton, 1975) and other brachycephalic breeds (Stiles, 2013), usually involving the medial aspect of the lower eyelid. Mean palpebral fissure length in the Persian is approximately 1 mm longer than in other cat breeds, though fissure length is comparable between Persians with and without entropion (Stades et al., 1992). Pronounced facial "jowls" in the intact male Maine Coon cat are implicated as a predisposing breed-related factor (Williams & Kim, 2009). While intact male cats are a clinical rarity these days, that same facial conformation may accompany entropion in the occasional feral tomcat as well. After accounting for breed predisposition (16%), Williams divided the remaining patients in his study of 50 entropic cats into two etiologic groups: young cats (32%) with chronic surface irritation from conjunctivitis, corneal ulceration, or corneal sequestration; and older cats (52%) with eyelid laxity or enophthalmos from reduced orbital tissue volume (Williams & Kim, 2009). Entropion due to lack of eyelid support also accompanies congenital microphthalmia and acquired phthisis bulbi. These observations support the prevailing theory that feline entropion is more likely a consequence of chronic, painful ocular disease than faulty conformation (Barnett & Crispin, 1998; Manning, 2014; Nasisse, 1991; Roberts & Lipton, 1975; Weiss, 1980), and may also explain why cats tend to develop entropion later in life compared to dogs (Read & Broun, 2007).

Surgical correction of entropion would seem a simple matter in cats considering their lack of predisposing conformational features such as macroblepharon and lateral canthal laxity, which commonly accompany canine entropion. However, failure to eliminate the cause of eyelid spasm leads to recurrence (Barnett & Crispin, 1998) – and the amount of eyelid tissue that must be resected to sufficiently evert the lid is often surprisingly greater than that required in a similarly entropic dog (Manning, 2014; Mitchell & Oliver, 2015; Williams & Kim, 2009). If the entropion resolves following application of a topical anesthetic, definitive surgical correction should be postponed until the underlying cause of the blepharospasm is identified and treated. Vertical mattress sutures or staples may be used to temporarily evert or "tack" the eyelids, limiting damage to the ocular surface in the interim. Subdermal injection of a hyaluronic acid filler

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Figure 28.6 **A**, **B**. Chronic bilateral entropion in a 2-year-old Persian with secondary keratitis. **C**. Entropion of the lower eyelid in a 6-year-old Domestic Shorthair with a history of chronic conjunctivitis. **D**. Postoperative appearance of the same eye following a modified Hotz-Celsus technique combined with lateral canthal closure.

(Restylane Silk®, Galderma Laboratories, Fort Worth, Texas, USA) was used to correct lower lid entropion of senile (n=8), primary (n=3), and cicatricial (n=1) origin in 12 cats (McDonald & Knollinger, 2018). Using only manual restraint, 0.1–0.3 mL of filler was injected into the subdermal space 1–2 mm ventral to the eyelid margin using a 27- or 30-gauge needle. With a median follow-up time of 259 days, 9 cats (75%) were asymptomatic following the initial injection. Of the remaining cats, 1 required a second injection, 1 required a third injection, and the single cat diagnosed with severe entropion required definitive surgical correction 2 weeks following the initial treatment. The risk of sarcoma formation following injection of subdermal fillers in cats is unknown, although Wolfer reported that subdermal collagen injected in the shoulder area of cats failed to elicit a positive skin reaction (Wolfer, 2002).

Most cases of feline entropion can be successfully corrected using a Hotz-Celsus procedure (Mitchell & Oliver, 2015; Williams & Kim, 2009), but recurrences are possible. White et al. (2012) reported the need for a second surgery in 3 of 26 eyes corrected using only a Hotz-Celsus procedure, 2 within 3 months of the initial procedure. With the observation that perfect eyelid apposition in the immediate postoperative period failed to permanently correct entropion in 5 of

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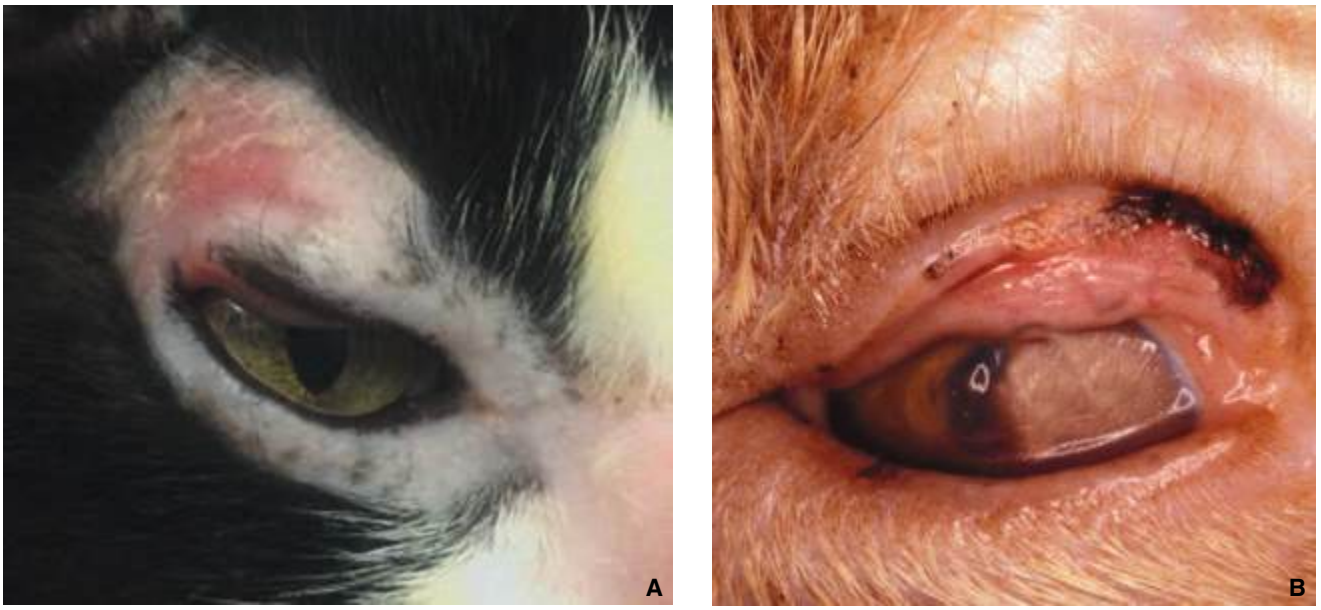


Figure 28.7 **A**. Cicatricial ectropion. Upper lid eversion in a 9-year-old Domestic Shorthair 1 month after burns suffered in a housefire. (Courtesy of Dr. Alyson Coppens.) **B**. Upper lid contracture and secondary keratitis following chemical burns in a 9-month-old Domestic Shorthair.

50 patients (Williams & Kim, 2009), some ophthalmologists recommend intentional overcorrection, aiming to create a mild ectropion at the completion of surgery (Mitchell & Oliver, 2015; Williams & Kim, 2009). To correct medial entropion and properly position the lower nasolacrimal punctum in brachycephalic cats, the Hotz-Celsus technique can be modified by excising a triangular rather than elliptical section of skin, with the tip of the triangle opposite the lower lacrimal punctum (Gelatt & Gelatt, 2011). In some cats it may be necessary also to address excess lid length to successfully correct the entropion. Success rates of 88.6% (White et al., 2012) to 95.2% (Read & Broun, 2007) are seen when the Hotz-Celsus procedure is combined with a lateral wedge resection, shortening the lower eyelid by as much as 5 mm. In a retrospective comparison of surgical techniques used to correct lower lid entropion in 124 cats, investigators preferred the Hotz-Celsus combined with lateral canthal closure; only 1 of 127 eyes required a second surgery (White et al., 2012). These authors also advocate prophylactic lateral canthal closure in the asymptomatic fellow eye to decrease its risk of future entropion. One study reported successful correction of entropion in 2 cats using a carbon dioxide laser at 8 W with continuous wave mode to excise the tissue ellipse in the lower lid (Serrano & Rodríguez, 2014). The unsutured wounds healed by second intention within 1 month.

Ectropion

Primary ectropion is virtually nonexistent in cats (Stiles, 2013). Eyelid eversion is more likely a consequence of cicatricial scarring following periocular abscessation, thermal burns, or chemical scalds (Fig. 28.7). A localized lesion can be corrected using a V-to-Y blepharoplasty, but the procedure must include resection of the scarred tissue to adequately alleviate the everting tension. The V-to-Y plasty also alleviates iatrogenic ectropion following overzealous entropion surgery. A local transposition flap, axial pattern flap, or lip-to-lid mucocutaneous subdermal plexus flap is an option in the patient with extensive scarring (Pavletic, 2018).

Cilia Disorders

The cat has no true eyelashes, only a row of thicker facial hairs that serve as rudimentary lashes along the upper lid. Other than the trichiasis associated with eyelid agenesis, feline cilia disorders are uncommon. An ectopic cilium causing a nonhealing ulcer has been reported in a Siamese cat (Hacker, 1989), a Burmese (Manning, 2014), and a hairless Sphynx (Soler & Alessio, 2018). Whereas ectopic cilia tend to erupt in young dogs, the cats in these reports were 6, 3, and 4.5 years of age, respectively. The ectopic cilia were successfully eliminated using either cryoepilation or en bloc resection.

Reports of feline distichiasis are equally rare, although images of distichiasis in the DSH, Burmese, and Birman appear in veterinary ophthalmic atlases (Barnett & Crispin, 1998; Esson, 2015; Ketring & Glaze, 2012; Mitchell & Oliver, 2015; Fig. 28.8). A case series detailing the use of cryotherapy for the treatment of distichiasis included 2 cats, a Siamese and a Burmese (Wheeler & Severin, 1984). Clinical signs of ocular discharge and keratitis resolved in a 2-year-old DSH cat after successful treatment of its bilateral distichiasis using transconjunctival electrocautery (Reinstein et al., 2011).

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Figure 28.8 Distichiasis. Several cilia extend from the meibomian gland openings along the lower eyelid margin, accompanied by a slight serous discharge. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

Dermoid

A dermoid is a form of choristoma, a congenital malformation in which fully differentiated tissue develops in an aberrant location. An ocular dermoid contains elements of normal skin, including keratinized epithelium, hair, glandular tissue, and fat. Embryologically, epidermal and connective tissue inclusions may form during closure of the fetal clefts, or pockets of dermal tissue may develop later in gestation following abnormal invagination of ectodermal tissue (Cook, 2013). Ocular dermoids are considered rare in cats. The anomaly may develop spontaneously in any breed, although a multifactorial mode of inheritance with a threshold phenomenon has been proposed in the Birman breed (Hendy-Ibbs, 1985).

There are conflicting statements in the literature regarding the principal location of feline ocular dermoids. Referencing early reports (Carter & Himes, 1971; Labue et al., 1985), two papers identified the temporal perilimbal conjunctiva and cornea as the most likely site in cats (Glaze, 2005; LoPinto et al., 2016). Barnett and Crispin (1998), as well as Mitchell and Oliver (2015), declared the skin and conjunctiva of the lateral canthus most frequently affected, and in their feline atlases included examples of lateral canthal dermoids in Birman and Persian kittens, respectively. A report of ocular anomalies in three related Burmese litters included a lateral canthal dermoid in one kitten, plus dermoids of the bulbar conjunctiva and external nares in others (Christmas, 1992). An incomplete lateral canthus with "minimal" dermoid formation occurred in three Burmese cats, along with protrusion of the gland of the third eyelid (Koch, 1979). A temporal epibulbar dermoid extended into the upper eyelid in another cat (Carter & Himes, 1971), with a corresponding conjunctival dermoid in the opposite eye. Bilateral lateral canthal dermoids accompanied multiple ocular anomalies in an 18-month-old DSH cat with microphthalmia, ankyloblepharon, corneal dermoids, and facial deformities resembling Goldenhar syndrome in humans (Berkowski et al., 2018).

Although enlargement of a dermoid is not likely, hair on its surface will grow, often irritating the eye and drawing attention to an anomaly that can be overlooked in the neonate. Excess tearing, conjunctivitis, and keratitis may occur. Surgical excision is advisable in most cases, but the proper technique must be determined on an individual basis. A lateral canthal dermoid may simply require a wedge-shaped excision and two-layer closure, with a figure-of-eight suture at the margin to ensure perfect apposition (Gelatt & Gelatt, 2011). Patients with concurrent conjunctival and/or corneal involvement are best referred to an ophthalmologist to ensure complete excision and restoration of normal anatomic relationships during repair of the operative site. Surgical excision is curative.

Blepharitis

Inflammation of the eyelids may occur as an isolated problem or as a component of generalized dermatologic disease. The causes of blepharitis are as varied as the causes of dermatitis in general, and in the cat are usually infectious, allergic, or immune-mediated in origin (Table 28.1). Cats presenting with blepharitis should be examined carefully to identify accompanying dermatologic lesions, the distribution of which may aid in diagnosis. If concurrent skin lesions are present and the eye itself is spared, consultation with a veterinary dermatologist is advisable.

Fungal Blepharitis

Dermatophytosis is a common cutaneous fungal infection in cats, colloquially referred to as "ringworm." Over 90% of feline cases are caused by *Microsporum canis*, with *M. gypseum* and *Trichophyton mentagrophytes* accounting for the remainder (Moriello et al., 2017). Infection results from contact with another affected cat or from environmental contamination. There is indirect evidence that Persian cats are predisposed to infection (Lewis et al., 1991). Lesions occur most commonly on the face, ears, and muzzle, then progress to the paws. Eyelid lesions include variably shaped areas of alopecia, erythematous patches, and crusted plaques. Pruritus is minimal to absent. The Wood's lamp is an excellent screening tool, revealing apple green fluorescence of the infected hair shaft. Sterile hemostats or a clean toothbrush can be used to collect hairs and scales for fungal culture. Although dermatophytosis in most healthy animals is self-limiting within 4 months of onset (Moriello & DeBoer, 1995),

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Table 28.1 Blepharitis associated with feline dermatologic diseases.

Primary Sign	Disease	Agent	Additional Features	Other Sites
Erythema, scales, crusts	Dermatophytosis	*Microsporum canis* (90%), *M. gypseum*, *Trichophyton mentagrophytes*	Alopecia, broken hairs, asymmetric lesions, zoonotic	Ears, muzzle, then paws
	Demodicosis	*Demodex cati*, *D. gatoi*, third unnamed mite	Patchy alopecia	Chin, ear canal, distal limbs
	Pemphigus foliaceus		Bilateral symmetry, variable pruritus	Claw folds, head, and ears
	Idiopathic facial dermatitis		Persians, Himalayans, "dirty face"	
	Bacterial folliculitis	*Staphylococcus* spp.		
Pruritus	Demodicosis	*D. gatoi*	Self-induced alopecia	Lateral thorax, medial limbs
	Feline scabies	*Notoedres cati*	Crusts, zoonotic	Proximal pinna, face, neck
	Atopy		< 2 yrs of age, alopecia, face and neck, eosinophilic plaque	Lateral thorax, ventral abdomen, back legs
	Food hypersensitivity		> 2 yrs, alopecia, face and neck, eosinophilic plaque	Gastrointestinal signs
	"Sticktight" fleas	*Echidnophaga gallinacean*	Preference for face	
Hyperpigmentation	Lentigo simplex		Lid margins, yellow cats	Lips, gingiva, nose
Depigmentation	Topical drug reaction		Marginal erythema	Conjunctiva
	Systemic lupus erythematosus		Siamese, erythema, crusts, scales	Glomerulonephritis, hemolytic anemia, neurologic signs
	Periocular leukotrichia		Siamese	
Erosion/ulceration	Solar dermatitis		White cats	Ears, nose, squamous cell carcinoma precursor
	Herpetic dermatitis	Feline herpesvirus-1	Dorsal muzzle, upper lip	Conjunctiva, cornea
	Mosquito hypersensitivity		Pruritus, alopecia	Bridge of nose
	Leishmaniosis	*Leishmania infantum*, *L. mexicana* (USA)	Uveitis, conjunctivitis	Gingivostomatitis, distal limbs, lymphadenopathy
Nodules	Feline leprosy	*Mycobacterium lepraemurium*	Adult males < 5 yrs, 2° ulcers, abscesses	Systemic disease rare
		M. visibile	Older cats, USA	Multi-organ dissemination
	Systemic mycoses	*Histoplasma capsulatum*, *Cryptococcus neoformans*	Chorioretinitis, uveitis	Multi-organ dissemination
	Feline pox	Cowpox virus	Eurasia; ulcers, then scabs	Systemic disease rare
	Leishmaniosis	*L. infantum*	Uveitis, conjunctivitis	Nose, lips, distal limbs
		L. mexicana	Endemic in Texas	Ears, muzzle

Source: Adapted from Bettenay et al. (2018), pp. 150–156.

topical and systemic treatment is recommended to shorten the disease course as well as limit spread to other animals and their human caretakers. Spot treatment of only visible lesions is not recommended in cats. Twice-weekly lime sulfur dips or miconazole-chlorhexidine shampoos remain the most effective choices for topical therapy in the United States; enilconazole is recommended in other parts of the world. Topical therapy is combined with noncompounded itraconazole (5–10 mg/kg orally every 24 hrs with food) or terbinafine (20–30 mg/kg every 24 hrs; Moriello et al., 2017).

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A pulsed regimen of oral 10% itraconazole solution administered for 7 days at 5 mg/kg every 24 hrs on alternate weeks over a 5-week period produced a clinical cure in 97.5% of infected cats (Puls et al., 2018). Oral griseofulvin is effective, but has been largely replaced by newer drugs with fewer side effects (Frymus et al., 2013). Treatment should be continued until diagnostic testing confirms a cure.

Systemic mycotic infections are relatively uncommon in cats. *Cryptococcus neoformans* and *Histoplasma capsulatum* infections are more often diagnosed than those of *Blastomyces dermatitidis* or *Coccidioides immitis*. The predominant ocular manifestations of these deep mycoses are chorioretinitis and anterior uveitis, but papules and nodules can develop on the face, nose, pinnae, and eyelids (Davies & Troy, 1996; Gilor et al., 2006; Greene & Troy, 1995; Miller et al., 2013c). Nodules may be singular or multiple and are often ulcerated (Miller et al., 2013c). In endemic areas, these pathogens should be considered in any cat exhibiting raised erythematous nodules of the eyelid and palpebral conjunctiva **(**Fig. 28.9**)**. Facial nodules and ulcers commonly associated with the subcutaneous fungus *Sporothrix schenckii* can also extend to the eyelids (Schubach et al., 2004).

Parasitic Blepharitis

Feline demodicosis is an uncommon dermatologic disease caused by the mites *Demodex cati*, *D. gatoi*, and a third unnamed *Demodex* sp. (Kano et al., 2012). Localized disease affects the eyelids, periocular area, head, and neck, with patchy alopecia, erythema, scaling, and crusting (Chesney, 1989; Fig. 28.10). *D. gatoi* is contagious to other cats and infestation is distinguished by moderate to severe pruritus. Generalized demodicosis is usually associated with underlying systemic diseases, including diabetes mellitus or infection with feline leukemia virus or feline immunodeficiency virus. Even in generalized disease, lesions predominate on the face and head. Diagnosis is based on the presence of mites in skin scrapings, hair plucks, or acetate tape preparations. *D. gatoi* may also be demonstrated using fecal flotation, since mites are ingested by the pruritic, overgrooming cat (Silbermayr et al., 2013). Localized *D. cati* lesions are typically self-limiting, but can be treated with topical rotenone ointment (Stiles, 2013), lime sulfur, pyrethrin-containing ear medications, or amitraz in mineral oil (1 : 9; Miller et al., 2013e). For generalized *D. cati* infestations, alternatives to weekly 2% lime sulfur dips include oral aqueous ivermectin (0.2–0.3 mg/kg every 24–48 hrs; Beale, 2012), oral milbemycin oxime (1–2 mg/kg every 24 hrs), injectable doramectin (600 µg/kg subcutaneously once weekly), topical imidacloprid-moxidectin applied every 7–14 days (Moriello, 2011), or oral fluralaner (single 28 mg/kg oral dose; Matricoti & Maina, 2017). The treatment of choice for *D. gatoi* consists of at least four weekly 2% lime sulfur dips (Moriello, 2011). Treatment of either mite should continue until two consecutive skin scrapings, taken 2 weeks apart from the same site, are negative.

Notoedric mange or feline scabies is a highly contagious yet uncommon disorder caused by *Notoedres cati* (Foley, 1991). Affected animals typically have large numbers of



Figure 28.9 Mycotic blepharitis. A 3-year-old Domestic Shorthair exhibits multiple erythematous nodules of the eyelid and conjunctiva associated with systemic histoplasmosis.



Figure 28.10 Demodicosis. Periocular skin scrapings were positive for *Demodex* spp. in a 13-year-old diabetic Domestic Longhair with periocular alopecia, erosion, and crusting. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

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mites that are easily found on skin scrapings or acetate tape impressions. Lesions first appear on the proximal edge of the ear, then spread rapidly to the face, eyelids, and neck. The infestation is intensely pruritic, accompanied by heavy crusts, thickened skin, and hair loss. Differentials include atopy, food hypersensitivity, and pemphigus foliaceus (Miller et al., 2013f). Six to eight weekly applications of lime sulfur to all in-contact cats may be necessary to eliminate the mites. Less labor-intensive alternatives include topical selamectin (6–12 mg/kg once or twice at a 14- or 30-day interval; Itoh et al., 2004), topical imidacloprid/moxidectin (Advantage® Multi, Bayer, Leverkusen, Germany, 0.1 ml/kg once; Hellman et al., 2013), subcutaneous doramectin (0.2–0.3 mg/kg once; Delucchi & Castro, 2000), oral ivermectin (0.2 mg/kg twice weekly for four doses; Sivajathi et al., 2015), or subcutaneous ivermectin (0.2–0.3 mg/kg at 14-day intervals; Miller et al., 2013f).

Bilateral red-orange pinpoint lesions developed in the periocular skin of two DSH cats infested with trombiculid mites, more commonly referred to in North America as grass itch mites or chiggers (Takahashi et al., 2004). Pruritus and self-induced excoriations were also noted. Mites were identified in skin scrapings. One cat was treated with topical 0.1% trichlorfon every 2 days for eight applications. Lesions resolved in the second cat following three doses of ivermectin administered once weekly, along with topical ivermectin applied daily for 1 month.

Eyelid nodules can develop from aberrant migration of dipterous fly larvae, most notably *Cuterebra* spp. in the cat (Slansky, 2007). Cats probably become infected as they prowl in rodent or rabbit habitats contaminated by fly eggs. The exact manner in which the larvae of these nonbiting flies enter the body is unknown, but it is assumed that they enter through the body's natural openings or are ingested during grooming. Cases tend to be more common during mid-summer and fall months when the flies are most active. The typical presentation is a subcutaneous swelling with a well-defined fistula or pore through which the developing third-stage larva can be seen (Rutland et al., 2017). Surgical removal of the larva is indicated, first enlarging the pore, then extracting the larva with gentle traction. Crushing the larva during removal or failing to remove the larva in its entirety can cause a Type 1 hypersensitivity reaction. The residual lesion is treated as an open wound. Preliminary data suggest that monthly heartworm preventatives may abort the development of new lesions (Miller et al., 2013f).

Infestation with *Echidnophaga gallinacean*, the sticktight flea, occurs in cats housed near poultry. This flea species prefers the facial region, attaching to the eyelids, pinnal margins, and muzzle (Miller et al., 2013f). Pruritus is a characteristic feature. The small red flea bodies may be mistaken for crusts in the erythematous periocular skin. Treatment options include spot-on products containing imidacloprid/moxidectin or selemectin, applied topically every 2 weeks for two to three treatments (Bettenay et al., 2018).

Hypersensitivity to antigens in mosquito saliva can cause a pruritic, erosive, crusting dermatitis in some cats (Bloom, 2006; Nagata & Ishida, 1997). Lesions are most common on the bridge of the nose, but the histologically eosinophilic reaction can extend into the periocular area. The cat should be isolated from mosquitoes if possible, particularly overnight when the insects are most actively feeding. Oral or injectable corticosteroids may reduce the pruritus and inflammation. The essential oil in catnip, nepetalactone,

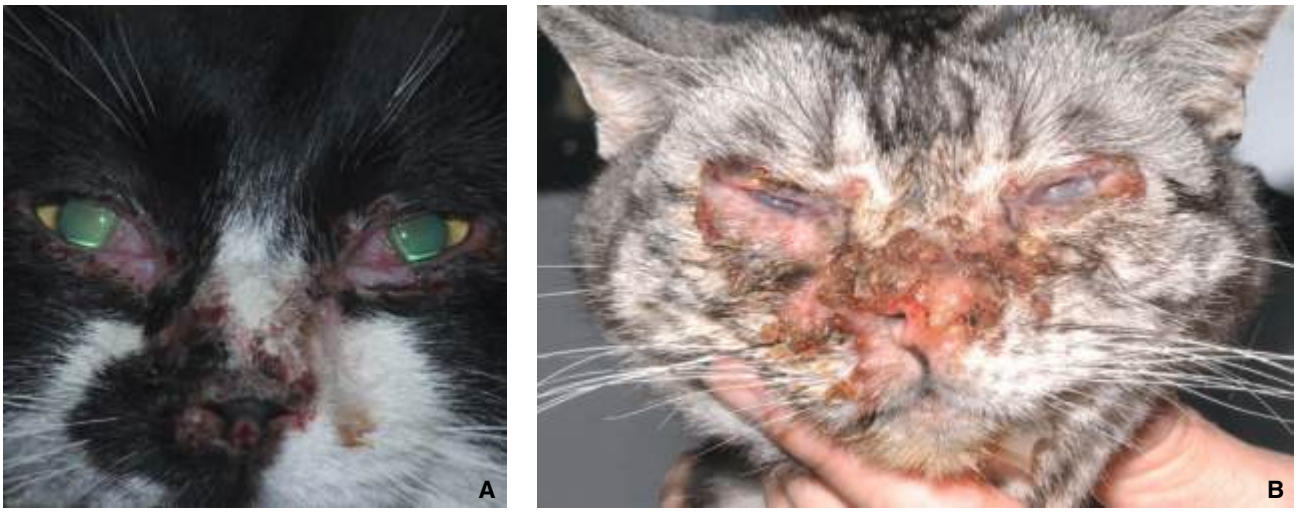


Figure 28.11 **A**. Herpetic dermatitis. Erosive periocular and facial dermatitis developed in a 2-year-old American Shorthair treated with systemic corticosteroids for a fever of unknown origin. **B**. This severe ulcerative dermatitis of the periocular skin, nasal planum, and muzzle was characterized by eosinophilic infiltration and polymerase chain reaction–confirmed feline herpesvirus-1 DNA. (Courtesy of University of California Davis Veterinary Ophthalmology Service.) Both patients responded favorably to famciclovir therapy.

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reportedly repels mosquitoes (Webb & Russell, 2007). Insect repellants containing DEET or permethrins should not be used in cats.

Viral Blepharitis

FHV has been identified as a cause of dermatologic lesions, particularly those involving the facial skin of domestic (Hargis & Ginn, 1999; Hargis et al., 1999; Holland et al., 2006; Suchy et al., 2000) and wild (Junge et al., 1991; Munson et al., 2004) felidae. This is not surprising when one considers the marked epithelial tropism of this virus and the fact that herpes simplex virus (HSV) is a well-known cause of dermal (especially labial) lesions such as "cold sores" or "fever blisters" (Maggs et al., 1998). Feline herpetic dermatitis typically but not always involves facial skin and is both proliferative and ulcerative, with papules, crusts, and ulcers (Fig. 28.11). Concurrent or preceding upper respiratory or ocular signs can be noted. Skin biopsy is critical for diagnosis and will reveal a markedly destructive eosinophilic furunculosis. The likelihood of an etiologic diagnosis will be improved if the pathologist is provided with the clinical suspicion and directed to look for pathognomonic intranuclear inclusion bodies. Failing that, polymerase chain reaction (PCR) assessment of fresh or paraffin-embedded biopsy samples for the presence of FHV-1 DNA is very helpful. Unlike ocular disease, where the high rate of viral shedding seen in normal cats dramatically reduces the diagnostic utility of PCR, FHV-1 PCR appears to be extremely useful for herpetic dermatitis. In one study (Holland et al., 2006), FHV-1 DNA was detected in all 9 biopsy specimens from 5 cats with herpetic dermatitis, but in only 1 of 17 biopsy specimens from the 14 cats with nonherpetic dermatitis, and in none of 21 biopsy specimens from 8 cats without dermatitis. When results of histologic examination were used as the gold standard in that study, the sensitivity and specificity of the PCR assay were 100% and 95%, respectively. An Italian group using a different PCR assay to assess biopsies from cats with a variety of eosinophilic dermatopathies found FHV-1 DNA in 12 of 64 biopsies (Persico et al., 2011). Treatment can be challenging; in fact, lack of response to empirical therapy for dermatitis should encourage consideration of the diagnosis of herpetic dermatitis. Twice-daily administration of famciclovir at 90 mg/kg orally is recommended for control of herpetic dermatitis. Lower doses appear less successful, and a protracted course may be necessary (Malik et al., 2009; Thomasy et al., 2016). Corticosteroids are contraindicated. Recurrence seems common.

Feline infection with cowpox virus occurs regionally in the United Kingdom, western Europe, and Asia (Möstl et al., 2013). The disease is extremely rare in North America, where other orthopoxviruses such as raccoonpox are implicated (Yager et al., 2006). Free-roaming cats acquire the virus from small rodents, developing an ulcerated, crusted skin nodule on the head or forelimb at the primary site of viral inoculation and replication. Within 1–2 weeks, multiple pruritic skin lesions appear on the face and paws, starting as macules or small erythematous nodules that ulcerate and scab (Bennett et al., 1990). Unilateral erosive, crusted lesions affected the upper and lower eyelids of a 4-year-old DSH (Barnett & Crispin, 1998). Bilateral periocular erosive lesions with marked swelling have been described in two cats (Allgoewer & Bomhard, 2009). Eyelid lesions predominated in a cat with a mixed infection of pox and canine distemper viruses (Wiener et al., 2013). Histopathologic confirmation is based on intracytoplasmic eosinophilic viral inclusion bodies within biopsied tissue. Lesion crusts may be submitted for pox-specific PCR in lieu of biopsy (Bettenay et al., 2018). Superficial lesions usually heal spontaneously within 4–5 weeks with supportive care.

Protozoal Blepharitis

Five species within the genus *Leishmania* have been identified in cats. *Leishmania infantum* is the predominant pathogen in the Mediterranean basin, Middle East, and China, but only *L. mexicana* is established in North America (specifically Texas; Barnes et al., 1993; Trainor et al., 2010). In addition to *L. infantum*, there are regionally endemic *Leishmania* species in South America. The disease is transmitted by phlebotomine sand flies. Tissue damage is due to granulomatous inflammation and immune complex deposition. Skin lesions and lymphadenopathy occurred in more than half of the 46 published clinical cases of feline leishmaniosis in Europe; ocular lesions appeared in one-third of affected cats (Pennisi et al., 2015). Although uveitis is the most common ocular lesion, blepharitis and conjunctivitis have been described in a number of clinical cases (Migliazzo et al., 2015; Navarro et al., 2010; Trainor et al., 2010). Cutaneous papules, nodules, exudative crusts, and ulcers often develop on the head and may affect the periocular skin (Soares et al., 2013). The most common histopathologic feature is diffuse granulomatous inflammation with macrophages that contain *Leishmania* amastigotes (Navarro et al., 2010). When blood, skin, bone marrow, and conjunctiva were submitted for PCR testing, 80% of infected cats were positive in only 1 of the 4 tissues, prompting a recommendation for multiple tissue submissions in order to minimize false negative results (Chatzis et al., 2014). Western blot offered better sensitivity and specificity compared to that of enzyme-linked immunosorbent assay (ELISA, MiraVista Diagnostics, Indianapolis, IN, USA) and immunofluorescent antibody (IFA) for serologic diagnosis of feline leishmaniosis (Persichetti et al., 2017). The most frequently used treatment regimen is either long-term oral administration of allopurinol (10 mg/kg every 12 hrs or 20 mg/kg every 24 hrs) as monotherapy, or allopurinol as maintenance treatment after a course of subcutaneous injections of meglumine antimoniate (Pennisi & Persichetti, 2018). Skin lesions in one cat resolved following three 4-week courses of treatment with 5 mg/kg meglumine

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antimoniate subcutaneously combined with 10 mg/kg of ketoconazole orally once daily, with a 10-day drug-free interval between each treatment period (Hervás et al., 1999). Clinical improvement occurs within a few weeks following start of therapy, but relapses appear common once treatment is discontinued. Topical treatment of cutaneous *L. mexicana* infection with clotrimazole and paromomycin was ineffective (Barnes et al., 1993).

Bacterial Blepharitis

Bacterial infections occur most commonly as a consequence of cat fight injuries. *Pasteurella multocida* is the most common organism cultured from cat bite wounds (Freshwater, 2008). Other isolates include *Staphylococcus pseudintermedius*, β-*hemolytic Streptococcus*, and various anaerobic species (Roy et al., 2007). The treatment of choice for a discrete abscess is surgical drainage, flushing the site thoroughly with sterile saline, balanced electrolyte solution, or dilute (1 : 50) povidone iodine solution (Davidson, 1998). A 7–10-day course of oral amoxicillin-clavulanate is recommended following drainage of the abscess or in patients with diffuse cellulitis (Roy et al., 2007). A study of antibacterial susceptibility of *P. multocida* isolated from the gingival margins of 368 cats (of 409 cats sampled) compared benzylpenicillin (100%), amoxicillin-clavulanate (100%), cefazolin (98.4%), and azithromycin (94%; Freshwater, 2008). Cats should also be tested for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) 60 days after being bitten by another cat (Goldkamp et al., 2008).

Pyoderma and bacterial folliculitis were considered rare in cats (Hill et al., 2006; White, 1991) until a 20% prevalence was revealed in a retrospective study of 52 cases identified in a dermatology referral population (Yu & Vogelnest, 2012). The median age of 4.5 years at diagnosis is likely linked to the age of onset of underlying primary dermatoses, of which hypersensitivities were most common (Yu & Vogelnest, 2012). A second cohort of cats older than 9 years of age also exists (White, 1991). Lesions most commonly occur on the face and include erythematous papules, crusts, secondary excoriations linked to pruritus, and alopecia. Pustules are seldom, if ever, present. Of the 62% of patients with facial lesions, 7 of 19 cats with specified lesion distribution demonstrated periocular involvement (Yu & Vogelnest, 2012). Diagnosis is based on cytologic examination of adhesive tape preparations, with neutrophils and intracellular bacterial cocci almost always present. Clinical response to amoxicillin-clavulanic acid administered for a minimum of 3 weeks was seen in 61% of patients (Yu & Vogelnest, 2012). Incomplete control of the underlying primary dermatoses may explain confirmed recurrences in 10% of cats within the study.

Cutaneous nodules are characteristic of mycobacterial infections in cats, including feline tuberculosis, caused almost exclusively by *Mycobacterium microti* or *M. bovis* (Gunn-Moore et al., 1996, 2011), and feline leprosy syndrome, attributed to various mycobacteria including *M. lepraemurium* (Gunn-Moore, 2014; Gunn-Moore et al., 2011). Single or multiple ulcerated or fistulated nodules have been described on the face and in the eyelids of cats infected with *Mycobacterium lepraemurium* (Malik, 2006). Diagnosis is based on detection of acid-fast bacilli in smears from fine-needle aspirates, crush preparations of biopsy specimens, or histologic sections. With commonly used in-house stains such as Diff-Quik (Baxter Diagnostics, Bellevue, WA, USA), mycobacteria are "negatively stained," appearing as clear individual or bundled rods within macrophages (O'Brien et al., 2012). Wide surgical excision of solitary nodules is the treatment of choice, with pre- and postoperative antimicrobial therapy using clofazimine, combined with clarithromycin or rifampin (O'Brien et al., 2012). Treatment must be continued for several months, or at least 2 months beyond lesion resolution.

Immune-Mediated Blepharitis

Of the various generalized autoimmune dermatoses that may involve the eyelids, pemphigus foliaceus is most common in the cat (Miller et al., 2013a). The disorder develops at any age. In a series of 57 cats, 80% developed bilaterally symmetric focal crusting lesions on the head, face, and ears, with periocular involvement in 10% (Preziosi et al., 2003). Lesions often appear first in the pre-auricular skin (Bettenay et al., 2018), accompanied by changes across the bridge of the nose and nasal planum. Claw folds are also commonly affected as the disease progresses. Diagnosis is based on histopathology. Prognosis is favorable when treated with triamcinolone, prednisolone, prednisolone plus chlorambucil, or cyclosporine (Miller et al., 2013a). Immunosuppressive therapy is usually continued indefinitely at the lowest possible dosage needed to maintain disease remission. Pemphigus foliaceus-like drug eruptions have been described in 5 cats, linked with ampicillin (Mason & Day, 1987), cimetidine (McEwan et al., 1987), ipodate, methimazole, and itraconazole and/or lime sulfur dips (Preziosi et al., 2003). Pemphigus erythematosus can mimic pemphigus foliaceus, although lesions are usually restricted to the head and neck (Scott et al., 1980; Fig. 28.12). Pemphigus vulgaris is extremely rare in cats, as is systemic lupus erythematosus (SLE). The Siamese cat is reportedly predisposed to SLE (Bettenay et al., 2018). Mucocutaneous ulceration may accompany crusting and scaling of the eyelids. Characteristic histopathology and a positive antinuclear antibody (ANA) test are suggestive, but three or more organ systems must be involved to substantiate a diagnosis of SLE.

Allergic Blepharitis

Localized and regional erythema, edema, and pain can develop rapidly following stings by bees, wasps, and other hymenopteran insects (Fitzgerald & Flood, 2006). The majority of insect stings are self-limiting events that resolve

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Figure 28.12 Pemphigus erythematosus in an adult Domestic Longhair. Erythematous macular dermatitis and excoriations affect the eyelids, nose, muzzle, and pinnae. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

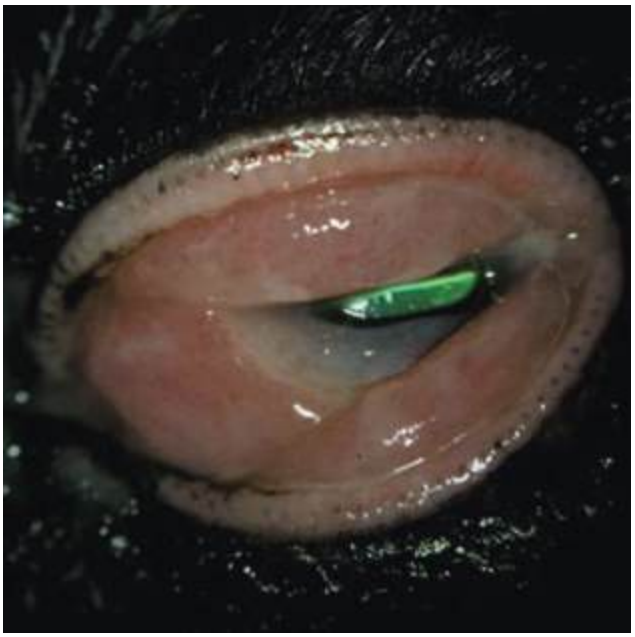


Figure 28.13 Blepharitis attributed to adverse drug reaction. Repeated application of topical trifluridine inflamed the eyelids and conjunctiva of a 2-year-old Domestic Shorthair. The marginal depigmentation is a reliable feature of drug-related blepharitis.

in a few hours without treatment. Conservative therapy consists of systemic antihistamines, cold compresses, and occasionally topical corticosteroid ointment. Patients should be monitored in the early stages for progressive signs suggestive of anaphylaxis. Facial and periocular edema developed in 5.7% of cats following vaccination. Young adult cats that received multiple vaccines per visit were at greatest risk (Moore et al., 2007).

Although acute hypersensitivity to a topical medication can produce immediate, transient conjunctival and eyelid swelling, the disorder is more often a delayed lymphocyte-mediated reaction, the result of repeated or prolonged drug application. The telltale eyelid abnormalities include marginal erythema, swelling, and depigmentation, often exaggerating the meibomian gland orifices (Fig. 28.13). A wider zone of periocular alopecia may develop. Conjunctivitis invariably accompanies the lid changes. An owner may note that redness and discomfort increase throughout the day, as the medication is repeatedly applied. Any active ingredient or preservative has the potential to irritate the ocular surface in the individual patient. Commonly implicated medications include neomycin, gentamicin, tetracycline, trifluridine, atropine, and dorzolamide. Blepharitis also occurs with topical cyclosporine use, though the reaction more likely reflects the type of oil used to compound the product rather than the cyclosporine itself.

Clinically, feline atopic dermatitis and food allergy appear to be indistinguishable (Hobi et al., 2011; Miller et al., 2013e). Young cats appear predisposed to atopic dermatitis, with the majority showing clinical signs between 6 and 24 months of age (Roosje et al., 2000). The mean age of onset of adverse food reactions was 3.5 years (Vogelnest & Cheng, 2013), thought to reflect the prolonged sensitization period before clinical signs develop. The Siamese and its crosses may be predisposed to food allergy (Carlotti et al., 1990). Signs tend to be nonseasonal in either hypersensitivity disorder (Ravens et al., 2014; Vogelnest & Cheng, 2013). The most common and consistent clinical sign of both is pruritus, often localized to the face and neck (Foil, 1988). Crusted, erythematous papules, self-induced excoriations, and patchy alopecia often develop in the pre-auricular area and may extend into the eyelids (Ravens et al., 2014; Vogelnest & Cheng, 2013). Some cats also develop lesions of the eosinophilic granuloma complex, especially eosinophilic plaques. Latimer and Dunstan (1987) described bilateral eosinophilic plaques of the eyelids in a DSH cat. Cytology of skin scrapings revealed eosinophils, while histologic sections of affected skin contained eosinophils, mast cells, and plasma cells. In a multicenter study of feline hypersensitivity dermatoses, conjunctivitis occurred in 19% of cats with non-flea-associated pruritic dermatitis (Hobi et al., 2011). Diagnosis of atopy is based on history, clinical signs, and exclusion of other causes of pruritus (Miller et al., 2013e). The only way to definitively diagnose food allergy is through a food elimination trial (Bryan & Frank, 2010). Symptomatic treatment of pruritus with oral or injectable glucocorticoids, cyclosporine, antihistamines,

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or serotonin antagonists is used in conjunction with allergen-specific immunotherapy to manage feline atopy (Ravens et al., 2014). Avoidance of the offending food is required to effectively manage food hypersensitivity. Systemic antipruritic therapy may be required when allergen avoidance is impossible, but about 50% of cats with food sensitivity do not respond to systemic glucocorticoids (White & Sequoia, 1989). Studies of oral antihistamines found that 73%, 50%, 41%, and 35% of allergic pruritic cats responded to chlorpheniramine, 2 mg/cat every 12 hrs (Miller & Scott, 1990); clemastine, 0.68 mg/cat every 12 hrs (Miller & Scott, 1994); cetirizine, 5 mg/cat every 24 hrs (Griffin et al., 2012); and cyproheptadine, 2 mg/cat every 12 hrs (Scott et al., 1998), respectively. A more recent study found no statistically significant difference between cetirizine and placebo in control of feline atopic pruritus (Wildermuth et al., 2013).

Miscellaneous Blepharitis

Solar dermatitis is a consequence of chronic sun exposure occurring in white- or orange-faced cats (Foil, 1995; Miller et al., 2013c). Lesions first appear on the margins of the ear pinna, but the eyelids (particularly the lower lids) may also be affected. Erythema and fine scaling are followed by skin peeling and crusts, consistent with sunburn. The actinic dermatitis may be a precursor to squamous cell carcinoma (SCC), since cancerous lesions appear at a younger age if preceded by solar damage (Gomes et al., 2000). Affected cats should be kept indoors from 11 a.m. to 2 p.m., when solar intensity and ultraviolet (UV) exposure are greatest, and should not be allowed to sunbathe by open doors or windows. The potential for ocular irritation limits the use of periocular topical sunscreens. Treatment with oral carotenoids (Irving et al., 1982) and retinoids (Evans et al., 1985) to prevent progression of precancerous lesions in cats has been ineffective. Topical immunomodulators such as imiquimod 5% cream (Alomar et al., 2007) and Cyclooxygenase-2 (COX-2) inhibitors such as 1% diclofenac gel (Bardagi et al, 2012; Burrows, 2014) have potential benefit, but have not been critically evaluated for treatment of solar dermatitis in cats.

Idiopathic facial dermatitis of Persian and Himalayan cats is believed to have a genetic basis (Bond et al., 2000). The median age of onset is 12 months and cats of either sex may be affected. Although serous or mucoid ocular discharge may accompany the periocular lesions, an ophthalmologist is likely to be consulted when facial fold inflammation is erroneously attributed to excess ocular discharge rather than the primary dermatitis. The disorder is commonly referred to as dirty face syndrome, due to the blackish waxy crusts that adhere to the hair in a symmetric pattern around the eyes and facial folds. With chronicity, the skin beneath the crusts becomes increasingly inflamed and often pruritic (Fig. 28.14). Secondary bacterial or *Malassezia* infection increases the severity of the lesions. Some cats develop submandibular lymphadenopathy. A consistently successful



Figure 28.14 Idiopathic facial dermatitis in a 4-year-old Persian cat. This incurable breed-related disorder may be misdiagnosed as facial scalding, with characteristic black crusts that account for the name "dirty face syndrome."

treatment regimen has not been found. Clinical signs have been palliated using various combinations of systemic antibiotics, ketoconazole, prednisolone, cyclosporine, allergen-specific immunotherapy, topical tacrolimus, and anti-seborrheic cleansing wipes (Bond et al., 2000; Miller et al., 2013b). Therapeutic response is limited and relapses can be expected if therapy is discontinued.

Pigmentary Disorders

Lentigo simplex is characterized by well-circumscribed areas of macular melanosis affecting the eyelid margins as well as the lips, gums, and nose (Fig. 28.15). Orange-colored cats are most commonly affected, with lesions first appearing in cats less than 1 year of age (Scott, 1987). Over time, the pigmented foci may increase in size and number, but there is no apparent progression to melanoma. This cosmetic disorder requires no treatment.

Periocular leukotrichia occurs transiently in female colorpoint cats, predominantly the Siamese (Foil, 1995; Scott, 1987). The disorder is characterized by patchy or complete lightening of hair color around the eyes. Stressors including estrus, pregnancy, or systemic illness are thought to initiate the change. Normal coloration generally returns within 1–2 hair growth cycles.

Meibomian Gland Disorders

Localized swelling of individual meibomian or accessory eyelid glands is uncommon in cats. In those rare instances, acute bacterial infection of a meibomian gland (internal hordeolum) or gland of Zeis (external hordeolum) or chronic inspissation of a meibomian gland's secretions (chalazion)

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Figure 28.15 Lentigo simplex is a benign cosmetic disorder characterized by macular melanosis of the eyelids, usually seen in orange-colored cats.

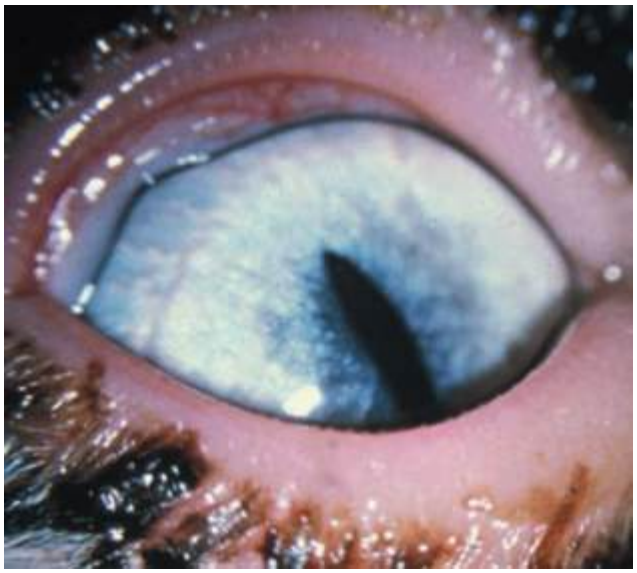


Figure 28.16 Meibomitis is less conspicuous in cats than in dogs, appearing in this 6-month-old Persian as a roughened lid margin, with caseous material plugging the meibomian gland orifices.

mimics that seen in the dog. The hordeolum is treated with warm compresses, combined with a topical antibiotic and corticosteroid ointment. Systemic therapy is seldom indicated for singular lesions. If complicated by secondary inflammation and discomfort, the individual chalazion can be curetted through a conjunctival incision.

Cats also rarely demonstrate diffuse infection or inflammation of the meibomian glands and surrounding tissues, termed meibomitis or marginal blepharitis, or the notable periocular erythema and eyelid swelling that characterize the canine disorder (Fig. 28.16). While both species develop nodular conjunctival swellings due to the accumulation of meibomian secretions, the proposed pathogenesis of feline lipogranulomatous conjunctivitis (see below) differs from the staphylococcal hypersensitivity commonly implicated in canine meibomitis. As a result, the symptomatic canine regimen of systemic antibiotics combined with corticosteroids may not be as effective in cats with meibomian gland disease. If initial response to oral amoxicillin-clavulanate, doxycycline, or a cephalosporin is limited, oral prednisolone should be added to the regimen, beginning with an induction dose of 2.2 mg/kg/day for 3–5 days, then tapering over several weeks until clinical signs resolve. Compared with dogs, cats require about twice the oral glucocorticoid dose for anti-inflammatory or immunosuppressive induction (Lowe et al., 2008). Keep in mind that corticosteroid administration reliably reactivates latent FHV-1.

Lipogranulomatous Conjunctivitis

Named for its characteristic conjunctival reaction rather than its meibomian gland association, lipogranulomatous conjunctivitis is a distinctive inflammatory disorder concentrated within the palpebral conjunctiva adjacent to the eyelid margin and meibomian glands. The problem tends to occur in older cats, with a mean age of 11 years (range 6–16 years; Kerlin & Dubielzig, 1997; Read & Lucas, 2001), and in predominantly white or white-faced cats or those with limited pigmentation of the eyelid margins (Read & Lucas, 2001). One source reported a higher incidence in the Persian (Mitchell & Oliver, 2015), although no Persians appeared in a retrospective study of 13 cats (Read & Lucas, 2001). Lesions occur unilaterally or bilaterally, but are usually more extensive in the upper eyelid. Of 21 eyes in 13 cats, lesions were never identified in the lower eyelid alone (Read & Lucas, 2001), perhaps reflecting the lesser meibomian gland development in the cat's lower lid (Samuelson, 2007). Increased tearing, mucoid discharge, and blepharospasm are common presenting signs. Smooth, nonulcerated, cream- or white-colored 2–3 mm conjunctival nodules are found adjacent to the eyelid margin, usually numerous and closely packed, but occasionally coalescing into much larger nodules that extend the length of the lid (Fig. 28.17). On rare occasion the nodules may distort the overlying eyelid skin (Manning, 2014).

Histologic features include variably sized lipid lakes within the submucosal connective tissue, surrounded by macrophages, multinucleated giant cells, and low numbers of plasma cells and lymphocytes (Kerlin & Dubielzig, 1997; Read & Lucas, 2001). Periglandular fibrosis is common. Inflammation is negligible within the meibomian glands themselves, but abnormally keratinized squamous epithelium within the meibomian gland ducts suggests that solar radiation may play a role in the disorder, sufficiently damaging the glands so that sebaceous secretions leak into the

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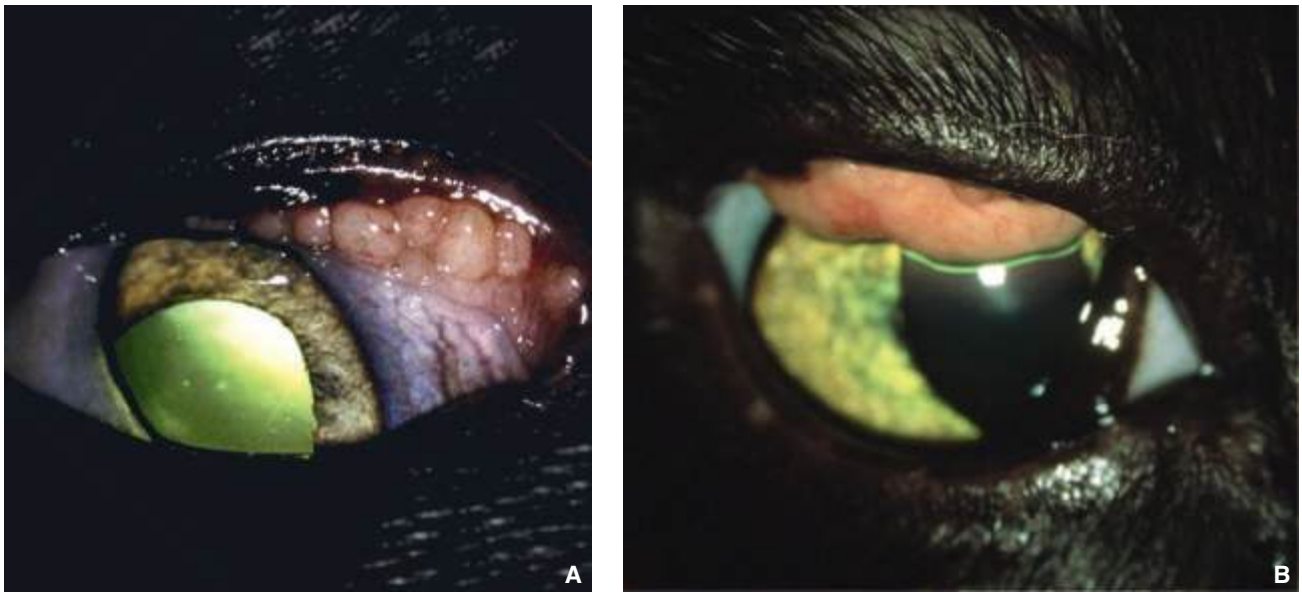


Figure 28.17 Lipogranulomatous conjunctivitis. **A**. Lipid-laden macrophages and retained lipid secretions create multifocal conjunctival nodules overlying the meibomian glands in a 12-year-old Domestic Shorthair. **B**. Secretions may also coalesce to create larger lobules that protrude beyond the lid margin, as in this 13-year-old Domestic Shorthair.

surrounding tissue (Read & Lucas, 2001). Concurrent ocular or periocular neoplasia was present in 5 of the 21 cats initially described with lipogranulomatous conjunctivitis (Kerlin & Dubielzig, 1997; Read & Lucas, 2001).

Although the pathogenesis of lipogranulomatous conjunctivitis differs from that of classic meibomitis, its inflammatory component may respond to a combined oral regimen of doxycycline and prednisolone, as previously described. Doxycycline provides an inherent anti-inflammatory benefit as well as a restorative effect on lipid quality within meibomian gland secretions (Pflugfelder et al., 2014). Warm compresses may also be of benefit. In poorly responsive or severely affected patients, surgical excision of the conjunctival nodules may be considered. The palpebral conjunctiva is incised along each side of the row of nodules, parallel to the eyelid margin, and the strip of affected conjunctiva and subconjunctival tissue is excised. The open wound is treated with topical antibiotic ointment for 7–10 days. Clinical signs resolved following surgical excision of the conjunctival nodules in 8 patients, with no significant recurrence during a 4–21-month postoperative period (Read & Lucas, 2001). Consideration should be given to the potential impact of this surgery on tear film quality and stability.

Eyelid Cysts and Nodules

Apocrine hidrocystomas arise from modified sweat glands (of Moll) within the skin near the eyelid margin. These benign, cystic tumors have also been referred to as cystadenomas (Dubielzig et al., 2010). Persian cats represent over 80% of reported cases (Cantaloube et al., 2004; Giudice et al., 2009; Kahane et al., 2014; Yang et al., 2007), with rare instances in the Himalayan (Chaitman et al., 1999) and the DSH (Newkirk & Rohrbach, 2009; Sivagurunathan et al., 2010). Older cats are typically affected, with reported cases ranging in age from 3 to 15 years, for a mean of 9.6 years. No sex predisposition is seen. Early lesions appear flat, but typical hidrocystomas are raised, reddish-brown to black cystic nodules distributed in the skin along the eyelids, especially around the medial canthus. Two patients demonstrated epiphora and blepharospasm (Kahane et al., 2014; Yang et al., 2007), but no other instances of pain or pruritus have been reported. Aspirates of the fluid help differentiate the cysts from melanoma, with macrophages of variable reactivity, phagocytosis of black-colored debris, and numerous cholesterol clefts (Kahane et al., 2014). The color of the thick, cell-poor fluid within the cyst lumen is attributed to hemosiderin and ceroid pigments. Definitive diagnosis requires excisional biopsy and histopathology characterized by multiple cystic structures of various sizes expanding the dermis, with intraluminal hyaline to granular material (Chaitman et al., 1999). The lesions have been interpreted as either retention cysts, based on epithelial flattening and dermal fibrosis, or benign adenomas, owing to high proliferative indices and epithelial papillary projections into the cyst lumen, with the latter interpretation prevailing (Cantaloube et al., 2004; Giudice et al., 2009). Treatment is determined by the number and size of the lesions and their effect on eyelid function. Small and random cysts may be monitored without treatment. Individual cysts may be drained by fine-needle aspirate, but recurrence is common within a matter of weeks to months (Chaitman et al., 1999; Kahane et al., 2014). Surgical excision

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can be considered for individual lesions, but new cysts appeared within 8–10 months in two cats (Cantaloube et al., 2004). Two other patients exhibited postoperative disease-free intervals lasting 5 years after surgical removal (Chaitman et al., 1999; Newkirk & Rohrbach, 2009). Following incision and drainage of the cyst, the residual tissue can be treated cryosurgically using either liquid nitrogen or nitrous oxide (Sivagurunathan et al., 2010), or photoablated using a 1450 nm diode laser (Echague et al., 2005). Cysts have been successfully ablated, with at least a 12-month disease-free interval, following injection of 20% trichloroacetic acid (TCA) into the drained lesion, taking care to avoid contact of the acid with the cornea (Yang et al., 2007). Anecdotal reports suggest that 1% polidocanol is an effective alternative sclerosing agent for cyst ablation.

Eyelid nodules developed in a 10-year-old DSH with feline progressive histiocytosis (Treggiari et al., 2015), a slowly progressive disease characterized by solitary or multiple skin nodules, particularly of the head, neck, and limbs. Nodules often disseminate to internal organs, including liver, spleen, and bone marrow, accounting for the mean survival of 13 months (Affolter & Moore, 2006). In the late stage of the disease, progressive histiocytosis is indistinguishable from histiocytic sarcoma. Eyelid nodules are also seen in feline leprosy (Malik et al., 2013), systemic mycotic infections (Miller et al., 2013d), feline pox (Bennett et al., 1990), and leishmaniosis (Poli et al., 2002), as previously described.

Eyelid Neoplasia

Eyelid tumors are less common in cats than dogs, but are more likely to be malignant when they do occur (Martins & Barros, 2014; McLaughlin et al., 1993; Newkirk & Rohrbach, 2009; Williams et al., 1981). Histologically malignant or potentially malignant tumors accounted for 91% of the eyelid masses in one study (Newkirk & Rohrbach, 2009; Table 28.2). Cats older than 10 years are most frequently affected, but no sex or breed predilections for eyelid neoplasms have been identified (McLaughlin et al., 1993).

SCC is the most common eyelid neoplasm of the cat. The frequency of SCC in early reviews of feline eyelid neoplasia ranged from 36% in a series of 36 cats to 65% in a group of 85 cats (McLaughlin et al., 1993). In a more recent report of 43 cats with eyelid tumors, 28% were diagnosed with SCC (Newkirk & Rohrbach, 2009). That study also reiterated the higher incidence of SCC in comparatively older cats and in white cats. White cats of any haircoat length have a 13 times greater risk of developing SCC than cats of other colors (Dorn et al., 1971). The Siamese cat's coloration reportedly decreases its risk of SCC (Miller et al., 1991). Solar dermatitis often precedes the development of SCC and likely increases the odds of lower eyelid involvement (Dorn et al., 1971; Gomes et al., 2000). The tumor occurs at or adjacent to the eyelid margin, appearing erythematous, either slightly raised or depressed, and commonly ulcerated, often with a crusted surface (Fig. 28.18). Lesions typically progress from erythema and crusting to superficial, then deep erosions. Large, eroded nodules are less common. Conjunctival epithelial dysplasia often accompanies the eyelid lesions (Dubielzig et al., 2010). Local invasion can be extensive, with orbital and regional lymph node involvement, but metastasis is rare until late in the disease. Tumor recurrence is common. In a retrospective study of feline eyelid tumors, 7 of 9 cats with SCC for which follow-up was available were euthanized, with an average survival time of 7.4 months (Newkirk & Rohrbach, 2009).

Cytologic examination of tissue scrapings or aspirates may demonstrate atypical keratinocytes, with asynchronous nuclear and cytoplasmic maturation in which fully keratinized cells retain large nuclei (Webb et al., 2009). Histopathology is required for definitive diagnosis. Irregular masses or cords of keratinocytes proliferate downward into the dermis, accompanied by keratin formation, keratin "pearls," intercellular bridges, mitoses, and atypia (Webb et al., 2009).

SCC is best managed by complete excision with wide, 4–5 mm surgical margins (Murphy, 2013). This approach is most likely to be curative, but excision of larger lesions will require reconstructive techniques to maintain a functional eyelid – or may even dictate enucleation of a visual eye. A variety of techniques have been described for eyelid reconstruction or wound closure following "en bloc" tumor excision in companion animals, including lip-to-lid subdermal plexus flaps (Dias et al., 2017; Hunt, 2006; Pavletic et al., 1982), local transposition flaps combined with third eyelid advancement (Schmidt et al., 2005), semicircular flaps (Pellicane et al., 1994), split eyelid flaps (Hagard, 2005; Lewin, 2003), bridge flaps (Doherty, 1973), interpolation skin flaps (Allen et al., 1997), oral mucosal–free grafts (Peña & Garcia, 1999), and caudal auricular axial pattern flaps (Stiles et al., 2003). A local transposition flap is least likely to devitalize, but its size is more limited than that of an axial pattern flap (Pavletic, 2018).

Reports of nonsurgical options generally refer to sites other than the eyelid, including the pinnae and nasal planum. Cryosurgery may be an option for superficial tumors (deQueiroz et al., 2008). In one study of 102 cats treated cryosurgically, median remission time was 26.7 months, with eyelid and ear lesions responding most successfully. A major limitation is the inability to assess lesion margins, illustrated by tumor recurrence in 17 of 102 cats at a median of 6.6 months after treatment (Clark, 1991). Brachytherapy with radioactive gold-198 seeds resulted in complete regression within 6 weeks following implantation in an extensive lower lid SCC. No tumor regrowth occurred in a 10-month postoperative period, when this 19-year-old DSH cat was euthanized for an unrelated disease (Hardman & Stanley, 2001). Five cats with

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Table 28.2 Frequency of feline eyelid tumors.

Tumor Type	McLaughlin et al. (1993) Total No. (%) Veterinary Medical Data Program*	McLaughlin et al. (1993) Total No. (%) Purdue Comparative Oncology Program	Newkirk & Rohrbach (2009) Total No. (%)	Martins & Barros (2014) Total No. (%)
Squamous cell carcinoma	56 (65%)	13 (36%)	12 (28%)	14 (54%)
Mast cell tumor	3 (4%)	4 (11%)	11 (26%)	0
Hemangiosarcoma	2 (2%)	0	6 (14%)	6 (23%)
Carcinoma/adenocarcinoma	5 (6%)	0	4 (9%)	0
Apocrine hidrocystoma	0	1 (3%)	3 (7%)	0
Peripheral nerve sheath tumor	0	0	3 (7%)	0
Lymphoma	0	4 (11%)	3 (7%)	0
Hemangioma	1 (1%)	0	1 (2%)	0
Melanoma	2 (2%)	3 (8%)	0	0
Fibrosarcoma	4 (5%)	3 (8%)	0	3 (12%)
Squamous papilloma	0	3 (8%)	0	0
Basal cell carcinoma	2 (2%)	0	0	1 (4%)
Basal cell epithelioma	0	2 (6%)	0	0
Sebaceous adenoma/epithelioma	3 (4%)	2 (6%)	0	1 (4%)
Histiocytic sarcoma	0	0	0	1 (4%)
Histiocytoma	0	1 (3%)	0	0
Neurofibroma	1 (1%)	0	0	0
Fibroma	2 (2%)	0	0	0
Trichoepithelioma	1 (1%)	0	0	0
Total benign	8 (10%)	9 (25%)	4 (9%)	2 (8%)
Total malignant	74 (90%)	27 (75%)	39 (91%)	24 (92%)

* Four tumors reported as "undetermined" are omitted from the original data.



Figure 28.18 Squamous cell carcinoma. The most frequent eyelid neoplasm in cats can appear (**A**) erosive, as in this localized lower eyelid lesion in a 12-year-old Domestic Shorthair; (**B**) multifocal, involving the medial canthus and lower eyelid in an 11-year-old Domestic Shorthair; or (**C**) nodular, infiltrating the lower eyelid, conjunctiva, and nictitans in a 17-year-old Domestic Shorthair (C reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

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periocular SCC treated using accelerated, hypo-fractionated electron beam radiation showed complete tumor response; disease-free intervals (DFI) ranged from 21 to > 987 days, with a mean DFI of 326 days (Melzer et al., 2006). However, radiation therapy delivered to the periorbital region has been associated with adverse ocular effects that include conjunctivitis, ulcerative keratitis, keratoconjunctivitis sicca (KCS), and cataracts (Pinard et al., 2012). A study of 20 feline cutaneous SCCs treated by photodynamic therapy included 4 eyelid tumors. Complete response occurred in 100% of treated tumors, with an overall 1-year control rate of 75% and a median time to recurrence of 172 days (Buchholz et al., 2007). In another report of photodynamic therapy, an eyelid SCC in a 14-year-old cat, previously treated with cryotherapy and radiation, demonstrated only partial response, apparent discomfort, and progressive disease (Frimberger et al., 1998). A study of photodynamic therapy that included 20 eyelid tumors among 38 cats documented complete tumor regression in 61% and partial regression in another 22%, with a mean progression-free interval of 35 months (Flickinger et al., 2018). Photodynamic therapy is not recommended for large, invasive tumors in which penetration depth of the photo-activating light is insufficient. Beta radiation using an ophthalmic applicator imbedded with strontium-90 can be used for superficial SCC lesions of 3 mm or less in depth (Murphy, 2013). In studies of nasal planum plesiotherapy with strontium-90, complete remission was achieved in 43 of 49 cats with no recurrence of disease for a median of 1071 days (Hammond et al., 2007), and in 13 of 15 cats with no recurrence for a median of 652 days (Goodfellow et al., 2006). Due to limited depth of penetration, radiofrequency hyperthermia should likewise be reserved for only the most superficial dermal lesions (Grier et al., 1980).

Intralesional chemotherapy was considered safe and effective in cats with nasal planum SCC (Théon et al., 1996), but the only mention of the modality in relation to the eyelid described a suspected injection-site sarcoma following treatment of a medial canthal SCC in a 14-year-old DSH (Martano et al., 2012). Electrochemotherapy is advocated to improve the response of SCCs to systemic chemotherapeutic agents. Complete tumor regression occurred in 21 of 26 (81%) cats (including 12 cats with periocular SCC) treated with intravenous bleomycin and permeabilizing electric pulses delivered across the tumor by modified caliper electrodes. Median time to progression in the periocular cohort was 24 months (compared to 4.7 months for bleomycin alone; Spugnini et al., 2015).

Basal cell carcinoma usually appears round and well circumscribed, but its tendency to ulcerate can make it difficult to clinically distinguish from SCC (Stiles, 2013). The tumor may also appear melanotic, cystic, and alopecic (Diters & Walsh, 1984). This carcinoma is generally benign, with slow, indolent growth and very rare metastasis from nonocular sites (Fehrer & Lin, 1986). Most are small and singular and can be successfully treated by surgical excision or cryotherapy. However, a large, expansive basal cell tumor in a 15-year-old DSH required radical resection of the upper lid and reconstruction utilizing a lip-to-lid subdermal plexus flap (Dias et al., 2017). A 12-year-old cat with a chronic ulcerated basal cell carcinoma obscuring the right eye was treated by surgical excision combined with radiation therapy and chemotherapy. The facial mass regressed, but the cat died 6 months later with pulmonary metastases (Day et al., 1994).

In the eyelid, mast cell tumors often appear as single, pink, hairless, slightly raised, and sometimes ulcerated masses, near to but typically sparing the lid margin (Fig. 28.19). Appearance does vary in the lid as in other cutaneous sites, ranging from clustered, ulcerated masses to large subcutaneous tumors. The age of onset tends to be significantly younger (6.5 years) than the average age of cats with all other types of tumors (11.7 years; Newkirk & Rohrbach, 2009). One study suggested an increased susceptibility to cutaneous mast cell tumors in the Siamese, Burmese, Russian Blue, and Ragdoll breeds (Melville et al., 2015). Mast cell tumors generally have one of the more favorable prognoses of the common eyelid neoplasms in the cat. In a retrospective study of feline cutaneous mast cell tumors, recurrence was documented in an eyelid following incomplete surgical excision (Wilcock et al., 1986), but generally benign behavior was ascribed to feline mast cell tumors in this and subsequent reports (Buerger & Scott, 1987; Molander-McCrary et al., 1998). In a study limited to feline periocular mast cell tumors, local tumor control following surgical excision (combined with strontium-90 irradiation or cryotherapy in 3 patients) was achieved in 22 of 23 cats, with a median follow-up time of 711 days. This impressive success rate was achieved despite incomplete surgical excision in 50% of cases. Cats in this series had a median survival time of 945 days, with no metastasis to peripheral lymph nodes or abdominal viscera in any cat at any time (Montgomery et al., 2010).

Eyelid fibrosarcomas in older cats are generally solitary, nodular, alopecic, and may be ulcerated (Brown et al., 1978; Miller et al., 1991; Stiles, 2013). Age of onset averages 10.4 years (Harasen, 1984). This tumor is typically well differentiated, slow growing, and characterized histopathologically by immature fibroblasts interspersed among bundles of collagen. Wide surgical excision is the treatment of choice (Allen et al., 1997), with prognosis correlated with the tumor's mitotic index (Bostock & Dye, 1979). Feline sarcoma virus-induced multicentric fibrosarcomas tend to occur in cats under 5 years of age. These patients have a poor prognosis regardless of therapy, since replication and expression of the sarcoma virus are linked with concurrent FLV infection and a much more aggressive, invasive form of tumor (Gardner et al., 1971; Harasen, 1984).

In a survey of feline peripheral nerve sheath tumors (PNST), 6 of 59 (10.2%) were associated with the eye

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Figure 28.19 Mast cell tumors range from small, lightly pigmented, alopecic nodules adjacent to the lid margin (**A**), seen in a 5-year-old Domestic Shorthair, to extensive subcutaneous masses (**B**), involving the entire upper eyelid in an 8-year-old Domestic Shorthair.

(Schulman et al., 2009). Synonyms include schwannoma, neurilemmoma, neurogenic sarcoma, neurofibroma, or neurofibrosarcoma. The feline eyelid appears particularly prone to this tumor, with the upper lid more commonly affected than the lower (Dubielzig et al., 2010; Hoffman et al., 2005; Fig. 28.20). Characterized as a low-grade spindle cell tumor, it is locally infiltrative but unlikely to metastasize. Recurrence after excision occurs in nearly all cases treated conservatively (Hoffman et al., 2005; Newkirk & Rohrbach, 2009). The wide surgical margins required to eliminate the tumor usually necessitate removal of a visual eye (Hoffman et al., 2005).

Less common feline eyelid tumors are described in individual case reports or are included in retrospective studies of feline neoplasia. A hemangiosarcoma in the lower eyelid of a 15-year-old DSH (Hartley & Ladlow, 2007), histologically well differentiated within the periocular dermis, was successfully treated by enucleation and an axial pattern flap in deference to the owner's insistence on a single surgical procedure (Hartley & Ladlow, 2007). A slow-growing pigmented rhabdomyoma in the upper lid of a 4-year-old mixed-breed cat, with aggregates of well-differentiated neoplastic skeletal myocytes, was successfully excised by H-plasty (Ollivier & Dubielzig, 2011). Anaplastic large cell lymphoma (B-cell type) was diagnosed in the upper eyelid of a 7-year-old domestic longhaired (DLH) cat and an 8-year-old DSH (Ota-Kuroki et al., 2014) and B-cell lymphoma was described in the eyelid of a 14-year-old male DSH with a concurrent scapular mass (Newkirk & Rohrbach, 2009; Fig. 28.21). Cutaneous papillomas are characterized as well circumscribed, pedunculated, and alopecic (Stiles, 2013). A smooth, hairless, dome-shaped sessile papilloma containing intranuclear viral inclusion bodies accompanied an upper eyelid xanthogranuloma (Carpenter et al., 1992). Three palpebral melanomas were included in a survey of 29 cats with ocular, oral, and dermal melanomas (Patnaik & Mooney, 1988). Metastasis occurred in all 3 cats, with mean time to death of 409 days. Sebaceous gland tumors rarely occur in cats (Newkirk & Rohrbach, 2009; Stiles, 2013), a notable distinction from dogs, in which meibomian gland adenoma is the most common eyelid tumor.



Figure 28.20 A peripheral nerve sheath tumor infiltrates the upper eyelid in a 15-year-old Siamese.

Diseases of the Nasolacrimal System

The nasolacrimal drainage system consists of the upper and lower lacrimal puncta, the lacrimal canaliculi, the lacrimal

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Figure 28.21 Multifocal pink nodules developed along the eyelids in a 15-year-old Domestic Shorthair, diagnosed as high-grade large cell lymphoma on fine-needle aspirate. (Courtesy of Dr. Melanie Ellis.)

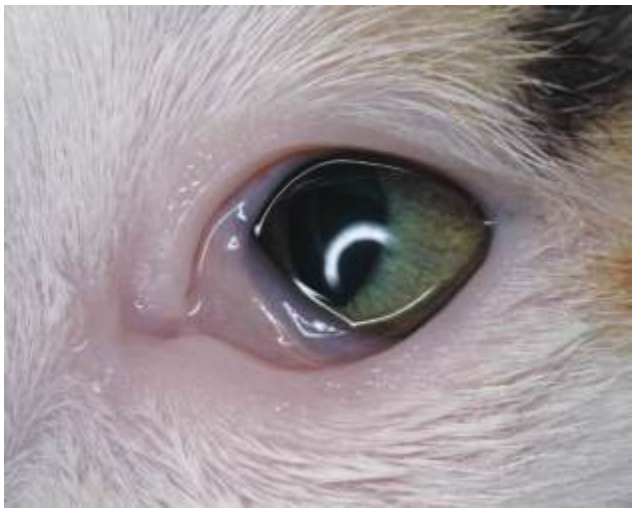


Figure 28.22 Epiphora. Third eyelid prominence and nasolacrimal punctal occlusion result from herpesvirus-induced symblepharon in a 10-month-old Domestic Shorthair.

sac, and the nasolacrimal ducts, which terminate distally in the nasal cavity vestibule beneath the ventral concha. The normal feline nasolacrimal system has been superbly illustrated using computed tomography and three-dimensional reconstruction (Nöller et al., 2006). From its origin at the lacrimal sac, the cat's nasolacrimal duct descends vertically toward the second premolar and there, at an angle of approximately 90°, changes to a horizontal course that parallels the hard palate (Gelatt et al., 1972). In one area, the nasolacrimal duct and the canine tooth are separated by only a thin alveolar socket, explaining why tooth extraction in this area may be problematic (Nöller et al., 2006). In brachycephalic cats, the upper canine teeth are displaced dorsally, forcing the nasolacrimal ducts to adopt a V-shaped course that adversely alters tear drainage (Breit et al., 2003; Schlueter et al., 2009)

Nasolacrimal disorders occur infrequently in cats and are usually characterized by epiphora (Stiles, 2013). Congenitally imperforate lacrimal puncta are rare and involve the upper punctum more often than the lower (Barnett & Crispin, 1998). In addition to the altered nasolacrimal course in brachycephalic breeds, other conformational features such as medial entropion, a shallow lacrimal lake, and tight apposition of the eyelid against the eye may contribute to epiphora. Symblepharon formation from prior conjunctivitis may result in punctal occlusion and epiphora in any cat (Fig. 28.22). A canine tooth root abscess in a 10-year-old cat resulted in epiphora due to extralumenal compression of the nasolacrimal duct (Anthony et al., 2010). In another 10-year-old cat, epiphora and nasolacrimal compression were consequences of excessive inflammation following tooth extraction (Calline et al., 2013). Obliteration of the nasal turbinates and secondary nasolacrimal obstruction caused chronic epiphora in a 12-year-old DLH cat with generalized osteosclerosis (Hanel et al., 2004). Local neoplasia such as SCC may involve the nasolacrimal system and produce partial or complete obstruction (Peiffer et al., 1978). Dacryocystitis, with a more florid mucoid to mucopurulent discharge, is also rare in cats (Rickards, 1973), presumably because the relatively short nasolacrimal duct provides less opportunity for obstruction (Stiles, 2013). Examples of feline dacryocystitis are included in various veterinary ophthalmic atlases (Barnett & Crispin, 1998; Esson, 2015; Ketring & Glaze, 2012; Mitchell & Oliver, 2015). Epiphora due to nasolacrimal disease must be differentiated from excessive lacrimation secondary to surface irritation or ocular pain. A single case of unilateral feline epiphora that occurred only while eating was attributed to idiopathic, paradoxical lacrimation or "crocodile tears" (Hacker, 1990).

In most cases, nasolacrimal blockage is difficult, if not impossible, to resolve. Irrigation of the nasolacrimal system produces only temporary improvement in most brachycephalic cats. The rare congenitally imperforate punctum is corrected by carefully excising the overlying mucus membrane, identified by the transient bleb that forms when the system is flushed through the opposite punctum. Restoration of punctal patency in cases of symblepharon is unlikely. Surgical conjunctivorhinostomy has been used with variable success to circumvent the obstructed system and divert tears into the nasal cavity (Covitz et al., 1977; Gelatt & Gelatt, 2011). Endoscopic and fluoroscopic-guided stenting of the nasolacrimal apparatus shows promise in nasolacrimal disease management, resolving obstruction in two cats as part of an ongoing clinical trial at the University of California

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Davis School of Veterinary Medicine in the USA (D.J. Maggs, personal communication).

Diseases of the Third Eyelid

The third eyelid, also called the nictitating membrane, membrana nictitans, or haw, consists of a semilunar fold of conjunctiva supported by a T-shaped piece of elastic cartilage (Schlegel et al., 2001) curved to conform to the shape of the underlying globe. Its serous gland surrounds the base of the cartilage and contributes to the cat's aqueous tear film. Removal of the third eyelid gland decreased average tear production by 16% in one study (McLaughlin et al., 1988). A study of tear film proteins following removal of the third eyelid, but not its gland, demonstrated significant reductions in matrix metalloproteinase activity (Petznick et al., 2012). The epithelium overlying the third eyelid contains numerous goblet cells on the palpebral surface, while aggregates of lymphoid tissue are present on both the inner and outer surfaces of the membrane (Schramm et al., 1994).

The third eyelid is normally unobtrusive in the cat, visible only with changes in position of the globe, for example enophthalmos or exophthalmos, or following loss of the sympathetic tone required to maintain its tonic retraction. Third eyelid protrusion is commonly seen in association with painful ocular disease. Gross thickening or swelling accompanying neoplasia or inflammation may also increase third eyelid visibility. Debility, weight loss, and diminished retrobulbar fat do not appear to appreciably influence third eyelid position in the cat compared to the dog (Barnett & Crispin, 1998).

The normal membrane sweeps diagonally across the cornea from its inferonasal location, refreshing the tear film and physically protecting the cornea. There is conflicting information in the literature regarding movement of the third eyelid in cats. Some describe a mechanism for active protrusion effected by abducens-innervated striated muscle fibers from the levator palpebrae superioris and lateral rectus muscles that attach to the third eyelid (Barnett & Crispin, 1998). A passive mechanism of third eyelid movement is supported by a morphologic study of the feline third eyelid, which found only smooth muscle strands extending into the third eyelid, with no striated muscle fibers extending into or within the membrane (Nuyttens & Simoens, 1995).

Horner's Syndrome

Horner's syndrome results from the interruption of the efferent sympathetic nervous system to the eye anywhere along its three-neuron pathway, from the hypothalamus and midbrain to the globe (Neer, 1984). First-order Horner's syndrome is invariably associated with additional neurologic deficits that may include ataxia, paresis, postural deficits, altered mental status, and involvement of other cranial nerves (De Risio & McConnell, 2009). Horner's syndrome can be the sole neurologic abnormality when either second- or third-order neurons are affected. In the cat, protrusion of the third eyelid and miosis are the most consistent features, with variable ptosis and enophthalmos (Kern et al., 1989; Fig. 28.23). The fur surrounding the affected eye of a Siamese cat lightened in color, attributed to peripheral vasodilation and a local increase in skin temperature in the absence of sympathetic vascular innervation (Jones & Studdert, 1975).

The literature includes many examples of feline Horner's syndrome, with causes that include trauma (both exogenous and iatrogenic), neoplasia, and inflammation (especially of the middle ear). Horner's syndrome is a common complication following surgery for middle ear disease, especially ventral bulla osteotomy, occurring in 53% of cases in one study (Bacon et al., 2003). The cause of Horner's syndrome could not be determined in 42% of the cats in Kern's retrospective study, making idiopathic disease the most common explanation for third-order Horner's syndrome (Kern et al., 1989; Table 28.3). Prognosis for spontaneous recovery is generally favorable in cases of trauma, infection, and inflammation, but not so in neoplastic disease (Kern et al., 1989; Van den Broek, 1987). Speed and degree of resolution are highly variable, reflecting the extent of nerve damage. Reported periods of time required for resolution range from 1 day (Kneller et al., 1972) to 6 months (Guth & Bernstein, 1961). When signs persist beyond 6 weeks following bulla osteotomy, patients are unlikely to recover fully (White, 2003). Specific treatment of



Figure 28.23 Horner's syndrome. Enophthalmos, ptosis, third eyelid protrusion, and miosis characterize the sympathetic defect in this 6-year-old Domestic Longhair with a mediastinal mass. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

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Table 28.3 Causes of feline Horner's syndrome.

Etiology	Location	Reference
Traumatic	Head	Bistner (1978); De Lahunta (1983); Morgan & Zanotti (1989)
	Neck	De Risio & McConnell (2009); Frye (1973); Holland (1996); Jones & Studdert (1975)
	Brachial plexus	Kern et al. (1989)
Neoplastic	Cranial mediastinum	Morgan & Zanotti (1989)
	Brachial plexus	Fox & Gutnick (1972)
	Cervical spine	Van den Broek (1987)
	Salivary gland	Pauli & Carter (1970)
	Oral/pharyngeal	Jones & Studdert (1975); Manning (1998)
	Orbital	Murphy et al. (1989b); Slatter (1990)
	Thyroid	De Lahunta et al. (2015)
	Otitis media	Cook (2004); Garosi et al. (2012); Ilha & Wisell (2013); Morgan & Zanotti (1989)
Inflammatory/ Infectious	Nasopharyngeal polyps	Kudnig (2002)
	Tick paralysis	Holland (2008)
	Orbital abscess	De Lahunta (1983); Slatter (1990)
Structural	Spinal cord	Lu et al. (2002)
	Cartilaginous embolus	MacKay et al. (2005); Turner et al. (1995)
	Ear ablation	Bacon et al. (2003); Smeak (2011); Spivack et al. (2013); Williams & White (1992)
	Bulla osteotomy	Anders et al. (2008); Faulkner & Budsberg (1990); Smeak (2011); Spivack et al. (2013); Trevor & Martin (1993)
Iatrogenic	Mandibular reduction	Baines & Langley-Hobbs (2001)
	Polypectomy	Bradley et al. (1985); Muilenburg & Fry (2002); Parker & Binnington (1985)
	Carotid/venous catheterization	De Lahunta et al. (2015); Kneller et al. (1972)
	Ear cleaning	Morgan & Zanotti (1989)
	Thyroidectomy	Birchard et al. (1984); Mallery et al. (2003); Wells et al. (2001)
	Parathyroidectomy	Kallet et al. (1991)
Idiopathic		Kern et al. (1989); Morgan & Zanotti (1989); Van den Broek (1987)

Horner's syndrome is seldom indicated. If third eyelid protrusion is sufficient to compromise vision, topical 2.5% phenylephrine can be applied every 8–12 hours or to effect.

Idiopathic Third Eyelid Protrusion

A syndrome of idiopathic third eyelid protrusion without other ocular abnormalities has long been recognized in the domestic cat. Also known as "haws syndrome," the condition is always bilateral, of acute onset, and without any age, breed, or sex predilection (Nasisse, 1991). Increased peristalsis, soft stools, and/or diarrhea are present in some cats, suggesting a more generalized sympathetic neuropathy or dysautonomia. An infectious cause has been proposed due to the appearance of the disorder in more than one cat in multicat households. In a study of 50 cats with diarrhea and bilateral third eyelid protrusion, investigators isolated an agent resembling a torovirus from 7 cats (Muir et al., 1990). A subsequent study failed to identify torovirus in any of the 51 cats sampled, but did find virus-like particles in the feces of 1 of 15 affected cats, 6 of 21 cats previously affected, and 4 of 15 healthy control cats (Smith et al., 1997). Intestinal parasites have been anecdotally implicated in the pathogenesis, prompting some clinicians to advocate deworming of affected animals. The protrusion can be symptomatically managed by application of 2.5% phenylephrine ophthalmic solution. Spontaneous resolution is likely, but clinical signs may persist for several weeks to even a few months.

Dysautonomia (Key-Gaskell syndrome) also causes bilateral third eyelid protrusion, but pupillary dilation and reduced tear production typically accompany this rare systemic disorder affecting both the sympathetic and parasympathetic nervous systems (Bromberg & Cabaniss, 1988; Canton et al., 1988). Accompanying clinical signs of dysautonomia include depression, dysphagia, vomiting, constipation, megaesophagus, and bradycardia (Kidder et al., 2008), with a reported 70% mortality rate (Sharp et al., 1984).

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Prolapsed Third Eyelid Gland

Prolapse of the gland of the third eyelid is uncommon in cats compared with dogs (Fig. 28.24). The Burmese breed predominates in reports of the disorder (Albert et al., 1982; Chahory et al., 2004; Christmas, 1992; Koch, 1979), but the problem is also documented in the Persian and DSH cats (Chahory et al., 2004; Schoofs, 1999). While glandular prolapse in dogs typically occurs during the first 1–2 years of life, cats tend to be older at presentation, illustrated in Chahory's report of 3 adult cats, 3 years (n=1) and 6 years (n=2) of age (Chahory et al., 2004). Glandular prolapse in the Burmese is reported in kittens (Christmas, 1992; Koch, 1979) as well as adult cats (Chahory et al., 2004). The gland should be surgically repositioned in order to preserve its substantial contribution to the cat's tear volume, with reported success using either the Morgan pocket technique (Chahory et al., 2004; Schoofs, 1999) or an anchoring procedure such as the modified Blogg technique (Albert et al., 1982; Christmas, 1992). KCS developed in one cat following surgical removal of the gland (Albert et al., 1982).

Cartilage Eversion

Eversion of the third eyelid cartilage is also rare in cats, perhaps a reflection of the elastic nature of their cartilage compared to the hyaline cartilage of the dog (Schlegel et al., 2001) and the firm adhesion between the cartilage and overlying conjunctiva (Williams et al., 2012). The problem has been reported in the British Blue (Williams et al., 2012), Persian (Chahory et al., 2004), and Burmese (Albert et al., 1982). The condition may be mistaken for protrusion of the third eyelid gland on cursory examination, since the combination of bent cartilage and overlying conjunctiva also creates a mass-like effect at the medial canthus. Glandular prolapse may also accompany cartilage eversion (Albert et al., 1982; Chahory et al., 2004; Koch, 1979). The scrolled portion of the cartilage is surgically excised via a surgical approach from the bulbar surface of the third eyelid, as described in dogs, although the feline cartilage may not be as easily separated from the overlying conjunctiva (Williams et al., 2012). The use of thermal cautery to remodel the cartilage has not been reported in the cat (Allbaugh & Stuhr, 2013).



Figure 28.24 Prolapse of the third eyelid gland in a 3-year-old Burmese. The gland in the opposite eye prolapsed 4 years later. Both were successfully corrected using a pocket technique.

Neoplasia

Although third eyelid neoplasia is uncommon in cats (Dees et al., 2016; Stiles, 2013), a variety of tumors have been described that affect either the surface tissues and substantia propria or the gland of the third eyelid. Differentials for third eyelid masses include eosinophilic conjunctivitis (Pentlarge, 1991), epitheliotropic mastocytic conjunctivitis (Beckwith-Cohen et al., 2017), and adnexal cryptococcosis (Martin et al., 1997).

Hemangiomas involving the leading edge of the third eyelid were described in 3 of 8 cats in a retrospective study of feline conjunctival hemangioma and hemangiosarcoma (Pirie & Dubielzig, 2006). The average age of affected cats with hemangioma was 11.8 years and neutered male cats were overrepresented in the study as a whole (n=7). The prototypical mass was described as a superficial reddish exophytic nodule originating in the poorly pigmented tissue of the third eyelid leading margin. In the one patient with postoperative follow-up, no recurrence was reported despite incomplete excision. A hemangiosarcoma appeared as a multilobulated red mass arising near the leading margin of the third eyelid in a 15-year-old DSH (Multari et al., 2002). No recurrence was reported in the 7 months following surgical excision and adjunctive cryotherapy. Two third eyelid hemangiosarcomas were included in Newkirk's retrospective study of feline eyelid tumors (Newkirk & Rohrbach, 2009). The tumor was completely excised in an 8-year-old DSH, with a DFI of ≥ 15 months. The second hemangiosarcoma in the series occurred in an 18-year-old DLH cat with incomplete surgical margins and no follow-up.

A mast cell tumor developed as a fleshy mass from the bulbar third eyelid conjunctiva in a 3-year-old Himalayan cat (Larocca, 2000). There was no recurrence in the year that followed excision. Histopathology strongly resembled the benign histiocytic mastocytomas described in Siamese cats under 4 years of age that tend to regress without treatment (Wilcock et al., 1986). A presumptive mast cell tumor of the third eyelid was also reported in a mixed-breed cat with generalized cutaneous mast cell tumors (Crafts & Pulley, 1975).

SCC of the third eyelid appears to be most often associated with extension from the eyelids (Stiles, 2013). SCC was cited

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in a retrospective study of malignant third eyelid tumors in dogs and cats that included 5 European Shorthair cats (Schäffer et al., 1994). A 13-year-old mixed-breed cat was euthanized 1 month after incomplete excision of a third eyelid SCC due to tumor recurrence (Newkirk & Rohrbach, 2009). The base of the third eyelid was affected along with the cornea and bulbar conjunctiva in a 14-year-old DSH with concurrent corneal hemangioma (Perlmann et al., 2010). Histopathology confirmed third eyelid involvement in 5 of 20 eyes included in a study comparing orbital SCC with feline restrictive orbital myofibroblastic sarcoma (Diehl et al., 2018).

Orbital infiltration and widespread metastasis to the brain and lungs were reported in a 10-year-old cat with melanoma that appeared to originate from the third eyelid surface (Roels & Ducatelle, 1998). A retrospective study of feline conjunctival melanoma included 4 cases originating in the conjunctiva overlying the third eyelid, with recurrence documented in 2 of these patients (Schobert et al., 2010).

A retrospective study of intraocular and periocular lymphoma documented third eyelid involvement in 3 of 15 study cats (Ota-Kuroki et al., 2014). Two of the tumors were classified as B-cell-type anaplastic or diffuse large cell lymphoma and 1 was classified as peripheral T-cell lymphoma. A 12-year-old DSH with a 4-week history of a swollen third eyelid was diagnosed with B-cell lymphoma. The cat survived for over 2 years despite neoplastic cells in the vasculature, its death attributed to unrelated causes (McCowan et al., 2014). Third eyelid lymphosarcoma was also diagnosed in two 12-year-old DSH cats included in a retrospective study of feline eyelid tumors (Newkirk & Rohrbach, 2009). Both cats were euthanized within 6 weeks of the diagnosis of B-cell lymphoma in one cat and T-cell lymphoma in the other. A DSH of unspecified age with a histologic diagnosis of high-grade lymphosarcoma died 2 months after laser excision of the affected third eyelid (Dees et al., 2015). Third eyelid lymphoma was included in Schäffer's retrospective study of canine and feline malignant third eyelid tumors (Schäffer et al., 1994).

Singular case reports described a fibrosarcoma of the third eyelid in a cat (Buyukmihci, 1975) and a third eyelid teratoma containing foci of haired skin, mucinous glands, skeletal muscle, cartilage, trabeculae of bone, respiratory epithelium, and poorly differentiated spindle cells in a 9-week-old DSH kitten (Andrie et al., 2018).

Compared to third eyelid gland neoplasms in dogs, those in cats are more likely to metastasize, recur, and substantially shorten patient survival times (Dees et al., 2016). An 11-year-old DSH died with widespread metastasis 6 months after diagnosis of a third eyelid gland adenocarcinoma (Komáromy et al, 1997), and a 13-year-old DSH died 2 weeks after a biopsy confirmed recurrence of a third eyelid gland adenocarcinoma incompletely excised 1 year beforehand (Newkirk & Rohrbach, 2009). A retrospective study of third eyelid gland neoplasms in dogs and cats included 18 cats of various breeds and an average age of 12.8 years (Dees et al., 2016). All feline third eyelid gland tumors were malignant. Adenocarcinoma was the most common neoplasm (n=15), with confirmed metastasis in 1 cat at the time of surgery and suspected metastasis in 3 additional cases. In 1 of these cats, mass excision had been described as complete, with greater than 1 mm tissue margins free of neoplastic cells. Local recurrence was confirmed in 2 cases, 1 of which was again described with complete surgical margins. Of 8 cases with available follow-up, the average survival time with third eyelid gland adenocarcinoma was 335 days. SCC was the second most common third eyelid gland neoplasm, affecting the 3 remaining cats in the study. Surgical margins were incomplete in all 3 cases, with orbital infiltration in 2 cats. Metastasis was suspected in 1 cat and local recurrence was suspected in another. Average survival time for cats with SCC of the third eyelid gland was 217 days (range 62–372 days).

With the exception of severe, irreparable trauma, the only indication for third eyelid removal is advanced and invasive neoplasia (Gelatt & Brooks, 2011). The membrane is excised at its base to ensure complete removal of its gland and cartilage, and the conjunctival wound is ideally sutured to prevent potential herniation of orbital fat. The third eyelid can also be excised using a carbon dioxide laser. The third eyelid is elevated with forceps and the base is cut and cauterized simultaneously using a linear continuous setting and 6 W of power, with little to no hemorrhage and a conjunctival wound that heals by second intention (Dees et al., 2015).

Ocular Surface Disease

Ocular surface disease is common in cats. Owing to the frequency with which bacterial and viral pathogens have been documented in cats with conjunctivitis and corneal disease, it is prudent to consider feline surface disease infectious until proven otherwise. Unlike the dog, in which most surface infections are linked with predisposing abnormalities of the adnexa and tear film, several primary pathogens are implicated in diseases of the feline conjunctiva and cornea. The most important of these are *Chlamydia felis (C. felis)*, a conjunctival pathogen, and FHV-1, a causative agent of conjunctival or corneal disease (or both). While initial clinical signs reflect a direct cytopathic effect on ocular surface epithelium, and less commonly and less severely pathology within the underlying corneal stroma or conjunctival lamina propria, long-term consequences of these infections may include altered surface anatomy, tear film deficiency and dysfunction, persistent or recurrent immunologic reactions, altered corneal clarity, and diminished tissue viability.

Acknowledging the infectious nature of feline surface disease is a far cry from making a definitive etiologic diagnosis. The reliability of diagnostic tests is reduced by the presence

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of *C. felis* and FHV-1 at the ocular surface of normal cats and the inability to differentiate wild-type organisms from vaccinal strains. Chronic disease is the most challenging to define, since available tests may not yet take into account newly identified chlamydial species, and because FHV-1 can be notoriously elusive in these cases. As a consequence, diagnosis is often better based on clinical acumen rather than analytic data, relying on familiarity with an organism's biologic behavior, careful assessment of clinical signs, and response to an optimal therapeutic regimen established for the suspected pathogen.

This section emphasizes the role of infectious agents in feline ocular surface disease, categorized by disorders in which conjunctival disease predominates, disorders in which conjunctival and corneal disease are likely to coexist, or disorders in which corneal pathology prevails (Table 28.4). The operative words are predominate and prevail. Considering the close anatomic and physiologic relationships between the conjunctiva and cornea, severe or chronic disease in one will inevitably impact the other to some degree.

Conjunctival Disease

Conjunctivitis is arguably the most common ocular complaint in cats. This is particularly true when including those cases where conjunctivitis is diagnosed based on a cursory ocular examination that disregards the link between conjunctival hyperemia and other disorders such as keratitis or uveitis, or one that fails to differentiate conjunctival from episcleral vessels in the glaucomatous eye. Feline conjunctivitis should be considered infectious until proven otherwise. The most commonly implicated primary pathogens are *Chlamydia felis (C. felis)* and FHV-1; the latter is also capable of infecting the feline cornea. Based on the volume of experimental and clinical data substantiating the role of these two pathogens in feline ocular surface disease, a practical clinical approach is first to eliminate keratitis, uveitis, or glaucoma as the primary diagnosis, and then to rule out less common causes of conjunctivitis in cats such as foreign body, neoplasia, eyelid or cilia disorders, tear film dysfunction, or allergy. Conjunctivitis can then be considered most likely caused by *C. felis* or FHV-1, with chlamydial conjunctivitis being nonulcerative, seen in the absence of keratitis, and more likely dominated by chemosis than intense hyperemia. By contrast, herpetic conjunctivitis often has more intense hyperemia than it does chemosis and can be ulcerative, especially in primary infections. There is often coincident keratitis, therefore FHV-1 is described more fully in the keratoconjunctival disease section that follows. Other conjunctival pathogens include *Mycoplasma* spp., feline calicivirus, and *Bordetella bronchiseptica*. Though implicated in feline conjunctivitis, the role of agents such as *Salmonella typhimurium* or *Bartonella* spp. is inconsequential or unsubstantiated.

Table 28.4 Ocular surface disease in cats, based on predominant area of involvement.

Conjunctival Disease
• *Chlamydia* spp.
• *Mycoplasma* spp.
• Calicivirus
• *Bordetella bronchiseptica*
• Symblepharon
• Lipogranulomatous conjunctivitis
• Epitheliotropic mastocytic conjunctivitis
• Neoplasia
Keratoconjunctival Disease
• Feline herpesvirus-1
• *Mycoplasma* spp.
• Eosinophilic keratoconjunctivitis
• Tear film disorders
• Dermoid
Corneal Disease
• Corneal sequestrum
• Acute eruptive bullous keratopathy
• Corneal ulceration
• Florida keratopathy
• Corneal dystrophy/degeneration

Chlamydia felis

Chlamydiae are obligate, intracellular Gram-negative bacteria that demonstrate a predilection for conjunctival epithelial cells. Though previously separated into two genera, *Chlamydia* and *Chlamydophila*, classification based on contemporary genome sequencing has reverted to the single genus *Chlamydia*. The most significant feline pathogen is *Chlamydia felis (C. felis)*, with a worldwide prevalence of 3.12%–23% in cats with acute and chronic conjunctivitis (Gruffydd-Jones et al., 1995; Hanselaer et al., 1989; Iwamoto et al., 2001; Kang et al., 2016; Low et al., 2007; Mochizuki et al., 2000; Rampazzo et al., 2003; Ravicini et al., 2016; Shewen et al., 1980; Sykes et al., 1999a; Volopich et al., 2005; Wills et al., 1988a). The organism also persistently infects respiratory, gastrointestinal, and genitourinary epithelial cells, a factor that likely accounts for the relapse of clinical signs following topical therapy. As many as 25 different genotypes of *C. felis* exist, and multiple genotypes may coexist in a cattery (Laroucau et al., 2012). Coinfections with more than one strain can occur. Other chlamydiae have been reported in cats with conjunctivitis, albeit rarely. DNA resembling that of the human pathogen, *Chlamydophila pneumoniae*, was identified in 5 of 49 European cats with conjunctivitis (Sibitz et al., 2011). Two parachlamydial organisms – *Neochlamydia hartmannellae* and *Parachlamydia acanthamoebae* – have also been detected

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using PCR in cats with conjunctivitis and keratoconjunctivitis, respectively. These organisms are typically found within amoebae, but coinfections have not yet been documented in cats (Richter et al., 2010; Von Bomhard et al., 2003).

Chlamydia psittaci var. *felis* (as the organism we now call *C. felis* was likely then known) was first isolated from cats with respiratory disease in 1942 (Baker, 1942). The organism was erroneously classified as a virus and its clinical disease was labeled feline pneumonitis. That designation was abandoned over time, as *C. felis* was determined to be a more significant conjunctival than respiratory pathogen. Some cats develop rhinitis with sneezing and nasal discharge, but lower respiratory signs of cough and dyspnea are unlikely (Bart et al., 2000). Cello (1967) described feline conjunctivitis attributed to *C. psittaci*.

C. felis infection occurs primarily through close contact with other infected cats and their ocular secretions, or less commonly via aerosol transmission. The organism can also be spread by contaminated fomites, but survives only a few days at room temperature and is inactivated by most disinfectants. Following exposure, infectious elementary bodies attach to and enter epithelial cells, then differentiate into reticulate bodies that undergo binary fission within a cytoplasmic vacuole or inclusion. Organisms mature into elementary bodies, infecting adjacent conjunctival epithelial cells following cell lysis. *C. felis* also spreads via the bloodstream to other tissues, including the tonsil, lung, liver, spleen, gastrointestinal tract, and kidney (Gruffydd-Jones et al., 2009). The incubation period is approximately 3–5 days following experimental infection, but clinical signs may take 5–14 days to appear following natural infection (Wills et al., 1984).

Infection with *C. felis* is more common in young cats, especially those 2–12 months of age (Wills et al., 1988a). Although maternal antibody is thought to protect most kittens less than 12 weeks of age, they may be infected by the queen at birth, based on occasional isolation of *C. felis* from cats with neonatal conjunctivitis (Cello, 1967; Sykes, 2001). It is unknown whether venereal transmission occurs in cats, but the organism has been identified in vaginal and rectal secretions of infected cats. Clinically normal cats with high chlamydiae-specific antibody titers can shed and transmit chlamydia (Ström Holst et al., 2011). Cats older than 5 years of age are less likely to be infected with *C. felis* (Sykes, 2014b). In contrast, the majority of cats harboring DNA of *Neochlamydia hartmannellae* are 10 years of age or older (Von Bomhard et al., 2003).

Clinical signs of acute chlamydial infection often develop unilaterally, then appear in the second eye a few days later. Characteristics include blepharospasm, serous ocular discharge, and chemosis, the latter often masking the intensity of concurrent conjunctival hyperemia. The discharge may become purulent with chronicity or coinfection by opportunistic resident flora (Fig. 28.25). Conjunctival follicle formation has been described, but lymphoid hyperplasia is more likely a nonspecific sign of chronic antigenic stimulation rather than a reliable indicator of *C. felis* infection. Upper respiratory signs are mild to absent. Mild fever, submandibular lymphadenopathy, and lameness have been reported in rare instances (Lim & Maggs, 2012; Ramsey,

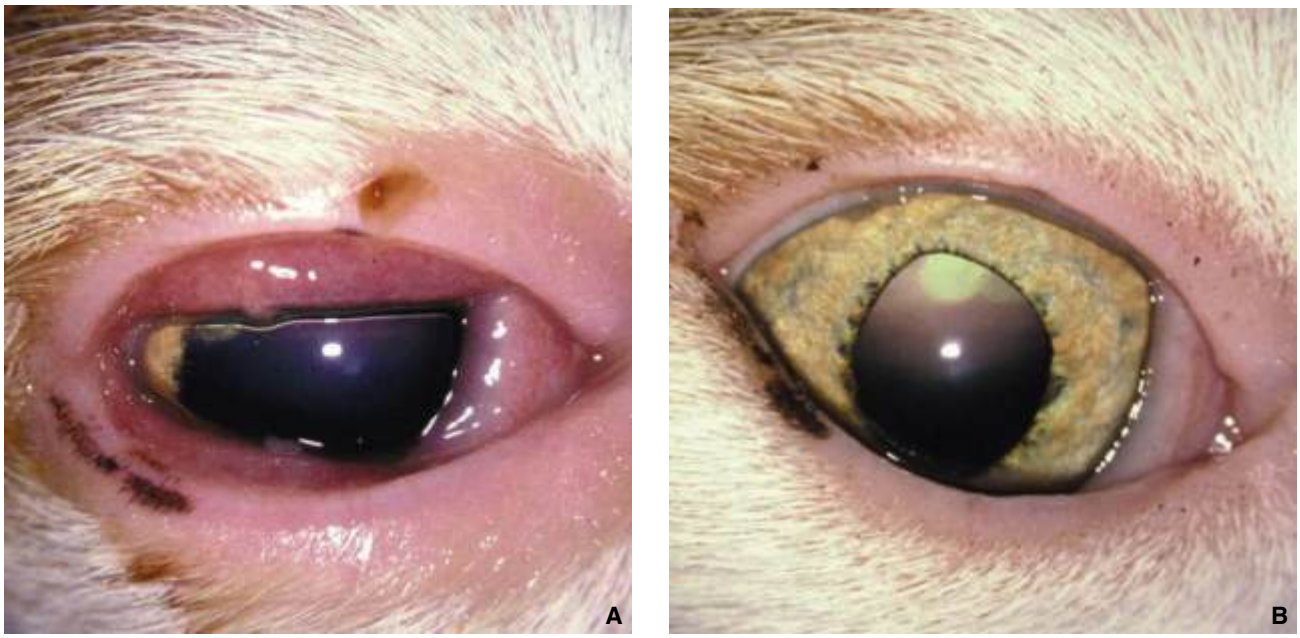


Figure 28.25 Polymerase chain reaction–positive *Chlamydia felis* conjunctivitis in a 6-year-old Domestic Shorthair. **A**. Initial presentation with conjunctival hyperemia and chemosis. **B**. Following a 30-day regimen of oral doxycycline.

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2000; TerWee et al., 1998). Cats with conjunctivitis that are also sneezing are 2.2 times more likely to be positive for FHV-1 than *C. felis* (Sykes et al., 1999b). Coinfection with C. felis and FHV-1 appears to be uncommon (Cai et al., 2002; Low et al., 2007; Rampazzo et al., 2003; Volopich et al., 2005; Von Bomhard et al., 2003).

Following initial infection, signs usually regress spontaneously within 2–6 weeks, and may improve more rapidly in older cats than in kittens (Ramsey, 2000). Conjunctivitis may persist in a milder form for many months, alternate between active and quiescent phases, or resolve completely. Coinfections with other pathogens may increase the severity of disease and duration of shedding. For example, cats may routinely shed *C. felis* for at least 60 days following infection (Lim & Maggs, 2012). When concurrently infected with FIV, the organism can be recovered from the conjunctiva of cats for as long as 215 days (O'Dair et al., 1994). It is unclear if chronic conjunctivitis is the result of reinfection from infected in-contact cats or recrudescence stemming from persistence of the organism in nonocular tissues (Ström Holst et al., 2011). Treatment of the affected as well as all in-contact cats would therefore appear to be the most successful approach to managing feline chlamydiosis.

A variety of diagnostic tests have been used to confirm infection with *C. felis*, each with limitations. In chronic cases, detection of the pathogen may be compromised by concurrent histopathologic changes in the conjunctiva (Kielbowicz et al., 2014). Basophilic intracytoplasmic inclusions, often located adjacent to the nucleus, may be identified by light microscopy in Giemsa-stained conjunctival scrapings collected 2–9 days after the onset of clinical signs. This method is relatively insensitive due to the transient nature of the inclusions and the improbability of finding inclusions in chronically infected cats. If available, direct fluorescent antibody or immunocytochemical stains may increase the sensitivity and specificity of this method. However, topical application of fluorescein dye to the ocular surface prior to sample collection may result in a false positive IFA test. Chlamydial inclusions must also be differentiated from cytoplasmic inclusions known as "blue bodies" that may develop following use of topical ointments (Streeten & Streeten, 1985).

Assays utilizing PCR are the preferred method for confirming active chlamydial infection, even in chronically affected cats (Dean et al., 2005; Helps et al., 2001; McDonald et al., 1998; Sandmeyer et al., 2010; Sykes et al., 1997, 1999b). Chlamydial DNA can be detected in conjunctival swabs, scrapings, or biopsies, although no significant difference was found in the *C. felis* detection rate between samples collected from the oropharynx, conjunctiva, nose, or tongue of cats with upper respiratory disease (Schulz et al., 2015). Vigorous swabbing is recommended to ensure that adequate numbers of epithelial cells are collected. Since a test for *C. felis* may not detect other chlamydial species such as *C. pneumoniae*, each individual laboratory should be consulted to establish the genus or species specificity of its available assay. The results of PCR may be arbitrarily affected by laboratory performance (Sandmeyer et al., 2010), falsely positive due to prior inoculation with an attenuated live chlamydial vaccine (Sykes, 2014b), or slightly inhibited by treatment with topical fusidic acid (Segarra et al., 2011). The study by Segarra and colleagues also demonstrated that topical proxymetacaine and fluorescein did not interfere with the ability of real-time PCR to detect *C. felis* (or FHV-1). Since healthy cats can be PCR positive on occasion, results must always be interpreted in light of the patient's history and clinical signs.

Conjunctival swabs are the preferred sample for chlamydial culture, although nasal and pharyngeal swabs may also yield positive results. The method is probably better suited to the laboratory than the clinical setting. In order to maintain organism viability, special transport media is required and the sample should be processed within 24 hours of collection. The culture process is technically demanding and time consuming, requiring embryonic yolk sacs or specific cell lines for growth, and the addition of fluorescent antibody to identify chlamydial inclusions within the infected cell culture. False negatives occur if viability is affected during transport or in chronic infections, when organism numbers are low. As a result, PCR assays are usually more sensitive than cell culture for confirmation of natural infection with *C. felis* (Sykes et al., 1999b).

Other diagnostic methods such as ELISA to detect chlamydial antigen in conjunctival swabs or serology to detect circulating chlamydial antibodies are considered inferior to PCR or culture as diagnostic tools. In general, ELISA assays have lower sensitivity and specificity when compared to culture (Pointon et al., 1991; Wills et al., 1988b). Inconsistent rises in immunoglobulin (Ig) M and variable or prolonged increases in IgG concentrations confound the interpretation of acute and convalescent chlamydial antibody titers (Sykes, 2014b). However, very high antibody titers ($\geq$ 1:512) may support the role of *Chlamydia* spp., since these levels have been associated with clinical illness and/or chlamydial shedding in group-housed cats with conjunctivitis (Gruffydd-Jones et al., 2009; Low et al., 2007; Ström Holst et al., 2011). Positive titers may also reflect recent vaccination. Complement fixation is unreliable for detecting recent *C. felis* infection (Cello, 1971). When the limitations of all available tests are considered, some simply rely on clinical signs and response to therapy as a means of diagnosis.

Systemically administered doxycycline is the drug of choice for feline chlamydial infections, producing rapid improvement in clinical signs and likely clearing the organism from ocular as well as systemic sites. Both hyclate and monohydrate salts are effective (Lappin et al., 2017). Kittens over 4 weeks of age can be treated with doxycycline without enamel discoloration. Oral administration of doxycycline at

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5–10 mg/kg every 12 hours for 3–4 weeks results in clinical resolution in most cats (Sykes, 2014b). Clinical signs diminish within 24–72 hours of the start of treatment. Client compliance may improve using a once-daily regimen of oral doxycycline (10 mg/kg every 24 hours), but treatment must then be continued for at least 28 days to eliminate the organism (Dean et al., 2005). Since some group-housed cats require treatment for as long as 6–8 weeks to clear the infection (Gruffydd-Jones et al., 1995), a general rule is to treat for a minimum of 3 weeks and at least 2 weeks beyond the resolution of clinical signs.

Cats are prone to drug-induced esophageal strictures due to delayed transit of capsules and tablets (Westfall et al., 2001), particularly with doxycycline hyclate (German et al., 2005; Melendez et al., 2000) and clindamycin hydrochloride (Beatty et al., 2006). As a precaution, tablets and capsules should be coated with a lubricating substance, such as butter, or administered in a pill treat, then followed by at least 2 mL of liquid or a small amount of food (Bennett et al., 2010; Lappin et al., 2017). Aqueous-based compounded formulations of doxycycline reportedly lose antibacterial activity after 7 days (Papich et al., 2013).

Oral pradofloxacin suspension (5–7.5 mg/kg every 24 hrs for 6 weeks) is an acceptable alternative in cats unable to tolerate doxycycline (Hartmann et al., 2008a; Sturgess et al., 2001; Sykes, 2014b). Some sources recommend oral amoxicillin-clavulanate in kittens less than 4 weeks of age to avoid the enamel discoloration associated with tetracycline administration (Sturgess et al., 2001; Sykes, 2014b), but not all ophthalmologists concur (D.J. Maggs, personal communication). Oral enrofloxacin (5 mg/kg every 24 hrs for 14 days) compared favorably with doxycycline in experimentally infected cats (Gerhardt et al., 2006), though persistent infections were documented in both groups at the study's end. Even though pradofloxacin is reportedly less effective than doxycycline (Hartmann et al., 2008b), it is preferred over enrofloxacin due to the latter's potential retinal toxicity. Ocular improvement with oral azithromycin can be rapid, but clinical signs often relapse, since the drug does not reliably eliminate *C. felis* systemically. In one study, comparable improvement in clinical signs was noted with doxycycline and azithromycin, and shedding ceased by day 7 and day 6, respectively. But while the doxycycline-treated cats remained negative for the remainder of the study, the azithromycin-treated cats shed *C. felis* intermittently (Owen et al., 2003). Despite this failing, azithromycin may still be useful in differentiating chlamydial from viral conjunctivitis. A therapeutic trial (5 mg/kg daily for 5 days, then every 72 hrs for a total of 3 weeks) may be less difficult for the patient and owner, taking into account the 3-day duration of azithromycin's tissue levels following a single 5 mg/kg oral dose. Rapid improvement lends support to a diagnosis of *C. felis*, makes FHV-1 highly unlikely as the active etiologic agent, and eliminates the burden of prolonged once- or twice-daily therapy. If clinical signs relapse, subsequent treatment with doxycycline is indicated. A 4-week course of amoxicillin-clavulanate therapy in experimentally infected cats prevented the recurrence of *C. felis* for 6 months after treatment (Sturgess et al., 2001), leading some to recommend its use as a safe alternative to tetracyclines in very young kittens (Sykes, 2005). However, a panel report summarizing antimicrobial use guidelines states that amoxicillin is ineffective against *C. felis* and that amoxicillin-clavulanate is inferior to other drugs used to treat *C. felis* (Lappin et al., 2017).

Topical therapy is not recommended as a sole route for the treatment of cats with chlamydiosis. Treatment with tetracycline or erythromycin ointment 2–4 times daily for as long as 60 days can improve clinical signs, but will not eliminate infection (Donati et al., 2005; Sparkes et al., 1999). Therefore, these formulations are probably best used in conjunction with systemic therapy to promote therapeutic drug concentrations at the ocular surface, control secondary infections not susceptible to doxycycline, and lubricate the inflamed tissues (Lim & Maggs, 2012). Other common topical antibacterial agents such as gentamicin, triple antibiotic, chloramphenicol (Sykes, 2014b), and fusidic acid (Sparkes et al., 1999) are ineffective against *C. felis*. Hypersensitivity to topical tetracycline can occur, characterized by marginal blepharitis and increasingly severe conjunctival hyperemia with successive applications of the drug (Ramsey, 2000). The ointment base alone may also contribute to ocular irritation following topical application (Eördögh et al., 2016).

Maternal antibodies usually protect kittens from infection by *C. felis* until 7–9 weeks of age (Wills et al., 1984). Natural infection confers little protection against reinfection, although there may be an age-related resistance based on the lower prevalence of chlamydiosis in older cats. Both inactivated and attenuated live chlamydial vaccines may reduce the severity of clinical signs by decreasing *C. felis* replication, but they do not completely prevent infection or shedding of the organism after challenge (Masubuchi et al., 2010; Mitzel & Strating, 1977; Wills et al., 1987). This noncore vaccine is generally reserved for cats with high risk of exposure to *C. felis*, such as those residing in multicat households and catteries or those entering shelters. The initial vaccination is given between 8 and 10 weeks of age, with a second injection 3–4 weeks later. Annual boosters are recommended for cats at continued risk of exposure. In catteries in which chlamydiosis is endemic, all cats should first be treated with doxycycline for at least 4 weeks, then vaccinated (Gruffydd-Jones et al., 2009). Transmission can be minimized by good hygiene, single housing, separation of naïve from infected cats, and appropriate disinfection of facilities and shared utensils.

Some chlamydial species are zoonotic, with *C. psittaci* being of particular concern, but verified cases of *C. felis*-related conjunctivitis in humans are seemingly very rare. Past reports linking *C. felis* to human conjunctivitis often

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relied on culture without speciation or on serology with potential cross-reactivity with other chlamydiae. For example, an elevated antibody titer was identified in the owner of a cattery with endemic chlamydiosis (Studdert et al., 1981). In a more convincing report of *C. felis*-associated human conjunctivitis, the organism detected in the patient's conjunctiva was genetically indistinguishable from the isolate recovered from the patient's cat (Hartley et al., 2001). As a precaution, proper hand washing should be encouraged in owners of affected cats, as well as in veterinary staff handling young cats with chronic conjunctivitis.

Mycoplasma felis

Mycoplasma spp. have traditionally been considered causative agents of feline conjunctivitis (Blackmore et al., 1971; Campbell et al., 1973b; Heyward et al., 1969; Tan & Markham, 1971; Tan & Miles, 1973), but their role as primary pathogens has been difficult to substantiate, since they may also be found as apparently commensal organisms of the feline conjunctiva and upper respiratory tract. The prevalence of *Mycoplasma* spp. in the conjunctival flora of normal cats ranges from 0% to 34% (Campbell et al., 1973a; Shewen et al., 1980; Sjödahl-Essén et al., 2008), but virtually all cats harbor *Mycoplasma* spp. in their upper respiratory tracts (McManus et al., 2014; Sykes, 2014b). Several studies document an increased prevalence of *Mycoplasma* spp. in cats with conjunctivitis or upper respiratory tract disease when compared with healthy cats (Haesebrouck et al., 1991; Holst et al., 2010; Low et al., 2007). *Mycoplasma felis* and *M. gateae* are the species most often mentioned in association with feline conjunctivitis, but one study utilizing PCR also detected *M. canadense*, *M. cynos*, *M. lipophilum*, and *M. hyopharyngis* in affected cats (Hartmann et al., 2010).

Early experimental studies established infection in some kittens (Blackmore & Hill, 1973; Haesebrouck et al., 1991; Tan, 1974), but failed to produce conjunctivitis in any adult cats (Cello, 1957). In light of this apparent age-related difference in disease susceptibility, it is possible that an immature or altered immune response is a critical factor in the pathogenesis of mycoplasmal conjunctivitis. It is also feasible that *Mycoplasma* spp. act as secondary invaders in the presence of other pathogenic viruses or bacteria (Schneck, 1972; Sykes, 2014b).

Clinical signs ascribed to infection with *Mycoplasma* spp. are nonspecific and include unilateral or bilateral conjunctivitis, accompanied by serous to mucopurulent discharge, conjunctival hyperemia, and chemosis (Fig. 28.26). In one experimental study, conjunctival hyperemia developed 2–3 days after inoculation and disappeared without treatment within 7 days (Haesebrouck et al., 1991). Papillary hypertrophy lends a velvety texture to the conjunctival surface. An adherent conjunctival pseudomembrane may be misinterpreted as a thick white exudate. Corneal stromal ulcers with neutrophilic cellular infiltrates and keratomalacia have been seen in association with *Mycoplasma* spp. infection (Gray et al., 2005; Ketring & Glaze, 2012; Sykes, 2014b), but predisposing factors such as coinfection with FHV-1 are probably required for mycoplasmal invasion of the cornea to occur.

Although cytology of conjunctival scrapings has been suggested as a diagnostic tool, *Mycoplasma* spp. are not

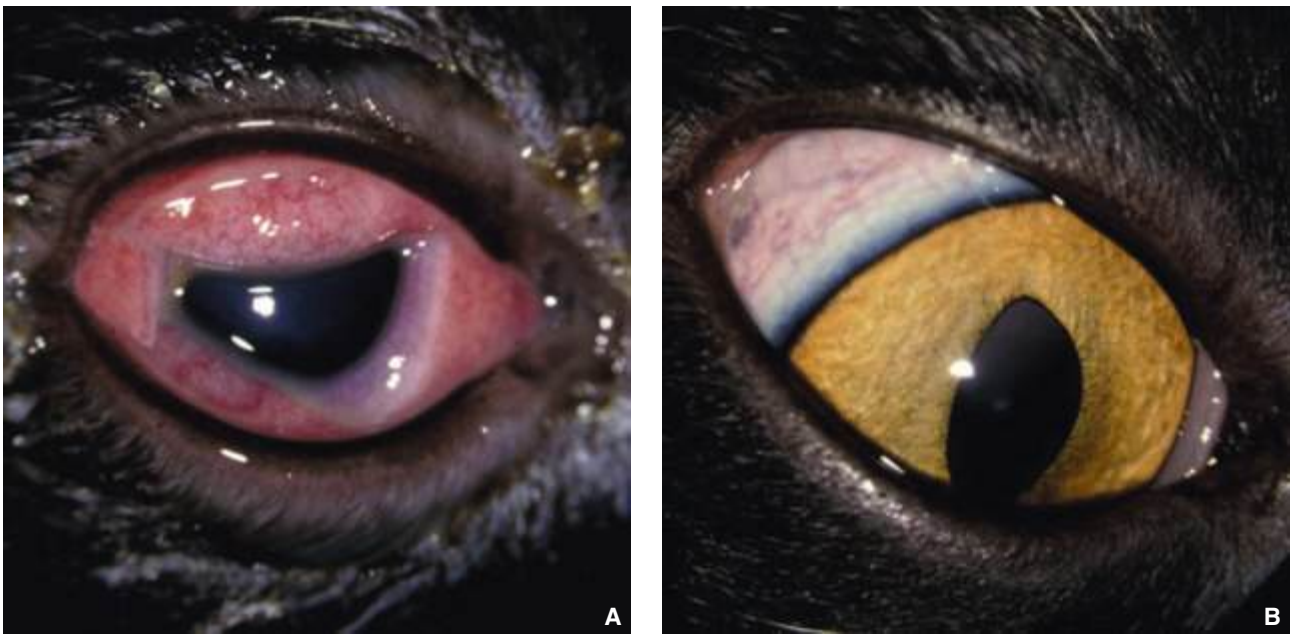


Figure 28.26 Polymerase chain reaction–positive *Mycoplasma* spp. conjunctivitis in a 2-year-old Domestic Shorthair. **A**. Initial presentation with conjunctival hyperemia and chemosis. **B**. Day 16 of an oral azithromycin regimen.

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dependably visible by light microscopy because of their small size (Sykes, 2014b). Mycoplasmal inclusions were identified in only 3 of 6 cats positive for *M. felis* by PCR analysis, leading authors of a cytologic study of feline conjunctivitis to conclude that cytology was unreliable in diagnosing *M. felis* infection (Hillström et al., 2012). Lack of a cell wall also precludes the use of Gram stain for identification. When found, the organisms appear as multiple punctate, darkly staining coccoid inclusions within the cytoplasm of conjunctival epithelial cells.

Most *Mycoplasma* spp. require special media and handling for successful culture, a method that may take days to weeks to complete. Conjunctival swabs are a poor source of culture material compared to blood, synovial fluid, or other bodily fluids. Since the organisms are cell associated, the conjunctival surface must be vigorously swabbed to obtain an adequate cellular sample. Culture of this commensal organism does not necessarily substantiate its role in a patient's clinical disease. Although PCR assays provide more rapid detection of *Mycoplasma* spp. (Chalker et al., 2004; Soderlund et al., 2011), the clinical significance of positive results is still unclear.

Tetracyclines and fluoroquinolones are active against most *Mycoplasma* spp. isolates (Sykes, 2014b). Treatment should be continued for at least 2 weeks, although the optimal duration of therapy in systemic infections is unknown. In a prospective study of *M. felis* infection in shelter cats, real-time PCR determined that a 14-day doxycycline regimen was more effective than a 7-day regimen in reducing the *M. felis* load, though 25% of the cats treated for 14 days were still infected at the study's conclusion (Kompare et al., 2013). In a study of feline conjunctivitis, a 3-week course of pradofloxacin or doxycycline was required to eliminate detectable *Mycoplasma* DNA (Hartmann et al., 2008a). A 3- or 4-week regimen of oral doxycycline (10 mg/kg every 24 hrs) seems a reasonable choice to treat *M. felis* infections, since it is also the treatment of choice for *C. felis*. Conjunctivitis also responds to topical tetracycline 4 times daily, though cats occasionally demonstrate topical sensitivity to the drug. Some *Mycoplasma* spp. are resistant to macrolides (Sykes, 2014b), so response to topical erythromycin or systemic azithromycin is not necessarily predictable.

There is no vaccine against feline *Mycoplasma* spp. Prevention focuses on the management of concurrent diseases or infections that predispose to secondary mycoplasmal infection. Reduced crowding and careful environmental hygiene may also reduce the incidence of *Mycoplasma* infections. Zoonotic potential appears limited, but *M. felis* was isolated from the joints of an immunocompromised woman with septic arthritis (Bonilla et al., 1997).

Feline Calicivirus

Feline calicivirus (FCV) is a nonenveloped RNA virus, widespread in the feline population. Between them, FCV and FHV-1 are estimated to account for up to 90% of upper respiratory tract infections in domestic cats (Di Martino et al., 2007; Ford, 1997). Like other RNA viruses, FCV is capable of rapid mutation, creating considerable antigenic diversity between strains. Multiple variants derived through mutation of an infecting FCV strain can simultaneously affect a single cat (Johnson, 1992; Radford et al., 1998). Disease prevalence due to FCV is highest among cats housed in large groups, with estimates ranging between 25% and 40% in colonies and shelters (Bannasch & Foley, 2005; Coutts et al., 1994; Helps et al., 2005; Wardley et al., 1974).

Infection occurs through direct contact of oral or nasal secretions from infected animals with conjunctival, oral, or nasal mucosa. The oropharynx is the primary site of viral replication. Most cats shed virus for at least 30 days following infection, but some may become lifelong carriers, infecting naïve cats through chronic intermittent shedding (Wardley, 1976). The virus is thought to elude host immune responses due to changes in capsid protein, ultimately localizing in the tonsillar epithelium of healthy carriers (Coyne et al., 2007). Unlike *C. felis, M. felis*, and FHV-1, FCV is environmentally resilient, able to survive on dry surfaces at room temperature for 28 days, and resistant to routine disinfectants (Clay et al., 2006; Doultree et al., 1999). FCV also remains infectious in flea feces for up to 8 days, with proven transmission occurring in kittens following contact with infected fleas (Mencke et al., 2009). The risk of FCV infection increases with group housing, coinfection with *M. felis*, and intact reproductive status (Berger et al., 2015).

Clinical findings depend on the virulence of the FCV strain, the age of the affected cat, and elements of the animal's husbandry (Radford et al., 2009). Acute oral and upper respiratory disease occurs mainly in kittens following an incubation period of 2–10 days, with transient viremia occurring 3–4 days after infection (Hurley & Sykes, 2003). The virus induces necrosis of epithelial cells, creating vesicles on the margin of the tongue that coalesce into geographic, map-shaped ulcers, considered the hallmark of FCV infection. These erosive or ulcerative lesions typically heal within 2–3 weeks (Sykes, 2014c). Mild upper respiratory disease with sneezing and serous nasal discharge accompanies oral ulceration (Gaskell et al., 2006). Less common manifestations of FCV include pneumonia, lameness secondary to acute synovitis, and chronic stomatitis. An uncharacteristically severe and often fatal form of FCV infection known as virulent systemic disease (VSD) causes widespread vasculitis, with fever, oral and pedal ulceration, head and limb edema, pleural effusion, hepatic necrosis, and bleeding due to coagulopathy (Coyne et al., 2006).

Despite its ability to induce epithelial cell necrosis, FCV has been considered a rather inconsequential ocular pathogen, causing ocular discharge and only mild, if any, conjunctivitis in experimentally infected cats (Hoover & Kahn, 1975; Lesbros et al., 2013; Poulet et al., 2005; Ramsey, 2000; TerWee et al., 1997). More significant ocular surface disease has been

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described in recent reports, including moderate to severe erosive conjunctivitis (Gerriets et al., 2012) and conjunctivitis sufficiently severe to obscure the corneal surface (Stiles, 2014). These findings may reflect coinfections with other agents of feline upper respiratory disease (Gerriets et al., 2012), more virulent strains of FCV, and/or variations in host immune responses (Stiles, 2014). Notably, no corneal ulcers were found in cats infected with only FCV. In another study of 89 cats with clinical signs consistent with naturally acquired FCV infection and in which FCV DNA was detected by PCR, 38% had ocular discharge, 44% demonstrated conjunctivitis, and 3% were described as having keratitis (Berger et al., 2015). However, coinfection with at least one other agent of feline upper respiratory disease was documented in 40% of these 89 cats, no doubt influencing the array of clinical signs described. Based on a reported odds ratio of 5.3 for the development of oral ulceration versus 0.82 for conjunctivitis (Berger et al., 2015), FCV should be considered highly unlikely when assessing a patient with conjunctivitis in the absence of concurrent oral ulceration. In the more virulent systemic form of FCV, crusting and ulcerative dermatitis can occur around the eyes, as well as on the nose, lips, and footpads. However, the severity of the accompanying systemic disease should differentiate this dermatologic manifestation from the erosive blepharitis seen with FHV-1.

Detection of FCV is optimized using combinations of quantitative reverse transcription PCR (RT-qPCR) or by combining RT-qPCR with cell culture to confirm the presence of replicating virus (Meli et al., 2018). Calicivirus RNA can be detected in conjunctival and oral swabs, cutaneous scrapings, and blood by use of PCR. The likelihood of FCV detection using virus isolation is improved when swabs from both the conjunctiva and oropharynx are tested (Marsilio et al., 2005). Since the seroprevalence of FCV is high due to natural infection and vaccination, evidence of FCV antibodies by virus neutralization or ELISA does not reliably indicate infection (Lappin et al., 2002).

Therapeutic options are limited. Contemporary topical and systemic antiviral agents used to treat FHV-1 inhibit DNA synthesis and are therefore ineffective against FCV, an RNA virus. Recombinant feline interferon-omega (rfeIFN-ω) inhibits FCV replication *in vitro* (Fulton & Burge, 1985), but topical therapy failed to improve clinical signs or reduce viral shedding in cats with keratoconjunctivitis when applied twice daily for 14 days (Slack et al., 2013). An initial subcutaneous injection followed by topical ocular, intranasal, and oral administration at 8-hour intervals for 21 days also failed to reduce clinical signs in cats with acute upper respiratory disease. However, reduced FCV copy numbers determined by quantitative PCR suggested that IFN might speed the reduction of viral load in infected cats (Ballin et al., 2014).

All healthy cats should be vaccinated against feline calicivirus. Modified live virus vaccines, particularly those administered intranasally, are preferred in shelters due to rapid seroconversion (Lappin et al., 2009). While vaccination provides protection against acute oral and upper respiratory tract disease, it does not prevent cats from becoming infected or from subsequently shedding FCV (Radford et al., 2006). Lifetime immunity is not likely in cats that recover from caliciviral disease, since the genome of this RNA virus continually mutates, altering the antigenic character of the infecting strain.

Bordetella bronchiseptica

Although *Bordetella bronchiseptica* is considered an important cause of respiratory disease in cats, this aerobic Gram-negative coccobacillus is likely to cause only mild ocular discharge and conjunctivitis. The disease is especially prevalent in shelters, breeding colonies, and research facilities where stress and close contact facilitate airborne transmission. In a study of 742 cats in the United Kingdom, *B. bronchiseptica* was isolated from 0% of pet cats, 19.5% of cats from rescue shelters, and 13.5% of cats in research colonies (Binns et al., 1999). The reported prevalence of infection in shelters ranges from 0% to 50% (Burns et al., 2011; Di Martino et al., 2007; Hoskins et al., 1998; Spindel et al., 2008; Veir et al., 2008).

This highly contagious organism is shed in oral and nasal secretions and also grows in natural water sources. Strains that infect dogs can be transmitted to cats, and vice versa (Dawson et al., 2000). Once inhaled, the bacteria adhere to respiratory cilia and secrete toxins damaging to the underlying respiratory epithelium. The incubation period ranges from 2 to 10 days. Clinical signs vary in severity, but sneezing is a conspicuous feature of feline infection, in contrast to the paroxysmal cough exhibited by dogs (Binns et al., 1999). Disease is usually confined to the upper respiratory tract, but fatal bronchopneumonia does occur in kittens. Ocular signs consist of conjunctivitis accompanied by serous to mucopurulent ocular discharge.

Bordetellosis is confirmed by aerobic bacterial culture and PCR assays performed on nasal and oropharyngeal swabs. Dacron or rayon swabs are preferred for culture, since growth may be inhibited by cotton swabs (Sykes, 2014a). Positive PCR results can occur for at least 3 weeks after intranasal vaccination (Iemura et al., 2009). Serology is of limited value for diagnosis because of the high prevalence of antibodies in the feline population.

Many infections are mild or self-limiting. Systemic antibacterial treatment is usually reserved for kittens less than 6–8 weeks of age, patients with respiratory disease lasting longer than 7–10 days, or those with signs of bronchopneumonia. Doxycycline is the antibiotic of choice, dosed at 5 mg/kg orally every 12 hours for 21 days (Baral, 2012). Specific treatment of the conjunctivitis is not required, since the organism does not colonize the ocular surface. Supportive care can be provided with a topical mucinomimetic such as sodium hyaluronate. Routine vaccination against *B. bronchiseptica* is not

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recommended in pet cats, but should be considered in animals group housed in facilities with a record of confirmed bordetellosis.

Other Infectious Agents Linked with Conjunctivitis

Excluding C. *felis* and *M. felis*, primary bacterial infections of the feline conjunctiva are rare. Infrequent opportunistic bacterial infections of the conjunctiva may occur following trauma, with adnexal abnormalities such as entropion, as coinfections with FHV-1 and *C. felis*, or as a consequence of postviral alterations in tear quantity or quality. The percentage of positive aerobic bacterial cultures was comparable in 2 of 3 studies characterizing the conjunctival flora of cats with conjunctivitis, with recovery rates of 34% in 38 cats (Nasisse et al., 1993) and 39% in 41 cats (Hartmann et al., 2010). *Staphylococcus* spp. predominated in these cases, followed by *Streptococcus* spp. and *Micrococcus* spp. Although a third study had a much lower percentage of positive cultures, recovered organisms mirrored those of the other studies, including *Staphylococcus epidermidis*, beta-hemolytic *Streptococcus*, and nonhemolytic streptococci (Shewen et al., 1980).

Natural and experimental infection with *Salmonella typhimurium* causes moderate to severe conjunctivitis in cats, though its clinical relevance as an ocular pathogen is debatable. Nevertheless, the conjunctiva is thought to be a portal for enteric infection and may serve as a source of Salmonella excretion (Fox et al., 1984). In a single case report, the organism was cultured from conjunctival and rectal swabs of an adult female cat with unilateral conjunctivitis (Fox & Galus, 1977). Clinical signs were limited to the eye, resolving with a 10-day regimen of oral and topical chloramphenicol. Interestingly, the conjunctivitis developed after the cat was relocated, and coinfection with established primary pathogens was not convincingly excluded. The absence of inclusions in conjunctival scrapings was used to rule out *C. felis* and *M. felis*, but FHV was not investigated.

Leishmania amastigotes were identified in a conjunctival biopsy from a 21-year-old European Shorthair cat that presented with exophthalmos and profound conjunctival thickening, resulting in a hyperemic, irregularly thickened mass that encircled most of the anterior globe (Ketring & Glaze, 2012). Accompanying ocular signs included corneal cellular infiltration, exudative retinal detachments, and extraocular myositis.

Neonatal Conjunctivitis

Neonatal conjunctivitis is a syndrome of acute conjunctival inflammation in neonatal kittens (Nasisse, 1991). Copious, typically purulent ocular discharge is a consistent finding. The condition is classically described in kittens prior to eyelid separation at 10–14 days of age, when the accumulating exudate distends the eyelids. The causes and treatment of neonatal conjunctivitis are summarized in the section describing abnormalities of eyelid opening.

Eosinophilic Conjunctivitis

On occasion, eosinophilic conjunctivitis appears as an autonomous clinical entity, without signs of the keratitis that shares its name – and likely its etiopathogenesis. One or both eyes may be affected in cats ranging in age from 1 to 15 years (Allgoewer et al, 2001; Pentlarge, 1991). The conjunctival surface often has a distinctive velvety texture, with concurrent swelling and hyperemia that also extend to the third eyelid (Fig. 28.27). Mucoid to mucopurulent discharge is common, as are depigmentation, thickening, and erosion of the lower eyelid margin and medial canthus (Allgoewer et al., 2001). Conjunctival scrapings are characterized by a preponderance of eosinophils and mast cells (Allgoewer et al., 2001; Pentlarge, 1991). Eosinophils, lymphocytes, plasma cells, mast cells, and macrophages are seen histologically (Allgoewer et al., 2001). The same Type I and IV hypersensitivity reactions proposed for eosinophilic keratitis could explain the cellular profile of eosinophilic conjunctivitis (Prasse & Winston, 1996). The role of FHV in eosinophilic conjunctivitis is as yet undetermined, but electron microscopy and PCR failed to detect FHV in Allgoewer's 12 cats. Topical or systemic anti-inflammatory drugs resolve clinical signs in as little as 3–6 weeks (Allgoewer et al., 2001; Larocca, 2000), but most cats require indefinite maintenance therapy to prevent relapse, similar to that subsequently described in detail for eosinophilic keratitis.

Allergic Conjunctivitis

Eosinophilic infiltration of the conjunctiva has been attributed to allergic disease (Lavach et al., 1977), but the finding



Figure 28.27 Eosinophilic conjunctivitis in a 7-year-old Domestic Shorthair with a 3-year history of ocular disease. Generalized conjunctival thickening and a suede-like surface texture obscure the underlying keratitis. A conjunctival scraping contained eosinophils, lymphocytes, and plasma cells.

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of a single eosinophil in the conjunctival cytologic specimens of 91 cats with chronic conjunctivitis suggests that allergy is an infrequent cause of feline conjunctivitis (Nasisse et al., 1993). Allergic conjunctivitis must be bilateral, unless the reaction can be attributed to a topical drug hypersensitivity in the individual eye. Clinical signs include periocular erythema, conjunctival hyperemia, chemosis, the presence of lymphoid follicles, and serous to mucoid ocular discharge. Since allergic conjunctivitis often accompanies allergic dermatitis, there may be concurrent inflammation of the skin, paws, ears, nares, and pharynx. Given the lack of specific clinical signs, a diagnosis of allergic conjunctivitis is often one of exclusion, first ruling out more common causes of a red eye on the basis of a thorough history and a complete ophthalmic examination. A dermatologist is an indispensable collaborator in the atopic patient that may require allergy testing or an elimination trial. If an antigen cannot be identified or eliminated, empirical therapy is like that for any other immune-mediated conjunctivitis. Topical dexamethasone or prednisolone is the mainstay of treatment, applied more frequently at first, then tapered to the lowest dose needed to control clinical signs. The selected steroid preparation ideally excludes any antibiotic in order to reduce risk of a delayed-type hypersensitivity with continued treatment. If clinical signs exacerbate with steroid therapy, reactivation of a latent herpesvirus infection may be responsible. Topical cyclosporine has an anti-eosinophilic property and has been used to treat feline eosinophilic keratoconjunctivitis (Spiess et al., 2009), but its efficacy in allergic conjunctivitis is untested. Consider use of proprietary Optimmune® (Merck Animal Health, Madison, NJ, USA), since many of the compounded products are dissolved in potent allergens such as peanut oil, olive oil, and corn oil. Controlled studies of topical antihistamines and mast cell stabilizers have not been performed in cats, nor do anecdotal reports suggest that they are uniformly effective in controlling clinical signs.

Epitheliotropic Mastocytic Conjunctivitis

Clinical signs of epitheliotropic mastocytic conjunctivitis resemble those of eosinophilic conjunctivitis, albeit in an uncommonly severe proliferative form, with conjunctival hyperemia, thickening, and mucoid ocular discharge (Beckwith-Cohen et al., 2017). Third eyelid abnormalities feature prominently, with either solitary nodules that expand the third eyelid or smaller, sometimes ulcerated nodules proliferating within the third eyelid conjunctiva. Its proliferative character may be clinically misinterpreted as SCC (Maggs et al., 2018a). In a report of 15 cats ranging in age from 7 months to 17.5 years, 3 also had eosinophilic keratitis and 3 demonstrated lesions of the facial skin or eyelids, including depigmentation of the eyelid margins (Beckwith-Cohen et al., 2017). Though more often unilateral than bilateral, the proliferative character of epitheliotropic mastocytic conjunctivitis mimics that of vernal conjunctivitis in humans, a disorder in which seasonal allergies play a crucial role (Jun et al., 2008). Histologically, lesions are characterized by mixed inflammatory infiltrates with an abundance of intra- and subepithelial mast cells and papillary epithelial hyperplasia. In the inaugural report, topical treatment with tacrolimus or corticosteroid was effective in controlling clinical signs, but some cats required long-term therapy to prevent relapse (Beckwith-Cohen et al., 2017).

Parasitic Conjunctivitis

Feline conjunctivitis has been associated with the nematode *Thelazia californiensis*, particularly in the western United States (Knapp et al., 1961), while *Thelazia callipaeda* is considered an emerging pathogen in Europe (Dorchies et al., 2007; Maia et al., 2016; Motta et al., 2014; Rodrigues et al., 2012; Soares et al., 2013). *Fannia* spp. flies serve as vectors of *T. californiensis*; *T. callipaeda* is transmitted by the fruit fly *Phortica variegata* (Otranto & Dantas-Torres, 2015; Otranto et al., 2006). Transmission of the parasite occurs when flies feed on lacrimal secretions, depositing third-stage larvae that develop into adult worms within the conjunctival cul-de-sac. Cases are often diagnosed in the late summer and autumn when the fly vectors are most active (Farkas et al., 2018). Clinical signs include serous to purulent discharge, blepharospasm, conjunctival hyperemia, and chemosis (Dumitrache et al., 2018), although an occasional cat is asymptomatic (Papadopoulos et al., 2018). The threadlike, motile whitish worms are physically removed from the conjunctival cul-de-sac using forceps. Experimentally, they are known to survive at least 9 months in a definitive host (Farkas et al., 2018). Monthly administration of milbemycin oxime has been suggested to prevent reinfection (Motto et al., 2012). Thelaziosis is a zoonotic disease (Shen et al., 2006).

The larvae of *Cuterebra* spp. may be deposited within the conjunctival tissue, leading to severe inflammation (Stiles, 2013). Treatment consists of manual removal of the larva, followed by application of a topical antibiotic coupled with a topical or systemic anti-inflammatory drug until the conjunctivitis has resolved.

Conjunctival Neoplasia

Melanoma

In the first description of feline conjunctival melanoma, tumor infiltrated both bulbar and palpebral conjunctiva in a 6-year-old female cat (Cook et al., 1985). In subsequent reports, patients ranged in age from 2 to 19 years, with a 12–14-year mean (Patnaik & Mooney, 1988; Schobert et al., 2010). The bulbar conjunctiva is the predominant site of origin. Of 27 reported conjunctival melanomas, 17 originated in bulbar conjunctiva (Patnaik & Mooney, 1988; Payen et al., 2008; Schobert et al., 2010), 5 developed in conjunctiva overlying the third eyelid (Roels & Ducatelle, 1998; Schobert

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et al., 2010), 3 arose in palpebral conjunctiva (Schobert et al., 2010), and the site of origin was undetermined in 2 (Cook et al., 1985; Schobert et al., 2010; Fig. 28.28). All 13 tumors of bulbar conjunctival origin extended deeply into the orbit in one study (Schobert et al., 2010). Most tumors are heavily pigmented; only 5 amelanotic tumors have been described (Schobert et al., 2010). Histologically, the majority exhibit pigmented round cell populations with multinucleated tumor cells, rarely admixed with spindle cells (Schobert et al., 2010). All meet the cytologic criteria of malignancy (Payen et al., 2008; Schobert et al., 2010), but no particular histologic morphology appears to predict the likelihood of recurrence, metastasis, or death (Schobert et al., 2010).

Feline conjunctival melanoma exhibits a slightly higher metastatic risk (14% vs. 10%) and a decidedly higher mortality rate (61% vs. 5%) than affected dogs (Schobert et al., 2010.) There are only two cases in the peer-reviewed literature claiming a successful outcome following surgical excision, the first based on lack of tumor recurrence in an 11-month postoperative period (Cook et al., 1985). In the second case, a well-differentiated and histopathologically delimited superior bulbar conjunctival mass was successfully excised in an adult female DSH, with no recurrence at 34 months (Payen et al., 2008). Wilcock mentioned two unpublished cases that recurred within 3 months of initial excision, but were cured by exenteration (Wilcock et al., 2002). In 3 cats, bulbar conjunctival tumors recurred following surgical excision and metastasized despite subsequent enucleation (Patnaik & Mooney, 1988). Two of these 3 cats were euthanized 3 months following diagnosis; the reported 409-day mean survival time was skewed by one owner's reluctance to consider euthanasia (Patnaik & Mooney, 1988). Of 13 patients with adequate follow-up in Schobert's review, 4 tumors recurred locally, 2 spread to submandibular lymph nodes, and 1 metastasized to the abdomen. Eight cats died, with a mean postdiagnosis survival time of 11 months, although necropsy was not performed to substantiate metastatic melanoma as the cause of death (Schobert et al., 2010). One patient with tumor originating in third eyelid conjunctiva showed overt metastasis at the time of diagnosis (Roels & Ducatelle, 1998).

Conjunctival melanoma must be differentiated from the equally rare limbal (epibulbar) melanocytoma that originates from neoplastic transformation of perilimbal melanocytes located near Descemet's membrane (Grahn & Peiffer, 2007). These benign tumors are characterized by variably pigmented neoplastic cells that extend in a fan shape into the deep corneal stroma and also extend outwardly, deep to the limbus, into the sclera, episclera, and conjunctiva (Harling et al., 1986). In an atypical case described as a limbal melanoma, a 13.5-year-old DLH with a 3×3 cm amelanotic scleral tumor and concurrent eyelid infiltration died of apparent distant metastasis 6 months after presentation (Day & Lucke, 1995), behavior more like that of the conjunctival melanomas described above.



Figure 28.28 Malignant melanoma of the conjunctiva in an 11-year-old Domestic Shorthair. A darkly pigmented third eyelid is accompanied by bulbar and palpebral conjunctival pigmentation and thickening. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

Lymphoma

Feline conjunctival lymphoma is an uncommon isolated tumor, described in 2 individual case reports (n=2) and in 2 case series (n=4; Fig. 28.29). Bilateral palpebral conjunctival



Figure 28.29 Conjunctival lymphoma was diagnosed in a 9-year-old Domestic Shorthair based on biopsy of a mass that distended the superior palpebral and bulbar conjunctiva.

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masses developed in an FeLV/FIV-negative 13-year-old DSH (Radi et al., 2004). The tumors were surgically excised, without subsequent treatment or follow-up. Both tumors were highly cellular, packed with sheets of atypical lymphocytes and immunohistochemically characterized as B-cell lymphoma. B-cell Hodgkin's-like lymphoma was diagnosed in a 7-year-old DSH with a superior palpebral conjunctival mass and concurrent reactive lymphadenopathy. Chemotherapy was ineffective, but the cat remained disease free for the 3 years for which it was monitored following orthovoltage radiation therapy (Holt et al., 2006). A single example of conjunctival lymphoma, with marked lobulated thickening of the superior palpebral conjunctiva in an 11-year-old cat, appeared in a review of 9 patients with presumed solitary ocular lymphoma (Wiggans et al., 2014a). This T-cell tumor was characterized by a monomorphic population of large round atypical lymphoid cells, accompanied by a mixed inflammatory infiltrate. Transient response occurred following radiation therapy and repeated courses of chemotherapy, but bilateral metastasis to the mandibular lymph nodes occurred 467 days after initial diagnosis and the patient was euthanized 82 days later. B-cell tumors developed in the upper palpebral conjunctiva (n=2) and the third eyelid conjunctiva (n=1) of DSH cats ranging in age from 10 to 12 years (McCowan et al., 2014). Of these 3 patients, one FIV-positive cat with radiation-responsive palpebral conjunctival lymphoma died 6 months after diagnosis. The cat with third eyelid conjunctival lymphoma died of unrelated causes 2 years later, while the third patient lived more than 4 years following enucleation. Because local spread to mandibular lymph nodes occurs in both feline and canine patients with conjunctival lymphoma, cytologic examination of local lymph node aspirates is recommended to stage the disease accurately at initial diagnosis (Wiggans et al., 2014a).

Vascular Tumors

Conjunctival vascular tumors of endothelial origin tend to be superficial exophytic masses, red to reddish-brown in color and either smooth or multilobulated in character. A case series of vascular tumors characterized 6 hemangiomas and 2 hemangiosarcomas in domestic cats averaging 10.6 years of age (Pirie & Dubielzig, 2006); 6 of the 7 cases with known sex were neutered male cats, mirroring a similar sex bias reported with cutaneous vascular neoplasia (Miller et al., 1992). The hemangiomas developed along the leading edge of the third eyelid (n=3), the temporal bulbar conjunctiva (n=1), and the inferior palpebral conjunctiva (n=1); the anatomic site of 1 hemangioma was unknown. The hemangiosarcomas arose from bulbar conjunctiva, 1 superiorly and 1 inferiorly. Hemangiosarcomas tended to have a more chronic course, existing 10.5 months prior to presentation versus 3.5 months for hemangiomas. Conjunctival vascular tumors have a favorable prognosis. Treatment of choice is surgical excision with adjunctive cryotherapy. In Pirie's review, no recurrence was reported following excision of the 6 hemangiomas, regardless of whether surgical margins were clean or dirty. Both hemangiosarcomas recurred following incomplete excision and adjunct treatment with cryotherapy or neodymium:yttrium-aluminum-garnet (Nd:Yag) laser. One case successfully resolved following a second excision; the other was enucleated after the hemangiosarcoma recurred a second time. No metastasis or death linked to the primary tumor was documented in the 5 cases for which follow-up information existed. Another hemangiosarcoma arising from the conjunctiva of the anterior third eyelid occurred in a 15-year-old DSH. The small red multilobulated mass resolved following surgical excision and cryotherapy, with no recurrence in the 7 months following surgery (Multari et al., 2002).

Squamous Cell Carcinoma

SCC is most likely to affect the palpebral conjunctiva and third eyelid as a consequence of eyelid tumor expansion. SCC has not been reported as a primary conjunctival tumor in cats, with the exception of a single case report of a 14-year-old DSH in which SCC and hemangioma developed on the cornea and conjunctiva without apparent eyelid involvement (Perlmann et al., 2010). No evidence of recurrence or metastasis was evident in the 8 months following exenteration.

Conjunctival Surface Adenocarcinoma

Adenocarcinoma of the conjunctival surface has been described in 10 cats of various breeds ranging in age from 3 to 18 years, with a mean of 10.7 years (Naranjo et al., 2009; Fig. 28.30). The conjunctiva overlying the third eyelid is the most frequent location, but tumor cells can also infiltrate the perilimbal cornea and third eyelid gland. Local recurrence is frequent; enucleation or exenteration may be required.



Figure 28.30 Conjunctival apocrine adenocarcinoma in a 14-year-old Domestic Shorthair.

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Keratoconjunctival Disease

Although corneal and conjunctival disease can occur independently of each other, it is more common, especially with inflammatory disorders, to see coincident involvement of both tissues (i.e., keratoconjunctivitis), albeit with one tissue sometimes more affected than the other. As with conjunctivitis, feline keratoconjunctivitis is typically infectious in nature, with the most important primary corneal pathogen in cats being FHV-1. While many other pathogens worsen corneal ulceration, FHV-1 is the only organism known to initiate ulcers in cats. Experimental studies fulfilling Koch's postulates, as well as clinical reports, suggest that *C. felis* is not a primary corneal pathogen (Owen et al., 2003; Rude, 1986; Wills, 1986).

Feline Herpesvirus Type 1

FHV-1 is a DNA virus and a member of the alphaherpesvirus subfamily of herpesviruses. Typical of members of this subfamily, the hallmark biologic features of FHV-1 are "tight" host species specificity, rapid intracellular replication within epithelial cells, and establishment of lifelong latency within neural cells. By contrast, FHV-1 is extremely labile in the environment, surviving only about 12 hours in dry environments and 18 hours in more moist conditions. It is susceptible to most disinfectants and to desiccation. Of importance when considering opportunities for nosocomial infection within an ophthalmic clinic, FHV-1 is rapidly killed by fluorescein stain and proparacaine, but can be recovered from eyewash for 5 days (Storey et al., 2002). Because of this short environmental survival, the major route of infection is via direct transfer of virus-containing macrodroplets between oral, nasal, and conjunctival mucosal surfaces of cats. It appears that cats do not form aerosols of any of the respiratory viruses during normal respiratory movements. An estimated 75%–97% of the world's cat population is seropositive, and the virus is considered to be responsible for 45% of all upper respiratory infections (Ellis, 1981; Maggs et al., 1999b; Studdert & Martin, 1970) and the majority of corneal ulcers (Hartley, 2010a) in cats.

Viral replication occurs primarily within the epithelium of the upper respiratory tract and eye, principally the conjunctiva, nasal turbinates, and nasopharynx, with more limited replication in the corneal epithelium (Li et al., 2015). Like species specificity, tissue specificity is likely mediated by virus–host cell surface receptor interactions (Maeda et al., 1998). Cell damage occurs through lysis or rupture of the cell membrane at the time of viral release, a phase of infection called "productive" or "cytolytic," causing erosion and ulceration of mucosal epithelium. Initiation of clinical disease is independent of the presence of conjunctival or upper respiratory flora, as shown by infection of germfree cats (Hoover et al., 1970), and a study of anaerobic bacterial involvement in ulcerative keratitis failed to show coincident presence of FHV-1 DNA (assessed using PCR) or cultivable virus (assessed using virus isolation; Ledbetter & Scarlett, 2008). However, the role of secondary bacteria in the severity and progression of ulcerative corneal disease should not be underestimated.

During acute replication within peripheral epithelial cells, some viral particles ascend neural axons to the nucleus, where they may establish lifelong latency. Latency is defined as a state where virus cannot be cultured (i.e., nonproductive infection), viral transcription is limited to only latency-associated transcripts (LATs), and there is no clinical disease. The LATs of FHV-1 have been characterized (Ohmura et al., 1993) and identified within trigeminal ganglia of cats without signs of ocular disease (Townsend et al., 2004). Traditionally, latency has been thought to occur in the vast majority (probably about 80%) of infected cats (Gaskell & Povey, 1977), but to occur solely in the trigeminal ganglia (Gaskell et al., 1985; Nasisse et al., 1992; Ohmura et al., 1993; Reubel et al., 1993; Townsend et al., 2004; Weigler et al., 1997). However, studies utilizing PCR in cats known to be infected with FHV-1 but not showing clinical signs have also identified viral DNA in the autonomic ganglia, optic nerve, olfactory bulb, vestibular ganglia, conjunctiva, and cornea (Nasisse et al., 1998; Parzefall et al., 2010; Reubel et al., 1993; Stiles & Pogranichniy, 2008; Stiles et al., 1997; Townsend et al., 2004, 2013; Weigler et al., 1997). Although virus in these cases may have been latent, gene expression, antigen immunohistochemistry, and histologic responses were not always assessed, and so persistent rather than truly latent virus may be more likely. Persistent virus is discussed more fully later in this chapter. Regardless, the finding of virulent and viable virus in the corneas of normal cats (Stiles & Pogranichniy, 2008) has important clinical implications for diagnostic testing of abnormal cats and for harvesting of tissues for corneal transplantation in cats.

Periodic reactivation of latent FHV-1 occurs after physiologic stresses such as rehousing, transport, parturition, and lactation, or following systemic administration of corticosteroids or epinephrine (Gaskell & Povey, 1977; Hickman et al., 1994). Indeed, corticosteroid administration has been advocated as a method of detecting carriers in endemic populations (Hickman et al., 1994). Once spontaneous or pharmacologic reactivation occurs, the virus is believed to descend the same sensory nerve axons that it ascended during primary infection, and thereby to reach the peripheral epithelial tissues again. This is the so-called round trip theory. Viral reactivation may occur in the absence of clinical signs or with a diverse range of recrudescent ocular, dermatologic, or upper respiratory signs associated with the recurrence of cytolytic (productive) replication in the mucosal epithelia. Clearly, this provides a highly adapted and successful means of perpetuating an environmentally labile virus within a host population. The "round trip" axonal

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transport theory led to the claim that viremia is unimportant in the pathogenesis of FHV-1 in cats. However, in other species infected with herpesviruses and in cats infected with viruses other than FHV-1, viremia allows dissemination of the virus to all organs, and can cause abortion, encephalitis, disseminated intravascular coagulation, and generalized organ failure (Kimura et al., 1991; Nawynck & Pensaert, 1995; Simons et al., 2005; van der Meulen et al., 2006b). Furthermore, FHV-1 DNA has been detected in the blood of cats exhibiting clinical signs of herpetic disease (Cullen et al., 2005b; Lim & Cullen, 2005; Powell et al., 2010) as well as apparently normal cats (Cullen et al., 2005a; Powell et al., 2010), and in distant sites such as bone or tendon in some cats that underwent mucosal infection (Swenson et al., 2012). However, these have not been consistent findings (Burgesser et al., 1999). In cats undergoing experimental primary infection with FHV-1, viral DNA was detected at least once in the blood of all cats between 2 and 15 days after inoculation (Westermeyer et al., 2009). However, in the same study, FHV-1 DNA was never detected and live virus was not isolated (cultured) from blood mononuclear cell samples from any adult, shelter-housed cat undergoing presumed recrudescent disease. This suggests that a brief period of viremia may occur during primary herpetic disease, but maybe not during recrudescence.

In addition to the latent and cytolytic phases of the FHV-1 life cycle, a "persistent" state is also proposed. Persistency mimics some aspects of latency, especially the inability to culture viable (virulent) virus. However, persistent virus is distinct from latent virus because genes in addition to LATs are expressed, and it is associated with (and likely induces) a chronic, often low-grade, inflammatory response. Persistency is the purported mechanism for chronic, typically nonulcerative, immunopathologic diseases such as herpetic stromal keratitis, lymphocytic/plasmacytic conjunctivitis, and potentially eosinophilic keratoconjunctivitis, herpetic dermatitis, and herpetic uveitis.

Finally, there is a growing appreciation that FHV-1 may cause disease through an additional mechanism – so-called metaherpetic disease. Metaherpetic disease arises from permanent or semi-permanent anatomic changes as a result of cytolytic and/or immunopathologic disease. Given the sometimes protracted delay following primary herpetic infection before metaherpetic disease becomes evident, as well as the likely inability to detect virus at that time, proving causal association is sometimes difficult. Some examples of suggested metaherpetic disease include (1) symblepharon following the exposure of corneal and/or conjunctival stroma due to ulcerative herpetic disease; (2) chronic conjunctival goblet cell depletion and tear film dysfunction following apparent clinical recovery from primary herpetic disease (Lim et al., 2009); (3) neurogenic dry eye as a result of corneal anesthesia secondary to herpetic injury to the trigeminal nerve (Sebbag et al., 2018a); and (4) band keratopathy or corneal sequestra as a result of exposure and structural alteration of the anterior stroma following chronic herpetic corneal ulceration (Nasisse et al., 1989b, 1998). Fig. 28.31 summarizes the viral states associated with latency; primary, recrudescent, and persistent infections; and metaherpetic disease.

There appears to be a real but relatively minor relationship between chronic herpetic diseases and coinfection with FeLV and FIV (Nasisse et al., 1993). Cats with chronic FHV-1 infection are more likely to be infected with FeLV or FIV than normal cats. Experimentally, FIV-infected cats exposed to FHV-1 develop more severe disease, although the length of the illness or level of FHV-1 shedding is not different (Reubel et al., 1992). *In vitro*, FHV-1 has been shown to enhance activation of gene sequences of FIV (Kawaguchi et al., 1991, 1992). Coinfection rates of FHV-1 with other agents of upper respiratory disease such as FCV, *C. felis*, *Bordetella bronchiseptica*, and *Mycoplasma* spp. range widely (Cai et al., 2002; Gerriets et al., 2012; Hillström et al., 2012; Litster et al., 2015b; Low et al., 2007; Nasisse et al., 1993; Rampazzo et al., 2003; Schulz et al., 2015; Volopich et al., 2005; Von Bomhard et al., 2003; Wieliczko & Ploneczka-Janeczko, 2010) and the likely clinical significance of coinfections is not known.

Clinical signs of infection with FHV-1 vary greatly depending on the cat's age, viral inoculum, and immune status.

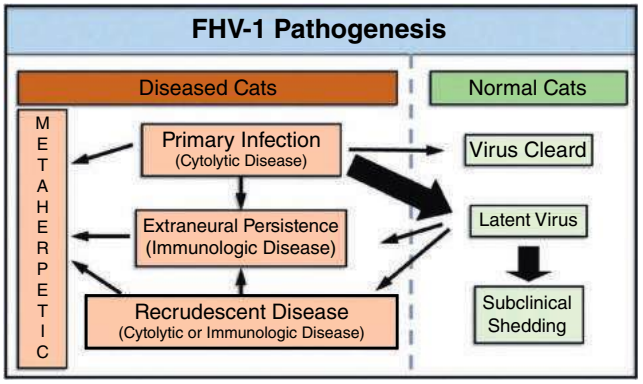


Figure 28.31 Proposed pathogenesis of feline herpesvirus type 1 (FHV-1). Following primary infection, the majority of cats become latently infected for life. The majority of these cats then shed virus subclinically. The remaining cats undergo recrudescent disease, develop metaherpetic syndromes, and/or have persistent virus in nonneuronal sites. In each of these phases except latency, the virus causes disease via one of three very different mechanisms, each requiring a very different therapeutic approach. The three mechanisms are cytolytic disease (i.e., cell rupture due to viral replication; e.g., corneal ulceration), immunologic disease (i.e., viral antigens driving immune-mediated tissue destruction; e.g., herpetic stromal keratitis), or metaherpetic syndromes resulting from permanent anatomic changes wrought by the virus (e.g., symblepharon). (Reproduced with permission from Maggs, D.J., Miller, P.E., & Ofri, R. (2018) *Slatter's Fundamentals of Veterinary Ophthalmology*, 6th ed. St. Louis, MO: Elsevier.)

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Following primary infection of FHV-1-naïve kittens, there is widespread and rapid viral replication in the epithelium of nasal mucosa and conjunctiva, marked upper respiratory and conjunctival inflammation, fever, anorexia, and lethargy. Pneumonia can occur (Love, 1971). Morbidity is high but mortality is uncommon, especially with supportive care. Tissue damage is due to viral cytolysis with subsequent ulceration of these mucosal surfaces, and sometimes symblepharon formation. By contrast, FHV-1 replicates to a more limited extent in corneal epithelium; however it can cause ulceration, notably dendritic lesions (Nasisse, 1990; Nasisse et al., 1989b; Fig. 28.32). The cause of the branching pattern of these ulcers is unknown, but is considered to be pathognomonic for herpetic infections of all species (Nasisse, 1990; Roberts et al., 1972). Dendritic corneal lesions occur in a biphasic pattern on days 3 and 12 of primary infection, the latter peak likely reflecting virus released from replication within and rupture of conjunctival epithelium (Nasisse et al., 1995). Little, if any, viral replication occurs within the corneal stroma (Nasisse et al., 1989b). Primary disease is usually self-limiting within 10–20 days (Thomasy et al., 2011).

Recrudescent disease is seen in some latently infected cats following periods of viral reactivation. The severity of disease and the tissues involved in these recrudescent episodes range widely among individuals and even among disease episodes. Disease may result from cytolytic, immunopathologic, or metaherpetic mechanisms. Conjunctivitis is usually milder and less ulcerative than seen in the acute infection. However, substantial conjunctival thickening and hyperemia can occur secondary to inflammatory cell infiltration. Corneal infections may again involve epithelial tissues, in which case dendritic and later geographic corneal ulceration may be seen, as in primary infections (see Fig. 28.32). Stromal keratitis may occur and is likely immunopathologic; that is, immune mediated but not necessarily autoimmune in origin (Fig. 28.33). Histologic observations from cats with chronic, naturally occurring stromal keratitis reveal fibrosis, collagen degeneration, and numerous lymphocytes, plasma cells, and macrophages (Nasisse et al., 1995). Experimentally, stromal keratitis does not occur during primary infection unless the normal immune response is suppressed by corticosteroids. In this scenario, the development of stromal keratitis is preceded by chronic epithelial ulceration and delayed viral clearance (with prolonged viral shedding), and acquisition of viral antigen by the corneal stroma. The subsequent stromal accumulation of polymorphonuclear cells, and T- and B-lymphocytes, correlates temporally with the return of normal immune function, eventually leading to stromal inflammation and fibrosis. The events surrounding experimental FHV-1 stromal keratitis are most compatible with a delayed-type hypersensitivity response (Th_1 cell-mediated, macrophage effector cells; Nasisse et al., 1995).

A major paradox exists with respect to the diagnosis of FHV-1 (Maggs et al., 1999b). Cats experiencing *primary* FHV-1 infection shed virus in sufficient quantities that viral detection is relatively easy. However, clinical signs during this phase of infection tend to be characteristic and self-limiting, making definitive diagnosis less necessary. By contrast, during the *more chronic* FHV-1-associated syndromes, the diversity and ambiguity of clinical signs make viral identification more desirable, especially if specific antiviral therapy is being considered. However, the elusive nature of the virus in these chronic syndromes makes this difficult. Indeed, the diagnosis of FHV-1 in individual cats represents one of the greatest challenges in the management of chronic FHV-1-related diseases. Although the specificity and extreme sensitivity of PCR have improved detection of the virus, this has also confirmed that the virus can be demonstrated in a large minority of apparently normal cats (Townsend et al., 2004).



Figure 28.32 Cytolytic disease associated with feline herpesvirus-1 infection. **A**. Primary conjunctivitis in a 3-month-old Domestic Shorthair, with early adhesions due to conjunctival epithelial ulceration. **B**. Pathognomonic dendritic ulceration in a 1-year-old Somali. **C**. Geographic corneal ulceration in a 2-year-old Domestic Shorthair following topical treatment of herpetic conjunctivitis with dexamethasone.

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Figure 28.33 **A**. Herpetic stromal keratitis with edema, white blood cell infiltration, and vascularization. (Courtesy of University of California Davis Veterinary Ophthalmology Service.) **B**. Chronic stromal keratitis in an 11-year-old Domestic Shorthair, with diffuse edema, fibrosis, cellular infiltration, vascularization, and multifocal sequestration.

This must be considered when interpreting the results of diagnostic assays in individual cats with disease. Additionally, we know that herpes simplex virus-1 (HSV-1), and therefore possibly FHV-1, can be stimulated to reactivate by irritation of the peripheral sensory neurons (Anderson et al., 1961; Harbour et al., 1983; Hill et al., 1978). Therefore, it is possible that virus detected at a peripheral site in a diseased animal may be there as a *result* rather than a *cause* of the disease being investigated. Finally, PCR assay in common usage can differentiate vaccine from wild-type virus (Maggs & Clarke, 2005). Therefore, whenever viral DNA is detected in a cat with disease, there are at least four possible explanations: (1) its presence is *coincidental* (i.e., unrelated to the primary disease process); (2) its presence is a *consequence* of the primary disease process; (3) it is vaccine virus; or (4) it is the *cause* of the primary disease process. There are also times when the PCR assay, despite its sensitivity, can be falsely negative. Therefore, whether virus is found or not (i.e., irrespective of the PCR test result), the clinician must still decide whether specific antiviral treatment is warranted. Currently, other than clinical acumen, there is no laboratory test that will answer that question.

Currently available tests rely on the demonstration of an immunologic response (usually in serum) to the organism, or the detection of whole, cultivable virus by virus isolation, its antigens by IFA, or its DNA by PCR (Nasisse & Weigler, 1997; Table 28.5).

Cytology typically reveals predominantly neutrophilic inflammation and is unrewarding for the diagnosis of FHV-1, since intranuclear inclusions are seen infrequently (Hillström et al., 2012; Nasisse et al., 1993; Volopich et al., 2005). IFA testing of samples collected by corneal or conjunctival scraping was one of the original methods used to detect FHV-1 in cats (Carlson & Scott, 1978). It is essential to collect samples for IFA testing before the instillation of fluorescein dye, as this will interfere with interpretation of the assay (da Silva Curiel et al., 1991). The principal limitations of the IFA test for FHV-1 diagnosis include lack of sensitivity (Nasisse et al., 1989b) and, like all other viral detection methods, the number of normal cats that are positive by this assay. In one study, the IFA test was positive in 50% of cats in which acute FHV-1 infection was suspected and 36% in which chronic FHV-1 infection was suspected; however, 28% of clinically normal cats were also IFA positive (Maggs et al.,

Table 28.5 Properties of and diagnostic considerations for four laboratory tests offered for diagnosis of feline herpesvirus in cats; none is ideal.

	Virus Isolation	Polymerase Chain Reaction	Immunofluorescent Antibody Assay	Serology
Detects	Virus	Viral DNA	Viral protein	Host response
Viable virus needed?	Yes	No	No	No
Vital stains alter result	Yes	?No	Yes	No
Transport	Complex	Simple	Simple	Simple

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1999b). Virus isolation has long been the gold standard for alphaherpesvirus diagnosis. Samples should be collected with dacron swabs with plastic handles, since cotton and alginate swabs, as well as wooden swab handles, can be inhibitory to some herpesviruses (Johnson & Johnson, New Brunswick, NJ, USA; Crane et al., 1980; Hanson & Schipper, 1976). Samples must also be collected before the application of fluorescein or rose Bengal (and likely lissamine green) stains, as vital stains can inhibit viral replication (Storey et al., 2002). Virus isolation is not routinely advocated for clinical specimens due to the logistic difficulty of transporting and processing samples in a timely fashion. As for other viral detection tests, the number of normal cats that shed FHV-1 render virus isolation not useful in the diagnosis of individual cats, although it remains a useful research and epidemiologic tool. FHV-1 can be detected in approximately 11% (Maggs et al., 1999b) to 24% (Stiles & Pogranichniy, 2008) of normal cats and only 0% (Stiles & Pogranichniy, 2008) to 18% (Maggs et al., 1999b) of cats showing clinical evidence of FHV-1-related disease. Likewise, serologic titers have not proven useful in the diagnosis of FHV-1 infection (Maggs et al., 1999b), principally because they cannot separate vaccinal titers from response to wild-type virus, and because titers tend to be of low magnitude (especially when measured by serum neutralization), even after primary infection. Interest in vaccinology has stimulated new investigations of the value of titers for predicting resistance to infection (Lappin et al., 2002; Scott & Geissinger, 1999). A large number and variety of PCR assays for the detection of FHV-1 have been described and these have produced a very wide range of data regarding FHV-1 detection in normal and abnormal eyes. With FHV-1 DNA detectable at the peripheral surfaces of up to 50% of normal cats, diagnostic testing of individual patients seems of little benefit (Townsend et al., 2004; Table 28.6).

Although quantitative PCR (qPCR) in experimentally infected animals suggested that there may be a critical concentration of viral DNA within host tissues, below which is likely to represent coincident or consequential virus and above which is more likely to represent causative virus (Vogtlin et al., 2002), this has not been borne out in spontaneously infected client-owned cats (Low et al., 2007).

Table 28.6 Reported polymerase chain reaction (PCR) detection rates for various tissue types, pathology, and sample types. Results are reported on a per eye or per sample basis, not per cat.

	PCR Detection Rates		
Tissue and Pathology	**Swab/brush**	**Scraping**	**Biopsy**
Normal cornea			6%,[1] 32%,[2] 46%,[3] 49%[4]
Normal conjunctiva	3%,[5] 6%,[6] 8%,[7] 20%,[8] 31%[9]		12%[3]
Sequestrum	27%[10]		18%,[3] 44%,[11] 55%[1]
Feline eosinophilic keratitis/conjunctivitis		55%,[12] 76%[1]	
Conjunctivitis	10%,[13] 14%,[9] 18%,[14] 24%,[6] 33%[8]		54%[3]
Diseased but not specified	18%,[15] 25%,[16] 33%,[17] 47%,[18] 58%,[19] 89%,[15] 91%[20]		

1. Nasisse et al. (1998).
2. Stiles & Pogranichniy (2008).
3. Stiles et al. (1997).
4. Townsend et al. (2004).
5. Low et al. (2007).
6. Fernandez et al. (2017).
7. Cullen et al. (2005a).
8. Rampazzo et al. (2003).
9. Burgesser et al. (1999).
10. Grahn et al. (2005).
11. Cullen et al. (2005b).
12. Déan & Meunier (2013).
13. Hillström et al. (2012).
14. Lim & Cullen (2005).
15. Hara et al. (1996).
16. Gerriets et al. (2012).
17. Polak et al. (2014).
18. Von Bomhard et al. (2003).
19. Schulz et al. (2015).
20. Burns et al. (2011).

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Treatment

Treatment of herpetic disease in cats inevitably involves the use of supportive care (e.g., topical antibiotics if secondary infection or corneal ulceration is present, artificial tears if lacrimal insufficiency exists, etc.), but may also require antiviral therapy. For a more complete review of antiviral drugs and their mode of action, refer to the antiviral drug section of Chapter 8, Part 2. Understanding the pathophysiologic mechanisms likely at play in each patient with herpetic disease is essential when tailoring treatment to individual patients. Central to this decision-making is the understanding that disease syndromes represent a "snapshot" of the current balance between the viral virulence and the host immune response, with an inadequate (or pharmacologically suppressed) immunologic response permitting viral replication, and viral replication sometimes producing antigens that inspire an exuberant (immunopathologic) host response (Fig. 28.34). In cytolytic disease, where cell rupture occurs as a direct result of viral replication and virus can often be cultured from diseased tissue, antiviral drugs are recommended and immunomodulatory therapy is generally contraindicated. In immunopathologic disease, where the host's reaction to viral antigens or altered autoantigens is believed to be the major cause of disease, virus is less reliably isolated (but can sometimes still be detected by PCR) and ulceration is less common. Here, antiviral drugs are typically ineffective when used alone, and concurrent immunomodulatory therapy is often required. However, if used without the "backdrop" of an antiviral agent, immunomodulatory therapy may encourage cytolytic disease. With metaherpetic disease, antiviral or immunomodulatory therapies alone or together are typically ineffective, and therapy specific to the anatomic and/or physiologic disruption is required.

Antiviral Therapy

There are currently no antiviral drugs developed for cats infected with FHV-1; all drugs used were developed for humans infected with other herpesviruses, principally HSV types 1 and 2. Experience shows that the metabolism and safety of these drugs in cats are not readily predicted from their behavior in humans, and that their efficacy against FHV-1 is not predicted from their efficacy against human herpesviruses. Therefore, careful *in vitro* investigation of efficacy against FHV-1, followed by safety and pharmacokinetic trials, subsequent placebo-controlled efficacy studies in experimental animals, and finally judicious clinical trials in client-owned animals should always precede widespread clinical use and anecdotal reporting.

Although opinions vary as to when and why antiviral therapy should be instituted in cats believed to be experiencing herpetic diseases, it appears reasonable that antiviral agents should be considered when signs are severe, persistent, or recurrent, particularly when there is corneal involvement,

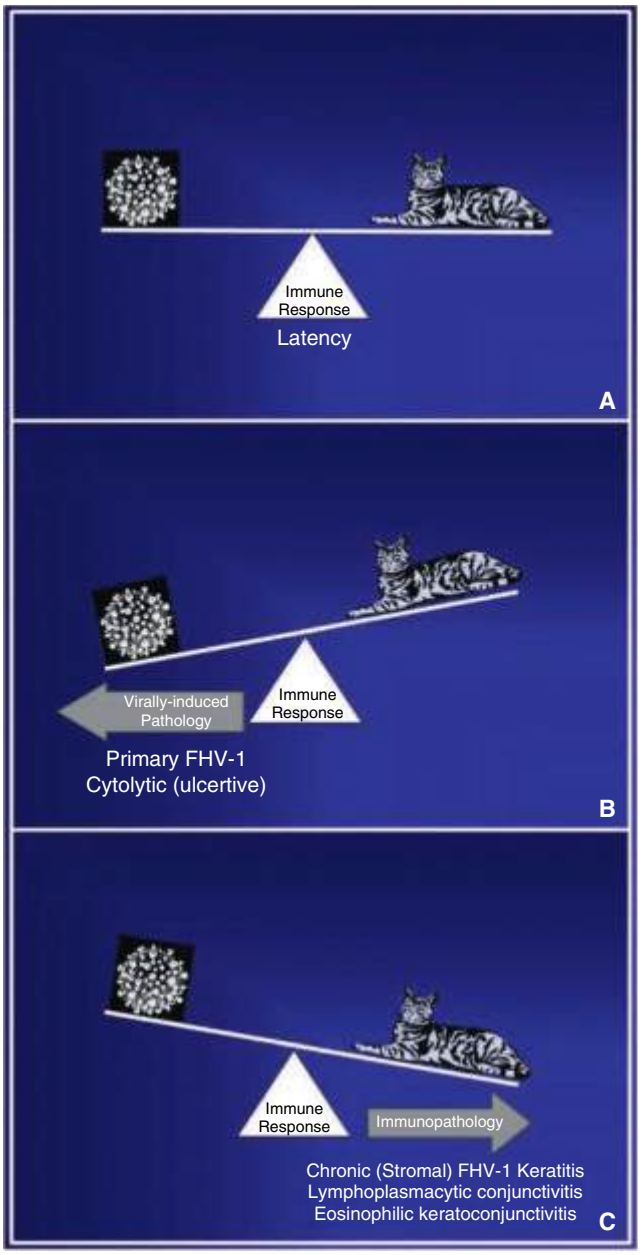


Figure 28.34 Herpetic seesaw. Central to decision-making regarding treatment for individual cats with herpetic disease is an understanding that disease syndromes represent a "snapshot" of the current balance between viral virulence and host immune response. **A**. Latency represents a state where virus and host are living in "harmony." **B**. Reduced immunity, as seen in young immunologically naïve kittens, stress, pharmacologic immunosuppression, and so on, will "tilt the balance" toward the virus and, if severe enough, promote productive (cytolytic) viral replication and tissue injury. Antiviral drugs may be indicated. Therapy with steroids is contraindicated. **C**. Viral replication sometimes produces antigens that recruit an exuberant (immunopathologic) host response. Therapy with corticosteroids may be indicated, but may reduce immunologic response sufficiently that cytolytic disease recurs (see B). Therefore, concurrent antiviral drugs are often recommended.

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and especially ulceration. Because epithelial replication, latency and reactivation, and persistence are such interdependent and sequential phases of herpetic disease, interruption of any one of them is expected to limit the virus's abilities to cause subsequent disease. Therefore, aggressive treatment of FHV-1-associated disease may limit disease progression and minimize frequency and severity of recurrences. This seems to be borne out by data that show a significant direct (positive) correlation between clinical score and viral DNA copy number 30 days after experimental infection, which suggests that the quantity of viral DNA that becomes latently established in the ganglia is related to the severity of the acute clinical infection (Townsend et al., 2013).

Some important general concepts about antiviral agents assist with prescribing and expectations of this class of drugs:

- Because herpesviruses reside intracellularly (and specifically within the host cell nucleus) and utilize host cellular machinery, antiviral agents tend to exhibit greater host toxicity than do antibacterial drugs. This limits many agents to topical application, and some are cytotoxic even when administered by that route.
- All antiviral agents to date are virostatic and therefore act only on replicating virus. As a result, they are more likely to induce viral resistance if under-dosed, must be dosed (orally or topically) very frequently, and are expected to have no effect against latent (nonreplicating) virus.
- No antiviral drug has proven antibacterial activity; concurrent antibacterial therapy should be considered on a case-by-case basis.
- Antiviral drugs should be administered at the appropriate dose until clinical remission is noted and then for an additional period determined by how challenging it was to gain remission. Like all other antimicrobial drugs, the dose of antiviral drugs should *never* be tapered, as this is a means by which the development of resistance is encouraged, especially with static drugs.

The effect of some antiviral drugs on FHV-1 replication *in vitro* has been studied and their potency relative to each other and relative to HSV-1 reported (Table 28.7). Antiviral efficacy is expressed as the IC_{50} (or the concentration at which viral replication is inhibited by 50%). Note, therefore, that a *lower* IC_{50} equates to a *more* efficacious antiviral drug.

The following antiviral agents have been studied to varying degrees for their efficacy against FHV-1, their pharmacokinetics in cats, and/or their safety and efficacy in treating cats infected with FHV-1.

Idoxuridine

Idoxuridine is a nonspecific inhibitor of DNA synthesis, affecting any process requiring thymidine. Host cells, therefore, are similarly affected, systemic therapy is not possible, and corneal toxicity can occur. It has been used as a 0.1% ophthalmic solution or 0.5% ophthalmic ointment. This drug is reasonably well tolerated by most cats and seems efficacious in many. No veterinary data regarding dose are available but, based on pharmacologic principles and data from humans, it likely should be applied to the affected eye at least 5–6 times daily. In a retrospective case series of cats with ocular disease attributed to FHV-1, 0.1% idoxuridine solution was used every 4–6 hours, with improvement or resolution of clinical signs in 3 cats and worsening or no improvement in 4 cats (Stiles, 1995).

Vidarabine

Vidarabine, like idoxuridine, is nonselective in its effect and so is associated with notable host toxicity – especially if administered systemically. Because it affects a viral replication step different from that targeted by idoxuridine, vidarabine may be effective in patients whose disease seems resistant to idoxuridine. As a 3% ophthalmic ointment, vidarabine may be better tolerated than many of the other topical antiviral preparations. Again, no veterinary data are available regarding dose, but it should probably be applied to the affected eye at least 5–6 times daily. In a retrospective case series of cats with ocular disease attributed to FHV-1, 3% vidarabine ointment was used every 4–6 hours, with improvement noted in 1 cat and worsening or no improvement noted in 2 cats (Stiles, 1995).

Trifluridine

Trifluridine is too toxic to be administered systemically, but topically administered trifluridine is considered one of the most effective drugs for treating HSV-1 keratitis. This is in part due to its superior corneal epithelial penetration (O'Brien & Edelhauser, 1977). This makes it the preferred topical agent for stromal keratitis (although the systemic agent famciclovir may be even more effective). *In vitro*, trifluridine is also one of the more potent antiviral drugs for FHV-1. A 1% ophthalmic solution is used in human herpetic keratitis at least 5–6 times daily. Unfortunately, it often causes marked ocular irritation in cats. In a retrospective case series of cats with ocular disease attributed to FHV-1, 1% trifluridine solution was used every 4–8 hours, with improvement in 1 cat and worsening or no improvement in 2 cats (Stiles, 1995).

Cidofovir

Cidofovir is available for intravenous or intravitreal injections in humans infected with herpesviruses, principally cytomegalovirus. However, this drug has also been dissolved in artificial tears to form a 0.5% or 1.0% solution and applied topically in experimental animal models of human herpetic keratoconjunctivitis, where it was equally effective when administered only twice daily as trifluridine was when administered 4–9 times daily (Kaufman et al., 1998;

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Table 28.7 Efficacy of various antiviral drugs against feline herpesvirus (FHV-1) and the human virus for which they were developed, herpes simplex virus (HSV-1). Efficacy is reported as median (range) concentration (μM) at which *in vitro* viral replication is inhibited by 50% (IC_{50}), therefore a *lower* IC_{50} equates to *greater* efficacy. Drugs are ranked (left to right) in order of decreasing efficacy against FHV-1. Note the different ranking for HSV-1.

	IC_{50} (μM)												
	HPMPA[1,2]	**IDU**[3–5]	**GCV**[5–7]	**PCV**[1,5,8–11]	**PMEDAP**[6,12]	**BDVU**[1, 4,13]	**TFU**[1,4,14,15]	**CDV**[5,6,9,11,16,17]	**VDB**[4,15]	**ADV**[6,18]	**ACV**[1,5,6,9,11,13,14,19]	**PFA**[5,6,13]	**RGV**[20,21]
FHV-1	0.23	5.6 (4.3–6.8)	8.9 (5.2–13)	14 (1.2–130)	14	18 (5.1–30.1)	19 (0.67–1350)	19 (7.9–168)	21	73	150 (16–11 x 10^4)	187 (140–230)	216
HSV-1	22	2.1	0.39	1.5	6.9	0. 3	0.5	19	30	21	0.8	68	68

ACV, acyclovir; ADV, adefovir; BDVU, bromovinyldeoxyuridine; CDV, cidofovir; GCV, ganciclovir; HPMPA, (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl) adenine; IDU, idoxuridine; PCV, penciclovir; PFA, foscarnet; PMEDAP, 9-(2-phosphonylmethoxyethyl)-2, 6-diaminopurine; RGV, raltegravir; TFU, trifluridine; VDB, vidarabine.

1. Williams et al. (2004).
2. Andrei et al. (1992).
3. Babiuk et al. (1975).
4. Nasisse et al. 1989a).
5. Maggs & Clarke (2004).
6. van der Meulen et al. 2006a).
7. Chen et al. (1989).
8. Lauter et al. (1976).
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10. Groth et al. (2014).
11. Hussein & Field (2008).
12. De Clercq et al. (1987).
13. Gadler et al. (1984).
14. Williams et al. (2005).
15. Ayisi et al. (1985).
16. Sandmeyer et al. (2005a).
17. Bronson et al. (1989).
18. Bestman-Smith & Boivin (2002).
19. Collins (1983).
20. Pennington et al. (2016).
21. Zhou et al. (2014).

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Romanowski et al., 1999). This is believed to be due to the long tissue half-lives of the metabolites of cidofovir (Neyts et al., 1991). The efficacy of a 0.5% solution compounded in methylcellulose artificial tears and applied topically twice daily to cats experimentally infected with FHV-1 was associated with reduced viral shedding and clinical disease in a prospective, masked placebo-controlled study (Fontenelle et al., 2008b). However, there are occasional reports of its experimental topical use in humans being associated with stenosis of the nasolacrimal drainage system components (Gordon et al., 1994; Sherman et al., 2002), and it is not commercially available as a topical ophthalmic agent in humans. Therefore, although the *in vitro* and short-term *in vivo* efficacy of cidofovir against FHV-1 are proven, cats should be monitored for nasolacrimal cicatrization. Unlike most compounded agents, there are also data on the efficacy of cidofovir over time and under various storage conditions. Cidofovir 0.5% compounded in normal saline (not methylcellulose as was studied *in vivo*) retained efficacy under all combinations of storage conditions tested: in plastic or glass; refrigerated (4 °C), or frozen at –20 °C or –80 °C; and for 1, 2, 4, or 6 months; however, changes in drug properties likely to be related to safety of clinical use after storage were not studied (Stiles et al., 2010).

Acyclovir

Acyclovir is the prototype of a group of antiviral drugs known as acyclic nucleoside analogues. Members of this group all require three phosphorylation steps for activation, the first of which must be catalyzed by a viral enzyme, thymidine kinase. This increases their safety and permits them to be systemically administered to humans. Unfortunately, the activity of the FHV-1 thymidine kinase enzyme on acyclovir is much less than that of the HSV-1-encoded enzyme, which likely explains the relative lack of efficacy of acyclovir against FHV-1 (Hussein et al., 2008a, 2008b). In addition to relatively low antiviral potency against FHV-1, acyclovir has poor bioavailability and is potentially toxic when systemically administered to cats. Oral administration of 50 mg/kg acyclovir to cats was associated with peak plasma levels of only 33 µM, approximately one-third the IC_{50} for this virus (Owens et al., 1996). Common signs of toxicity are referable to bone marrow suppression. With the advent of the apparently safer and more effective famciclovir, systemic administration of acyclovir seems difficult to justify. However, acyclovir is available in some countries as an ophthalmic ointment, which reduces systemic toxicity concerns but not necessarily questions of antiviral efficacy against FHV-1. Regardless, a 0.5% ointment used 5 times daily in naturally infected cats was associated with a median time to resolution of clinical signs of 10 days (Williams et al., 2005). Importantly, cats treated only 3 times daily took approximately twice as long to resolve and did so only once therapy was increased to 5 times daily. These data reinforce the general premise that antiviral agents must be given at the appropriate dose and dose frequency because they are virostatic.

Valacyclovir

Valacyclovir is a prodrug of acyclovir that is – in humans and cats – more efficiently absorbed from the gastrointestinal tract than is acyclovir and, following absorption, is converted to acyclovir by a hepatic hydrolase (de Miranda & Burnette, 1994). As a result, plasma concentrations of acyclovir that surpass the IC_{50} for FHV-1 can be achieved after oral administration of this drug. However, in cats experimentally infected with FHV-1, valacyclovir induced fatal hepatic and renal necrosis, along with bone marrow suppression, and did not reduce viral shedding or clinical disease severity (Nasisse et al., 1997). Therefore, despite its superior pharmacokinetics, valacyclovir should never be administered to cats. This serves as a very poignant reminder of how toxic acyclovir is in cats if a sufficiently high plasma concentration is achieved.

Ganciclovir

Ganciclovir is another acyclic nucleoside analogue available for oral or intravenous administration in humans, where it is associated with more severe neurologic toxicity, neutropenia, and bacterial infections than is acyclovir (Burns et al., 2002; Ernst & Franey, 1998). Like acyclovir, a prodrug of ganciclovir (valganciclovir) is available. The safety and pharmacokinetics of ganciclovir or valganciclovir have not yet been studied in cats. A 0.15% ophthalmic gel is available for humans, and there are anecdotal reports of good efficacy and tolerability in cats infected with FHV-1.

Famciclovir

Famciclovir is a highly bioavailable prodrug of penciclovir (Fig. 28.35). Penciclovir is effective against FHV-1 *in vitro*. In humans metabolism of famciclovir to penciclovir is complex, requiring di-deacetylation to BRL42359 in the blood, liver, or small intestine, with subsequent oxidation to penciclovir by aldehyde oxidase in the liver (Clarke et al., 1995; Filer et al., 1994; Vere Hodge et al., 1989). Neither famciclovir nor BRL42359 has any *in vitro* antiviral activity against FHV-1 (Groth et al., 2014), therefore complete metabolism to penciclovir is required. However, hepatic aldehyde oxidase activity in cats is about 2% of that seen in humans and is lower than in any other species reported to date (Dick et al., 2005). Famciclovir pharmacokinetics in the cat are extremely complex and nonlinear (i.e., doubling of famciclovir dose does not lead to doubling of plasma penciclovir concentration), presumably due to saturation of the hepatic oxidase (Sebbag et al., 2016b). As a result, very high plasma concentrations of BRL42359 accumulate in the cat (Sebbag et al., 2016b). Fortunately, this compound demonstrates very little cytotoxicity *in vitro* (Groth et al., 2014). Although there is a growing body of literature describing the pharmacoki-

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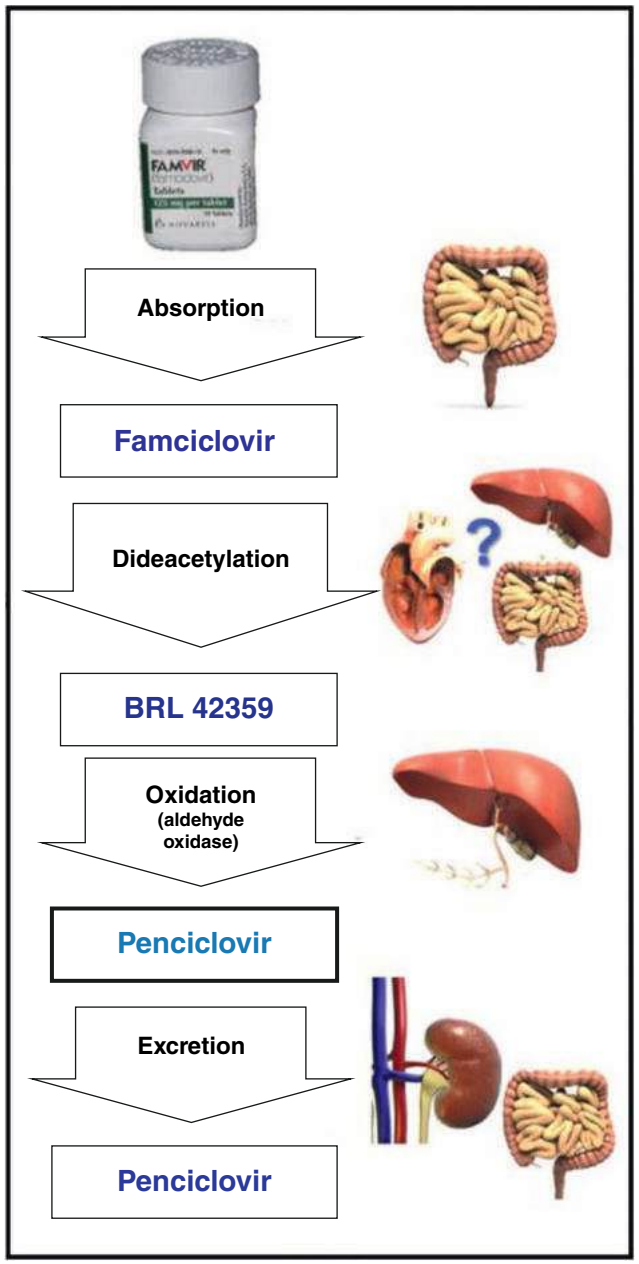


Figure 28.35 The absorption, metabolism, and excretion pathway of famciclovir in humans. Following oral administration, famciclovir is absorbed across the intestine and undergoes di-deacetylation. The exact site at which this step occurs is unclear, but may be in the enterocytes, bloodstream, or liver. The inactive metabolite BRL42359 is then oxidized by a hepatic aldehyde oxidase to the active antiviral compound penciclovir, which is ultimately excreted in feces and urine. Based upon famciclovir, BRL42359, and penciclovir concentrations in feline plasma following oral administration of famciclovir, similar steps likely occur in cats. (Anatomic images courtesy of www.MedicalGraphics.de (license # CC BY-ND 3.0 DE). Reproduced with permission from Thomasy, S.M. & Maggs, D.J. (2016) A review of antiviral drugs and other compounds with activity against feline herpesvirus type 1. *Veterinary Ophthalmology*, **19**(Suppl. 1), 119–130, Fig. 1.)

netics and pharmacodynamics of famciclovir and penciclovir in cats, recommendation of an appropriate famciclovir dose requires knowledge of a number of factors that are still not well characterized for famciclovir/penciclovir in cats, or, in some cases, for antiviral drugs in general in any species. These include:

- Knowledge of whether penciclovir concentrations in plasma, tears, or the infected tissues themselves are most relevant.
- Selection of an appropriate target penciclovir concentration based on *in vitro* IC_{50}s (which range from 304 to 3500 ng/mL; Groth et al., 2014; Hussein & Field, 2008; Maggs & Clarke, 2004; Williams et al., 2004).
- Knowledge of whether the targeted IC_{50} should be exceeded by the trough or the peak penciclovir concentrations, and for how long.

Together, these uncertainties have led to much controversy about the optimum famciclovir dose in cats, with reported doses ranging from 8 mg/kg once daily (Malik et al., 2009) to 140 mg/kg thrice daily (Thomasy et al., 2016). However, the following data should be used to inform dose selection.

In the only masked, placebo-controlled efficacy trial to date, cats known to be infected with FHV-1 and given approximately 90 mg famciclovir per kg thrice daily orally achieved an approximate peak plasma penciclovir concentration of 2100 ng/mL (Thomasy et al., 2011). Relative to control cats, treated cats had significantly reduced clinical signs, decreased serum globulin concentrations, reduced histologic evidence of conjunctivitis, decreased viral shedding, and reduced serum FHV-1 titers, as well as increased goblet cell density (Thomasy et al., 2011). A subsequent study showed that administration of a single dose of 40 mg/kg to uninfected healthy cats achieved nearly identical plasma penciclovir concentrations to those achieved with a single dose of 90 mg/kg (Thomasy et al., 2012b). A third study (Thomasy et al., 2012a) revealed that cats receiving 40 mg/kg thrice daily had tear penciclovir concentrations likely to be effective against FHV-1 (using a target IC_{50} of 304 ng/mL; Hussein et al., 2008a) for at least 3 hours after each dose (i.e., for ≥ 9 hours/day). In the most comprehensive pharmacokinetic study to date, healthy cats were administered famciclovir at 30, 40, or 90 mg/kg twice or thrice daily, and plasma and tear famciclovir, BRL42359, and penciclovir concentrations were measured (Sebbag et al., 2016b). This resulted in the recommendation that cats should receive 90 mg famciclovir per kg twice daily, because this regimen achieved comparable plasma and tear penciclovir concentrations to those achieved with 90 mg/kg thrice daily, whereas the lower doses tested did not result in adequate tear penciclovir concentrations, even when administered thrice daily.

Perhaps most revealing so far are data from a retrospective study comparing outcomes when famciclovir was

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administered to client-owned cats with spontaneously arising disease presumed to be herpetic. Cats received famciclovir at approximately 40 (33 cats) or 90 mg/kg (26 cats) thrice daily (Thomasy et al., 2016). Median duration of therapy required for clinical improvement was significantly longer in cats administered 40 versus 90 mg/kg. Furthermore, cats in the 90 mg/kg group showed significantly greater and faster improvement than cats in the 40 mg/kg group. The reduction in treatment duration with the higher famciclovir dose was estimated to decrease overall client costs due to a reduction in total famciclovir administered and potentially the number of recheck examinations required. These data suggest that 90 mg/kg three times a day is clinically and cost effective. Meanwhile, pharmacokinetic data (Sebbag et al., 2016b) suggest that tear and plasma penciclovir concentrations are similar whether cats receive 90 mg/kg famciclovir 2 or 3 times daily. When assessed in tandem, data from these two studies (Sebbag et al. 2016b; Thomasy et al., 2016) suggest that 90 mg famciclovir per kg twice daily is likely to be effective in treating cats with herpetic disease. Adverse events (most commonly gastrointestinal) potentially attributable to famciclovir were reported in 17% of cats receiving 40 or 90 mg famciclovir per kg thrice daily, but the prevalence was not different between the two dose groups and the signs were generally mild and transient or reversible upon discontinuation of the drug (Thomasy et al., 2016). Assessing all *in vivo* tolerance data for famciclovir, this drug appears to be markedly safer than acyclovir (Owens et al., 1996) or valacyclovir (Nasisse et al., 1997), the only other systemic antiviral drugs to be orally administered to cats (Malik et al., 2009; Nasisse et al., 1997; Owens et al., 1996; Sebbag et al., 2016b; Thomasy et al., 2007, 2011, 2012a, 2012b, 2016). However, patients administered famciclovir should be closely monitored, and assessment of a complete blood count, serum biochemistry panel, and urinalysis should be considered in cats with known concurrent disease or cats expected to receive famciclovir for long periods. As in humans (Boike et al., 1994), reduction in dose frequency should be considered in cats with renal insufficiency. Like all antiviral drugs, famciclovir should be administered at the appropriate dose until clinical remission is noted, and then for an additional period determined by how challenging it was to gain disease control. Like all other antimicrobial drugs, the famciclovir dose should *never* be tapered, as this is a means by which the development of resistance is encouraged, especially because this is a virostatic drug. Given that when given at appropriate doses, famciclovir achieves antiviral concentrations of penciclovir in the tears (Sebbag et al., 2016b), topical application of an ophthalmic antiviral drug concurrent with famciclovir at 90 mg/kg orally twice daily appears unnecessary. However, because famciclovir does not appear to fully protect or permit regeneration of conjunctival goblet cells (Lim et al., 2009; Thomasy et al., 2011), concurrent topical administration of a hyaluronate-containing artificial tear preparation is recommended (Cullen et al., 1999). Data to date reveal that prophylactic administration of famciclovir to cats in shelters is not useful and cannot be recommended (Cooper et al., 2018; Litster et al., 2015a).

Lysine Therapy

Much has been written regarding L-lysine and its putative efficacy against FHV-1 in cats. As with the antiviral drugs, initial interest arose from *in vitro* data and clinical trials in humans. Lysine's antiviral effect is believed to arise because arginine is an essential amino acid for FHV-1 (Maggs et al., 2000) and HSV-1 (Griffith et al., 1981; Tankersley, 1964) replication, and assumes that lysine antagonizes arginine availability to or utilization by these viruses during protein synthesis. This was hypothesized to affect protein synthesis of the virus more than the host because viral proteins had a higher arginine-to-lysine content than did human (and feline) proteins (Kaplan et al., 1970). But recent analysis suggests that the difference in the amino acid content of feline herpesviral and cat proteins is minimal (Bol & Bunnik, 2015). This may explain why *in vitro* replication of HSV-1 (Griffith et al., 1981; Tankersley, 1964) and FHV-1 (Maggs et al., 2000) is notably suppressed in the presence of markedly elevated lysine concentrations in combination with exceptionally low arginine concentrations, but this is not borne out with more physiologic amino acid concentrations (Cave et al., 2014). *In vivo* data in cats are also contradictory. Stiles et al. (2003) demonstrated the safety and efficacy of oral administration of lysine to cats prior to primary exposure to FHV-1. Cats receiving 500 mg L-lysine every 12 hours orally, beginning 6 hours prior to experimental inoculation with FHV-1, exhibited less severe conjunctivitis than did cats receiving placebo. However, viral shedding, as determined by virus isolation, did not differ between groups. Subsequently, Maggs et al. (2003) demonstrated that oral lysine supplementation helps to prevent viral reactivation and/or shedding in latently infected cats. Despite significant elevations in plasma lysine concentration, no change in plasma arginine concentration or any ill effect attributable to lysine administration was observed in either study, other than perhaps some mild and reversible gastrointestinal disturbance in Stiles's study. There is also one study in which bolus administration of lysine was tested in 144 naturally infected shelter-housed cats (Rees & Lubinski, 2008). Cats received oral boluses of 250 mg (kittens) or 500 mg (adult cats) of lysine once daily for the duration of their stay at the shelter and outcomes were compared with those of an untreated control group. A significant treatment effect was not shown for the incidence of infectious upper respiratory disease (IURD), the need for antimicrobial treatment for IURD, or the interval from admission to onset of IURD. However, it was not determined whether and to what extent these cats were shedding or infected with FHV-1 (or other pathogens).

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The safety and efficacy of incorporating lysine into cat food have also been assessed. Results of an initial safety trial were encouraging (Fascetti et al., 2004). Cats fed a diet supplemented with up to 8.6% (dry matter) lysine showed no signs of toxicity, had normal plasma arginine concentrations, and had normal food intake. Mean plasma lysine concentration of these cats was increased to levels similar to that achieved with bolus administration. In a subsequent study (Maggs et al., 2007), 25 cats with enzootic upper respiratory tract disease were fed a diet supplemented to 5.1% lysine, while 25 cats remained on a basal ration (~1% lysine). The study was conducted for 52 days, at the beginning of which cats were subjected to rehousing stress (which is known to cause viral reactivation). Ironically, food (and therefore lysine) intake decreased coincident with peak disease and viral presence. As a result, cats did not receive lysine at the very time they needed it most. Perhaps partly because of this, disease in cats fed the supplemented ration was *more* severe than that in cats fed the basal diet. In addition, viral shedding was *more* frequent in cats receiving the supplemented diet. To further assess these unexpected outcomes, a similarly designed experiment (Drazenovich et al., 2009) was performed in a local humane shelter with a more consistent "background" level of stress and with greater numbers enrolled compared to the initial rehousing study (Maggs et al., 2007). In all, 261 cats were enrolled, each for 4 weeks. Despite plasma lysine concentration in treated cats being greater than that in control cats, again *more* treated cats than control cats developed moderate to severe disease and shed FHV-1 DNA at certain points throughout the study (Drazenovich et al., 2009).

In summary, there is considerable variability among these studies, especially with respect to methodology, study population, and dose and method of lysine administration. However, taken together, data from these studies suggest that lysine is safe when orally administered to cats and, provided that it is administered as a bolus, may reduce viral shedding in latently infected cats and clinical signs in cats undergoing primary exposure to the virus. If lysine is administered to cats, owners should not be advised to restrict their cat's arginine intake, as is done in humans. Feeding a single arginine-deficient meal to a cat can induce fatal encephalopathy (Morris & Rogers, 1978).

The Interferons

The IFNs are a group of cytokines that have diverse immunologic and antiviral functions. The IFNs are divided into four groups – α, β, γ, and ω IFNs – and numerous subtypes. Viral infection stimulates cells to secrete IFN into the extracellular space, where it binds to specific receptors on neighboring cells and, through mechanisms not fully understood, prevents or limits the spread of infection (i.e., it is not virucidal). Knowledge and consideration of this mode of action allow the clinician to set and maintain reasonable expectations of how effectively the IFNs may work when used therapeutically, and in which patients with which stage of disease they might be expected to be most effective. Although IFNs may play important *physiologic* roles in the control of viral infections, *in vitro* and clinical trials investigating potential *therapeutic* applications have produced conflicting and not strongly supportive results (Sandmeyer et al., 2005b; Siebeck et al., 2006; Weiss, 1989). Similarly, the few peer-reviewed *in vivo* studies do not lend strong support to use of these drugs (Cocker et al., 1987; Haid et al., 2007; Nasisse et al., 1996). In perhaps the most comprehensive prospective, randomized, placebo-controlled, double-masked clinical trial (Ballin et al., 2014), 37 cats were randomly assigned to receive placebo or recombinant feline IFNω (2.5 MU/kg) subcutaneously, followed by 0.5 MU topically at 8 hr intervals via the conjunctiva, intranasally, and orally for 21 days. All cats received additional treatment with antibiotics, expectorants, and inhalation of nebulized physiologic saline with chamomile. Clinical signs were evaluated over 42 days. All cats demonstrated improvement in clinical signs during the course of the study, with no significant difference in any of the assessed variables when comparing the two groups. Given the lack of rigorous supporting data to date, further research is necessary before use of this group of compounds can be recommended, especially in the more chronic or recrudescent clinical syndromes in those client-owned cats commonly seen by ophthalmologists.

Mycoplasma-Associated Ulcerative Keratitis

One report described seven cats with extensive corneal ulceration characterized by stromal loss, cellular infiltration, and keratomalacia (Gray et al., 2005). Either *Mycoplasma felis* (n=6) or *M. gateae* (n=1) was cultured and confirmed by 16S rRNA gene sequencing in all cases. An opportunistic role was again suspected, since all patients had either a history of corneal disease and/or prior treatment with corticosteroids. But the unique presentation, coupled with resolution of the corneal disease only after treatment with *Mycoplasma*-specific antimicrobial agents, suggests that *M. felis* and *M. gateae* could be clinically relevant corneal pathogens in certain circumstances.

Symblepharon

Adhesion of the palpebral, bulbar and/or third eyelid conjunctiva to itself or to the cornea is termed symblepharon. The epithelial ulceration that predisposes to the adhesions is most often a consequence of neonatal herpetic keratoconjunctivitis, but symblepharon could follow any severe conjunctivitis that effaces the epithelial surface, including chemical or thermal burns. Clinical signs are determined by the severity and location of the symblepharon and range from subtle alterations in depth of the conjunctival

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cul-de-sac to blinding corneal opacification. Common signs include a reduced palpebral fissure, a prominent third eyelid, and epiphora due to nasolacrimal punctal occlusion (Fig. 28.36). Changes in corneal clarity may be focal or diffuse, faintly hazy to fully opaque. The junction of cornea and sclera is less distinct. The conjunctival vessels that overlie the corneal surface may be misinterpreted as a refractory keratitis, since conventional therapy will not alter these permanently transposed vessels. Symblepharon is not painful, once the causative inflammation resolves.

Symblepharon is easier to prevent than to treat. Early recognition and appropriate treatment of neonatal conjunctivitis are essential. In cases of acute conjunctival damage, the raw surfaces must be separated until re-epithelialization occurs. Soft contact lenses and methylmethacrylate conformers have been used for that purpose following chemical injury in people (Kaufman & Thomas, 1979). Otherwise the opposing tissues must be pried apart, sometimes several times daily, using a sterile cotton swab or forceps inserted between the topically anesthetized layers. A topical antibacterial ointment directed against the cat's common conjunctival pathogens should be generously applied to coat the ulcerated tissue and further discourage adhesions. Surgical treatment of chronic symblepharon is usually reserved for patients with impaired vision or altered eyelid function (Gelatt & Brooks, 2011), since the success of surgery is often dismal. Reformation of corneal adhesions is common, a complication attributed to altered limbal stem cells that impact corneal epithelialization. Amniotic membrane has been sutured to the cornea following dissection of sym-



Figure 28.36 A common sequela of neonatal feline herpesvirus-1 infection, symblepharon can restrict eyelid mobility, obliterate the conjunctival cul-de-sac, limit tear drainage, and impact corneal clarity and vision. **A**. This young Maine Coon illustrates a reduced palpebral fissure and gross corneal opacity in the left eye. **B**. The temporal limbus is obscured in a young Domestic Shorthair, with an accompanying inclusion cyst and focal sequestrum. **C**. Diffuse corneal adhesions hide intraocular detail in a 4-month-old Domestic Shorthair.

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blepharon, effectively reducing readhesion in one cat (Barros et al., 2005). A 1-year-old cat with a pseudopterygium-like annular veil of conjunctival tissue over healthy, unaffected cornea was successfully treated by surgical inversion and transpalpebral fixation of the conjunctival tissue to reform the fornices (Allbaugh et al., 2017).

Eosinophilic Keratitis/Proliferative Keratoconjunctivitis

Eosinophilic keratitis is a gradually progressive, infiltrative disease that derives its name from the eosinophils found in cytologic and histopathologic samples of the affected cornea and adjacent conjunctiva (Fig. 28.37). The disorder was first described in 1978, in three separate case reports presented at the Midwest Veterinary Ophthalmology meeting in Columbus, Ohio, USA (Brightman et al., 1979; Prasse & Winston, 1996). Subsequent accounts describing similar clinical features but varying cellular characteristics suggest that more than one type of proliferative keratoconjunctivitis may exist (Nasisse, 1991).

The age of affected cats ranges from 7 months (Morgan et al., 1996) to 17 years (Stiles & Coster, 2016), with a trend toward young adult males of ≤ 4–6 years of age. The DSH and DLH breeds predominate, but the disease has also been reported in the Persian, Siamese, Himalayan, Turkish Angora, Maine Coon, and Russian Blue breeds.

The disorder is more often unilateral than bilateral, affecting only one eye approximately 75% of the time (Dean & Meunier, 2013; Morgan et al., 1996). The classic lesion appears commonly in the dorsolateral cornea, but any and all corneal quadrants may be affected. In a retrospective series of 15 cats, the predominant lesion occurred laterally (n=5), medially (n=4), dorsally (n=4), ventrally (n=1), or centrally (n=1; Paulsen et al., 1987). Pinpoint cream-colored nodules in the perilimbal conjunctiva and subtle superficial vascularization in the adjacent cornea may be overlooked at the onset. As the infiltrative process progresses, an irregular pink to flesh-colored vascularized corneal mass develops, bordered by a zone of corneal edema. Perhaps the most distinguishing feature of eosinophilic keratitis are the raised, variably sized, friable white plaques that develop atop the corneal infiltrate and adjacent bulbar conjunctiva, described as cheesy or cottage cheese like (Bedford & Cotchin, 1983; Collins et al., 1986). These plaques are the product of sloughing corneal excrescences that contain necrotic acellular material and eosinophils (Prasse & Winston, 1996). Retrospective studies describe corneal ulceration in 13% (Paulsen et al., 1987), 24% (Morgan et al., 1996), and 28.6% of patients (Spiess et al., 2009). In comparison, corneal ulceration was a more prevalent feature in a series of 45 cats, with an ulcer either preceding or present at the time of diagnosis in 66.7% of patients (Dean & Meunier, 2013). When present, epithelial defects are usually located at the leading edge of the infiltrative lesion, but punctate areas of fluorescein retention also occur over the surface plaques, corresponding to the excrescences of eosinophils and amorphous eosinophilic material noted above (Prasse & Winston, 1996). Blepharospasm, ocular discharge, and conjunctival hyperemia are variable, usually intensifying over time. The nictitating membrane may appear thickened. As a general rule, systemic evidence of eosinophilic disease is rare, although circulating eosinophilia, allergic bronchitis, and eosinophilic enteritis have occurred (Morgan et al., 1996). Concurrent dermatologic lesions of feline eosinophilic granuloma complex have never been reported.

Diagnosis of eosinophilic keratitis is confirmed by cytologic examination of superficial corneal scrapings. Smears often contain epithelial cells, eosinophils, mast cells, neutrophils, and lymphocytes, along with nuclear debris and eosinophilic granules from disrupted cells (Prasse & Winston, 1996). Eosinophils may not be the predominant cell type (Dubielzig et al., 2010), but a single eosinophil is considered diagnostic (Spiess et al., 2009). Histologically both epithelial



Figure 28.37 Eosinophilic keratitis. **A**. Raised white plaques and vascularization in the temporal cornea of a 2-year-old Domestic Shorthair. **B**. Distinctive temporal plaque formation with mild vascularization in a 6-year-old Domestic Shorthair. **C**. Generalized stromal infiltration with widespread yet indistinct surface plaques and prominent vascularization in a 2-year-old Domestic Shorthair.

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thinning and hyperplasia are seen, with mast cells and fewer eosinophils found between epithelial cells. Superficial corneal excrescences containing eosinophils and varying amounts of amorphous eosinophilic material and granules often lack epithelium, corresponding to the focal areas of fluorescein retention within the corneal lesion. Plasma cells are numerous within the corneal stroma beneath these excrescences. Inflammatory cells may extend into deep stroma, with numerous eosinophils, plasma cells, and mast cells, but infrequent lymphocytes, neutrophils, and macrophages. Lymphocytes may form nodular aggregates in rare instances (Prasse & Winston, 1996). Two reports of proliferative keratitis described an amorphous eosinophilic material between and beneath epithelial cells, but only small lymphocytes, histiocytes, plasma cells, and a few mast cells in the surrounding superficial stroma (Bedford & Cotchin, 1983; Pentlarge & Riis, 1984). Differential diagnoses for eosinophilic/proliferative keratoconjunctivitis include fungal keratitis, neoplasia, foreign body granuloma, endogenous or exogenous corneal trauma with second intention healing (O'Connell et al., 2017; Paulsen et al., 1987), or a lepromatous granuloma (Lamagna et al., 2009).

The etiopathogenesis of eosinophilic keratoconjunctivitis is unknown, although there is a suspected association with FHV-1 infection based on positive IFA or PCR assays in 33.3% (Morgan et al., 1996), 54.5% (Dean & Meunier, 2013), and 76.3% of affected cats (Nasisse et al., 1998). The presence of eosinophils in cytologic specimens of cats with conjunctival and corneal lesions also correlates highly with detection of FHV-1 DNA (Volopich et al., 2005). Physical disruption of the epithelium does not appear to be a critical step in eosinophilic keratitis; neither prior nor active corneal ulceration was universally present in the FHV-positive cats of these reports. Aqueous tear production is normal (Hodges, 2005; Morgan et al., 1996). Two disease mechanisms have been proposed for eosinophilic keratoconjunctivitis based on the cell types within the lesion: a Type I hypersensitivity reaction mediated by IgE, with mast cell and eosinophil degranulation resulting in chronic tissue injury; or a Type IV delayed hypersensitivity reaction mediated by sensitized T-lymphocytes and interleukins that also drives eosinophil-related corneal injury (Prasse & Winston, 1996). If the presence of FHV-1 DNA in corneal scrapings substantiates its role in eosinophilic keratoconjunctivitis, then direct cytolysis may contribute to corneal damage. The toxic effect of eosinophil granule protein deposition on epithelial cell viability and migration may also play a role in corneal ulceration, as seen in human atopic keratoconjunctivitis (Messmer et al., 2002; Stiles & Coster, 2016).

Eosinophilic keratoconjunctivitis is more likely controllable rather than curable, based on a 65.5% recurrence rate once treatment is discontinued (Morgan et al., 1996). Time to recurrence in that study ranged from 1 to 60 months, with a mean of 9.8 months. Others have reported recurrences at 5 weeks (Bedford & Cotchin, 1983), 3 months (Brightman et al., 1979), 12 months (Pentlarge & Riis, 1984), and 15 months (Paulsen et al., 1987).

Local immunosuppression remains the mainstay of treatment. Traditionally topical corticosteroids such as 1% prednisolone acetate or 0.1% dexamethasone are applied every 6–12 hours in a gradually tapering regimen, dictated by clinical response. Treatment is recommended for several weeks beyond resolution of clinical signs. A low-frequency maintenance regimen may be required, for instance application 3 times weekly, should clinical signs relapse following cessation of therapy. Only 3 of 31 cats treated with topical corticosteroids alone failed to improve in the long term (Morgan et al., 1996). Improvement is also reported with subconjunctival triamcinolone (4 mg) and unspecified oral corticosteroid administration (Brightman et al., 1979; Morgan et al., 1996). In cats with a history of corneal ulceration, documented FHV-1 infection, or concurrent ulceration, topical or systemic antiviral therapy is a prudent addition to any immunosuppressive regimen (Lim & Maggs, 2012). Some advocate initiating treatment with antiviral medication alone, adding steroids or other immunomodulators only if clinical signs fail to improve (Ofri, 2013).

Other immunomodulatory or anti-inflammatory drugs have also been used to manage eosinophilic keratoconjunctivitis. Read et al. (1995) reported improvement in 5 cats treated with topical cyclosporine, either with 0.2% ointment (n=1) or 1% corn oil-based cyclosporine solution (n=4). Topical application of 1.5% corn oil-based cyclosporine A solution every 8–12 hours reduced clinical signs in 31 (88.6%) of 35 cats, but only 19 of these cats were treated with cyclosporine alone. The 4 cats that failed to respond to topical cyclosporine alone subsequently improved with either topical dexamethasone, oral famciclovir, or oral megestrol acetate (Spiess et al., 2009). Marginal blepharitis developed during treatment in 2 (5.7%) of 35 cats, most likely a reaction to the drug vehicle rather than the active ingredient. Cyclosporine may be better suited for long-term maintenance once the keratoconjunctivitis has been initially controlled with steroids (Barnett & Crispin, 1998; Sanchez, 2014). There are no published reports documenting the response of eosinophilic keratoconjunctivitis to topical tacrolimus. One cat treated with an unspecified topical nonsteroidal anti-inflammatory drug (NSAID) failed to improve (Morgan et al., 1996).

Early reports of eosinophilic keratitis relied almost exclusively on oral megestrol acetate to control clinical signs (Bedford & Cotchin, 1983; Brightman et al., 1979; Kipnis, 1979; Paulsen et al., 1987). This oral progestogen should be used with caution, since its glucocorticoid activity at high or prolonged doses can cause adrenocortical suppression (Chastain et al., 1981; Middleton et al., 1987) and impaired glucose metabolism leading to diabetes mellitus (Mansfield et al., 1986; Middleton & Watson, 1985). Male cats appear to

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have a higher risk of developing diabetes compared to females (McCann et al., 2007). These endocrine effects may be reversible, since glucose and cortisol levels returned to baseline 3 months after discontinuing therapy in cats treated with 5 mg megestrol acetate daily for 2 weeks, then 5 mg three times weekly for 1 year (Peterson, 1987). Other adverse effects include increased appetite, weight gain, temperament changes, cutaneous xanthomatosis, mammary hyperplasia, mammary neoplasia, and pyometra (Romagnoli, 2015). Single case reports of ocular effects describe diabetic retinopathy (Herrtage et al., 1985) and lipid-laden aqueous humor (Ghaffari, 2008). With informed client consent, I (MBG) continue to recommend oral megestrol acetate in cats with widespread surface involvement, concurrent corneal ulceration, or a history of herpetic keratoconjunctivitis, since clinical improvement is rapid and risk of exacerbating herpetic disease appears subjectively low. Following an induction regimen of 5 mg daily for 5 days, then 5 mg every other day for 5 doses, dosage is quickly tapered to the lowest level needed to sustain clinical remission. Only 2.5–5 mg megestrol acetate as infrequently as once monthly may prevent relapses once clinical signs are controlled.

A topical regimen of megestrol acetate also appears to successfully control eosinophilic keratitis while limiting the risk of systemic side effects (Stiles & Coster, 2016). Topical application of a 0.5% compounded ophthalmic formulation of megestrol acetate every 8–12 hours reduced or resolved eosinophilic plaques and corneal vascularization in 15 (88%) of 17 cats within a mean of 6 weeks. Frequency of therapy required to maintain remission ranged from twice daily to once weekly. Serum glucose measured in 9 cats remained within the normal range, while control of preexisting diabetes in a 10th cat was unaffected in the 10-month mean follow-up period. Polydipsia, polyphagia, and weight gain did not occur, but adrenocortical function was not objectively assessed.

A novel regimen utilizing feline stem cells resolved clinical signs of eosinophilic keratitis in 5 cats previously unresponsive to topical corticosteroid (n=1), topical cyclosporine (n=5), and/or oral megestrol acetate (n=1; Villatoro et al., 2018). Two bulbar subconjunctival injections of adipose-derived feline mesenchymal stem cells were administered 2 months apart, with no other topical or systemic therapy in the 11-month follow-up period. Two cats improved substantially within 1 month of the first injection. Complete clinical remission was seen in all cats at 6 months, lasting through the 11-month recheck. The mechanism of the therapeutic effect is unknown, but stem cells have both inherent immunomodulatory and anti-inflammatory characteristics (Carrade & Borjesson, 2013).

Dry Eye Disease Syndromes

Dry eye disease in humans is increasingly being seen more broadly as dysfunction of the integrated functional lacrimal unit, with each patient existing somewhere along a spectrum from predominantly evaporative dry eye disease (which in veterinary medicine has traditionally been called exposure keratitis) to forms in which aqueous deficiency is the predominant driving factor (which in veterinary medicine has traditionally been called keratoconjunctivitis sicca). Qualitative tear film deficiency obviously exerts influences along this spectrum too. Adoption of this approach in veterinary medicine and especially in feline ophthalmology will encourage a deeper understanding of the pathophysiology unique to each case and a more thoughtful, contemplative, and holistic approach to management of each patient. Unlike dogs, tear film dysfunction and dry eye disease in cats are less commonly recognized, remain very poorly understood, seem to be associated with more subtle clinical signs, and are often poorly responsive to therapies typically effective in dogs. In dogs, dry eye disease carries with it strong connotations of aqueous tear film deficiency consequent to immune-mediated destruction of the lacrimal glands and is typically responsive to cyclosporine. By contrast, this appears to be a very rare syndrome in cats. Rather, those cases of dry eye disease in cats in which an etiopathogenic diagnosis is made appear more likely to result from dysfunction of the meibomian glands, goblet cells, or trigeminal nerve, and it appears that this dysfunction may result from metaherpetic (anatomic/physiologic postherpetic) damage (Cullen et al., 2005a; Lim & Cullen, 2005; Lim et al., 2009; Sebbag et al., 2018a). Of particular relevance is a specific metaherpetic syndrome in which virally induced damage to the trigeminal nerve axons and their ganglion is believed to reduce corneal sensation and thus reduce reflex tearing in humans (M'Garrech et al., 2013) and maybe in cats (Sebbag et al., 2018a). Neurogenic KCS may occur secondary to diseases disrupting parasympathetic innervation of the lacrimal glands such as dysautonomia (Kidder et al., 2008).

The essentials of tear film testing are identical in cats and in dogs. In particular, nothing can replace a thorough and directed assessment of the ocular surface and tear film, with special attention to each of the elements involved in the secretion, distribution, retention, and drainage of tears. However, it was only recently that normative values of some tear tests in routine use in dogs and humans (Table 28.8) as well as normal goblet cell density values for various conjunctival regions (Fig. 28.38) were published for cats (Sebbag et al., 2015, 2016a).

As determined by intraclass correlation coefficients and 95% limits of agreement, test–retest repeatability for all tear tests assessed was poor, despite the researchers being able to keep constant more variables than would typically be possible in the clinic (Sebbag et al., 2015). This suggests that while data from this population can be used to set normal values in cats, monitoring of disease progression or response to therapy by comparing Schirmer tear test 1 (STT-1) results between visits in individual patients is of lesser value. When neuro-

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Table 28.8 Results of the Schirmer tear test (STT-1), phenol red thread test (PRTT), tear film breakup time (TFBUT), tear film osmolarity (TearLab System, OcuSense, San Diego, CA, USA), and meibometry (MB 560, Courage-Khazaka Electronic, Cologne, Germany) in 120 normal cats (Sebbag et al., 2015).

Tear Test	Median	95% Central Range	95% Limits of Agreement	Intraclass Correlation Coefficients
STT-1 (mm/min)	18	9–34	−11 to +11	0.44
PRTT (mm/15 sec)	29	15–37	−10 to +13	0.19
TFBUT (sec)	12.4	9.1–17.7	−6.2 to +5.9	0.2
Osmolarity (mOsm/L)	322	297–364	−39 to +57	0.19
Meibometry (MU)	32	11–114	−52 to +66	0.51

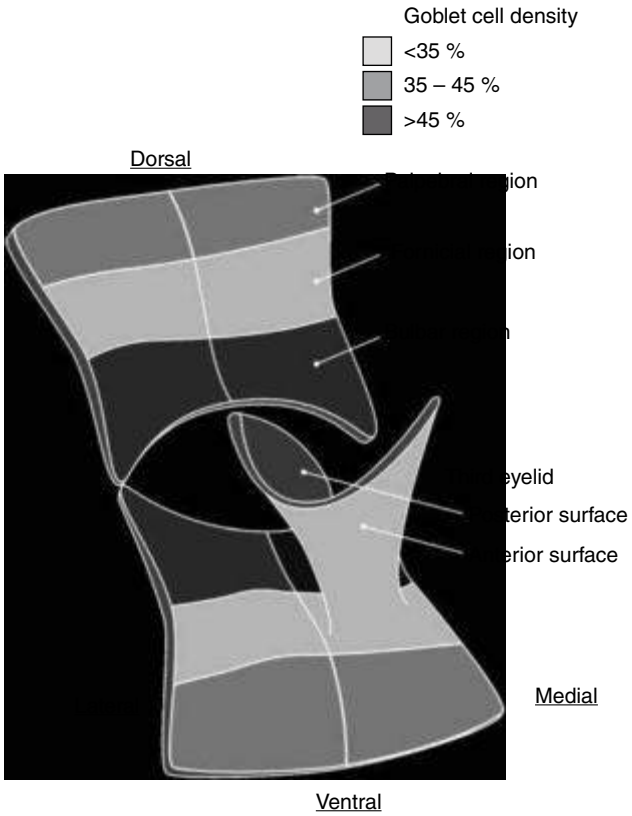


Figure 28.38 Schematic representation of the feline conjunctiva showing goblet cell density (GCD) for each of 13 areas evaluated in 21 eyes of 14 cats without clinical evidence of ocular surface disease and without histologic evidence of conjunctival disease. Increasing shade intensity represents increased GCD expressed as a percentage of basal epithelial cells based upon a count of 200 adjacent basal epithelial cells. Counts were not performed for the ventromedial bulbar conjunctiva (shown in white). GCD of the fornicial conjunctiva and anterior surface of the third eyelid (> 45%) was significantly greater than GCD of the palpebral conjunctiva (35%–45%), which was significantly greater than GCD of the bulbar conjunctiva and posterior aspect of the third eyelid (< 35%). (Reproduced with permission from Sebbag, L., Reilly, C.M., Eid, R., et al. (2016) Goblet cell density and distribution in cats with clinically and histologically normal conjunctiva. *Veterinary Ophthalmology*, **19**(Suppl. 1), 38–43, Fig. 4.]

genic dry eye disease is suspected in cats, it appears, in addition to a very thorough clinical exam as well as STT-1 and tear film breakup time (TFBUT) measurements, that assessment of corneal touch threshold (CTT) and a stimulated STT (similar in intent to the originally described STT-3) may be useful. The goal of this revised STT-3 is to cause reflex tearing by stimulation of a nerve other than the trigeminal nerve while a STT strip is in place in the conjunctival fornix. One described way of doing this is to place a cotton ball soaked in alcohol in front of but not touching the cat's nose for 1 minute prior to and during performance of an otherwise standard STT-1 (Sebbag et al., 2018a). Cats with a functional lacrimal gland and intact efferent sympathetic and parasympathetic pathways, and therefore capable of tear production and secretion but lacking the normal trigeminal reflex to initiate or promote such tearing, have dramatic increases in their STT result in response to this olfactory stimulation. It may be that the percentage increase in tearing that occurs in affected eyes is of more interest and potentially more diagnostic than is the absolute STT result achieved. In cats in which chronic conjunctivitis is believed to have altered conjunctival mucin stores and/or release, TFBUT should be assessed, sometimes along with conjunctival biopsy and goblet cell density (GCD) calculation in addition to routine histologic assessment so as to quantify such loss (Cullen et al., 2005a; Lim & Cullen, 2005; Lim et al., 2009; Sebbag et al., 2016a).

Given the permanent anatomic, likely meta-herpetic, changes associated with tear film dysfunction in cats, therapy at present is extremely limited and largely focused upon tear film supplementation. There is some evidence that hyaluronate will not only increase tear film stability in the short term, but also cause/facilitate goblet cell regeneration (Cullen et al., 1999; Moore & Collier, 1990).

Corneal Disease

Normal Cornea

The feline cornea is almost circular in shape, with a mean horizontal diameter of 16.5 ± 0.6 mm and a mean vertical

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diameter of 16.2 ± 0.61 mm (Carrington & Woodward, 1986). The thickness of the cornea increases over the first 4 months of life, measuring 379 µm at 9 weeks of age (Moodie et al., 2001). Values reported for the adult cat's central corneal thickness range from 546 µm using ultrasonic pachymetry (Chan-Ling et al., 1985; Gilger et al., 1993; Schoster et al., 1995) to 767 µm measured histologically (Samuelson, 2013). Comparable *in vivo* values are reported using contemporary modalities: 585 µm (Cleymaet et al., 2016), 600 µm (Famose, 2014), and 629 µm (Alario & Pirie, 2013) by spectral domain optical coherence tomography (SD-OCT) and 606 µm based on Scheimpflug imaging (Cleymaet et al., 2016). Corneal curvature also changes over the first 12–15 months of life, decreasing from a steeply curved, astigmatic state in the young kitten to a roughly spherical shape with 39 D of refractive power in the adult (Moodie et al., 2001). Normal endothelial cell density in cats ranges from 2668 ± 211 cells/mm^2 (Peiffer et al., 1981) to 2846 ± 403 cells/mm^2 (Kafarnik et al., 2007). With age, endothelial cell density decreases while endothelial cell size and pleomorphism increase (Franzen et al., 2010).

The central cornea is less sensitive in brachycephalic than DSH cats (Blocker & van der Woerdt, 2001). In one study performed with a Cochet-Bonnet aesthesiometer, the mean CTT (g/mm^2) for the central cornea of DSH cats was approximately 1.7, while that of the peripheral cornea was 5 (Blocker & van der Woerdt, 2001). Values for brachycephalic cats, specifically Persian and Himalayan, were 4 and 6.2, respectively. In a second study, the length of the Cochet-Bonnet aesthesiometer filament was used to compare corneal sensitivities (Wagner et al., 2003). The central corneal sensitivity in the DSH was 3.58 cm, whereas that of Persian cats was 2.97 cm. Cats with centrally located corneal sequestra had an even lower mean sensitivity of 2.0 cm in this region. In both studies, the sensitivity of the peripheral cornea was significantly lower than that of the central cornea in all groups tested. Using *in vivo* confocal microscopy, corneal subepithelial/subbasal nerve fiber densities measured in mm/mm^2 were found to be higher in DSH cats (15.49/18.4) compared with Persian cats (9.5/12.28) and with both mesocephalic and brachycephalic dogs (Kafarnik et al., 2008).

The cat's ability to remodel its cornea after significant wounding is almost legendary. Following experimental deep lamellar keratectomy in 3 young cats, confocal microscopy showed regeneration of normal epithelium, restoration of normal stromal thickness and lamellar organization, return of normal keratocytes, and reappearance of corneal nerves in the regenerated stroma, all within 40–60 days (Acosta et al., 2006). Cats also exhibited significant stromal regeneration 6 months following experimental photorefractive keratectomy, with return to preoperative corneal thickness and clarity (Nagy et al., 2007). A study comparing pigs and cats as models for corneal transplantation found that cats provided uneventful surgeries and clear transplants, with functional results similar to those achieved in human subjects (Brunette et al., 2011). Feline endothelial cells do not actively divide, but rather enlarge and migrate to maintain a functional monolayer (Van Horn et al., 1977). Stromal swelling will occur when endothelial cell density falls to less than 40%–45% of normal (Landsham, 1988). Endothelial permeability returned to normal by 3 months and the endothelial pump rate was restored within 5 months in a study of 10 cats following mechanical damage to the entire endothelial surface (Huang et al., 1989). Chronic corneal irritation rarely stimulates the deposition of melanin pigment (Nasisse, 1991).

DNA of FHV-1 and FeLV has been detected in clinically normal feline corneas. In 17 cats serologically positive for FeLV, 11 had PCR-confirmed FeLV within the cornea. Immunohistochemical staining of the corneas also documented FeLV gp70 in the corneal epithelium of 9 of the FeLV-positive cats (Herring et al., 2001). Two studies also determined that about half of clinically normal feline corneas are positive for FHV-1 DNA when evaluated by PCR (Stiles et al., 1997; Townsend et al., 2004). Virulent FHV-1 identified in the corneas of asymptomatic cats is capable of replicating, but it is unclear if this represents a low-level persistent infection or viral latency (Stiles & Pogranichniy, 2008). Corneal donors should be appropriately screened to avoid iatrogenic transmission of these infectious agents. A negative ELISA test is considered sufficient for excluding or significantly decreasing the likelihood of FeLV transmission by keratoplasty (Herring et al., 2001).

Within the conjunctival cul-de-sac are opportunistic pathogens capable of colonizing the damaged cornea, although the overall prevalence of conjunctival bacterial flora is lower in cats than in other domestic species (Campbell et al., 1973a; Espinola & Lilenbaum, 1996; Gerding et al., 1993; Martin, 2009; Shewen et al., 1980) and the conjunctival surface demonstrates periodic sterility (Kielbowicz et al., 2015). *Staphylococcus* is the predominant isolate, the relative frequency of specific organisms varies between studies. For example, *Staphylococcus epidermidis* has been detected in 4% (Shewen et al., 1980), 21% (Kielbowicz et al., 2015), and 45% (Espinola & Lilenbaum, 1996) of conjunctival samples of healthy cats. Fungi have been isolated from the conjunctival sacs of healthy cats, including *Aspergillus* spp. in 8% of those sampled (Samuelson et al., 1984).

Corneal Ulceration

Until proven otherwise, it is fair to assume that a cat's superficial corneal ulcer is a consequence of FHV-1 infection (Hartley, 2010a), the characteristics and treatment of which have been detailed previously. Poorly adherent epithelial margins are also common in herpetic ulcers. The indolent-type ulcer or spontaneous chronic corneal epithelial defects (SCCED) of middle-aged and older dogs, characterized by

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failure of epithelial adherence to the underlying stroma, seldom, if ever, occurs in cats. Accordingly, keratotomy with a burr or needle has little place in the management of feline ulceration and has been implicated in sequestrum formation when performed (La Croix et al., 2001).

A subjective clinical impression that deep corneal ulceration occurs less commonly in cats than in dogs is indirectly supported by the lower number of feline ulcers that appear in retrospective studies of surgically managed corneal disease (Balland et al., 2016; Bussieres et al., 2004; Chow & Westermeyer, 2016; Hansen & Guandalini, 1999; Vanore et al., 2007; Watté et al., 2004). Management of stromal ulcers in cats is not unlike that in dogs, details of which can be found in Chapter 19. Keep in mind that herpetic ulcers involve loss of only corneal epithelium. Stromal involvement implies the persistence of another inciting cause or opportunistic infection by bacteria or fungi that adhere to damaged tissue. Bacterial involvement should always be suspected whenever there is corneal stromal loss, corneal malacia, or stromal leukocytic infiltration. Fungal keratitis demonstrates similar clinical features, but occurs less commonly; details are outlined in a subsequent section. Corneal "melting" occurs when an imbalance between endogenous matrix metalloproteinases (MMP), bacterial proteolytic enzymes, and the proteinases present in the cornea and precorneal tear film leads to the destruction of corneal collagen (Famose, 2015; Ollivier et al., 2007).

Other potential causes of ulceration include eyelid abnormalities, quantitative or qualitative tear deficiencies (Cullen et al., 1999), foreign bodies, neurologic deficits that alter eyelid function or corneal sensitivity (Kern & Erb, 1987), and trauma. With perhaps the exception of trauma, these precipitating factors appear less frequently in cats than in dogs. As in other species, evaluation of the cat with a suspected corneal ulcer should include close visual inspection of the eyelids, conjunctiva, and third eyelid to rule out entropion, marginal defects, masses, or foreign bodies. Evaluate corneal sensation and the cat's ability to blink completely across the central cornea. Since corneal ulceration increases reflex tearing, inappropriately dry periocular fur demands determination of tear volume, objectively measured using the STT. Tear quality is another important parameter to consider, although assessment of TFBUT is problematic with the roughened, irregular surface of an ulcerated eye. A normal STT measures 14.3 ± 4.7 mm/min; TFBUT in young, healthy cats is 16.7 ± 4.5 sec (Cullen et al., 2005a). Before application of fluorescein dye to document the extent of epithelial loss, any off-white to yellow cellular infiltrates and/or soft, mucinous, necrotic (malacic) tissue within or surrounding the ulcer bed must be documented. Corneal cytology can provide rapid confirmation of infectious agents and guides initial selection of antimicrobials. Corneal swabs or scrapings are also submitted for bacterial culture and susceptibility to assure an appropriate medical regimen. Since adequate sampling may be compromised by the fragile nature of the corneal defect or by previous antibacterial use, corneal cytology and culture may not reliably detect sepsis in all patients (de Bustamante et al., 2018).

In a Swiss review of septic keratitis, bacterial isolates from feline corneal ulcers included *Staphylococcus* spp. (65.6%), *Streptococcus* spp. (12.5%), *Pasteurella* spp. (6.3%), aerobic spore formers including *Bacillus cereus* (6.3%), *Pseudomonas* spp. (3.1%), *Escherichia* coli (3.1%), and unspecified Gram-positive anaerobic rods (3.1%; Suter et al., 2018). Gram-positive organisms also predominated in another study of feline infected corneal ulcers, but Gram-negative bacteria were more frequently isolated compared to Suter's study: *Staphylococcus* spp. (51%), *Streptococcus* spp. (8%), *Pseudomonas aeruginosa* (13.5%), and *Pasteurella multocida* (10%; Lin & Petersen-Jones, 2008). Colonization of the interlamellar stromal spaces by *Pseudomonas aeruginosa* and *Sphingobacterium multivorum* created an infectious crystalline keratopathy, characterized by a white crystalline opacity that branched from the margins of corneal sequestra in 2 cats (Ledbetter et al., 2017). At least one species of obligate anaerobic bacteria was isolated from 3 cats with ulcerative keratitis, including *Peptostreptococcus* spp., *Fusobacterium nucleatum*, and *Bacteroides vulgatus*. Positive anaerobic cultures were more likely in patients following ocular trauma, preexisting corneal disease, and chronic dermatologic disease (Ledbetter & Scarlett, 2008). *Clostridium* spp. were isolated in 2 cats with corneal sequestra (Featherstone & Sansom, 2004).

Although *Chlamydia* and *Mycoplasma* are classified as conjunctival pathogens, genetic markers of these organisms have been identified in cats with corneal disease. PCR assays performed on corneal scrapings or keratectomy samples from 20 cats with corneal erosions detected *Chlamydiales* order-specific DNA in 1 cat and *Parachlamydia acanthamoebae* DNA in 3 cats (Richter et al., 2010). None of the corneal erosions was positive for *C. felis*. *Neochlamydia hartmannellae*, an endosymbiont of the amoeba *Hartmannella vermiformis*, was detected in the conjunctiva of cats with keratitis and/or conjunctivitis (Von Bomhard et al., 2003). However, corneal lesions were not specifically sampled, nor did the study document coinfection with *H. vermiformis*, an established cause of amoebic keratitis in humans (Pinna et al., 2017). While the findings in the two studies indicate exposure to these obligate intracellular bacteria, the clinical significance and pathogenesis are undetermined. A more convincing role for *Mycoplasma* was reported in 7 cats with severe stromal ulceration and/or keratomalacia (Gray et al., 2005; Fig. 28.39); 4 of the affected cats had a history of herpetic keratitis and all 7 had been treated with topical or systemic corticosteroids and/or antibiotics ineffective against *Mycoplasma* prior to referral. Growth on culture from corneal specimens of each cat was consistent with *Mycoplasma*. The bacterial isolates were further characterized as *M. felis*

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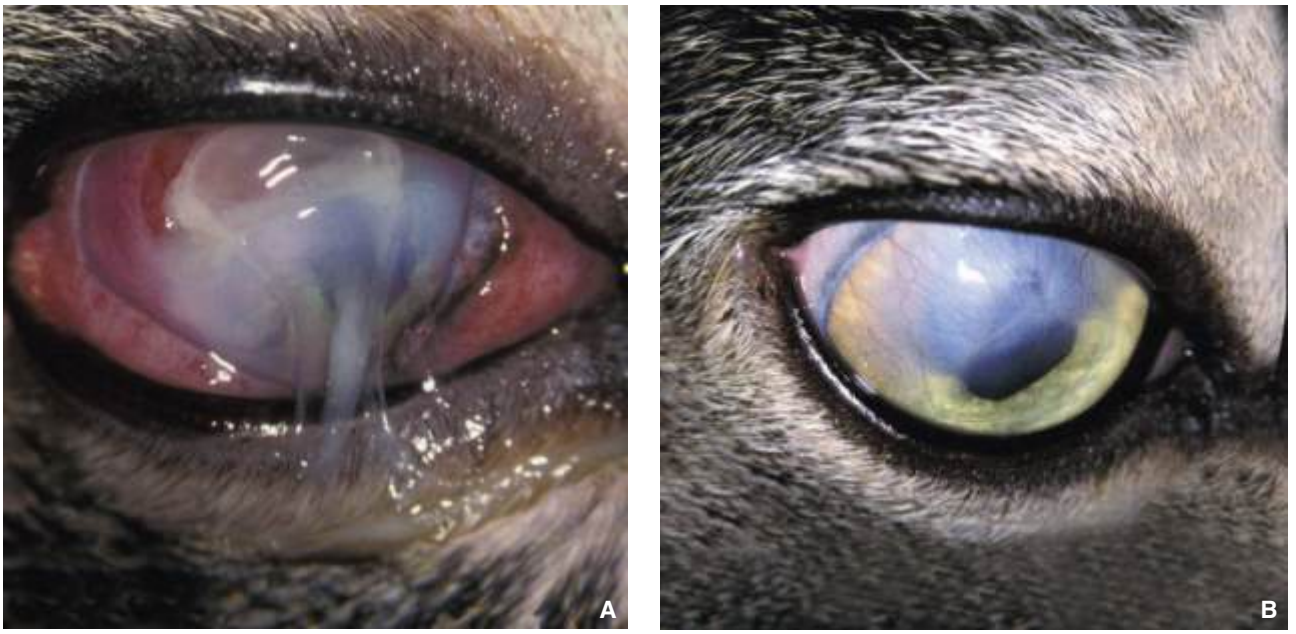


Figure 28.39 **A**. *Mycoplasma* spp. was cultured from the axial cornea of this 16-year-old cat with diffuse keratomalacia and corneal vascularization. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.) **B**. The same eye, day 53 of treatment.

(n=6) and *M. gateae* (n=1) based on 16S rRNA gene sequencing. All cats responded to topical therapy appropriate for *Mycoplasma*. Recommended treatment options are topically applied tetracycline or azithromycin or systemically administered pradofloxacin (Maggs, 2018b). One study found that systemically administered doxycycline did not achieve therapeutic concentrations in the tears of cats (Hartmann et al., 2008b), thereby limiting its efficacy unless the corneas were sufficiently vascularized (Maggs, 2018b). However, a subsequent study after oral administration of 4.2–5 mg/kg doxycycline every 12 hrs for 6 consecutive days in cats documented tear concentrations up to ninefold greater than those previously reported (Sebbag et al., 2018b). Although not considered the primary etiologic agents in these cases, *M. felis* and *M. gateae* were regarded as clinically relevant threats to corneal integrity.

Corneal infection by the protozoa *Encephalitozoon* (*Nosema*) was characterized by numerous stellate superficial corneal opacities that resembled lipid deposits in a 3-year-old DSH (Buyukmihci et al., 1977). The diagnosis was made histopathologically, and keratectomy was curative.

Extensive corneal destruction may occur in kittens, the consequences of which have been labeled feline early-life ocular disease (Jacobi & Dubielzig, 2008a; Fig. 28.40). Histomorphologic changes included broad corneal perforation, extensive uveal prolapse, and collapse of the globe in 6 eyes from 6 cats, ranging in age from 7 weeks to 2 years at the time of enucleation. The lens was missing and presumably extruded through the corneal defect in 4 of the eyes. Uveal extramedullary hematopoiesis occurred in 3 eyes, presumably



Figure 28.40 Feline early-life ocular disease in a 4-week-old feral Domestic Shorthair, characterized by extensive corneal destruction resulting in corneal perforation and uveal prolapse.

a result of stem cell stimulation by inflammatory cytokines (Mudhar et al., 2005). The authors warned that these hematologic precursor cells could be misinterpreted as a round cell neoplasm. Although symblepharon in 3 of the cats implicated FHV-1 in the disorder, a definitive cause could not be determined in any of the cases. A secondary bacterial infection of a traumatic or primary herpetic ulcer could explain the progressive corneal destruction.

Therapy with fortified gentamicin solution combined with a penicillinase-resistant compounded cephalosporin has been recommended for initial treatment of bacterial keratitis pending identification of the infecting organism and its

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antibiotic susceptibility (Kern, 2004). Gentamicin ophthalmic solution, commercially produced as a 3 mg/mL concentration, can be fortified by adding 50 mg of parenteral antibiotic to produce a final concentration of 11 mg/mL (Kern, 1990). Ciprofloxacin and gentamicin were both effective against all *Streptococcus*, *Pseudomonas*, and *Pasteurella* isolates, plus 93% and 90% of *Staphylococcus* isolates, respectively, from 54 cats with ulcerative keratitis (Lin & Petersen-Jones, 2008). In the same study, cephalothin was effective against 93% of *Staphylococcus* spp. isolates. Of the antibiotics commercially available for ophthalmic use, erythromycin was least effective, with 50% or more of bacterial isolates showing resistance. In a more recent study of septic keratitis that included 28 cats (Suter et al., 2018), resistance to gentamicin was noted in 1 of 14 staphylococcal isolates and in 3 of 3 streptococcal isolates. Cephalosporin resistance was reported in 2 of 14 staphylococcal isolates, but none (0 of 3) of the streptococcal isolates.

Deep ulcers of at least 40% stromal loss, including 4 corneal perforations, were successfully managed in 13 cats with topical and systemic medications alone (de Bustamante et al., 2018). The topical regimen consisted of serum (n=12), atropine (n=10), and antibiotics (n=13), specifically ofloxacin and cefazolin (n=10), ciprofloxacin and cefazolin (n=1), ofloxacin only (n=1), or ciprofloxacin only (n=1), applied every 2–6 hours. The median course of topical antibiotic therapy was 30 days, ranging from 16 to 103 days. Concurrent systemic therapy included antibiotics (n=7), prednisolone (n=5), robenacoxib (n=2), and/or buprenorphine (n=8). Gradual reduction in corneal stromal malacia, cellular infiltration, and vascularization was seen, with a mean of 21 days to corneal re-epithelialization. All 13 cats retained a comfortable and visual eye.

Corneal cross-linking (CXL) has been used to successfully arrest corneal melting (keratomalacia) in cats. The technique improves biomechanical stability by creating intrafibrillar covalent bonds in the stromal collagen fibers using UV-A light to photoactivate riboflavin applied to the cornea. A pilot study of CXL included 3 cats with unilateral progressive corneal melting (Spiess et al., 2014). A stable cornea was observed within 2–4 days in 2 cats, based on subjective assessment of corneal contour, ulcer depth, cellular infiltrates, and keratomalacia. With up to 75% stromal loss across the entire cornea, the third cat required 12 days for stromal stabilization and developed a corneal sequestrum in the early post-treatment period that spontaneously extruded. A subsequent prospective study of CXL enrolled 7 cats with a median age of 10 years, a median ulcer depth of 50%, and a median ulcer area of 144 mm^2 (Pot et al., 2014). Median times to stromal stabilization and complete epithelial closure were 12 days and 20 days, respectively, with no treatment failures; 2 of 7 cats in the CXL treatment group (and 1 of 4 in the control group) developed a corneal sequestrum during the corneal healing process. A third study using an accelerated CXL protocol in 10 cats with unilateral melting ulcers reported epithelial healing at day 8 in 9 of 10 patients and at day 15 in the 10th cat (Famose, 2015). Cellular infiltration resolved in all cats by day 8. At day 31, all treated eyes were sighted, with variable degrees of corneal fibrosis. None of the treated cats in this study developed a sequestrum.

In some cases, medical-grade adhesives may be used as an alternative to surgery to provide structural support for deep stromal ulcers and a physical barrier against cellular infiltration and subsequent enzymatic destruction (Fogle et al., 1980). A superficial ulcer in an 11-year-old Burmese healed within 6 weeks following application of isobutyl cyanoacrylate, with a mild vascular reaction and a small residual leukoma (Bromberg, 2002). Stromal ulcers resolved in 100% (7 of 7) of cats following epithelial debridement and application of butyl-2-cyanoacrylate adhesive (Watté et al., 2004). Glue retention times ranged from 8 to 55 days, with residual corneal opacity in 2 patients and symblepharon formation in 1 patient with concurrent conjunctival necrosis and perilimbal stromal ulceration.

In chronic superficial corneal ulcers refractory to medical treatment, mean time to healing following simple debridement of the ulcer with a sterile cotton swab was 30 days (range 7–240 days; La Croix et al., 2001). Mean healing time when debridement was combined with grid keratotomy was 42 days (range 21–63 days); 31% of these cats developed a corneal sequestrum. Ulcers in 2 cats healed within 2 weeks following superficial keratectomy. In 2015, Jégou and Tromeur corroborated the efficacy of superficial keratectomy for chronic superficial ulcers in a study of 36 cats (41 eyes), in which 32.5% healed within 2 weeks and 85% resolved within 4 weeks. Mean time to healing was 22 days (range 7–74 days). Corneal transparency was very good to excellent in 83% of patients following surgery.

Surgical grafting may be indicated if an ulcer is rapidly progressing, if > 66% of the corneal thickness has been lost, or when medical therapy fails to resolve the ulcer (Hartley, 2010b). A variety of procedures have been used successfully in cats, including conjunctival (Hakanson & Meredith, 1987; Hakanson et al., 1988; Scagliotti, 1988; Soontornvipart et al., 2003), amniotic membrane (Arcelli et al., 2009; Barachetti et al., 2010; Barros et al., 2005; Cognard & Barnouin, 2017; Knollinger et al., 2018), corneal (Hacker, 1991; Hansen & Guandalini, 1999; Peña Gimenez & Fariña, 1998; Townsend et al., 2008), and synthetic or bioengineered grafts (Table 28.9; Balland et al., 2016; Bussieres et al., 2004; Chow & Westermeyer, 2016; Dulaurent et al., 2014; Featherstone et al., 2001; Goulle, 2012; Vanore et al., 2007), surgical details of which can be found in Chapter 19. A study of cryopreserved feline corneoscleral tissue concluded that cornea stored at –20 °C for up to 10 years could still be used for tectonic support without loss of structural or microbiologic integrity (Costa et al., 2016).

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Table 28.9 Biomaterial grafts for feline deep corneal ulcers.

Graft Material	No. of Cases	Concurrent Device or Surgery	Success Rate (%)	Reference
Small intestinal submucosa	2		100	Featherstone & Sansom (2000)
	5	Conjunctival flap (1/5)	80	Featherstone et al. (2001)
	2	Conjunctival flap	100	Bussieres et al. (2004)
	2	Third eyelid flap	100	Vanore et al. (2007)
	7	Third eyelid flap	100	Goulle (2012)
Porcine urinary bladder matrix	2	Third eyelid flap	100	Balland et al. (2016)
	12	Bandage lens, tarsorrhaphy	83	Chow & Westermeyer (2016)

Miscellaneous Corneal Infections

Corneal abscesses have been rarely described in the cat (Campbell & McCree, 1978; Moore & Jones, 1994). Presumed to be bacterial in origin, the typically fluorescein-negative stromal lesions are creamy white to yellow in color due to neutrophilic infiltration, with notable edema, vascularization, and discomfort. The alleged cause in each report was a focal penetrating injury that quickly epithelialized, encasing bacteria within the deeper cornea. Although cytology, culture, and susceptibility testing are indicated, sampling is often constrained by the intact epithelium or the depth of the abscess. Therapy may be directed against the organisms most commonly isolated from feline ulcers: *Staphylococcus* spp., *Streptococcus* spp., and *Pasteurella multocida*, the latter frequently associated with cat claw injuries (Moore & Jones, 1994). A bactericidal antibiotic that penetrates intact corneal epithelium, such as a fluoroquinolone, is an appropriate empirical choice. Treatment with topical and subconjunctival gentamicin was curative in one reported case. The second, a 13-year-old DSH, failed to respond to oral ampicillin and topical gentamicin over a 5–day period, but healed by granulation 10 days after the abscessed tissue was surgically excised.

Acid-Fast Granulomatous Keratitis

Intracorneal granulomas associated with acid-fast bacilli have been described in a 2-year-old and a 16-year-old cat living in the northwestern United States (Dice, 1977). The progressive "fleshy" intrastromal lesions histologically resembled cutaneous granulomas of feline leprosy (Gunn-Moore, 2014), with neutrophils and mononuclear inflammatory cells interspersed between sheets and clumps of pale-staining histiocytes containing acid-fast bacilli. The granulomas were surgically excised after medication failed to alter the clinical course. A case report from Italy also describes a 2-year-old European Shorthair cat with a nodular vascularized mass arising in the dorsal bulbar conjunctiva and invading the adjacent cornea and sclera (Lamagna et al., 2009). The lesion was histologically characterized by multifocal to coalescing pyogranulomas made up of multinucleated giant cells and vacuolated macrophages containing acid-fast bacilli. *Mycobacterium* 16S rRNA gene-specific PCR was positive. A regimen of systemic clindamycin and doxycycline combined with topical tetracycline was recommended but declined. The lesion reportedly was unchanged 1 year later. The clinical appearance and progressive nature of the granulomas in these cats distinguish their proven mycobacterial disease from that theorized in patients with Florida spots.

Fungal Keratitis

Mycotic keratitis is rare in cats, although the presence of fungi in conjunctival swabs has been demonstrated in 40% of healthy cats (Samuelson et al., 1984). Reported fungi isolated from normal feline eyes include *Penicillium*, *Cladosporium*, *Aspergillus*, and *Scopulariopsis* spp. (Gerding et al., 1993; Samuelson et al., 1984). In general, predisposing factors for fungal keratitis include tear film insufficiency, treatment of corneal ulceration with topical antimicrobials and/or corticosteroids, exposure to environmental vegetative material, and the presence of fungal organisms within the normal conjunctival flora (Binder et al., 2011). In humans, two forms of keratomycosis are described. Infections due to filamentous fungi such as *Aspergillus* spp. are usually initiated by trauma, whereas those associated with yeast-like fungi such as *Candida* spp. usually develop secondary to existing ocular problems, including tear deficiency, or systemic disorders such as diabetes mellitus (Mahmoudi et al., 2018; Thomas, 2003). Both forms have been reported in cats. Infections with filamentous fungi predominate; individual case reports of feline keratomycosis include infections by *Acremonium* spp., *Aspergillus flavus*, *Cladosporium* spp., and *Aspergillus fumigatus* (Binder et al., 2011; Labelle et al., 2009; Miller et al., 1983; Schmidt, 1974). *Candida* spp. infection was reported in not only the corneas but also the vitreous and retinas of a 12-year-old diabetic cat with concurrent hyperadrenocorticism (Gerding et al., 1994).

Clinical signs often include unusually severe blepharospasm, with conjunctival hyperemia and variable discharge.

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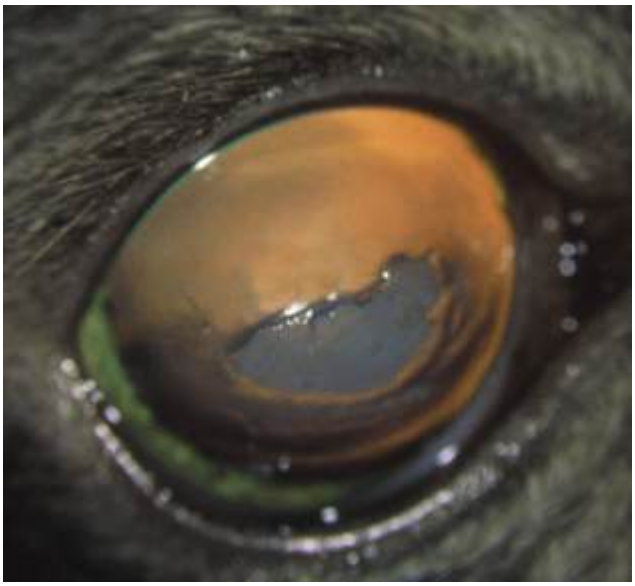


Figure 28.41 Mycotic keratitis in a 7-year-old Domestic Shorthair with a raised, dull corneal plaque composed of mats of fungal hyphae, masking the underlying stromal ulcer.

Corneal ulceration may be accompanied by a raised, opaque surface plaque with irregular margins and multifocal satellite lesions of gray-white stromal infiltrates. A pigmented plaque suggests infection by dematiaceous fungi (Bernays & Peiffer, 1998). Keratomalacia can lead to rapid stromal loss. Secondary corneal vascularization and anterior uveitis are common (Fig. 28.41).

Rapid confirmation is based on cytologic evidence of fungal hyphae in corneal scrapings. The specific fungus is ideally identified by culture, but samples may require prolonged incubation. PCR is an emerging option for faster and thus clinically relevant fungal identification (Binder et al., 2011; Labelle et al., 2009). Published data are available regarding the antifungal sensitivities of many fungi. Topical 1% voriconazole successfully resolved the *Acremonium flavus* infection in 29 days (Labelle et al., 2009). The *Acremonium*-related ulcer progressed to 70% corneal depth in some areas despite topical 1% miconazole therapy. Treatment was switched to topical 1% voriconazole, with resolution of the infection 48 days after initial presentation (Binder et al., 2011).

Florida Spots

A seemingly benign corneal disease referred to as Florida spots or tropical keratopathy has long been recognized in cats in the southeastern United States and the Caribbean basin (Peiffer & Jackson, 1979). Similar lesions have also been described in cats living in Brazil (Barros & Safatle, 1997) and Israel (Sarfaty, 2009). The disorder is characterized by singular or multiple gray to white corneal opacities located within the anterior stroma of one or both eyes (Fig. 28.42). The lesions are variably sized, from 1 to 8 mm in diameter, round to irregular in shape, and often appear most dense at their center. The periphery of adjacent lesions may overlap. The cornea is otherwise unremarkable, with no signs of vascularization or inflammation, and the affected cats show no discomfort. The condition progresses slowly, if at all. The lesions are not altered by topical antibacterial, antifungal, or corticosteroid therapy (Stiles, 2013).

The cause of the keratopathy is unknown. In an early description of the disorder, *Rhinosporidium* was implicated based on the presence of encapsulated anterior stromal vacuoles, some of which contained basophilic spherical material interpreted as endospores (Peiffer & Jackson, 1979). Another study demonstrated acid-fast material within the stromal lamellae and described non-membrane-bound, rod-like structures suggestive of mycobacterial organisms within stromal vacuoles (Fischer & Peiffer, 1987). A histopathologic

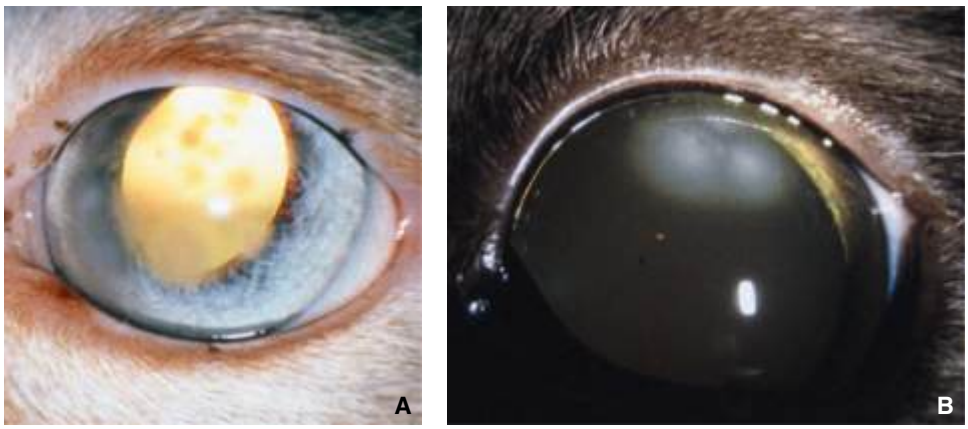


Figure 28.42 Tropical keratopathy (Florida spots). **A**. Multiple opacities in the cornea of a 5.5-year-old Domestic Shorthair appear pale against the medial iris and dark against the tapetal reflection. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.) **B**. Multiple pale stromal infiltrates with typically denser centers are present in the dorsal cornea of an otherwise asymptomatic feline eye.

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study of 6 cats from St. Kitts described the keratopathy as an anterior stromal collagen disorder with varying degrees of epithelial hyperplasia (Bolfa et al., 2018). Affected corneas were often thinner by 4%–18%, attributed to consolidation of corneal stroma, with dense accumulations of collagen in the superficial layers. Variation in collagen fibril diameters and spacing was thought to contribute to the corneal opacities. No evidence of inflammation, edema, vascularization, fibrosis, acid-fast, or fungal organisms was found in this latest study. Passing reference to lipids within tissues include descriptions of birefringent extracellular granules within the epithelial basal lamina (Whitley & Gilger, 1999), lightly staining material adjacent to keratocytes (Fischer & Peiffer, 1987), and empty epithelial basement membrane vacuoles attributed to loss of lipids during processing (Bolfa et al., 2018). Other suggested but unproven factors include exposure to UV light (Bolfa et al., 2018), toxic effects of fire ant (*Wasmania auropunctata*) venom (Sarfaty, 2009), and microtrauma associated with dust or other airborne pollutants (McLendon et al., 1993).

Corneal Sequestrum

A sequestrum is characterized histologically by stromal collagen degeneration and distinguished clinically by discoloration of the affected corneal stroma, its color progressing from subtle amber and bronze to jet black over time. Synonyms for the condition include corneal sequestration, corneal mummification, corneal nigrum, and corneal necrosis. Long considered a uniquely feline disease, histopathologic features of corneal sequestration have been rarely described in dogs (Bouhanna et al., 2008; Dubielzig et al., 2010) and horses (McLellan & Archer, 2000). The unmistakable stromal discoloration is seldom, if ever, seen in these other species.

Corneal sequestration occurs in cats of all ages, with the apparent exception of neonates, and exhibits no gender predilection (Lightowler et al., 1987; Morgan, 1994; Pentlarge, 1989; Souri, 1975; Startup, 1988). Reported ages range from 5 months (Startup, 1988) to 18 years (Graham et al., 2017), with a mean age of 5.2–5.6 years (Cullen et al., 2005b; Featherstone & Sansom, 2004; Gelatt et al., 1973; Morgan, 1994; Pentlarge, 1989). Brachycephalic breeds appear predisposed to sequestrum formation. Persian cats have the highest reported incidence, followed by Siamese, Burmese, Himalayan, and DSH breeds (Featherstone & Sansom, 2004; Gelatt et al., 1973; Morgan, 1994; Pentlarge, 1989; Startup, 1988).

Once encountered, the clinical appearance of a corneal sequestrum is unmistakable. The lesion usually develops unilaterally. Bilateral lesions can arise simultaneously or sequentially, but tend to occur most often in Persians or other brachycephalic breeds (Featherstone & Sansom, 2004). An oval to circular pigmented lesion commonly develops in the central or paracentral cornea, its color progressing from translucent amber to darker bronze, then to an impervious jet black with chronicity (Fig. 28.43). The location may vary depending on the inciting cause. The margins of the discoloration are typically ill-defined in the early stages, but become more distinct over time. A subtle bronze tint often extends peripherally into the stroma surrounding a discrete sequestrum. The size of the sequestrum varies, with diameters ranging from 1 to 10 mm in one study (Andrew et al., 2001). Depth of the lesion also varies and can extend from the superficial stroma to Descemet's membrane (Souri, 1972). In Andrew's report of 17 affected corneas, the sequestrum occupied the superficial stroma in 8 eyes, the anterior one-third of the stroma in 3 eyes, and the middle one-third of the stroma in 6 eyes (Andrew et al., 2001). As the sequestrum progresses and opacifies, lesion depth becomes increasingly difficult to determine without the benefit of advanced imaging modalities such as ultra-high-resolution ultrasound (Bentley et al., 2003). High lesion reflectivity and total signal absorption prevented determination of lesion depth in 3 of 5 corneas examined by OCT (Famose, 2014). The lesion may appear raised above the surrounding cornea as corneal epithelium migrates beneath the sequestrum, separating it from the deeper stroma. Accompanying clinical signs include blepharospasm, ocular discharge, and conjunctival hyperemia. The corneal epithelium is usually absent over and immediately surrounding the sequestrum, but uptake of fluorescein may be limited by the stromal necrosis or may be difficult to visualize over the sequestrum itself. The lesion may stain diffusely with 0.5% rose Bengal (Gelatt et al., 1973). Although corneal ulceration is common, corneal perforation is rare (Featherstone & Sansom, 2004). On occasion, stromal discoloration can occur beneath intact epithelium (Featherstone & Sansom, 2004; Gelatt et al., 1973; Stiles, 2013). Corneal vascularization varies from mild to severe, with no clear relationship to duration of the sequestrum (Featherstone & Sansom, 2004). There may be rare instances of nonhealing corneal ulcers that mimic the refractory behavior of a sequestrum and demonstrate stromal necrosis histopathologically, but lack the characteristic corneal discoloration (Jégou & Tromeur, 2015).

Histopathologically, the epithelium overlying the sequestrum is usually absent and poorly adherent at the lesion margins. The sequestrum itself is characterized by coagulation necrosis and lacks keratocytes, inflammatory cells, and blood vessels. Its lamellar structure is still discernable, but indistinct (Dubielzig et al., 2010). Often bordering the stromal necrosis is a foreign body–like reaction, with lymphocytes and plasma cells in early lesions, macrophages, neutrophils, and giant cells in more chronic cases (Pentlarge, 1989), and considerable karyorrhexis and karyolysis at the junction of diseased and normal tissue (Gelatt et al., 1973). Vascularization or granulation tissue commonly encompasses or undermines the sequestrum. Mineralization is a rare occurrence (Gemensky & Wilkie, 2001).

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Figure 28.43 Corneal sequestrum. **A**. Early stromal bronzing associated with a central corneal ulcer in an adult Persian. **B**. Central corneal sequestrum in an adult Himalayan. (Courtesy of Dr. Eric Smith.) **C**. The same cat, 1 year later. **D**. Temporal sequestrum secondary to chronic entropion in an 8-year-old Domestic Shorthair. **E**. Vascularized, extruding sequestrum in a 7-year-old Himalayan.

The etiopathogenesis of sequestrum formation remains speculative, although some form of chronic corneal insult is thought to initiate the process. Apoptosis may contribute to sequestration based on ultrastructural changes in keratocytes that include clumping and margination of chromatin and shrunken cytoplasm (Cullen et al., 2005b). Early reports proposed a local metabolic defect (Souri, 1975), a hereditary basis in colorpoint breeds (Vawer, 1981), or a primary stromal dystrophy (Bistner, 1983; Gelatt et al., 1973; Startup, 1988). Brachycephalic breed-related adnexal abnormalities including lagophthalmos, entropion, and medial canthal trichiasis are repetitively linked with corneal sequestration. Corneal sensitivity, particularly that of the central cornea, is known to be poorer in healthy Persians than in healthy DSH cats (Blocker & van der Woerdt, 2001), but no statistical difference was found in the central corneal sensitivity of normal Persians versus those with sequestra (Wagner et al., 2003). Morgan diagnosed KCS in 4 of 42 cats with sequestra (Morgan, 1994). Conjunctival goblet cell atrophy and an accelerated TFBUT were reported in 1 cat with a corneal sequestrum (Cullen et al., 1999). A subsequent prospective study of 11 cats with sequestra identified a trend of decreased goblet cell/epithelial cell ratios in the conjunctiva and an accelerated TFBUT of 14 seconds (versus 21 seconds in normal controls), but the differences were not statistically significant (Grahn et al., 2005). While the investigators attributed the variations to the concurrent corneal and conjunctival inflammation rather than an initiating event in the sequestrum's pathogenesis (Johnson et al., 1990), tear film dysfunction remains an emerging focus of investigation in this and other ocular surface diseases. A slight but statistically insignificant increase in tear protein concentration occurs in affected cats (Davidson et al., 1992). Total tear lipid content was significantly lower in affected than control eyes when evaluated with high-performance liquid chromatography (Featherstone et al., 2004). Iatrogenic sequestration has been reported following debridement or grid keratotomy of nonhealing corneal ulcers. A sequestrum developed in 10% (2 of 21) of eyes following debridement alone and 31% (4 of 13) of eyes treated by grid keratotomy (LaCroix et al., 2001). Chemical cauterization has also been incriminated as an iatrogenic stimulus (Startup, 1988).

FHV-1 is implicated as a factor in sequestrum formation. Chronic corneal ulceration precedes sequestration in some cats (Featherstone & Sansom, 2004) and FHV-1 DNA has been identified in experimentally induced (Nasisse et al., 1989b) and naturally occurring sequestra (Featherstone & Sansom, 2004; Morgan, 1994; Nasisse et al., 1998; Stiles, 1995; Stiles et al., 1997; Volopich et al., 2005). Acknowledging that herpesvirus is only one of many causes of corneal

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damage that may precipitate sequestrum formation, Nasisse hypothesized that upregulation of pro-inflammatory cytokines following keratocyte infection could explain the similarity in histologic features between a sequestrum and the collagen damage seen in herpes-induced stromal keratitis (Nasisse et al., 1998). Interestingly, the prevalence of FHV-1 DNA is greater in sequestra from domestic breeds than in Persians or Himalayans (Nasisse et al., 1998; Stiles et al., 1997), lending support to the fundamental role of conformation in sequestrum formation in the brachycephalic breeds of cat. Bacterial or fungal organisms identified on culture (Featherstone & Sansom, 2004; Gelatt et al., 1973) or histopathology (Dubielzig et al., 2010) are generally considered opportunistic rather than causative, although Cullen's finding of *Toxoplasma gondii* DNA in 4 of 9 affected corneas prompted her call for further study of its significance (Cullen et al., 2005b).

The nature of the stromal discoloration likewise remains a mystery. Melanin was proposed in one study based on spectroscopic identification of chromophores with similar light absorption and microscopic detection of melanin-like particles (Featherstone et al., 2004), but a subsequent electron microscopic study failed to identify melanin granules (Cullen et al., 2005b). Another theory implicated tear-derived porphyrins in the stromal discoloration, based on their role in murine chromodacryorrhea (Wilcock, 2007), but no porphyrins were found in normal feline lacrimal glands, corneas, or corneal sequestra to support that hypothesis (Newkirk et al., 2011). An early case report identified iron in a sequestrum (Ejima et al., 1993). Scanning electron microscopy in a later study discounted iron as a factor in the discoloration, despite absorbance spectra indicating the presence of iron, copper, and traces of other metals in the necrotic tissue (Featherstone et al., 2004). Ultrastructural electron-dense particles suggested mineralization, but specific elements were not identified (Cullen et al., 2005b). Feline tear composition remains an area of interest as a source of the discoloration, suggested by the brown color of affected cats' ocular discharge and the staining of contact lenses, conjunctival grafts, and small intestinal submucosal grafts that occurs during treatment (Featherstone et al., 2004). An endogenous corneal defect involving epinephrine metabolism has also been proposed (Gelatt et al., 1973), based on corneal and conjunctival discoloration in human eyes treated with topical epinephrine that oxidatively converts to melanin via an unstable adrenochrome pigment (Kaiser et al., 1992).

Treatment must address causative factors as well as the sequestrum itself. For instance, partial permanent tarsorrhaphy or correction of medial entropion may minimize corneal insult in brachycephalic patients. Because a superficial sequestrum may eventually slough as the corneal epithelium undermines the necrotic tissue, some clinicians advocate a conservative medical approach that combines a topical prophylactic antibiotic, a topical hyaluronan-based lubricant, and a topical or oral antiviral if herpesvirus is suspected. A review of medical treatment in 37 cases recommended a broad-spectrum topical antibiotic every 6 hrs for 10 days, followed by repeated daily administration of artificial tears and a topical acetylcysteine-containing collyrium every 8 hrs (Dalla et al., 2007). A feline dietary supplement containing vitamins, minerals, and protein, and an Elizabethan collar completed the regimen. Reported times to recovery for 1–3 mm diameter lesions were 1 month in 32%, 2 months in 27%, 5 months in 14%, 7–10 months in 5%, and 12 or more months in 18%, with a leukoma as the therapeutic endpoint. Recurrences were seen in 3 Persians 1, 4, and 5 years later – in the opposite eye. Boydell reported that topical application of 3000 units/mL of IFNα-2b 4 times daily eliminated corneal discoloration in eyes with sequestra (Boydell & Roxburgh, 1999). Spontaneous healing is often a prolonged process and less likely to occur with deep stromal lesions. If the sequestrum is beginning to separate from the surrounding cornea, it may be possible in a tractable patient to debride the loose tissue with scissors or a diamond burr following topical anesthesia, repeating the process in subsequent visits until the removal is complete (Schmidt, 1989).

Definitive removal of the sequestrum is indicated in persistent or deep lesions, especially as corneal inflammation progresses and pain increases. Lamellar keratectomy is the technique of choice for definitive surgical excision, removing the sequestrum in its entirety while preserving as much healthy cornea as possible (Sanchez, 2014; Fig. 28.44). Time to healing is significantly shorter following surgical removal (3.8 weeks) than with medical therapy alone (11.2 weeks; Morgan, 1994). After Blogg suggested that recurrence could be prevented using a conjunctival graft over the keratectomy site (Blogg et al., 1989), a variety of therapeutic options have been proposed to expedite corneal healing and discourage sequestrum recurrence. These include a bandage contact lens, third eyelid flap, temporary tarsorrhaphy, cyanoacrylate adhesive, conjunctival pedicle graft, corneal-conjunctival transposition, small intestinal submucosal graft, amniotic membrane transplant, and bovine pericardial graft.

Of 35 eyes treated by keratectomy, a sequestrum recurred in 2 cats following a third eyelid flap, in 1 cat following a conjunctival graft, and in 1 cat after a corneoscleral transposition, for a 12% recurrence rate (Morgan, 1994). Featherstone reported an overall recurrence rate of 20% in 80 eyes treated either medically (n=6), by keratectomy alone (n=44), or by combining keratectomy with a conjunctival (n=24) or porcine small intestinal submucosal graft (n=6). A sequestrum recurred in 7 of 35 eyes in which a bandage contact lens was placed, including 3 eyes with a small intestinal submucosal (SIS) graft. The difference in sequestrum recurrence between grafted eyes (17%) and those without grafts (25%) was statistically insignificant. Notable observations included postoperative discoloration of 4 contact lenses, 3 porcine SIS grafts,

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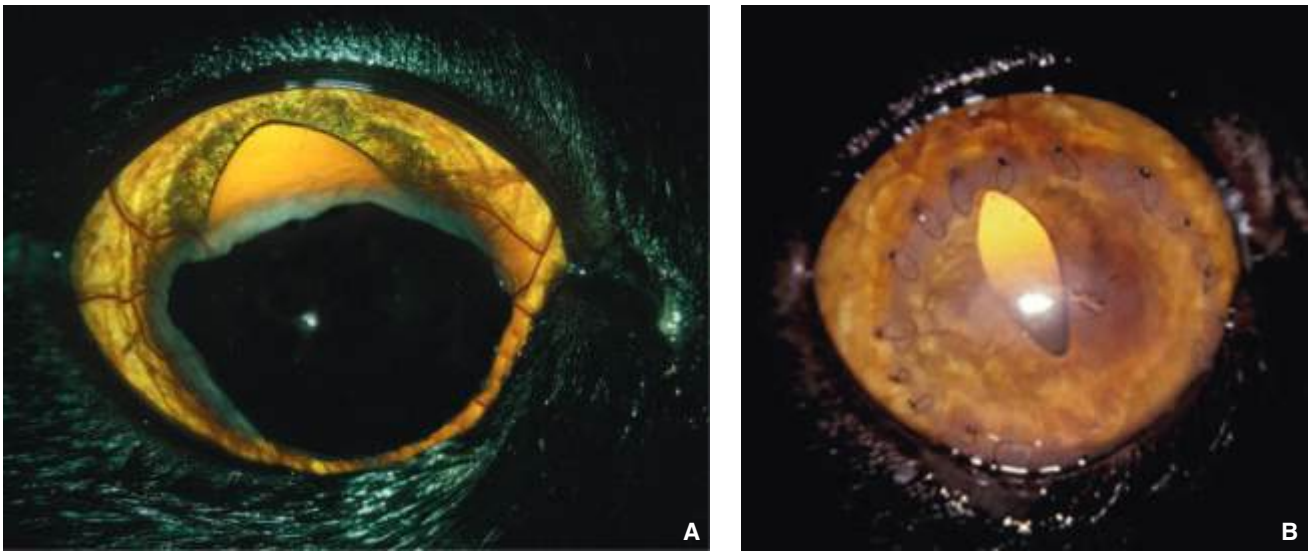


Figure 28.44 Corneal sequestrum of 1-year duration in a 6-year-old Domestic Shorthair. **A**. Preoperative appearance. At surgery the lesion extended to Descemet's membrane. **B**. 8 weeks after deep lamellar keratectomy and fresh lamellar corneal graft.

a single conjunctival island graft, and 2 conjunctival pedicle grafts (Featherstone & Sansom, 2004). Since SIS takes on characteristics of the tissue into which it is grafted, investigators warned that the biomaterial may be prone to discoloration, especially if the existing sequestrum is incompletely excised (Featherstone et al., 2001). A multilayered SIS graft and third eyelid flap were used following sequestrum excision in 34 feline eyes, with recurrence of a sequestrum in 4 cases (Goulle, 2012). A study of corneal reconstruction in dogs and cats using porcine urinary bladder submucosa (ACell Vet®, ACell, Columbia, MD, USA) included sequestrum excision and ACell® grafting in 32 feline eyes (Chow & Westermeyer, 2016). A sequestrum recurred in the graft bed of 1 cat 14 months after initial sequestrum excision and ACell application. Final results of the study were not tabulated according to specific corneal disease treated, which in addition to sequestrum (n=32) included corneal perforation (n=9), descemetocele (n=2), and deep corneal ulceration (n=1). Nevertheless, overall postoperative opacification in 38 cats following an ACell graft was negligible to mild in 66% (n=25), moderate in 24% (n=9), and severe in 11% (n=4). Another study using ACell Vet following sequestrum excision in 7 cats reported a 100% success rate, with residual scarring classified as mild (n=2), moderate (n=2), and severe (n=3; Balland et al., 2016). Transplantation of equine amniotic membrane resulted in good corneal transparency 12–20 weeks postoperatively following regression of secondary granulation tissue, with no recurrence of sequestra in 5 of 7 eyes (Barachetti et al., 2010). However, the authors advised against use of amnion in very deep or nonvascularized sequestra based on graft failure in the 2 remaining cats. Bovine pericardium has also been used to successfully graft the corneas of 3 cats after sequestrum excision, with focal corneal scarring reported 2 months after surgery (Dulaurent et al., 2014).

There were no recurrences following keratectomy and corneoconjunctival transposition in 17 eyes, all of which recovered with negligible corneal scarring in a median of 34 days (Andrew et al., 2001). In a larger retrospective report of corneoconjunctival transposition after keratectomy (Graham et al., 2017), sequestra recurred in 8.3% of cats (9 of 109 eyes). Though not statistically significant, the study suggested that younger cats are more likely to develop a recurrent sequestrum. A sequestrum occupying 40% of the corneal surface in a 1-year-old Persian was excised and successfully repaired using a bidirectional corneoconjunctival transposition, with no recurrence in the 6 months following surgery (Yang et al., 2019). Grafts were optically transparent within 2 months following keratectomy and lamellar keratoplasty using frozen canine (n=4) or feline corneal tissue (n=2) in 6 Persian eyes (Peña Gimenez & Fariña, 1998). Severe corneal edema and vascularization were described in an 8-year-old Burmese following penetrating keratoplasty using fresh canine cornea, but only a faint corneal nebula remained 16 months after surgery (Townsend et al., 2008). Laguna et al. (2015) performed lamellar (n=17) and full-thickness (n=1) keratoplasties with fresh homologous tissue in 2 cases, frozen homologous tissue in 6 eyes, and frozen heterologous grafts in 10 eyes. Faint corneal opacity remained in 83%, but a sequestrum recurred in only 1 eye.

The presence of residual pigmentation following keratectomy is thought to increase the risk of sequestrum recurrence (Blogg et al., 1989; Irving & Johnstone, 1988; Lightowler et al., 1987; Morgan, 1994), with a 38% recurrence following incomplete keratectomy in one study (Featherstone & Sansom, 2004). The authors also cautioned

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against transection of conjunctival pedicles in grafted eyes based on formation of a corneal abscess in 1 eye and recurrence of sequestration in 3 eyes after severing the grafts' blood supply (Featherstone & Sansom, 2004).

Acute Bullous Keratopathy

Acute bullous keratopathy (ABK) is a rare but distinctive feline disorder characterized by sudden onset of profound but relatively well-circumscribed corneal edema, with coalescing fluid bullae that disrupt and weaken the stroma's lamellar structure and dramatically alter corneal contour (Fig. 28.45). Synonyms include eruptive bullous keratopathy and acute corneal hydrops, the latter term favored by Pederson et al. (2016) based on similarities with acute corneal hydrops in humans and differences from the bullous keratopathy described in the Manx cat. The disorder tends to present unilaterally in young adult cats (Pederson et al., 2016). However, both eyes may be involved concurrently or sequentially (Glover et al., 1994; Pierce et al., 2016), and cats as old as 15 years have been affected (Pederson et al., 2016).

In one study, 13 of 21 (61.9%) eyes had a history of prior and/or concurrent ocular disease including keratitis, anterior uveitis, corneal sequestrum, granulomatous conjunctivitis, and glaucoma (Pederson et al., 2016). In another study that excluded patients with a history of chronic ocular disease, superficial corneal ulceration was present in 4 of 17 eyes (Pierce et al., 2016). Nonspecific findings accompanying the acute corneal change include excessive tearing, blepharospasm, and conjunctival hyperemia. The extremely edematous stromal bulla develops within hours and without warning. The lesion may vary from only a few millimeters in diameter to one that encompasses the entire corneal surface (Pierce et al., 2016). There is typically a distinct junction between the lesion and the normal cornea that surrounds it. The protruding tissue is initially gray to blue in color, but becomes progressively clearer as the edema coalesces and fluid bullae separate the stromal lamellae. Untreated, ABK can rapidly lead to corneal perforation. The condition may be misinterpreted as a collagenolytic stromal ulcer, although the latter is typically characterized by a gelatinous, sagging stroma with inflammatory cell infiltrates rather than sizable pockets of edema. The clinical features of ABK differ from the slowly progressive edema of Manx cats, even though the advanced stage of that heritable stromal dystrophy is also described as a bullous keratopathy (Bistner et al., 1976).

The underlying cause of ABK is unknown. Proposed etiologies include a defect of Descemet's membrane and the adjacent endothelium; a primary or inherited stromal dystrophy; or endothelial dysfunction (Moore, 2005; Pederson et al., 2016). In humans, breaks in Descemet's membrane are seen in cases of keratoconus complicated by acute hydrops (Fan Gaskin et al., 2014). An initial study of feline ABK found no abnormalities of Descemet's membrane or the endothelium in the 2 eyes submitted for histopathologic examination (Glover et al., 1994). Histologic ruptures of Descemet's membrane and the associated endothelium have since been described, accompanied by marked stromal edema and focal loss of keratocytes (Dubielzig et al., 2010, Fragola et al., 2017; Pierce et al., 2016). SD-OCT identified fluid pockets that severely disrupted stromal organization, but the thickness of the bulla prevented endothelial evaluation (Famose, 2014). SD-OCT documented a focal detach-



Figure 28.45 Acute bullous keratopathy characterized by a well-defined protrusion of markedly edematous, structurally compromised corneal stroma in (**A**) a 3-year-old Domestic Shorthair and (**B**) a 6-year-old Domestic Shorthair. Both cats were treated successfully using a third eyelid flap.

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ment of Descemet's membrane adjacent to a deep stromal opacity in the cornea of a 1-year-old DSH cat with ABK in the opposite eye. It is unknown whether the lesion represented an *in vivo* precursor to ABK, since the cat was lost to follow-up (Schlesener et al., 2018). There is little to no histologic evidence of inflammation, with only occasional leukocytes or small pockets of neutrophils within the tissue (Dubielzig et al., 2010; Glover et al., 1994). Cytology, culture, and serology have failed to detect any bacterial, viral, protozoal, and fungal organisms (Glover et al., 1994; Pierce et al., 2016). Any concurrent systemic disease appears to be coincidental based on the diversity of reported diagnoses (Pederson et al., 2016; Pierce et al., 2016).

Martin's observation that ABK might be linked to treatment with topical and/or systemic dexamethasone (Martin, 2009) was followed by a report of ABK in 2 cats treated with systemic prednisolone and cyclosporine (Evans et al., 2008) and a retrospective study documenting the use of topical and/or oral steroids in 9 of 19 cats (47.3%) with ABK (Pederson et al., 2016). However, a review of ABK in 10 cats with systemic disease requiring immunosuppressive therapy concluded that systemic cyclosporine therapy was a significant risk factor for ABK ($P<0.001$) while systemic prednisolone was not ($P=0.10$; Pierce et al., 2016).

In acute hydrops of the human eye, the break in Descemet's membrane is thought to heal by reattachment of the membrane to the posterior stroma, followed by migration of the endothelium and subsequent fibroplasia over the remaining gap (Fan Gaskin et al., 2014). The size of the defect understandably influences the healing time. Some instances of feline ABK have responded to medical treatment using topical 5% sodium chloride and/or antibacterials (oxytetracycline, neomycin-polymyxin B-bacitracin, and/or tobramycin) administered for weeks to months. At last recheck in one study, 3 of 6 medically treated eyes with adequate post-therapeutic follow-up were sighted (Pierce et al., 2016). Smaller lesions are realistically the only candidates for medical management alone. For more extensive lesions, surgical options are generally grouped into those that provide tectonic support, including conjunctival pedicle and corneal grafts, and those that tamponade the bullous tissue, including nictitating membrane flaps and tarsorrhaphies. Although conjunctival pedicle grafts have been the predominant technique employed in single (Pattullo, 2008; Schlesener et al., 2018) and small-group case studies (Glover et al., 1994), failures have been reported (Glover et al., 1994). A frozen lamellar corneal graft was used to successfully treat ABK in 2 young DSH cats (Hansen & Guandalini, 1999). Convincing evidence of the effectiveness of a nictitating membrane flap for ABK was provided in a retrospective study of 21 eyes (Pederson et al., 2016). The flap was combined with a topical and/or oral antibacterial in all patients and left in place for a median of 15 days (range 6–30 days). Additional topical medications such as 5% sodium chloride were infrequently prescribed. Resolution of ABK occurred in 90.5% of the treated eyes (Pederson et al., 2016). Conjunctival or corneal grafts are indicated in instances of corneal perforation. Enucleation may be required in patients with extensive perforating lesions.

Corneal Dystrophies and Degenerations

Corneal dystrophy is defined as a primary inherited, bilaterally symmetric corneal disease, unassociated with prior inflammation or systemic disease. Feline corneal diseases that conform to this definition are rare (Fig. 28.46A). The familiar stromal lipid dystrophies of dogs are virtually unheard of in cats. The only reports of dystrophy in cats describe endothelial dysfunction and secondary stromal edema. An inbred line of Manx cats developed marked corneal edema and disintegration of stromal collagen, beginning at 4 months of age (Bistner et al., 1976; Dice, 1980). A recessive mode of inheritance was proposed. The disease inevitably progressed over a 2-year period, culminating in bullous keratopathy. Secondary epithelial changes included intracellular edema and separation of the basal cells from their basement membrane. The pathogenesis of the edema is unknown, since the original report found no ultrastructural abnormalities within the endothelium. The condition has seldom been documented since its original description. Endothelial dystrophy also occurs in DSH cats, with stromal edema beginning in the central cornea at 3–4 weeks of age, progressing peripherally but ultimately sparing the perilimbal cornea (Cooley & Dice, 1990; Crispin, 1982; Olin & TenBroeck, 1973). Bullous keratopathy and epithelial thinning are late complications. The earliest histopathologic change is cytoplasmic vacuolation of the endothelial cells (Crispin, 1982). There is no specific treatment, although penetrating keratoplasty may be a viable alternative in cats (Bahn et al., 1982; Brunette et al., 2011).

Lipid keratopathy/degeneration is also rare in the cat and is almost always associated with prior damage to the cornea (Crispin, 2002; Fig. 28.46B). In contrast to heritable corneal dystrophies, acquired corneal degenerations may be unilateral or bilaterally asymmetric. Lipid and/or mineral deposition accompanies corneal inflammation and vascularization. The infiltrate can develop without concurrent systemic lipid abnormalities, but hyperlipidemia may modify the appearance and progression of the keratopathy (Crispin, 1982). Few examples of feline lipid degeneration exist in the literature. A lipid infiltrate was considered a complication of chemical irritation in a Siamese cat (Kipnis, 1975). A 3-year-old DSH developed progressive corneal lipid infiltration and vascularization 4 months after a traumatic ulcer complicated by an anterior synechia (Carrington, 1983). Histopathology of the excised refractile lesion showed crystalline and globular lipids along with subepithelial lymphocytes, plasma cells, and activated keratocytes. The lesion recurred 3 weeks after

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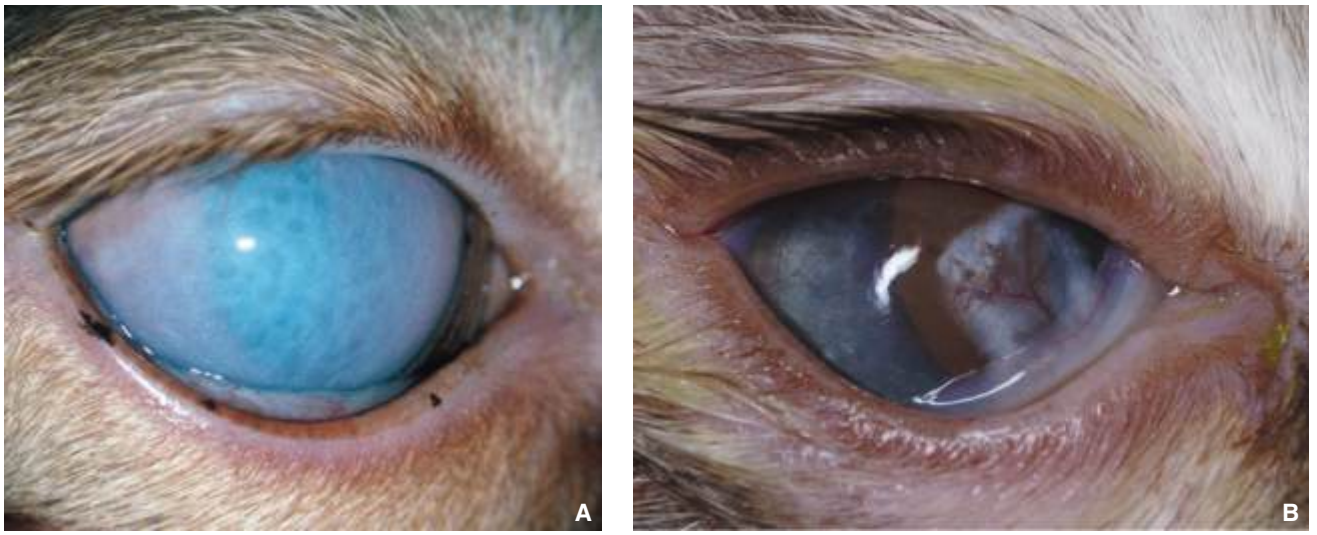


Figure 28.46 Corneal dystrophy/degeneration. **A**. Presumed endothelial dystrophy in a 3-year-old Domestic Shorthair with bilateral progressive corneal edema beginning at 4 months of age. **B**. Corneal degeneration with lipid deposition and vascularization following corneal ulceration in a 3-year-old Siberian cat.

surgery, likely influenced by a concurrent twofold elevation in fasting serum cholesterol. A fan-shaped refractile lipid infiltrate developed in the vascularized cornea of a DSH following a cat claw injury (Crispin, 1993). A 5-year-old DSH with a vascularized corneal sequestrum also developed a lipid infiltrate (Featherstone & Sansom, 2004). Under natural conditions, stromal calcification or band keratopathy is rare in cats, but has been described in association with experimental stromal FHV-1 infections (Nasisse et al., 1989b). In another example of corneal mineralization, authors theorized that topical steroid therapy potentiated the necrosis and initiated the mineralization of a corneal sequestrum in an 8-month-old cat with a history of FHV-1 keratoconjunctivitis (Gemensky & Wilkie, 2001). Subepithelial mineral deposits were described in conjunction with a corneal hemangiosarcoma in a 10-year-old DSH (Cazalot et al., 2011). Corneal degeneration must be differentiated from infectious crystalline keratopathy that appears as a white branching refractile stromal opacity, usually at the margin of a corneal ulcer, facet, or sequestrum (Ledbetter et al., 2017). Corneal infection by the protozoa *Encephalitozoon* (*Nosema*) is also characterized by stellate superficial corneal opacities that resemble lipid deposits (Buyukmihci et al., 1977).

Bilateral arcus lipoides corneae, characterized by a circumferential perilimbal lipid infiltrate, was described in an 18-month-old Persian with hypercholesterolemia that followed bacterial pyelonephritis and septicemia (Crispin, 1993). Two instances of transient corneal lipidosis have been reported in cats followed intravenous lipid therapy for permethrin toxicosis (Seitz & Burkitt-Creedon, 2016; Yuh & Keir, 2018). Slit-lamp examination revealed bilateral diffuse corneal opacification 36–42 hours after administration of a 20% lipid emulsion in both cats, accompanied by marked hypertriglyceridemia. The corneal changes spontaneously resolved within 3–7 days as the serum triglyceride levels decreased.

Corneal cloudiness is a common feature in cats with lysosomal storage diseases, including GM1- and GM2-gangliosidosis, α-mannosidosis, and mucopolysaccharidosis I and VI. Each of these recessively inherited inborn errors of metabolism is linked to a specific enzymatic deficiency that causes accumulation of a substrate – lipid, glycoprotein, or mucopolysaccharide – within the lysosomes (Skelly & Franklin, 2002). The ground-glass appearance of the corneas (Haskins et al., 1979) is attributed to the presence of vacuolated stromal cells (Haskins et al., 1983), disruption of the orderly collagen structure within the stroma (Alroy et al., 1999), and alterations in collagen fibrils following transformation of keratocytes to myofibroblasts (Yuan et al., 2016).

Corneal Dermoids

Although the lateral canthus may be the most common location for feline ocular dermoids (Barnett & Crispin, 1998), corneal dermoids have been described in the DSH and Birman breeds (Hendy-Ibbs, 1985) and lateral limbal dermoids have been seen in Burmese and DSH cats (Koch, 1979; Nasisse, 1991). Bilateral corneal and lateral canthal dermoids also accompanied multiple ocular anomalies in an 18-month-old DSH cat with microphthalmia, ankyloblepharon, and facial deformities resembling Goldenhar syndrome in humans (Berkowski et al., 2018). Lamellar keratectomy is the treatment of choice. If the excision includes both cornea and conjunctiva, the conjunctiva should be tacked at the limbus to prevent inadvertent conjunctival adhesions to the

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denuded stroma. The corneal defect will epithelialize rapidly, but the site should be monitored for vascular incursion that can increase postoperative corneal opacity.

Corneal Neoplasia and Nodules

Neoplasia of the feline cornea is rare. Expansion of a conjunctival, limbal, or intraocular tumor into the cornea is considered far more likely than development of a primary neoplasm in this normally avascular tissue (Fischer et al., 2002). Feline corneal tumors resulting from the extension of ocular or periocular tumors include SCC (Fischer et al., 2002), limbal melanoma (Harling et al., 1986), lymphoma (Corcoran et al, 1995; Ota-Kuroki et al., 2014), anterior uveal melanoma (Dubielzig et al., 2010), and post-traumatic ocular sarcoma (Dubielzig, 1990).

Squamous neoplasms of the ocular surface have a preference for areas of epithelial transition and are therefore frequently limbal in location (Fischer et al., 2002). SCC originated at the limbus and extended into the cornea in two DSH cats, 13 and 16 years of age, each with a history of progressive keratitis appearing as raised foci of granulation-like tissue unresponsive to symptomatic steroid therapy (Scurrell et al., 2013). No complications were documented in the 6 months following enucleation in 1 cat. The second cat was euthanized 3 months following enucleation due to pain and weight loss. Histopathology demonstrated intraocular invasion of the iridocorneal angle and anterior uvea, with formation of a retrocorneal neoplastic membrane in each eye. A primary corneal SCC was diagnosed histopathologically in a 15.5-year-old cat with a history of chronic herpetic keratitis and clinical signs that included corneal edema, vascularization, pigmentation, and a central descemetocele (Nappier et al., 2017). The tumor penetrated the cornea and infiltrated the iridocorneal angle. The cat was euthanized due to progressive renal disease, with no evidence of local invasion or metastatic SCC in the brief 2-week period following enucleation.

Appearing as two distinct but adjoining masses occupying most of the cornea surface, an SCC and hemangioma were simultaneously diagnosed in the cornea of a 14-year-old DSH (Perlmann et al., 2010). The tissue of origin could not be determined, though a conjunctival origin for the SCC and a limbal origin for the hemangioma were proposed. No local recurrences or metastases were noted in the 8 months following exenteration. Another example of a "collision tumor" was included in a retrospective study of corneal vascular neoplasia, with a coexisting SCC and hemangiosarcoma in a 7-year-old DSH (Shank et al., 2019); 3 of 4 additional cats in the study were diagnosed with corneal hemangiosarcoma, 2 of which were centered in the cornea. A corneal hemangioma in the remaining cat displayed less than 10% limbal attachment. No follow-up information was available for any of the 5 study subjects. A presumed primary hemangiosarcoma appeared as a rapidly growing, raised, multilobulated red mass in the cornea of a 10-year-old DSH, once again with a history of chronic keratitis (Cazalot et al., 2011). No local recurrences or metastases were observed in the 18 months following enucleation, the latter performed when the tumor recurred 3 weeks following keratectomy.

An intermediate-grade corneal fibrosarcoma appeared as a slow-growing pink exophytic mass in the axial cornea of a 12-year-old DSH with a prior history of corneal sequestration (Strong et al., 2016). No evidence of local recurrence or metastases was noted 6 months after diagnosis and enucleation. A smooth, pink exophytic perilimbal fibrosarcoma invaded the cornea of a 4-year-old DSH, with no recurrence following keratectomy and sclerectomy (Barnett & Crispin, 1998).

Limbal melanocytoma is also referred to as limbal or epibulbar melanoma. This pigmented subconjunctival tumor originates from neoplastic transformation of melanocytes located close to the limbus near Descemet's membrane (Grahn & Peiffer, 2007). The tumor tends to develop in the dorsolateral aspect of the globe, extending into the deep cornea in a fan-shaped pattern and spreading outward onto the adjacent episcleral surface, deep to the limbus and conjunctiva (Fig. 28.47). As in dogs, feline limbal melanocytomas are generally regarded as benign and slow growing, unlikely to infiltrate intraocularly or metastasize (Grahn & Peiffer, 2007; Harling et al., 1986). Even so, there are 2 reports of distant metastases attributed to limbal-based melanomas in cats. A 13.5-year-old DLH cat with documented local tumor recurrence and distant metastases died 6 months after initial presentation. Notably, the tumor in this case was amelanotic, with 2–3 mitotic figures per high-power field (Day & Lucke, 1995). In another example of metastatic potential, a 6-year-old DLH cat died 32 months after initial tumor excision and cryotherapy (Betton et al., 1999). Although there was no local tumor recurrence, postmortem examination documented metastases to spleen, liver, lungs, heart, bone, all lymph nodes, adrenal glands, and both eyes. Considering the long clinical latency, the authors suggested revising the description for feline limbal melanoma from benign to malignant, with delayed growth of metastases. Differential diagnoses for limbal melanocytoma include extraocular extension of uveal melanoma, conjunctival melanoma, and staphyloma (Grahn et al., 2005; Skorobohach & Hendrix, 2003). Management of limbal melanocytomas includes periodic photographic surveillance, partial or full-thickness surgical excision with or without grafting, laser ablation (Sullivan et al., 1996), cryotherapy (Harling et al., 1986), or various combinations of these modalities. A pigmented spot persisted at the tumor site following lamellar sclerectomy and cryosurgery, but no additional growth was noted in the 32 months following surgery in a 6-year-old DLH (Betton et al., 1999). Autologous third eyelid cartilage was used to repair the corneoscleral defect following full-thickness

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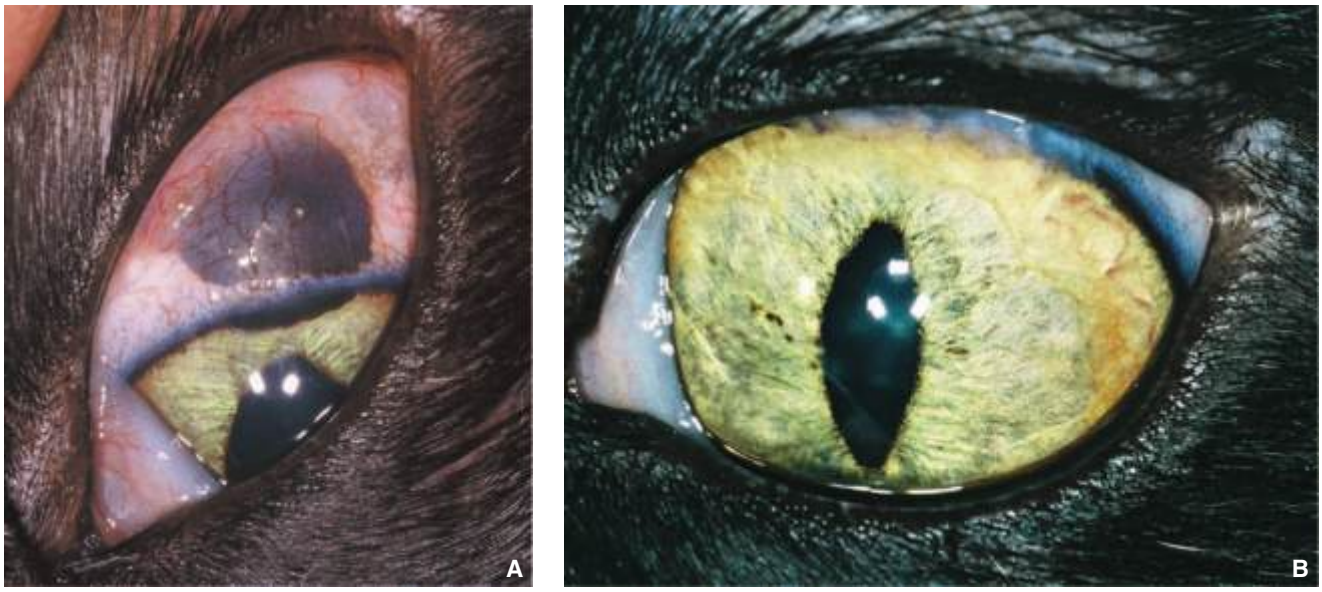


Figure 28.47 **A**. A subconjunctival limbal melanocytoma extends into the deep cornea in a fan-shaped pattern. **B**. The same eye following excision and repair using a full-thickness scleral homograft. (Courtesy of Dr. Caryn Plummer.)

excision of a limbal melanoma in a 12-year-old DSH, with no recurrence in an 85-day postoperative observation period (Kanai et al., 2006). A 2.5-year DFI was reported after tumor excision, adjunctive Nd:YAG laser therapy, and repair of the surgical defect with a biosynthetic graft (ACell Vet) in a 4-year-old DSH (Plummer et al., 2008).

A proliferative corneal lesion originating at the temporal limbus and histologically resembling fibrous histiocytoma has been described in a DSH cat (Smith et al., 1976). Like its canine counterpart, the mass was characterized by lymphocytes, plasma cells, histiocytes, and active fibroplasia. Keratectomy of the lesion was curative. Mild perilimbal infiltration in the anterior third of the corneal stroma developed in conjunction with bilateral temporal episcleral nodules in a 7-year-old European Shorthair cat (Grillot et al., 2018). The smooth, subconjunctival nodules were characterized by cellular aggregates of various inflammatory cells, especially macrophages and lymphocytes, intermingled with fibroblastic fibers, consistent with nodular granulomatous episcleritis. The lesions resolved in response to a tapering regimen of topical dexamethasone, with no recurrence in a 6-month post-treatment period.

Diseases of the Anterior Uvea

The neonatal feline iris appears blue to blue-gray, developing its adult coloration around 8 weeks of age. The mature feline iris is lightly colored, with a spectrum that includes blue, green, yellow, and gold, or combinations thereof. The overall lighter coloration may reflect a greater proportion of pheomelanin to eumelanin within the iris stroma (Alario et al., 2013). The colored feline iris also lacks a pigmented cell layer in the anterior iris stroma typical of brown-eyed dogs and has less pigmentation surrounding its iridal vessels (Alario et al., 2013). As in other species, pigmentation in blue eyes is limited to the iridal posterior neuroepithelium and absent within the iris stroma (Alario et al., 2013). Using magnification and oblique illumination, the fine texture of the feline iris is more easily visualized compared to that of the darker brown canine iris. Particular attention should be given to the ridges and crypts that characterize the anterior iris face, since edema and cellular infiltrates often obscure these fine details early in uveal inflammatory disease. Vessels situated within the iris stroma are more superficial in cats compared to dogs (Alario et al., 2013). The serpentine character of the major arterial circle in the peripheral iris is also easily appreciated in these lightly colored eyes.

The cat's vertically elliptic pupil is regulated by two autonomically innervated antagonistic muscles. The iris sphincter is parasympathetically controlled via the oculomotor and short ciliary nerves. The cat has only two short ciliary nerves that exit the ciliary ganglion: the nasal nerve that innervates the medial half of the sphincter and the malar nerve that supplies the lateral half (Scagliotti, 1980). A lesion affecting a single short ciliary nerve produces a hemi-dilated pupil with a D or reverse-D shape, determined by the nerve and the eye affected. For example, a lesion involving the nasal nerve produces a D-shaped pupil in the right eye and a reverse-D in the left. The dilator muscle is sympathetically innervated via the cranial cervical ganglion and ophthalmic nerve.

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Developmental or Structural Disorders

Variations in Iris Color

Heterochromia refers to a difference in color within the iris of one eye (heterochromia iridis) or between the two eyes (heterochromia irides). The variation is most common in white cats of any breed (Fig. 28.48) and in those breeds with predominantly white coats, including the Turkish Van, Turkish Angora, Japanese bobtail, and Khao Manee.

Pale iris coloration is a distinguishing feature of cats with Chédiak-Higashi syndrome, first recognized in blue-smoke Persians (Collier et al., 1979; Kramer et al., 1977). Affected irises are pale yellow-green rather than the bold yellow or copper of unaffected animals (Fig. 28.49). The irises of affected cats also appear thin, with a basket-weave pattern visible to the unaided eye.

Uveal Pigmentation in White and Siamese Cats

Blue-eyed white cats lack pigment in their iris and choroidal stroma due to the absence of pigmented cells normally derived from the embryonic neural crest. Presumably the progenitor cells either fail to migrate to the ocular tissue, fail to differentiate into uveal pigment cells, or fail to survive (Cable et al., 1995). The Siamese cat is also deficient in ocular pigment, but its blue eyes are the result of defective pigment production (Thibos et al., 1980). Pigment cells within the Siamese iris and choroid contain little to no pigment.

The causative mutation for the *siamese* temperature-sensitive allele has been identified in tyrosinase (TYR), an enzyme required for melanin production in mammals (Lyons et al., 2005). The TYR gene corresponds to the *color* locus in cats, and its alleles, from dominant to recessive, are designated as C (full color) > c^b (*burmese*) ≥ c^s (*siamese*) > c (*albino*) (Imes et al., 2006). In the Siamese, there is also a relative decrease of pigmentation in the iridal and retinal pigment epithelia that originate from the embryonic eye cup, in contrast to the normal pigmentation of these cells in the white cat (Thibos et al., 1980).



Figure 28.48 Iris heterochromia in a white Domestic Shorthair cat. (Courtesy of Dr. Caryn Plummer.)

The presence of blue irides in cats is often linked with other functional abnormalities. The white (W) pigment gene in cats is autosomal dominant over color, but distinct from albinism. Unlike dogs homozygous for the merle gene, homozygous blue-eyed white cats do not typically have visual deficits (Levick et al., 1980), but are instead prone to deafness (Bergsma & Brown, 1971; Mair, 1973). As early as 1868, Darwin noted in his book *The Variation of Animal and Plants under Domestication* that "white cats, if they have blue eyes, are almost always deaf." The prevalence of deafness is greater when blue eyes are bilateral (65%/85%) than if unilateral (39%/40%; Bergsma & Brown, 1971; Mair, 1973). While white coat color is clearly a dominant trait, inheritance of blue eyes and deafness is described as autosomal non-Mendelian, with incomplete penetrance (Kral & Lomber, 2015). Evidence supports a pleiotropic gene, with heritability coefficients of 0.75 for blue eyes and 0.55 for deafness, but investigators have not ruled out a polygenic effect (Geigy et al., 2007). Congenitally deaf cats exhibit superior localization of peripheral visual stimuli and enhanced visual sensitivity to motion compared to cats with normal hearing, a phenomenon attributed to cross-modal plasticity and reorganization of specific regions of the auditory cortex (Butler et al., 2017; Lomber et al., 2010). It is often suggested that the blue-eyed, deaf white cat is the feline homologue of Waardenburg's syndrome, although



Figure 28.49 Chédiak-Higashi syndrome (CHS). This blue-smoke-colored 4-year-old Persian has a pale yellow iris with a basket-weave appearance typical of the disorder. Its cataract is unrelated to the CHS. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

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cats do not demonstrate the spectrum of facial features noted in the human condition (Faith, 1979). The feline albino locus (C) also produces a solid white haircoat and blue irises, but deafness has not been associated with albinism (Oetting et al., 2003).

Neuroanatomic abnormalities in the visual pathways of blue-eyed Siamese cats give rise to crossed eyes (convergent strabismus or esotropia), nystagmus, and decreased stereopsis (Johnson, 1991; Kaas, 2005). Part of the temporal retina that normally projects to the ipsilateral lateral geniculate nucleus (LGN) instead projects to the contralateral LGN (Guillery & Kaas, 1971; Hubel & Wiesel, 1971; Kalil et al., 1971; Leventhal, 1982). While abnormal retinogeniculate pathways exist in every Siamese cat, the degree of involvement varies (Cooper & Pettigrew, 1979; Stone et al., 1978). The abnormal projections originate from a vertical strip of retina about 20–25° in width located just temporal to the area centralis (Guillery & Kaas, 1971). Compared to a normally pigmented cat, the Siamese demonstrates a more gradual transition from the contralateral pattern of projection typical of the nasal retina to the mostly ipsilateral projection of the temporal retina (Stone et al., 1978).

The abnormal contralateral projection creates a mirror or inverted image of the normal representation (Guillery et al., 1974). While this misalignment would be expected to create substantial visual impairment in the Siamese, adjustments in the cortex reduce the behavioral impact of the misdirected projections. The cats either suppress a portion of the input to the visual cortex (i.e., the Midwest cat; Kass & Guillery, 1973) or rearrange the relay of the abnormal projections in the visual cortex (i.e., the Boston cat; Hubel & Wiesel, 1971). Most Siamese cats probably possess a mixed pattern of cortical organization that combines both mechanisms (Cooper & Blasdel, 1980). Nevertheless, Siamese cats lack both binocular vision (Kaas & Guillery, 1973) and stereoscopic depth perception (Packwood & Gordon, 1975) and are virtually blind in the nasal hemifield when they view the world with only one eye (Elekessy et al., 1973; Guillery & Casagrande, 1977). Reduced numbers of receptors and ganglion cells in the Siamese retina, including a lower percentage (8%) of W- and X-type ganglion cells compared to normal cats (32%; Chino et al., 1977; Stone et al., 1978), may be responsible for other alterations in vision such as a decrease in visual resolution (Blake & Antoinetti, 1976).

Esotropia or convergent strabismus may accompany these neuroanatomic abnormalities, developing during the third month of age (Blake & Crawford, 1974; Fig. 28.50). Since the patterns of visual activation by each eye are independent and lack binocular interaction in the visual cortex, there is no advantage to normal ocular alignment. The convergent strabismus may in fact be beneficial, providing an overlapping albeit independent view of a few degrees of frontal vision (Guillery & Casagrande, 1977; Kaas, 2005). Surgical correction of the strabismus is neither indicated nor recommended (Johnson, 1991; Stiles, 2013). Nystagmus may be more common than strabismus (Johnson, 1991). Contradictory stimuli reaching the rostral colliculus and tectum may initiate the involuntary ocular oscillations, but an exact mechanism is yet to be determined (Apkarian, 1996).



Figure 28.50 Esotropia in a feral Domestic Shorthair cat of unknown age.

Albino cats, with no retinal pigmentation, have a more extensive abnormal projection from the contralateral eye to the LGN than the Siamese (Creel et al., 1982b; Leventhal et al., 1985; Pospichal et al., 1995). Misrouted projections of the central visual pathways are also present in cats with Chédiak-Higashi syndrome (Creel et al., 1982a).

Congenital Iris Anomalies

Persistent pupillary membranes (PPMs) are relatively uncommon in cats when compared to dogs. There is no apparent breed or sex predisposition. Normally the pupillary membrane regresses during late fetal development and into the immediate postnatal period (Cook, 2007). PPMs are vestiges of this embryonic vascular network, originating at the iris collarette, a region of the iris face midway between the pupillary margin and peripheral iris base. The point of origin helps differentiate PPMs from postinflammatory adhesions (synechiae) that typically incorporate the pupillary margin. PPMs are either confined to the iris surface (Fig. 28.51) or extend from the iris face to the posterior cornea or to the anterior lens capsule, where they produce nonprogressive opacities at the attachment site (Fig. 28.52). The residual strands are variably pigmented, thick or thin, singular or multiple, and may even appear as a fiber web spanning the pupil. Thin, lightly pigmented iris

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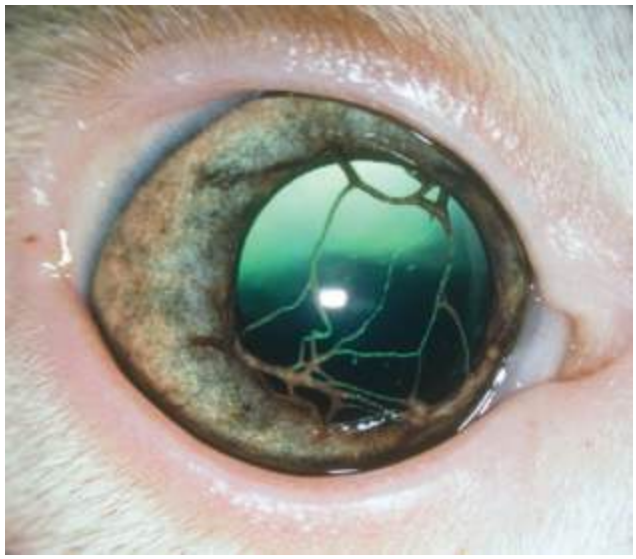


Figure 28.51 A network of persistent pupillary membranes originates at the iris collarette and spans the pupil in this adult Domestic Shorthair.



Figure 28.52 A central corneal scar results from persistent pupillary membranes that extend from iris to cornea in a 6-month-old Domestic Shorthair.

face PPMs may continue to regress in kittens up to 3–4 months of age, but are permanent thereafter. Those PPMs with corneal or lens attachments do not regress. Any associated corneal opacity is likely fibrotic and variably pigmented, but secondary edema is conceivable in severely affected eyes. Anterior capsular fibrosis and pigmentation accompany iris-to-lens PPMs, but true subcapsular cataract formation is unlikely. Patency of a PPM was noted in a blue-eyed 3-year-old DSH cat during a fluorescein angiography study of normal feline eyes (Alario et al., 2013). Treatment of PPMs is seldom indicated. Although pharmacologic dilation might improve vision in the rare patient with extensive axial opacities, secondary tension on the membranes could potentially aggravate the corneal or lens lesions (Hendrix, 2007). Most PPMs are identified in otherwise normal eyes, but also coexist in domestic and exotic cats with other ocular anomalies such as lenticonus (Bauer et al., 2015), persistent hyperplastic tunica vasculosa lentis/primary vitreous (Allgoewer & Pfefferkorn, 2001), and various ocular colobomas, including eyelid agenesis (Bellhorn et al., 1971; Cutler, 2002; Schäffer et al., 1988). Two of four DSH kittens in Martin's study of feline colobomatous syndrome exhibited deep endothelial opacities consistent with prior PPM attachments (Martin et al., 1997).

Rare instances of anterior segment dysgenesis (ASD) have been described in cats, with broad adherence of the iris to the posterior cornea (Dubielzig et al., 2010; Hamoudi et al., 2013; Williams, 1993). Synonyms include anterior segment cleavage syndrome and Peters' anomaly. The space normally representing the anterior chamber is narrowed or nonexistent. Notable corneal opacification is associated with segmental histologic defects in Descemet's membrane and the corneal endothelium, where the uveal and corneal tissues blend. Concurrent anomalies may include microphthalmia (Berkowski et al., 2018) and failure of separation of the cornea and lens (keratolenticular dysgenesis; Berkowski et al., 2018; Peiffer, 1983b). The 18-month-old DSH in Berkowski's report also demonstrated corneal dermoids and craniofacial defects reminiscent of Goldenhar syndrome in humans (Berkowski et al., 2018). In general, ASD begins with abnormal kerato-lenticular separation, followed by mechanical impairment of axial neural crest cell migration (Cook, 1995). The cause of the anomaly in cats is unknown, but *in utero* exposure to teratogens (Cook & Sulik, 1988) and heritability (Hamoudi et al., 2013) have been implicated.

Congenital iris and ciliary body cysts occur in cats on rare occasion (Stiles, 2013), a consequence of incomplete fusion of neuroectoderm destined to form the bilayered iris and ciliary epithelia. Like the adult counterpart, these early cysts are smooth and spherical and tend to remain attached to the posterior iris or the pupillary margin (Peiffer, 1977). Examination of the cyst with a focal light source may reveal its translucent nature, but feline cysts tend to be more heavily pigmented and not as easily transilluminated as those seen in dogs. Treatment is seldom indicated, but surgical removal (Belkin, 1983) and deflation using a diode laser (Gemensky-Metzler et al., 2004) have been described.

Iris colobomas are characterized by a notch-like defect in the pupil, most often occurring in the ventromedial iris (Barnett & Crispin, 1998). The iris defect may be full or partial thickness, the latter not only altering the pupil shape but also exposing the posterior pigmented layers of

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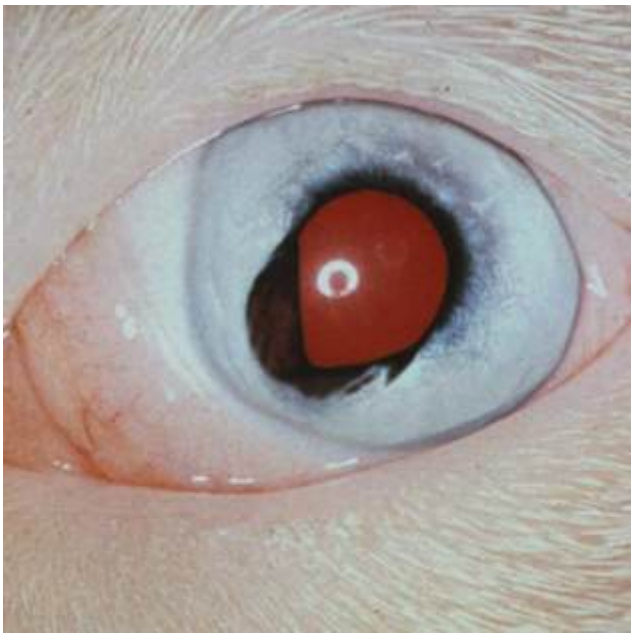


Figure 28.53 Iris coloboma in a 1-year-old Domestic Shorthair, altering the pupil shape and exposing the posterior pigmented layer of the iris. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

the iris (Fig. 28.53). Though rare in cats, iris colobomas may be associated with other colobomatous defects of the eyelid (Bellhorn et al., 1971; Cutler, 2002), choroid/sclera, and optic disc (Bellhorn et al., 1971). Image degradation attributed to an iris coloboma was proposed as a cause of LGN atrophy in a 6-month-old cat, although the study failed to rule out additional ocular abnormalities either clinically or histologically (Richards, 1977). Presumed iris hypoplasia accounted for constant mydriasis in 2 of 4 normally sighted Korat kittens in which only a small circumferential rim of iris tissue could be visualized and the major arterial circle could not be identified (Slenter et al., 2018). Other congenital pupillary abnormalities such as corectopia (abnormal pupil position) are equally rare, and may be confused with the convergent strabismus seen in the Siamese (Fig. 28.54).



Figure 28.54 The left pupil tilts along its vertical axis and is offset nasally in a 4-month-old Burmese with bilateral corectopia.



Figure 28.55 Iris atrophy in a 16-year-old Tonkinese, through which the tapetal reflection can be seen. A dark-walled iris cyst arises at the medial pupillary margin.

Acquired Iris Abnormalities

Iris Atrophy

Iris atrophy occurs in cats less frequently than in dogs. The problem is generally one of older cats, but iris thinning and loss of surface texture can also follow chronic uveitis or glaucoma. Blue-eyed cats may be more commonly affected (Stiles, 2013). Iris innervation appears to play a role in the structural integrity of the primate anterior uvea, but ciliary ganglionectomy failed to affect the ocular smooth muscles or cause iris degeneration in cats as it did in monkeys (Armaly, 1968). Iris atrophy may be focal or diffuse, recognized by an irregular pupillary margin, by distinct defects in the iris stroma, or by thinning that simply permits visualization of the tapetal reflection through the stroma (Fig. 28.55). Any clinical significance is usually limited to the relative mydriasis and incomplete pupillary constriction that accompany the iris sphincter defect, predisposing to photophobia due to unrestricted light entry. The mydriasis may also be misinterpreted as an afferent or efferent neurologic deficit if the atrophy is not recognized on cursory examination.

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Iris Cysts

Acquired iris cysts are more common than those that occur congenitally. The pigmented epithelium of the iris (or, less commonly, the ciliary body's inner epithelium) may undergo spontaneous cystic hyperplasia in the absence of inflammation or other predisposing factors. Cysts are also a consistent finding in cats with a history of blunt ocular trauma (Dubielzig et al., 2010). In contrast to canine iris cysts, those in cats tend to be bilateral, multiple, elongate, or ovoid in shape, more darkly pigmented, and seldom, if ever, free-floating (Belkin, 1983; Dubielzig et al., 2010; Peiffer, 1977; Fig. 28.56). With a mean age at presentation of 10.25 years, Burmese (n=21) and female cats (n=23) were overrepresented in a retrospective study of 36 cats with uveal cysts (Blacklock et al., 2016). Cysts tended to arise at the ventral (n=20) or medial (n=11) pupillary margin or at multiple sites around the pupil (n=12). Large or multiple cysts may displace the iris anteriorly, causing modest elevations in intraocular pressure (IOP) by compromising the iridocorneal angle and/or predisposing to collapse of the ciliary cleft, particularly after pharmacologic pupil dilation (Blacklock et al., 2016; Gemensky-Metzler et al., 2004). In 7 cats with anterior iris displacement, mean IOP increased from 19.5 to 24.6 mmHg following pupillary dilation with tropicamide (Gemensky-Metzler et al., 2004).

A cyst is more likely than a neoplasm if similar changes are noted in the contralateral eye or if the mass appears within the pupillary space (Fragola et al., 2018). Because feline cysts are often characterized by multiple pigmented walls within a single cyst, multilayered cyst walls, and/or a hyperplastic iris pigmented epithelium, transilluminating the cyst with a bright light may not be as reliable as in other species in distinguishing a cat's cyst from a uveal melanoma (Fragola et al., 2018). This difficulty has been substantiated in 2 studies in which patients were either referred because of a suspected tumor (Gemensky-Metzler et al., 2004) or eyes were regrettably enucleated on that suspicion (Fragola et al., 2018). In the latter review of 14 enucleated eyes, the examining clinician specifically stated that the lesion did not transilluminate in 6 cases. Other misleading clinical features included a darkly pigmented lesion (n=11) or a mass effect within the iris (n=6), the latter ultimately attributed on histopathology to distortion of the iris leaflet by a retro-iridal cyst. High-resolution ultrasound (HRUS) may help differentiate cysts from solid masses, but standard ultrasound failed to conclusively make that distinction in 2 cases (Fragola et al., 2018). Even HRUS may not adequately differentiate a thick-walled feline cyst from a cystic neoplasm (Fragola et al., 2018).

Treatment is seldom necessary. The exception may be in patients with multiple or sizable cysts that displace the iris anteriorly, especially if IOP is increased. Less likely are cysts that impair vision or mechanically damage the corneal endothelium. Although cysts have been irrigated, aspirated, and surgically extracted from the feline eye (Belkin, 1983; Peiffer, 1977), contemporary treatment is more likely to utilize a semiconductor diode laser to noninvasively rupture and coagulate the cysts. Cysts in 7 cats were successfully deflated using the diode laser under an operating microscope (Gemensky-Metzler et al., 2004). For pulsed application through a 0.3 or 0.8 mm spot, an average of 97 spots was required to coagulate all the cysts in an eye, with average power and duration settings of 700 mW and 1000 msec,

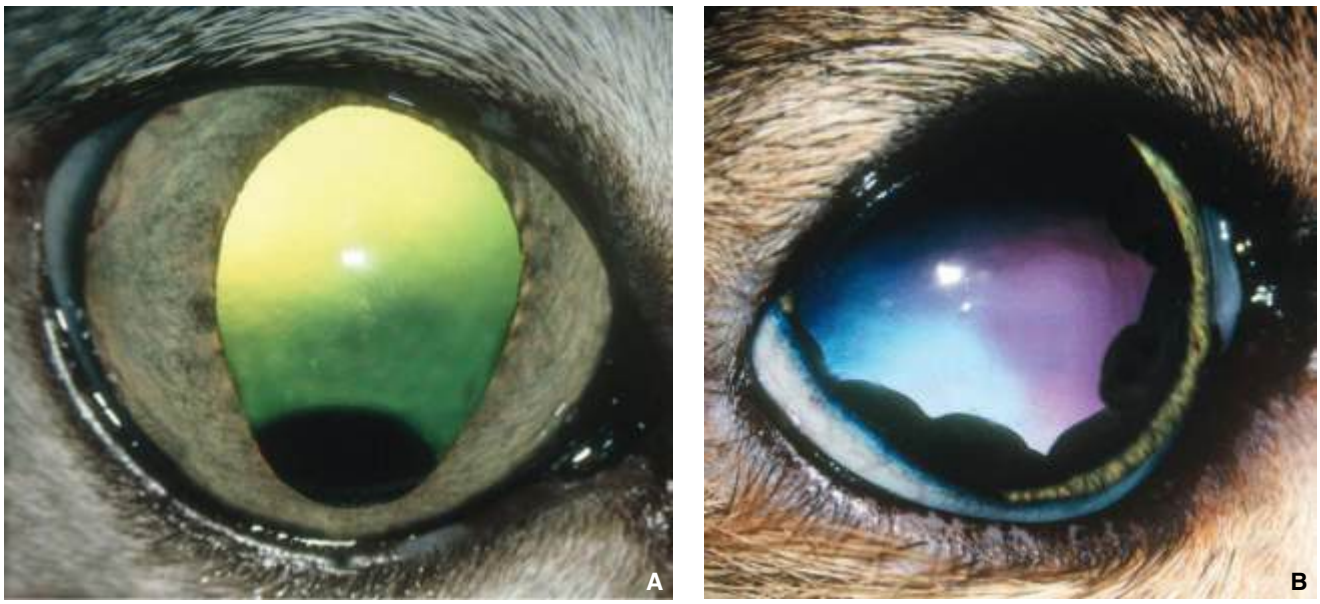


Figure 28.56 **A**. A single darkly pigmented iris cyst remains attached within the posterior chamber. **B**. A shallow anterior chamber resulted from multiple, dark-walled iris cysts within the posterior chamber, seen only after pupillary dilation in this adult Domestic Shorthair.

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respectively. Post-treatment anterior chamber debris was minimal with the exception of transient pigmented strands in 1 cat and permanent focal endothelial pigmentation in another.

Anterior Uveitis

Inflammation of the iris and ciliary body – that is, anterior uveitis – is one of the most common and significant ocular diseases in cats, with an immediate impact on ocular function and patient comfort. Uveitis can be a standalone condition affecting the eye only, or can be part of a more generalized systemic syndrome in which the eye is one of several organs involved. In order to return the eye's vascular tunic to normal, the attending clinician is obligated to recognize the clinical signs of uveitis in a timely fashion and treat the uveal inflammation to its conclusive resolution. But cats do not easily divulge their secrets. The red, cloudy eye that characterizes canine uveitis is seldom as obvious in the feline patient. The cat's already subtle ocular hyperemia is also masked by the limited visibility of the sclera when the eyelids are in a normal position. Feline corneal edema is likewise subtle, often requiring close examination of the perilimbal region to appreciate a change. Overt discomfort may be less common than lethargy – and who takes note of a sleeping cat? Uveitis may therefore go unnoticed and untreated until secondary complications of glaucoma and cataract call attention to the problem. With few pathognomonic signs, documenting the cause of feline uveitis may be the most daunting task. Even with extensive diagnostics, a cause may not be discovered in as many as 70% of cats with uveitis (Davidson et al., 1991a; Jinks et al., 2016), leaving only symptomatic therapy to combat the inflammation, without eliminating its underlying stimulus. Reduced but not resolved, the inflammation may ultimately lead to complications such as glaucoma that compel the enucleation of a blind, painful eye.

A variety of topics are fundamental to understanding the how and why of uveitis and its impact on ocular form and function. The reader is referred to Chapters 6, 7, and 9 to review the basic mechanisms of ocular immunity, microbiology, and inflammation, respectively. Chapter 21 applies these fundamentals to a discussion of uveitis in the dog. Because anterior uveitis may be the first outward sign of serious, and potentially fatal, systemic disease in the cat, Chapter 37, Part 2 reviews the salient general features of diseases known to cause uveitis in cats.

Clinical Features of Feline Uveitis

The clinical signs of anterior uveitis are similar regardless of the species of animal or underlying cause. The most reliable indicators of intraocular inflammation are the presence of aqueous flare, signaling breakdown of the blood–aqueous barrier, and decreased IOP, a consequence of ciliary body dysfunction.

Hyperemia results from vasodilation of conjunctival and episcleral vessels. Ciliary flush refers to a rose-red coloration of the perilimbal sclera that reflects dilation and congestion of the deeper uveal vasculature. Corneal opacification results from edema produced when toxins, inflammatory mediators, and cellular precipitates damage the endothelium. Vessels may invade the deeper corneal layers, while inflammatory cells (keratic precipitates) often settle on the cornea's inner surface. As noted previously, conjunctival hyperemia and corneal edema are typically more subtle in cats compared to dogs with anterior uveitis.

Breakdown of the blood–aqueous barrier increases aqueous turbidity, elevating aqueous protein (flare) and permitting inflammatory cells and fibrin to enter the eye. Cells may settle on the corneal endothelial surface or the anterior lens capsule, or diffuse into the anterior vitreous. The fine surface texture of the iris disappears and its color changes due to edema and cellular infiltrates. With chronicity, a pre-iridal fibrovascular membrane may develop, creating fine vessels on the iris surface that may ultimately extend over the iridocorneal angle and compromise aqueous outflow (Peiffer et al., 1990). The iris reddening that accompanies these new vessels, referred to as rubeosis iridis (Gartner & Henkind, 1978), is easily observed in the lightly colored feline eye. A common sequela of pre-iridal membranes is eversion of the pupillary margin.

The pupil is classically constricted and sluggish in its reactions owing to tissue edema and stimulation of the iris sphincter by inflammatory mediators, notably prostaglandins. Pupillary dilation is often incomplete following application of less potent diagnostic mydriatics such as tropicamide. Comparing the extent of postmydriatic pupillary dilation with that of the contralateral normal eye is particularly helpful in supporting a diagnosis of uveitis when other clinical signs are vague. Edema and cellular infiltrates within the iris stroma may alter pupillary shape, but iris-to-lens adhesions (i.e., posterior synechiae) are more likely to distort the pupil's vertical ellipse as the uveitis persists.

Decreased IOP follows ciliary body dysfunction and reduced aqueous production. Prostaglandins, one of several ocular inflammatory mediators, may also decrease IOP by enhancing aqueous outflow through the uveoscleral pathway. In subtle uveitis, IOP may be within the normal range (approximately 10–20 mmHg), but notably lower (> 20%) than the normal eye.

Clinical signs of uveitis also include nonspecific indications of pain such as tearing, blepharospasm, and subtle enophthalmos with third eyelid prominence. Because cats are solitary survivors, they are often notoriously secretive about revealing discomfort and disabilities, appearing lethargic or reclusive rather than overtly painful. Patients

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with severe or chronic intraocular inflammation, particularly those complicated by glaucoma, may exhibit decreased interaction or playfulness, uncharacteristic sleep patterns, reduced grooming, and even altered litter box use.

Abnormalities in the eye associated with chronic anterior uveitis include pigmentary changes in the iris, cataracts secondary to toxic influences on lens epithelium, and lens luxations owing to degeneration of the ciliary processes and lens zonules. Glaucoma results from impaired aqueous flow through the pupil or through the iridocorneal angle due to posterior and peripheral anterior synechiae and pre-iridal fibrovascular membranes. Iris bombé, a forward ballooning of the iris caused when aqueous is trapped posteriorly by 360° iris-to-lens adhesions, is uncommon in the cat, probably because its pupil is not as intimately associated with the axial lens curvature throughout its vertical ellipse as is the circular pupil of the dog (Fig. 28.57). A shrunken, hypotonic globe (phthisis bulbi) can occur in cats due to postinflammatory uveal degeneration and atrophy, but glaucoma and buphthalmos are more common endpoints.

Classification of Uveitis

In an attempt to effectively investigate and treat a complex problem, uveitis has been categorized in a number of ways. Emphasis is appropriately given to causes of uveitis, with broad categories that reflect exogenous etiologies that arise outside the eye, such as trauma, and endogenous causes that originate from within the eye, spreading from the bloodstream or from neighboring structures, including a plethora of infectious, neoplastic, and immune-mediated disorders (Table 28.10). Although many diseases are known to cause uveitis in the cat, idiopathic uveitis remains the most common diagnosis in clinical practice and an etiologic conclusion substantiated by reviews of feline uveitis throughout the years (Chang & Carter, 2009; Chavkin et al., 1992; Colitz, 2005; Davidson et al., 1991a; Jinks et al., 2016; Lappin et al., 1992a; Peiffer & Wilcock, 1991; Powell & Lappin, 2001a; Roze, 2008; Table 28.11).



Figure 28.57 The iris balloons forward when aqueous is trapped by extensive posterior synechiae in a rare instance of iris bombé in an adult feral cat.

Other considerations include the principal part of the uveal tract involved, the duration of the inflammation, and whether the problem is unilateral or bilateral. These features may aid in ranking differential diagnoses. For instance, causative agents such as FIV may predominate in the anterior uvea, systemic mycoses characteristically originate in the posterior uvea, and feline infectious peritonitis (FIP) frequently results in panuveitis. Exogenous uveitis is likely to be acute and self-limiting, uveitis associated with systemic disease tends to be subacute, and idiopathic cases typically are chronic or recurrent (Maggs, 2009). Although unilateral uveitis is more likely with exogenous causes or idiopathic disease and bilateral uveitis tends to have a systemic cause, it is important to thoroughly and repeatedly monitor the second eye to rule out asymmetric development of clinical signs. A retrospective study of 45 cats with anterior uveitis described characteristics of those with concurrent systemic disease (n=18) and those diagnosed with idiopathic uveitis (n=25; Gemensky et al., 1996). Cats with systemic disease were younger, with a mean age of 7.6 years versus 9.6 years in the idiopathic group. Two-thirds (67%) of cats with systemic disease had bilateral ocular involvement, while only 48% of the idiopathic group were bilaterally affected. The male to female ratio of the study group was high overall (2.75:1) and even higher for cats with systemic disease (3.5:1).

Systemic Evaluation

Once uveitis has been diagnosed, an investigation of its cause is essential. A complete ophthalmic examination will rule out exogenous causes such as trauma or reflex uveitis associated with corneal ulceration. The cat's history is scrutinized to establish its habitat, travel history, vaccination status, and prior injuries or diseases. A thorough physical examination should be performed to assess the cat's general health and to direct subsequent testing. A minimum database that includes a complete blood count, serum biochemistry profile, urinalysis, and serology for FeLV and FIV is indicated in patients with systemic signs of illness, those with bilateral endogenous uveitis characterized by cells and fibrin in the anterior chamber and/or concurrent posterior segment inflammation, and those with uveitis that fails to respond as expected to symptomatic therapy. The investigation may ultimately include thoracic and abdominal radiography, abdominal ultrasound, and aspirates of lymph nodes,

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Table 28.10 Potential causes of feline uveitis.

Exogenous Factors	Endogenous Factors	
Traumatic	**Infectious**	**Idiopathic**
Blunt injury	Bacterial	Lymphocytic-plasmacytic uveitis
Penetrating wound	*Bartonella* spp.	
Ocular surgery	*Leptospira* spp.	**Immune-mediated**
	Mycobacterium spp.	Lens-induced
Toxic	Septicemia of any cause	Phacolytic (cataract)
Drug-related	Septic lens implantation syndrome	Phacoclastic (lens trauma)
Parasympathomimetics (pilocarpine)	*Ehrlichia* spp.*	Periarteritis nodosa
Prostaglandin analogs (latanoprost)	*Borrelia burgdorferi**	
Tiletamine/zolazepam (Telazol®)	Viral	**Metabolic**
Radiation therapy	Feline infectious peritonitis	Systemic hypertension
	Feline leukemia virus	Hyperlipidemia
Reflex uveitis	Feline immunodeficiency virus	
Ulcerative keratitis of any cause	Feline herpesvirus*	**Neoplastic**
	Feline sarcoma virus§	Lymphosarcoma
	Protozoal	Melanoma
	Toxoplasma gondii	Other primary intraocular tumors
	Leishmania spp.	Other metastatic tumors
	Mycotic	
	Aspergillus spp.	
	Blastomyces dermatitidis	
	Coccidioides immitis	
	Cryptococcus spp.	
	Histoplasma capsulatum	
	Candida albicans	
	Parasitic	
	Dirofilaria immitis	
	Encephalitozoon cuniculi	
	Ophthalmomyiasis interna (*Diptera* spp.)	
	Cuterebra spp.	

*Seroprevalence data only; §Experimental.

masses, and draining tracts for cytologic examination. Serology to confirm or eliminate infectious disease is dictated by systemic signs of illness, abnormalities in the minimum database, or likelihood of exposure based on geographic location, as with systemic mycoses. Since positive serologic tests for infectious agents occur in healthy cats as well as diseased cats, the results do not necessarily correlate to clinical disease of the eye in individual cats (Lappin, 2000). Aqueous, vitreous, or subretinal aspirates may be indicated in cases of exudative uveitis when other diagnostic efforts have been exhausted. Aqueous cytopathology is primarily useful in the diagnosis of lymphoma (Linn-Pearl et al., 2015). Otherwise, cytologic assessment of aqueous humor failed to identify a cause for anterior uveitis in 10 of 10 cats in one study (Wiggans et al., 2014b) and 32 of 39 cats in another (Linn-Pearl et al., 2015). The aqueous humor of cats with idiopathic uveitis tends to have greater numbers of large, reactive lymphocytes and plasma cells, while cats with FIP demonstrate predominantly neutrophilic inflammation (Wiggans et al., 2014b).

Causes of Anterior Uveitis

Feline Leukemia Virus

FeLV has long been incriminated in feline ocular disease, yet less than 2% of cats with clinical FeLV infection demonstrate ocular signs (Brightman et al., 1991). While this retrospective study concluded that cats infected with FeLV have a twofold greater risk of developing eye disease than noninfected cats, the report also concluded that (1) FeLV causes no

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Table 28.11 Documented causes of feline uveitis: Clinical, histopathologic, and serologic diagnoses in cats with uveitis. Number positive/number tested (% of total patients in study, rounded to nearest whole number).

	Clinical and Serologic		Histopathologic	Serologic*		
Cause	**Davidson et al. (1991a)**	**Jinks et al. (2016)**	**Peiffer & Wilcock (1991)**	**Chavkin et al. (1992)**	**Lappin et al. (1992a)**	**Powell et al. (2010)**
Feline leukemia virus	6/53 (11%)	3/112 (3%)		5/84 (5%)	15/124 (12%)	1/104 (1%)
Feline immunodeficiency virus	6/28 (11%)	8/109 (7%)		19/83 (20%)	16/124 (13%)	4/104 (4%)
Feline infectious peritonitis		19/120 (16%)	34/158 (22%)			
≥ 1:1600	1/45 (1%)			3/74 (3%)	7/124 (6%)	
≥ 1:100				20/74 (27%)	27/124 (22%)	
Toxoplasma gondii	1/43 (1%)	22/93 (18%)	1/158 (1%)	73/93 (79%)	92/124 (74%)	24/104 (23%)
Bartonella spp.		19/44 (16%)				56/104 (54%)
T. gondii and *Bartonella* spp.		5/42 (4%)				
Feline herpesvirus						4/104 (4%)
Mycotic disease						
Cryptococcosis		1/8 (1%)	3/158 (2%)			
Histoplasmosis			5/158 (3%)			
Neoplasia		6/120 (5%)				
Iris melanoma	3/53 (6%)	1/120 (1%)				
Lymphoma	3/53 (6%)	3/120 (3%)	33/158 (21%)			
Metastatic adenocarcinoma		2/120 (2%)				
Multiple myeloma	1/53 (1%)					
Ocular sarcoma			3/158 (2%)			
Unspecified neoplasm			1/158 (1%)			
Hypertension	1/53 (1%)					
Traumatic			15/158 (10%)			
Lens-induced			12/158 (8%)			
Study conclusions						
Total patients in study	53	120	139	93	124	104
Idiopathic	31/53 (59%)	49/120 (41%)	51/139 (37%)			
Negative serology				9/93 (10%)	21/124 (17%)	33/104 (32%)
Definitive diagnosis	21/53 (40%)	37/120 (31%)	88/139 (63%)			

* Totals may include *T. gondii* and viral coinfections.

primary eye disease; (2) metastatic lymphoma is the apparent cause of anterior uveal infiltration seen in FeLV-positive cats; and (3) retinal lesions observed in anemic FeLV-infected cats are secondary to pancytopenia rather than a direct effect of the virus. Perhaps the most clinically important consequence of FeLV infection is immunosuppression that predisposes to secondary infectious disease and increases tumor risk by altering inherent tumor surveillance mechanisms (Hartmann, 2012). In a retrospective study of ocular lymphosarcoma in 15 cats, 2 of 4 cats tested for FeLV were positive (Ota-Kuroki et al., 2014). FeLV test results were only available for 17 of 49 cats included in a retrospective histopathologic study of ocular lymphosarcoma; 7 (41%) were FeLV positive (Corcoran et al., 1995).

The early stages of uveal lymphosarcoma may appear similar to any other uveitis, although the iris generally appears increasingly thickened and irregular as the disease progresses. Lesions usually appear flesh-colored and may have a velvety texture (Fig. 28.58). Dyscoria or anisocoria develops as neoplastic infiltration restricts pupil mobility or as a consequence of FeLV-related neurologic effects (Brightman et al., 1977). Histopathologically, anterior uveal tumor infil-

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Figure 28.58 **A**. Mild rubeosis iridis with fine keratic precipitates and a small pigmented clot in a 10-year-old Domestic Shorthair seropositive for feline leukemia virus (FeLV). **B**. Ocular lymphoma with diffuse iris infiltration, rubeosis iridis, and cellular exudation in a 7-year-old Domestic Shorthair seropositive for FeLV.

tration ranges from localized involvement, with an associated mild inflammatory reaction that includes inflammatory cells and fibrin in the anterior chamber, to more extensive neoplastic infiltration (Corcoran et al., 1995).

If a serum ELISA antigen test is positive, an immunofluorescent antibody test can be performed to confirm infection, or the ELISA can be repeated in 3 months (Willis, 2000). The incidence of FeLV infection has decreased over the years following the introduction of vaccination in the 1980s, coupled with quarantine and removal of infected cats (Louwerens et al., 2005). Although the incidence of FeLV antigen-expressing lymphoma has likewise declined, there is increasing evidence of a role of FeLV proviral DNA in the development of lymphoma in FeLV-antigen negative, regressively infected cats (Weiss et al., 2010). Aqueous paracentesis can be useful in making a cytologic diagnosis of ocular lymphosarcoma, as demonstrated in 9 of 39 cats with anterior uveitis (Linn-Pearl et al., 2015).

Feline Immunodeficiency Virus

Infection with FIV causes chronic immunosuppression in cats and in some cats a mild to moderately severe, chronic uveitis (Connaughton, 1989; Hardy, 1988; Hopper et al., 1989; Ishida et al., 1989; Pedersen et al., 1987; Yamamoto et al., 1989). Virus was recovered from the anterior chamber in 3 of 12 cats experimentally infected with FIV, and a lymphocytic-plasmacytic uveitis was documented histopathologically in 75% (9 of 12) of the animals euthanized ≥ 4 weeks following infection (Ryan et al., 2003). The ocular inflammation may result from direct viral damage or secondary opportunistic infections of the eye (English et al., 1990). Coinfection with *Toxoplasma gondii* increases the possibility of ocular disease (Davidson et al., 1993a, 1993b). An immunohistochemical and histopathologic study proposed a role for immune complexes in the anterior uveitis seen in 13 of 15 cats with chronic FIV infection (Loesenbeck et al., 1996).

Keratic precipitates tend to be uncommon and few in number when present (English et al., 1990). Nonspecific plasma cells and lymphocytes are likely to characterize aqueous cytology (Fig. 28.59). While cellular infiltrates in the anterior vitreous (i.e., pars planitis) occur often with FIV, other evidence of posterior segment disease is infrequent (Willis, 2000). As with any chronic uveitis, formation of posterior synechiae, cortical cataracts, and secondary glaucoma are likely. FIV-infected cats are about five times more likely to develop lymphoma or leukemia than noninfected cats (Gabor et al., 2001; Magden et al., 2013; Poli et al., 1994), with the potential for ocular involvement (Fischer et al., 1999; Stiles, 2014).

The mainstay for clinical diagnosis has been ELISA detection of circulating antibodies against FIV, with positive results confirmed by Western blot analysis (Willis, 2000). Negative test results are generally highly reliable. Unfortunately, vaccination of cats against FIV produces long-lasting antibodies indistinguishable from those used for the diagnosis of FIV infection (Levy et al., 2004), confounding the diagnosis. There are now point-of-care diagnostic kits that may reliably identify natural FIV infection regardless of vaccination history, likely because they target gp40 antibodies (Westman et al., 2015).

Feline Infectious Peritonitis

FIP is the result of a mutation in the ubiquitous feline coronavirus (FCoV). About 12% of FCoV-infected cats will

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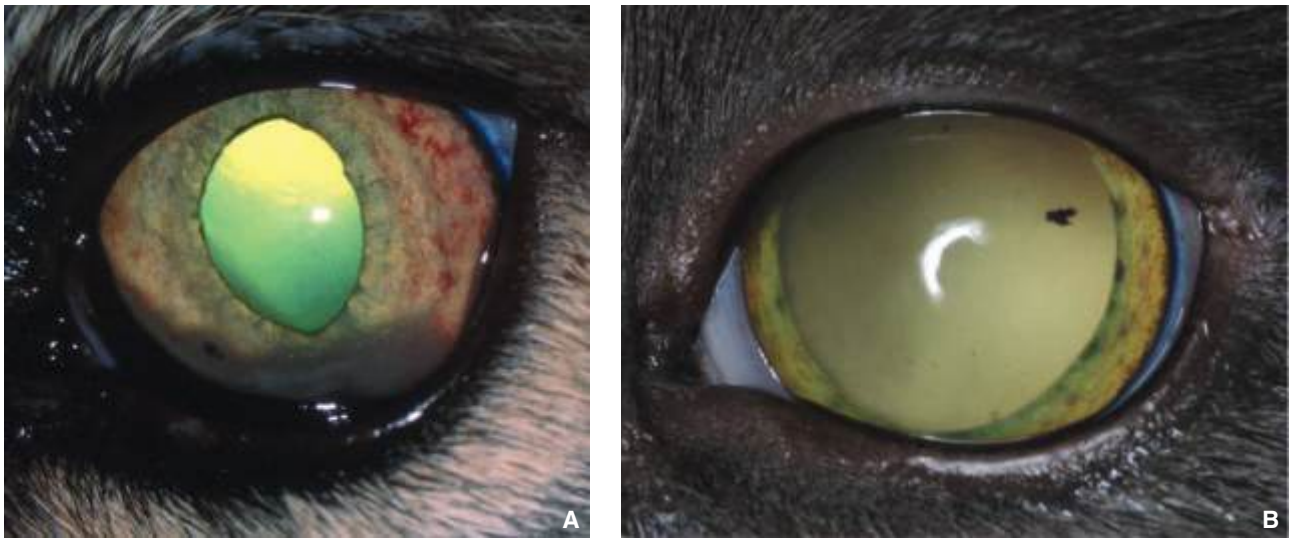


Figure 28.59 **A**. Rubeosis iridis and a fibrinous exudate in the ventral anterior chamber characterize the uveitis in a 10-year-old Domestic Shorthair seropositive for feline immunodeficiency virus (FIV). **B**. The tapetal reflection is muted by a cellular infiltrate in the anterior vitreous of a cat seropositive for FIV.

develop FIP (Addie et al., 1995). The majority (about 70%) of affected cats are less than 1 year of age (Hartmann, 2005). At-risk breeds include the Abyssinian, Bengal, Birman, Himalayan, Ragdoll, and Rex (Pesteanu-Somogyi et al., 2006). FIP has also been diagnosed in cheetahs and California mountain lions (Pedersen, 2014). The systemic disease is characterized by anorexia, weight loss, fever refractory to antibiotics, and variable peritoneal and thoracic effusions. The prognosis for cats with FIP is generally grave. Median survival after the onset of clinical signs was 21 days in cats with effusion, 38 days in cats with noneffusive disease, and 111 days in cats with mixed disease (Tsai et al., 2011).

Ocular manifestations are more common in the noneffusive ("dry") form of the disease (Pedersen, 1997; Tsai et al., 2011), occurring in about 60% of affected cats without effusions but in fewer than 9% of patients with effusions (Pedersen, 2009). However, a more recent study suggests that eye involvement in the effusive form may be underestimated, as 29% of cats confirmed with FIP showed eye involvement (Kipar & Meli, 2014). Clinical signs result from granuloma formation, immune complex deposition, and pyogranulomatous vasculitis (Evermann et al., 1995; Fig. 28.60). A mixed uveal inflammatory cell infiltrate made up of neutrophils and mononuclear inflammatory cells is seen histologically (Peiffer & Wilcock, 1991). An immunohistochemical study found that B cells and plasma cells predominated over T cells and macrophages in cases of severe ocular inflammation (Ziólkowska et al., 2017). The same study concluded that circulating FCoV-bearing macrophages gain access to the eye following breakdown of the blood–ocular barrier, via damaged ciliary epithelium and blood vessel walls within the severely inflamed ciliary body. Anterior uveitis and/or chorioretinitis may develop with or without concurrent systemic signs (Campbell & Reed, 1975; Carlton et al., 1973; Disque et al., 1968; Doherty, 1971; Gelatt, 1973; Hardy & Hurvitz, 1971; Kline et al., 1994; Poland et al., 1996; Sherding, 1979; Slauson & Finn, 1972; Sparkes et al., 1994; Wolfe & Griesemer, 1966). Ocular vasculitis leads to breakdown of the blood–aqueous barrier and fibrin exudation into the anterior chamber from uveal blood vessels (Andrew, 2000). Because of the granulomatous nature of the inflammatory response, "mutton fat" keratic precipitates tend to occur (Doherty, 1971). FIP may also cause a pyogranulomatous chorioretinitis and retinal vasculitis with clinically evident perivascular cuffing, exudative retinal detachments, and optic neuritis. The intraocular inflammation often progresses to panuveitis or panophthalmitis, with diffuse and severe corneal edema, marked anterior uveitis, marked cellular infiltration of the vitreous, chorioretinitis, and inflammatory retinal detachments (Stiles, 2013). Bilateral panuveitis accompanied widespread cutaneous papules and perivascular pyogranulomatous dermatitis in a 2-year-old Sphynx, with positive immunohistochemical staining for FCoV antigen in dermal macrophages (Bauer et al., 2013).

Antemortem diagnosis of FIP is challenging, especially in the noneffusive form of the disease. In most cases, the first step in FIP diagnosis is to perform hematology, biochemistry, and FCoV serology to assess the likelihood of the disease. The presence of FCoV antibodies only indicates that the cat is or has been infected with a coronavirus, though not necessarily the mutated form responsible for FIP (Andrew, 2000). Nevertheless, titers $\geq 1:3200$ are highly suggestive of FIP (Hartmann et al., 2003). A complete blood count often reveals a neutrophilia with left shift and nonregenerative anemia

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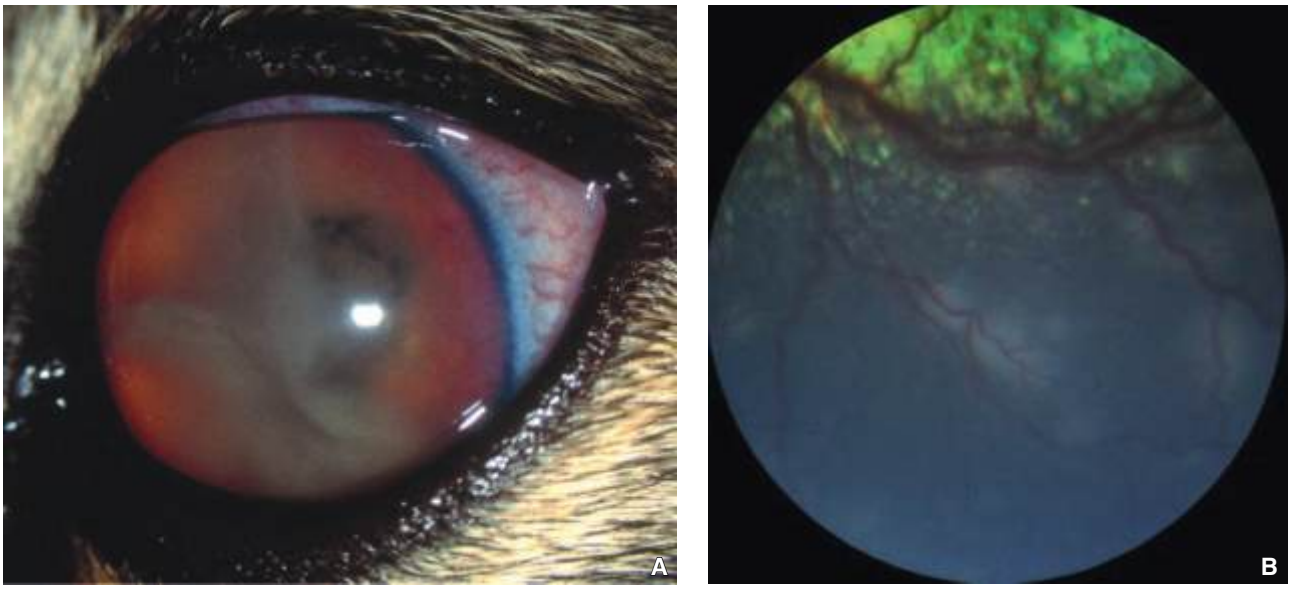


Figure 28.60 **A**. A fibrinous exudate obscures the severe rubeosis iridis that gives the eye its orange hue in an 11-month-old Domestic Shorthair with feline infectious peritonitis (FIP). **B**. Perivascular cuffing of retinal vessels in a 10-month-old Persian with FIP.

(Andrew, 2000; Barr, 1998). A normal lymphocyte count makes FIP unlikely (Addie et al., 2009). Hyperproteinemia resulting from polyclonal gammopathy occurs in approximately 50% of cats with effusive FIP and 70% of cats with noneffusive FIP (Barr, 1998). The albumin/globulin ratio has higher diagnostic value than protein or globulin concentrations alone, and FIP is considered highly unlikely at ratio values over 0.8 (Hartmann et al., 2003; Jeffery et al., 2012). Histopathologic identification of pyogranulomatous tissue infiltrates has been considered the most reliable indicator (Barlough & Stoddart, 1998), but one study found concordance with a final diagnosis of FIP to be poor (Giori et al., 2011). In that report, the highest concordance was found for serum concentration of alpha-1 acid glycoprotein (AGP) combined with immunohistochemistry. Other investigators consider serum AGP a powerful marker for FIP, but only when coupled with other high-risk factors (Saverio et al., 2007). The contemporary gold standard for FIP diagnosis is immunohistochemistry on effusions or lesions to detect FCoV antigen in infected macrophages (Pedersen, 2009), considered 100% predictive of FIP (Hartmann et al., 2003). Typical aqueous humor cytology is characterized by pyogranulomatous inflammation with macrophagic engulfment of neutrophils, absence of microorganisms, and giant cells (Felten et al., 2018). Wiggans et al. (2014b) found that neither clinical nor cytologic assessment of anterior chamber contents differed significantly between cats with idiopathic or FIP-associated uveitis. The diagnostic utility of an immunocytochemical assay using aqueous humor had an average accuracy of only 69.4% (Felten et al., 2018).

Currently there is no effective treatment for FIP and mortality is extremely high (Pedersen, 2014). Supportive treatment is aimed at suppressing the inflammation, usually with corticosteroids, although there are no controlled studies to prove benefit (Pedersen, 2014). Contemporary investigation now centers on antiviral therapy using nucleoside analogs (Pedersen et al., 2019) and protease inhibitors (Pedersen et al., 2018).

Feline Herpesvirus-1

While herpesvirus has long been linked with uveitis in humans (Wensing et al., 2018), its role in feline anterior uveitis is as yet unsubstantiated. FHV-1 was first considered a possible cause of endogenous uveitis after a study found that 14% of cats diagnosed with idiopathic uveitis had FHV-1 DNA in their aqueous humor (Maggs et al., 1999a). The study also found that local FHV-1 antibody production within the eye, based on the Goldmann-Witmer coefficient, occurred in more cats with idiopathic uveitis than cats without uveitis. FHV-1 has been isolated from the uveal tract of experimentally infected cats during the acute phase of the infection, and was also detected within the uvea by PCR assay (Townsend et al., 2013). However, another study found that only 3.8% of cats with uveitis had positive PCR FHV-1 results in either their blood (1.9%) or aqueous humor (1.9%), while 31.6% of healthy cats had positive PCR results (Powell et al., 2010).

Experimental Feline Sarcoma Virus

Feline sarcoma virus (FeSV) is an oncogenic RNA virus thought to have evolved by mutation from FeLV. The virus is responsible for spontaneous tumor formation in naturally infected cats. Although a role for FeSV in naturally occurring feline uveitis has not been documented, experimental

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subcutaneous injection does induce anterior uveitis (Lubin et al., 1983). Clinical signs of conjunctival hyperemia and ciliary flush appeared 37 days after inoculation, with subsequent development of iritis, posterior synechiae, pigment deposits on the lens capsule, and cataracts. Histopathologically, lymphocytic-plasmacytic inflammation was confined to the iris and ciliary body. Sarcomatous changes were noted in bizarre transformed cells and large multinucleated cells. The presence of large quantities of virus in the aqueous humor suggests that local virus replication occurs. Inflammatory changes are thought to reflect virus–antibody interactions or a cell-mediated immune response.

Toxoplasmosis

The cat is the definitive host for *Toxoplasma gondii*, an intracellular protozoan considered one of the most common parasitic infections of animals and humans. As carnivores, cats are probably infected during the first 6 months of life by ingesting tissue of infected intermediate hosts containing bradyzoite-laden cysts, or less commonly by contact with sporozoites in an environment contaminated by fecal oocysts. Transplacental transfer is considered uncommon, but has been demonstrated experimentally (Dubey et al., 1995a; Powell & Lappin, 2001b). The cytopathic effect associated with intracellular replication of the organism in target organs ranges from inapparent in adult cats to severe in neonatal or immunosuppressed animals. In a retrospective study of histologically confirmed toxoplasmosis in 100 cats, 36 had generalized multi-organ involvement, 26 had predominantly pulmonary lesions, 16 had gastrointestinal disease, and 7 demonstrated neurologic signs (Dubey & Carpenter, 1993). Cats with systemic toxoplasmosis classically demonstrate chorioretinitis characterized by multifocal hyporeflective lesions in the tapetal fundus and fluffy white infiltrates in the nontapetal region (Davidson, 2000; Fig. 28.61A). Ocular disease was demonstrated in 9 of 15 cats with systemic toxoplasmosis, with active chorioretinitis in 4 cats, inactive retinal lesions in 1 cat, and anterior uveitis in all 9 patients (Lappin et al., 1989a; Fig 28.61B).

While there is a clear association between panuveitis and systemic feline toxoplasmosis, the role of *T. gondii* in anterior uveitis in an otherwise healthy cat is somewhat controversial. A causative effect has been defended based on a higher seroprevalence of *T. gondii* in cats with uveitis than those without; the prevalence of local or intraocular antibody production, especially IgM, in cats with uveitis; the presence of *T. gondii* antigen and positive PCR (b1 gene) assays in the aqueous humor of cats with uveitis; and the apparent clinical improvement in uveitis of cats treated for toxoplasmosis (Chavkin et al., 1992; Lappin et al, 1992a, 1992b, 1993, 1996). The debate arises from the inability to histologically document the organism in the eyes of cats with only anterior uveitis, a shortcoming repeated in several retrospective histopathologic studies of feline anterior uveitis (Davidson et al., 1991a; Peiffer & Wilcock, 1991; Wilcock et al., 1990). Proposed alternative theories for *T.*

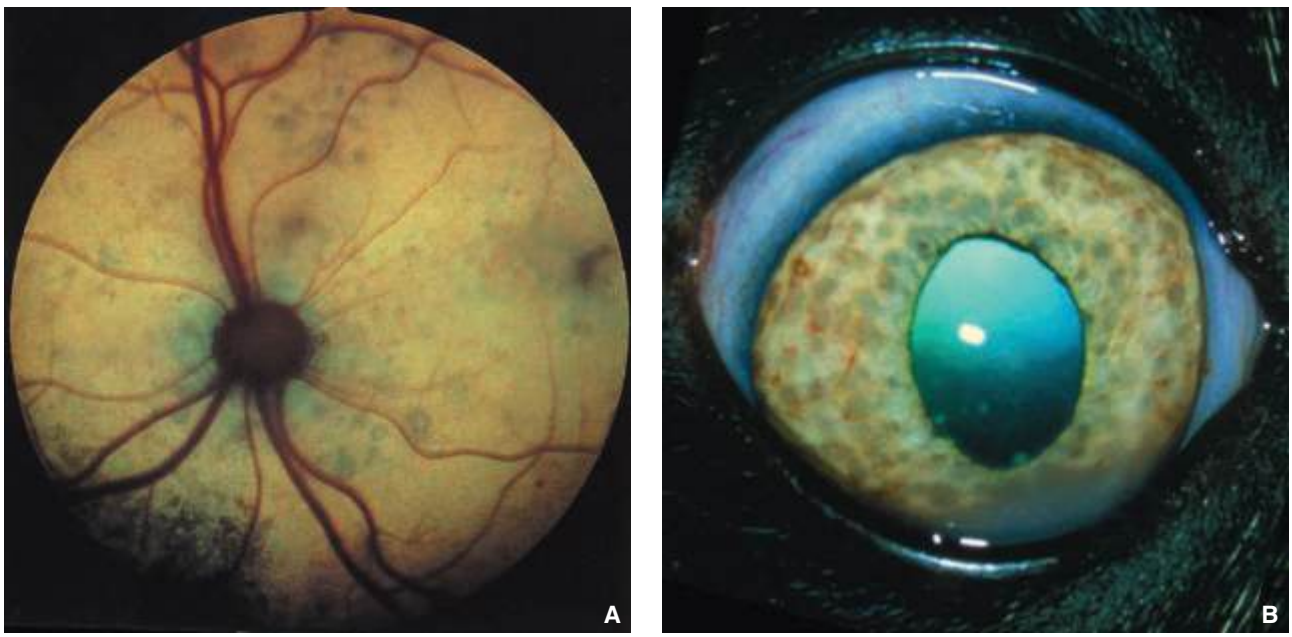


Figure 28.61 **A**. Intraretinal and subretinal exudates appear as dark foci scattered throughout the tapetal fundus in a 12-year-old Domestic Shorthair with a *Toxoplasma gondii* immunoglobulin (Ig) M titer of 1 : 64. **B**. Toxoplasmosis was diagnosed in a 4-year-old Domestic Shorthair with a rising serum IgM titer (to 1 : 16,384), rubeosis iridis, a fibrin clot, and multifocal gray iris nodules of inflammatory cells.

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gondii's role in feline uveitis look beyond a direct cytopathic effect of the replicating organism to include ocular homing of activated immune cells following exposure to *Toxoplasma* antigen in nonocular tissues, and/or autoimmunity arising from molecular mimicry between *Toxoplasma* antigens and uveal proteins (Davidson & English, 1998). Deposition of circulating antigens or antigen–antibody complexes within the uveal tract is less likely, since *T. gondii* antigen circulation is transient (Davidson et al., 1993a, 1993b). Increased antibodies to *T. gondii* without increased serologic response to other feline pathogens discounts the mechanism of nonspecific upregulation of immune response (Lappin et al., 1992a).

Presumptive diagnosis is based on the presence of compatible systemic or ocular findings, supportive serologic tests, and response to anti-*Toxoplasma* therapy, but definitive diagnosis is limited to those patients in which the organism is identified in ocular tissues. An IgM antibody titer ≥ 1:256 suggests recent infection (Lappin et al., 1989b), given that IgM antibodies are generally produced within 2–4 weeks following primary exposure, but only persist for 3 months. A rising IgG antibody titer between paired serum samples is also supportive of active infection. However, the widespread seroprevalence of *T. gondii* in the cat population and the persistence of IgG titers for 2 years or longer limit the diagnostic significance of a single positive IgG titer (Chavkin et al., 1994; Dubey et al., 1995b). In cats with anterior uveitis and a positive serum titer, it may be helpful to measure antibodies in the aqueous humor and serum concurrently, so that the relative level of antibodies in the eye can be determined through calculation of the Witmer-Goldmann coefficient (C-value; Davidson, 2000; Lappin et al., 1992b). A C-value greater than 1 suggests local antibody production, although a value greater than 8 has been recommended to account for technique inaccuracy (Chavkin et al., 1994). A PCR assay on blood and aqueous humor increased the detection rate of *T. gondii* in cats with uveitis when antibody titers were negative, but the diagnostic usefulness of that data requires further consideration (Powell et al., 2010).

Symptomatic treatment of the anterior uveitis combines topical corticosteroids and a mydriatic-cycloplegic, and may be sufficient in seropositive cats with only anterior uveitis (Davidson, 2000). Available systemic antibiotics used in the treatment of toxoplasmosis only suppress *T. gondii* tachyzoite replication and do not eliminate the organism. Clindamycin hydrochloride is the treatment of choice, dosed at 12.5 mg/kg orally twice daily for 14–21 days. Clindamycin is indicated in cats with posterior segment lesions, those with uveitis and concurrent systemic disease, and those patients in which response to topical therapy alone is limited. One study demonstrated resolution of anterior uveitis in 3 cats with systemic toxoplasmosis using clindamycin therapy alone (Lappin et al., 1989a).

Leishmaniasis

Leishmaniasis is a vector-borne zoonotic disease classically associated with the Mediterranean region, but now found in Central and South America and parts of Africa and Asia. *Leishmania infantum* is transmitted by phlebotomine sand flies and is the species most frequently reported in cats in the Old World and in Central and South America (Pennisi & Persichetti, 2018). Other *Leishmania* species may infect cats, including *L. mexicana* found in an endemic region of Texas. Although the dog is considered the main reservoir host of the parasite and experimental studies suggest a natural resistance of cats to infection (Simões-Mattos et al., 2005), the incidence of feline leishmaniasis has increased over the past two decades (Pennisi et al., 2015). Clinical disease in cats is commonly associated with impaired immunocompetence caused by FIV coinfection, immunosuppressive therapy, or concurrent diseases including neoplasia and diabetes mellitus (Pennisi, 2015).

In a literature review of 46 clinical cases of feline leishmaniasis (Pennisi et al., 2015), lymphadenopathy and nodular and/or ulcerative dermatitis are the most common clinical signs, occurring in 50% of patients. Visceral involvement is rare (Navarro et al., 2010). Ocular abnormalities are reported in one-third of affected cats. Unilateral or bilateral uveitis is the most common ocular lesion (Hervás et al., 2001; Leiva et al., 2005; Maia et al., 2015; Richter et al., 2014; Sanches et al., 2011; Verneuil, 2013), with instances of blepharitis, conjunctivitis, and keratitis also reported (Fig. 28.62).



Figure 28.62 Leishmaniasis in a 21-year-old European Shorthair with proliferative keratoconjunctivitis that obscures intraocular detail. Ultrasound revealed a concurrent retinal detachment. (Courtesy of Dr. Teresa Peña. Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

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Nonspecific signs of uveitis include subtle corneal edema, aqueous flare, rubeosis iridis, and posterior synechia with dyscoria (Verneuil, 2013), but exudative panuveitis with secondary glaucoma (Leiva et al., 2005) and pseudotumoral granulomatous iridocyclitis (Hervás et al., 2001) have also been described. In the latter case of a 6-year-old FIV-positive patient, an intense inflammatory reaction composed of macrophages and multinucleated giant cells containing *Leishmania* amastigotes produced a 1.42 cm whitish mass arising from the ciliary body and adhering to the iris. Ocular disease was the predominant manifestation of leishmaniasis in 3 cats, all of which demonstrated a combination of anterior uveitis, nodular blepharitis/conjunctivitis, and keratitis (Maia et al., 2015).

Hypergammaglobulinemia and nonregenerative anemia are common clinicopathologic findings in individual case reports. Diagnosis is based on serologic detection of specific antibodies to Leishmania antigen, with antibody levels ranging from low to very high in affected cats (Pennisi & Persichetti, 2018). In a recent study comparing the diagnostic performance of serologic methods, Western blot offered the best sensitivity and specificity in cats compared to ELISA and the immunofluorescent antibody test (IFAT; Persichetti et al., 2017). Skin biopsies and lymph node aspirates from sick cats usually have high parasite loads measured by quantitative real-time PCR (Migliazzo et al., 2015). *Leishmania* amastigotes have been demonstrated cytologically in conjunctival nodules, corneal infiltrates, and aqueous humor, and histopathologically in the uveal tissue of enucleated eyes. The associated inflammatory reaction is characterized as granulomatous or pyogranulomatous (Navarro et al., 2010).

Treatment of cats with clinical leishmaniasis is still empirically based on protocols prescribed in dogs. Long-term oral administration of allopurinol as monotherapy and maintenance treatment after a course of subcutaneous injections of meglumine antimoniate are the most frequent regimens described, but controlled studies of efficacy and safety have yet to be conducted in cats (Pennisi & Persichetti, 2018). Allopurinol dosed orally at 10 mg/kg every 12 hours resolved active uveitis, keratitis. and blepharitis within 2 months in a 7-year-old cat that was still alive 3 years after initial diagnosis (Richter et al., 2014). Life expectancy of cats with clinical leishmaniasis is usually good, with most living several years after diagnosis (Pennisi et al., 2015).

Cytauxzoonosis

Cytauxzoon felis is a tick-transmitted protozoan hemoparasite of wild and domestic cats. Infection results in an acute febrile illness, with profound depression, anorexia, dehydration, and reluctance to move. Pancytopenia is a common finding. The clinical signs are attributed to the organism's tissue phase in which schizont-laden macrophages occlude the vessels of virtually any tissue, particularly the lungs, spleen, and liver (Meinkoth & Kocan, 2005). Definitive diagnosis is based on identification of signet-ring shaped *C. felis* piroplasms within erythrocytes on routine blood smears. The mortality rate is alarmingly high, with death occurring within 3 weeks of infection. In a retrospective study of 34 naturally infected cats, 94% either died or were euthanized (Birkenheuer et al., 2006). There are however reports of survivors (Meinkoth et al., 2000) and asymptomatic carriers (Haber et al., 2007). Of 53 cats treated with atovaquone and azithromycin, 60% survived to discharge (Cohn et al., 2011).

Beyond third eyelid protrusion attributed to malaise, descriptions of ocular signs in published case series and case reports are nonexistent. Conjunctival hyperemia and episcleral vascular injection were reported in only one case (Meier & Moore, 2000). However, histopathologic identification of intraocular *C. felis* in 3 cats suggests that hemorrhagic panuveitis is a clinical possibility as treatment evolves and survival rates improve (Meekins & Cino-Ozuna, 2018). The study found schizont-laden macrophages throughout the uveal tract and within retinal blood vessels, with the potential for hyphema and hemorrhage within the iris stroma, vitreous, and retina. Retinal detachment could accompany choroidal hemorrhage and subretinal effusion due to hypoproteinemia.

Systemic Fungal Infections

The systemic mycotic agents include a group of dimorphic fungi (*Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*) usually encountered in specific geographic regions. Infection occurs by inhalation of infectious particles from the soil, although direct cutaneous infection has been reported with *Coccidioides* (Beaudin et al., 2005). Both histoplasmosis and blastomycosis have been diagnosed in indoor-only cats (Blondin et al., 2007; Houseright et al., 2015; Reinhart et al., 2012). Failure of the host immune system to contain the infection in the respiratory tract results in generalized dissemination to other body organs via blood and lymphatics. *Cryptococcus neoformans* and *C. gattii* are saprophytic yeasts with a worldwide distribution. Infection with this organism can occur by inhalation, with the nasal cavity as the primary site of infection in cats, or by direct cutaneous inoculation (Sykes & Malik, 2014). Rare instances of anterior uveal involvement in cats with aspergillosis (Barrs et al., 2012) and candidiasis (Gerding et al., 1994; Miller & Albert, 1988) have been described. As a species, cats are very susceptible to infection with *Histoplasma* and *Cryptococcus*, less susceptible to *Blastomyces*, and very resistant to infection by *Coccidioides*.

With regard to the eye, these disorders have in common the hematogenous dissemination from the primary respiratory site of infection to the posterior uvea and the formation of a granulomatous chorioretinitis (Fig. 28.63). In cryptococcosis, the organism can spread to the eye from the central nervous system along the optic nerve (Olander et al., 1963).

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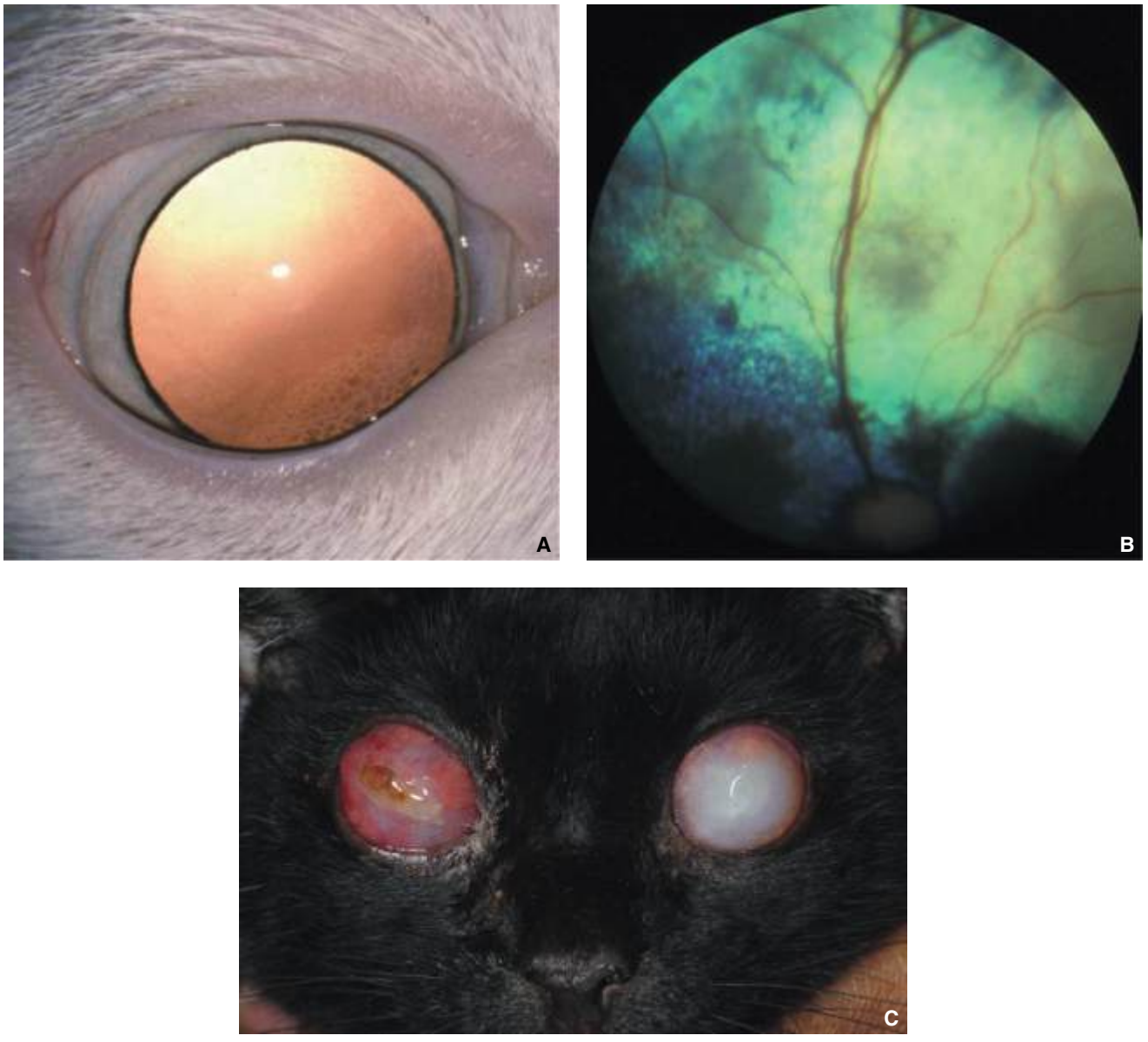


Figure 28.63 Mycotic uveitis. Panuveitis in a 5-year-old Domestic Shorthair with cryptococcosis, with (**A**) keratic precipitates anteriorly and (**B**) subretinal and choroidal granulomatous exudates obscuring the tapetal reflection. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.) **C**. An unusually severe bilateral panuveitis in a 3-year-old Domestic Shorthair with histoplasmosis.

Anterior uveitis is considered an extension of the posterior segment disease, is unlikely to exist without concurrent chorioretinitis, and does not necessarily express the granulomatous character of the concurrent fundic lesions. In all systemic mycoses, intraocular inflammation is caused by the presence of the organism within the eye rather than a nonspecific uveal response to systemic infection (Gionfriddo, 2000). The unique immunologic mechanisms of the eye, including anterior chamber-associated immune deviation (ACAID), may allow fungal organisms to persist in ocular tissues (English, 1999), with the potential for relapse of ocular signs once therapy is discontinued. One study determined that *H. capsulatum* within macrophages can evade immunologic responses and persist as subclinical foci of infection within various organs (Kaufmann, 2007).

While not the primary or predominant ocular manifestation, anterior uveitis of varying severity has been described in systemic fungal infections of cats. Cats with cryptococcosis demonstrated keratic precipitates, fibrin in the anterior chamber, fibrin and pigment on the anterior lens capsule, and posterior synechiae (Blouin & Cello, 1980; Fischer, 1971; Gwin et al., 1977; Rosenthal et al., 1981). A cat with dissemi-

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nated histoplasmosis exhibited aqueous flare, posterior synechiae, iris neovascularization, and nodules on the iris surface, with histologic evidence of *Histoplasma*-laden macrophages and lymphocytes throughout the eye (Peiffer & Belkin, 1979). Keratic precipitates, aqueous flare and cells, rubeosis iridis, and secondary cataract were seen in a *Toxoplasma*-seropositive cat with panuveitis secondary to histoplasmosis (Pearce et al., 2007). In a report of 8 cats with blastomycosis, anterior uveitis was diagnosed in 1 of 3 patients with ocular disease (Gilor et al., 2006). Miller and co-workers described unilateral anterior segment signs in 2 cats with ocular blastomycosis consisting of severe aqueous flare, keratic precipitates, posterior synechiae, and rubeosis iridis, and noted that posterior segment lesions were consistently more severe than those of the anterior segment (Miller et al., 1990). A seronegative Persian cat with coccidioidomycosis presented with unilateral anterior uveitis characterized by a large fibrin clot in the anterior chamber that progressed to granulomatous endophthalmitis despite therapy (Angell et al., 1985). Anterior uveitis and retinal detachment were present in 13% of cats in a retrospective study of 48 cats with coccidioidomycosis (Greene & Troy, 1995). Anterior uveitis developed in 2 of 3 cats with ocular coccidioidomycosis; bilateral fibrinous clots within the anterior chamber obscured intraocular detail in one cat, and keratic precipitates and mild aqueous flare characterized the uveitis in another (Tofflemire & Betbeze, 2010). Anterior uveitis was documented histopathologically in a cat with aspergillosis (Barrs et al., 2012).

The cornerstone of diagnosis is demonstration of the fungal organism in tissue or fluids by cytology or histopathology (Kerl, 2003). If organisms cannot be identified in cytologic preparations from nonocular sites of infection, subretinal or vitreous aspirates are much more likely to demonstrate fungal organisms than aqueocentesis. Latex agglutination assays to detect cryptococcal capsular antigen are both sensitive and specific (Trivedi et al., 2011). Assays to detect antibodies against *Histoplasma* and *Blastomyces* are of low sensitivity and specificity, do not discriminate between current disease and previous exposure, and are not recommended as a sole diagnostic test to determine infection (Bromel & Sykes, 2005a, 2005b; Werner & Norton, 2011). ELISA for the detection of *Histoplasma* spp. antigen in feline urine and serum is sensitive (94%) and specific (100%; Cook et al., 2012), although cats with only ocular signs may not demonstrate detectable antigenuria due to the localized nature of the infection (Smith et al., 2016). Even antigen testing of ocular fluids may not be adequate to diagnose histoplasmosis in cats with only ocular signs, nor does serial urine and/or serum antigen testing confirm complete resolution of infection (Smith et al., 2016). *Blastomyces* antigen assays have not been critically evaluated in cats. Low numbers of organisms make cytology relatively insensitive for diagnosis of coccidioidomycosis compared to other deep mycoses, but complement fixation to detect antibodies to *Coccidioides* spp. is positive in most cats, with titers ranging from 1 : 2 to 1 : 128 (Greene & Troy, 1995).

Itraconazole (ITZ) is considered the standard of care for the treatment of systemic mycoses in cats and is effective for cryptococcosis, histoplasmosis, blastomycosis, and coccidioidomycosis. Side effects are few, but the drug may be prohibitively expensive for some clients. Although ITZ does not penetrate the intact blood–brain or blood–ocular barriers as effectively as fluconazole, it may achieve levels adequate to treat central nervous system or ocular infection when there is associated inflammation that compromises barrier integrity (Foy & Trepanier, 2010). One study of ITZ for histoplasmosis reported relapse in only 2 of 8 cats within 6–10 months of cessation of therapy, but both had ocular involvement (Hodges et al., 1994). Fluconazole (FLU) has traditionally been recommended in patients with ocular and neurologic disease due to its ability to penetrate the blood–ocular and blood–brain barriers (Vaden et al., 1997). In one study, 28 of 29 cats with cryptococcosis, including a cat with optic neuritis, responded well to FLU, with virtually no side effects (Malik et al., 1992). In a study of histoplasmosis, cats treated with FLU (n=17) had similar mortality and recrudescence rates when compared with cats treated with ITZ (n=13; Reinhart et al., 2012). However, acquired resistance to FLU was suspected in a cat with histoplasmosis treated for 13 months (Renschler et al., 2017). Anterior uveitis resolved in 3 cats with coccidioidomycosis treated with FLU; chorioretinal granulomas diminished but persisted. FLU therapy was continued throughout the follow-up period in all 3 cats, ranging from 5 to 24 months (Tofflemire & Betbeze, 2010). Regardless of the antifungal drug chosen, treatment is prolonged and, in some cases, may even be lifelong in order to prevent recrudescence. For example, mean duration of therapy with ITZ was 137 days and with FLU was 171 days in a retrospective study of feline histoplasmosis (Ludwig et al., 2018). With severe posterior segment inflammation, oral corticosteroids at anti-inflammatory doses may be indicated in conjunction with antifungal therapy (Stiles, 2013). Because serial antibody or antigen testing may not confirm complete resolution of fungal infection (Hanzlicek et al., 2016), some investigators advocate the removal of blind eyes (Smith et al., 2016).

Bartonellosis

Bartonella spp. are Gram-negative bacteria that persist in erythrocytes and vascular endothelial cells, with phylogenetic similarities to *Rickettsiae* and *Brucella*. *Bartonella henselae* and *B. clarridgeiae* are the most likely species to be isolated from cats, although *B. koehlerae*, *B. quintana*, and *B. bovis* are reported to cause natural infections (Álvarez-Fernández et al., 2018). The organism is transmitted from cat to cat by fleas, is specifically harbored in flea excrement rather than saliva, and is inoculated through individual or communal grooming

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(Guptill, 2003). Regurgitation of *B. henselae* by cat fleas (*Ctenocephalides felis*) has been demonstrated experimentally, but flea-bite transmission has not been confirmed (Bouhsira et al., 2013). Infection of cats occurs worldwide, with the highest seroprevalence in warm, humid climates in which the flea vector thrives. In the United States, seroprevalence rates range from 5% to 93% (Nutter et al., 2004). Bacteremic prevalence rates for various combinations of *B. clarridgeiae*, *B. henselae*, and *B. koehlerae* often approach 50%–75% in feral cat populations worldwide (Chomel & Kasten, 2010). Existing data indicates that few cats naturally infected with Bartonella have notable clinical signs (Guptill, 2010).

A single case report provides the strongest evidence linking *Bartonella* spp. and anterior uveitis in the cat (Lappin & Black, 1999). A 6-year-old DSH with unilateral anterior uveitis was serologically negative for *T. gondii*, coronavirus, FIV, FeLV, and *C. neoformans*, but had a serum IgG antibody titer to *Bartonella* spp. of 1:128. Intraocular *Bartonella*-specific IgG production was also demonstrated in aqueous humor, with a Goldmann-Witmer coefficient (C-value) of 4.42. Anterior uveitis persisted despite topical prednisolone acetate and systemic prednisolone therapy, resolving only after the addition of oral doxycycline dosed at 50 mg every 12 hrs for 21 days. The cat remained asymptomatic during the 13-month follow-up period.

Subsequent studies have failed to demonstrate a statistically significant association of documented active *Bartonella* infection with uveitis in naturally infected cats (Guptill, 2010; Stiles, 2011). In a report of *Bartonella*-specific antibodies and DNA in the aqueous humor of cats, serum antibody titers and aqueous PCR results were similar between cats with uveitis and healthy shelter cats (Lappin et al., 2000). The significance of positive Western immunoblot test results, used alone to support the role of *Bartonella* spp. in a variety of feline ocular diseases including uveitis (Ketring et al., 2004), has been questioned in light of the widespread seroprevalence of the organism, as well as the low (18.8%) positive predictive value of the Western blot for the presence of *Bartonella* DNA in cat blood (Lappin et al., 2008). In a study comparing serum antibodies in cats with and without uveitis, the healthy group had a higher percentage of seropositive cats (70%) than the group with uveitis (55%; Fontanelle et al., 2008a). Uveitis was diagnosed in only 5 of 298 ill cats in a study using serology and culture to determine an association between *Bartonella* and disease in pet cats, but 4 of these 5 were both seronegative and blood culture negative for *B. henselae* and *B. clarridgeiae* (Sykes et al., 2010). Yet another study comparing serum antibodies and PCR amplification from blood and aqueous humor in 104 cats with uveitis and 19 healthy shelter cats found positive antibody titers in a higher percentage of cats in the healthy group than in the group with uveitis (Powell et al., 2010). In the same study, *Bartonella* spp. DNA was amplified from the aqueous humor of one healthy cat, but none of the cats with uveitis.

Measuring serum antibodies alone has limited value for determining whether an ill cat has an active *Bartonella* infection, since the positive predictive value of serologic tests for bacteremia in cats is only 39%–46% (Guptill, 2003). False negative tests are uncommon, however; the negative predictive value of serologic tests for bacteremia or the presence of DNA in cat blood is high, at 87%–97% (Lappin et al., 2008). Current or previous infection by *Bartonella* spp. is best determined by combining serologic antibody testing with blood culture performed on BAPGM media (www.galaxydx.com) or with PCR assay on blood to demonstrate *Bartonella* spp. DNA (Lappin, 2018). A panel consensus report endorsed by the American Association of Feline Practitioners (AAFP) recommends the following criteria for the diagnosis of feline bartonellosis: presence of a syndrome reported to be associated with *Bartonella* spp. infection; exclusion of other causes of the clinical syndrome; detection of a positive *Bartonella* spp. test; and response to administration of a drug with presumed anti-*Bartonella* activity (Brunt et al., 2006).

If fever or other acute signs attributed to bartonellosis are suspected, administration of doxycycline is usually effective, but does not eliminate infection (Lappin, 2018). The AAFP Panel Report recommends doxycycline at 10 mg/kg orally daily for 7 days, continuing treatment for a minimum of 28 days (or 2 weeks beyond resolution of clinical signs) if a positive response is achieved by day 7 (Brunt et al., 2006). If the initial response to doxycycline is limited, a fluoroquinolone is an appropriate second choice. Pradofloxacin at 7.5 mg/kg orally once daily is considered by many to be the optimal drug for the treatment of clinical bartonellosis, as it is least likely to induce resistant strains (Biswas et al., 2010). Azithromycin is now considered contraindicated because of rapid induction of resistance (Biswas et al., 2010). Use of imidacloprid-containing products (Advantage Multi topical solution or Seresto® collars, Bayer Animal Health) has been shown to prevent transmission of *B. henselae* among research cats (Bradbury & Lappin, 2010; Lappin et al., 2013).

Leptospirosis

One of three cats with clinical leptospirosis characterized by renal insufficiency without liver involvement also exhibited anterior uveitis (Arbour et al., 2012). A 9-year-old neutered male DSH with a history of hunting rodents presented with unilateral uveitis of 2 months' duration, along with forelimb lameness, polyuria, and polydipsia. Titers were positive for *Leptospira pomona*, *L. bratislava*, and *L. grippotyphosa*, persisting despite treatment with amoxicillin and extended doxycycline therapy. The uveitis waxed and waned throughout a 3-year follow-up period.

Bacterial Uveitis

Examples of uveitis associated with miscellaneous bacterial infections have been reported in individual cats. An 8-year-

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old DSH presented with multiple subcutaneous nodules, generalized lymphadenopathy, and a dilated right pupil secondary to peripapillary granulomatous chorioretinitis and bullous retinal detachment (Dietrich et al., 2003). Acid-fast bacilli were noted histopathologically and *Mycobacterium simiae* was cultured from a biopsied skin nodule. Complete clinical remission followed treatment with rifampicin, enrofloxacin, and clarithromycin, with chorioretinal scarring and optic atrophy, but no recurrence of active inflammation over a 22-month follow-up period.

An 8-year-old mixed-breed cat developed refractory unilateral anterior uveitis following full-mouth tooth extractions for treatment of root abscesses (Westermeyer et al., 2013). *Actinomyces* spp. was isolated from the oral abscesses as well as the enucleated eye, with histologically abundant filamentous organisms within the anterior chamber. The authors suspected that immunosuppressive steroid therapy used to manage concurrent inflammatory bowel disease may have contributed to the development of the uveitis.

A febrile 3-year-old DSH presented with bilateral panuveitis attributed to bacterial septicemia (Donzel et al., 2014). Aqueous and vitreous cytology revealed suppurative inflammation, with intracellular and extracellular cocci identified on culture as *Enterococcus faecalis*. No primary infection site was identified. The uveitis resolved in one eye in response to prolonged systemic antibacterial therapy, but a mature cataract and aqueous flare were still noted in the second eye 1 year after diagnosis. Blindness was permanent.

Ophthalmomyiasis

Ophthalmomyiasis is as rare in cats as it is in other species. The condition most commonly manifests as parasite migration in and beneath the sensory retina. Most affected cats are clinically asymptomatic and the telltale tracks of the migration are often coincidental findings on fundus examination. In addition to the retinal lesions, one case of ophthalmomyiasis interna had a large fibrinohemorrhagic clot in the anterior chamber, presumably induced by anterior uveal migration of the parasite (Gwin et al., 1984).

Several reports describe uveitis associated with intraocular *Cuterebra* larvae. The mode of entry is not readily apparent. Visualization of the parasite is often limited by the corneal edema and fibrin that commonly accompany the infestation (Fig. 28.64). While in one case the globe was salvaged by surgical extraction of the larva, corneal edema was permanent (Johnson et al., 1988). Another cat developed retinal degeneration and lost vision in the affected eye several weeks after outwardly successful removal of the larva (Harris et al., 2000). The uveitis resolved in another case in which the larva was surgically removed from the anterior chamber, and the cat remained sighted with normal retinal function (Stiles & Rankin, 2006). Coagulation necrosis and hemorrhage of the retina, choroid, and optic nerve were demonstrated histologically, along with the larva, in a cat euthanized because of worsening systemic and neurologic signs (Wyman et al., 2005).

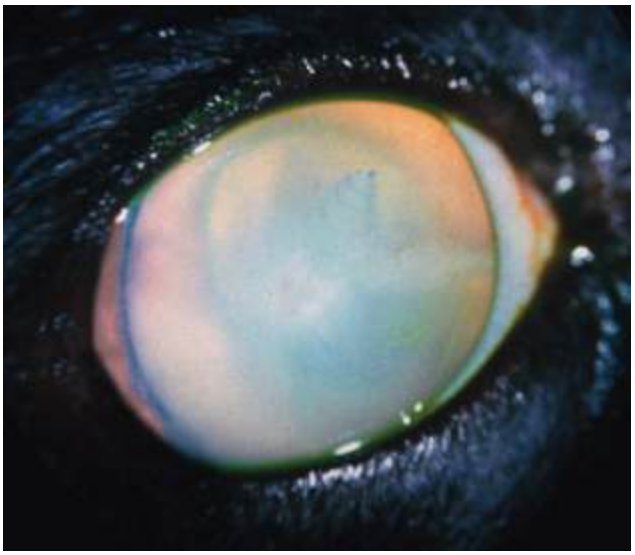


Figure 28.64 Anterior uveitis in a 1-year-old Domestic Shorthair with an intraocular Cuterebra larva.

Invasion of the globe by a nematode of the family *Metastrongylidae* has also been described in a cat (Bussanich & Rootman, 1983). The patient demonstrated ocular pain in association with inflammatory cells, fibrin, and blood within the anterior chamber. The eye eventually required enucleation.

Traumatic Uveitis

Uveitis is always initiated by tissue injury, disrupting the blood–ocular barrier and causing release of various chemical mediators that drive the inflammatory response (O'Connor, 1983). Nowhere is the concept of tissue injury more obvious than following an actual traumatic event. The injury may be blunt or perforating, including the effects of ocular surgery.

Blunt trauma originates from crushing bite wounds, automobile accidents, or impact with an unyielding implement such as a golf club, either unintentional or deliberate. The blunt force acutely distorts the eye; initial globe compression is followed by equatorial stretching and posterior displacement of the lens–iris diaphragm. Bleeding results from the direct rupture of uveal vessels or disinsertion of the iris or ciliary body roots. Equatorial deformation can also cause peripheral retinal tears. The sclera may rupture, especially at the posterior pole of the globe, near the optic nerve. Clinical signs include pain, eyelid swelling, subconjunctival hemorrhage, hyphema, and vitreous hemorrhage that may be severe enough to obscure other intraocular detail (Fig. 28.65). Loss of dazzle reflex, menace response, and indirect pupillary lens reflex to the healthy eye convey a poor prognosis for vision. Evaluation should include a fluorescein dye test and

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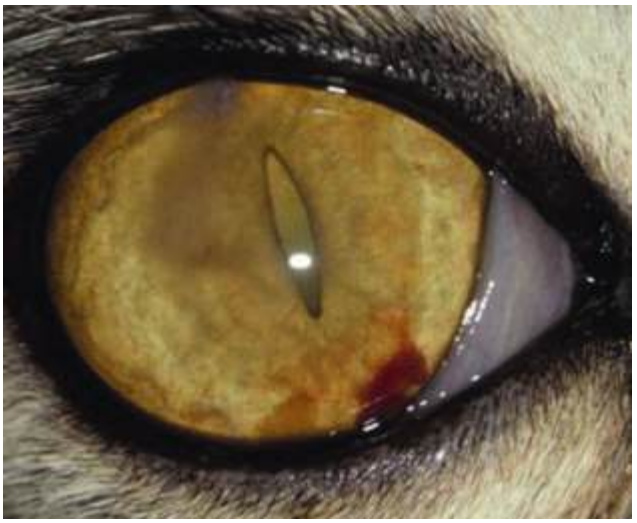


Figure 28.65 Anterior uveitis with miosis and mild hyphema followed a perforating corneal injury near the dorsal limbus in an adult cat.

tonometry. If the IOP is notably lower than the normal eye, if air bubbles are seen within the anterior chamber, or if the globe appears "wrinkled," ocular ultrasound should be considered to rule out scleral rupture. Eyes with confirmed scleral rupture are candidates for enucleation.

Functional outcome is often determined at the moment of impact, regardless of emergency response or hemorrhage resolution. If fluorescein is negative, topical corticosteroids are indicated for the traumatic uveitis. Topical atropine should be used cautiously in patients with complete hyphema, since the drug's effect on aqueous outflow may limit movement of red cells from the anterior chamber. Although systemic COX-2-selective NSAIDs have little effect on platelet function and may be used for analgesia and inflammation, drug labeling in the United States may not permit a regimen of adequate duration to successfully resolve the uveitis. Systemic prednisolone may be the better initial option if an extended treatment regimen is anticipated. An example of successful treatment of presumed traumatic uveitis and hyphema was reported in a purpose-bred kitten treated with topical prednisolone acetate, topical atropine, and oral meloxicam (Sorrell et al., 2008).

Penetrating or perforating corneal injuries are typically accompanied by some degree of uveitis, either initiated as a reflex mediated by the trigeminal nerve or driven by inflammatory mediators released upon entry of the claw, foreign body, or scalpel blade into the anterior chamber. Small, partial-thickness lacerations may only require medical management, as for a corneal ulcer, but unsealed full-thickness lacerations should be surgically repaired, as described in Chapter 19. Aftercare combines a topical prophylactic antibacterial solution, judicious application of topical atropine to reverse concurrent miosis, and an oral steroid or short-term systemic NSAID to reduce inflammation. Topical steroids or NSAIDs are less desirable in the acute management of traumatic corneal wounds due to altered tissue viability or unrealized sepsis, but either anti-inflammatory can be used following meticulous repair of surgical incisions.

Particular attention should be given to the integrity of the lens following a penetrating ocular wound. Punctate capsular defects may seal with fibrin, but larger wounds with cortical extrusion may necessitate lens extraction at the time of primary corneal repair. Intracameral tissue plasminogen activator (TPA) should be used cautiously in these patients, since reduction in anterior chamber fibrin is also likely to disrupt any fibrin seal overlying a capsular tear. Sequelae of capsular disruption range from variable cataract formation to chronic severe lens-induced (phacoclastic) uveitis driven by cortical material that continues to leak into the anterior chamber. A histopathologic study of 20 eyes examined for intractable inflammation and/or secondary glaucoma because of lens capsule rupture supported the hypothesis that early lens removal may be the best and only successful treatment for an injured lens (Wilcock & Peiffer, 1987). In an early clinical report of traumatic lens capsule disruption, 4 of 6 canine eyes treated medically required enucleation and another developed phthisis bulbi (Davidson et al., 1991b). Based on that experience, the authors concluded that prophylactic lens removal is indicated in patients with lens capsule tears of 1.5 mm or greater or those with substantial disruption of lens cortex. The only cat in the study, a 1-year-old DLH, was treated successfully by extracapsular lens extraction. Following those guidelines, 6 cats with corneal and lens lacerations were treated successfully by corneal repair and phacoemulsification, with all remaining visual at a median follow-up of 4 months (Braus et al., 2017). The authors remarked that "cats appear to develop less marked inflammation following lens trauma and lens surgery than do dogs," but also advised monitoring for post-traumatic ocular sarcoma formation following this type of injury, even with phacoemulsification. Not all ophthalmologists advocate lens extraction, however, as demonstrated in a retrospective study of 77 clinical cases of corneal laceration with lens capsule disruption that included 10 cats (Paulsen & Kass, 2012). In this study, patients with corneal injuries requiring surgical repair or those managed by lens removal developed vision-threatening complications at 3 and 4.5 times the rate of patients treated medically, respectively. Unfortunately, the specific response of the feline patients could not be determined from the study data as presented. Of particular significance in the management of this type of injury in cats is the association between traumatic lens capsule rupture and the development of feline ocular sarcoma, a particularly aggressive tumor discussed further in the section on intraocular neoplasia.

Septic implantation syndrome occurs when a penetrating wound inoculates bacteria within the lens. A unique pattern

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of slowly progressive or delayed-onset endophthalmitis is attributed to sepsis and the presence of bacterial antigens rather than release of lens proteins (i.e., phacoclastic uveitis; Bell et al., 2013; Dubielzig & Pirie, 2005). Clinical signs typically include fibrinous exudate on the lens capsule, especially associated with a focal cataract. The diagnosis is usually made on histopathologic examination of the enucleated globe, since clinical evidence of a bacterial infection within the lens is not readily apparent. Histologic findings include lens capsule rupture, degeneration of lens fibers (cataract), lenticular abscessation with neutrophils dissecting into the lens cortex, microorganisms embedded within the cortex but separate from inflammatory infiltrates, lymphoplasmacytic infiltrates in the iris stroma, and pre-iridal fibrovascular membranes (Bell et al., 2013; Dubielzig & Pirie, 2005). The first report of septic implantation syndrome included 2 cats with endophthalmitis and intralenticular bacterial colonies (Marlar & Dubielzig, 1995). A subsequent report described the histopathologic features of enucleated globes from 11 cats (Dubielzig & Pirie, 2005). A 13-year-old DSH with a 1 mm full-thickness corneal scar and focal incipient cataract consistent with a penetrating wound developed hypopyon, iris bombé, and secondary glaucoma 1 year after initial examination (Dalesandro et al., 2011). In a larger case series of septic implantation syndrome, 20 cats underwent unilateral enucleation for intractable uveitis and/or glaucoma (Bell et al., 2013). Clinical signs included uveitis (n=14), cataract (n=7), glaucoma (n=12), and corneal disease (n=5). The duration of ocular disease, from the earliest signs of uveitis or lens opacity until enucleation, ranged from 10 days to 1 year, with a median duration of 6 weeks. No breed or age predilections were identified, but male cats were overrepresented (70%). Infectious organisms identified within the lens of 14 cats included Gram-positive cocci (n=8), Gram-positive rods (n=4), and Gram-variable rods (n=2).

Cats appear to be particularly vulnerable to ocular injury associated with dental surgery. Scleral perforation and lens capsule rupture were histologically confirmed in 2 cats that developed exudative uveitis following extractions of maxillary premolar and molar teeth (Smith et al., 2003). Severe anterior uveitis developed in 1 patient within 7 days of the procedure, but did not appear in the second until 11 months later, the delay attributed to septic implantation syndrome. A third cat in the series recovered, with only localized cataract formation and a small amount of vitreous debris remaining 1 year later. Suppurative panophthalmitis with scleral and lens perforations was documented in 2 cats after multiple tooth extractions, with intervals of 7 and 42 days between the dental procedures and enucleations (Duke et al., 2014). A penetrating scleral wound was histologically confirmed in the enucleated eye of an 8-year-old DSH with intractable exudative uveitis and secondary glaucoma 5 days after receiving an intraoral maxillary nerve block (Perry et al., 2015). A subsequent retrospective study of 13 cats with ocular penetration during routine dentistry advised against transoral maxillary nerve blocks (Volk et al., 2019). Ocular signs developed at a median of 1.5 days following dentistry, with fibrinous uveitis, miosis, and vision loss. Response to therapy was poor, with 7 of 13 (54%) cats requiring enucleation. Scleral penetration was identified in 3 of 6 globes evaluated histologically, and lens capsule rupture and phacoclastic uveitis were confirmed in 4 eyes. Of the 5 cats managed medically, 4 exhibited persistent inflammation at last recheck. Active inflammation resolved in only 1 of the 13 patients in the study.

Drug-Related Uveitis

Bilateral anterior uveitis and hyphema were described in a cat anesthetized with a 1:1 combination of tiletamine and zolazepam (Telazol®, Zoetis, Parsippany, NJ, USA) administered intramuscularly for surgical sterilization. Clinical signs resolved within 24 hours, without evidence of residual damage (Schenk et al., 2017). The same report included a summary of surveys distributed to veterinarians practicing in shelters and high-volume spay-neuter practices in the United States, in which 9 of 20 respondents recalled instances of transient poststerilization hyphema. Of these, 7 used tiletamine/zolazepam in their anesthetic protocol. The etiology of the observation is unknown.

A transient increase in the permeability of the blood–aqueous barrier has been described in cats following topical application of 2% pilocarpine (Rankin et al., 2002). Topical prostaglandin analogues such as latanoprost may also disrupt the blood–aqueous barrier, exacerbating an existing uveitis (Willis, 2004) or complicating postoperative recovery following lensectomy (Arcieri et al., 2005). While these topical agents are seldom used in cats, the examples serve as reminders of the potential for drug-induced effects on uveal stability and reactivity.

Metabolic Uveitis

Burmese cats are at risk for developing lipid-laden aqueous, a condition attributed to anterior uveitis and an underlying disorder of lipid metabolism that results in increased serum triglyceride concentrations (Kluger et al., 2010). There is speculation that lipids may even incite the inflammation that facilitates their entry into the anterior chamber (Hendrix, 2013). Six Burmese cats had more than one episode of lipid aqueous in the same or contralateral eye, producing a characteristic milky-white appearance within the anterior chamber. All cats were less than 12 months of age, with females overrepresented (5 of 6). Clinical signs resolved in most cases within 24 hours. All resolved within 3 days and in most cases after topical 0.1% dexamethasone therapy. Based on an oral fat tolerance test, 4 of 5 cats tested were considered lipid intolerant. The dyslipidemia associated with the lipid aqueous is thought to be an inherited disorder that remains undefined.

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Hyphema is a relatively infrequent complication of systemic hypertension in cats. In a report of systemic hypertension in 69 cases, anterior migration of vitreous hemorrhage associated with retinal detachment accounted for hyphema in 10 eyes, but hyphema in 2 eyes appeared to result from iris hemorrhage (Maggio et al., 2000). The mechanism is most likely related to altered vascular permeability, but the fragile vessels that characterize secondary pre-iridal vascular membranes could account for spontaneous hemorrhage in cats with chronic retinal detachments.

Immune-Mediated Uveitis

Although an immune-mediated label has been applied to cases of idiopathic uveitis based on response to immunosuppressive therapy, confirmed instances of immune-mediated uveitis in cats are mainly limited to lens-induced inflammation. Slow leakage of lens proteins through the intact lens capsule of an advanced cataract causes phacolytic uveitis, a relatively uncommon problem in cats due to the low incidence of feline cataracts. Phacoclastic uveitis refers to a severe lens-related uveitis that follows lens capsule rupture, rapid leakage of large amounts of lens protein, and loss of T-cell tolerance (Wilcock & Peiffer, 1987). This form of uveitis, typically associated with perforating corneal lacerations, is discussed in more detail in "Traumatic Uveitis."

Periarteritis nodosa is a rare disease of cats in which small and medium arteries undergo fibrinoid necrosis. The disorder is thought to represent an immune complex-mediated vasculitis. Histologically, a neutrophilic infiltrate in the vascular tunica media is surrounded by a zone of lymphocytes and plasma cells. Vascular occlusion results from the formation of granulation tissue. Unilateral iritis was noted in one cat (Altera & Bonasch, 1966). Ocular lesions in another consisted of bilateral panuveitis with proteinaceous exudate within the anterior chambers and lymphocytic-plasmacytic infiltration of the ciliary bodies (Campbell et al., 1972). Other changes included the presence of cyclitic membranes, choroidal thickening by cellular infiltrates, and exudative retinal detachments. Vessels of the kidneys, lungs, and spleen were also affected. The diagnosis of feline periarteritis nodosa is usually a postmortem histopathologic determination.

Idiopathic Uveitis

While idiopathic disease is fundamentally a diagnosis of exclusion, in reality the label is commonly assigned to feline anterior uveitis, with no inciting cause identified in up to 70% of cases (Davidson et al., 1991a; Jinks et al., 2016). Histopathologic examination of affected eyes demonstrates lymphocytic-plasmacytic inflammation within the iris and ciliary body (Peiffer & Wilcock, 1991). In one study comparing cases of uveitis associated with systemic disease to those categorized as idiopathic, the latter were less likely to be bilateral (48% versus 67%), affected cats were generally older (9.6 versus 7.6 years), and 76% of patients were over 5 years of age (Gemensky et al., 1996).

Despite the prevalence of idiopathic uveitis in cats, there is a paucity of information regarding the mechanisms of inflammation in the feline eye. Interleukin 6 (IL-6) may be a mediator of feline uveitis, its activity detected in 22 of 27 (81.5%) aqueous humor samples from cats with uveitis (Lappin et al., 1997). COX-2 was detected in 55% (11 of 20) of eyes with lymphocytic-plasmacytic uveitis, 31% (4 of 13) with neutrophilic uveitis, and 1% (1 of 11) with uveitis associated with diffuse iris melanoma, suggesting that COX-2 is an inflammatory mediator in feline uveitis but not in diffuse iris melanoma. COX-2 was also detected in the cornea of 21 eyes with uveitis. Uveitis severity was positively correlated with COX-2 expression in both the uvea and the cornea (Sim et al., 2018). A recent study tested the hypothesis that feline lymphoplasmacytic uveitis is characterized by an influx or *in situ* induction of pro-inflammatory T cells (Crossfield et al., 2019). Immunohistochemical labeling was performed on eyes from normal cats and those diagnosed with idiopathic uveitis or FIP. The study concluded that pro-inflammatory Th17 cells are fundamental in the pathogenesis of noninfectious uveitis, based on the presence of the IL-17 marker in idiopathic but not FIP-associated uveitis. There was no significant difference between idiopathic and FIP groups in the frequency of cells labeled with FoxP3, a biomarker of regulatory T cells (Tregs) involved in immune system modulation and maintenance of self-tolerance, suggesting that a reduction in the frequency of regulatory T cells is not a contributing factor in the idiopathic form of the disease.

Various immunologic mechanisms have been proposed to explain idiopathic uveitis, though none has been specifically documented in the cat. While the distinction between autoimmune and immune-mediated uveitis is not always clear, the first refers to an autoimmune reaction to self-proteins (autoantigens), while the latter involves an aberrant inflammatory response to triggers that include microbes and tissue damage (Prete et al., 2015). Since the relative inaccessibility of the eye conveyed by its blood–ocular barriers limits the induction of peripheral tolerance, systemic T cells can be activated by a chance encounter with an ocular antigen or a microbial mimic (Caspi, 2006; Wildner & Diedrichs-Möhring, 2004). Such mimicry has been documented in the horse, in which the cornea and lens contain proteins very similar to those of *Leptospira interrogans* (Parma et al., 1997). The inhibitory ocular microenvironment may be able to control naïve T cells, but may not adequately regulate entering T cells that have already acquired an effector function peripherally (Caspi, 2014). Some investigators theorize that idiopathic uveitis ultimately traces back to an infectious etiology, through cytolytic tissue damage that exposes or alters ocular antigens, through uncontrolled and dysregulated host immune responses that continue after infection subsides, or as a result of persistent nonreplicating microor-

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ganisms or residual microbial antigens that reactivate resident memory T cells (Forrester et al., 2018).

Treatment of Anterior Uveitis

Treatment of uveitis is ideally tailored to each cat, taking into consideration the cause of the uveitis, its severity and duration, the portion of the uveal tract affected, and the presence of other ocular or systemic diseases. Considering the incidence of idiopathic disease, the treatment of uveitis remains largely symptomatic. Local – and sometimes systemic – immunosuppression is the treatment of choice in cases for which no cause has been determined. The use of antibiotics is not indicated unless a bacterial or protozoal infection is suspected or confirmed.

The mainstay of uveitis therapy is the corticosteroid. With the exception of patients with corneal ulceration, topical corticosteroid therapy should commence in all cases of uveitis while the cause of the inflammation is investigated. Numerous preparations are available for topical use, but the preferred formulations are 1% prednisolone acetate suspension or 0.1% dexamethasone solution, both of which penetrate intact corneal epithelium. Severe inflammation demands frequent topical application, starting as often as every 2 hours and tapering as clinical response is noted. When compared to 0.1% dexamethasone, topical administration of 1% prednisolone acetate suspension more effectively reduced aqueous flare in healthy cats following paracentesis-induced breakdown of the blood–aqueous barrier (Rankin et al., 2011). Dexamethasone 0.1% is also available combined with antibiotics including tobramycin or neomycin/polymyxin B, but the latter should be used with caution, having been implicated in anaphylactic reactions in cats following topical application (Hume-Smith et al., 2011; Plunkett, 2000).

Systemic corticosteroid administration is generally contraindicated in systemic infections, but should be considered in patients with severe uveitis or with concurrent choroiditis once infectious disease has been excluded. The exception may be FIP, in which systemic steroids are often used to palliate the associated vasculitis. Some ophthalmologists advocate systemic corticosteroids combined with an antifungal regimen in patients with mycotic chorioretinitis (Stiles, 2013). Oral corticosteroids should also be delayed in patients suspected of ocular lymphosarcoma until a multidrug chemotherapeutic regimen can be considered, since prior treatment with corticosteroids significantly reduced survival time in a cohort of cats in remission following chemotherapy (Taylor et al., 2009). Orally administered prednisolone significantly decreased intraocular inflammation in clinically normal cats with paracentesis-induced blood–ocular barrier breakdown, but no treatment effect was seen with oral prednisone (Rankin et al., 2013). Oral prednisolone may begin at 1–2 mg/kg every 12 hours in patients with severe inflammation, or 0.5 mg/kg once daily when a more moderate anti-inflammatory effect is needed. Reduction of dose and frequency should be carried out as soon as clinical response allows.

NSAIDs inhibit the formation of prostaglandins that act as potent inflammatory mediators within the eye, but they are not immunosuppressive, making them less desirable for the management of uveitis in the majority of cats. A number of topical NSAIDs have been developed that improve ocular bioavailability and reduce systemic side effects, but only 0.03% flurbiprofen and 0.1% diclofenac sodium have been evaluated in cats. In a paracentesis-induced inflammatory model, 0.1% diclofenac reduced aqueous flare comparable to 1% prednisolone acetate, whereas 0.03% flurbiprofen and 0.1% dexamethasone did not significantly decrease flare at any time point in the 26 hours post centesis (Rankin et al., 2011). Topical NSAIDs may be applied up to 4 times daily, dictated by the severity of the inflammation, but systemic absorption has been documented at that frequency. When administered topically to both eyes of healthy cats 4 times daily for 14 days, flurbiprofen reached higher plasma concentrations compared to diclofenac, with mean values of 423 ng/mL and 150 ng/mL, respectively (Lanuza et al., 2016). Flurbiprofen also persisted in the circulation up to 48 hours after application was discontinued, whereas diclofenac was cleared in 50% (3 of 6) of cats in 24 hours and all cats by 48 hours. Systemic absorption of topical diclofenac was also demonstrated in healthy cats treated 4 times daily for 7 days, with a concurrent decrease in glomerular filtration rate (GFR; Hsu et al., 2015). Although the investigators considered the reduced GFR to reflect iatrogenic volume depletion associated with multiple blood draws, they recommended caution when using topical diclofenac in systemically ill cats. Neither study demonstrated clinically relevant effects on serum blood urea nitrogen or creatinine (Hsu et al., 2015; Lanuza et al., 2016). Unlike their systemic counterparts, topical NSAIDs may be used in conjunction with topical corticosteroids without adverse effect, providing a synergistic but not additive anti-inflammatory effect.

In the United States, meloxicam and robenacoxib are the only systemic NSAIDs licensed for use in cats, labeled for the control of postoperative pain associated with orthopedic surgery, ovariohysterectomy, and castration. Meloxicam can be administered once perioperatively as a subcutaneous injection, and robenacoxib can be administered orally once daily as a flavored tablet for no more than 3 consecutive days. In some parts of the world, however, meloxicam is approved for indefinite use in cats for the alleviation of inflammation and pain associated with chronic musculoskeletal disorders, dosed at 0.1 mg/kg on day 1, followed by 0.05 mg/kg orally once daily. In a paracentesis-induced inflammatory model, meloxicam significantly decreased intraocular inflammation in clinically normal cats, dosed at 0.1 mg/kg beginning 2 days prior to paracentesis and continuing 2 days after paracentesis, with efficacy similar to that of oral prednisolone

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(Rankin et al., 2013). Oral robenacoxib failed to significantly decrease the extent of the paracentesis-induced blood–ocular barrier breakdown in healthy cats, dosed at 6 mg once daily for 3 days beginning 1 day prior to anterior chamber paracentesis. However, low levels of drug were detected in the aqueous of 5 of 6 treated cats, indicating that the drug can cross the intact blood–ocular barrier (Sharpe et al., 2018). Although topical corticosteroids can be safely used in conjunction with systemic NSAIDS (and vice versa), the two classes should never be given together systemically due to substantial risk of gastrointestinal ulceration.

Abrupt cessation of anti-inflammatory therapy, whether topical or systemic, may be associated with a "rebound" of inflammation. Treatment should be continued for at least 2 weeks beyond resolution of clinical signs. Determination of that endpoint should include an objective assessment of IOP, since subtle hypotony may be the only indication of active inflammation as treatment progresses. Cats with chronic idiopathic uveitis are likely to exhibit a relapse of clinical signs below a critical topical or systemic dose. The previously effective dose should be reinstated and, in all likelihood, maintained indefinitely.

Recrudescence of ocular herpesvirus may occur during treatment of uveitis, often manifest as corneal ulceration. Corticosteroid therapy should be discontinued and the ulcer allowed to resolve before reinitiating anti-inflammatory therapy. Antiviral therapy may speed resolution of the ulcer. A topical NSAID should then be used to manage the uveitis. Unfortunately, this class of drugs will also reactivate FHV in some cats, as demonstrated with human HSV (Trousdale et al., 1980).

Atropine (1%) is a parasympatholytic mydriatic-cycloplegic agent that decreases ocular pain by reducing iris and ciliary muscle spasm. Concurrent pupillary dilation discourages adhesions of iris to lens (posterior synechia) that alter normal aqueous circulation and mechanically compromise vision. The drug also reduces vascular endothelial permeability and stabilizes the blood–aqueous barrier (Van Alphen & Macri, 1966). Treatment should begin with topical application 1–2 times daily, decreasing frequency as dilation occurs. Possible adverse systemic effects with frequent topical use include reduced tear production, ileus, and dementia. An ophthalmic ointment is recommended in cats to decrease the likelihood of copious salivation that occurs when the bitter drug is licked off the nose following passage through the nasolacrimal system. IOP should be determined before initiating atropine, since its cycloplegic effect also increases resistance to aqueous outflow. Atropine is contraindicated in patients with secondary glaucoma. If IOP is high normal, shorter-acting tropicamide is a safer alternative. Although a less potent mydriatic-cycloplegic than atropine, any adverse effects are likely to last only 4–6 hours. IOP should be regularly monitored and either drug discontinued if IOP rises above normal.

If fibrin is present in the anterior chamber and does not resolve on its own within a few days of formation, TPA can be injected into the anterior chamber at a dose of 25 µg in a volume of 0.10 mL (Stiles, 2013). The fibrin usually resolves within 1–2 hours if it has not been present for more than 7–10 days.

As a general rule, therapy for uveitis should be initially aggressive, slowly tapering the frequency of administration as clinical signs subside. Recurrences of inflammation following cessation of treatment suggest the need for prolonged if not indefinite maintenance therapy. Ongoing diligence regarding recurrences of inflammation, elevations in IOP, and onset of systemic disease is essential in the management of cats with uveitis.

Anterior Uveal Neoplasia

Both primary and secondary uveal neoplasms occur in cats, affecting the anterior uvea more commonly than the choroid (Stiles, 2013). In 2011, the pathology database of the University of Wisconsin-Madison Comparative Ocular Pathology Laboratory (COPLOW) included 2614 cases of primary ocular neoplasia in cats. Tumors of the globe accounted for 2136 (82%) of all cases and 82% of these were melanocytic (n=1754). In general, intraocular tumors occur most commonly in middle-aged and older cats, with mean and median ages of 10.6 and 11 years, respectively (Dubielzig, 2011). There is no apparent breed or sex predilection (Dubielzig, 1990; Dubielzig et al., 2010; Mould et al., 2002; Peiffer et al., 2002; Williams et al., 1981). Early detection and timely intervention are crucial responses, owing to the locally invasive nature and metastatic potential of most feline intraocular tumors.

Feline Diffuse Iris Melanoma

Although examples of feline malignant uveal melanoma appeared in early case reports (Cardy, 1977; Peiffer et al., 1977; Souri, 1978), case series (Bellhorn & Henkind, 1970), and general reviews of feline neoplasia (Engle & Brodey, 1969; Patnaik et al., 1975; Saunders & Barron, 1958; Whitehead, 1967), it was not until Acland's account of 4 cats with slowly progressive iris infiltration that the unique clinical and histopathologic characteristics of feline diffuse iris melanoma (FDIM) were brought to light (Acland et al., 1980). Now considered the most common form of anterior uveal melanoma in cats, FDIM usually develops in cats over 9 years of age (Dubielzig et al, 2010; Mould et al., 2002), though ages at histopathologic diagnosis range from 2.8 to 23 years (Wiggans et al., 2016).

Invasive, metastatic anterior uveal melanomas developed following experimental injection of FeSV into the anterior chamber of kittens (Albert et al., 1981; Shadduck et al., 1981), but there is no compelling evidence of the role of retroviruses in the naturally occurring disease. One study sug-

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gested a link between anterior uveal melanoma and retrovirus infection after identifying FeLV-FeSV DNA in formalin-fixed enucleated globes, but only 3 of 36 samples were positive (Stiles et al., 1999). Negative FeLV-targeted immunohistochemistry and PCR on 10 formalin-fixed FDIM samples in a subsequent study also failed to substantiate an association (Cullen et al., 2002). Contemporary investigation centers on mutation analysis and gene expression of the feline tumor (Rushton et al., 2017, 2019b). Although feline ocular melanomas do not show any of the mutations typical of human melanomas (Rushton et al., 2017), expression patterns of various genes involved in tumor induction and progression differ between cats with diffuse iris melanoma and normal cats (Rushton et al., 2019b). Most notable is the overexpression of KIT, a gene that encodes for a stem cell growth factor receptor and is incriminated in cell proliferation within human uveal melanoma (Mouriaux et al., 2003).

Diffuse iris melanoma begins as focal or multifocal areas of iris pigmentation that appear as flat brown spots within the lightly colored feline iris. This earliest benign stage is referred to as iris melanosis, when pigment is strictly confined to the iris surface (Fig. 28.66A). Rare amelanotic variants may be clinically misinterpreted as inflammatory disease (Bjerkas et al., 1997). Over months to years, the

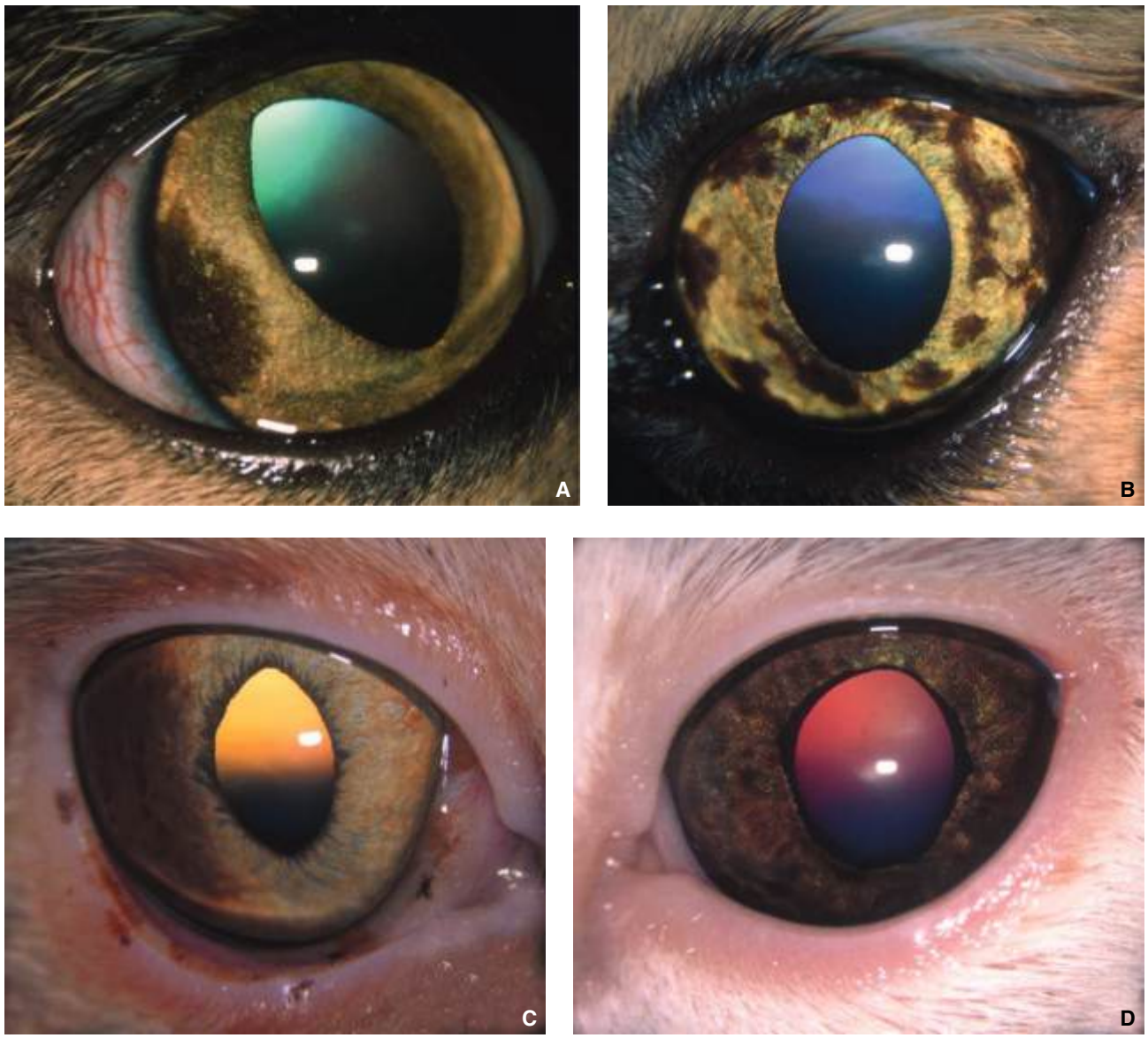


Figure 28.66 **A**. A flat area of pigmentation is interpreted as iris melanosis in an 8-year-old Domestic Shorthair (DSH). **B**. Multiple flat, pigmented foci are randomly scattered across the iris face in a 9-year-old DSH. **C**. The dull color and suede-like texture of the iris pigmentation in a 6-year-old DSH suggest a transformation to melanoma. **D**. Diffuse iris melanoma was confirmed histologically in a 10-year-old DSH with generalized iris thickening, ectropion uveae, and subtle pigmented cells on the anterior lens surface.

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extent and intensity of the pigmentation increase as individual spots enlarge or the number of pigmented sites increases (Fig. 28.66B). Serial photography is recommended to document these slow, modest changes. The transformation to diffuse iris melanoma is marked by the infiltration of pigmented cells into the iris stroma, a histologic determination that may include a change in cell morphology from a small angular cell to a rounded cell with a rounded nucleus and prominent nucleolus (Dubielzig & Lindley, 1993; Fig. 28.66C). Changes in pupil shape and reactivity may result as the iris thickens. Progressive infiltration of the iris, ciliary body, iridocorneal angle, and sclera follows, often complicated by glaucoma (Wilcock et al., 1990; Fig. 28.66D). Although one study listed uveal inflammation as a histopathologic parameter detected in 30 of 47 eyes with FDIM (Wiggans et al., 2016), uveitis is not a common clinical feature, nor have previous histopathologic reports characterized a significant inflammatory component in cases of FDIM (Duncan & Peiffer, 1991; Kalishman et al., 1998; Mould et al., 2002; Patnaik & Mooney, 1988).

There is no reliable way to predict the progression of disease in individual cats. In some, the pigmented foci may remain static for the life of the cat, or may expand over several years with no effect on vision or health (Kalishman et al., 1998). Clinically it seems that lesions progress more rapidly in younger cats, though that observation is yet to be corroborated in the literature. Rates of metastasis range from 19% to 63% (Duncan & Peiffer, 1991; Patnaik & Mooney, 1988; Wiggans et al., 2016), the higher percentages likely biased by the advanced tumor stage at which enucleation was performed in the early studies. The scleral venous plexus provides the most likely route of extraocular metastasis. Because the globe itself is devoid of lymphatics, only tumors that gain access to the conjunctival and periocular lymphatics by first breaching the sclera are likely to involve regional lymph nodes (Duncan & Peiffer, 1991). Metastasis occurs more often to the liver than to the lungs (Dubielzig et al., 2010), but lesions have also been found in the kidneys, spleen, omentum, diaphragm, pericardium, parietal pleura, hilar lymph nodes, and brain (Bertoy et al., 1988). Abdominal ultrasound should therefore be included when staging patients with diffuse iris melanoma. One report of a 10-year-old DSH 5 months after enucleation described widespread metastases that included the head and proximal diaphysis of the radius (Planellas et al., 2010). A latent period of up to 3 years can occur between diagnosis of melanoma and detection of metastatic disease. Even then, the role of metastatic disease in the death of these elderly cats has not always been clear (Kalishman et al., 1998; Wiggans et al., 2016).

The clinical dilemma centers on the timing of enucleation in patients suspected of FDIM. On merely the suspicion of diffuse melanoma, is it best to remove a functional eye early in the disease process to eliminate any chance of metastasis, or can one safely and ethically justify a conservative course of periodic examination that monitors progression but risks metastatic disease? There is as yet no definitive clinical means to determine when melanosis transforms into melanoma, since the fundamental infiltration of pigmented cells into the iris stroma is only detectable histologically. Slit-lamp examination, gonioscopy, and tonometry can identify changes suggestive of transformation that include iris thickening; development of a dull, velvety texture as iris surface detail is effaced; altered pupillary shape or mobility; exfoliation of pigmented cells into the aqueous; iridocorneal angle infiltration, with pectinate ligament pigmentation; and change in IOP. Aqueocentesis and "vacuuming" of the iris surface to recover cells for cytologic examination are seldom diagnostic. In one study of the diagnostic utility of aqueocentesis, an aspirate of a ciliary body mass confirmed a malignant amelanotic melanoma, but the accompanying aqueous cytology revealed only mononuclear inflammatory cells (Linn-Pearl et al., 2015). Microsurgical surface biopsy of pigmented foci can be safely performed, with a low risk of significant intraocular hemorrhage, but overall diagnostic benefit has not been established. Iris biopsies in 6 cases of hyperpigmentation were consistent with melanosis (n=3) or FDIM (n=2, subsequently confirmed on histopathology of the enucleated eyes), with the remaining sample too small to interpret (Featherstone et al., 2016). Complications associated with the biopsies included mild intraoperative hemorrhage (n=3), fibrin clot formation (n=2), corneal ulceration (n=1), and postoperative ocular hypertension (n=1).

An important differential diagnosis is an iridociliary cyst with unusually thick black walls that limit transillumination and disguise its cystic nature. On suspicion of intraocular melanoma, 14 neoplasia-free eyes containing one or more iridociliary cysts were mistakenly enucleated, 9 of these by or on the recommendation of a board-certified veterinary ophthalmologist (Fragola et al., 2018). A cyst is more likely than a melanoma to originate from behind the iris, appear within the pupil, or also affect the contralateral eye.

The only clinically measurable prognostic indicator described for FDIM has been the presence of secondary glaucoma, a feature of advanced disease that conveys a poor prognosis and reduced survival time (Kalishman et al., 1998). Only 4 of 19 cats (21%) with diffuse iris melanoma and secondary glaucoma survived, compared to 11 of 15 cats (73%) with tumor alone (Kalishman et al., 1998). Surprisingly, a recent study, in which 68% of FDIM-affected eyes were diagnosed with glaucoma, did not identify a significant association between glaucoma and metastases (Wiggans et al., 2016).

Various histologic and immunohistochemical characteristics have been proposed as indicators of metastatic risk following diagnosis of FDIM, though again there is discrepancy in the predictive value of individual parameters between studies. One report found a significantly higher mitotic index in neoplasms with a fatal outcome and an increased

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likelihood of metastatic disease in cats with neoplastic cells in the scleral venous plexus (Duncan & Peiffer, 1991). Other studies echoed the utility of the mitotic index in determining metastatic potential (Day & Lucke, 1995; Dubielzig & Lindley, 1993). Kalishman et al. (1998) considered the extent of tumor infiltration in the globe at the time of enucleation, comparing survival rates of affected cats to those of age-matched controls. The overall survival of affected cats was significantly shorter than that of control cats. However, those cats with melanoma confined to the iris, even to the level of the posterior iris epithelium, had a survival rate comparable to the control group. Prognosis progressively declined if the tumor invaded the ciliary body or the ciliary body and sclera, with median postenucleation survival times of 5 years and 1.5 years, respectively. Wiggans et al. (2016) reported increased rates of metastasis in eyes with extrascleral extension, tumor necrosis, a mitotic index of greater than 7 mitoses per 10 high-power (400×) fields, and choroidal invasion, but failed to corroborate scleral venous plexus invasion as a negative prognostic indicator. The study also identified three immunohistochemical predictors of metastasis, with increased metastatic rates associated with labeling of melan-A (a melanocyte antigen) and E-cadherin (an adhesion protein), and decreased rates with homogenous labeling of PNL2 (an antibody directed against melanocyte antigen). Cell-free DNA (cfDNA) does not appear to be a useful diagnostic or prognostic marker in cats with FDIM, despite reports of its predictive value in humans with ocular melanomas (Metz et al., 2013). No significant differences were found in the plasma concentration or integrity of circulating cfDNA between cats with iris melanoma, iris nevus, or controls, or between cats with and without metastases (Rushton et al., 2019a).

Enucleation remains the treatment of choice for FDIM. Evisceration and intraocular prosthesis are not advised in patients with suspected FDIM. There are no controlled studies documenting the ability of iridectomy, laser ablation of discrete lesions, or melanoma vaccine to arrest FDIM progression in cats. The efficacy of surgical excision or laser ablation may be limited by the multifocal nature of the disease, the involvement of the iris root and pectinate ligaments, and the dissemination of neoplastic cells via the aqueous humor (Mould et al., 2002). While the safety of melanoma vaccine was established in a study of 24 cats with malignant melanoma, including 4 cats with ocular/periorbital melanoma, vaccine efficacy and patient survival are as yet undocumented (Sarbu et al., 2017). Adverse effects of the vaccine in 7 cats (11.4%) included pain on administration, muscle fasciculations, transient inappetence, depression, nausea, and mild injection-site pigmentation. Initial data regarding gene expression in feline iris melanoma suggest a potential chemotherapeutic target in the KIT gene that encodes for a stem cell growth factor receptor (Rushton et al., 2017, 2019b).

Atypical Uveal Melanoma

Considered a separate entity from FDIM, this form of melanoma originates multifocally from any portion of the uveal tract other than the anterior iris (Dubielzig et al., 2010; Fig. 28.67). In a report of 6 cats ranging in age from 8 to 16 years, tumors were mainly centered in the ciliary body (2 of 6) and the choroid (3 of 6; Harris & Dubielzig, 1999). Histologically these tumors contain primarily round, heavily pigmented cells, without the anaplastic nuclear features of advanced diffuse iris melanoma. The risk of metastasis, which appears substantial despite these bland cellular characteristics, is likely related to the advanced stage at which this particular form of melanoma is recognized, a consequence of its origin posterior to the iris. There was suspicion of metastases in 2 of 4 cats with sufficient follow-up, with abdominal masses appearing in each cat 6 and 19 months following enucleation (Harris & Dubielzig, 1999).

Feline Ocular Post-Traumatic Sarcoma

Feline ocular sarcomas are the second most common primary intraocular tumor, after diffuse iris melanoma (Dubielzig, 2002). These malignant tumors are frequently preceded by ocular trauma or chronic uveitis, with an intervening latent period that averages 7 years (Dubielzig et al., 2010).

Although indistinguishable in clinical behavior and appearance, there are three histologic subtypes of feline ocular post-traumatic sarcoma (FOPTS; Dubielzig et al., 2010). The most common is a spindle cell variant, thought to arise from neoplastic transformation of lens epithelial cells and sharing characteristics with vaccine-associated sarcomas in cats (Dubielzig et al., 1990; Zeiss et al., 2003). Immunohistochemical markers for both T and B cells implicate neoplastic lymphocytes as the cell of origin in the round



Figure 28.67 An atypical uveal melanoma originates in the ciliary body and infiltrates the inferior iris of a 9-year-old Domestic Shorthair.

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cell variant (Naranjo et al., 2007). The osteo-chondrosarcoma variant is least common and is characterized by malignant mesenchymal cells of unknown origin that produce cartilage and/or osteoid matrix within the tumor. The gross clinical presentation is that of a white to pink mass, often originating in the posterior segment and proliferating circumferentially until it fills the entire globe. Chronic, relatively unresponsive uveitis, intraocular hemorrhage, and glaucoma are common secondary features (Fig. 28.68).

The first example of FOPTS may have been described as a chondrosarcoma in a 2-year-old cat that died 2 weeks after enucleation (Barron & Saunders, 1959). In retrospect, the tumor's invasiveness, associated lens capsule rupture, and tumor cells within the choroidal and scleral vessels fit the picture of post-traumatic sarcoma (Beckwith-Cohen et al., 2014). An osteosarcoma was reported in a phthisical feline eye injured 8 years beforehand (Woog et al., 1983). A link between trauma and sarcoma was reiterated in 3 feline eyes enucleated several years following injury, with histologic evidence of lens rupture, circumferential distribution of sarcoma within the globes, and optic nerve infiltration (Dubielzig, 1984). The potential role of chronic intraocular inflammation in sarcoma formation was subsequently introduced in a study of 13 cats with ocular sarcomas, 5 with histories of trauma and 6 with chronic uveitis of undetermined cause (Peiffer et al., 1988); 9 cats had tumors that characteristically lined the globe interior, with long-standing lens ruptures. Of the 13 cats, 7 died within months of enucleation owing to tumor recurrence or metastasis, with extension of tumor into the optic nerve of 4 cats. Dubielzig et al. (1990) described the morphologic variants of FOPTS in 13 cases (including the 3 cases reported in 1984), with spindle cell fibrosarcoma predominating (8 of 13); 11 cats in the series had a history of prior ocular disease, and trauma was documented in 5 of these patients. Postoperatively, 73% (8 of 11) were euthanized for tumor-related problems. An additional 10 cases ranging in age from 7 to 16 years had latent periods of 8 weeks to 8 years between injury or onset of inflammation and tumor development (Dubielzig et al., 1994). Tumor lined the globe interior in 9 eyes and extended beyond the sclera or into the optic nerve in 8 patients. Individual case reports also document the aggressive nature of this feline tumor (Barrett et al., 1995; Hakanson et al., 1990; Miller & Boosinger, 1987; Stoltz et al., 1994), including the first report of metastasis of a post-traumatic chondrosarcoma (Moreira et al., 2018).



Figure 28.68 A post-traumatic sarcoma in an 8-year-old Domestic Shorthair appears as a flesh-colored vascularized mass that effaces the temporal and ventral iris. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

Chronic lens rupture is a feature in the majority of reported feline sarcomas. Ruptured lens capsules were detected in 28 of 30 intraocular sarcomas included in a morphologic and histochemical survey of 75 feline intraocular neoplasms (Grahn et al., 2006). Observations in another study of feline sarcomas included lens rupture (n=5), advanced cataract (n=2), lens extraction (n=2), and absence of the lens (n=1; Dubielzig et al., 1994). An immunohistochemical investigation of 38 cases supported a lens epithelial cell origin for all but the round cell variant of sarcoma (Cassotis et al., 1999a). Zeiss et al. (2003) also substantiated a lens epithelial cell origin in 3 of 9 sarcomas. Lens epithelial cells exhibited increasing epithelial–mesenchymal transition as spindle cell variants progressed from the earliest metaplasia to advanced tumor growth beyond the eye (Takahashi et al., 2015). Such epithelial–mesenchymal transition is thought to contribute to tumor metastasis and chemoresistance as polarized epithelial cells lose their adhesion properties. Other characteristics identified in post-traumatic sarcomas that favor tumorigenesis include increased expression of telomerase activity and loss of cell cycle control (Carter et al., 2005).

In addition to obvious perforating lens trauma such as cat claw injuries, increased risk of feline sarcoma is suspected in association with lens extraction (Naranjo et al., 2007, 2011), and following intravitreal gentamicin injection to chemically ablate the ciliary body in cases of chronic glaucoma (Duke et al., 2013; Naranjo et al., 2007; Stoltz et al., 1994). One study documented post-traumatic sarcomas in 10 cats following lens extraction, with an average interval of 4.8 years between lens surgery and enucleation (Naranjo et al., 2011). In another, 5 of 8 cats treated by intravitreal injection were diagnosed with malignant tumors: 3 post-traumatic sarcomas and 2 melanomas (Duke et al., 2013). It is unclear in either instance whether the tumors were initiated by the therapeutic procedures or stemmed from an earlier event that caused the lens abnormalities and/or glaucoma in the

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first place. An orbital extraskeletal osteosarcoma developed in conjunction with a postoperative conjunctival cyst 5 years after enucleation for diffuse iris melanoma in a DSH cat. The authors proposed that the myofibroblastic collagen-rich matrix within the cyst wall acted as an inflammatory nidus, stimulating tumor growth similar to that of post-traumatic ocular sarcoma (Groskopf et al., 2010).

Metastasis occurs primarily by extension into the orbit through the sclera at the limbus or posterior pole or along the optic nerve to the brain (Peiffer et al., 1988). A potential hematogenous route is also suggested by tumor cells found within choroidal and scleral vessels. Metastasis to lymph nodes is rare. There is, however, one report of intrathoracic metastasis of a presumed post-traumation ocular chondrosarcoma in a young DSH cat (Moreira et al., 2018). If the owner is not committed to diligent monitoring, it is prudent to enucleate blind, traumatized feline globes, particularly those with lens capsule rupture. Approximately 8% of prophylactically enucleated feline globes in the COPLOW collection had an early spindle cell variant of post-traumatic sarcoma (Dubielzig et al., 2010).

Other primary sarcomas occur rarely in cats. An anterior uveal spindle cell tumor in a 10-year-old DSH first appeared as a nonpigmented solitary nodular mass, later complicated by secondary glaucoma (Fig. 28.69). The tumor was characterized as a Schwann cell variant of a peripheral nerve sheath tumor, resembling the spindle cell tumor of blue-eyed dogs (Evans et al., 2010). Primary intraocular chondrosarcomas distinct from the post-traumatic variety developed in four DSH cats ranging in age from 9 to 16 years (Beckwith-Cohen et al., 2014). Three cats exhibited white, friable masses filling the vitreous and intraocular chambers; the fourth had a well-demarcated mass of the iris and ciliary body. Histologically, neoplastic spindle cells were surrounded by a chondromatous matrix that compressed rather than infiltrated the ocular tissues, with no evidence of lens capsule rupture or extension beyond the globe. Two cats were alive 6 months and 3 years following enucleation; one diabetic cat died 6 months after enucleation of undetermined cause. The fourth patient was lost to follow-up. A myxoid leiomyosarcoma was thought to arise from the iris dilator muscle of a 6-year-old DSH with unilateral hyphema, iris bombé, and secondary glaucoma. The tumor was characterized by loosely arranged spindle cells diffusely infiltrating all intraocular tissues except the lens (Labelle & Holmberg, 2010).



Figure 28.69 A spindle cell tumor infiltrates the medial iris in a 12-year-old Domestic Shorthair. The mass was characterized as a Schwann cell variant of a peripheral nerve sheath tumor. (Courtesy of Dr. Paige Evans. Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

Iridociliary Epithelial Tumors

Primary ciliary body adenomas and adenocarcinomas are uncommon in cats, constituting 3.7% of feline ocular neoplasms in the COPLOW collection (Dubielzig et al., 2010). Early reports described a ciliary body carcinoma in a 7-year-old male cat (Cotchin, 1957) and ciliary body adenocarcinomas in 2 DSH cats, 8 and 10 years of age (Peiffer, 1983a). These slow-growing, nonpigmented vascularized masses typically originate from the ciliary pars plicata, fill the posterior chamber, cradle the lens equator, then appear within the pupillary space or extend into the anterior chamber through the iris root (Fig. 28.70). On rare occasion the mass extends posteriorly, invading the choroid with the potential for retinal detachment (Peiffer, 1983a). Secondary glaucoma may occur with infiltration of the iridocorneal angle, but uveitis is uncommon. In a histopathologic study of 17 eyes from



Figure 28.70 From its origin in the ciliary body, a nonpigmented vascular iridociliary adenoma extends into the posterior chamber and distorts the adjacent iris in a 9-year-old Domestic Shorthair.

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cats with ciliary body neoplasia, only 2 showed scleral invasion, a tendency associated with adenocarcinoma rather than adenoma (Dubielzig et al., 1998). One tumor recurred following attempted local excision, but enucleation appeared otherwise adequate for removing all neoplastic tissue in the cats. Metastasis is considered unlikely (Dubielzig et al., 1998), although one cat died 3 months after enucleation with metastases to the lungs, liver, and kidney and another succumbed to a chronic wasting disease of undetermined cause 1 year following enucleation (Peiffer, 1983a).

Metastatic Uveal Neoplasia

Lymphosarcoma is the most frequent metastatic intraocular tumor and the second most common intraocular neoplasm in cats (Dubielzig et al., 2010). The age of affected animals in one study ranged from 9 months to 18 years, with a mean of 9 years (Corcoran et al., 1995). Iris infiltration may be nodular (Fig. 28.71A, B) or diffuse (Fig 28.71C). Perivascular infiltration by neoplastic cells (Cello & Hutcherson, 1962) may contribute to a significant breakdown of the blood–aqueous barrier and the accompanying hypopyon, fibrin, and/or

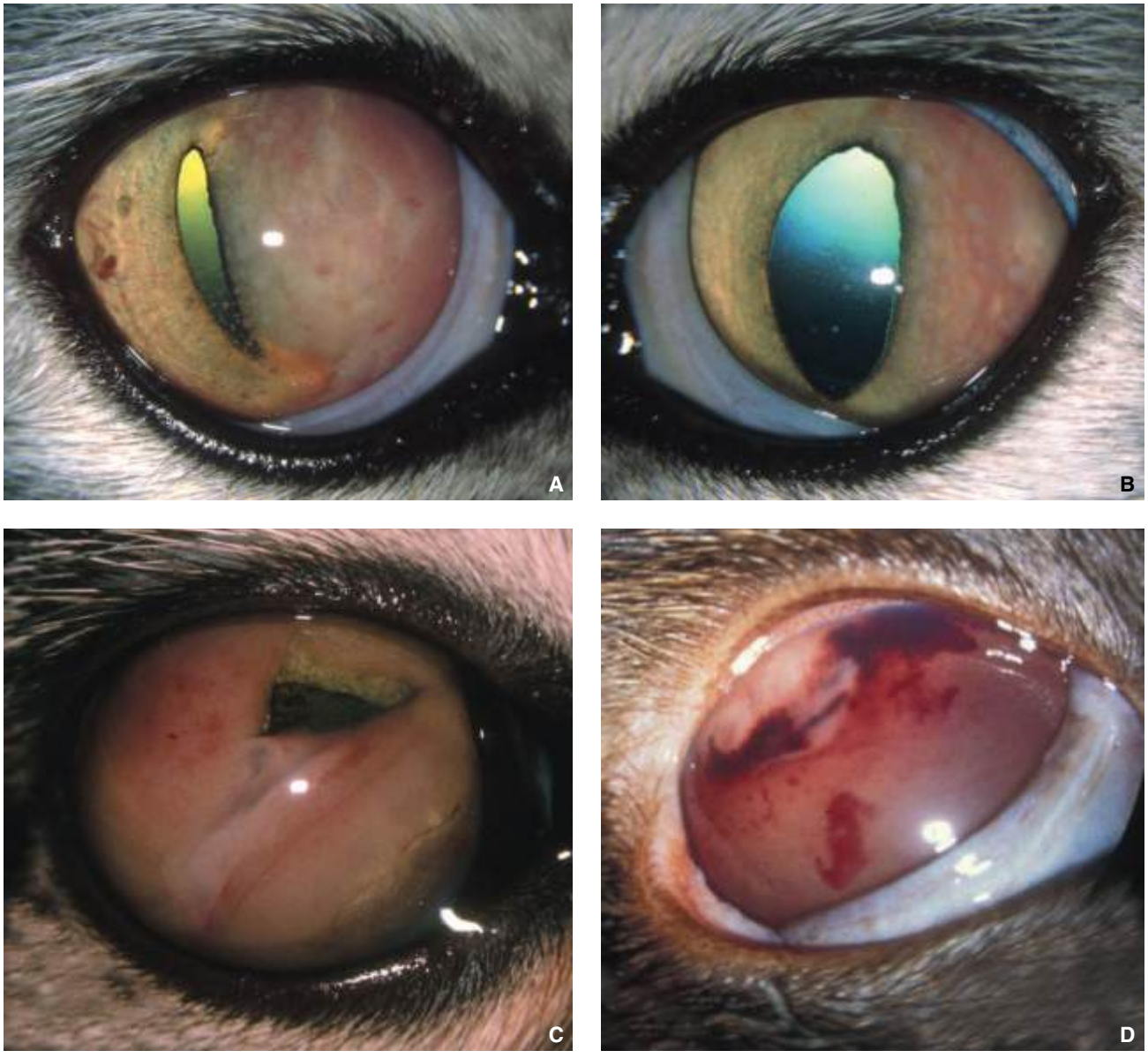


Figure 28.71 The right (**A**) and left (**B**) eye of a feline leukemia virus–negative 6-year-old Domestic Shorthair with abdominal lymphadenopathy and localized iris infiltration secondary to lymphosarcoma. **C**. Diffuse iris infiltration and a fibrinous exudate due to lymphosarcoma in a 9-year-old Domestic Shorthair. **D**. A pale mass in the temporal iris is accompanied by hyphema and fibrin in a 16-year-old Siamese with metastatic mammary adenocarcinoma. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

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hyphema within the anterior chamber. Lymphoplasmacytic uveitis is seen in approximately half of uveal lymphomas (Dubielzig et al., 2010). Bilateral anterior uveitis was the predominant ocular sign in a caracal diagnosed with large granular lymphoma (Aitken-Palmer et al., 2011). In a retrospective review of canine and feline ocular lymphoma, only 1 of 6 cats with intraocular lymphoma was affected bilaterally, but it too was characterized as a T-cell, large granular lymphocytic lymphoma (Ota-Kuroki et al., 2014). Ocular changes were documented in 12 (48%) of 26 cats newly diagnosed with lymphoma, with uveitis (anterior/posterior) as the predominant sign in 58% of patients. In the same report, complete remission of anterior uveitis occurred in 1 of 2 cats receiving chemotherapy (Nerschbach et al., 2016). An aberrant pupillary shape was described bilaterally in a 7-year-old European Shorthair cat, the "D" and "reverse-D" appearance ultimately attributed to iris stromal infiltration rather than neurologic disease (Nell & Suchy, 1998). Choroidal metastases tend to be multifocal owing to the segmental anatomy of the choroidal vasculature (Grahn et al., 2019). Retinal lymphoma, usually accompanied by some degree of uveal involvement, accounts for only 1.3% of cases of feline ocular lymphoma (Malmberg et al., 2017). Secondary glaucoma develops owing to extensive cellular infiltration of the aqueous outflow pathway or, less commonly, to peripheral anterior synechiae (Carlton, 1976; Corcoran et al., 1995).

Although the tumor may first appear in the globe, uveal lymphoma is generally considered a manifestation of multicentric disease (Dubielzig et al., 2010; Grahn et al., 2019; Stiles, 2013). B-cell lymphoma (n=7) occurred about twice as frequently as the T-cell phenotype (n=4) in a retrospective survey of feline intraocular neoplasms (Grahn et al., 2006). Overt signs of neoplasia such as peripheral lymphadenopathy are less likely in cats, since the abdominal form of lymphoma accounts for nearly 80% of feline cases (Vail & Young, 2007). Ocular signs preceded systemic disease in more than half of the 49 cats in Corcoran's retrospective study of ocular lymphoma and its histopathologic features (Corcoran et al., 1995). A 13-year-old Persian with unilateral uveitis and histologically confirmed large cell uveal lymphoma subsequently developed neurologic disease due to cerebral B-cell lymphoma, but all other organs were unremarkable (Giordano et al., 2013). Reported cases of presumed solitary intraocular lymphoma are exceedingly rare, representing only 0.06% of all feline lymphoma patients (Wiggans et al., 2014a). Initial systemic evaluation including cytologic examination of fine-needle aspirates of nonocular tissues failed to document lymphoma in any other organs of a 10-year-old DSH with anterior uveitis, glaucoma, and lens luxation, but its disease-free status following enucleation could not be substantiated when the cat was lost to follow-up (Wiggans et al., 2014a). Survival times were known in 10 of the 49 cases included in Corcoran's study, ranging from 0 days to 2.6 years, with a mean of 13.9 months (Corcoran et al., 1995).

Aqueocentesis may be particularly useful in the diagnosis of ocular lymphoma (Aitken-Palmer et al., 2011; Olin, 1977; Sandmeyer et al., 2017), with neoplastic lymphocytes demonstrated in the aqueous of 7 of 39 cats in one study (Linn-Pearl et al., 2015). Rapid processing of the sample is recommended to avoid adverse effects of ethylenediaminetetraacetic acid (EDTA) on cells within the collection tube. Diagnostic quality may improve using a cyto-centrifuge slide preparation to concentrate the cells within a 0.1–0.2 mL aqueous sample (Linn-Pearl et al., 2015).

Uveal metastases of various tumors other than lymphoma have been reported in the cat (Fig 28.71D). In a retrospective study of 164 cases of feline ocular metastases, carcinomas accounted for 78% of the cases, followed by sarcomas (15.3%), undifferentiated tumors (5.5%), and melanomas (1.2%). Clinical findings included hyphema, uveal infiltration/masses, synechiae, and secondary glaucoma, with a median age of 13 years in affected cats (Bedos et al., 2017). One or both eyes may be involved, with extensive and widespread invasion of blood vessels. The choroid rather than the anterior uvea is more often the target of these metastatic neoplasms, with a funduscopic pattern of choroidal infarction characterized by wedge-shaped areas of tapetal discoloration and profound vascular attenuation (Dubielzig et al., 2010; Fig. 28.72). Embolization of branches of the short posterior ciliary arteries create the sectorial loss of perfusion known as Amalric's wedge (Henkind, 1966). Secondary

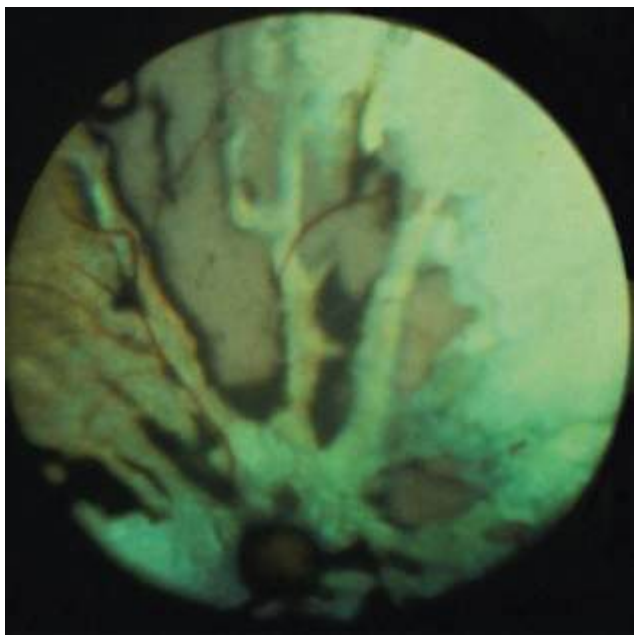


Figure 28.72 Tumor embolization of retinal and choroidal vessels creates a wedge-shaped area of chorioretinal degeneration in a 14-year-old Domestic Shorthair with metastatic intestinal adenocarcinoma. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

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intraocular tumors can also result from direct invasion of the eye by lesions originating on the ocular surface or in periocular sites.

SCC diffusely infiltrated the ciliary body, choroid, and optic nerve of both eyes in a blind, ataxic 9-year-old domestic cat. The primary site was not determined, but the uveal involvement suggested a hematogenous route to the eye (Cook et al., 1984). Intraocular infiltration of a corneolimbal SCC occurred in 2 cats, both with a history of chronic keratitis. The tumors infiltrated the drainage angle and iris, forming retrocorneal neoplastic membranes. One cat was euthanized 3 months following enucleation with suspected orbital involvement (Scurrell et al., 2013). A suspected primary corneal SCC also invaded the iridocorneal angle and iris in a 15-year-old DSH cat (Nappier et al., 2017). Local infiltration of the skull and cavernous sinus by SCC indirectly impacted the uvea in one cat, causing complete unilateral ophthalmoplegia and Horner's syndrome, with blindness attributed to concurrent optic nerve involvement (Murphy et al., 1989b).

A ciliary body tumor developed in a 13-year-old DSH with widespread metastasis of a mammary adenocarcinoma (West et al., 1979). A sweat gland adenocarcinoma metastasized to the choroid and optic nerve of a 15-year-old Siamese, creating intraocular hemorrhage and retinal detachment (Moise et al., 1982). Ischemic chorioretinopathy, especially notable in the tapetal fundus, was described in 4 cats with metastatic bronchogenic carcinoma (Cassotis et al., 1999b). Clinically, all cats demonstrated unilateral ocular involvement, but bilateral choroidal metastases were documented histologically in 1 patient. In addition to the ocular disease, 3 of the 4 cats developed abnormalities in the distal extremities or appendicular musculature. A 14-year-old DLH developed focal iris swelling, anterior uveitis, and retinal detachment associated with a mediastinal pulmonary bronchogenic adenocarcinoma (Gionfriddo et al., 1990). A focal gray-red iridal mass also developed in an 8-year-old domestic cat in association with a widely disseminated adenocarcinoma thought to be of pulmonary origin (Murphy et al., 1989a). Ocular metastasis of primary, but otherwise unspecified, lung tumors was reported in 7 cats with iris thickening/masses, uveitis, hemorrhage, and glaucoma (Mould & Billson, 2006). Histologically, a pattern of sheet-like growth occurred along the endothelial surface of blood vessels, especially of the choroid, and along intraocular surfaces including the iris and ciliary body.

A soft tissue fibrosarcoma originating over the hip of a 14-year-old Korat metastasized widely despite surgical excision and adjunct chemotherapy, with a fleshy mass infiltrating the iris and ciliary body of one eye (Fulton et al., 1991). A subretinal tumor and retinal detachment developed in a 6-year-old DSH diagnosed with a vaccine-associated fibrosarcoma. Despite repeated surgical excision, radiation, and chemotherapy, the cat also developed pulmonary and subcutaneous metastases (Cohen et al., 2003). Bilateral iris masses developed in a 6-year-old DSH 15 months after amputation of a forelimb diagnosed as subcutaneous fibrosarcoma (Mowat et al., 2012). Histopathology confirmed concurrent infiltration of the choroid, optic nerve, lung, and kidney.

Bilateral hypopyon and iris thickening were attributed to myeloproliferative disease in a 6-year-old Siamese cat, with diffuse infiltration of the bone marrow, lymph nodes, spleen, liver, and eyes by stem or reticulum-type cells that distinguished the disease from lymphoma (Slatter et al., 1974).

Glaucoma

Causes

Glaucoma in the cat is less common than in the dog, and most cases of feline glaucoma appear to be secondary. There are surprisingly few clinical and histopathologic reports in the literature regarding feline glaucoma (Beckwith-Cohen et al., 2019; Brown et al., 1994; Coop & Thomas, 1958; Gelatt & Ladds, 1971; Hampson et al., 2002; Jacobi & Dubielzig, 2008b; Kuehn et al., 2016; McCalla et al., 1988; McLellan et al., 2004; McLaughlin et al., 1987; Ridgeway & Brightman, 1989; Trost et al., 2007; Wilcock et al., 1990). As with dogs, most cats with glaucoma are presented late in the disease, and the initial events that induced the glaucoma may be masked by secondary changes. It is likely that glaucoma in the cat is under-diagnosed due to its insidious onset and gradual progression (McLellan & Miller, 2011).

An attempt to classify the different types of feline glaucoma from the available literature is summarized in Table 28.12. Congenital glaucomas may be either unilateral or bilateral and occur because of developmental abnormalities of the aqueous humor outflow pathways (Fig. 28.73). ASD, a heterogenous spectrum of developmental disorders

Table 28.12 Types and causes of glaucoma in cats.

Congenital
Secondary to structural anomalies (anterior segment dysgenesis, feline neovascular vitreoretinopathy)
Primary glaucoma
Open/normal-angle with or without collapsed ciliary cleft
Narrow/closed-angle (Burmese)
Pectinate ligament dysplasia (Siamese – LTBP2 mutation)
Secondary glaucoma
Anterior uveitis (chronic)
Lens luxations (trauma, primary, cataract)
Phacolytic/phacoclastic uveitis (lens perforation)
Hyphema (systemic hypertension, bleeding disorders, trauma)
Intraocular neoplasia (primary or secondary)
Aqueous misdirection syndrome

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Figure 28.73 Bilateral congenital glaucoma characterized by buphthalmos and corneal edema in a 12-week-old Domestic Longhair kitten.

that affects the cornea, iris, lens, and iridocorneal angle, occurs due to abnormalities of neural crest and neuroectodermal cell differentiation during embryogenesis. Inappropriate aqueous outflow leads to elevations in IOP and pronounced buphthalmos in young cats. A variety of syndromes in human ophthalmology have been reported, with analogous conditions sporadically reported in cats (Lazard & Peiffer, 2010; Peiffer, 1983b). A recent report described a case of Type 1 Peter's anomaly in a kitten (Park et al., 2018b). A newly recognized form of congenital glaucoma associated with a neovascular vitreoretinopathy and ASD occurs rarely in kittens and young cats without history of trauma, systemic disease, or intraocular inflammation or neoplasia (Beckwith-Cohen et al., 2019). This diagnosis is made based on distinct histopathologic features, including an avascular peripheral retina with gliosis and epiretinal neovascularization of the retina. It is unknown if the feline patients in this case series developed glaucoma due to ASD or secondary to extensive peripheral anterior synechia and intraocular inflammation.

Primary glaucoma has been reported, but appears to be much less common than secondary glaucoma in the cat. In a histopathologic study of 131 enucleated glaucomatous feline eyes, a primary cause was suspected in only 3 cases in which the associated inflammatory changes were considered to be either absent or mild, and because iridocorneal angle closure or obstruction was not a prominent histopathologic feature of the disease (Wilcock et al., 1990). In another study of 82 cats (93 eyes), glaucoma appeared to be primary in only 5 eyes based upon clinical examination (Blocker & van der Woerdt, 2001). Breed predispositions for glaucoma have been described in the Siamese (Brown et al., 1994; McLellan et al., 2004; Peiffer, 1982), Persian and European Shorthair (Trost et al., 2007; Walde & Rapp, 1992), and Burmese (Hampson et al., 2002). In most cats with primary glaucoma, the iridocorneal angle is open (Wilcock et al., 1990). However, a description exists of a group of closely related Siamese with primary congenital glaucoma (PCG) resulting from pectinate ligament dysplasia (McLellan et al., 2004). In an additional report, Burmese cats were reported to have narrow- or closed-angle glaucoma (Hampson et al., 2002). Open-angle glaucoma was described in a histopathology report of 8 cats, 6 of which were DSH or DLH, and 2 of which were Burmese (Jacobi & Dubielzig, 2008b). The gonioscopic appearance of the normal feline iridocorneal angle and ciliary cleft reveals a long, slender, and slightly branching pectinate ligament that is usually the same color as the iris and a pigmented trabecular meshwork (Fig. 28.74). Visualization of the iridocorneal angle and pectinate ligament is often possible without a goniolens.

Recently, a mutation in *LTBP2*, a known gene implicated in human PCG, was established as a cause of PCG in domestic cats (Kuehn et al., 2016). A 4 base pair (bp) insertion was identified in exon 8 of *LTBP2* in affected individuals generating a frame shift that completely alters the downstream open reading frame and eliminates functional domains. The phenotype was initially observed in a pair of Siamese cats, but is independent of the Siamese genetic background. The mode of inheritance is fully penetrant, autosomal recessive. Elevated IOP, globe enlargement, and elongated ciliary processes are consistently observed in all affected cats by 8 weeks of age. In fact, mean IOP at age 10 weeks is significantly higher in kittens with PCG (19.8 mmHg) than in normal kittens (13.2 mmHg) of the same age, and this disparity continues to widen as age-matched kittens age (Adelman et al., 2018). While normal kittens will reach their adult IOP by 3 months of age, PCG kittens' IOP continues to rise. Lens zonular instability is a common feature, although the more pronounced clinical signs (i.e., anterior or posterior lens subluxation and luxation) occur within the first 2 years of life. Neither episcleral vascular congestion nor signs suggestive of ocular pain are apparent and there is not usually evidence of intraocular inflammation. Gonioscopy reveals open or slightly narrowed iridocorneal angles, with subtle dysplasia of the pectinate ligament that is normally characterized by sparse and delicate fibers that span the entrance to the ciliary cleft. This feature is consistent with goniodysgenesis, supported by the extreme narrowing of the ciliary cleft reported previously on HRUS of the ocular anterior segment. Thus, this form of PCG is attributed to arrest (histologically confirmed) in the early postnatal development of the aqueous humor outflow pathways in the anterior segment of the eyes of affected animals. Additional clinical features noted in affected animals include prominent, elongated ciliary processes, spherophakia, iris hypoplasia, and iridodonesis. Corneal edema is not a prominent feature of this condition, and when it occurs is generally associated with lens instability and corneal endothelial contact by an anterior luxated or subluxated lens. Mild to pronounced optic nerve head cupping is apparent by 6 months of age. PCG cats with

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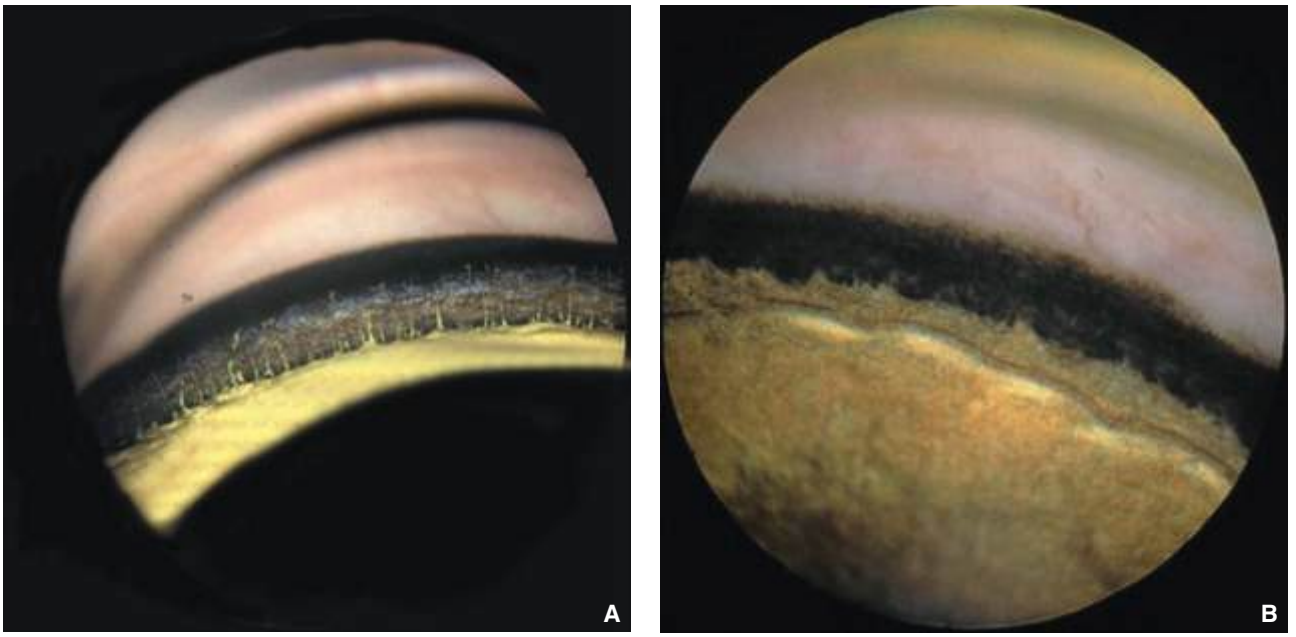


Figure 28.74 **A**. A gonioscopic view of the normal feline iridocorneal angle in a 3-year-old Domestic Shorthair illustrates fine, widely spaced pectinate ligaments spanning the wide ciliary cleft, with the pigmented trabecular meshwork in the background. **B**. Photomicrograph of a normal feline iridocorneal angle and ciliary cleft (hematoxylin and eosin). (Reproduced with permission from Stiles, J. (2013) Feline ophthalmology. In: *Veterinary Ophthalmology* (eds. Gelatt, K.N., Gilger, B.C., & Kern, T.J.), 5th ed., pp. 1477–1559. Ames, IA: Wiley-Blackwell.)

buphthalmos and increased corneal diameter have marginally thinner corneas and a significant decrease in corneal sensitivity as assessed with esthesiometry compared to normal age-matched cats (Telle et al., 2019).

Most cases of feline glaucoma are secondary to either anterior uveitis or intraocular neoplasia (Blocker & van der Woerdt, 2001; Wilcock et al., 1990). In two separate histopathologic studies, the majority of glaucoma cases occurred secondary to chronic, idiopathic, lymphocytic-plasmacytic uveitis (Gelatt & Ladds, 1971; Peiffer & Wilcock, 1991). However, other causes were FIP, iridal melanoma, FeLV-associated lymphosarcoma, trauma, and lens-induced uveitis.

Anterior uveitis may lead to glaucoma through the deposition of inflammatory cells within the iridocorneal angle and ciliary cleft, the development of peripheral anterior synechiae or postinflammatory fibrovascular membranes that traverse the iridocorneal angle, and collapse of the ciliary cleft (Peiffer & Wilcock, 1991; Wilcock et al., 1990), all of which block the outflow of aqueous humor (Fig. 28.75). On gonioscopy, the iridocorneal angle may appear to be unusually wide because of angle recession and globe enlargement. However, the ciliary cleft is collapsed and peripheral anterior synechiae may be scattered among the pectinate ligaments.

Intraocular neoplasia is the other predominant cause of feline secondary glaucoma. While any intraocular neoplasm may cause secondary glaucoma, diffuse iridal melanoma presents the highest risk. The second most common neoplasm to cause glaucoma is lymphosarcoma (Peiffer & Wilcock, 1991; Wilcock et al., 1990). Intraocular neoplasia can cause impaired aqueous humor outflow via several mechanisms, including infiltration of the trabecular meshwork and ciliary cleft by neoplastic cells, direct damage to the trabecular cells, formation of peripheral anterior synechiae, formation of pre-iridal fibrovascular membranes, and secondary inflammation from neoplastic factors and necrosis.

Other, less common causes of feline secondary glaucoma include corneal perforation with anterior synechia (and subsequent angle and cleft closure) and traumatic lenticular rupture (McCalla et al., 1988). The severe inflammation after corneal and lens perforations may induce pupillary seclusion due to annular posterior synechiae. The cat's vertical, slit-shaped pupil appears to be more difficult to occlude except in cases of severe inflammation.

Anterior lens luxation may cause feline secondary glaucoma by obstructing aqueous outflow (Olivero et al., 1991). Because the feline anterior chamber depth is greater than the canine, glaucoma secondary to anterior lens luxation is less common in the cat than in the dog (Sapienza, 2005). Lens subluxations or luxations may occur in cats with chronic glaucoma and buphthalmic globes. Buphthalmos may contribute to zonular disinsertion and lens instability, resulting in an anterior lens luxation. Therefore, determining whether the lens displacement or the glaucoma was the primary event is critical for treatment and prognosis.

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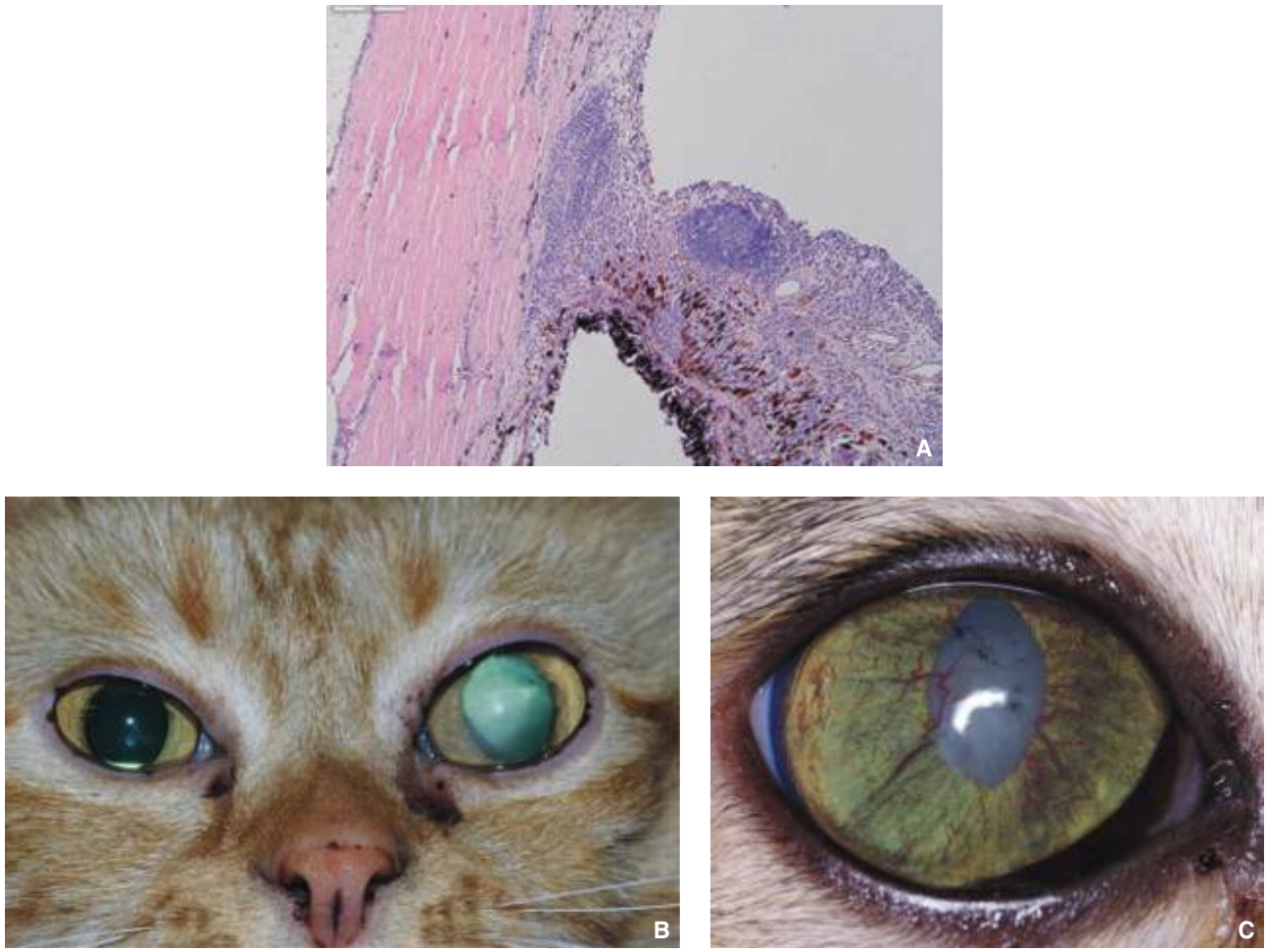


Figure 28.75 **A**. Photomicrograph from a feline globe with glaucoma secondary to chronic uveitis. A lymphoplasmacytic infiltrate is present in the iris and sclera. The iridocorneal angle and ciliary cleft are obstructed by the inflammatory infiltrate (hematoxylin and eosin). (Reproduced with permission from Stiles, J. (2013) Feline ophthalmology. In: *Veterinary Ophthalmology* (eds. Gelatt, K.N., Gilger, B.C., & Kern, T.J.), 5th ed., pp. 1477–1559. Ames, IA: Wiley-Blackwell.) **B**. Feline eyelid conformation can mask buphthalmos and episcleral congestion, illustrated in the left eye of a 6-year-old Domestic Shorthair with glaucoma secondary to idiopathic uveitis. **C**. Idiopathic uveitis and secondary glaucoma in a 2-year-old Domestic Shorthair with cataract, rubeosis iridis, lens capsule vascularization, and an intraocular pressure of 42 mmHg.

Glaucoma due to aqueous humor misdirection, sometimes termed malignant glaucoma, has been described in the cat (Czederpiltz et al., 2005; LaCroix et al., 2003; Miller et al., 1999). The pathogenesis appears to be misdirection of the aqueous humor posteriorly into the vitreous humor through small breaks in the hyaloid near the vitreous base. The resultant increased vitreal pressure causes anterior displacement of the lens–iris diaphragm, marked shallowing of the anterior chamber, and subsequent closure of the iridocorneal angle. Typical clinical signs include mydriasis, a shallow anterior chamber visible on slit-lamp biomicroscopy, and IOP elevations that range from mild to marked (Fig. 28.76). In a study of 32 cats (LaCroix et al., 2003), the mean age at presentation was 12 years, with female cats significantly more affected than males. The IOP ranged from 12 to 58 mmHg at presentation, with an IOP of 20 mmHg or higher in 32 of 40 affected eyes. Ultrasonography and histopathologic examinations have revealed a thickened anterior vitreal face interposed between the lens and ciliary body, partial ciliary cleft collapse, and cavitated vitreal regions corresponding to fluid pockets. Medical therapy to reduce aqueous humor production or improve aqueous outflow has variable results in these cases. In many cats the progression of disease is relatively slow, and topical medications such as timolol maleate and dorzolamide maintain relatively normal IOPs for prolonged periods. Surgical pars plana vitrectomy (Miller et al., 1999) or lensectomy and anterior vitrectomy (Czederpiltz et al., 2005; Miller et al., 1999; Sapienza, 2005) in some cats have been successful in controlling IOP. A case series evaluating lensectomy and posterior capsulotomy with or without vitrectomy or endoscopic cyclophotocoagulation described the postoperative course of 7 cats (9 eyes)

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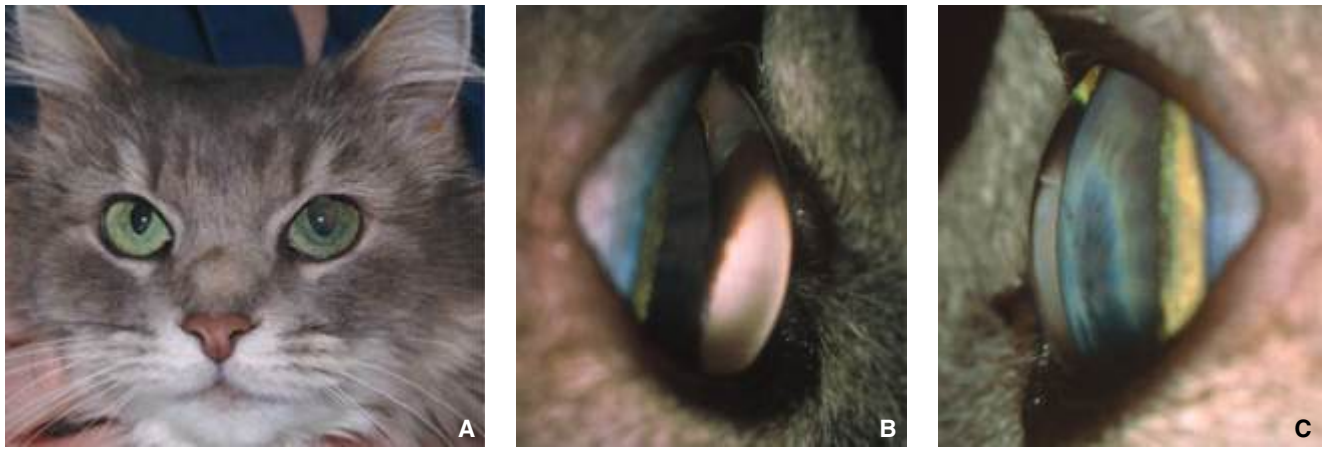


Figure 28.76 Feline aqueous humor misdirection syndrome (FAHMS). **A**. Subtle mydriasis is a common presenting sign of FAHMS, as seen in the left eye of a 12-year-old Domestic Shorthair with an intraocular pressure (IOP) of 31 mmHg. **B**. A lateral view of the right eye in a 10-year-old Domestic Shorthair demonstrating the normal depth of the anterior chamber. **C**. A lateral view of the left eye of the same cat, showing the extremely shallow chamber that characterizes FAHMS, with an IOP of 34 mmHg.

with aqueous misdirection in which medical therapy alone was insufficient to control elevations in IOP (Atkins et al., 2016). All of the cats were visual 1 year after surgery and all but 1 eye was normotensive, suggesting that surgical management may be a useful option in these cases.

Clinical Signs and Intraocular Pressure Measurement

The criteria for making a diagnosis of glaucoma in the cat is the same as in other animal species; however, clinical signs in the cat may be more subtle and therefore easily overlooked. Often, the clinical signs have been present for extended periods of time and the eyes are already permanently blind (Blocker & van der Woerdt, 2001; Dietrich, 2005). In one study, the most common complaints and clinical signs were cataract, corneal edema, mydriasis, buphthalmos, "cloudy eye," and blindness (Blocker & van der Woerdt, 2001). Conjunctival or episcleral hyperemia was often absent. Cats frequently do not develop the conspicuous corneal edema that occurs in dogs, which may indicate the ability of the feline corneal endothelium to pump against significant hydrostatic pressure or signal lower elevations of IOP. In acute glaucoma, pupillary dilation is the most common finding and may be the only sign observed (Brooks, 1990). Buphthalmia, exposure keratitis with vascularization, and lens luxation (usually subluxation and anterior luxation) are common sequelae to chronic intraocular hypertension (see Fig. 28.76). Buphthalmia, however, is easily overlooked, because the orbit and eyelids effectively camouflage the enlarged globe. Retinal degeneration is recognized ophthalmoscopically by vascular attenuation and tapetal hyperreflectivity. Because the small optic papilla of the cat normally lacks myelin, optic nerve cupping is often difficult to visualize. Even so, the atrophic optic nerve head is darker in color.

The circadian rhythm of IOP in normal cats has been evaluated (Del Sole et al., 2007). The peak IOP occurred between 9 p.m. and 12 a.m., while the lowest values occurred between 9 a.m. and 6 p.m. Mean IOP as measured with applanation tonometry in this study was 18 mmHg over the 24-hour period. Another study evaluating IOP in normal cats by use of applanation tonometry reported values of 9–31 mmHg (Miller et al., 1991). An experimental study determined that applanation tonometry in the cat underestimates IOP, such that the Tono-Pen XL® (Reichert Technologies, Ametek, Berwyn, PA, USA) reading should be multiplied by 1.6 to approximate the actual IOP (Passaglia et al., 2004). In a study to establish reference values of IOP in normal cats by use of a rebound tonometer (TonoVet®, Icare, Vantaa, Finland), the mean value was 21 mmHg (Rusanen et al., 2010). The rebound tonometer was found to correlate well with direct manometry in the clinically important pressure range. Another study compared the TonoVet to the Tono-Pen XL and concluded that both instruments produce reproducible IOP measurements in cats, but that the TonoVet readings were much closer to the true IOP than those of the Tono-Pen XL (McLellan et al., 2013). The TonoVet is superior in accuracy to the Tono-Pen XL for the detection of ocular hypertension and/or glaucoma in cats in a clinical setting.

Treatment

The goals for treatment of feline glaucoma are the same as in other species. The foremost considerations are to correct, when possible, the underlying cause and to reduce IOP. Glaucoma secondary to idiopathic uveitis is sometimes effectively treated using aggressive anti-inflammatory therapy.

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Topical corticosteroids can be very effective; however, they have some limitations and potential sequelae. Long-term topical dexamethasone has been reported to cause elevated IOP in normal cats (Zhan et al., 1992), although a more recent study evaluating the effects of topical corticosteroid therapy on the IOP of both normal cats and cats with PCG suggests that the incidence of steroid-induced IOP elevation in cats is lower than that of previously published feline studies (Gosling et al., 2016). Normal cats in that study (2 of 5) that exhibited a response to topical corticosteroids had only small elevations that were considered clinically unimportant. Cats with preexisting compromise in aqueous humor outflow (in PCG) may show a greater clinically relevant response than normal cats (Gosling et al., 2016). The use of topical steroids in cats may on occasion cause recrudescence of latent herpesvirus infections. If lens luxation or rupture is the cause of the glaucoma, lens extraction is beneficial. In the study by Blocker and van der Woerdt (2001), 58% of the eyes maintained an IOP within the normal range and appeared comfortable with medical therapy alone.

In *acute* cases of glaucoma, when the IOP is greater than 50 mmHg and is accompanied by mydriasis, a hyperosmotic agent, such as intravenous mannitol or oral glycerin, may be generally indicated to lower the IOP and to preserve optic nerve and retinal functions. Because the efficacy of osmotic agents relies on established blood–aqueous and blood–vitreous barriers, their effect is diminished in the face of intraocular inflammation (Willis, 2004). Withholding water from the patient for up to 4 hours is required to produce the desired hypotensive effect (Dugan et al., 1989). In a recent study on the effects of latanoprost on IOP in PCG cats as well as normal cats, administration of latanoprost resulted in an acute lowering of IOP in glaucomatous cats, which subsequently diminished over a period of 3 weeks (McDonald et al., 2016). This suggests that cats with PCG, not necessarily cats with other forms of inherited glaucoma or secondary glaucoma, may respond to topical latanoprost in acute instances. However, no consistent reduction in IOP was observed over time and cats experienced profound miosis followed by a marked rebound mydriasis. There was no IOP-lowering effect seen in normal cats.

Medical therapeutic options include systemic and topical carbonic anhydrase inhibitors, topical beta-blockers, topical alpha-2 agonists, parasympathomimetics, and prostaglandin analogues. Systemic carbonic anhydrase inhibitors are not recommended in cats due to side effects including decreased appetite, vomiting, and lethargy (Blocker & van der Woerdt 2001). Options for topical carbonic anhydrase inhibitors are dorzolamide and brinzolamide. Application of 2% dorzolamide or 1% brinzolamide results in a significant decrease in IOP and/or in aqueous humor flow rate in normotensive cats (Dietrich et al., 2007; Rainbow & Dziezyc, 2003; Rankin et al., 2012; Slenter et al., 2020). The addition of 0.5% timolol maleate to dorzolamide significantly reduces IOP over that seen with dorzolamide alone (Dietrich et al., 2007; Slenter et al., 2020). In a retrospective study, dorzolamide appeared to effectively decrease IOP in glaucomatous cats (Blocker & van der Woerdt, 2001), and in a study using dorzolamide in cats with PCG, IOP was significantly reduced with every 8-hour treatment (Sigle et al., 2011). While dorzolamide appears to be efficacious when used in the cat, administration of 1% brinzolamide topically every 12 hours did not significantly reduce IOP in normotensive cats (Gray et al., 2003).

The topical beta-blockers most commonly used in veterinary medicine are betaxolol and timolol (Willis, 2004). There are currently no reports on the efficacy of betaxolol in feline patients. When timolol maleate 0.5% was administered to normotensive cats, the IOP was decreased by 22% (Wilkie & Latimer, 1991a). A significant miosis was also induced. With a gel-forming solution of timolol maleate 0.5% administered once daily to normal or glaucomatous cats an inconsistent IOP-lowering effect was observed, suggesting that this formulation administered once daily would be of limited clinical benefit to PCG cats (Kiland et al., 2016). Apraclonidine is an alpha-2 agonist that has been evaluated for its effects on IOP in cats. When 0.5% apraclonidine was administered to normotensive cats, a significant decrease in IOP was noted (Miller & Rhaesa, 1996). However, severe side effects, including a decreased resting heart rate and vomiting, were also noted. Therefore, apraclonidine is not recommended for use in cats.

Use of 2% pilocarpine, a direct-acting parasympathomimetic agent, has been reported to decrease IOP by 15.2% in normotensive cats (Wilkie & Latimer, 1991b). Pilocarpine has been shown in dogs to increase the permeability of the blood–aqueous barrier (Krohne, 1994), which makes it a less desirable choice for use in cases of glaucoma secondary to uveitis. Additionally, pilocarpine may be very irritating, has the potential for systemic side effects, and is not generally recommended for treating feline glaucoma.

Topical application of prostaglandins has been shown to produce a sustained decrease in IOP in the cat (Bito et al., 1983). However, the commercially available prostaglandin analogues, latanoprost (Studer et al., 2000), bimatoprost, and unoprostone isopropyl (Bartoe et al., 2005), have had no effect on the IOP of normal cats, although they do cause miosis. This lack of effect may be because decreases in IOP in cats appear to be mediated through prostanoid E and D receptors (Bhattacherjee et al., 1999; Chen & Woodward, 1992; Woodward et al., 1989). While latanoprost is a highly selective prostanoid F receptor agonist (Studer et al., 2000), the receptors for bimatoprost and unoprostone isopropyl have not yet been determined (Bartoe et al., 2005). The effect of travaprost on IOP has not been reported in the cat.

When medical therapy fails to control IOP, surgical options may be considered. In globes that retain vision, cyclophotocoagulation is a surgical option to decrease the production of aqueous humor. Cyclophotocoagulation may be performed

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with the Nd:YAG or diode laser (Abrams, 2001; Rosenberg et al., 1995). The diode laser causes fewer complications because of decreased bystander tissue damage. However, complications may still occur and include postoperative increases in IOP, corneal ulcers, intraocular hemorrhage, cataract, and retinal detachment (Cook, 1997). The risk of lens damage from laser energy with possible development of intraocular sarcoma has not been evaluated in cats. A case report describes diode laser cyclophotocoagulation performed twice in a cat with primary glaucoma, with suboptimal results (Trost et al., 2007). Diode cyclophotocoagulation may be preformed either transsclerally or endoscopically, the latter requiring a surgical approach to the interior of the globe and lensectomy. The use of gonioshunts in cats with glaucoma is a feasible treatment option, although reports in the literature are sparse (Park et al., 2018a). An Ahmed glaucoma valve was placed with an adjunctive atelocollagen-glycosaminoglycan matrix surrounding the implant to encourage the development of normal tissue over the implant (rather than scar tissue) in an effort to prevent collapse and contraction of the bleb, a common source of implant failure in a single feline patient with narrow iridocorneal angles. The cat, a Russian Blue, healed well and remained normotensive for 7 months of available follow-up (Park et al., 2018a). The authors of that report noted that the tight eyelids of the cat may make the insertion of drainage devices difficult.

In permanently blind eyes, surgical therapy for glaucoma is indicated, particularly if the IOP cannot be maintained within a comfortable range (< 25 mmHg). Enucleation is indicated in blind, painful, or buphthalmic eyes, and is the procedure of choice for eyes with intraocular neoplasia or infections. An orbital prosthesis can be placed for improved cosmesis. However, use of methyl methacrylate as an orbital prosthesis is not recommended in cats, because 40% of cats in one study experienced complications (Nasisse et al., 1988). Evisceration with intraocular prosthesis may be considered if neoplasia or infection is not present; however, the cosmetic effects may not be as pleasing as they are in the dog, and cats have a higher rate of postoperative prosthesis failure (17%; Hamor et al., 1993). Pharmacologic ablation of the ciliary epithelium by intravitreal injection of gentamicin was historically considered another treatment option for blind eyes (Bingaman et al., 1994). Nevertheless, this procedure is not recommended because of the potential for sarcoma formation from possible lens damage (Dubielzig et al., 1990; Duke et al., 2013).

Diseases of the Lens and Cataract Formation

Congenital Cataracts and Lens Anomalies

Multiple ocular defects rarely occur in the cat, but the few reported cases have all included some form of lenticular abnormality. Microphakia with elongated ciliary processes and subsequent anterior lens luxation has been described in three unrelated Siamese and a DSH cat (Aguirre & Bistner, 1973; Molleda et al., 1995). In one case, cataracts were present (Aguirre & Bistner, 1973). Bilateral aphakia associated with retinal detachment has been reported in a DSH; however, the retinal detachment was considered to be secondary (Peiffer, 1983b). A condition characterized by sagittal lenticular elongation and contact of the abnormal lens with ectatic axial cornea has been described in a 4-month-old Persian kitten (Peiffer, 1983b). The defect was termed keratolenticular dysgenesis and was presumed to represent anomalous formation of the lens vesicle from surface ectoderm.

Congenital cataracts occasionally occur in domestic cats (Fig. 28.77; Peiffer & Gelatt, 1974, 1975; Rubin, 1986; Schwink, 1986). Incomplete posterior nuclear cataracts, which were presumed to be congenital, have been described in several Birman kittens (Schwink, 1986). The cataracts involved primarily the area of the Y sutures, in the form of either linear or triangular opacification. In a third report, both complete and incomplete triangular cortical cataracts were described in several Himalayan kittens (Rubin, 1986). These were also located in the posterior cortex, and because one parent had posterior triangular lenticular opacities, a recessive mode of inheritance was suspected. Congenital cataracts have been described as a frequent manifestation of the Chédiak-Higashi syndrome in the cat (Collier et al., 1979). The cataracts vary in size, but typically involve the posterior nucleus, sutures, cortex, and capsule.



Figure 28.77 Congenital cataracts. Immature cataracts were present bilaterally in a 4-month-old Himalayan kitten. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

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Bilateral macrophakia has been reported in 3 cats (Benz et al., 2011b). All cats had visual deficits and the vitreous was completely replaced by the lens. Retinal degeneration was also present in all cats.

Primary and Secondary Cataract Formation

In contrast to in the dog, primary and inherited cataracts are rare in the cat. Primary cataracts have been documented in a number of feline breeds, including the Persian, Himalayan, Russian Blue, British Shorthair, Birman, and Bengal (Bourguet et al., 2018; Narfström, 1999; Nygren et al., 2018; Peiffer & Gelatt, 1975; Rubin, 1986; Schwink, 1986). Most of these primary cataracts are congenital. Bengal cats display cataracts that are presumed to be inherited (Bourguet et al., 2018). These cataracts are either nuclear with small perinuclear posterior foci or posterior polar subcapsular. Vision loss is not reported. The hereditary cataracts that affect Russian Blues are probably inherited through a simple recessive mode, although that is yet to be confirmed (Nygren et al., 2018). Cataracts in this breed range from mild (small triangular Y-shaped or circular opacities at the border of the posterior nucleus and the anterior part of the posterior cortex) to severe (the majority or the entirety of the nucleus and cortex). Visual impairment is noted in the more advanced instances.

Most cataracts in the cat are secondary and are classified according to association with trauma, anterior uveitis, glaucoma, or lens luxation. An epidemiologic study of cats with cataracts in France reported that of the referral population, 13% (268 of 2054) were affected with cataract due to uveitis (35.8%), congenital abnormalities (15.7%), age-related degeneration (senility; 10.8%), presumed heredity (8.2%), trauma (7.8%), lens luxation (3.3%), glaucoma (1.5%), and diabetes mellitus (0.4%), with the remainder having an unknown etiology (16.4%) (Guyonnet et al., 2019). Uveitis-related cataracts raise the risk and concern for lens subluxation/luxation and glaucoma.

Traumatic cataracts are relatively common in the cat and are often sequelae to perforating ocular injury, particularly from cat claws or thorns (Fig. 28.78). Traumatic cataracts tend to be focal, occurring primarily in the region of the insult, and often are associated with focal posterior synechiae. Traumatic cataracts generally are slowly progressive or nonprogressive. When the lens capsule rupture is sufficiently large, lens protein may escape, thereby causing severe uveitis. Bacteria may be inoculated into the lens with a penetrating wound, leading to septic lens implantation syndrome (Dalesandro et al., 2011; Dubielzig & Pirie, 2005; Marlar & Dubielzig, 1995). Septic implantation syndrome exhibits a unique pattern of slowly progressive or delayed-onset endophthalmitis with lens capsule rupture, lenticular abscess, and intralenticular microorganisms (Bell et al., 2013). Lens abscesses may develop weeks or months after traumatic inoculation of the microorganism into the lens,



Figure 28.78 Traumatic cataract in an adult Domestic Shorthair following a penetrating injury, with a corneal scar at 10 o'clock, anterior capsular pigmentation, an immature cortical cataract, and subsequent risk of post-traumatic sarcoma.

and the course of the condition is distinctly different from the pattern seen with lens-induced uveitis. Finrinous exudate is usually observed on the lens capsule associated with a focal cataract. Lens material may be seen in the anterior chamber or adhered to the capsule, and secondary glaucoma commonly accompanies the intractable uveitis.

The most common cause of secondary feline cataracts is chronic anterior uveitis. Cataracts due to uveitis are typically slow to progress, begin in the cortex, and may be associated with posterior synechiae, rubeosis iridis, and pre-iridal and pupillary inflammatory membranes. Lens luxation is a common sequela (Fig. 28.79).

Several types of metabolic/toxic cataracts have been reported in the cat. Kittens fed a commercially available kitten milk replacer developed cataracts consisting of diffuse anterior and posterior lens opacification and vacuolation of the posterior Y sutures (Remillard et al., 1993). These lens opacities resolved in older kittens, becoming residual perinuclear halos and a few incipient cortical opacities. Investigators concluded that their diet contained inadequate levels of arginine.

Infectious causes of cataract in the cat appear to be uncommon. A study from Austria demonstrated the presence of *Encephalitozoon cuniculi* within the cataractous lenses of 19 eyes from 11 cats (Benz et al., 2011a). The organism was confirmed by PCR and sequencing in 18 of 19 lenses and 10 of 19 aqueous humor samples. All cats had positive serum antibody titers. All cats underwent phacoemulsification and

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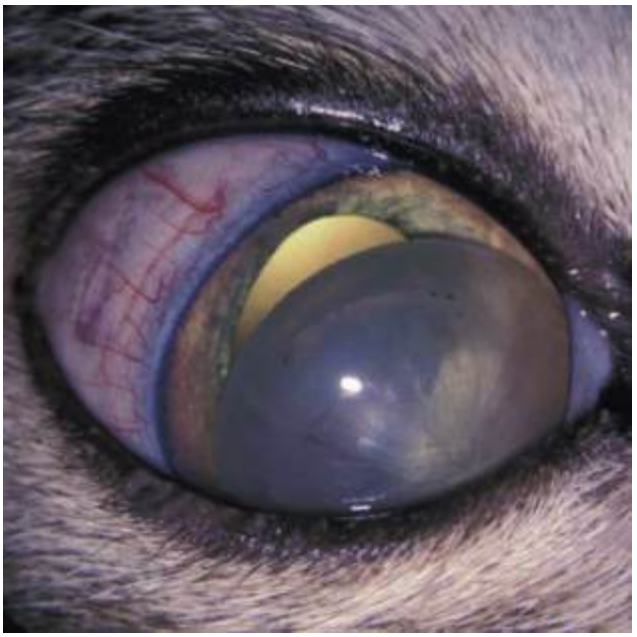


Figure 28.79 Subtle rubeosis iridis and lens capsule pigmentation accompany secondary cataract formation and anterior lens luxation in a 7-year-old Domestic Shorthair with unilateral idiopathic uveitis.

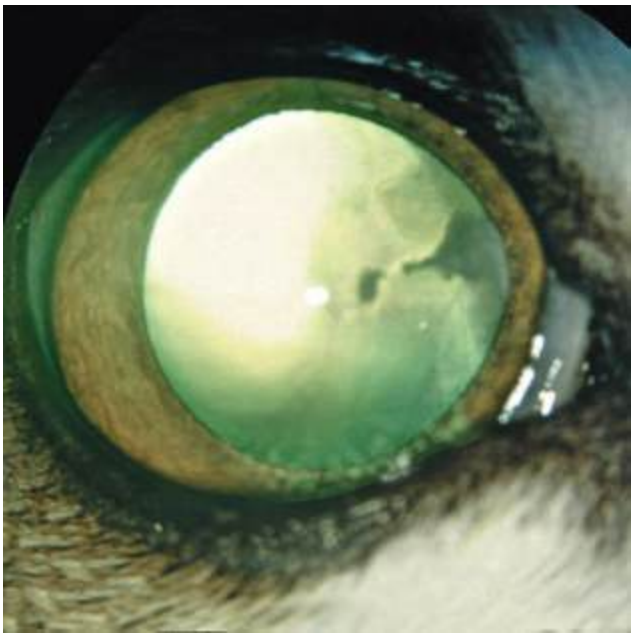


Figure 28.80 A 4-year-old European Shorthair demonstrates a dense lens opacity in the nasal cortex caused by *Encephalitozoon cuniculi*, confirmed histologically and serologically following lens extraction of the progressive cataract the following year. (Courtesy of Dr. Barbara Nell. Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

subsequently had clinical improvement in the anterior uveitis that was present preoperatively.

Theoretically, the feline lens should respond to elevated blood glucose levels by cataract formation, but diabetic cataracts are uncommon (Salgado et al., 2000). When they do occur, feline diabetic cataracts have been described as progressing more slowly than canine diabetic cataracts (Peiffer & Gelatt, 1975). Because the onset of diabetes mellitus usually occurs in cats older than 7 years, low activity of aldose reductase in the lenses of older cats may explain why diabetic cataracts are a rare occurrence in this species (Richter et al., 2002). Diabetes mellitus and bilateral cataracts have been reported in an 18-week-old DLH kitten (Thoresen et al., 2002).

A kitten with cataracts and nutritional secondary hyperparathyroidism and hypocalcemia has been documented (Stiles, 1991). The immature cataracts appeared as axial posterior subcapsular opacities. Bassett (1998) described a kitten with cataracts and hypocalcemia and hyperphosphatemia due to primary hypoparathyroidism. The cataracts were bilateral, incipient to immature, anterior and posterior subcapsular opacities typical of the lenticular changes noted in cats with hypocalcemia (Peterson et al., 1991). Normal cats, in a long-term investigation using topical 0.1% dexamethasone to elevate IOP, developed cataracts (Zhan et al., 1992). The lens changes in these cats consisted of subcapsular opacities.

In a study that examined the lenses of 2000 normal cats, 50 cats with diabetes mellitus and 100 cats following a dehydrational crisis, all cats over 17 years of age had some lens opacity, although the opacities were typically small and not of clinical significance (Williams & Heath, 2006). The ages at which the prevalence of cataract was 50% was 12.7 years for normal cats and 5.6 years for diabetic cats. Cats with a history of severe dehydration had no greater prevalence of cataract than normal cats.

Lens Luxation

Feline lens luxations are most commonly associated with chronic uveitis and glaucoma (see Fig. 28.79). In a retrospective study (Olivero et al., 1991), the most common age at presentation was 7–9 years. Siamese cats were overrepresented, as were male cats. An apparently primary zonular degeneration occurred in aged felines, but was infrequent (2.4% of cases). In a report of 10 related DSH cats spanning three generations, 9 cats had primary lens instability (Payen et al., 2011). A zonular defect caused by a possible dominantly inherited genetic disorder was suggested.

As in other species, complications of lens luxation in the cat are direct corneal endothelial cell damage, secondary glaucoma, persistent uveal inflammation, and vision loss (Fig. 28.80). Because the feline anterior chamber depth is greater than that of dogs, glaucoma due to anterior lens luxation is less common in the cat than in the dog (Sapienza,

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2005). Specific treatment is by intracapsular lens extraction, and the prognosis depends on the duration and the underlying cause. In one study 89.5% of the cats undergoing lensectomy benefited from the procedure (Olivero et al., 1991). Primary lens luxations generally have an excellent prognosis after surgery. The prognosis in other types is less favorable, but lens luxation secondary to idiopathic uveitis can be successfully treated surgically if attentive therapy for the underlying uveitis is concurrently provided.

Cataract Surgery and Lensectomy

Feline cataract surgery is performed in a fashion identical to canine cataract surgery, but reports of clinical operative series are limited. A series of dogs and cats that received phacoemulsification following corneal and lens laceration suggests that cats have an excellent prognosis following surgical repair (Braus et al., 2017). All cats (n=6) in that series were visual for the duration of follow-up. Phacoemulsification is an effective procedure in the cat (see Chapter 22). The success rate for cataract surgery in the cat appears better than it is in the dog. Clinical impressions suggest this is, in part, because the feline uvea responds less intensively to surgical trauma, and because postoperative inflammation can be controlled more easily. Cats with preexisting chronic uveitis and secondary cataract have a less favorable prognosis following phacoemulsification, in the author's (CEP) experience. Opacification of the posterior lens capsule has been investigated in normal cats after extracapsular lensectomy (Cobo et al., 1984). The postoperative changes appear to result from transformation of the residual lens epithelial cells into fibroblasts containing contractile elements, proliferation of a pigment-contacting membrane from the iris and ciliary body, and migration of pigment cells from the iris or ciliary body (or both). Using keratometry and A-mode ultrasonography in normal cats, the dioptric power of a prototype posterior chamber intraocular lens was determined to be 53–55 D, which is substantially higher than that required in dogs (Gilger et al., 1998b). However, experimental implantation of posterior chamber prototype intraocular lenses revealed that a 52–53 D intraocular lens is required to achieve emmetropia (Gilger et al., 1998a).

Diseases of the Posterior Segment

The posterior segment includes the vitreous, ocular fundus, and optic nerve. As in other species, the ocular fundus in the cat is divided into the tapetal fundus, the nontapetal fundus, the optic nerve head or optic disc, and the retinal vasculature. The feline vascular pattern is holangiotic, with three major pairs of cilioretinal arterioles and larger venules that emerge near the optic nerve head periphery. The tapetal fundus appears to be more consistent in the cat than in the dog, appearing as a highly reflective, usually yellow-green, triangular area in the dorsal fundus (Fig. 28.81A). Partial to complete lack of the tapetum occasionally occurs in blue-eyed cats. The area centralis, which is an area of high cone concentration, is located approximately 3 mm lateral to the optic nerve head. Conus or peripapillary hyperreflective areas as well as pigmented areas immediately adjacent to the optic disc are not uncommon. The nontapetal fundus is usually heavily pigmented, appearing as a dark brown area surrounding the tapetal fundus. In color-dilute cats, the nontapetal fundus is nonpigmented focally or diffusely, thereby permitting visualization of the deeper choroidal vasculature (Fig. 28.81B). The optic disc is typically situated in the tapetal fundus; it is small, circular, nonmyelinated, and somewhat

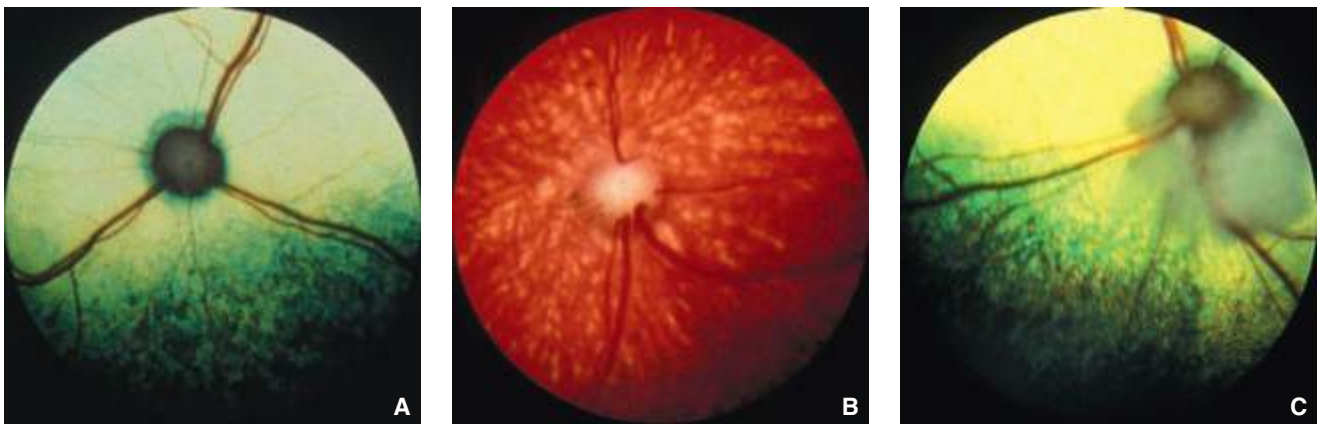


Figure 28.81 **A**. The normal feline fundus is characterized by a brightly reflective yellow-green tapetum dorsally, a pigmented nontapetal region ventrally, and three major paired vessels. The nonmyelinated disc often appears gray in color. **B**. In color-dilute cats, deeper choroidal vessels are often visible due to lack of melanin in the ventral retinal pigmented epithelium. This cat's lack of tapetum also exposes the dorsal choroidal vasculature. **C**. On rare occasion, a myelin variation in the nerve fiber layer alters the appearance of the normal, distinctly circular, nonmyelinated optic disc.

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gray. Occasionally, myelination of the nerve fiber layer may occur about the optic disc and is considered a variation of normal (Fig. 28.81C). Retinal vessels do not cross the optic disc as they do in the dog.

Vitreous

Congenital and Developmental Disorders

Persistent hyaloid arteries appear to be rare in the cat. Ketring and Glaze (1994) have documented a 2-year-old DSH with a persistent hyaloid artery and anterior lens luxation. Barnett and Crispin (1998) have documented a 7-month-old Ragdoll kitten with a unilateral persistent hyaloid artery. Persistent hyperplastic tunica vasculosa lentis and persistent primary vitreous has been reported in 2 cats (Allgoewer & Pfefferkorn, 2001).

Acquired Disorders

Vitreal infiltrates of inflammatory and red blood cells may occur. Inflammatory cell infiltrates typically occur in cases of chronic anterior uveitis or posterior uveitis, particularly pars planitis. Accumulation of inflammatory cells on the posterior lens capsule and within the anterior vitreous, often termed snowbanking or snowballing, is frequently noted with pars planitis.

Vitreal hemorrhage is the condition most likely to be encountered clinically. Hemorrhage may be caused by inflammation, trauma, neoplasia, clotting disorders, systemic hypertension, and severe anemia.

Asteroid hyalosis occurs less frequently in cats than in dogs, but is occasionally seen in middle-aged to older cats. It may be unilateral or bilateral. Ophthalmomyiasis interna, with larvae in the posterior segment, has been reported (Brooks et al., 1984; Gwin et al., 1984; Johnson et al., 1988; Kaswan & Martin, 1984; Wyman et al., 2005). Prognosis for sight and retention of the globe is guarded and dependent upon the degree of damage the organism causes during its migration through and occupancy of the eye. *Cutarebra* spp. are the most commonly reported larvae in the globes of cats.

Retina and Choroid

Congenital, Developmental, and Acquired Disorders

Focal retinal, choroidal, and optic disc colobomas are rare in the cat. These defects usually occur in association with the colobomatous syndrome in cats with eyelid agenesis. In some eyes focal retinal dysplasia is also present, and vision may or may not be impaired. In one report, 4 kittens from a litter of 5 were examined and found to have lesions that included eyelid agenesis, microphthalmia, choroidal colobomas, focal retinal dysplasia, and optic disc coloboma (Fig. 28.82; Bellhorn et al., 1971; Martin et al., 1997).

Retinal Dysplasia

Retinal dysplasia is loosely defined as anomalous retinal development with resultant aberrant organization of retinal elements to form rosettes, folds, and gliosis (Fig. 28.83). The causes of retinal dysplasia are numerous, but in the cat the

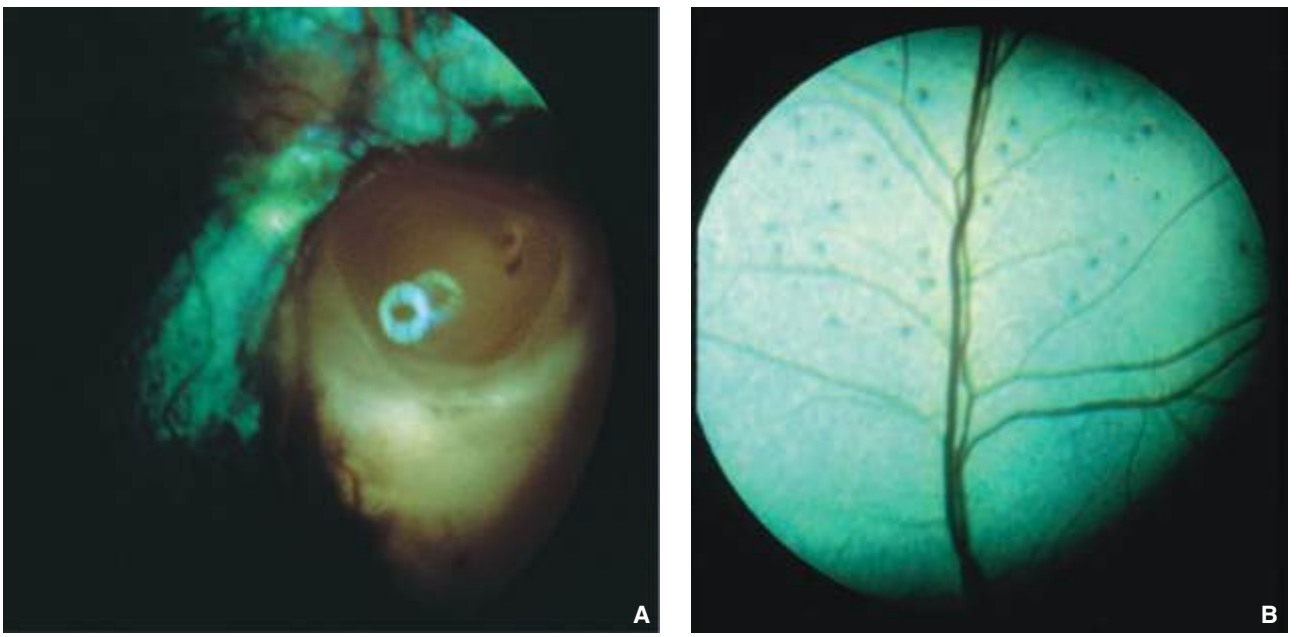


Figure 28.82 Colobomatous syndrome. **A**. A kitten with a large coloboma involving the optic nerve and adjacent choroid. **B**. Retinal dysplasia associated with colobomatous syndrome in a kitten. (Reproduced with permission from Stiles, J. (2013) Feline ophthalmology. In: *Veterinary Ophthalmology* (eds. Gelatt, K.N., Gilger, B.C., & Kern, T.J.), 5th ed., pp. 1477–1559. Ames, IA: Wiley-Blackwell.)

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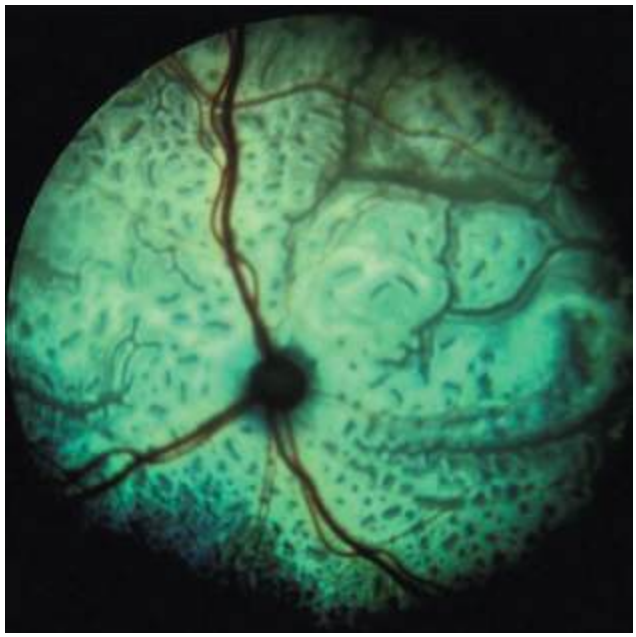


Figure 28.83 Congenital retinal folds appear as dark spots and branching lines that obscure the underlying tapetum in a 4-month-old Domestic Shorthair with retinal dysplasia and congenital cataracts. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

condition has most often been associated with intrauterine or early neonatal viral infections. Retinal dysplasia has also been reported in feline colobomatous syndrome (see previous section). When injected intraocularly or intraperitoneally to fetal or neonatal kittens, FeLV produces retinal dysplasia characterized by disorganization and necrosis of retinal tissue, with reorganization into cell clumps and dysplastic rosette structures (Albert et al., 1977). Full-thickness retinal folds that include the retinal pigment epithelium (RPE) may also be seen. Retinal dysplasia is accompanied by RPE proliferation and migration into the mature retina. The severity of FeLV-induced retinal dysplasia parallels that of the intraocular inflammation with which it is invariably associated. A less consistent effect of experimental intraocular infection is the development of retinal neoplasia characterized by large pleomorphic cells that are often multinucleate. The apparent malignant transformation of retina into structures containing cells arranged around a central lumen and limited by what appears to be the external limiting membrane has been likened to the Flexner-Wintersteiner rosettes that characterize human retinoblastoma.

Impaired development of retinal, cerebral, and cerebellar tissues has been associated with perinatal feline panleukopenia infection (MacMillan 1974, 1980; Percy et al., 1975). The dysplastic retina is characterized by thinning of the sensory retina, with disruption of normal architecture and rosette formation. As with dysplasia induced by FeLV infection, RPE migration is a concomitant finding.

Genetic retinal dysplasia, common in the dog, has not been well documented in cats. A suspected multifocal retinal dysplasia in related Somali cats has been reported (Narfström, 1999). Retinal dysplasia was associated with a congenital staphyloma, iris coloboma, and cortical cataract in a DSH cat (Skorobohach & Hendrix, 2003).

Bilateral optic nerve aplasia has been described in a Domestic Longhair kitten (Barnett & Grimes, 1974). The absence of optic nerves and tracts was confirmed histopathologically, and associated ocular defects included absence of the ganglion cell layer and presence of rosettes in the peripheral retina. That the dam and littermates were normal argues against a genetic basis for this condition. Optic nerve hyperplasia has also been recognized in conjunction with retinal lesions in a cat after fetal infection with panleukopenia virus (Greene et al., 1982).

Taurine Deficiency Retinopathy

Taurine is a sulfur-containing amino acid essential to cats because they have limited ability to synthesize it from cysteine, which is a precursor amino acid for most animal species. Taurine is stored in the liver, but the highest tissue concentrations are found in the heart muscle and retina, where especially high concentrations are found in the photoreceptor cells (Sturman et al., 1978). A dietary taurine level of 500–750 ppm has been suggested as being necessary to prevent feline retinal disease. The function of taurine is not fully understood, but it has been speculated to act as a neurotransmitter and to have a protective influence on cell membranes.

The retinopathies known as nutritional retinal degeneration and feline central retinal degeneration (FCRD) appear to be identical and associated with inadequate levels of dietary taurine. The first report of feline retinal disease that, in retrospect, probably related to the amino acid taurine was described by Bruckner (1949). In 1964, Scott and colleagues described a nutrition-linked retinal degeneration in cats fed a semipurified diet containing casein; because the abnormalities included conjunctivitis, keratitis, and squamous metaplasia of the oral cavity, vitamin A deficiency was suspected as the cause. A subsequent study by Morris (1965), who described the ophthalmoscopic changes, demonstrated the photoreceptor degeneration. At approximately the same time, a unique feline retinopathy characterized by bilateral degeneration of the central sensory retina, FCRD, was described (Bellhorn & Fischer, 1970). This condition occurred infrequently among cats fed seemingly appropriate diets, but in unrelated animals. In studies of the photoreceptor function in cats with nutritional retinal degeneration, Rabin and colleagues (1973) documented that focal degeneration in the area centralis preceded the advanced retinal degeneration, and they concluded that FCRD was, in fact,

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the initial stage of the nutritional degeneration. Aguirre (1978) documented that the various stages of central retinal degeneration were associated with feeding dog food to cats. The deficient dietary element was identified as taurine, an amino acid that was eventually shown to be essential to cats and to be critical for retinal and cardiac function (Anderson et al., 1979; Barnett & Burger, 1980; Bedford, 1983; Bellhorn et al., 1974; Berson et al., 1976, 1981; Blake & Bellhorn, 1978; Hayes, 1982; Hayes et al., 1975a, 1975b; Knopf et al., 1978; O'Donnell et al., 1981; Orr et al., 1976; Pasantes-Morales et al., 1986; Pickett et al., 1990; Pion et al., 1987; Ricketts, 1983; Schmidt et al., 1976a, 1976b, 1977; Wen et al., 1979). As a result of these studies, the dietary levels of taurine were increased in commercial cat foods, and feline nutritional retinopathy has become rare. Still, occasional individual domestic and exotic (or zoo) cats may be presented with nutritional retinopathy when fed vegetarian, noncommercial, or home-made diets (Pickett et al., 1990).

The ophthalmoscopic appearance of taurine deficiency retinopathy is considered to be pathognomonic, and five progressive stages have been described. The earliest lesion, or stage 1, is increased granularity of the area centralis. Stage 2 is defined as an ellipsoidal, hyperreflective lesion (Fig. 28.84A). In stage 3, a second hyperreflective lesion becomes visible nasal to the optic papilla. The two lesions eventually coalesce to form a large, band-shaped area of hyperreflectivity dorsal to the optic papilla, or stage 4 (Fig. 28.84B). Stage 5 is generalized retinal degeneration, with attenuation or loss of retinal vessels. The ophthalmoscopically visible retinal lesions have been shown to have decreased rhodopsin levels (Jacobson et al., 1987).

The characteristic histopathologic feature of taurine deficiency retinopathy is degeneration of the central sensory retina, particularly the outer layers (photoreceptors, outer nuclear layer; Leon et al., 1995). Ultrastructurally, the photoreceptors are absent in the affected area, and hypertrophied RPE cells, presumably the result of excessive phagocytized material, are found near the external limiting membrane. Disorganization of cone disc material occurs in photoreceptors outside the area of the lesion. Electrophysiologic studies have revealed decreased amplitudes and increased implicit times of cone responses, but normal rod function. Angiographic abnormalities are absent. Through behavioral studies, visual acuity has been shown to be decreased, but most deficits are only detectable clinically during the advanced stages.

Dietary deficiency of taurine results in selective depletion of plasma and retinal amino acid levels within 5 weeks. Electrophysiologic studies have revealed an increase in cone implicit times, thus indicating that cone photoreceptors are initially affected. After 10 weeks of dietary deficiency, the amplitudes of both rod and cone electroretinograms are decreased (Schmidt et al., 1976a). Functional abnormalities are estimated to occur at least 10 weeks before photoreceptor cell death. Ophthalmoscopic signs of retinal disease become apparent between 3 and 7 months, with complete retinal degeneration becoming apparent by 9 months (Rabin et al., 1973). The histopathologic appearance is one of progressive photoreceptor degeneration, which is first recognized by

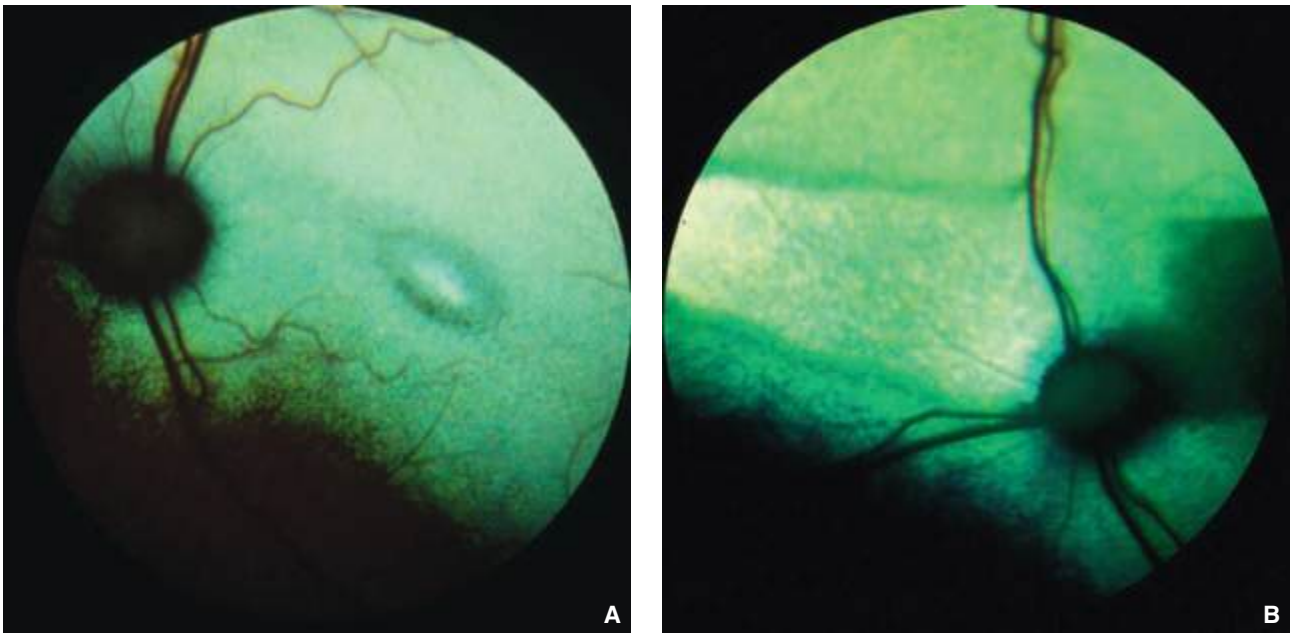


Figure 28.84 Taurine deficiency retinopathy. **A**. Early in the deficiency, bilaterally symmetric elliptical hyperreflective lesions develop in the area centralis temporal to the optic disc. **B**. As the degeneration progresses, lesions coalesce to create a horizontal hyperreflective band that extends nasally and temporally above the optic disc.

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vesiculation and disorientation of cone outer segment discs (Hayes et al., 1975b). Ultrastructural studies have also demonstrated that tapetal rods lose their normal lattice structure in the absence of taurine (Hayes et al., 1975a). The retinal effects of taurine deficiency are only partially reversible. The electroretinographic changes, and particularly those of the rods, are readily reversed after dietary correction, but the ophthalmoscopic lesions are permanent (Berson et al., 1981). Because taurine deficiency has been linked to feline cardiomyopathy, cardiac function should be evaluated in all cats affected with these ophthalmoscopic abnormalities (Pion et al., 1987).

Although taurine deficiency retinopathy occurs much less frequently today than it did before the dietary requirements for taurine in cats were understood, affected cats may still be seen. Cats that eat diets deficient in taurine are at risk and some cats eating an adequate diet may not absorb the amino acid normally. Any cat with suspected taurine deficiency should have plasma taurine levels evaluated. Normal values for cats fed dry food are 80–120 nMol/mL (University of California, Davis Amino Acid Laboratory). Values less than 40 nMol/mL are considered inadequate and consistent with a deficiency.

Inherited Rod-Cone Dysplasia, Dystrophy, and Degenerations

With the exception of those disorders with a nutritional basis, retinal degenerations are relatively rare in the cat, as evidenced by the infrequent reports in the literature (Barnett, 1965; Bedford, 1989; Carlile, 1981; Kelly & Lewis, 1985; Rubin, 1963; Rubin & Lipton, 1973; Souri, 1972; West-Hyde & Buyukmihci, 1982). The first report describing an apparently primary retinal degeneration in three cats appeared in 1963 (Rubin). The lack of historical evidence for nutritional deficiency, the ophthalmoscopic appearance of diffuse vascular attenuation, and histopathologically selective photoreceptor degeneration suggested a genetic basis. Photoreceptor degeneration, which is characterized ophthalmoscopically by tapetal hyperreflectivity and vascular attenuation, was described in several related Persian cats, with a suspected autosomal recessive mode of inheritance (Rubin & Lipton, 1973). A breeding colony of Persian cats was established, and an early-onset, autosomal recessive, progressive retinal atrophy was confirmed (Rah et al., 2005). The earliest clinical sign was reduced pupillary light reflex, which could be noted at age 2–3 weeks. By 16 weeks, retinal degeneration was complete. Histologically the lesions were primarily located in the photoreceptors, the outer nuclear layer, and the RPE. The specific genetic defect has yet to be identified. The retinal degeneration was found not to be associated with coat color or polycystic kidney disease, an inherited disease of Persian cats (Rah et al., 2006).

Electrophysiologic and histopathologic findings reported in a family of domestic cats with signs of retinal degeneration suggested a genetic basis, with a dominant mode of inheritance suspected (West-Hyde & Buyukmihci, 1982). The early onset described in this report, however, is most compatible with rod-cone dysplasia. Findings in one clinical report of feline retinal degeneration with a possible genetic origin suggest that the Siamese breed, at least in Great Britain, is at risk (Barnett, 1965). A more recent report of 26 cats in the United States with diffuse retinal degeneration also found the Siamese cat to be overrepresented (Giuliano & van der Woerdt, 1999). It was also found in this study that a variety of medications had been administered to the cats in the 12 months preceding examination, with enrofloxacin being the most common (see "Drug-Associated Retinal Toxicity"). Other than enrofloxacin toxicity (which was not recognized at the time of that publication), a cause for retinal degeneration could not be determined in this group of cats.

Rod-Cone Dysplasia in the Abyssinian

An autosomal dominant retinal dysplasia has been described in the Abyssinian breed (Curtis et al., 1987). Affected kittens as young as 4 weeks may show mydriasis and nystagmus, which is variable, intermittent, and often rapid. The first ophthalmoscopically visible lesions consist of tapetal dullness and loss of detail, present by 8–12 weeks of age. Progression of the disease is fairly rapid and is evidenced by tapetal hyperreflectivity, loss of pigmentation in the nontapetal fundus, and retinal vascular attenuation (Fig. 28.85). The disease is very advanced by 1 year of age. Secondary

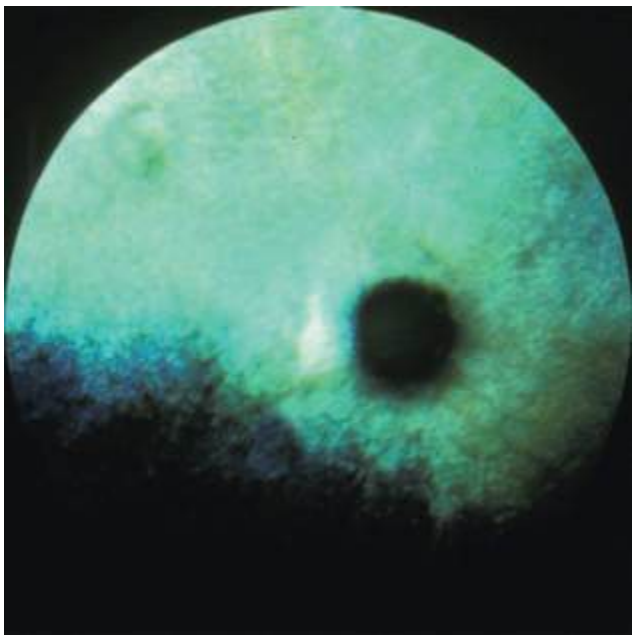


Figure 28.85 Generalized tapetal hyperreflectivity and profound retinal vessel attenuation are seen in a 7-month-old Abyssinian, characteristic of heritable rod-cone dysplasia. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

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cataracts have not been observed. The rods and cones are both affected, and disorganized outer segments as well as diminutive inner segments can be detected as early as 14 days of age (Leon & Curtis, 1990). The photoreceptor inner segments remain rudimentary, and the outer segments fail to elongate. Outer segment material is spare and consists mostly of whorls of disorganized and disoriented disc lamellae. Degeneration begins in the central retina and advances toward the periphery, with progressive loss of the photoreceptor cell layers. At 30 weeks of age, only two to five rows of nuclei in the outer nuclear layer remain in affected cats. This condition is appropriately described as a cone-rod dysplasia, since the cones have been documented to degenerate prior to the rods (Narfström et al., 2011). Affected cats have abnormal and retarded photoreceptor development, caused by a single base deletion and subsequent frameshift in the CRX gene, which is critical for photoreceptor development and maintenance. Affected kittens have no recordable cone electroretinograms (ERGs) and rod responses that are delayed in development, markedly reduced, and completely lost by 20 weeks of age (Occelli et al., 2016).

Rod-Cone Degeneration in the Abyssinian

A recessively inherited rod-cone degeneration in Abyssinian and Somali cats is termed *rdAc* (retinal degeneration in Abyssinian cats; Anderson et al., 1991; Carlile et al., 1984; Ehinger et al., 1991; Gorin et al., 1995; Jacobson et al., 1989; Minella et al., 2018; Narfström, 1985; Narfström & Nilsson 1986, 1989; Narfström et al., 1985, 2009; Wiggert et al., 1994). A single base pair change in the intron 50 of the centrosomal protein 290 (*CPE 290*) gene results in alternative splicing of the transcript, with subsequent introduction of a stop codon and truncation of the mature protein (Menotti-Raymond et al., 2007). The disease typically begins at 1.5–2 years of age, then progresses to complete retinal degeneration over the next 2–4 years. However, in a recent study the progression of disease was found to be quite variable (Narfström et al., 2009). Four distinct ophthalmoscopic categories have been described (Narfström, 1985). In the stage of suspected disease (S1), a subtle, gray discoloration of the peripapillary area on one or both sides of the optic disc is seen. The early stage (S2; Fig. 28.86A) is characterized by a more diffuse, gray tapetal discoloration, usually associated with mild vascular attenuation. In the moderately advanced stage (S3), hyperreflective areas become visible in a diffusely discolored tapetal fundus, and vascular attenuation is prominent. In the advanced stage (S4; Fig. 28.86B), generalized tapetal hyperreflectivity is accompanied by severely attenuated or absent retinal vessels. The appearance varies somewhat with the age of the animal, however, and younger cats demonstrate more prominent areas of hyperreflectivity in the midperipheral and peripheral fundus. Focal pale areas as well as heavily pigmented lesions occur in the nontapetal fundus of severely affected animals. Significant fluorescein angiographic changes are limited to vascular constriction. ERG amplitudes are proportionally reduced, starting in cats at 8–12 weeks of age, and are commensurate with the stage of disease. Loss of the b-wave amplitude correlates with a loss of rhodopsin (Narfström et al., 1985). One study found that Abyssinian cats heterozygous for the disease can be identified by their abnormal, dark-adapted ERGs, even though their fundi appear normal ophthalmoscopically (Ekesten & Narfström, 2004).

Another study found that heterozygous carrier cats could be differentiated from homozygous affected cats prior to clinically evident retinal degeneration by comparing the ERG b-wave to a-wave ratio (Hyman et al., 2005).

The initial histopathologic changes are disorganization of the photoreceptors, beginning in the midperipheral portions of the fundus, with reduced numbers of photoreceptor nuclei (Fig. 28.86C; Narfström & Nilsson, 1989). In the moderately advanced stage, the photoreceptor outer segments disappear, and the inner segments become extremely shortened in the peripheral and midperipheral retina. In the advanced stage, the outer segments are absent, the inner segments are reduced in number, and thinning of other retinal layers becomes apparent. As in the other stages, the central retina is less severely affected in the advanced stage.

In affected kittens, a high number of immature-appearing rod outer segment discs are present at 35 days postnatally, but the cones appear to be normal at this stage. In cats 5 months of age, affected rod outer segments demonstrate disintegration, as evidenced by vacuolization and clumping of the disc material and by formation of debris. In a study that utilized immunolabeling for green-sensitive and blue-sensitive cones, it was determined that by the age of 12 months cones are affected (Narfström et al., 2001). The inner retina is largely preserved throughout the disease.

Affected *rdAc* cats exhibit preservation of their central retinas until later stages of the disease, similar to children with Leber congenital amaurosis. The photoreceptor layer within the area centralis and visual streak of the ellipsoid zone remains notably thicker during the course of the disease than that in the midperipheral areas (Minella et al., 2018). The integrity of the ellipsoid zone is maintained in the better-preserved retinal regions, intimating that these parameters (thickness and rate of degeneration) may serve as markers of disease progression and/or treatment success.

Rhodopsin levels are reduced in affected cats as early as 6 months of age (20% reduction; by 2.5 years of age, 60% reduction; in a 7-year-old cat, not measurable; Jacobson et al., 1989). Gamma amino butyric acid (GABA) and its synthesizing enzyme, glutamate decarboxylase (GAD), gradually decrease in both the inner and outer layers of the retina in affected cats (Ehinger et al., 1991). Loss of the photoreceptors was a prerequisite for loss of GABA immunoreactivity. Loss of GABA was not likely the result of neuron loss, but it was related to the persistence of GAD-immunoreactive

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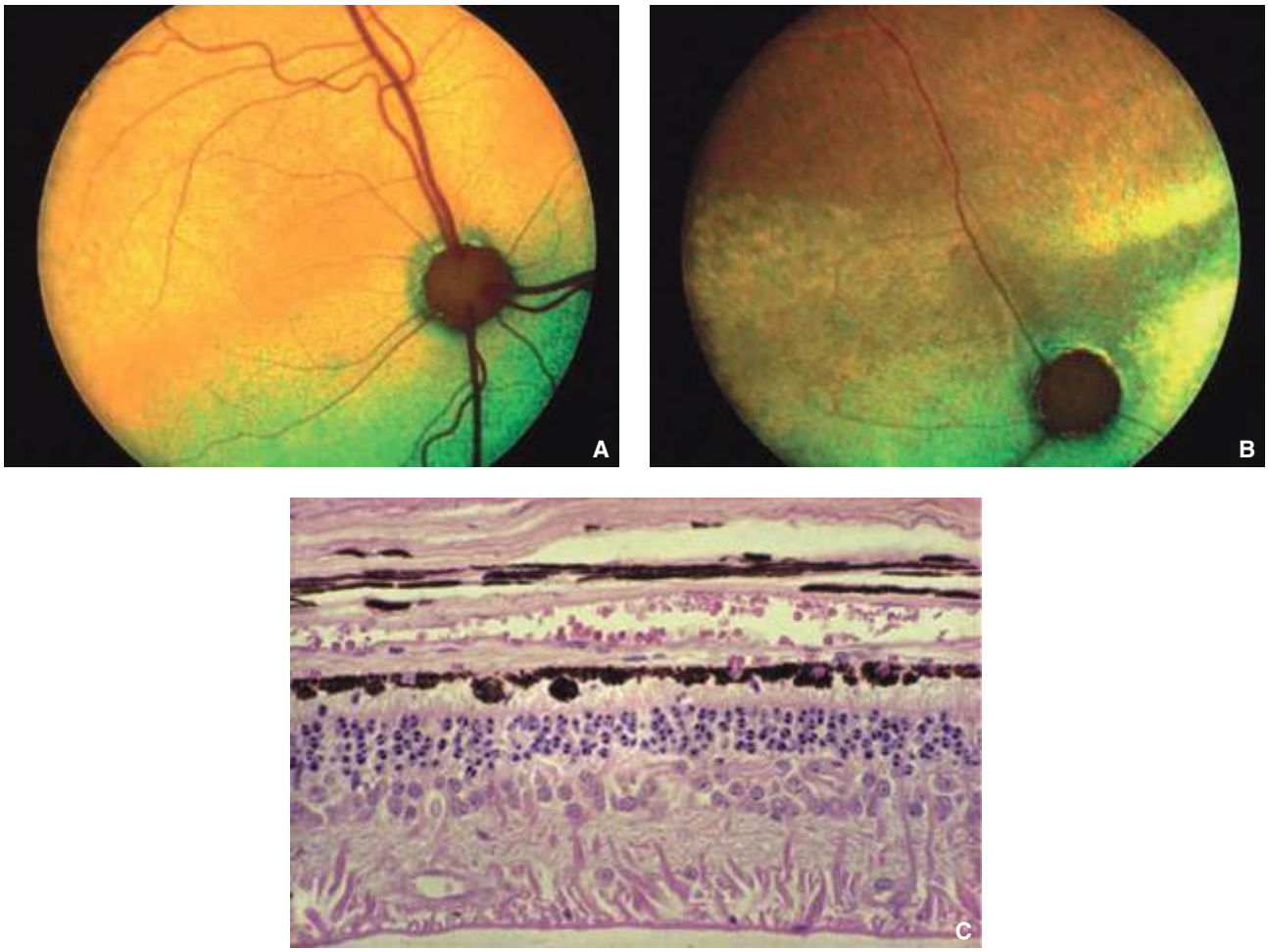


Figure 28.86 Fundus photographs of Abyssinian cats homozygous for inherited rod-cone degeneration. **A**. Early changes in a 2-year-old cat. There is a gray discoloration in the peripheral tapetal fundus, but retinal vasculature is normal. **B**. Late changes in a 6-year-old cat. There is marked hyperreflectivity and grayish discoloration to the tapetal fundus, and retinal vasculature is attenuated. **C**. Light micrograph of a 2.5-year-old cat in a moderately advanced stage of rod-cone degeneration. The inferior nontapetal fundus is shown. Note the reduced numbers of photoreceptor nuclei in the outer nuclear layer and the short and degenerating rod and cone outer and inner segments. There is hypertrophy of some retinal pigment epithelial cells and a few displaced photoreceptor cell nuclei are observed in the subretinal space. The inner retina is normal appearing (hematoxylin and eosin). (C courtesy of Dr. Kristina Narfström. Reproduced with permission from Stiles, J. (2013) Feline ophthalmology. In: *Veterinary Ophthalmology* (eds. Gelatt, K.N., Gilger, B.C., & Kern, T.J.), 5th ed., pp. 1477–1559. Ames, IA: Wiley-Blackwell.)

neurons. Measurements of the interphotoreceptor retinoid-binding (IRB) protein and message in affected cats indicate that levels of both are significantly reduced in kittens as young as 4 weeks old and at the earliest stage of retinal disorientation (Wiggert et al., 1994). Opsin messenger RNA was more abundant in affected cats at least 1 year before the onset of clinical visual impairment. The reduction in IRB protein gene expression below normal levels and before the onset of retinal degeneration suggests this may represent either a primary defect or an early disorder that itself could cause adverse effects. Subsequent sequence analysis has excluded phosducin as the gene for this recessive retinal degeneration in the Abyssinian breed (Gorin et al., 1995). Plasma lipid abnormalities have been recently reported in Abyssinian cats with hereditary rod-cone degeneration, and affected cats had lower levels of ώv3 polyunsaturated fatty acids, thereby suggesting a deficiency of the Δ-4 desaturase (Anderson et al., 1991).

Prevalence studies of the *rdAc* mutation document that the defective allele is present in moderate abundance in the Abyssinian breed in Europe and Australia (Narfström et al., 2009). The mutation is also present in a large number of cat breeds in addition to the Abyssinian and Somali in North America and Europe (Menotti-Raymond et al., 2010). The mutation was found in 14 of 41 breeds (34%) sampled, and was particularly high in Siamese and Siamese-related breeds. The mutation in the Siamese was only found in wedge-faced cats and was absent in the apple-head cats, suggesting a

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divergence of the gene pool in these two phenotypes of Siamese cats.

Progressive Retinal Atrophy in the Bengal Cat

Recently, an inherited form of early-onset retinal atrophy in the Bengal cat has been identified and characterized (Ofri et al., 2015). Pedigree analysis suggests that the condition is inherited in an autosomally recessive mode. Ophthalmoscopic signs of retinal degeneration are first noted in affected kittens by 9 weeks of age and progress noticeably over the following 4 months. Electroretinography reveals reduced rod and cone function at 7 and 9 weeks of age, respectively; rod responses are generally extinguished by 14 weeks of age and cone responses are minimal by 26 weeks of age. Changes in visual behavior are apparent by 1 year of age. Histologic degeneration, including reduced photoreceptor numbers, rapid deterioration of the photoreceptor layer, and severe outer retinal degeneration, is first observed by 8 weeks.

Other Retinal Degenerations

An isolated case of feline retinal degeneration has been described that has similarities to the rare human condition of gyrate atrophy (Valle et al., 1981). Common abnormalities include severe photoreceptor degeneration, decreased numbers of choriocapillaries and smaller choroidal vessels, increased plasma ornithine and glutathione levels, and undetectable ornithine aminotransferase activity. Cataracts, however, which are consistently found in the human condition, were absent. This appears to be an extremely rare condition in the cat.

A single case report describes a 4-year-old DSH cat with a 2.5-year history of progressive ataxia and a 1-year history of progressive vision loss (Barone et al., 2002). On necropsy, the cat was found to have adult-onset cerebellar abiotrophy and retinal degeneration. Although the two conditions could not be definitively linked, the authors speculated that an essential protein or process involved in neuronal pathways of the cerebellar Purkinje cells is also critical in retinal pathways.

Drug-Associated Retinal Toxicity

The most significant ocular drug toxicity to be identified in cats is enrofloxacin-associated retinal degeneration (Ford et al., 2007; Gelatt et al., 2001; Wiebe & Hamilton, 2002). Beginning in 1997, the enrofloxacin label dosing was changed from the previous recommendation of 2.5 mg/kg every 12 hours to a flexible dose ranging from 5 to 20 mg/kg as a split or single dose. Very soon afterward, cases of acute and severe retinal degeneration and blindness were observed in cats receiving enrofloxacin. In an experimental study in which young healthy cats were given enrofloxacin 50 mg/kg every 24 hours, vascular attenuation, and tapetal hyperreflectivity were noted on funduscopic examination beginning on day 2. By day 3 decreased b-wave amplitudes on ERG and generalized retinal degeneration on histopathology were present, worsening by day 7 (Fig. 28.87; Ford et al., 2007). Behavioral, neurologic, and musculoskeletal abnormalities also occurred.

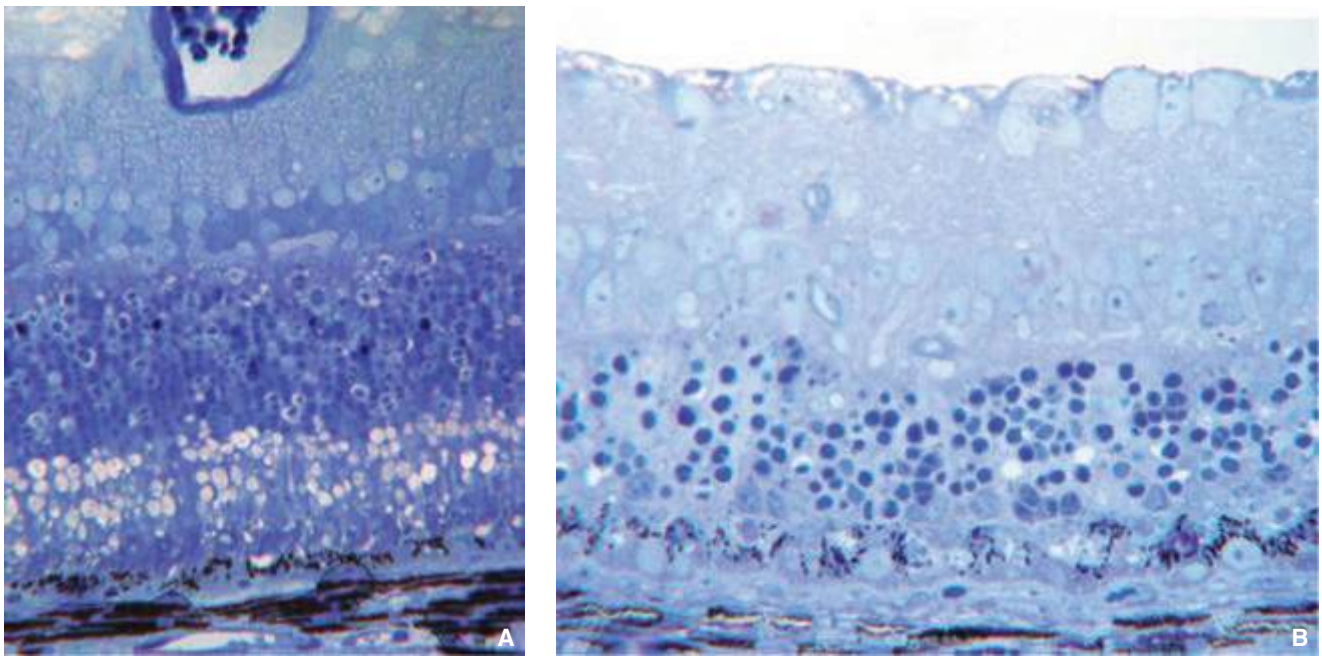


Figure 28.87 Enrofloxacin-associated retinal degeneration. **A**. Histopathologic degenerative changes are apparent in all layers of the retina by day 3 in a cat receiving 50 mg/kg enrofloxacin. **B**. Severe degeneration of the retina by day 7 in a cat receiving 50 mg/kg enrofloxacin (toluidine blue). (Courtesy of Dr. Richard Dubielzig. Reproduced with permission from Stiles, J. (2013) Feline ophthalmology. In: *Veterinary Ophthalmology* (eds. Gelatt, K.N., Gilger, B.C., & Kern, T.J.), 5th ed., pp. 1477–1559. Ames, IA: Wiley-Blackwell.)

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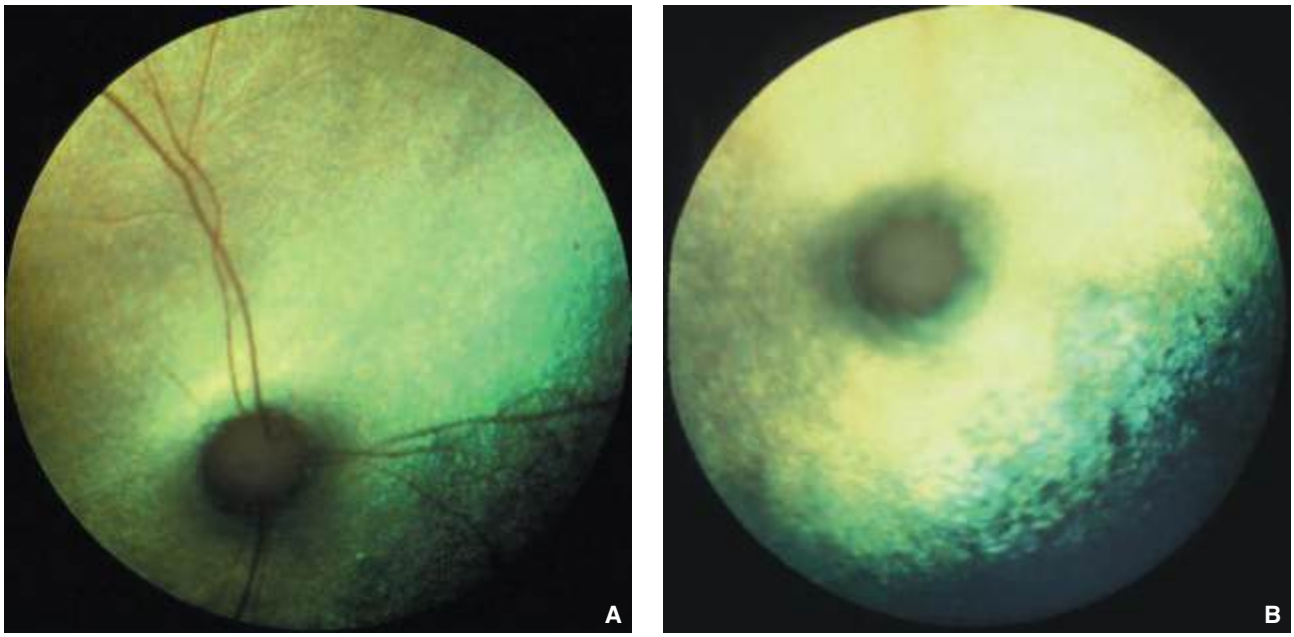


Figure 28.88 Enrofloxacin-associated retinal degeneration. **A**. Increased tapetal reflectivity (muted by a neutral density filter) and retinal vessel attenuation are seen in a blind 8-year-old Domestic Shorthair 6 days after discontinuing enrofloxacin administration. Vision changes were noted on day 4 of treatment. **B**. The same eye examined 8 months later illustrates the end-stage effect of the toxicity, with profound tapetal reflectivity and retinal vessel attenuation. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

In most cases seen to date, the blindness has been permanent, although a few cats have retained some vision. One of the remarkable findings of this toxicity is the rapidity with which the retina degenerates (Fig. 28.88). Tapetal hyperreflectivity and vessel attenuation are dramatic even in cats that have received enrofloxacin as a single dose. ERG responses are typically extinguished, even in cats that appear to retain some vision.

Although enrofloxacin has been the compound most identified with feline retinal degeneration, all of the fluoroquinolones must be considered potentially retinotoxic (Wiebe & Hamilton, 2002). The newer fluoroquinolone pradofloxacin was demonstrated to have no retinal toxicity in *young, healthy* cats at 6–10 times the recommended dose, based on ERG, OCT, and histopathology (Messias et al., 2008). Older cats and those with impaired renal or hepatic function may have reduced clearance and increased plasma levels of fluoroquinolones compared to young, healthy cats. There is limited information about the metabolism of enrofloxacin in cats, but approximately 40% of the drug is metabolized to ciprofloxacin in dogs, and this compound is further transformed to metabolites that are excreted in the urine. Decreased GFR in dogs increases the plasma levels of the primary metabolite of marbofloxacin (Lefebvre et al., 1998).

A molecular genetic basis for fluoroquinolone-induced retinal degeneration in cats has been documented (Ramirez et al., 2011). Distribution of fluoroquinolones to the retina is normally restricted by the transport protein ABCG2 at the blood–retinal barrier. In the cat, specific amino acid changes in this transport protein cause a functional defect that allows photoreactive fluoroquinolones to accumulate in the feline retina, leading to the formation of reactive oxygen species and retinal damage.

Risk factors for fluoroquinolone retinal toxicity in cats include old age, renal or hepatic impairment, dose and duration of drug administration, as well as route of administration. Intravenous administration was found to be a contributing factor to retinal toxicity in a study of 17 cats (Gelatt et al., 2001). The fluoroquinolones as a drug class, and particularly enrofloxacin, should be viewed as potentially dangerous to cats and used only when no alternative exists. Even then, the dose should be kept as low as possible, should never exceed the current manufacturer's recommended dose of 2.5 mg/kg every 12 hours, and should be administered for the minimum possible length of time.

A descriptive study of the globes from nondomestic felids (e.g., lions, tigers) that were collected following enucleation or euthanasia compared histopathologic findings in cats that were treated at some point in their lives with enrofloxacin and those that were not (Newkirk et al., 2017). None of the treated cats (n=36) exhibited vision loss and none of the globes examined displayed the hallmark of enrofloxacin-associated retinal toxicity, thinning of the outer nuclear layer. The authors of that report concluded that enrofloxacin is safe to use in nondomestic felids. This conclusion should be viewed with caution given the sporadic nature of fluoro-

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quinolone-associated retinal toxicity in the domestic cat population. The authors of this chapter have observed enrofloxacin-associated toxicity in ocelots and tigers that were given oral or injectable enrofloxacin at recommended dosages.

Concurrent administration of methylnitrosourea (a carcinogen) and ketamine hydrochloride caused severe retinal degeneration in cats (Schaller et al., 1981), while administration of methylnitrosourea alone did not damage the retina. The toxicity is characterized by photoreceptor and outer nuclear layer degeneration, which is evident by 5 days of exposure. The pathophysiologic mechanisms involved were not identified.

Griseofulvin toxicity led to bone marrow suppression and death in one cat (Rottman et al., 1991). The cat also presented with mydriasis and vision impairment. On histologic examination of the retinas, the photoreceptors were found to have generalized loss of distinction, but definitive degeneration was not documented.

Inflammation

Chorioretinitis refers to inflammatory conditions that arise in the choroid and extend into the retina. Retinochoroiditis refers to inflammations that originate in the retina and eventually involve the choroid, though the former is more common. Active chorioretinal inflammations are characterized ophthalmoscopically by edema, hemorrhages, inflammatory or neoplastic cell infiltration, mycotic and parasitic granulomas, and exudates or transudates. Chorioretinitis that has abated leaves scars, which appear ophthalmoscopically as areas of hyperreflectivity, with or without pigment deposition in the tapetal fundus, and areas of depigmentation or pigment clumping in the nontapetal fundus.

Viral chorioretinitis in the cat has been associated with FIP virus (see Fig. 28.60; Campbell & Schiessl, 1978), FIV (Hopper et al., 1989), and FeLV (Brightman et al., 1991; Corcoran et al., 1995).

Fungal chorioretinitis has been associated with cryptococcosis (see Fig. 28.63B, Fig. 28.89A; Davies & Troy, 1996; Dye & Campbell, 1988; Fischer, 1971; Gionfriddo, 2000; Gwin et al., 1977; Jacobs et al., 1997; Reed et al., 1963; Rosenthal et al., 1981; Wilkinson, 1979), histoplasmosis (Fig. 28.89B; Davies & Troy, 1996; Jasmin et al., 1969; Peiffer & Belkin, 1979; Wolf & Beldon, 1984), blastomycosis (Alden & Mohan, 1974; Breider et al., 1988; Davies & Troy, 1996, Hatkin et al., 1979; Jasmin et al., 1969; Miller et al., 1990; Nasisse et al., 1985; Neunzig, 1983; Sheldon, 1966), and coccidioidomycosis (Angell et al., 1985; Greene & Troy, 1995; Reed et al., 1963; Tofflemire & Betbeze, 2010).

The protozoal agent *Toxoplasma gondii* is a documented cause of chorioretinitis in cats (Campbell, 1974; Davidson et al., 1993a, 1993b, 1996; Dubey, 1986, 1988; Dubey & Carpenter, 1993; Heeley, 1975; Hirth & Nielsen, 1969; Lappin et al., 1989a; Petrak & Carpenter, 1965; Piper et al., 1970; Powell et al., 2010; Vainisi & Campbell, 1969). It has most often been confirmed in cats with systemic illness due to

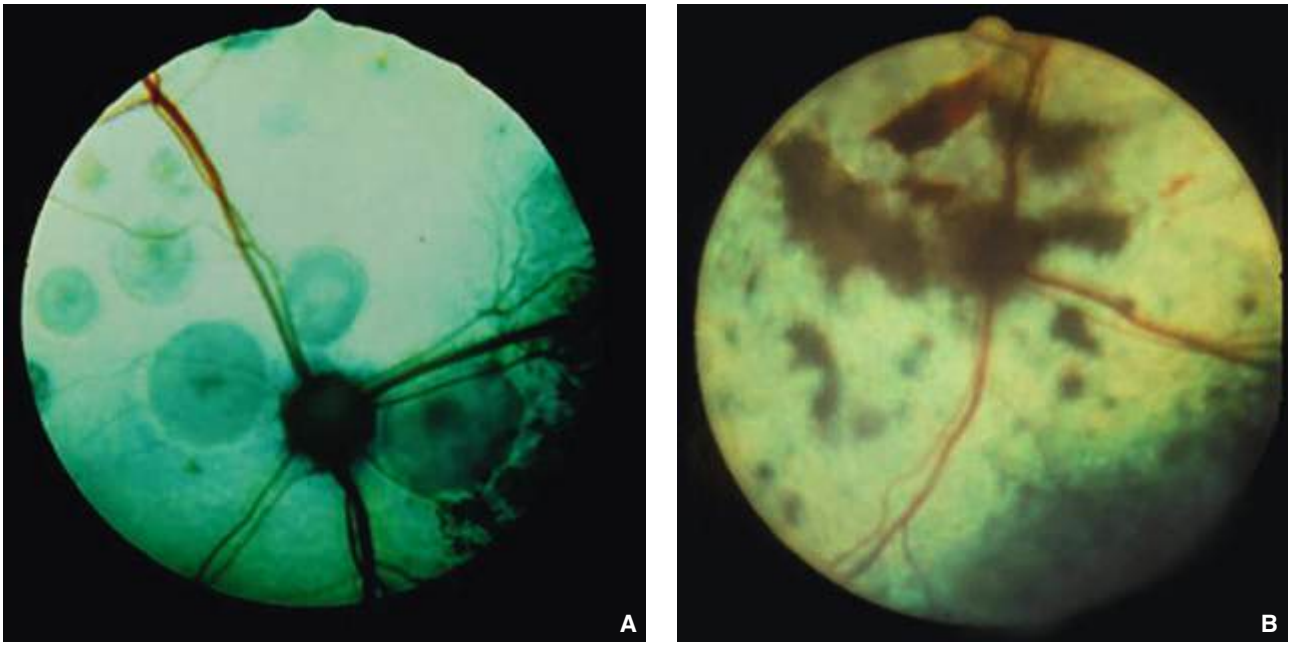


Figure 28.89 Mycotic chorioretinitis. **A**. Multifocal circles of subretinal edema surround darker focal granulomatous exudates in a 6-year-old Domestic Shorthair with cryptococcosis. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.) **B**. Multifocal darkly colored preretinal exudates and hemorrhages obscure the tapetal reflection and optic disc in a 2-year-old Domestic Shorthair with histoplasmosis.

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toxoplasmosis or in experimentally infected cats. The role of toxoplasmosis in causing ocular inflammation in otherwise healthy cats remains controversial and difficult to prove.

Feline chorioretinitis with retinal detachment has been associated with tuberculous *Mycobacterium bovis* (Formstron, 1994), as well as with the nontuberculous agent *Mycobacterium simiae* (Dietrich et al., 2003). Ocular mycobacteriosis is cats is often secondary to disseminated disease, usually following dermatologic or respiratory disease; however, it may occur in the absence of systemic disease or a classically recognized immune suppression (Stavinohova et al., 2019). It can involve any structure of the eye (uveitis, corneal granuloma, eyelid granuloma, retinal detachment, retinal granuloma, conjunctivitis, cataracts, lens luxations, and glaucoma). The main histopathologic features are granulomatous to pyogranulomatous chorioretinitis with retinal detachment with or without anterior uveitis, optic neuritis, scleritis, episcleritis, or retrobulbar cellulitis (Stavinohova et al., 2019). Prognosis is guarded, but good clinical outcomes may be achieved if lesions can be surgically removed and systemic medical therapy follows.

Parasitic infections such as dipteran larvae may cause chorioretinitis as the parasite migrates within or under the retina (Brooks et al., 1984; Kaswan & Martin, 1984).

Hypertensive Retinopathy

Systemic hypertension is a relatively common disease of aged cats and has most consistently been associated with chronic renal insufficiency and less frequently with hyperthyroidism (Elliott et al., 2001; Henik et al., 1997; Kobayashi et al., 1990; Littman, 1994; Maggio et al., 2000; Morgan, 1986; Sansom et al., 1994, 2004; Snyder, 1998; Stiles et al., 1994; Syme et al., 2002). Primary hypertension in cats may exist, but at this time remains undefined. Most hypertensive cats are at least 10 years old, often older. Acute blindness is the most common reason for presentation (Dukes, 1992; Kobayashi et al., 1990; Littman, 1994; Maggio et al., 2000; Morgan, 1986; Sansom et al., 1994; Turner et al., 1990). Other presenting signs may be those of renal disease, hyperthyroidism, or neurologic signs secondary to cerebrovascular accidents (hemorrhage, infarct, arteriolar spasm).

In cats with renal dysfunction, the presence or magnitude of hypertension is unrelated to azotemia. Persistent lack of urine-concentrating ability may be the only indication of chronic renal disease. The mechanism of systemic hypertension in cats with renal disease remains unclear. Renal disease leads to increased sodium chloride retention, which leads to increased intracellular calcium. This in turn increases arteriolar tone and sensitivity to vasopressors such as angiotensin II and catecholamines. Renal disease also causes activation of the renin-angiotensin-aldosterone system, which raises blood pressure by increasing stroke volume and total peripheral resistance. Angiotensin II is a potent vasoconstrictor, while aldosterone causes renal sodium chloride retention (Dukes, 1992). In one study of normotensive and hypertensive cats, hypertensive cats were found to have variable levels of renin-angiotensin-aldosterone activation (Jensen et al., 1997). Another experimental study had results that did support the renin-angiotensin-aldosterone system in sustaining hypertension in cats (Mathur et al., 2004).

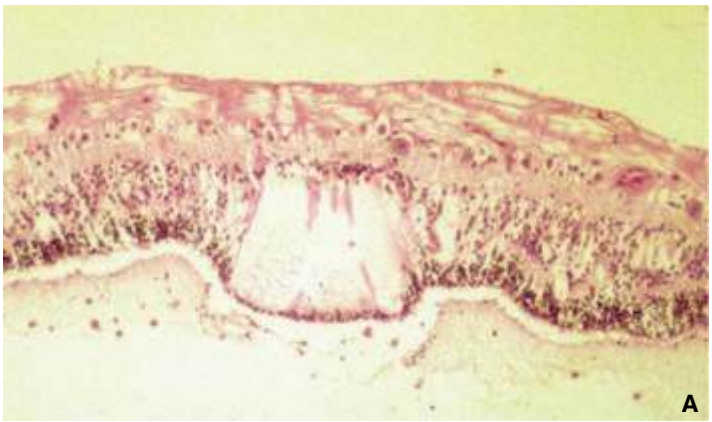
Hyperthyroidism may contribute to systemic hypertension through its effects on the heart. Hyperthyroidism increases stroke volume and cardiac output, leading to systolic hypertension. In chronic hypertension, small muscular arteries become fibrotic and sclerotic, leading to systolic and diastolic hypertension. Chronic hypertension causes left ventricular hypertrophy, which is often misdiagnosed as hypertrophic cardiomyopathy.

The eye, because of its small-caliber vessels, is a target organ for hypertensive damage (Henik et al., 1997; Stiles, 1991). Prolonged systemic hypertension leads to sustained vasoconstriction of retinal arterioles via autoregulation. Beyond certain critical pressures, autoregulation breaks down and vascular integrity is compromised. Occlusion of precapillary arterioles can lead to ischemia and retinal degeneration. Leakage of plasma and red blood cells occurs when endothelial cells and vascular smooth muscle become damaged (fibrosis and sclerosis). Leakage of plasma within the retina leads to retinal edema and foci of fluid accumulation within the neurosensory layer (Fig. 28.90). Retinal detachment is thought to be associated primarily with plasma effusion from diseased choroidal vasculature. Additionally, the RPE undergoes ischemic damage, contributing to retinal detachment (Crispin & Mould, 2001). Cotton-wool spots, or swollen axons, are a hallmark of hypertensive retinopathy in primates and may be seen early in the course of disease. This finding has not been reported in feline hypertensive retinopathy.

Clinically, the ocular manifestations of systemic hypertension can be severe and include retinal arterial tortuosity, intraretinal hemorrhage, preretinal hemorrhage, subretinal hemorrhage, retinal edema and focal bullae, retinal detachment, retinal degeneration, hyphema, anterior uveitis, and secondary glaucoma (Fig. 28.91; Elliott et al., 2001; Stiles, 1991). The iris and ciliary body vessels may be compromised, leading to bleeding within the vitreous cavity and posterior or anterior chambers. More commonly, hyphema is associated with massive posterior segment (retinal or choroidal) hemorrhage, with blood that migrates through the pupil. Hyphema that does not clear quickly can lead to synechiae and secondary glaucoma.

Frequently, the first indication of systemic hypertension is what appears to be an acutely blind animal. Even though cats may have an acute decompensation that leads to blindness, hypertensive retinopathy is usually one of gradual progression over several months and can be recognized before blindness occurs if fundic examination is performed. The

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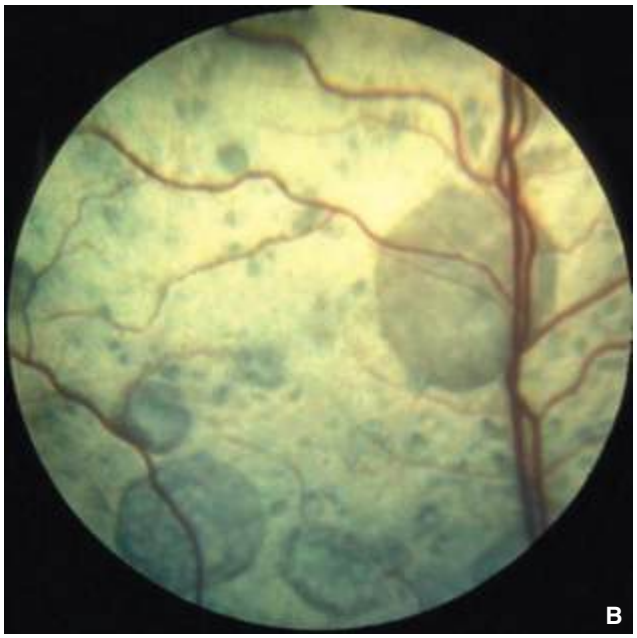




Figure 28.90 Hypertensive retinopathy. **A**. Photomicrograph of the retina from a 14-year-old Domestic Shorthair cat with hypertensive retinopathy. The retina is detached with a subretinal transudate present. Note the cystic spaces within the retina from the leakage of plasma (hematoxylin and eosin). (Reproduced with permission from Stiles, J. (2013) Feline ophthalmology. In: *Veterinary Ophthalmology* (eds. Gelatt, K.N., Gilger, B.C., & Kern, T.J.), 5th ed., pp. 1477–1559. Ames, IA: Wiley-Blackwell.) **B**. Multiple rounded foci of retinal edema alter the tapetal reflection in a 10-year-old Domestic Shorthair with a mean systolic blood pressure of 220 mmHg. **C**. Retinal edema creates vermiform folds in a 9-year-old Domestic Shorthair with a mean systolic blood pressure of 300 mmHg, together with pinpoint intraretinal hemorrhages and a focal detachment that blurs detail near the optic disc. (B and C reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

exception to this is bilateral, acute, serous retinal detachment without antecedent ocular abnormality, which is usually associated with a rapid increase in systemic blood pressure.

Recognition of animals at risk for systemic hypertension is an important factor in preventing blindness. Any cat over 10 years of age should have a fundic examination performed as well as blood pressure measurement at least once per year (Sansom et al., 2004; Young et al., 2019). Cats with renal disease or hyperthyroidism should have these tests performed at diagnosis and subsequently as the disease is managed.

Measurement of blood pressure in the cat is most easily accomplished in a clinical setting by use of indirect measurement with a Doppler ultrasonic detection device. The oscillometric devices may be less reliable in cats. Accurate readings can be difficult to obtain, because a stressed cat can have significant elevation of blood pressure (Belew et al., 1999). Repeated measurements in a calm environment may be needed to detect trends in blood pressure. Normal blood pressure for cats is usually defined as 120/80 mmHg. The Doppler is unreliable in obtaining a diastolic value, so the systolic value is typically used to assess blood pressure. One

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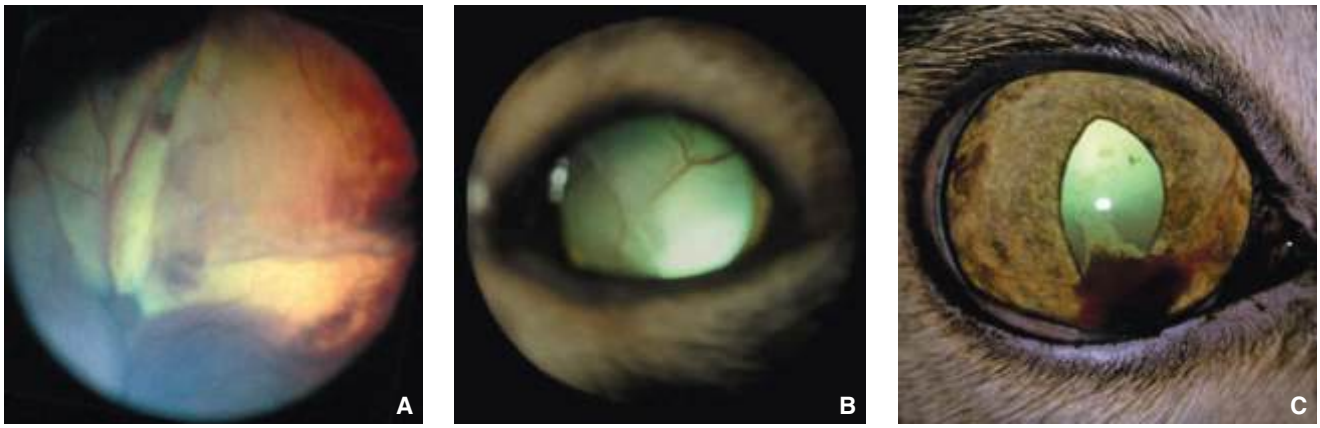


Figure 28.91 Hypertensive retinopathy. **A**. Bullous retinal detachment and subretinal hemorrhage in a 14-year-old Domestic Longhair with a systolic blood pressure of 280 mmHg. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.) **B**. Complete serous retinal detachment seen through the dilated pupil of a blind 13-year-old Domestic Shorthair with a systolic blood pressure of 270 mmHg. **C**. Hyphema accompanies systemic hypertension in an 11-year-old Domestic Shorthair.

study of 181 cats found that an age-related increase in blood pressure occurred in healthy cats, as it does in humans and dogs (Sansom et al., 2004). In this study, hypertensive retinopathy was reported to be common in cats 10 years of age or older; however, details of ophthalmic examinations were not provided. Systolic blood pressure values were found to be a better predictor of hypertensive retinopathy than diastolic or mean values.

Placement and size of the cuff are important in obtaining accurate blood pressure measurement. The cuff width should be 30%–40% of the circumference of the limb. The median artery of the forelimb has been shown to give the most accurate readings in cats (Belew et al., 1999). The cuff is placed over the median artery and the transducer is placed between the carpal and metacarpal pad. The hair should be clipped and a coupling gel applied prior to placing the transducer. Cuffs that are too large will give falsely low readings, whereas cuffs that are too small will give falsely elevated readings. If a proper cuff size falls between two available cuffs, the larger should be used. When making a judgment as to whether a cat is hypertensive, fear and excitement must be taken into account. Typically, systolic values greater than 160 mm Hg are considered hypertensive. Cats with hypertensive retinopathy often have systolic blood pressure values that approach or exceed 200 mmHg. The same size of cuff, the same limb, and preferably the same Doppler unit should be used each time when rechecking blood pressure in a patient (Haberman et al., 2004).

Treatment of hypertensive retinopathy includes controlling the underlying disease processes and treating the systemic hypertension. There is the potential in some animals for blindness to be reversible if systemic hypertension can be quickly controlled. Bullous retinal detachments can resolve if the underlying effusion is controlled. Depending on the length of time the retina has been detached, vision may be regained. There is some evidence that the feline retina begins to degenerate within the first week of detachment (Anderson et al., 1986), so immediate treatment is imperative. Retinal hemorrhages and edema can also resolve if blood pressure is controlled. As the systemic hypertension resolves with treatment, if the degree of ocular damage is limited, the examiner will note return of PLRs and resolution of hemorrhage, and possibly reattachment of the retina. Return of vision in all cases is dependent on the degree of damage the retina has undergone. Ideally, hypertension should be recognized and treated before severe ocular disease occurs. Even if vision is not restored, treating hypertension is important to prevent other serious effects such as neurologic disease. A recent study evaluating the visual outcome in cats with hypertensive chorioretinopathy reported that the presence of a menace response following treatment was positively correlated with presence of menace at presentation, time to reattachment, and gender (Young et al., 2019). Cats that were visual at presentation were, logically, more likely to be visual at last follow-up than cats that were acutely blind or blind for less than 2 weeks at presentation, and far more likely to be visual than cats that had been blind for more than 2 weeks. Following antihypertensive therapy, 69% of eyes with retinal detachment had reattached and 57.6% of eyes that had negative menace response at presentation recovered a menace response. In this study, 93.2% of eyes that were visual at the time of diagnosis maintained vision through the time of last follow-up. This supports the benefit of routine blood pressure screening in cats over 10 years of age (Sansom et al., 2004; Young et al., 2019). This may identify the presence of systemic hypertension prior to the point of retinal detachment and onset of blindness. Cats that did not have retinal detachment and were visual at the time of presentation were

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diagnosed with retinal disease due to hypertension as an incidental finding. Female cats with systemic hypertension were more likely to develop ocular signs and vision loss; however, the mechanisms and significance of this are unclear.

The calcium channel blocker amlodipine has been used very successfully in cats at a dose of 0.625–1.25 mg orally once daily, and has become the drug of choice for hypertensive cats (Cooke & Snyder, 1998; Elliott et al., 2001; Henik et al., 1997; Snyder, 1998; Young et al., 2019). Enalapril and propranolol were ineffective at controlling blood pressure in cats in one study (Jensen et al., 1997), whereas the use of benazepril was associated with a small but significant reduction in blood pressure in cats with renal compromise (Brown et al., 2001). Most cats of average weight will require 1.25 mg of amlodipine daily, while a few cats require 1.25 mg twice daily. In an experimental study of hypertensive cats treated with 0.25 mg/kg/day amlodipine, significant reductions in blood pressure were documented (Mathur et al., 2002). Cats should be reevaluated within 7 days after starting amlodipine. Adverse effects seem to be few in cats receiving amlodipine. Reported side effects include azotemia, lethargy, hypokalemia, reflex tachycardia, and weight loss. Clinicians are urged to consult the current internal medicine literature for further recommendations on the medical treatment of systemic hypertension and its underlying etiologies. Once cats are normotensive and are being maintained on an antihypertensive agent, they should be reevaluated at least every 6 months. All hypertensive cats should be evaluated for renal, endocrine, cardiac, and neoplastic disease.

Lipemia Retinalis

The term lipemia retinalis describes the ophthalmoscopic visibility of lipids and/or lipoproteins in retinal blood vessels. The condition is of diagnostic significance only, because an elevated blood lipid level has not been demonstrated to adversely affect retinal tissue. Theoretically, any condition predisposing a patient to elevated plasma lipoprotein levels could cause lipemia retinalis. Examples of diseases characterized by defective lipid synthesis or degradation are diabetes mellitus and hypothyroidism.

Lipemia retinalis occurs infrequently in the cat (Crispin, 1993; Ginzinger et al., 1996; Gunn-Moore et al., 1997; Jones et al., 1983; Wyman & McKissick, 1973). The condition has been experimentally induced in neonatal kittens by parenteral administration of large doses of methylprednisolone. Lipemia retinalis also occurs in cats secondary to primary, familial hypercholesterolemia (Ginzinger et al., 1996; Jones et al., 1983). In addition to lipemic retinal vessels, clinical manifestations include subcutaneous nodules over bony protuberances, particularly in the hock region of the rear legs. Histopathologically, these subcutaneous xanthomas resemble lipid granulomas. The cause is suspected to be a lipoprotein lipase deficiency. The result is fasting hyperlipoproteinemia because of elevations in the levels of plasma cholesterol and triglycerides. In normal cats, most triglycerides are contained in very low-density lipoproteins; in affected cats, most triglycerides and cholesterol are contained in chylomicrons. Both the ocular and dermatologic abnormalities resolve after feeding the cat a low-fat diet.

Anemic Retinopathy

Retinal hemorrhages were documented in 20 of 26 anemic cats, some of which were also thrombocytopenic (Fischer, 1970). Hemorrhages occurred at all depths in the retina and with equal frequency in both the tapetal and nontapetal fundus. The mechanism of retinal hemorrhage formation is thought to be anemia-induced hypoxia of retinal vessels, followed by compensatory venule dilation to maintain retinal perfusion and a subsequent increase in capillary fragility, which ultimately leads to hemorrhage. Anemic retinopathy occurs in a high percentage of cats with hemoglobin levels of less than 5 g/dL, and the condition is aggravated by concurrent thrombocytopenia.

Diabetic Retinopathy

Few cases of presumed diabetic retinopathy have been described (Hatchell et al., 1995; Herrtage et al., 1985). In one, retinal and vitreal hemorrhages as well as retinal detachments were the prominent ophthalmoscopic changes, and microaneurysms were present as well (Herrtage et al., 1985). With insulin therapy, the retinas partially reattached, with some return of vision. The cause of the diabetes in this case was prolonged administration of megestrol acetate. The severe ocular abnormalities in this cat were consistent with those of hypertension, which is a disease that was not excluded in this case by blood pressure measurement. Another report of retinal lesions in a pancreatectomized cat described microaneurysms, intraretinal hemorrhage, particularly in the area centralis, regions of capillary nonperfusion, intravascular microvascular abnormalities, and small foci of neovascularization (Hatchell et al., 1995).

In an experimental study, intraretinal oxygen levels were measured in diabetic cats (Linsenmeier et al., 1998). Oxygen levels were abnormally low in the inner half of the retina of diabetic cats, with some regional variation. Histologic changes included microaneurysms, leukocyte and platelet plugging of aneurysms and venules, and degenerating endothelial cells in capillary walls. In a recent study of 52 diabetic dogs, 11 (21%) developed retinal hemorrhages or microaneurysms, although in all dogs the lesions were small and did not interfere with vision (Landry et al., 2004).

Hyperviscosity Retinopathy

The retina of the domestic cat is sensitive to the effects of increased plasma viscosity. Ocular lesions in a cat with serum hyperviscosity syndrome caused by an IgG-secreting myeloma were retinal hemorrhages, optic disc swelling, and

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partial retinal detachment (Hribernik et al., 1982). Two cats with IgG monoclonal gammopathy were reported to have retinal hemorrhages and tortuous retinal vessels (Forrester et al., 1992). Another cat with hyperviscosity syndrome and an orbital plasmacytoma had dilated and tortuous retinal vessels (Ward et al., 1997). Common systemic clinical manifestations of hyperviscosity syndrome in the cat include listlessness, weight loss, neurologic signs, and heart murmur. The ophthalmic manifestations of serum hyperviscosity are ascribed to a decrease in retinal blood flow, thus causing secondary hypoxic damage to the retinal capillaries.

Ophthalmomyiasis Interna Posterior

In ophthalmomyiasis interna, there is intraocular migration of parasites, with the suffix posterior added to indicate posterior segment involvement. Five such cases, all with strikingly similar clinical findings, have been described in asymptomatic domestic cats (Brooks et al., 1984; Gwin et al., 1984; Kaswan & Martin, 1984). Ophthalmoscopic examination reveals multiple, criss-crossing, curvilinear tracks in the sensory retina (Fig. 28.92). The tracks are of uniform width, have distinct margins, and occur in both the tapetal and nontapetal fundus. Tapetal hyperreflectivity with foci of pigment deposition typifies the tapetal lesions, whereas lesions in the nontapetal fundus demonstrate pigment loss and clumping. Retinal hemorrhage and edema were interpreted as indicating recent migration. In one case, in which histopathologic results were available, degeneration of the outer retinal layers was present, thereby indicating that parasite migration probably occurred in the subretinal space. The actual parasite may or may not be seen at ophthalmoscopy.

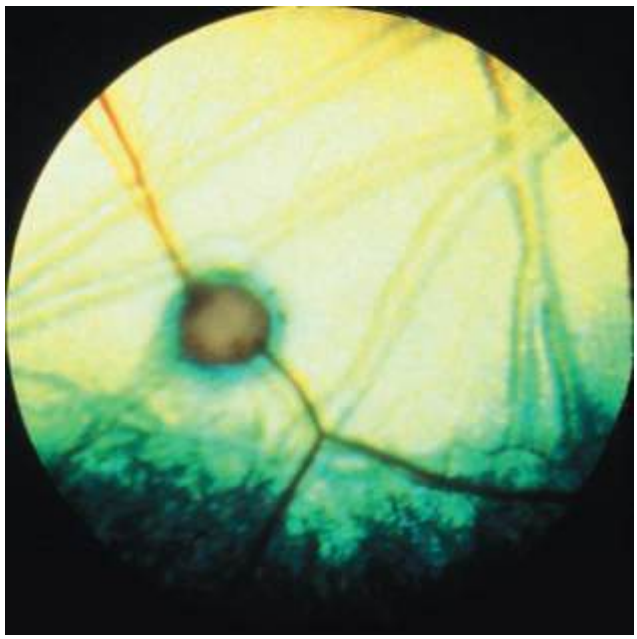


Figure 28.92 Ophthalmomyiasis. Well-demarcated hyperreflective "tracks" in the tapetal fundus from subretinal larval migration in a 2-year-old Domestic Shorthair. (Courtesy of Dr. Keith Collins. Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

One case has been reported in which a cat presented for anorexia and lethargy and the parasite was visualized in the fundus (Wyman et al., 2005). The cat was euthanized for the deteriorating condition and a *Cuterebra* spp. larva was identified. Coagulation necrosis and hemorrhage of the optic nerve, retina, and choroid as well as anterior uveitis were present on histopathology. No significant cerebrum or brainstem lesions were found.

Retinal Fold and Detachment

Retinal folds may occur as congenital lesions, but are also recognized in the cat as a secondary response to other ocular diseases (MacMillan, 1976). Five such cases have been described, with the histopathologic changes in 6 eyes having been studied. Ophthalmoscopically, acquired retinal folds may be focal or diffuse, and they occupy either the tapetal or nontapetal fundus. Their appearance is characteristic. Folds are recognized as irregular, vermiform lesions that are hyporeflective in the tapetal fundus and appear white to gray in the nontapetal fundus. Histopathologically, the photoreceptor, outer nuclear, and outer plexiform layers are elevated from the RPE. The inner retinal layers, however, remain normal.

The causes of retinal folding are variable. Folds may occur secondary to retinal detachment or as a sequela to intraocular inflammation (Fig. 28.93). Retinal detachment or separation of the sensory and epithelial retina in the cat has been described in association with a wide variety of ophthalmic and systemic abnormalities, including systemic hypertension, hyperviscosity syndromes, periarteritis nodosa, toxoplasmosis, trauma, cryptococcosis, blastomycosis, histoplasmosis, coccidiomycosis, FIP, ethylene glycol toxicosis, polycythemia, and primary as well as secondary intraocular neoplasms (Barclay & Riis, 1979; Lombard & Twitchell, 1978; Roberts, 1959). The specific pathologic mechanisms of detachment appear to be similar to those in other animal species. The specific responses of the feline retina to detachment, however, have some unique features (Anderson et al., 1986; Erickson et al., 1981). Degenerative changes rapidly occur at the epithelial cell–photoreceptor interface, and histopathologic changes are evident within 1 hour. By the third day of detachment, both rod and cone outer segments become degenerated and are replaced by membrane-bound sacs. Assembly of new outer segment material in the form of disorganized discs and membranous whorls continues for as long as 2 months. A significant decrease in the outer nuclear layer by the first month of detachment is attributable to necrosis and migration of photoreceptor cell nuclei into the subretinal space. Photoreceptor synaptic contact with second-order neurons is diminished by day 30 and absent by

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Figure 28.93 Retinal edema creates multiple folds appearing as thin dark lines throughout the tapetal fundus of a 10-month-old Himalayan with feline infectious peritonitis.

day 50. These findings appear to contrast with those in the dog, in which the outer nuclear layer survives for 6 months. Interestingly, cone inner segments, cell bodies, and synaptic terminals remain relatively well preserved at a time when rods are necrotic. The severity of changes correlates with the duration and height of the detachment. Early retinal pigment cell abnormalities are mounding of the apical cell surface, increased DNA synthesis, and eventually RPE proliferation. In chronic detachment, Müller cell proliferation and hypertrophy contribute to scar formation.

Posterior Segment Neoplasia

Primary neoplasms of the posterior segment appear to be quite rare in the cat. An astrocytoma of retinal origin has been described in one cat (Gross & Dubielzig, 1984). The presenting signs were leukocoria with a vascularized mass visible within the pupil. Histopathologically, the tumor infiltrated the optic nerve head, choroid, and vitreous humor. A choroidal melanocytoma has been reported in a cat (Semin et al., 2011). The cat later died from lymphoma and at necropsy no evidence of metastatic melanoma was detected.

Lysosomal Storage Diseases

Storage disorders are a group of progressive, inherited diseases caused by the deficiency of a specific lysosomal enzyme (Aguirre et al., 1983; Alroy et al., 1999; Blakemore, 1972, 1986; Breton et al., 1983; Burditt et al., 1980; Cork et al., 1978; Cowell et al., 1976; Cummings et al., 1988; Haskins et al., 1979, 1980; Hubler et al., 1996; Jezyk et al., 1977, 1986; Langweiler et al., 1978; Mazrier et al., 2003; Murray et al., 1977; Stramm et al., 1985, 1986; Vandevelde et al., 1982; Wenger et al., 1980). Disease ultimately results from abnormal accumulation of the deficient enzyme's substrate within lysosomes of affected cells. Lysosomal storage diseases reported to have ophthalmic manifestations are mucopolysaccharidosis I and IV, GM_1 and GM_2 gangliosidosis, mannosidosis, and mucolipidosis II. Table 28.13 lists the distinguishing features of each disease.

Diseases of the Optic Nerve and Central Nervous System

Congenital and Developmental Disorders

Colobomas of the optic disc and peripapillary region are rare in cats (Fig. 28.94; Bellhorn et al., 1971). Optic disc colobomas may occur in association with eyelid agenesis, as well as with other developmental anomalies (Martin et al., 1997).

Optic disc aplasia has been reported in a cat in which the retinal vasculature, nerve fiber layer, ganglion cell layer, optic nerves, and optic tract also failed to develop (Barnett & Grimes, 1974). Optic nerve aplasia may also occur if kittens are exposed to weekly doses of 500–1000 mg of griseofulvin during the first half of gestation (Scott et al., 1975). Additional abnormalities include cyclopia, anophthalmia, rudimentary optic tracts, and numerous central nervous system and skeletal abnormalities.

Optic disc hypoplasia may also occur, though uncommonly. The visual deficits depend upon the extent of the defect (Barnett & Crispin, 1998). Histologically, fewer retinal nerve fibers and ganglion cells are present.

Acquired Disorders

Optic Neuritis

Optic neuritis appears to be less common in the cat than the dog. Inflammation of the optic nerve may have a variety of causes in the cat. Viral, parasitic, and fungal infections can all cause optic neuritis. Of the viral diseases, FIP is most likely to affect the central nervous system and the optic nerve (Andrew, 2000). Associated ocular signs may include anterior uveitis, chorioretinitis, perivascular cuffing, and retinal detachment. The typical histopathologic findings consist of pyogranulomatous inflammation of the meninges (Foley & Leutenegger, 2001).

Toxoplasmosis may cause optic neuritis as well (Dubey & Carpenter, 1993). Upon histopathologic examination, tachyzoites have been noted within the optic nerve (Vainisi & Campbell, 1969). Of the systemic fungal infections, *Cryptococcus neoformans* is the most frequently recognized systemic fungal infection in cats (Pentlarge & Martin, 1986; Wilkinson, 1979). Optic neuritis is the second most

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Table 28.13 Lysosomal storage diseases with ocular manifestations.

			Affected Tissues		Clinical Signs		
Disease	**Breeds Affected**	**Deficient Enzyme**	**General**	**Ocular**	**General**	**Ocular**	**Ocular Pathology**
GM_1-gangliosidosis	Domestic Shorthair Siamese Korat	β-Galactosidaise	Liver (hepatocytes) CNS (neurons)	Cornea Lens Sensory retina	Ataxia, muscular tremor, hypermetria, weakness	Diffuse cornea opacification, dark spots in tapetum, pale spots in nontapetal fundus	Membrane-bound inclusions in keratocytes, especially adjacent to epithelium and endothelium; vacuolated endothelial cells and lens epithelium, membrane-bound inclusions in ganglion cell and inner nuclear layers
GM_2-gangliosidosis	Domestic Shorthair Korat	β-D-N acetylhexosaminidase	Liver (hepatocytes) CNS (neurons)	Cornea	Ataxia, hypermetria, head tremors, paralysis	Corneal cloudiness	Vacuoles in ganglion cells
α-Mannosidosis	Persian Domestic Shorthair	α-Mannosidase	Liver CNS Peripheral nerves Pancreas Salivary glands Kidney	Cornea Lens Retina Choroid	Stillbirth, neonatal death, tremor, ataxia, hypermetria, calvarial abnormalities	Diffuse stippling of the cornea, lenticular vacuoles along suture lines, mottled lesions in tapetal fundus	Vacuoles in ganglion cells, RPE, tapetum, and choroid
Mucopoly-saccharidosis I	Domestic Shorthair	α-L-Iduronidase	Skull (chondrocytes) CNS (neurons) Heart (fibroblasts)	Cornea	Short maxilla, frontal bossing, depressed nasal bridge, abnormal postural reactions, gait abnormalities	Corneal cloudiness, "ground-glass" appearance	Membrane-bound inclusions in keratocytes
Mucopoly-saccharidosis VI	Siamese	Arylsulfatase B	Blood (leukocytes) Liver (hepatocytes) Skin (fibroblasts) Heart (fibroblasts)	Cornea (sclera) Conjunctiva Uvea RPE	Facial dysmorphia, epiphyseal dysplasia, hip subluxation posterior paresis	Hypertelorism, diffuse corneal cloudiness, "granular" appearance	Vacuolated inclusions in connective tissue of cornea, conjunctiva, sclera, choroid, and iris and ciliary body keratocyte vacuolation in posterior cornea early; eventually entire cornea affected, vacuolated inclusions in ciliary epithelium and RPE, RPE hypertrophy
Mucolipidosis II	Domestic Shorthair	Failure of trafficking of several lysosomal enzymes	CNS Bones Heart	Retina	Failure to thrive as kittens, facial dysmorphia, long bone lesions, cardiac failure, respiratory infections	Retinal degeneration leading to blindness by age 4 months	Photoreceptor degeneration

CNS, central nervous system; RPE, retinal pigment epithelium.

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Figure 28.94 An optic disc coloboma in a 4-year-old Siamese appears as a small dark pit at the 6 o'clock position along the ventral margin of the optic nerve head. (Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)



Figure 28.95 Peripapillary edema associated with optic neuritis in a visually-impaired 3-year-old Domestic Shorthair with cryptococcal meningitis.

commonly reported ocular lesion in cases of feline cryptococcosis (Davies & Troy, 1996; Fig. 28.95).

Optic Nerve Atrophy

Atrophy of the optic nerve is the sequela to any process that damages the retinal ganglion cells or their axons. Examples of such causes include injury to the optic nerve during traumatic ocular proptosis, traction-related damage to the optic nerve at the level of the optic chiasm during enucleation of the contralateral eye (Stiles et al., 1993), and previous episodes of optic neuritis. Chronic glaucoma and retinal degeneration will also result in optic nerve atrophy.

Optic Nerve Neoplasia

Primary neoplasia of the feline optic nerve is uncommon (Buyukmihci et al., 2002). While no report defines the most common primary neoplasm of the feline optic nerve, meningioma is the most common primary neoplasm of the canine optic nerve (Andrews, 1973) and the most common feline intracranial neoplasm (Troxel et al., 2003). Astrocytomas or gliomas may also occur. Secondary neoplasia of the optic nerve is possible as well. Lymphoma is the most common secondary feline intracranial neoplasm and has been detected within cranial nerves (Andrews, 1973). Traumatic ocular sarcoma has a propensity for growth into and along the optic nerve, often into the brain, resulting in death (Dubielzig, 2002; Dubielzig et al., 1990). An intraocular myxoid leiomyosarcoma in a cat was reported to partially fill the globe and extend into the optic nerve. (Labelle & Holmberg, 2010).

Central Nervous System Blindness

Inflammations, infections, neoplasia, hypoxia, encephalopathies, head trauma, nutritional deficiencies, toxicities, and cerebrovascular accidents may all lead to blindness. Pupillary light and dazzle reflexes may remain intact or be absent, depending on the areas of the central nervous system that are affected. Specific central nervous system disorders that have been reported to cause blindness include *Cuterebra* larvae migration (Glass et al., 1998; Williams et al., 1998), hypovitaminosis A (Bartsch et al., 1975), hepatic encephalopathy from portosystemic shunt and shunt ligation (Kyles et al., 2002) and from hepatic lipidosis (Burrows et al., 1981), central nervous system blastomycosis (Miller et al., 1990), permethrin toxicity (Boland & Angles, 2010), and methylmercury toxicity (Gruber et al., 1978).

In a study that included 3 cats with postretinal blindness that were evaluated by magnetic resonance imaging (MRI), 1 cat had a nasal carcinoma with intracranial extension, 1 cat had a nasal osteosarcoma with intracranial extension, and 1 cat had a pituitary carcinoma (Seruca et al., 2010). All cats had sudden and permanent vision loss as the presenting clinical sign. In a study of 9 cats with intracranial meningioma, preoperative signs resolved after surgery, except for central blindness that persisted (Forterre et al., 2000).

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Diseases of the Orbit

Congenital and Developmental Disorders

Multiple abnormalities or colobomas of the eye and associated ophthalmic structures occur in the domestic cat. In one report, the breeds represented included the DSH and Persian (Bellhorn et al., 1971). The condition is characterized by congenital colobomatous defects in single or multiple ocular tissues, which may include the eyelid, iris, optic nerve, and sclera. Similar ocular anomalies have been reported in the snow leopard (Barnett & Lewis, 2002; Gripenberg et al., 1985). Another report described a litter of DSH kittens with multiple ocular anomalies (sufficient to produce blindness) that included microphthalmia, choroidal and optic disc colobomas, retinal dysplasia, and tapetal aplasia (Martin et al., 1997). The most consistent anomalies in these kittens were focal dorsolateral eyelid agenesis and trichiasis. Both heredity and *in utero* viral causes have been proposed for this syndrome, but no supporting evidence is currently available.

Griseofulvin Teratogenesis

The cat is particularly sensitive to the teratogenic effects of griseofulvin (Scott et al., 1975). When given to cats at a weekly dose of 500–1000 mg during the first half of gestation, griseofulvin produces ocular defects consisting of cyclopia, anophthalmia, and optic nerve aplasia. Extraocular defects include numerous central nervous system and skeletal abnormalities.

Acquired Disorders

Traumatic Proptosis

Considerable trauma to the orbit and head are required to proptose a cat's globe (Fig. 28.96). Concurrent facial fractures and optic nerve damage are more common than not. In one series of traumatic proptosis in 18 cats, no eyes regained vision (Gilger et al., 1995). Sexually intact males were more frequently affected, with vehicular trauma the most frequently established source of trauma. In 16 of 18 affected cats, facial bone fractures, hyphema, corneal perforation, and ocular desiccation were common. In only 2 of the 18 cats was replacement of the globe and temporary tarsorrhaphy attempted.

Orbital Inflammations and Infections

The feline orbit has relatively limited space compared with that of the dog. Hence, space-occupying orbital inflammations and neoplasms will produce exophthalmos, deviation of the globe, and protrusion of the nictitating membrane early in the disease process. Orbital surgeries are also more difficult to perform because of the limited peribulbar space.

Orbital cellulitis and abscessation caused by bacteria occur infrequently in the cat (Fig. 28.97), but are usually amenable to traditional therapy of drainage and antibiotic administration (Ramsey et al., 1996). In a study of orbital bacterial infections, 5 of 7 cats had positive bacterial isolation, with *Pasturella* and *Bacteroides* the most common genera (Wang et al., 2009). Retrobulbar steatitis resulting in exophthalmos and globe compromise has been reported from extension of otitis media and an inflammatory polyp (Fenollosa-Romero et al., 2018).

Onchocerca lupi was the causative agent of orbital cellulitis in 2 cats (Labelle et al., 2011). The organism was identified on histopathology and confirmed by molecular diagnostic techniques.



Figure 28.96 Proptosis in the cat is usually the result of severe head trauma with cranial and mandibular fractures, as seen in this adult Domestic Shorthair that had been struck by a car.



Figure 28.97 Orbital cellulitis in a 3-year-old Domestic Shorthair with periocular swelling, a prominent third eyelid, and lagophthalmos.

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Orbital infections caused by fungal agents are occasionally reported. Bilateral orbital cellulitis and exophthalmos caused by *Penicillium* sp. have been described in a domestic cat (Peiffer et al., 1980), as well as a retrobulbar mass caused by *Pythium insidiosum* (Bissonnette et al., 1991). *Aspergillus* spp. have been documented to cause orbital infections in several cats (Barachetti et al., 2009; Barrs et al., 2014; Hamilton et al., 2000; McLellan et al., 2006; Smith & Hoffman, 2010; Wilkinson et al., 1982). Clinical signs in these animals may include exophthalmos, corneal drying with possible ulceration secondary to lagophthalmos, ocular discharge, oral cavity ulceration, pain upon opening of the mouth, and nasal discharge if the infection involves the nasal cavity or sinuses. Sino-orbital aspergillus (SOA), a form of feline upper respiratory tract aspergillosis (URTA), is believed to occur from extension of the nasal disease, rather than the result of hematogenous spread. A recent study looking at computed tomography (CT) findings in cats with URTA revealed extensive bone lysis in addition to masses within the orbit, suggesting that fungal disease should be considered as an alternative differential to neoplasia (Barrs et al., 2014).

Surgical therapy alone, including orbital exenteration, has not typically been successful. In one report, a cat was successfully treated with posaconazole after surgery and treatment with itraconazole and amphotericin B failed (McLellan et al., 2006). In a report of 3 DSH cats with orbital aspergillosis, therapy with oral voriconazole was utilized in 2 of the cats (Smith & Hoffman, 2010). The drug resulted in serious systemic side effects that necessitated discontinuation of therapy.

Orbital foreign bodies have occasionally been reported in the cat (Kim et al., 2011; Lybaert et al., 2009; Tovar et al., 2005). CT successfully identified a linear metallic foreign body in 1 cat (Kim et al., 2011) and a linear wood foreign body in another cat (Lybaert et al., 2009), both of which were removed surgically with good results. Ocular and orbital ultrasound identified a retrobulbar abscess in 1 cat, but failed to demonstrate a plant foreign body (Tovar et al., 2005). The plant material penetrated the globe and was identified at enucleation.

A 13-year-old cat with a 1-week history of periorbital swelling and exophthalmos had a predominantly eosinophilic inflammatory cell infiltrate in the orbital tissue that was biopsied (Dziezyc & Barton, 1992). The cat was treated with oral prednisolone in a tapering dose over 4 weeks and had no recurrence in a 2-year follow-up. Orbital emphysema associated with frontal sinus penetration has also been reported in a cat (Wolfer & Grahn, 1995).

Feline Restrictive Orbital Myofibroblastic Sarcoma

Originally described as an idiopathic sclerosing orbital disease in 7 cats (6 DSH cats and one Persian) in one case series (Billson et al., 2006) and in one DSH cat in a single case report (Miller et al., 2000), feline restrictive orbital myofibroblastic sarcoma (FROMS) is an insidious condition that results in progressive fixation of the eyelids and orbital structures. The features of the condition are similar to those of sclerosing orbital pseudotumor in humans. In affected cats, extensive fibrosis with encapsulation of normal tissues progresses over weeks to months. In most cats, the condition became bilateral. Exposure keratitis, corneal ulceration, and corneal perforation were prominent features of the disease due to inability of the eyelids to move (Fig. 28.98). Although there were some inflammatory cells (lymphocytes, plasma cells, and occasional neutrophils) seen in affected tissues, invasion of collagenous tissue along existing tissue planes, rather than invasion of tissues, was the predominant feature. Some of the eyes examined histopathologically also had intraocular disease, including iritis, pre-iridal fibrovascular membranes, choroiditis, and partial retinal detachments. Other systemic disease was not found in affected cats, and complete blood counts, serum chemistries, and serology for infectious diseases failed to reveal a pattern. Treatment included oral corticosteroids, oral antibiotics, and radiation therapy in 1 cat. Additionally, 3 cats received surgical therapy, including entropion repair and temporary tarsorrhaphy. In all cases, response to treatment was poor: 6 of the 8 cats were euthanized, 1 cat later died from chronic renal failure, and 1 cat had bilateral exenteration performed.

In a report of the histopathologic features of tissues from affected cats, infiltration of neoplastic spindle cells was found



Figure 28.98 Feline restrictive orbital myofibroblastic sarcoma (FROMS) in a 12-year-old Domestic Shorthair with secondary exposure keratitis due to globe and eyelid immobility. (Courtesy of Dr. Marjorie Neaderland. Reproduced with permission from Ketring, K.L. & Glaze, M.B. (2012) *Atlas of Feline Ophthalmology*, 2nd ed. Ames, IA: Wiley-Blackwell.)

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in the orbit, eyelids, and periorbital skin, with collagen deposition and a few inflammatory cells (Bell et al., 2011), hence the moniker feline restrictive orbital myofibroblastic sarcoma. The spindle cells spread along fascial planes, but did not form a discrete mass. A recent report describing the CT and MRI findings in a cat with FROMS suggests that feline patients with orbital disease should undergo MRI with fat-suppression techniques, as increased signal intensity was present on short tau inversion recovery (STIR) images that was not apparent on regular weighted images (Thomasy et al., 2013). Initially, MRI of both orbits in that cat revealed extensive, irregular contrast-enhancing tissue without evidence of osteolysis, followed by extensive destruction of the bones of the orbit and maxilla shown on CT within 10 weeks. MRI images combined with orbital or eyelid biopsy showing spindle cell populations, even if bland, should suggest a diagnosis of FROMS (Thomasy et al., 2013). Strong intracytoplasmic immunohistochemical labeling for vimentin and smooth muscle actin in combination with a fibroblastic phenotype of the cells is helpful in the diagnosis (Thomasy et al., 2013).

Orbital Neoplasia

Orbital neoplasia is fairly common in cats. In one series, approximately two-thirds of the neoplasms were epithelial in origin, with SCC being the most frequent type (Fig. 28.99; Gilger et al., 1992). Approximately 15 different types of orbital tumors have been reported in the cat, including osteoma of the zygomatic arch, parosteal osteoma, and fibrosarcoma (Cottrill et al., 1987; Knecht & Greene, 1977; Peiffer et al., 1978; Pentlarge et al., 1989). Orbital lymphosarcoma may occur either unilaterally or bilaterally in the cat (Fig. 28.100). A well-differentiated teratoma causing exophthalmos in a 3-year-old cat has been reported (Wray et al., 2008). A recent report described a series of cats with clinical presentations resembling that of FROMS that were ultimately diagnosed with orbital invasive SCC, suggesting that SCC should be considered a differential diagnosis in cats with restrictive adnexal or orbital signs and corneal changes (Diehl et al., 2018). There were no statistically significant differences between clinical findings in FROMS cases and SCC cases, although exophthalmos and resistance to retropulsion were less common and overt eyelid and orbital masses were more common in SCC cases (Diehl et al., 2018). Both carry a guarded to poor prognosis.

In one cat with an orbital osteosarcoma, the imaging techniques of ultrasound, radiography, CT, and MRI were all performed and compared to the postmortem examination results (Ramsey et al., 1994). Only the use of MRI delineated the exact borders of the neoplasm. In a case series using CT for evaluating orbital disease in 13 cats, bony lysis was the feature that was most consistently associated with neoplasia, which was ultimately diagnosed in 11 of the cats (Calia et al., 1994). Indentation of the globe was most often seen with lymphoma. In a study of 13 cats using MRI to evaluate orbital disease, lymphoma, sarcoma, and carcinoma were the most commonly diagnosed neoplasms in the 11 cats that had tumors (Armour et al., 2011). A recent study that attempted to differentiate between inflammatory and neoplastic orbital conditions based on CT signs concluded that the most predictive CT signs for neoplasia were involvement of the anterior ocular structures of orbital bones (Lederer et al., 2015). However, bone lesions can also be seen in cases of chronic inflammation such as sinusitis. The most predictive CT sign for inflammatory conditions of the orbit was abnormal extraconal fat (Lederer et al., 2015).

While primary neoplasms are much more common in the feline orbit, metastatic tumors to the orbit have been reported, including a cat that developed orbital and calvarial



Figure 28.99 **A**. Orbital squamous cell carcinoma in a 14-year-old Domestic Shorthair with secondary exophthalmos, third eyelid protrusion, and exposure keratitis. **B**. Concurrent oral squamous cell carcinoma in the same cat.

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Figure 28.100 Orbital lymphoblastic lymphosarcoma in a 10-year-old Siamese with secondary exophthalmos, third eyelid protrusion, and conjunctival infiltration that obscures the globe.

metastases of its primary adenosquamous carcinoma (Binanti & Zani, 2015).

Depending on the tissue of origin and the invasiveness of an orbital tumor, therapeutic options may include surgery (orbitotomy with tumor resection or exenteration), radiation therapy, and/or chemotherapy.

Enucleation

Enucleation or exenteration in the cat must be approached with more caution than the same surgical procedure in the dog, because of the higher risk for damage to the optic chiasm (Donaldson et al., 2014; Stiles et al., 1993). The feline optic nerve is short and lacks the same degree of S-curve as present in the dog. Traction placed on the globe during enucleation may lead to optic chiasm damage and blindness in the fellow eye. In fact, in a retrospective study of 6 cats with mydriasis and/or visual deficits immediately following enucleation, optic chiasmal atrophy was noted on MRI (Donaldson et al., 2014). Acute afferent optic nerve deficits following enucleation, progressive optic nerve head atrophy, normal outer retinal function, and MRI demonstrating optic canal pathology are consistent with chiasmal injury due to traction on the optic nerve during enucleation (Donaldson et al., 2014). There is little free space in the feline orbit, so the use of large instruments or inappropriate technique may place undue traction on the optic nerve. This is especially true in cats with glaucoma and buphthalmic globes, a common reason for enucleation. It is recommended that careful technique is practiced when enucleating cats so that tissues can be identified and transected carefully, and that only a small hemostat be used to clamp the optic nerve, vessels, and retractor bulbi muscle behind and close to the globe. The hemostat should be removed prior to the use of a small scissors to cut these tissues, so that two instruments are not being introduced behind the globe. Rostral traction on the globe to facilitate optic nerve ligation is contraindicated in cats (Donaldson et al., 2014). Presurgical regional anesthesia with either a retrobulbar block or a peribulbar block should be performed in cats prior to enucleation; however, drug volume and systemic toxicity of the chosen anesthetic agent should be carefully considered. A cadaver study in cats showed that retrobulbar injection techniques and peribulbar injection techniques are likely to be equally effective in producing distribution of the anesthetic agent and subsequent regional anesthesia, although the peribulbar technique required a larger volume (Shilo-Benjamini et al., 2013).

In cases of enucleation or exenteration in which there is insufficient skin to close the orbital defect, a caudal auricular axial pattern flap may be useful (Smith et al., 1993; Spodnick et al., 1996; Stiles et al., 2003; Trevor et al., 1992). A skin graft from the neck and scapular region that includes the caudal auricular artery is harvested and rotated into the orbital defect. The most common complication of this procedure is distal flap necrosis from loss of blood supply. An axial pattern flap based on the superficial temporal artery can also be used, and may have less of a tendency for distal flap necrosis (Fahie & Smith, 1997).

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Equine Ophthalmology

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Vision in Horses

Vision in horses is of paramount importance for their survival and for their utility. However, vision in this species and the effect of ophthalmic disease on vision has not been extensively studied (Miller & Murphy, 2011).

Horses evolved as open country prey species. They thus require vision adapted for an arrhythmically photic (diurnal and nocturnal) lifestyle (Brooks, 2002). Retinal cellular architecture in particular in the horse appears adapted to the detection of motion in low lighting conditions. This occurs at the expense of visual acuity and color perception. The horizontally elliptical pupil in equidae allows for scanning of a wide arc of horizon (Harman, 1999) (Fig. 29.1). Under bright daytime ambient lighting conditions, miosis from reflex papillary constriction will reduce the glare associated with tapetal reflectivity (Miller & Murphy, 2011). The visual disruption caused by glare is likely to be bettered by the presence of yellow pigment in the equine lens nucleus, which will limit transmission of short wave, high energy, blue light, and subsequently protect retinal photoreceptors under bright light conditions (Brooks, 2002; Miller & Murphy, 2011).

Globe position in adult horses allows horizontal monocular visual fields of approximately 146 degrees and a frontal binocular field of 65–80 degrees (Harman, 1999; Miller & Murphy, 2011), creating a panoramic visual field of some 350 degrees (Fig. 29.2). This is most extreme when the animal's head is down in grazing position. Blind spots occur behind the tail and immediately anterior to the interocular space. The vertical monocular visual fields are estimated to be some 178 degrees, which are likely to be variable depending upon the size of the pupillary aperture and the size and shape of the granulae iridica. The granulae iridica probably act as a natural visor under bright lighting conditions, protecting the retina from excessive light exposure, and under conditions of extreme miosis may create a functional bicoria (two pupils), aiding distance discrimination in a monocular field (Miller & Murphy, 2011).

Binocular vision in horses occurs when the head is elevated and the face aimed towards the object of interest. The wide peripheral vision of the horse occurs when the head is in the grazing position. It is not possible to use both forms of vision simultaneously.

Defence against predators in most prey species is crucially dependent on both visual perception and distance discrimination, often under poor lighting conditions. The relatively large eyes and extensive pupillary excursion in the horse allow for maximum light capture. The rod dominated retina (the rod : cone ratio is variably cited as 8 : 1 and 20 : 1) (Ehrenhofer et al., 2002; Wouters & De Moor, 1979b). Species-specific rod photopigment adaption may increase visual sensitivity in dim light. The presence of a dorsal fibrous tapetum in the macular areas of the fundus enhances light capture, but the resulting scatter of the reflected light is likely to reduce acuity, although this may be ameliorated to some degree by the reduced photoreceptor to ganglion cell ratio in the macular areas (Crispin et al., 1990).

Compared with primates, the rods and cones in the horse appear to be relatively evenly distributed throughout the neurosensory retina, although a specific increase in cone density is present in the macular areas, allowing enhancement of visual acuity and color perception in these areas (Ehrenhofer et al., 2002; Sandeman et al., 1996). The macular areas of the horse retina lie dorsal to the optic disc and are believed to be orientated in a plane roughly corresponding to the horizontally elliptical pupil (Brooks, 2002; Ehrenhofer et al., 2002: Guo & Sugita, 2000, 2002; Hebel, 1976; Wouters & De Moor, 1979). The macular areas correspond to the ventral visual fields. The horse has a relatively low ganglion cell density compared with other mammals. Retinal ganglion cell density is, however, increased in the macular areas, and decreases significantly towards the retinal periphery creating larger peripheral receptor fields (Guo & Sugita, 2000, 2002; Hebel, 1976). The horse optic nerve contains a relatively high proportion of axons of large retinal

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Figure 29.1 Horizontally elliptical pupil permits wide scanning of the horizon.



Figure 29.2 Lateral globe position creates a wide panoramic field of view.

ganglion cells, which are adapted for motion detection, depth perception, and sensitivity in dim light (Brooks et al., 1995; Harman, 1999). This functional and topographic arrangement of the retinal microanatomy will result in an increasing photoreceptor to ganglion cell convergence ratio towards the peripheral horse retina, with the increasingly large receptor fields causing a decrease in peripheral visual sensitivity both in terms of visual acuity, and point discrimination and depth perception, with increasing distance from the macular areas. Although this would appear to confer visual disadvantage on a prey species, peripheral sensitivity to motion may be maintained, and it is possible that other visual cues, such as luminescence and contrast, may become relatively important in peripheral vision of the horse. Horses react with reflex flight behavior as objects suddenly enter their peripheral visual fields, but they subsequently use binocular forward vision to identify and assess the object or threat.

Stereopsis (binocular vision) is likely important for many of the tasks ridden horses are required to do, particularly jumping obstacles. However, one-eyed horses will perform these tasks with competence, suggesting horses are capable of utilizing monocular cues in depth perception (Timney & Keil, 1996; Timney & Macuuda, 2001; Timney et al., 1992). Although there are many kinds of monocular cues, the most important are interposition, atmospheric perspective, texture gradient, linear perspective, size cues, height cues, and motion parallax.

Monocular Vision Cues

- *Interposition:* Overlap. When one object overlaps or partly blocks the view of another object, the covered object is judged as being farther away.
- *Atmospheric Perspective:* The air contains microscopic particles of dust and moisture that make distant objects look hazy or blurry. This effect is called atmospheric perspective, and is used to judge distance.
- *Texture Gradient:* When a surface is viewed from a slant, rather than directly from above. The texture becomes denser and less detailed as the surface recedes into the background, and this information helps to judge depth.
- *Linear Perspective:* Parallel lines, such as fences, appear to converge with distance, eventually reaching a vanishing point at the horizon. The more the lines converge, the farther away they appear.
- *Size Cues:* If two objects are the same size, the object that casts a smaller retinal image is perceived as farther away than the object that casts a larger retinal image. This depth cue is known as *relative size*, because we consider the size of an object's retinal image relative to other objects when estimating its distance. Another depth cue involves the *familiar size* of objects. Through experience, we become familiar with the standard size of certain objects. Knowing the size of these objects helps us judge our distance from them and from objects around them.
- *Height Cues:* Points nearer to the horizon are perceived as more distant than points that are farther away from the horizon. This means that below the horizon, objects higher in the visual field appear farther away than those that are lower. Above the horizon, objects lower in the visual field appear farther away than those that are higher. This depth cue is called *relative height*, because when judging an object's distance, we consider its height in our visual field relative to other objects.
- *Motion Parallax:* When objects at different distances appear to move at different rates when the observer is in

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motion. The rate of an object's movement provides a cue to its distance. The more distant objects appear to move at a slower pace.

Visual acuity in horses has been variably estimated to lie between 20/30 and 20/60 on the Snellen scale in the macular areas, with significant drop off in the periphery (Timney & Keil, 1990). Acuity has been estimated to improve as objects are elevated up to 70 cm from ground level (Hall et al., 2003). Accommodation is believed to be limited to +/-2 diopters, and is likely to be achieved by anterior translocation of the lens rather than by change in lens shape (Miller & Murphy, 2011; Sivak & Allen, 1975). Although published results vary, the overall consensus appears to be that the average resting refraction as measured by streak retinoscopy in greater than 50% of horses is near emmetropia, and astigmatism is uncommon, whereas the remainder are roughly equally divided into either myopic or hyperopic (McMullen & Gilger, 2006; Sivak & Allen, 1975; Stuhr et al., 1990). Whether errors of refraction are likely to be a significant cause of behavioral problems in horses is not known (Miller & Murphy, 2011).

The focal length of the vertebrate eye is a function of wavelength, i.e., the eye suffers from longitudinal chromatic aberration. Different wavelengths of light will be focused on different positions of the retina because of the differences in refractive index of the lens. Chromatic aberration of a lens is seen as "fringes" of color around the image, because each color in the optical spectrum cannot be focused at a single common point on the optical axis. Chromatic defocus is a particularly severe problem in eyes with high light-gathering ability, because depth of field is small because of a pupillary opening that is large in relation to the focal length of the eye. Calculations show that in such eyes only a narrow spectral band of light can be in focus on the retina. Well-focused images are created at the wavelengths of maximum absorbance of all spectral cone types. Multifocal lenses in eyes with mobile irises are correlated with pupil shapes that allow all zones of the lens, with different refractive powers, to participate in the imaging process, irrespective of the state of pupil constriction. Rings in the lens of the horse indicate areas of varying refractive index because of a multifocal lens system. Multifocal lenses compensate for chromatic aberration and allow for sharp images (Kroger et al., 1999).

Color Vision

Studies of color perception indicate horses possess dichromatic vision utilizing two populations of cones, a short-wavelength-sensitive (blue) cone with a peak sensitivity of approximately 428 nm, and a second cone with a peak sensitivity around 540 which is between the human red and green cones (Carroll et al., 2001; Macuda & Timney, 1998; Miller & Murphy, 2011; Pick et al., 1994; Sandeman et al., 1996; Smith & Goldman, 1999; Ver Hoeve et al., 1999). Therefore, horses likely have difficulties in seeing red and differentiating orange and blue (Miller & Murphy, 2011) (Fig. 29.3). Cone density is reduced in horses compared with humans, indicating horses may perceive colors as muted, with color dilution increasing towards the peripheral visual fields as retinal cone density decreases.

Despite an increasing body of knowledge relating to the visual physiology of the horse, major aspects of functional vision and the effects of ocular pathology on functional vision remain elusive. Ridden horses with major ophthalmic abnormalities, including extensive and bilateral lens opacification or peripapillary chorioretinal pathology, often show no behavioral evidence of visual compromise. On the contrary, horses with minor abnormalities such as central focal lens opacities or vitreal 'floaters', can exhibit behavior sug-

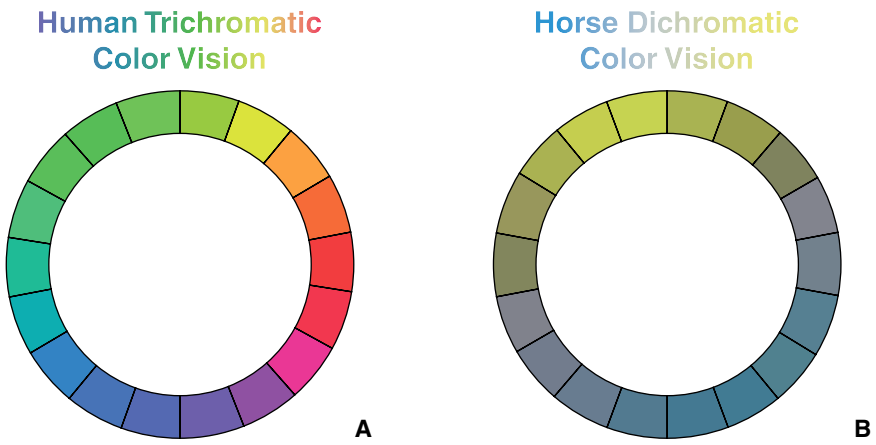


Figure 29.3 Comparison of normal human color vision (**A**) to dichromatic color vision of the horse (**B**). Horses are likely, therefore, to have difficulties in differentiating orange and blue. (*Source*: With permission from Miller, P. & Murphy, (2011) Equine vision. In: *Equine Ophthalmology* (ed. Gilger, B.), 2nd ed. Philadelphia: Elsevier.)

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gestive of visual dysfunction, e.g., 'head shaking', shying or exaggerated startle responses, whereas others with similar ocular abnormalities present no behavioral problems. Veterinary ophthalmologists are often asked to judge the effects of ocular disease on vision (and consequently the suitability and safety) in a particular horse, but this assessment is very difficult to make. However, some guidelines may be helpful:

- Retinal pathology encompassing the macular areas is likely to have significant effects on visual acuity and color perception in the affected eye.
- Peripapillary pathology, particularly where there is overt injury to the associated retinal blood vessels, is likely to be associated with some disruption of retinal ganglion cell transmission, creating a peripheral field deficit in the areas of origin of these ganglion cells.
- Multiple focal chorioretinitis lesions ('bullet hole' lesions) distributed in a horizontally linear pattern in the inferior peripapillary fundus can, for reasons unknown, be associated with significant visual disability.
- Older horses with age-related pigmentary retinopathy and retinal vascular attenuation may show signs of visual difficulty in dim lighting conditions.
- Dense opacities of the ocular media within the visual axis, particularly those involving the nodal point of the eye (posterior perinuclear lens), may disrupt light passage onto the macular areas of the retina and impair vision, or may create a frank blind spot.
- Acquired inclusions in the fluid media of the eye, mainly in the vitreal body, which move precipitately with ocular saccades, can be associated with head shaking behavior in some horses.

Clinical Assessment of Vision in Horses

Vision testing in horses is subjective, and there is at present no means of objectively assessing vision in the horse which is not overtly blind. Environmental observation (i.e., observing the horse in the stall, pasture, or while being worked), menace response, dazzle reflex, and maze testing (with or without unilaterally blindfolding the horse) together may provide some information regarding the presence or absence of vision. Determining total blindness is possible with these tests but determining whether a horse has decreased vision is not easily done. By extrapolation from human optometry, a positive menace response from 2 feet away is likely to indicate simply that the horse's visual acuity is *at least* 20/20,000, i,e., 100 times worse than the level recognized in humans as legally blind (20:200). Therefore, a positive menace reflex should be interpreted with caution (Miller & Murphy, 2011).

Obstacle course testing of horses is often proposed as a means of testing visual function in horses. However, although this procedure will detect most horses with frank blindness, the horse's use of nonvisual sensory cues arising from both the immediate environment and the handler, and the apparently complex and interactive use of visual cues by the horse, make this a highly unreliable method of estimating the extent of any visual disability in the horse.

At present, extrapolation from a fundamental understanding of the physiology of vision, in conjunction with a careful and systematic ophthalmic examination, is the most effective and objective means available to the clinician of determining the absolute presence or absence of significant visual disability in a horse with ocular pathology. Veterinarians should be cautious when giving opinions on the functional consequences of ocular pathology.

Examination of the Equine Eye

In order to perform a thorough examination of the equine eye, the patient must be adequately restrained. Chemical restraint greatly facilitates a complete ophthalmic examination of the horse. Typically, a short-acting sedative is administered intravenously (IV), followed by an auriculopalpebral motor block. Xylazine (0.3–0.4 mg/kg IV) is usually adequate for examination. Especially difficult equine patients may require either a higher dose of xylazine (1.1 mg/kg IV) or detomidine (0.02–0.04 mg/kg IV) or romifidine (40–120 µg/kg IV). If more invasive diagnostic or treatment procedures are to be performed, such as corneal scrapings or conjunctival biopsies or placement of a subpalpebral lavage system, most animals will require the more potent detomidine with or without the addition of butorphanol (0.01–0.02 mg/kg IV). Detomidine or romifidine at an appropriate dose usually results in rapid sedation without an excitation phase and a steady head position without movement (such as the jerks that are frequently observed with xylazine and butorphanol sedation) that is necessary when performing any procedure near an eye with impaired corneal integrity. Xylazine and butorphanol are effective sedatives but may induce head tremors or exaggerated response to stimuli (such as sound), which can be frustrating when performing a detailed ocular examination. Pretreatment with IV acepromazine (0.02–0.04 mg/kg IV) followed 10–15 minutes later with xylazine or detomidine may also reduce head tremors in horses. Difficult horses should be restrained in stocks, and a twitch may be used in conjunction with chemical restraint during the examination. As with small animals, the use of restraint and sedation in the horse depends on the individual's temperament, the experience of the handlers and examiner, and the facilities. Although likely not clinically significant, it should be noted that the use of sedatives may cause a change

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in intraocular pressure (IOP); a decrease in IOP is noted with most alpha-2 agonists (Stine et al., 2014; van der Woerdt et al., 1995).

Restraint and Nerve Blocks

The orbicularis oculi muscle closes the eyelids and, thus, can impair or even prevent ocular examination, especially in large animals. The pain in diseased eyes may be so intense that examining or manipulating the orbit and globe is difficult and potentially threatening to the integrity of the globe if the horse resists. The eyelids should never be forced open, however, because expulsion of intraocular contents can occur through a full-thickness corneal or scleral laceration. A motor block to facilitate opening of the eyelids and visualization of the globe will target either the auriculopalpebral or palpebral nerves (Fig. 29.4A, B). The palpebral nerve, which arises from the auriculopalpebral branch of the facial nerve, innervates the orbicularis oculi muscle. These motor fibers may be blocked at any point between the origin of the

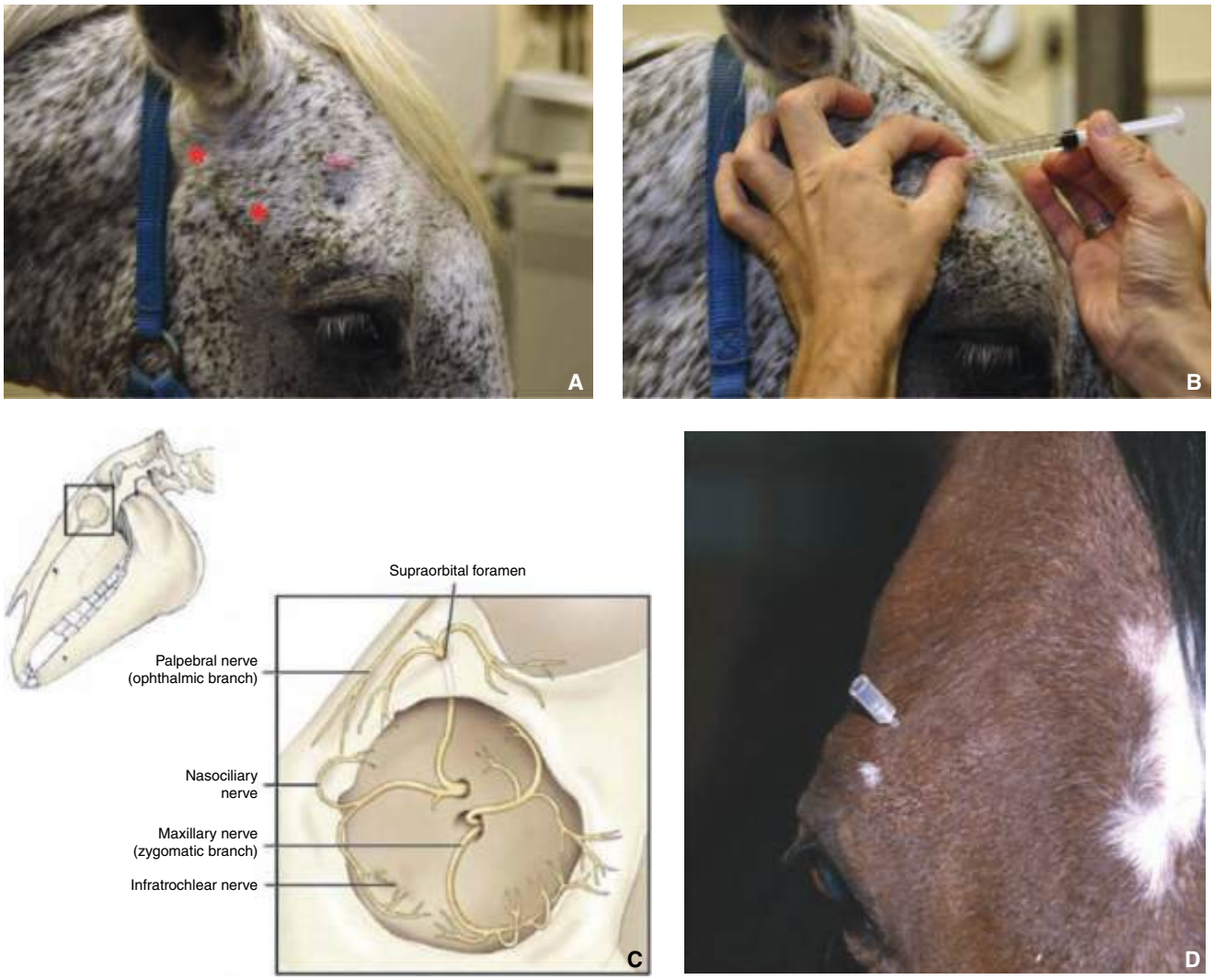


Figure 29.4 The nerve blocks used in the equine eye examination. **A.** The auriculopalpebral nerve block in a horse facilitates examination of the eye and is crucial when the cornea is fragile and near perforation. This figure illustrates the proximal placement of the block with the needle, while the arrows mark alternative locations that will elicit a similar response. **B**. The injection of anesthetic agent. **C.** The frontal (supraorbital) nerve is a branch of the trigeminal nerve and is blocked as it emerges from the supraorbital foramen within the frontal bone. (*Source*: With permission from Miller, P. & Murphy, C (2011) Equine vision. In: *Equine Ophthalmology* (ed. Gilger, B.), 2nd ed. Philadelphia: Elsevier.) **D.** The supraorbital nerve block is performed at the level of the supraorbital foramen (directly within the foramen if possible, in the region if not) and is useful for anesthesia of the upper eyelid. To locate the supraorbital foramen, the examiner places his/her thumb under the orbital rim, the middle finger in the supraorbital fossa, then places the index finger straight down midway between the thumb and middle finger to locate the supraorbital foramen.

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auriculopalpebral nerve and the palpebral nerve branch. There are three main points at which the auriculopalpebral or palpebral nerves can be blocked in the horse. The first is just anterior to the base of the ear where the auriculopalpebral nerve emerges from the parotid salivary gland and becomes subcutaneous on the lateral aspect of the coronoid process. Here local anesthetic may be injected into the depression just caudal to the ramus of the mandible at the ventral edge of the temporal portion of the zygomatic arch (Rubin, 1964). The rostral auricular artery and vein should be avoided. The second is just lateral to the highest point of the caudal zygomatic arch where the palpebral nerve can be "strummed" under the skin over the dorsal border of the bone (Manning, 1976). The third is where the palpebral nerve lies on the zygomatic arch caudal to the bony process of the frontal bone. Considering the branching of the motor fibers, more proximal blocks generally are preferred, because they affect more of the orbicularis oculi muscle. A 25-gauge, 5/8-inch needle is used to inject the 1–5 mL (usually 1–2 mL is sufficient) of anesthetic subfascially adjacent to the nerve, and the injection site is massaged to facilitate drug diffusion about the nerve. Lidocaine is most often employed for this procedure because of its rapid onset and reasonably long duration; however, procaine, bupivacaine, and mepivacaine can be used (Havener, 1994). With effective akinesia, ptosis, narrowing of the palpebral fissure, and occasionally, lower-lid ectropion result. These effects typically last from 45 minutes to 1 hour. A hospitalized horse receiving repeated auriculopalpebral nerve blocks occasionally becomes resistant, thereby taking longer to achieve akinesia and, sometimes, requiring higher doses of anesthetic. It appears that local tissues become resistant to drug penetration, and that accurate needle placement for injections thus becomes increasingly important. General anesthesia is rarely necessary to perform a thorough ophthalmic examination, but it is definitely required for the meticulous repair of many injuries to the eye and periocular region.

In some instances, it is helpful to desensitize the skin of the eyelids to facilitate examination of the eye or to enable surgical repair of an eyelid wound or placement of a subpalpebral lavage. Sensation to the eyelids is provided by the ophthalmic and maxillary divisions of the trigeminal nerve (i.e., cranial nerve V). In most domestic animals, the frontal, lacrimal, and infratrochlear nerves arise from the ophthalmic division of cranial nerve V, whereas the zygomatic nerve arises from the maxillary division (Cyce et al., 1987) (Fig. 29.4C). In the horse, the frontal nerve innervates most of the central upper lid, the lacrimal nerve innervates the lateral upper lid, the zygomatic nerve innervates most of the lateral lower lid, and the infratrochlear nerve innervates the medial canthus (Peterson, 1951; Manning, 1976; Wilkie, 1991). There are several different sensory blocks that may be employed in horses depending on the location of the eyelid lesion to be addressed. The central two-thirds of the upper eyelid is innervated by the frontal or supraorbital nerve, and is blocked by injecting 2 mL of 2% lidocaine into the supraorbital foramen (Manning, 1976) (Fig. 29.4D). This foramen can be identified as a small depression in the supraorbital process of the frontal bone, medial to its most narrow aspect. It can be palpated if the examiner places his or her thumb below the dorsal orbital rim and the middle finger in the supraorbital fossa. The examiner then places the index finger straight down midway between the thumb and middle finger to locate the supraorbital foramen. This is the most commonly employed sensory block of the eyelids in the horse. The lateral upper eyelid and lateral canthus are innervated by the lacrimal nerve, and can be blocked with a line block along the lateral third of the dorsal orbital rim. A block of the zygomatic nerve will anesthetize the lateral lower lid and is achieved with a line block along the ventrolateral orbital rim. The medial canthal region is innervated by the infratrochlear nerve and is desensitized by injecting anesthetic through the bony trochlear notch on the dorsal rim of the orbit near the medial canthus (Manning, 1976; Wilkie, 1991).

Ophthalmic Exam

A systematic approach should be taken to examination of the equine eye. Following assessmentof vision, and prior to instillation of any medication in or around the eye, the examiner should evaluate for symmetry of the head, bony orbits, eyelids, globes, and pupils in a well-lit environment. Ocular comfort may be assessed by assessment of the position of the eyelashes, position of the globe, ocular discharge, blink rate, and degree of blepharospasm. The upper eyelashes of the healthy horse are nearly perpendicular to the cornea, whereas a ventral or downward direction of the eyelashes may indicate discomfort, enophthalmos, or ptosis (Fig. 29.5). The menace response should be assessed before sedation and motor blockade of the eyelids. Sensation of ocular and adnexal structures should be evaluated prior to sensory blocks being performed. Pupillary light and dazzle reflexes may be performed at any time. An assistant is helpful when assessing consensual pupillary light reflexes (PLRs).

A focal light source (e.g., a transilluminator) and a direct ophthalmoscope are essential pieces of equipment for ophthalmic examinations in the horse. With adequate illumination, the periocular tissues, orbit, eyelids, conjunctiva, and ocular surface should be examined. If a lesion is present on the cornea or conjunctiva, a bacterial ± fungal culture and suceptibility may be indicated and should be collected before administration of topical agents to the eye.

The remainder of the ophthalmic examination should ideally be performed in a darkened environment. Examination of the nasolacrimal system, third eyelid, and conjunctiva is performed using magnification and/or slit lamp biomicroscopy.

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Figure 29.5 **A.** The upper eyelashes of the healthy horse, when viewed from the front, are nearly perpendicular to the cornea. **B.** A ventral or downward direction of the upper eyelashes, when viewed from the front, may indicate blepharospasm as seen in this horse with orbital disease and keratitis.

The anterior surface of the third eyelid can be better visualized by gently retropulsing the globe to produce passive prolapse of the nictitans. For evaluation of the posterior surface, grasp the third eyelid gently with Graefe fixation forceps or place a cotton-tipped applicator behind the nictitans to gently retract. Examine the cornea for abnormalities including opacities, ulcerations and structural defects, vasculature, edema, fibrosis and infiltrates by using transillumination with magnification and/or slit lamp biomicroscopy. When indicated, cytology is collected next, usually after application of a topical anesthetic. Fluorescein and/or Rose Bengal staining of the cornea follow. Next, evaluate resting pupil size, shape, and mobility and appearance of the anterior structures (iris, lens), including the assessment for aqueous flare. The attachment of the iridocorneal angle pectinate ligaments to Descemet's membrane at the iridocorneal angle can be visualized directly medially and laterally in the adult horse. Estimation of IOP with an applanation or rebound tonometer should also be performed. IOP should always be assessed with the horse's head held above its heart, otherwise artifactual elevation (up to 87%) may occur (Komaromy et al., 2006).

Pupillary Dilation

Mydriasis is required for complete examination of the lens and ocular posterior segment. The most common mydriatic used is tropicamide (Mydriacyl 1%, Alcon Laboratories, Fort Worth, TX, USA), which takes effect in approximately 10–20 minutes and lasts 4–6 hours in the horse (Gelatt et al., 1995; Gilger & Stoppini, 2011). If the horse has intraocular inflammation or uveitis secondary to corneal disease or trauma, a single application of tropicamide may not be sufficient to fully dilate the pupil. Topical phenylephrine (2.5% or 10%) does not cause mydriasis in normal horses, nor does it enhance the mydriatic effect of tropicamide (Hacker et al., 1987). Because of its longer duration of action, the use of atropine for routine examination is not recommended (Davis et al., 2003).

Diagnostics

After mydriasis has been achieved, the clarity, position, and size of the lens, vitreous body, optic nerve, retinal blood vessels, and the tapetal and non-tapetal fundus are evaluated. Examination of the ocular fundus can be performed with a direct, indirect, or panoptic ophthalmoscope, depending on the examiner's preference (Fig. 29.6). It may be helpful to initiate the fundic examination with indirect ophthalmoscopy with a 20-D, 14-D or 2.2 Pan-Retinal® lens (Volk, Mentor, OH, USA) followed by direct ophthalmoscopy to examine specific lesions further. Further details on the specific techniques of the ophthalmic examination are described in Chapter 10, Part 1.

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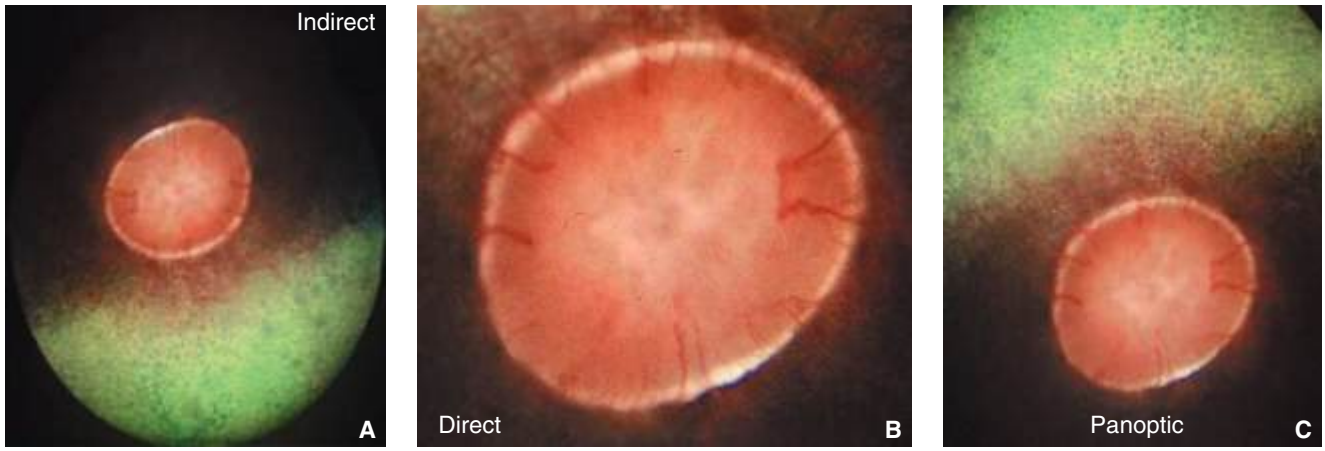


Figure 29.6 Appearance of the equine fundus when viewed with indirect ophthalmoscopy (**A**), direct ophthalmoscopy (**B**), and with a PanOptic™ ophthalmoscope (**C**).

Ocular Problems in the Equine Neonate

Ocular disorders of the equine neonate may be congenital, inherited, or acquired. Normal embryogenesis of the foal eye results in a fully developed globe and adnexa at birth. However, tear production and corneal sensitivity may be low initially, and lagophthalmos may be found in neonates (Adams & Mayhew, 1984; Brooks et al., 2000a). A menace response may not be fully developed until 10–14 days after birth (Latimer & Wyman, 1985). The PLRs, however, are intact, although may be sluggish initially (Anor et al., 1999; Barnett, 1975; Dwyer, 2011; Latimer & Wyman, 1985). In the neonatal foal, the horizontal axis of the pupil and globe deviates slightly medially and ventrally, with the eye reaching a normal adult position by 1 month of age (Adams & Mayhew, 1984). The neonatal iris may be slightly gray in color and the pupil round to oval in shape. Hyaloid artery remnants in foals may contain blood for several hours after birth but generally disappear by 3–4 months of age (Gelatt et al., 1993; Munroe, 2000). Lens sutures are often prominent in foals and should not be mistaken for a cataract (Roberts, 1992). The anterior suture has a variable configuration in shape, with the posterior suture varying in shape from "Y," sawhorse, to stellate patterns (Latimer et al., 1983). The anterior sutures are difficult to visualize in Thoroughbreds, but they are easier to identify in Standardbred and Saddlebred foals (Latimer et al., 1983).

Variations of the normal equine neonatal fundus are numerous, and primarily relate to coat color (also see later section on the adult ocular fundus). The optic disc is oval to round (most often), pink–orange in color, and located slightly temporal in the inferior quadrant of the non-tapetal fundus. The retinal vessels are small and extend only a short distance from the optic disc. No retinal vessels are found at the 6-o'clock position of the horse optic disc. The foal tapetal fundus is usually blue to blue–green, with small dots and end-on views of choroidal capillaries or "Stars of Winslow" distributed in a uniform pattern. Color-dilute neonates may have light yellow zones of tapetal color with red "Stars of Winslow," or have no tapetum with resultant exposure of the choroidal vasculature thereby creating a red fundic reflection (Gelatt et al., 1993). The entire tapetal region in white horses may appear yellow. The non-tapetal fundus is usually dark brown in neonates. Light gray linear streaks arcing horizontally nasally and temporally away from the optic disc margin may be seen in the non-tapetal fundus of foals, and represent axon bundles in the nerve fiber layer (Gelatt et al., 1993; Turner, 2004). Partial albinism will result in a lack of pigmentation in the retinal pigment epithelium (RPE) of the non-tapetal region permitting visualization of the choroidal vasculature.

Ophthalmic Exam in Neonates

An ophthalmic examination is a very important part of the neonatal physical examination, which is performed most commonly 12–36 hours after birth (Dwyer, 2011). Abnormalities are frequently noted on neonatal exams and these foals should be monitored regularly and carefully. A recent study of Standardbred foals examined within 48 hours of birth revealed ocular abnormalities in 37/102 (36.3%) individuals. Retinal and subconjunctival hemorrhages were present in 19/102 (18.6%), and in 13/102 (12.7%), respectively. In 4/102 (3.9%) animals, an entropion of the lower eyelid was present. Only one foal (1%) showed a congenital nuclear unilateral cataract. No other ocular abnormalities were detected. However, all foals showed various degrees of remnants of hyaloid system. One week after the first ocular examination, retinal hemorrhages had resolved in 100% of

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the eyes, whereas subconjunctival hemorrhages had disappeared in all eyes by the second week after the first examination (Barsotti et al., 2013). In another study, 39/70 neonatal foals with systemic disease had at least one ophthalmic lesion (Labelle et al., 2011). Of the 39 foals with ophthalmic disease, 24 (61.5%) had potentially vision-threatening lesions. Clinically important abnormalities included conjunctival hyperemia or episcleral injection (42.9%), uveitis (25.7%), ulcerative keratitis (18.6%), nonulcerative keratitis (14.3%), entropion (11.4%), retinal hemorrhage (11.4%), and cataract (8.6%). Foals with sepsis were significantly more likely to have uveitis than were those without sepsis. Foals with sepsis and uveitis were also significantly less likely to survive than were foals that had sepsis without uveitis. Acquired ophthalmic disease (52.9%) was significantly more common than congenital ophthalmic disease (12.9%).

Congenital Anomalies and Abnormalities

Congenital anomalies and abnormalities are not common in foals, but the eyes of newborn foals should be examined especially if vision problems are apparent.

Microphthalmos

Microphthalmos is a congenital globe condition in which the globe axial length is less than two standard deviations below the mean length (Fig. 29.7). Microphthalmos is common in foals and may be either unilateral or bilateral (Dziezyc et al., 1983; Munroe, 2000). Thoroughbreds appear to be at increased risk (Munroe & Barnett, 1984). Microphthalmos differs from phthisis bulbi, which is an initially normal-sized globe that degenerates and atrophies secondary to severe injury or insult. Microphthalmos may be spontaneous and idiopathic, or it may be secondary to uterine infection or drug toxicity. Microphthalmos may be an isolated finding, or it may be associated with other ocular abnormalities, such as cataracts and retinal dysplasia (Dziezyc et al., 1983). Microphthalmos associated with other ocular defects is termed a *complicated microphthalmos*; if the globe is simply small and visual, it is referred to as a *simple or pure microphthalmos* (Dziezyc et al., 1983). A small palpebral fissure and prominence of the nictitans may be noted in affected foals. Entropion may occur from a lack of support from the small globe and be associated with mild-to-severe ulcerative keratitis. Corneal ulceration resulting from entropion and microphthalmia may necessitate entropion repair in visual globes or enucleation of nonvisual globes.



Figure 29.7 **A.** Microphthalmos in a foal with nictitans protrusion and conjunctival exposure. The orbit is flattened on this side of the skull. **B.** Radiograph of the foal shows orbital malformation on the side with microphthalmos.

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The bony orbit and skull with the microphthalmic globe may become malformed as the foal ages (Fig. 29.7)

Orbit

Development of the bony equine orbit is influenced by globe development (Gelatt, 1993). Asymmetry of the face because of an underdeveloped bony orbit can be associated with congenital microphthalmos or phthisis bulbi resulting from severe globe trauma in a very young foal. Fractures of the orbital bones with or without globe damage caused by trauma from kicks or accidents may require surgical correction in foals (Brooks, 1999).

Strabismus

Strabismus refers to a deviation in alignment of one globe in relation to the normal visual axis. It is often recognized when compared with the relative position of the fellow globe. When the two eyes fail to focus on the same image point, the brain may ignore the input from the deviated eye to result in a form of vision loss termed amblyopia. The two eyes may be crossed (esotropia), turned outward (exotropia), or deviated up vertically (hypertropia) (Fig. 29.8), or deviated down vertically (hypotropia).

Binocularity is an acquired feature of vision that normally develops early in life. The development of binocular vision requires both eyes to have visual capability and to be properly aligned. With strabismus, visual confusion occurs as a result of the projection onto corresponding retinal areas of simultaneously perceived dissimilar images of two different spatial objects that would normally project onto noncorresponding retinal areas. A physiologic scotoma prevents perception of dissimilar images from the strabismic eye, however, and the foal is thus spared the visual confusion that results from strabismus. Foals with congenital or early onset strabismus do not receive the essential visual retinal stimulation for development of binocular vision and thus lack true stereopsis.



Figure 29.8 Strabismus (hypertropia) in a foal with congenital cataract.

Congenital strabismus and dorsomedial strabismus have been reported in Appaloosa foals with equine congenital stationary night blindness (Gelatt, 1993; Sandmeyer et al., 2007). Hypertropia associated with congenital cataracts may resolve after surgical removal of the cataract. Esotropia is common to Saddlebreds and has been reported in mules with an incidence of 0.5% (Munroe & Barnett, 1984). Surgical correction of strabismus by rectus muscle transposition is infrequently performed by veterinary ophthalmologists. Muscles can be weakened by moving the muscle insertion posteriorly or strengthened by shortening the muscle or advancing the insertion site anteriorly; alternatively, muscle insertions can be transposed to different locations to alter the functional pull of the muscles. The reader is advised to consult the literature and a veterinary or physician ophthalmologist before attempting to correct equine strabismus (Spaeth, 2003).

Dermoids

Dermoids (i.e., choristomas) of the eyelids, nictitans, cornea, and conjunctiva have been reported in foals (Gelatt, 1993; Greenberg et al., 2012; Gornik et al., 2015; Roberts, 1992). Corneal and conjunctival dermoids may look like aberrant pigmentation when associated hair follicle development is minimal. Glands and follicles appear as hypopigmented foci on pigmented dermoids (Fig. 29.9). Treatment depends on location. Superficial to deep keratectomy is indicated for corneal dermoids and excision with reconstructive blepharoplasty for eyelid dermoids is warranted to alleviate ocular irritation. Limbal dermoids have been noted with iridal hypoplasia and cataracts in Quarter Horses (Joyce, 1990).

Nasolacrimal System Atresia

Eyelid punctal atresia, nasolacrimal duct (NLD) agenesis, and nasal punctal atresia must be differentiated from acquired obstruction causing dacryocystitis of the nasolacrimal drainage system (Brooks, 2002; Gelatt, 1993; Roberts, 1992). NLD atresia, which is most commonly manifested by an imperforate nasal punctum, appears clinically as mild to moderate, unilateral, or bilateral epiphora at 4–6 months of

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Figure 29.9 Corneal dermoid in a foal. Note the pale spots within the pigmented lesion. These represent follicles.

age and, if not managed appropriately, will develop into severe mucopurulent discharge by 10–12 months of age caused by the development of secondary bacterial dacryocystitis (Fig. 29.10A). Culture and antibiotic sensitivity testing of the discharge and irrigated material are highly recommended. Contrast dacryocystorhinography with 4–6 mL of radiopaque solution may be necessary to confirm the diagnosis (Fig. 29.10B). Computerized tomography can aid diagnosis (Nykamp et al., 2004).

Eyelid punctal atresia may be noted visually at the medial canthus (lack of a punctal opening), because of distention of the conjunctiva over the atretic puncta after irrigation of the nasolacrimal system from the nasal puncta. A diagnosis of atresia of the nasal punctal may be presumed by noting the lack of a distal opening to the NLD within the mucocutaneous junction at the medial nares, failure of the irrigating solution to exit the nasal puncta during flushing of the proximal nasolacrimal system through the palpebral lacrimal puncta, and distention of the floor of the nasal vestibule in response to irrigation (Brooks, 2002). Agenesis of the osseous NLD is fortunately rare but may also accompany the eyelid or nasal puncta atresia.

Creation of a new proximal or distal opening and duct by catheter instillation is indicated for puncta atresia (Dziezyc, 1999; Giuliano, 2011). It may be possible to flush the nasolacrimal system from the patent nares or canthal puncta to cause a dilation of the mucosa over the site of the atretic punctum. Once the atretic site is identified, an incision through the eyelid conjunctiva or nasal mucosa with a scalpel, cautery, or laser ablation will establish patency (Stoppini, 2014). To treat definitively, a 5-French male silastic or plastic urinary catheter is placed normograde from a proximal nasolacrimal punctum and pulled through the nares and sutured in place (Fig. 29.10C). The catheter will need to remain in place for several weeks (4–8 weeks) to allow epithelialization of the new duct and puncta and resolution of the dacryocystitis. Topical and systemic antibiotics are given for 2–4 weeks (Giuliano, 2011). More severe cases of ductal atresia may require more advanced interventional procedures (Plummer et al., 2018). Canaliculorhinostomy has also been used successfully to relieve NLD obstruction in the horse (McIlnay et al., 2001).

Corneal Disease

Congenital corneal disease is uncommon in the horse, with megalocornea of multiple congenital ocular anomalies (MCOAs) of the Rocky Mountain Horse (Ramsey et al., 1999a, b) and dermoids (Latimer & Wyman, 1985; Latimer et al., 1983) being most common.

Heterochromia Iridis

Heterochromia iridis is variation in the normal, dark brown iridal color that may affect one or both eyes. It may be a combination of white and blue iris color with brown corpora nigra (i.e., “wall eye”), or it may be a white iridal color with brown corpora nigra (i.e., “china eye”) (Fig. 29.11). Heterochromia iridis is common to the Appaloosa and Paint breeds as well as individuals with palomino, pinto, and white coat colors (Gelatt, 1993). The fundus of foals with heterochromia iridis may display the subalbinotic qualities of non-tapetal hypopigmentation and tapetal hypoplasia. Occasionally, eyes with heterochromia iridis will show additional ocular abnormalities.

Aniridia

Aniridia, or complete absence of the iris, has been reported with congenital cataracts in Thoroughbreds, and as a sole lesion in Quarter Horses and Belgians (Gelatt, 1993; Munroe, 1997; Roberts, 1992; Ueda, 1990). Aniridia, which is characterized clinically by the visualization of ciliary body processes and edge of the lens has been reported to be inherited as an autosomal dominant trait in the Belgian Draft horse, the Quarter Horse, a Thoroughbred, and a Thoroughbred/Welsh cross (Eriksson, 1955; Joyce, 1990). In spite of the terminology, total aniridia is rare and the base of the iris is usually present histologically in most cases. Aniridia in foals is typically bilateral and the lens equator and ciliary processes are generally visible medially and laterally. Discomfort from true photophobia and glare in conditions of bright light may be present because of the inability to regulate light entering the eye. Tinted contact lenses could be used as therapy.

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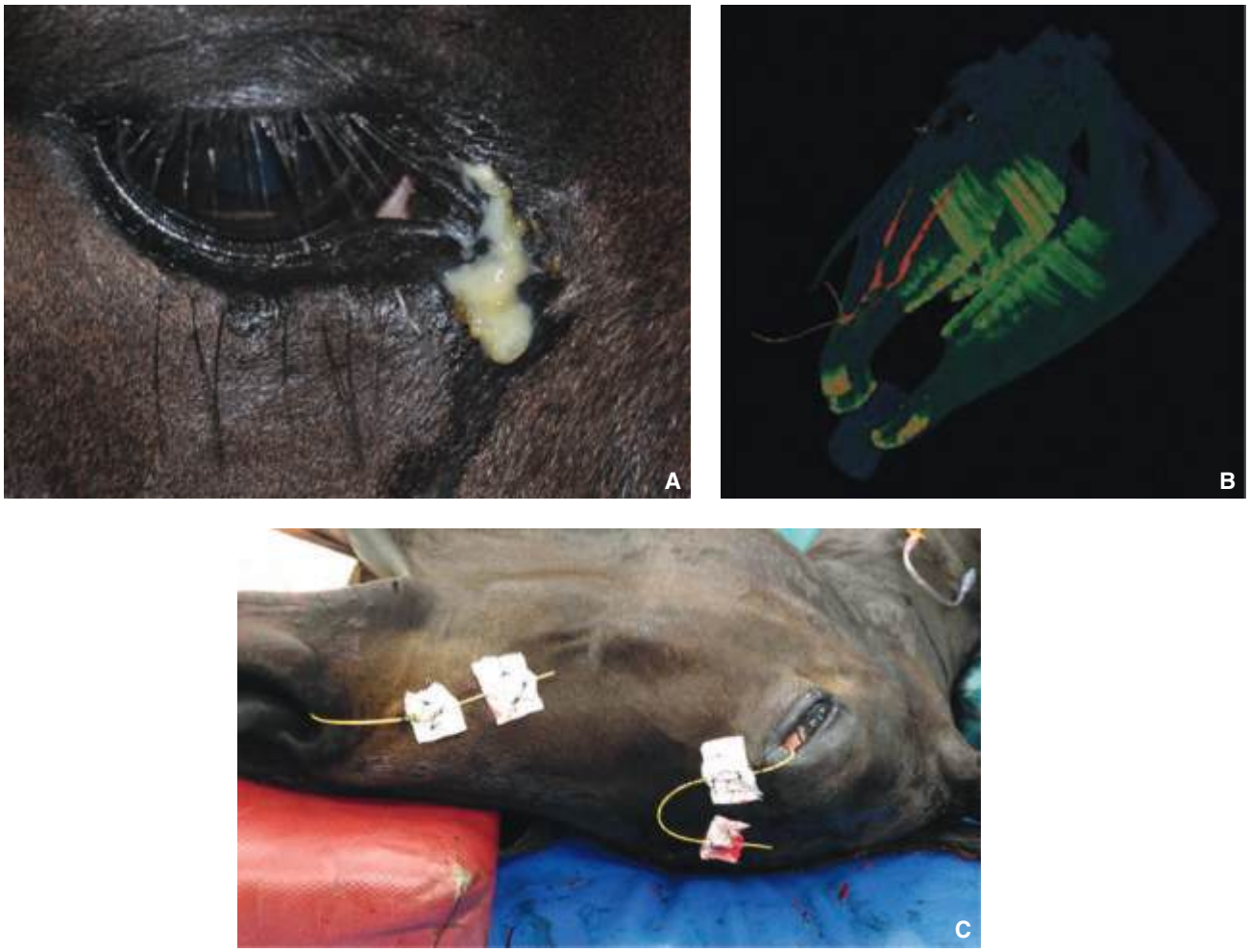


Figure 29.10 Nasolacrimal duct atresia in the foal. **A.** Mucopurulent discharge in a Thoroughbred yearling with unilateral nasolacrimal duct atresia. **B.** Three-dimensional colorized reconstruction of a computed tomography dacryorhinocystogram. These normal nasolacrimal ducts are red in color. Dacryorhinocystography, by radiography or computed tomography, is indicated to locate and characterize the obstruction when the nasolacrimal duct cannot be irrigated, either normograde or retrograde. **C.** 5-French ureteral catheter placed in nasolacrimal duct after neocanalization of the duct with agenesis. The tube is sutured adjacent to the medial canthus and the naris. Alternatively, the distal suture could be directed to exit through a skin incision through the false nostril. Typically, the tube is sutured into place for 4–8 weeks.

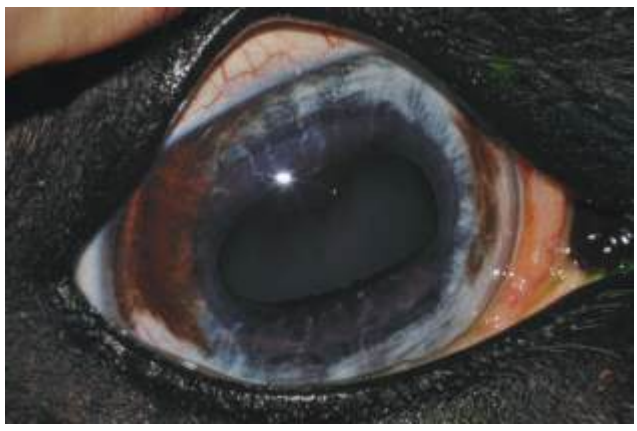


Figure 29.11 Heterochromia in a Quarter Horse. Note the distinct patches of brown and blue of the iris stroma.

Iridal Hypoplasia and Colobomata

Iris colobomas, both typical and atypical, may occur uncommonly in horses but should be differentiated from iris hypoplasia, which is an iris defect commonly observed in lightly pigmented irises (Fig. 29.12A, B). Iridal hypoplasia is a congenital underdevelopment of the iris stroma that appears as thin iris tissue often with holes or defects. In iridal hypoplasia of heterochromic eyes, the affected thin region of iris stroma may appear dark because of the exposure of the posterior pigmented epithelium of the iris and it may appear cyst-like if it balloons into the anterior chamber from the higher pressure of the posterior chamber (Buyukmihci et al., 1992). It is common in Appaloosas, Miniature Horses and ponies, and in blue and heterochromic eyes. A failure of the embryonic optic fissure to close can result in full-thickness

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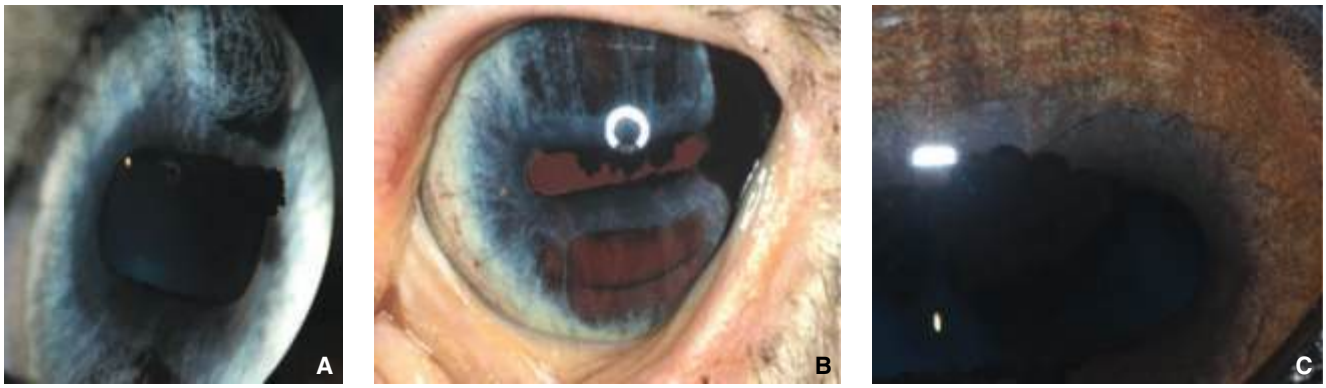


Figure 29.12 Congenital iris abnormalities in foals. **A.** Iris hypoplasia dorsally causes a cystic bulging of the dorsal iris stroma. **B.** In this foal, the hypoplastic iris is so thin that the equator of the lens is visible behind the iris. **C.** Persistent pupillary membranes originating at the iris collarette.

colobomatous defects of the iris stroma, pupillary margin, or both. Typical colobomas occur at the 6-o'clock position of the iris.

Persistent Pupillary Membrane

Persistent pupillary membranes (PPM) are remnants of the anterior tunica vasculosa lentis. They appear as strands of iridal tissue arising from the mid-iris collarette and, in most cases, passing to attach to the iris, though attachment to the lens or cornea is possible (Latimer et al., 1983) (Fig. 29.12C). Nonprogressive corneal opacity results if the PPM adheres to the cornea, or a focal cataract can result if it adheres to the lens. These membranes generally regress to some extent over the first 6–12 months of life, and they require no treatment. Iris-to-iris PPM are very commonly observed in the adult horse.

Anterior Segment Dysgenesis

Anterior segment dysgenesis (ASD) is characterized variably by observation of PPM and may be a component of the MCOA syndrome of Rocky Mountain Horses (Andersson et al., 2008; Ramsey et al., 1999a, 1999b). ASD is associated with a missense mutation in the *PMLE17* gene, oft referred to as the silver dapple gene in the horse (Brunberg et al., 2006). Breeds affected include the Shetland pony, Miniature Horses, Rocky Mountain Horse, Kentucky Mountain Saddle Horse, Mountain Pleasure Horse, Morgan Horse, Bashkir-Curly Horse, Naraganssett Pacer, and Haflinger (Komaromy et al., 2011; Plummer 2011). Chocolate coat color and flaxen mane and tail color are often associated with ASD (Fig. 29.13A). ASD is best described in the Rocky Mountain Horse where it appears to be a co-dominant trait (Ewart et al., 2000; Ramsey, 1999, Ewart 2000). Hypoplasia of the corpora nigra and iris, and temporal iris and ciliary body cysts are found in the heterozygous Rocky Mountain Horse (Fig. 29.13B, C). The homozygous state has congenital miosis with the pupil frequently nonresponsive to mydriatic drugs, deep anterior chamber, macrocornea, ciliary body and retinal cysts, cataract, lens luxation, RPE streaks, and retinal dysplasia/detachment (Komaromy et al., 2011; Ramsey, 1999b) (Fig. 29.13D). Also see Chapter 37, Part 3.

Hyaloid Artery Remnants

Hyaloid artery apparatus consists of the hyaloid artery and the "posterior pupillary membrane" (posterior tunica vasculosa lentis) (Munroe, 2000). Remnants of some segment of this apparatus are apparent to some degree in both eyes of ~80% of Thoroughbred neonates younger than 4 days old. It was perfused with blood in about a third of the eyes at birth and became nonperfused by 48 hours postpartum. These remnants appear as white linear opacities at the surface of the posterior lens capsule. Hyaloid artery remnants may attach to the posterior lens capsule as Mittendorg's dot, or appear as a white structure on the surface of the optic disc as Bergmeister's papilla (Cutler et al., 2000; Munroe, 2000). The vitreal segment of the hyaloid artery is red when perfused and forms a nonpigmented, tube-shaped structure when nonperfused (Cutler et al., 2000) (Fig. 29.14A). Persistence of any part of the hyaloid artery system does not generally cause problems, although small posterior axial cataracts may be present in some eyes as a result (Cutler et al., 2000).

Persistent primary vitreous is an uncommon finding in the horse and appears as an optically dense membranous or tubular structure attached to the posterior lens capsule or, unusually, to the centre of the optic disc (Matthews, 2004a). Persistent hyperplastic primary vitreous, in which dense proliferating fibrovascular mesenchyme-derived tissue remains attached to the posterior lens capsule, causing a pronounced leukocoria, is a very rare finding in the horse.

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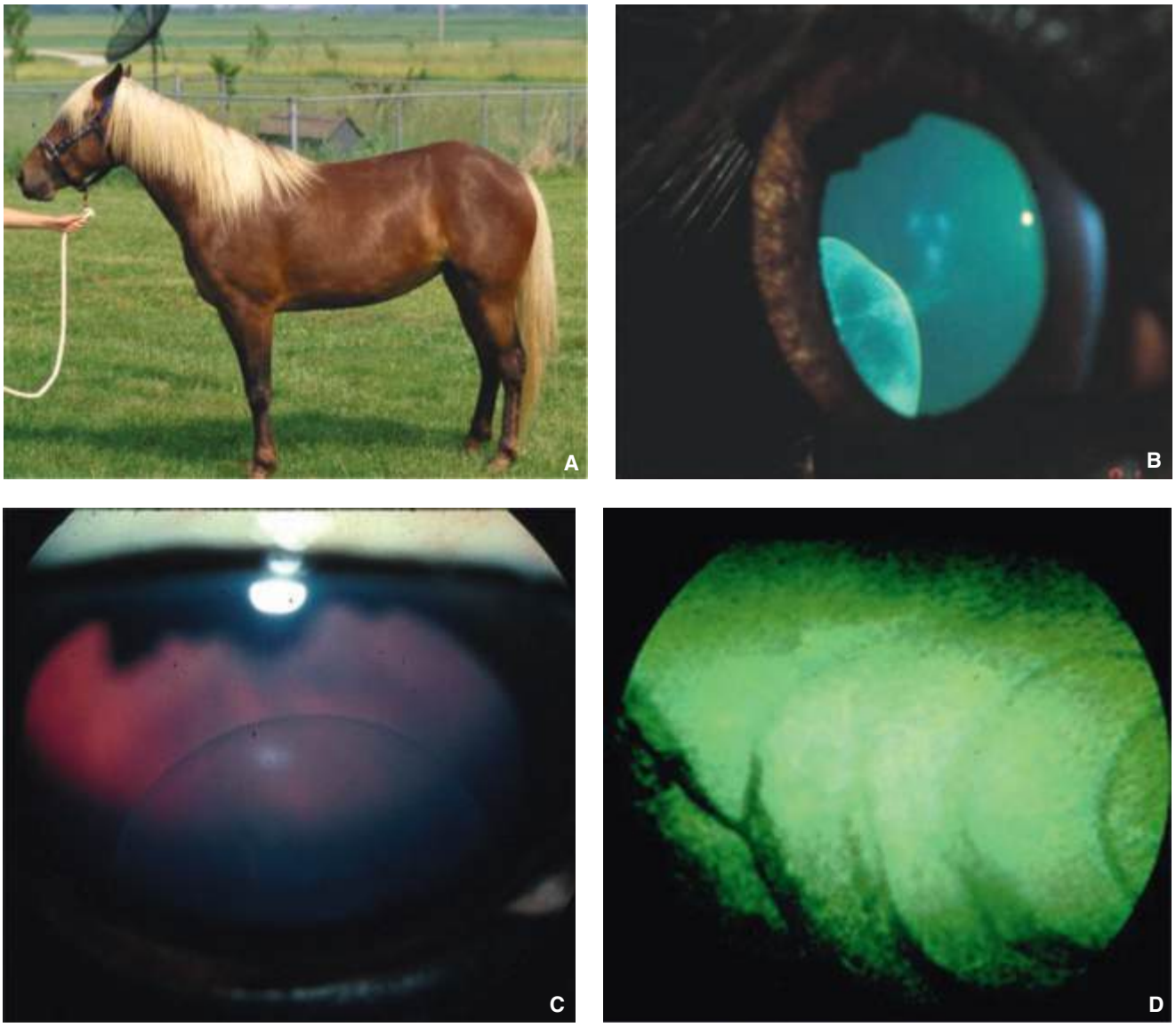


Figure 29.13 Foals affected with multiple congenital ocular anomalies (MCOA). **A.** Individuals with the silver dapple coat color (mutations at the *PMEL* locus) may be affected with anterior segment dysgenesis. Homozygotes tend to be more severely affected than heterozygotes. The chocolate coat color with a flaxen mane and tail is a silver dilute version of a black horse. **B.** Temporal nonpigmented ciliary body cyst in a heterozygous Rocky Mountain Horse. **C.** Large nonpigmented uveal cyst in a silver dapple Miniature Horse. **D.** Retinal pigment epithelium streaks and retinal dysplasia in a homozygous affected Miniature Horse with anterior segment dysgenesis and MCOA.

Cataracts

Congenital defects of the lens may be caused by genetic causes (inherited), toxins, nutritional imbalance, ionizing radiation, inflammation or other idiopathic causes, although these causes have not been well characterized in horses. However, cataracts are the most common congenital abnormality in foals, representing approximately 35% of all congenital ocular defects (Latimer & Wyman, 1985; Latimer et al., 1983; Munroe & Barnett, 1984; Turner, 2004) (Fig. 29.14). Other lens anomalies that have been described in horses include spherophakia, lenticonus, and coloboma. Inherited congenital cataracts have been documented in Thoroughbreds, Quarter Horses, and Morgans (Beech & Irby, 1985; Beech et al., 1984; Colitz & McMullen, 2011). Rocky Mountain Horses can also develop congenital cataracts and lens luxation associated with ASD (Ramsey et al., 1999a). A dominant mode of inheritance has been reported in Belgian as well as in Thoroughbred horses (Gelatt, 1993; Roberts, 1992). Morgan horses have nonprogressive, nuclear, bilaterally symmetrical cataracts that do not seriously interfere with vision (Beech et al., 1984) (Fig. 29.14C).

Healthy foals with cataracts, visual impairment, the personality to tolerate handling and administration of topical

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therapy, and free of active uveitis are candidates for cataract surgery (Brooks, 2005a). Brisk PLRs and a dazzle blink response usually indicate a functional retina. However, a preoperative electroretinography is recommended to confirm retinal function. Ocular ultrasonography is indicated as well to rule out the presence of retinal detachment. Foals should be carefully evaluated for any subclinical infectious systemic diseases, such as *Rhodococcus* pneumonia, because sight-threatening postoperative endophthalmitis may result 7–10 days after surgery if the condition is not detected and treated preoperatively (Brooks, 2005a).

The most common technique for removing congenital cataracts in foals is phacoemulsification. Recent advances in the surgical technique have increased the success rate in foals to nearly 80% (Brooks, 2005a; Dziezyc et al., 1991; Whitley et al., 1990). The logistics of general anesthesia and surgery as well as the surgical success rate are most favorable in foals younger than 6 months of age. Postoperative iridocyclitis is generally quite minimal compared with that found in the dog. However, diligent medical therapy and monitoring is warranted. Corneal ulcers, hyphema, and infectious endophthalmitis are serious potential postoperative complications in foals. The visual outcome of cataract surgery can be difficult to evaluate in young horses as well. Foals left aphakic after cataract surgery are profoundly hyperopic, but in many cases have appropriate visual behavior (Brooks, 2005a; Dziezyc et al., 1991; Farrall & Handscombe,1990; Millichamp & Dziezyc, 1996; Whitley et al., 1990). The placement of artificial intraocular lenses is advocated at present. However, the most ideal dioptric strength to employ is still a matter of debate (Harrington, et al., 2013; McMullen, 2010a; Meister et al., 2018; Townsend et al., 2013).

Congenital Non-Cataractous Abnormalities of the Lens

Ectopia lentis is a rare anomaly caused by failure of the lens vesicle to enter the optic cup during early embryogenesis. The result is the development of disordered lens tissue in a shallow anterior chamber, appearing clinically as dense and generalized anterior segment opacification (Barnett et al., 1995).

Coloboma of the lens, a notch-like discontinuity in the peripheral outline of the lens probably arising from a primary absence of zonule fibres, has been reported as an isolated abnormality in otherwise normal eyes (Gerhards et al., 1992). Coloboma of the lens, lenticonus, and microphakia have been recorded in association with complex microphthalmos in foals (Garner & Griffiths, 1969).

Anterior subepithelial lens cyst is a very rare abnormality which appears to adversely affect vision in some cases (Fig. 29.14D). These cysts arise at the anterior pole of the lens and bulges into the anterior chamber. The capsule is not involved in our experience. Lens cysts may arise from displaced lens capsule and separated lens epithelial cells. Surgical excision of the cyst and entire lens is possible (Brooks, 2002).

Congenital subluxation of both lenses has been reported in an Arab-cross foal with no other ocular abnormalities (Matthews et al., 1983a).

Congenital Glaucoma

Glaucoma is an elevation in IOP that is detrimental to normal ocular function. The reference ranges for normal IOP in horses ranges from 17 to 28 mmHg (Dziezyc et al., 1992; Knollinger et al., 2005; Miller et al., 1990a; van der Woerdt et al., 1995). Elevation in IOP that is incompatible with ocular health results from an obstructed outflow of aqueous humor, eventually resulting in optic nerve damage and blindness. Congenital glaucoma is generally associated with developmental anomalies of the iridocorneal angle (Barnett et al., 1988; Gelatt, 1993; Halenda et al., 1997). No particular breed predisposition has been reported for glaucoma in equine neonates. Glaucoma can also be a sequela to severe or untreated anterior uveitis in foals.

Clinical signs of glaucoma include generalized corneal edema, narrowing or fibrosis of the iridocorneal angle, deep linear and branching corneal band opacities of Descemet's membrane and the posterior stroma, lens luxations, optic nerve cupping, and a fixed, dilated pupil (Barnett et al., 1988; Gelatt, 1993; Halenda et al., 1997). The linear corneal band opacities are a consistent feature of equine glaucoma, and histopathologically represent thin areas of Descemet's membrane. Buphthalmia will occur if IOP is persistently elevated (Fig. 29.15).

Though glaucoma can be treated medically, surgical therapy may be best for foals with ASD. This is a difficult disease to manage in the foal, with little to no chance of preserving vision even if the condition is both detected and treated surgically early in its course. Therapy is directed at decreasing the IOP by reducing the production of aqueous or, more importantly, by increasing outflow of aqueous humor.

Aqueous production should be reduced with a beta-adrenergic antagonist and a topical carbonic anhydrase inhibitor. Topical cholinergics and prostaglandin drugs may exacerbate iridocyclitis and should only be used with caution.

Surgical therapy for equine glaucoma is directed at reducing the production of aqueous humor by damaging the ciliary body with laser energy (i.e., cyclophotocoagulation). High-flow gonioimplants may be considered to increase the aqueous outflow in foals; modified canine or dual-tube gonioimplants have been used successfully in glaucomatous horses (Brooks, 2002). Chronically painful and blind, buphthalmic globes should be enucleated.

Congenital Disorders of the Posterior Segment

Fortunately, congenital abnormalities of the equine posterior segment are uncommon and rarely have clinical significance,

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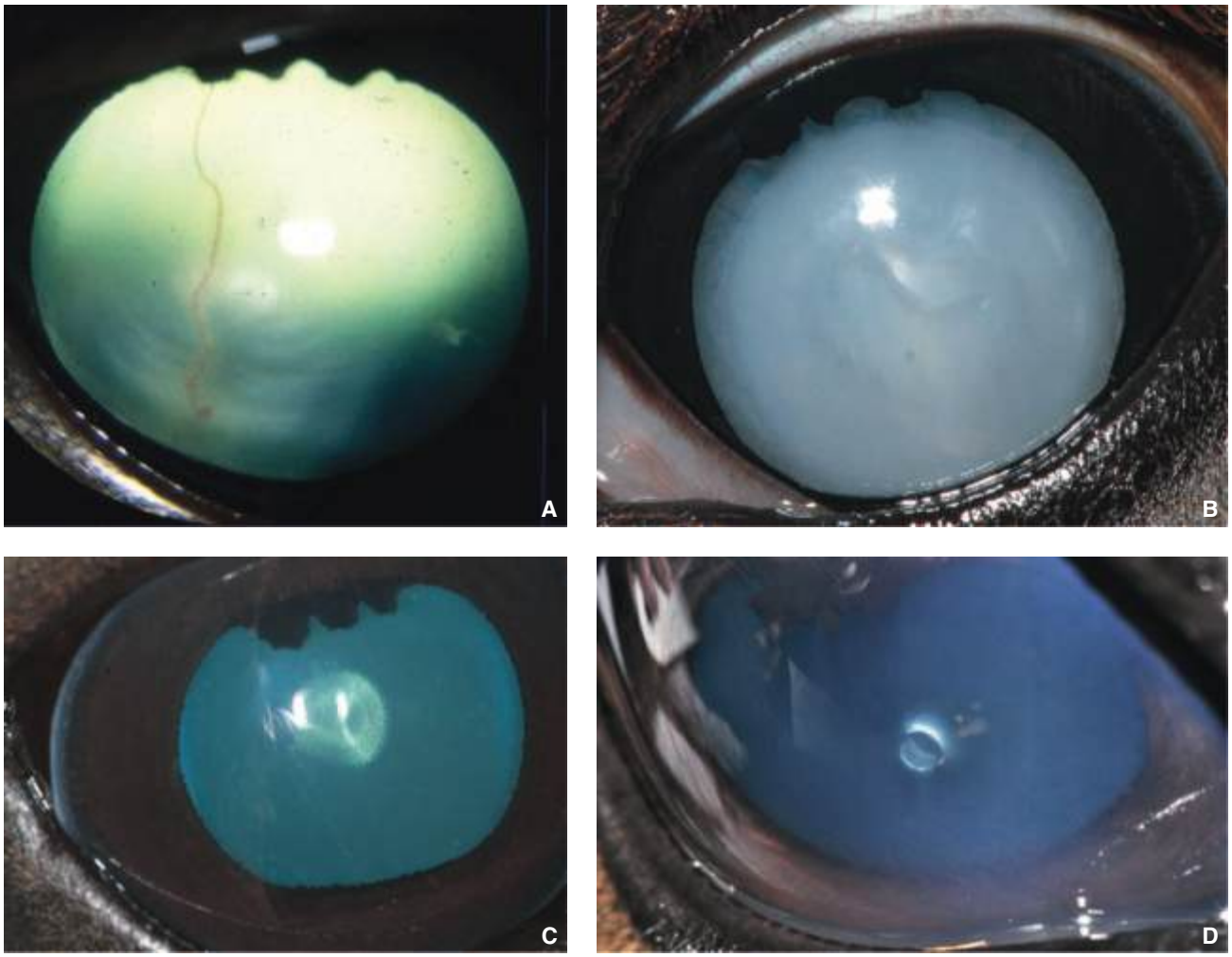


Figure 29.14 Congenital cataracts in foals. **A.** Remnants of the tunica vasculosa lentis remains perfused on the posterior lens capsule of this yearling. **B.** Advanced immature cataract in a Thoroughbred foal. **C.** Inherited nuclear cataract in a Morgan Horse. **D.** Axial anterior lens cyst.



Figure 29.15 Corneal edema from congenital glaucoma in a foal.

such as the case with focal colobomas (Fig. 29.16A). Other defects, such as congenital retinal detachment, retinal dysplasia, congenital stationary night blindness, and the MCOA syndrome (i.e., the Rocky Mountain Horse syndrome) may be associated with vision loss (Ramsey et al., 1999a; Wilkie, 2011).

Retinal dysplasia is an *in utero* developmental or postinflammatory problem of the retina in which the sensory retina is "folded" to form rosettes of neural tissue. Retinal dysplasia in foals is generally bilateral and often associated with other congenital ocular problems (Gelatt, 1993; Roberts, 1992). Heritability studies are lacking but the incidence of retinal dysplasia in foals is low, suggesting minimal genetic influence. Retinal dysplasia can appear as either single or multiple, or linear or geographic foci or regions of hyporeflective folds or hyperreflective thinning on ophthalmoscopy (Fig. 29.16B).

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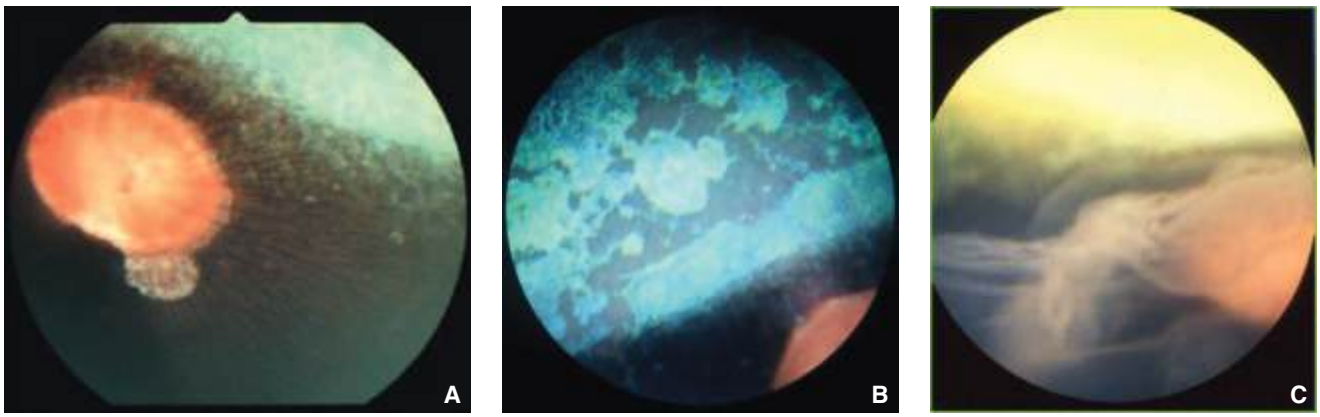


Figure 29.16 Ocular fundus abnormalities in the foal. **A.** Focal peripapillary retinal pigment epithelium coloboma. This is a common congenital abnormality without known clinical significance. **B.** Retinal dysplasia in a Thoroughbred foal. **C.** Congenital retinal detachment in a foal. The retina is torn and appears as a convoluted opaque membrane.

Retinal detachments may be either unilateral or bilateral, and they can be associated with other ocular abnormalities (Fig. 29.16C). The detached retina can be observed through the dilated pupil as a floating veil of opaque tissue in the vitreous. If the detachment is bilateral, the foal will be blind at birth and may have nystagmus. Congenital, inflammatory, and traumatic causes have been reported (Cutler et al., 2000; Matz-Rensing, 1996; Rebhun, 1992a). Standardbreds appear predisposed (Cutler et al., 2000). They may also be hereditary or associated with multiple ocular abnormalities.

Atypical retinal colobomas have been noted, both singly or in groups, in the tapetal and non-tapetal fundic regions in foals. They are usually reported to be unilateral (Rebhun, 1992a). Visual hemifield deficits were reported in one horse with a large coloboma near the optic nerve head (Rebhun, 1992a).

Congenital stationary night blindness has been reported in Appaloosas, Quarter horses, Miniature Horses, and horses with leopard complex spotting (Bellone et al., 2008; Ludwig et al., 2015; Rebhun et al., 1984; Sandmeyer et al., 2007, 2012; Witzel, 1978; Witzel et al., 1977). It has also been reported in a Thoroughbred and a Paso Fino (Nunnery et al., 2005). The fundus appears to be structurally normal, with characteristic, a-wave-dominant electroretinographic patterns confirming the diagnosis. A defect in neural transmission between the photoreceptor layers and the bipolar cells is suspected. Vision is severely diminished in reduced light levels, but functional in bright light. Day blindness, though infrequent, has also been reported (Gelatt, 1993). Microphthalmia, strabismus, and nystagmus may be present as well. The mode of transmission is still under investigation. However, homozygosity for the incompletely dominant allele LP (also responsible for leopard complex spotting) is associated with congenital stationary night blindness (Audo et al., 2009; Bellone et al., 2008; Munroe, 1997; Munroe & Barnett, 1984; Sandmeyer et al., 2005; Witzel et al., 1977). Decreased expression of the *TRPM1* gene is likely responsible for both ocular and pigmentation changes (Bellone et al., 2008).

Optic nerve hypoplasia and optic nerve atrophy in foals may be secondary to developmental or inflammatory processes. Foals with optic nerve hypoplasia display smaller-than-normal discs, have slow PLRs, mydriasis, and depending on the degree of hypoplasia, may retain some vision. Foals with optic nerve atrophy will be blind with fixed, dilated pupils, have pale discs with no retinal vessels, and posterior depression of the optic disc of several diopters. Blind foals may display a searching nystagmus. Bilateral optic nerve colobomas were noted in one Quarter Horse filly (Bildfell et al., 2003). The cause is a congenital lack of retinal ganglion cell development or excessive destruction of embryonic ganglion cells.

Acquired Ocular and Adnexal Problems in the Foal

Blepharitis

Dermatophytosis, dermatophilus, and staphylococcal folliculitis can cause the blepharitis or eyelid inflammation of foals (Munroe, 1997). Alopecia, excoriation, and depigmentation are associated with fly-bite blepharitis in foals (Latimer et al., 1983). Trauma, fire, and excessive head rubbing are associated with blepharitis in foals and adult horses (Fig. 29.17A, B).

Entropion/Ectropion

Entropion is inversion of the margin of the lower or upper eyelids. It may occur in foals as a primary anatomic condition

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or be secondary to the enophthalmos associated with microphthalmos or prematurity/dysmaturity. Severe lid scarring after eyelid trauma can cause entropion. Rolling in of the eyelid margin may occur with dehydration or malnutrition in systemically compromised foals. It is the most common eyelid abnormality in foals and is most commonly exhibited in only the lower eyelid. However, it may affect the upper eyelid in Miniature Horses (Fig. 29.17C, D). Ocular pain may cause spastic entropion which may exacerbate the degree of anatomic entropion present. Entropion may result in increased lacrimation, blepharospasm, conjunctivitis, or corneal ulceration. Treatment involves physical eversion of the eyelid margin with temporary, nonabsorbable sutures in a vertical mattress pattern (4-0 silk) or with surgical staples until the underlying etiology has resolved or the foal has outgrown its entropion (Miller, 1999; Plummer, 2005). Permanent reconstructive entropion surgeries should be reserved for full grown individuals (Plummer, 2005). Blepharoplastic procedures may be necessary in cases of primary anatomic entropion or in those resulting from extensive trauma.

Ectropion is eversion of the lower or upper eyelid margins and generally follows scarring of the eyelids from severe trauma or burns. It is less common than entropion (Fig. 29.17E and Fig. 29.18). Surgical correction is necessary for ectropion if blepharospasm, corneal ulcers, or exposure keratoconjunctivitis are present.

Eyelid Trauma

Traumatic eyelid lacerations and forehead trauma can occur in foals and adults (Fig. 29.19). Upper eyelid lesions are more serious than lower eyelid injuries, because upper eyelid provides the greater degree of globe protection and its movement distributes tear film to prevent exposure keratitis. Thus, preserving the eyelid margins to prevent trichiasis and exposure-induced ulcerative keratitis is critical (Miller, 1999; Plummer, 2005). Excision of lacerated pedicles of eyelid marginal tissue should be avoided. The prominent blood supply to the eyelids generally allows acceptable and functional surgical repair, as well as quick healing. Wounds should be gently cleansed with 0.5% povidone-iodine solution, and systemic antibiotics should be administered. Two-layer closure of skin–orbicularis muscle and tarsoconjunctival layers is recommended to maximize healing and return to function (Miller, 1999; Plummer, 2005).

Dacryocystitis

Dacryocystitis is inflammation of the tear drainage system. Obstruction of the nasolacrimal apparatus is the most common cause of dacryocystitis and secondary infection often develops. Copious mucoid to mucopurulent discharge at the medial canthus is the typical presenting sign. This condition is treated by flushing of the tear drainage system to re-establish patency and then administering systemic antibiotics and anti-inflammatory medications. Topical steroids and mucolytic agents if they are formulated as solutions or suspensions so that they can pass through the duct may be helpful.

Conjunctivitis and Subconjunctival Hemorrhage

Conjunctivitis caused by environmental irritants (e.g., hay, sand, dirt, ammonia, pollen, ash) is common in neonates, with recumbent foals being at particular risk. Conjunctival inflammation secondarily associated with pneumonia or other systemic infectious and inflammatory conditions is often found in older foals (i.e., 1–6 months of age). Contributing etiologic agents may include adenovirus, equine herpesvirus (EHV)-1, equine viral arteritis, influenza virus, *Streptococcus equi* subspecies *equi* (Strangles), *Rhodococcus*, and *Actinobacillus* spp. (Brooks, 2002; Gelatt, 1993). Epiphora, chemosis, and hyperemia are typical clinical signs. If bacterial conjunctivitis is present, the ocular discharge will become mucopurulent. Conjunctival cytology and culture can be useful in making the diagnosis of infectious conjunctivitis. Therapy begins by flushing the conjunctival sacs to remove any underlying irritant. Patency of the NLD should be established, because duct obstructions can exacerbate conjunctivitis. Broad-spectrum antibiotic ophthalmic solutions or eye lubricants are indicated, and corticosteroid ophthalmic preparations are useful if there are no corneal ulcers present.

Subconjunctival or episcleral hemorrhages can result from birthing trauma and generally resolve in 7–10 days. No treatment is necessary. Traumatic hemorrhages are generally quite large and must be differentiated from the petechial or ecchymotic hemorrhages suggestive of a coagulation disorder. Episcleral hemorrhages are also associated with neonatal maladjustment syndrome in foals (Latimer et al., 1983).

Ulcerative Keratitis in Foals

A corneal ulcer is present when there is a break in the corneal epithelium, most commonly caused by trauma. The clinical appearance of a corneal ulcer, to the casual observer, includes increased lacrimation, blepharospasm, photophobia, conjunctival hyperemia, and ocular cloudiness, likely from development of corneal edema, aqueous flare, and possibly hypopyon (depending upon the degree of associated anterior uveitis). Foals, especially those under intensive care, should be monitored for the development of corneal ulcers. Foals with corneal ulcerations generally will exhibit less intense pain, blepharospasm and tearing than their adult counterparts (Brooks et al., 2000a). This is likely because of immature sensory innervation. The corneal

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Figure 29.17 Eyelids abnormalities. **A.** Blepharoedema from self-trauma in a foal. **B.** Blepharitis with lid swelling, skin ulcerations and hair loss after a fire. **C.** Severe lower lid entropion and blepharitis in a foal. A corneal ulcer is present. Note the corneal edema and infiltrate ventrally. **D.** The entropion was corrected with temporary tacking vertical mattress sutures. **E.** Cicatricial ectropion from a barn fire. Lid movement was normal but forehead scarring prevented the upper lid from protecting the cornea.

surface of superficial ulcers can appear dull, cloudy, and roughened. In rapidly progressive or infected ulcers, the corneal stroma may appear "melting," as the result of keratomalacia (Fig. 29.20A).

Although many types of ulcers in foals are sterile, every corneal wound is susceptible to infection with bacterial and fungal pathogens. Diagnostic testing to look for involvement of these agents should always be performed. A superficial corneal ulcer that does not improve rapidly in 24–48 hours, rough ulcer margins, increasing stromal opacification, deepening of the ulcer, and difficulty maintaining mydriasis are often signs of ulcer infection (Brooks, 2002). The diagnosis

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Figure 29.18 Lower lid ectropion in a horse.

of a corneal ulcer is confirmed with the application and retention of fluorescein dye on the cornea (Fig. 29.20B). It is strongly recommended that swabs for microbiologic cultures and susceptibilities as well as corneal scrapings for cytology be obtained to initiate appropriate medical therapy (Fig. 29.20C).

Medical therapy for foals with ulcerative keratitis does not differ substantially from that initiated for corneal ulcers in adults. Bacterial and fungal growth must be halted or prevented with antimicrobial agents. Anterior uveitis must be controlled for comfort and to prevent blinding sequelae. Anterior uveitis in foals with corneal ulcers should be treated with both topical atropine and systemic nonsteroidal anti-inflammatory drugs (NSAIDs). However, the dose and frequency should be carefully administered and the foals monitored closely because they are more susceptible to the development of gastric ulcers from stress which may be exacerbated by NSAIDs and gastrointestinal stasis from atropine (Williams et al., 2000). A reduction in the tear film and stromal protease activity is also critical to healing of corneal ulcers in foals, particularly because they are prone to the development of melting ulcers. Melting ulcers in foals may be sterile (whereas those in adults are usually infected). However, they may progress rapidly and catastrophically if the enzymes responsible for corneal degradation are not arrested. The appearance of a gray, mucoid, gelatinous corneal exudate should prompt immediate action. Autogenous serum from the foal or its mare may also be quite effective in arresting corneal melting when administered topically every hour. Five percent acetylcysteine or 0.17% dipotassium ethylenediaminetetraacetic acid (EDTA) may be used as well until stromal liquefaction is reduced. Combinations of these anticollagenase drugs should also be considered if the ulcers are rapidly progressive. Surgery should be considered if the integrity of the cornea is deeply compromised. Treatment must be sustained until the stroma has firmed and the epithelium has completed regenerated.

Noninfectious Persistent Corneal Erosions in Neonates

Very slow-healing, persistent, superficial corneal ulcers are commonly encountered in recumbent, premature, and neonatal foals. These ulcers or erosions often fail to vascularize and affected foals may not exhibit a great deal of discomfort. Diminished corneal sensitivity and low tear production in these foals may be associated with the delayed corneal

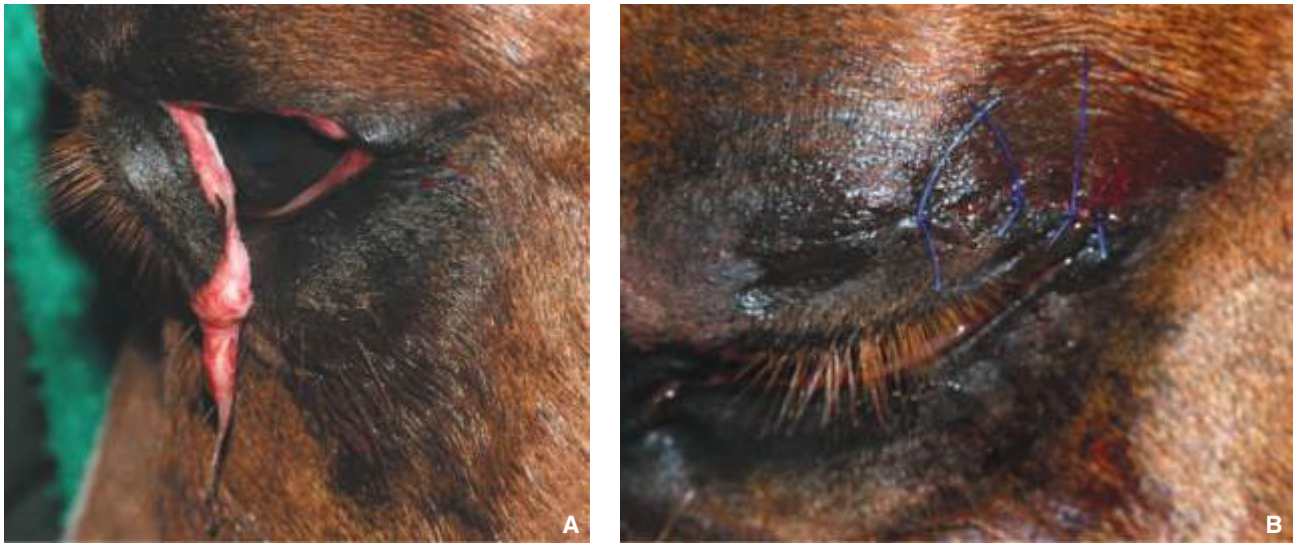


Figure 29.19 **A.** Severe upper lid laceration in a horse. **B.** Surgical repair of the laceration improved function and appearance.

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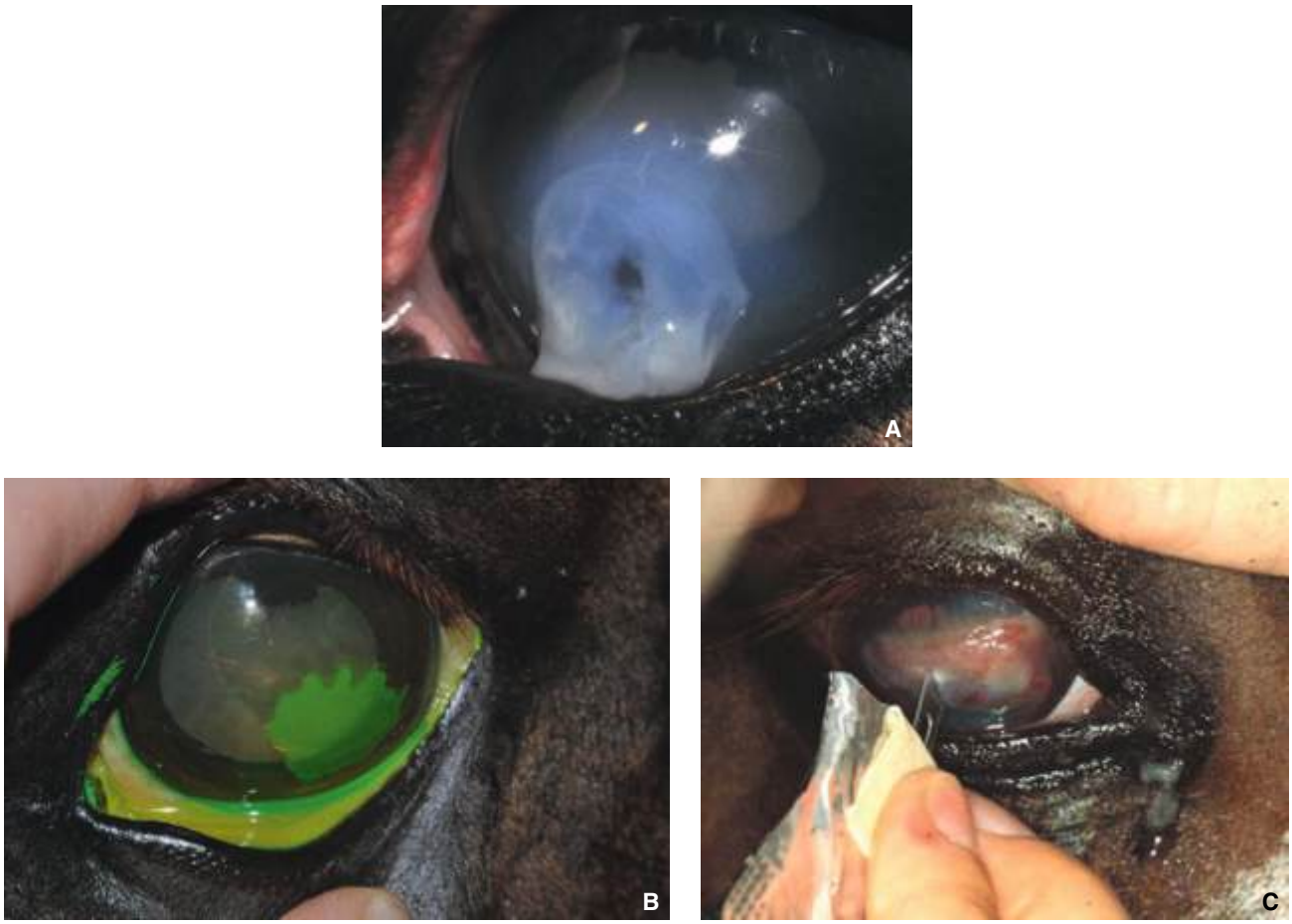


Figure 29.20 Corneal ulcerations in foals. **A.** Melting ulcer (keratomalacia) in a foal. The dark foci is a very thin area in the center of the wound; **B.** Fluorescein retention delineates the borders of a corneal ulcer. **C.** For corneoconjunctival cytology, scrapings may be obtained using a Kimura platinum spatula, a Dacron swab, the blunt end of a Beaver blade, or a cytobrush. This image shows use of the back-end of a scalpel blade to collect cells and material from the periphery of a corneal wound.

healing of these superficial ulcers (Brooks et al., 2000a; De Haas, 1962; Mackie, 1978). These ulcers are noninfectious initially but susceptible to secondary infection as an open wound. Infections will cause slow healing of a corneal ulcer, and corneal cytology and culture are recommended for all foals with slow-healing persistent ulcers. Distichia or ectopic cilia are infrequently found among foals, but they can cause persistent ulcers. The conjunctival sacs and the area posterior to the nictitans should be carefully checked for foreign objects (e.g., dirt, sand). If the foals are blinking poorly, or keratoconjunctivitis sicca or entropion is present, corneal ulcers will also heal slowly.

Therapy is directed at treating any underlying cause (such as tacking sutures from entropion), removing abnormal epithelium, and promoting adhesion of the epithelium to its basement membrane and the stroma. The cornea should be topically anesthetized and the loose abnormal epithelium gently debrided with dry, soft cotton swabs. Debridement may need to be repeated or may require a more aggressive approach and the use of a diamond burr to minimize any suprastromal membrane that may be inhibiting epithelial migration and adhesion.

Contact lenses and collagen shields are available in sizes suitable for foals (diameter, 26–32 mm), and they can serve as corneal bandages to aid the healing of superficial ulcers by supporting epithelial cell migration. Eye masks that cover the ulcerated eye are recommended to diminish environmental dust and fly exposure and to reduce the risk of damage from the foal rubbing its eye.

Antibiotic solutions are indicated to prevent infection. Triple antibiotic solutions are appropriate, although solutions containing gentamicin should be avoided as they can retard corneal healing (Berry et al., 1995). Five percent sodium chloride ophthalmic preparations are beneficial in removing the superficial corneal edema associated with persistent ulcers, and topical autogenous serum or plasma with its growth factors and anticollagenase activity can promote epithelial growth and prevent stromal melting from tear proteases

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(Berman et al., 1975; Brooks, 2004 Cutler, 2004; Haffner et al., 2003; Kirschener, 1989; Ollivier, 2004; Ollivier et al., 2004; Phan et al., 1989). If healing stagnates despite debridement and medical therapy, a keratectomy may be indicated.

Iridocyclitis in Foals

Systemic disease can cause blinding iridocyclitis in foals; therefore, early recognition, diagnosis, and therapy are imperative. Septic foals or those with another systemic inflammatory disease such as pneumonia may be afflicted with anterior uveitis as a manifestation of their systemic disease. *Salmonella* sp., *Rhodococcus equi*, *Escherichia coli*, *Streptococcus equi* subspecies *equi*, *Actinobacillus equuli*, adenovirus, and equine viral arteritis have all been associated with uveitis in affected foals (Gelatt, 1993).

Lacrimation and blepharospasm are usually the signals of ocular involvement and will accompany corneal edema, conjunctival hyperemia, ciliary injection, aqueous flare, hyphema, fibrin, and hypopyon in eyes with iridocyclitis. Miosis is evident initially as the hallmark of uveitis and it can result in dyscoria as well as in anterior and posterior synechiae. Fibrin and pigment deposition on the anterior lens capsule and cataract formation are sequelae to anterior uveitis in foals.

As long as a corneal ulcer is absent, topical corticosteroids are the treatment of choice for anterior uveitis and these are usually accompanied by mydriatic/cycloplegics, and systemic NSAIDs (as long as the systemic condition of the foal warrants their use). If a corneal ulcer is present, this precludes the use of topical corticosteroids but not topical NSAIDs.

Many foals with systemic disease will develop fibrinous uveitis (Fig. 29.21). Fibrin may fill the anterior chamber and span the pupil, increasing the chances of synechia and cataract formation. If routine anti-inflammatory therapy does not result in rapid degradation of the anterior chamber fibrin (48–72 hours), intracameral administration of 25–150 µg tissue plasminogen activator (tPA) via 27 or 30-gauge needle introduced into the anterior chamber at the limbus under heavy sedation or general anesthesia may be used to accelerate fibrinolysis and clear the anterior chamber of foals with severe iridocyclitis. Tissue plasminogen activator should be avoided if recent hemorrhage (<48 hours) is present, but can still be effective up to 2 weeks after clot formation.



Figure 29.21 Fibrinous uveitis in a foal with *Rhodococcus* pneumonia. Fibrin in the anterior chamber is obscuring visualization of the iris and pupil.

Depending on the cause, the overall prognosis for anterior uveitis is guarded in foals, depending upon its severity and response to therapy. The owner should be educated about the possibility of vision loss and other potential complications.

Diseases of the Retina/Optic Nerve in Foals

Hypoxic ischemic encephalopathy or neonatal maladjustment syndrome is commonly associated with small and round retinal hemorrhages, hemorrhages on the optic disk, pupil asymmetry, corneal edema, and ulcerative keratitis. Hemorrhages associated with hypoxic ischemic encephalopathy disappear in several days if the foal survives (Cutler et al., 2000; Gelatt, 1993; Munroe & Barnett, 1984).

Chorioretinitis may be noticed in foals born to mares suffering from respiratory and other systemic diseases during late gestation (Rebhun, 1992a). Peripapillary, small, circular lesions with a hyperpigmented center and a depigmented peripheral ring characterize these chorioretinal scars (Slater et al., 1995).

Hemorrhage in the posterior segment (retina, vitreous) is common in neonates. In recent studies, as many as 11%–13% of neonates examined had retinal hemorrhages, which are typically attributed to birthing trauma (Barsotti et al., 2013; Labelle et al., 2011) (Fig. 29.22).

Equine Orbit in Adults

The adult equine orbit is 62.1 mm in width, 59.4 mm in height and 98.3 mm in depth (Samuelson, 1999). The globe of the equine eye is larger in the horizontal (48.4 mm) than the vertical (47.6 mm) diameter (Prince et al., 1960). The mean anterior to posterior diameter is 43.7 mm. The volume of the equine globe ranges between 45.0 and 50.9 mL (Lavach, 1987). The volume of the anterior chamber is 3.04 ± 1.27 mL and the volume of the vitreal chamber is 26.15 ± 4.87 mL. The orbits and globes of the horse skull are directed anteriorly, slightly dorsal, and are positioned 80 degrees lateral to the midline to allow for wide panoramic vision. The orbits of the skull are bony cavities formed by the frontal, lacrimal, zygomatic, temporal, sphenoid, and

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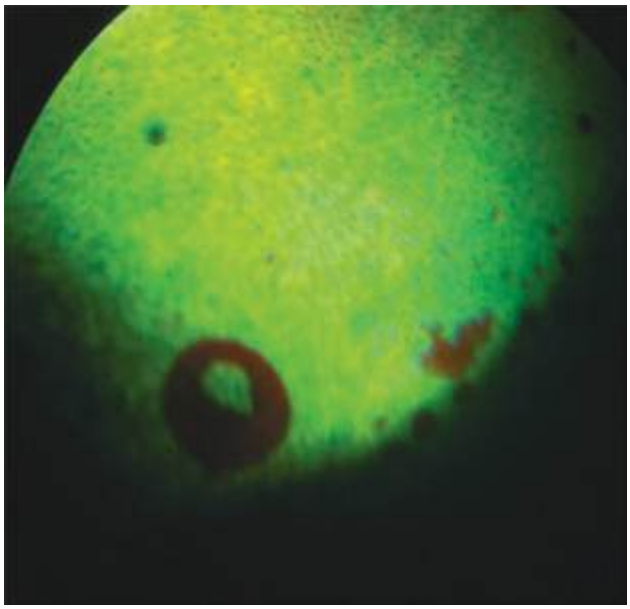


Figure 29.22 Retinal hemorrhages from birthing trauma in a foal.

palatine bones, and function to protect the globe (Diesem, 1968; Prince et al., 1960; Samuelson, 1999). The orbits of the horse are open anteriorly, closed posteriorly, possess a soft tissue ventral floor, and contain osseous canals, fissures, and foramina (Diesem, 1968; Prince et al., 1960; Samuelson, 1999). Sinuses surround the orbit.

The anterior rim of the bony orbit is complete in the horse (Diesem, 1968; Prince et al., 1960; Samuelson, 1999). The nasal wall is extensive and formed by the frontal, lacrimal, and presphenoid bones. The roof or dorsal wall is formed by the frontal and, to a small degree, the lacrimal bone. The orbital floor or ventral wall consists anteriorly of the zygomatic bone and the zygomatic process of the temporal bone, with the larger posterior orbital floor consisting of soft tissue formed by periorbital fascia (Koch, 1980). The zygomatic arch, formed by the zygomatic process of the frontal bone, the frontal process of the zygomatic bone, and the zygomatic process of the temporal bone, closes the temporal orbital wall (Koch, 1980; Samuelson, 1999). This complete bony orbital rim anteriorly and bony orbital walls posteriorly is a factor in the horse sustaining comparatively more orbital fractures than in other domestic animals. Because of this bony protection and strong extraocular muscles, horses rarely develop other orbital trauma other than penetrating injury.

The zygomatic process of the frontal bone contains the supraorbital foramen which carries sensory nerve fibers to the upper eyelid (Diesem, 1968; Koch, 1980; Prince et al., 1960; Samuelson, 1999). The frontal sinus is contained inside the frontal bone. The lacrimal bone forms the nasal part of the anterior orbital rim and the anterior ventral surface, contains the entrance to the lacrimal canal, and is the site of origin for the ventral oblique muscle. The sphenoid bones form the nasal, posterior, and ventral orbital boundaries. The optic nerve and internal ophthalmic artery pass in the optic canal of the presphenoid bone and enter the orbit at the optic foramen. The basisphenoid bone is associated with the orbital and round foramina, the alar canal, the maxillary artery and nerve, and the cavernous sinus.

The extreme posterior orbit contains the ethmoidal foramen with the ethmoidal vessels and nerve, the optic foramen with the optic nerve and internal ophthalmic artery, the orbital foramen with cranial nerves III through VI, the round foramen and the maxillary nerve, and the rostral alar foramen with the external ophthalmic and maxillary arteries (Prince et al., 1960; Samuelson, 1999). The maxillary, sphenopalatine, and major palatine foramina, and their associated blood vessels and nerves are found ventral to the anterior portion of the orbital cavity in the pterygopalatine fossa (Prince et al., 1960; Samuelson, 1999).

The orbital system functions as a precise and complex unit. An extensive system of orbital connective tissues forms a framework for the compartmentalization and support of all orbital structures in order to maintain appropriate anatomic relationships, and to allow for the precise and coordinated globe movements (Dutton, 1996; Koch, 1980). The essential components of the orbital connective tissues are the periorbita, the orbital septum, and the episcleral fascia or Tenon's capsule. Periosteum lines the orbital bones, and the optic and orbital foramina (Dutton, 1996; Samuelson, 1999). Applied to the inner surface of the periosteum are multiple layers of orbital connective tissue called periorbita. The inner layers of the periorbita continue anteriorly as the orbital septum, which separates from the periosteum at the lid margin to continue into the lid as the tarsal plate. The optic nerve is contained within a dural sheath that is continuous at the orbital apex with the periosteum of the optic canal. Well-developed fascial slings of the orbital septum form suspensory complexes with orbital fat to maintain precise extraocular muscle alignment as the globe moves (Dutton, 1996). Tenon's capsule is also termed episcleral fascia and is located between the conjunctiva and sclera. Tenon's capsule begins anteriorly at the perilimbal sclera and extends around the globe to the optic nerve where it blends with fibers of the dural sheath and sclera (Dutton, 1996; Samuelson, 1999). It is firmly adherent to the episcleral tissue anterior to the scleral insertions of the rectus muscles (Dutton, 1996; Koch, 1980; Samuelson, 1999).

The frontal sinus is located dorsal and ventral to the medial orbit. The maxillary sinus is located ventral and nasal to the orbit. The bony plate between the orbit and maxillary sinus is very thin (Dutton, 1996). The anterior maxillary sinus can be located just ventral to the intersection of a line between the medial canthus and infraorbital foramen, and a perpendicular line from the fourth cheek tooth (Lavach, 1987) (Fig. 29.23). Trephination dorsal to a line between the

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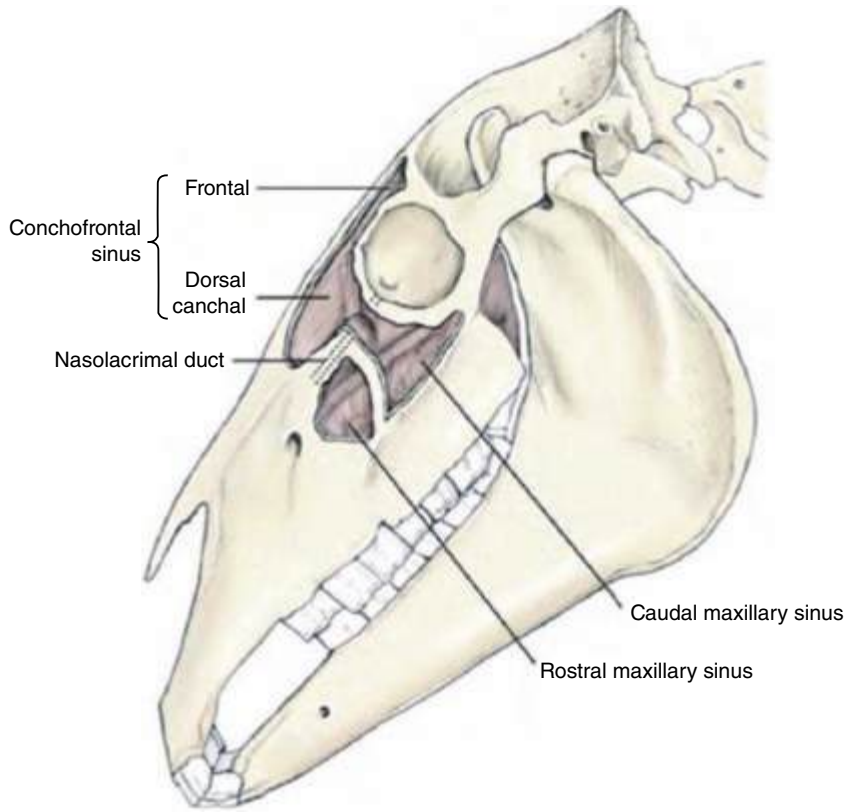


Figure 29.23 Periorbital sinuses. The frontal (conchofrontal), maxillary (caudal and rostral), and sphenopalatine, are in close anatomic proximity to the orbit. (*Source*: With permission from Gilger, B (2011) Diseases and surgery of the orbit. In: *Equine Ophthalmology* (ed. Gilger, B.C.), 2nd ed. Philadelphia: Elsevier.)

infraorbital foramen and medial canthus can result in NLD damage. The center of a line between the medial canthus and facial crest indicates the location of the caudal maxillary sinus. The sphenopalatine sinus is located medial and ventral to the orbit. With the exception of the anterior maxillary sinus, all sinuses in the horse communicate with one another (Diesem, 1968; Lavach, 1987). Sinus disease involving the frontal, maxillary, or sphenopalatine sinuses may intrude upon the orbit of horses (Diesem, 1968; Lavach, 1987). The large paranasal sinuses adjacent to the orbit are a common location for infection, neoplasia, and other clinical abnormalities that result in swelling of tissues that frequently impinge on the orbital structures.

The lacrimal gland, orbital fat, and connective tissue fascia completely fill the orbital spaces between the globe, extraocular muscles, optic and other cranial nerves, and orbital vascular elements of horses to provide a cushion that protects these delicate structures from injury during ocular movements. The lacrimal gland is situated dorsolaterally between the zygomatic process and the globe (Diesem, 1968). It is separated from the globe by periorbital fascia and opens via 12–16 small ducts along the lateral part of the conjunctival sac in a line anterior to the dorsal conjunctival fornix (Diesem, 1968). Care should be taken when making conjunctival flaps or when placing subpalpebral lavage systems in this area as damage to these ducts could result in a tear insufficiency problem. There is no orbital salivary gland in the horse (Diesem, 1968). A cushion of fat lies in the ventral equine orbit (Diesem, 1968).

Orbital disease processes can occur within the extraocular muscle cone (i.e., intraconal), between the muscle cone and periorbital sheath, or external to the periorbital sheath (i.e., subperiosteal). Infectious, traumatic, inflammatory, or neoplastic disease processes involving the eyelids, paranasal sinuses, tooth roots, guttural pouch, or nasal cavity may extend into the orbit, thereby causing exophthalmus or strabismus (or both). Strabismus in adult horses may be associated with visual difficulties and abnormal head posture (Lavach, 1987). Fractured walls of the paranasal sinuses can result in orbital emphysema, and tooth-root abscesses may cause sinus and orbital disease.

Orbital disease processes can result in exophthalmos because of space-occupying orbital lesions, or enophthalmos if the volume of the orbital contents decrease because of malnutrition or pathology (Fig. 29.24). Both the degree and direction of exophthalmos depend on the size and location of the lesion. Intraconal lesions cause anterior displacement of the globe, whereas lesions of the medial orbit displace the

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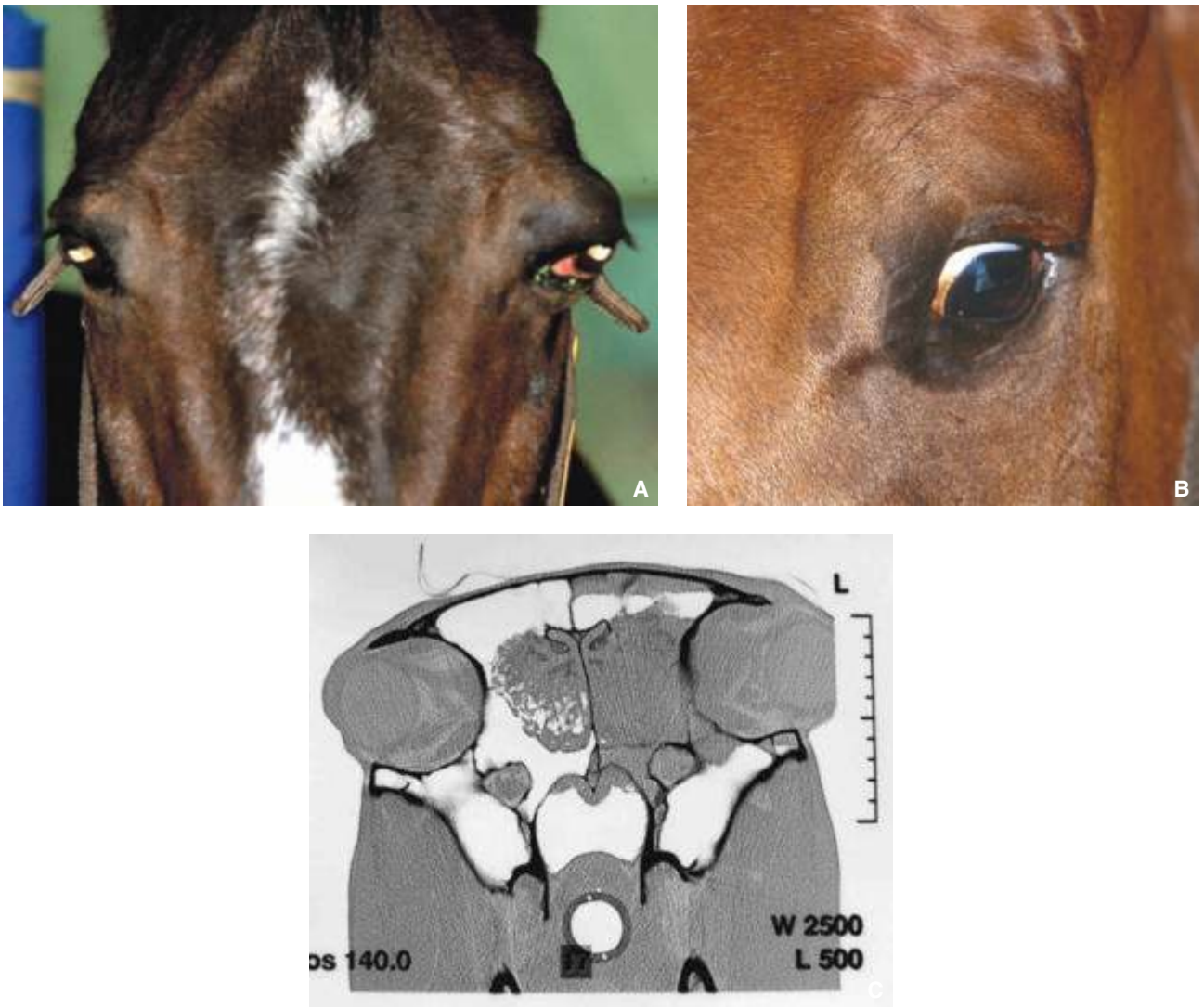


Figure 29.24 Differences in orbital tissues can result in exophthalmos or enophthalmos. **A.** Exophthalmos of the left eye in a horse with an orbital neoplasm. **B.** Enophthalmos in a horse after trauma. **C.** Computed tomography image of the horse in (**A**) indicates an orbital tumor originating in the nasal passage and extending into the adjacent sinuses and orbit causing the exophthalmos.

globe laterally. The nictitating membrane usually protrudes with exophthalmos, and if the exophthalmos is severe, exposure keratitis can then result because of inability of the lids to cover the cornea. Large space-occupying masses, such as tumors, bone fragments, or hematomas, can limit globe motility and impair the ocular circulation (Kafarnik, 2014). The size of the exophthalmic globe is normal and should not be confused with the globe enlargement (i.e., buphthalmos) noted in advanced equine glaucoma.

Diagnostic Procedures

Making the diagnosis of orbital disease usually requires imaging techniques in addition to a complete ophthalmic examination. Commonly used diagnostic imaging tools include orbital ultrasound and skull radiographs. Although commonly used, the extent and severity of injury are not well characterized by these modalities. When possible, computed tomography (CT) is the imaging modality of choice in equine orbital disease (Fig. 29.24C and Fig. 29.25D). Radiographic examination of the skull may be used to evaluate the horse with orbital disease. However, the extensive overlap of the many bones of the skull makes interpretation challenging (Fig. 29.25A). Meticulous attention to detail in film handling and patient positioning as well as a thorough knowledge of normal orbital anatomy are required. Increased soft-tissue densities and lytic bone changes are often associated with neoplasia and chronic inflammatory diseases, and soft-tissue calcification can occur in orbital cellulitis. Contrast radiography of the orbit may assist in localization of space-occupying masses or foreign bodies.

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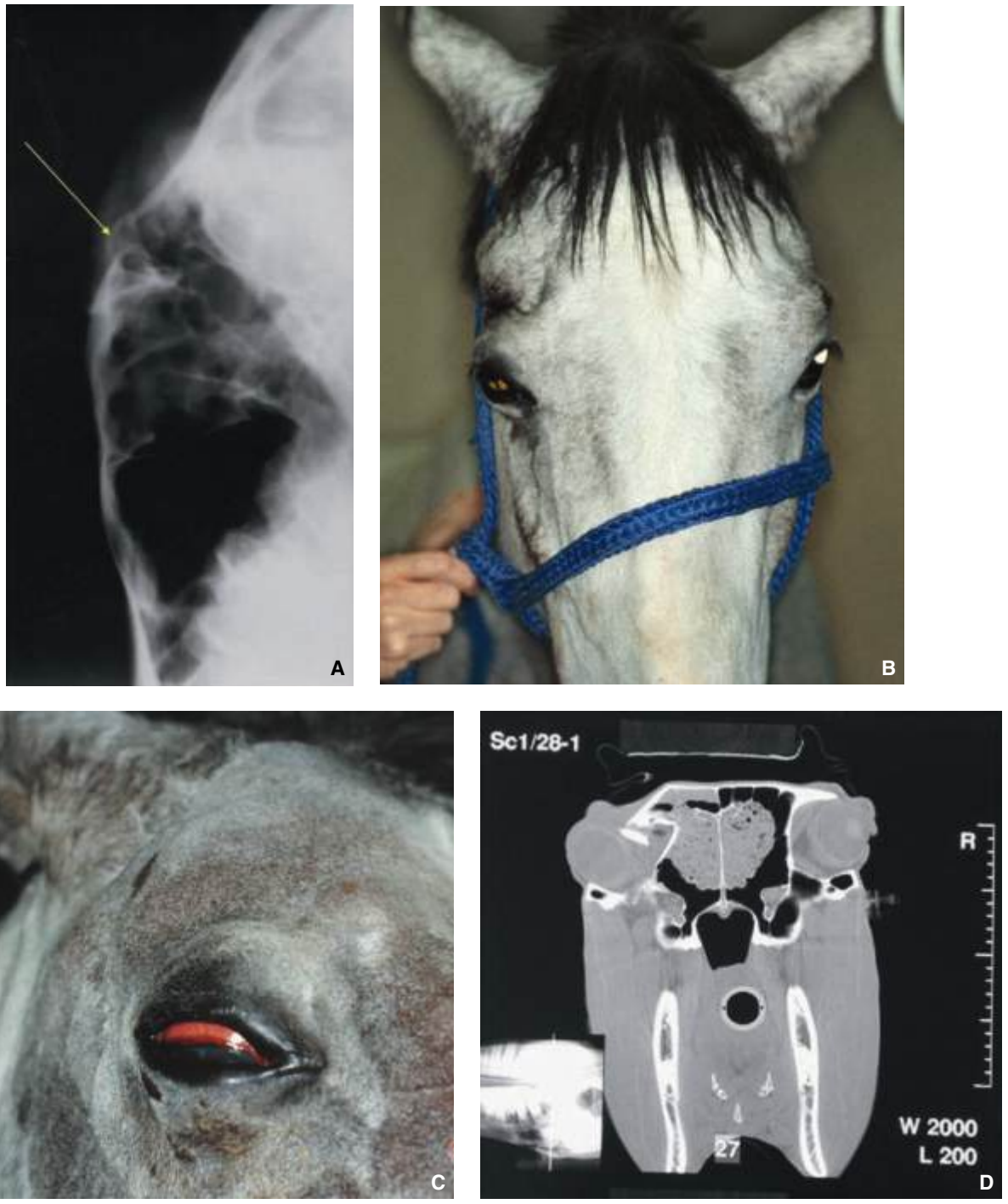


Figure 29.25 Radiographs of orbital fractures can be difficult to interpret. **A.** Radiograph of a fractured and ventrally deviated dorsal orbital rim. Overlapping bone and periosteal reaction and soft tissue swelling make interpretation challenging. **B, C.** Fracture of the dorsal orbital rim of a horse had resulted in ventral deviation of the globe and ventral strabismus. Fractures of the dorsal orbital rim are most common in horses, likely because the dorsal orbital rim protrudes externally and laterally, and thus is highly vulnerable to trauma. **D.** Transverse computed tomography (CT) image of a horse with left-sided orbital fractures. When available, CT is the imaging modality of choice in equine orbital disease.

Ultrasonography is a noninvasive, painless procedure that can both qualitatively evaluate various orbital abnormalities (Michau, 2005; Rogers et al., 1986; Scotty, 2005a; Scotty et al., 2004). Diagnostic ultrasonography is indicated when a globe is exophthalmic or the posterior segment is obscured by opacities of the cornea, lens, or vitreous. This technique

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allows visualization of the retrobulbar soft-tissue space and differentiation between solid, soft-tissue lesions and cystic orbital lesions. However, evaluation of the extent of disease is not possible with ultrasonography (Rogers et al., 1986; Scotty, 2005a; Scotty et al., 2004).

The advent of high-resolution CT and magnetic resonance (MR) imaging has dramatically enhanced evaluation of the character and extent of orbital disease (Michau, 2005; Morgan et al., 1994). CT is the modality of choice when evaluating the orbit, especially if there is concern about bone involvement. MR is useful for characterizing soft tissue disease. Both are superior to radiography and ultrasonography in that they can create 3-Dimensional reconstruction of the orbit and thereby permit better understanding of the anatomy and disease (Michau, 2005; Morgan et al., 1994; Ramirez & Tucker, 2004). The requirement of general anesthesia and cost may be limitations to the use of these modalities.

Aspiration of fluid or biopsy of a mass behind the globe should be performed for culture, cytology, and histopathology. These tests are indicated in cases of exophthalmos to diagnose and differentiate space-occupying masses. An 18-gauge, 10 cm, slightly curved needle inserted 1 cm lateral to the lateral canthus and then directed posteriorly, in a line parallel to the medial canthus or a needle directed ventrally into the supraorbital fossa posterior to the globe, may be used to blindly sample the retrobulbar space. Care must be taken to prevent damage to the globe, orbital vessels, or optic nerve. It is far preferable to employ ultrasound or CT guidance when sampling the retrobulbar space.

Retrobulbar Nerve Blocks

Orbital or retrobulbar anesthesia can reduce eye and third eyelid movement, and decrease corneal sensation for short ophthalmic procedures such as eyelid laceration repair, nictitans removal, corneal foreign body removal, intraocular injections or aqueocentesis, and iris cyst laser ablation (Gilger & Davidson, 2002). Retrobulbar nerve blocks can facilitate general anesthesia required for enucleation surgery by minimizing the depth of the plane of anesthesia necessary. Retrobulbar blocks are standard of care for enucleation and exenteration procedures and should be performed in all cases undergoing these surgeries. For the supraorbital technique, a 22-gauge 3.5-in (8.5 cm) spinal needle is inserted through the surgically prepped skin of the supraorbital fossa just caudal to the posterior aspect of the dorsal orbital rim. The needle is advanced until it reaches the retrobulbar muscle cone. This can be detected by slight dorsal movement of the eye. Once positioned, 10–12 mL of an anesthetic agent (lidocaine, bupivacaine, or mepivicaine) is injected into the orbit. Slight exophthalmos and mydriasis will occur with a properly placed block. The four-point block involves placing the needle through the conjunctival fornices and dividing the volume of the block among the quadrants (dorsal, ventral, medial, lateral). The anesthetic typically takes effect in 5–10 minutes and lasts 1–4 hours depending upon the agent used (Gilger & Davidson, 2002).

Surgical Techniques for the Orbit

Enucleation refers to surgical removal of the globe, conjunctiva, and nictitating membrane. Usually, this procedure is necessary because of severe corneal infection and endophthalmitis, corneal or adnexal neoplasia, orbital neoplasia, or severe ocular trauma causing a painful, blind eye. This procedure does not necessarily indicate a failure of ophthalmic care; it may be a necessary and planned treatment for specific conditions. There are two basic approaches to enucleation in the horse: the transpalpebral technique, and the subconjunctival technique. The transpalpebral technique is most useful in cases of severe corneal infection and of conjunctival, nictitating membrane or corneal neoplasia, but it does leave a larger orbital soft-tissue defect than the subconjunctival technique. The subconjunctival approach is quicker and associated with less hemorrhage. It should be used when a cosmetic shell is to be placed to maintain the integrity of the lid margin. Orbital silicone prosthetic implants to improve cosmesis (decrease orbital "pitting" or "sinkage") may be used with either method (Hamor et al., 1993). However, there is an increased risk of postsurgical infection when orbital prostheses are placed (Huppes et al., 2017).

Orbital exenteration is a surgical technique used to remove malignant tumors of the orbit that extend beyond the confines of the globe or are likely to be unresponsive to chemotherapy or radiation therapy (or both). In this procedure, the entire orbital contents, including the periorbita, are surgically removed. Periosteal elevators may be needed to remove the periorbital fascia; the remaining tissue is excised using scalpel or scissors. Finally, a permanent tarsorrhaphy is performed to close the orbit if the lids were not involved in the disease process. A skin graft can be used to cover the open socket if too much eyelid was removed to allow primary closure, or the socket can be left to heal with second intention and the development of granulation tissue. Should large amounts of periocular skin need to be removed, a modification of the exenteration/enucleation procedure can be used. A portion of the dorsal orbital rim can be removed and combined with mesh skin expansion to facilitate skin closure of large defects (Beard et al., 2002).

The intraocular (sometimes referred to as intrascleral) prosthesis has been used in the horse as a cosmetic alternative to enucleation (Michau & Gilger, 2004). The intrascleral prosthesis replaces the intraocular contents, which are removed by evisceration. Implants of 38–44 mm in diameter are recommended for adult horses, but they should not be placed in eyes with severe corneal disease, intraocular neoplasia, or infectious panophthalmitis. The prosthesis provides a cosmetically acceptable globe with normal lid

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movements and globe motility. The main complications are extrusion of the implant and postoperative infection.

Extrascleral shell implants or conformers consisting of hydroxyapatite, porcelain, or methylmethacrylate shells can be made by ocularists to cover a disfigured or phthisical globe (Gilger et al., 2003). The surface of the shell is painted, and the prosthesis is subsequently placed into the conjunctival sac. The lids and nictitating membrane hold the conformer in place. Daily cleaning and expense are the main limitations, but the cosmetic results are quite good. Ocular conformers for horses are commercially available.

Orbitotomy is indicated when orbital conditions are unresponsive to medical therapy, and/or the cause of the disease cannot be ascertained. Orbital exploration is indicated for biopsy or excision of orbital masses, drainage of infectious processes, and retrieval of foreign bodies. Orbital surgery may also be necessary in the horse to repair periorbital fractures (Caron et al., 1986; Koch, 1980). Surgical procedures used for equine orbital exploration may make a dorsal approach or an osteotomy of the zygomatic process of the frontal bone (Caron et al., 1986; Koch, 1980; Lavach & Severin, 1977). The dorsal approach involves a curvilinear skin incision over the dorsal orbital region, just lateral to the external sagittal crest of the frontal and parietal bones and curving laterally caudal to the zygomatic process of the frontal bone. Lateral retraction of the attachments of the interscutularis and temporalis muscles to the temporal and frontal bones allows the extraocular muscle cone to be exposed. Alternatively, resection of the nasal and temporal aspects of the zygomatic process of the frontal bone using an oscillating bone saw may be performed. The orbital mass is then biopsied and debulked. If the tumor is extensive and the eye incapable of vision, the globe should be enucleated and the orbit exenterated.

Paranasal Sinuses

Periorbital sinuses, the frontal (conchofrontal), maxillary (caudal and rostral), and sphenopalatine, are in close anatomic proximity to the orbit (Fig. 29.23). Primary sinus diseases may secondarily affect one or both orbits. Sinusitis or empyema (i.e., purulent material within the sinus) is one of the most common non-neoplastic diseases of the equine head. Clinical signs of sinus disease include possible exophthalmos, from pressure or swelling that extends to the orbital contents, unilateral nasal discharge, facial swelling, and decreased nasal airflow (Nickels, 2006). Deformation or protrusion of maxillary bone may also be present. Orbital disease is usually associated with chronic sinus disease and can result in unilateral or bilateral blindness from compression of adjacent optic nerve(s) and optic chiasm (Barnett et al., 2008). Diagnosis is based on typical clinical signs of sinusitis and on skull radiographs or, preferably, CT. In primary infectious maxillary sinusitis, the fluid should be drained, the sinus lavaged, and appropriate systemic antimicrobial agents given. In secondary infectious sinusitis, the primary underlying disease, such as dental disease, facial fractures, granulomatous disease, or neoplasia, should be corrected if possible (Nickels, 2006).

Other diseases of the periorbital sinuses that can affect orbital contents include maxillary sinus cysts that are slow growing, expansible masses that must be differentiated from neoplasia. *Dentigerous cysts*, or cysts from the dental arcade, occur uncommonly in the horse but may result in exophthalmos or deformation of the orbit. Exophthalmos occurs in approximately 20% of cases of sinus neoplasia (Dixon & Head, 1999; Head & Dixon, 1999). Unilateral nasal discharge, facial swelling, and epistaxis are also common clinical signs in cases of neoplasms of the sinonasal structures (Dixon & Head, 1999; Head & Dixon, 1999). The most common neoplasms of the periorbital sinuses that cause exophthalmos are, in order of frequency, adenocarcinoma, adenoma, osteoma, squamous cell carcinoma, fibrosarcoma, undifferentiated sarcoma, lymphosarcoma, and esthesioneuroblastoma.

Orbital Inflammation and Cellulitis

Perforation by a foreign body, direct trauma, and seeding by septic emboli are among the more common causes of orbital cellulitis. Extension of inflammatory and infectious conditions from adjacent sinuses and cavities also occurs commonly. If septic endophthalmitis is untreated or is poorly responsive to therapy, it may progress to panuveitis and orbital cellulitis (Fig. 29.26). Enucleation to prevent microbial colonization of deeper tissues may be necessary. In contrast, orbital cellulitis does not readily induce uveitis within



Figure 29.26 Septic endophthalmitis extending into periocular tissues has resulted in orbital cellulitis.

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the globe. Granulomas resulting from *Actinomyces* spp., the nematode *Habronema*, and phycomycosis may occur. Orbital cellulitis is manifested by blepharedema, swelling of the supraorbital fossa, exophthalmos, orbital pain, epiphora or mucoid discharge, and protrusion of the nictitians, conjunctival hyperemia and chemosis, and sometimes lagophthalmos. Fever, elevated white blood count, and general malaise may also be present with orbital cellulitis. Orbital ultrasonography, CT, and fine needle aspiration may be helpful in the diagnosis (Van Den Top et al., 2007). Aggressive use of NSAIDs and broad-spectrum antibiotics are indicated. Rarely is there a discrete fluid pocket in the abscess, so attempts at drainage are usually not fruitful or effective (Gilger, 2011). However, debridement of any visible necrotic tissue is recommended. If there is no response to therapy and the globe is damaged, then enucleation or exenteration may be needed.

If sinusitis is present, trephination into the affected sinus for the culture of exudate as well as irrigation and drainage is indicated. Fluid-filled swellings should be aspirated and specimens submitted for microbiologic culture and cytology. Orbital cellulitis caused by traumatic orbital contusions can be associated with fractures of the orbital rim, and retrobulbar hemorrhage from trauma can result in exophthalmos.

Ethmoid hematomas are well-encapsulated masses originating in or around the ethmoid labyrinth or occasionally from the paranasal sinuses from the mucosal lining of the ethmoid conchae and less commonly from the walls of the maxillary and frontal sinus of mature horses. The cause is unknown, but hemorrhage occurs in the submucosa of an endoturbinate or a sinus, causing the mucosa to stretch and thicken, forming the capsule of the hematoma and contributing factors such as chronic infection, repeated episodes of hemorrhage, congenital or neoplastic changes have been proprosed. An enlarging lesion may extend dorsally into the frontal sinus or ventrally into the sphenopalatine sinus or into the maxillary sinus, nasal cavity or orbit as it enlarges. Extensive lesions have been associated with exophthalmos.

In Europe, hydatid cysts have been reported in the orbit (Barnett et al., 1988). These cysts have caused exophthalmos and optic nerve atrophy.

Orbital Fractures and Trauma

Fractures of the orbital bones may present with asymmetry of the globes or face, epistaxis, exophthalmos, eyelid and conjunctival swelling, depression or concavity of the periorbital region, crepitus, and sometimes, pain on periorbital palpation. Fractures of the dorsal orbital rim are most common (Fig. 29.25) because the dorsal orbital rim protrudes externally and laterally and is thus highly vulnerable to trauma. These fractures may result in displacement, impingement, functional restriction, or laceration of the globe. Damage to the intraosseous NLD, globe, optic nerve, paranasal sinuses, or some combination of these can also occur (Blogg et al., 1990; Caron et al., 1986; Koch, 1980). Ophthalmic complications include corneal ulcers, iridocyclitis, entrapment of the globe by bone fragments, and blindness (Blogg et al., 1990; Caron et al., 1986). In most cases, the injury causing the fracture is not observed. Instead, the horse is found with a swollen periobital area. Fractures from vehicular accidents or from falling over backward and hitting the poll of the head may result in fractures to the basioccipital bone and consequently basisphenoid bone in the inner orbit. This can result in blindness if it involves the sphenoid foramina.

Diagnosis and assessment of orbital rim fractures should be accomplished by a thorough ophthalmic examination and digital palpation. The horse should be adequately tranquilized and restrained, and after use of topical anesthetic, a lubricated gloved finger should carefully palpate the orbital rim and wall. Pressure on the globe or orbital rim should be avoided. Imaging by radiography, and preferably CT, should be performed prior to considering surgical intervention. Skyline views are helpful for the orbital rim, but they can be difficult to interpret. A CT scan is nearly always recommended when orbital fractures are present (Fig. 29.25D).

Periorbital fractures should be repaired quickly, because fibrous union of the fractured pieces begins within 1 week after injury making elevation and realignment difficult. Minor orbital rim fractures that are closed and nondisplaced may not require surgical correction unless fracture fragments are impinging on the globe or perfect cosmesis is required. Any section of bone that is impinging on the globe or orbital contents needs to be reduced or removed. When the ultimate cosmetic outcome is desired, closed fracture reduction is highly desirable. With the horse placed under general anesthesia, zygomatic process fractures may be reduced or closed by manipulation of the bone piece into position using a bone hook (Caron et al., 1986; Gilger, 2011). Monofilament stainless-steel wire suture (20–22-gauge), cerclage wire, small orthopedic pins, as well as orthopedic bone plates and cancellous bone grafts, are used to stabilize bone fragments and to immobilize and repair extensive orbital fractures. More complex fractures of the dorsal orbital rim may be reduced with a malleable plate or bone plate (Koch et al., 1980). Small bone fragments should be removed lest they become sequestra. Open fractures typically are managed by debridement and cleaning of the wound, reduction of displaced by viable bone fragments, and removal of small, grossly contaminated fragments. Depending on the extent of contamination, some or all of the wound is left open for adequate drainage, or drains are placed to facilitate healing. Surgical exploration may reveal fractures to be more extensive than detected at radiography. Incomplete fractures may not be visible without subperiosteal dissection. Failure to repair large fractures can result in permanent facial deformity (Blogg et al., 1990; Caron et al., 1986; Koch, 1980).

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Fractures that expose the periorbital sinuses may result in emphysema and epistaxis. Sinus fractures are considered open wounds and should be treated aggressively. A drain may be placed if there is any evidence of infection (purulent exudate, cytologic evidence of bacteria or fungus), and creation of drainage should be considered (externally or into the nasal cavity) if there is inadequate drainage (Gilger, 2011).

The equine globe does not tolerate much intraocular hemorrhage and, in many cases, will undergo phthisis bulbi if this occurs. Enucleation should be performed without undue delay in severely traumatized globes, because bacteria can spread along the optic nerve to the brain (Lavach, 1987) (Fig. 29.27).

The complete bony orbital rim of the horse generally protects against traumatic globe proptosis, but this problem has been reported on occasion with severe injuries. In most instances the degree of damage sustained by the orbit and the globe necessitates enucleation, but in the rare instance that the proptosed globe is intact, it should be evaluated for integrity, hyphema, pupil size, and corneal dessication. It is likely that ocular venostasis resulting from eyelid entrapment of the globe will have developed. Miosis with severe hypotony and hyphema is indicative of severe trauma and poor prognosis for a viable globe. Disruption of its intraocular blood supply and severe intraocular hemorrhage usually results in phthisis bulbi. The proptosed globe should be replaced into the orbit with the horse under general anesthesia. A temporary tarsorrhaphy will protect the cornea, and topically applied antibiotics and atropine as well as systemically administered NSAIDs and antibiotics will decrease the swelling and minimize the risk of infection.



Figure 29.27 Globe rupture flowing orbital trauma. Note the extensive subconjunctival hemorrhage and the rupture along the dorsotemporal limbus. The prognosis for this globe is grave and should be enucleated.

Orbital Neoplasia

Neoplasia of the equine orbit is much less common than in other domestic species. The most common primary neoplasms of the orbit are neuroendocrine tumors and extra-adrenal paraganglioma (Basher et al., 1997; Dopke et al., 2005; Matiasek et al., 2007; Miesner et al., 2009). Anaplastic sarcoma, lymphoma, and squamous cell carcinoma (SCC) are also common. Extension of adnexal SCC into the orbit carries a poor prognosis (Fig. 29.28). Other reported tumors of the equine orbit have included lipoma, adenocarcinoma, lymphosarcoma, melanoma, meningioma, hemangiosarcoma, sarcoid, multilobular osteoma, neurofibroma, medulloepithelioma, and Schwannoma (Basher et al., 1997; Davis et al., 2002; Lavach, 1987, Lavach & Severin, 1977; Rebhun & Del Piero, 1998; Richardson & Acland, 1983; Sweeney & Beech, 1983). Progressive exophthalmos, displacement of the nictitans, conjunctival hyperemia and chemosis, orbital swelling, bone surface distortion, blindness, strabismus, anisocoria, behavioral abnormalities and less commonly, epistaxis and signs referable to the involvement of adjacent cavities, are reported symptoms in horses with orbital tumors (Basher et al., 1997; Gilger, 2011). Blindness may result from intracranial compression of the optic nerve by pars intermedia masses. Biopsy for histopathologic evaluation should be performed early when there is clinical suspicion. Local lymph nodes should be evaluated by palpation and cytology if abnormalities are suspected. CT is the best method to determine the extent of the tumor and the most appropriate treatment (Davis et al., 2002; Miesner et al., 2009; Tucker & Farrell, 2001). Orbital ultrasound is generally only helpful in the diagnosis of orbital neoplasia to direct fine needle aspiration for cytologic examination. A biopsy is the only definitive method to confirm the presence of neoplasia. Treatment consists of surgical removal with or without adjunctive therapies. Although surgical removal and salvage of the eye is possible early in the disease process, many cases require exenteration of the orbit.

Orbital Fat Prolapse

Orbital fat may herniate through weakened episcleral fascia or from trauma, resulting in lobular, subconjunctival masses that may resemble tumors (Bedford et al., 1990; Munroe & Belgrave, 1988) (Fig. 29.29). Aspiration, biopsy, and cytologic evaluation of these masses reveal the presence of adipose cells. Fat prolapse may occur iatrogenically after excision of the third eyelid. The affected tissue can usually be excised and the conjunctival rent sutured to prevent recurrent herniation.

Diseases and Surgery of the Eyelids

Diseases of the eyelids are a very common problem in horses, especially traumatic eyelid lacerations and neoplasia.

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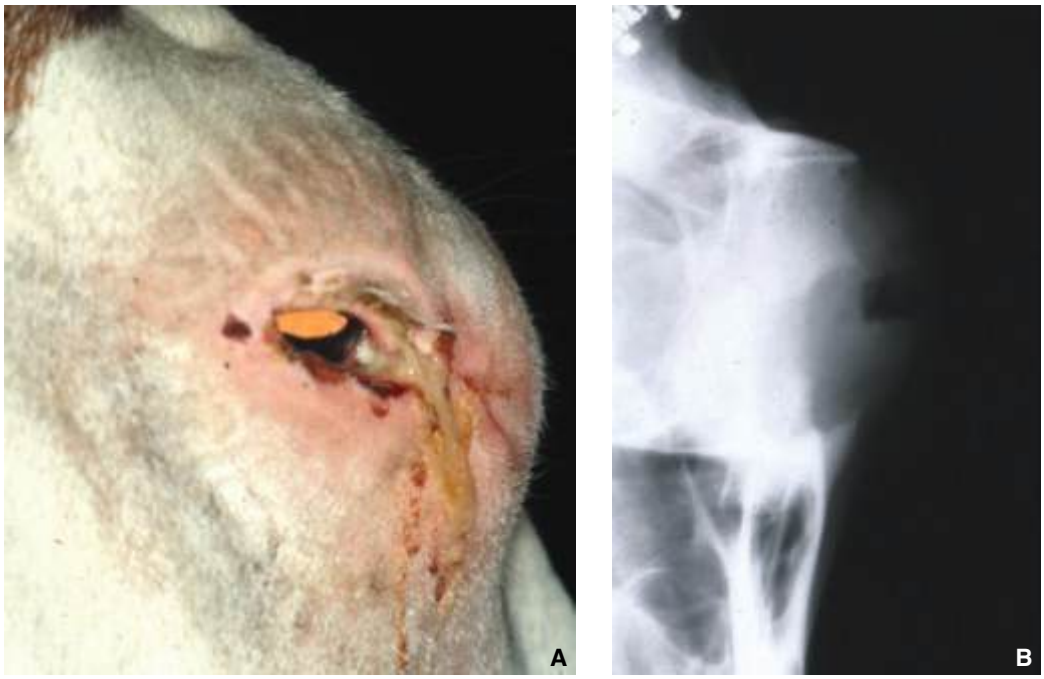


Figure 29.28 **A.** Extension of squamous cell carcinoma from the eyelids and the nictitans into the orbit. **B.** Radiography revealed extensive lysis of the bony orbit.



Figure 29.29 Orbital fat prolapse in a horse. Note the smooth swelling visible posterior to the nictitans.

Appropriate initial management of these conditions is very important because dehiscence of wounds or recurrence of neoplasia result in conditions that are much more difficult to manage and can threaten the integrity of the eye.

Entropion

Entropion is an inward rolling of the eyelid margin. It can be a primary anatomic problem in foals, or it can be secondary to poor condition, dehydration, and muscle weakness in "downer foals." Entropion in adults may be cicatricial from previous eyelid trauma, or it may be acquired or spastic secondary to chronic ocular irritation causing spasms of the orbicularis oculi muscle (Miller, 1999; Moore, 1992). Clinical signs include epiphora, blepharospasm, conjunctivitis, and ulcerative keratitis, but these signs may vary with the extent of the entropion.

Blepharoplastic surgical correction of entropion in neonatal foals is not recommended (Plummer, 2005). Foals should be managed medically with ocular lubricants and temporary tacking as they mature and grow. Nonabsorbable vertical mattress sutures to temporarily evert the eyelid margin in foals can be placed to give the foal some time to grow or regain condition. Permanent surgical correction is usually not necessary.

Before attempting entropion therapy, concurrent ocular problems such as blepharitis, distichiasis, and corneal disease should be identified and treated. The amount of surgical correction for entropion in mature horses must be estimated before general anesthesia and after local nerve block and a topical anesthetic has been applied to the ocular surface (Miller, 1999; Moore, 1992; Plummer, 2005). It is important to determine how much of the entropion is anatomic and how much is secondary to spasm from ocular pain. For optimal results, surgical techniques should always undercorrect slightly.

The modified Hotz-Celsus procedure is simple and can be adapted to most types of entropion in the horse. An initial incision, running parallel to and 2–3 mm from the eyelid

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margin to a depth that includes orbicularis oculi muscle, is made, with the length of the incision being determined by the amount of eyelid margin involved. The ends of the first incision are joined by a second, parallel, elliptical skin incision, with the width previously determined by evaluating the degree of eversion necessary to correct the entropion. Closure is accomplished with simple interrupted 4-0 nonabsorbable sutures. The suture ends adjacent to the eyelid margin should be trimmed short. If the entropion is the result of a focal cicatrix, removal of that scar tissue and undermining of the skin from its underlying attachments is critical to releasing tissue for the repair.

Eyelid Lacerations

Eyelid trauma and lacerations are common in the horse. Close confinement in box stalls and trailers during transport, the prominent lateral positioning of eyes, and the horse's characteristic acute "flight response" in which horses react to stimuli by exaggerated movements of their heads contribute to the propensity for eyelid trauma (Giuliano, 2011). Lacerations can develop from blunt trauma from a crushing injury against the orbital rim, direct contact with sharp objects (e.g., nail, metal edge), and ripping of the eyelid which usually results when the eyelid margin is caught on a hook with subsequent rapid head movement by the horse (Giuliano, 2011). A complete ocular examination is very important to assess corneal integrity, anterior chamber clarity and depth, and scleral continuity because damage to the globe, orbital cellulitis, orbital or periorbital fractures, corneal ulceration, uveitis, hyphema, or posterior segment injuries such as retinal detachment may accompany the lid damage. Lid lacerations may be accompanied by orbital cellulitis and periorbital fractures (Miller, 1999). The severity of the initial appearance of the lesion does not correlate with overall prognosis (Giuliano, 2011). Damage to the upper eyelid is most significant, however, because most of the globe coverage and protective functions of the eyelids are performed by the upper eyelid. Medial canthal lacerations may result in damage to the nasolacrimal canaliculi. Small eyelid punctures may introduce infectious orbital or retrobulbar cellulitis with fever and exophthalmos (Brooks, 1999). These wounds should be cultured for bacteria and fungi, surgically debrided only minimally, and covered with warm compresses. Systemically administered antibiotics and NSAIDs aid resolution of this condition. In some cases, however, surgical drains may need to be placed.

Due to the excellent blood supply to the eyelids, most lacerations can be repaired to achieve a relatively well-functioning and cosmetic eyelid. Therefore, every attempt should be made to surgically repair all eyelid lacerations, taking care to avoid cutting any hanging eyelid pedicles (Fig. 29.30A). Failure to repair a laceration, or amputation of a torn eyelid pedicle rather than a surgical repair, can result in exposure-induced corneal disease (Fig. 29.30B). Eyelid lacerations must be repaired quickly to avoid lid infection, reduce eyelid edema, and minimize scarring of the lid as well as corneal dessication and ulceration. Because of the abundant vasculature present in the eyelids, minimal debridement of a laceration generally is necessary (Plummer, 2005). Small lid lacerations can be repaired under local anesthesia and mild sedation. Accurate two-layer closure of the tarsoconjunctiva (continuous absorbable suture, such as 6-0 polyglactin 910 [Vicryl®, Ethicon, Somerville, NJ, USA] in a simple continuous pattern) and skin–orbicularis muscle (nonabsorbable suture) aids the healing process, because it minimizes formation of scar tissue and lid deformity and encourages quick return of normal eyelid function. The eyelid margin should be meticulously apposed as the first step in eyelid repair with a figure-of-eight suture pattern of nonabsorbable 4-0 to 6-0 suture (Rebhun, 1980a) (Fig. 29.30C). Additional simple interrupted skin sutures are placed as needed to close the remainder of the eyelid defect. Large eyelid lacerations with loss of tissue or those of a long-standing nature require general anesthesia and sophisticated blepharoplastic grafting procedures (Henriksen, 2013). Incorrect closure of the eyelid margin or failure to use a two-layer closure may lead to dehiscence or chronic corneal irritation. Skin sutures should be left in place for at least 14 days, in some instances longer if the wound strength is still compromised.

Lacerations of the margin or body of the nictitating membrane should be carefully repaired to avoid corneal irritation. The posterior face of the nictitating membrane should always be examined for injury and foreign material. Removal of the nictitating membrane should be performed only if it is severely damaged.

Blepharitis

Primary bacterial blepharitis is uncommon in the horse. Eyelid abscesses associated with foreign bodies, subpalpebral lavage systems, and bony sequestra have been reported. Dermatophytosis resulting from *Trichophyton* or *Microsporum* sp. may cause blepharitis as well, but usually there are skin lesions elsewhere on the body concurrently (Latimer et al., 1983). Topical antifungal agents such as miconazole or thiabendazole ointments may be indicated in those cases. *Histoplasma farciminosus* and *Cryptococcus mirandi* are reported to cause blepharitis in the horse and require systemic antifungal therapy (Moore, 1992).

Habronemiasis is a common cause of equine granulomas of the eyelids, conjunctiva, lacrimal caruncle, medial canthus, and nictitans. In tropical and subtropical climates, infection of periocular tissue by *Habronema* larvae is a common cause of conjunctivitis or blepharitis. However, the condition is being more widely recognized in temperate climates (Verhaar et al., 2018). Nonhealing, elevated, and

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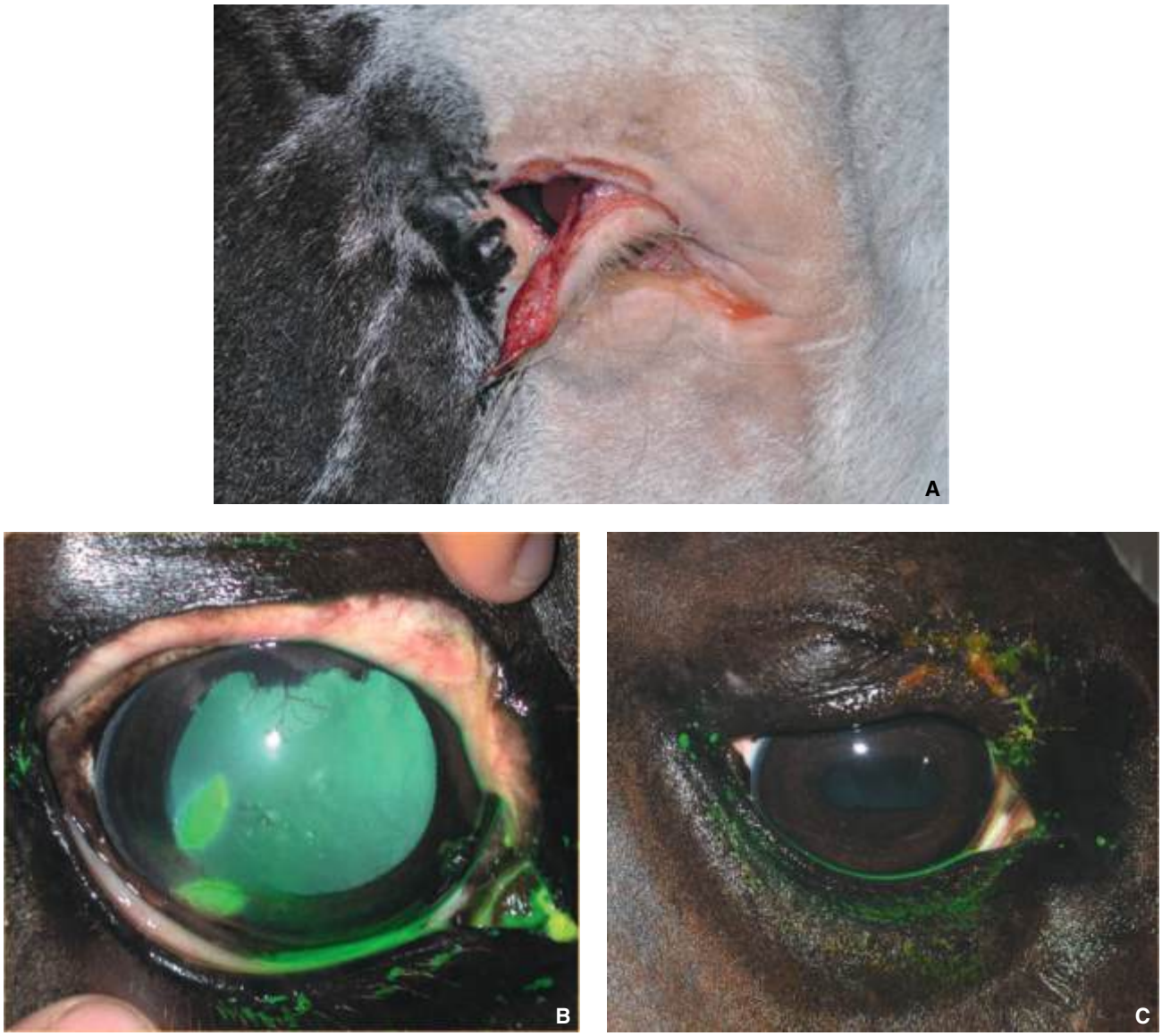


Figure 29.30 Eyelid lacerations are often full-thickness and require exact reconstruction. **A.** Upper eyelid laceration with a hanging pedicle. This should be reapposed rather than excised. **B.** This horse had an upper eyelid laceration and the pedicle was excised. Note the complete absence of the eyelid margin. Superficial keratitis and ulcerations developed secondary to exposure and qualitative tear film deficiency. **C.** Meticulous apposition of the eyelid margin is critical to postoperative function and comfort, particularly with upper eyelid wounds.

ulcerated periocular granulomas with fistulous tracts and a yellow, caseous exudate ("sulfur-like" granules) consisting of gritty foci of necrotic mineralized tissue are found on horses during the warm weather months (Fig. 29.31A). House and stable flies serve as vectors to transmit eggs and larvae to these warm, moist periocular sites. Dying microfilariae are believed to incite immune hypersensitivity. Cytology from affected sites reveals numerous eosinophils, mast cells, PMNs, and plasma cells. Larvae may be identified on histopathology of affected tissue but when they are not, it can be difficult to differentiate habronemiasis from a hypersensitivity reaction, mastocytoma, nodular necrobiosis, or fungal granulomas because of the nonspecific, but exuberant eosinophilic reaction that the horse produces (Moore, 1992). Topical therapy for solitary, focal lesions of habronemiasis consists of a mixture containing 135 g of nitrofurazone ointment, 30 mL of 90% dimethyl sulfoxide (DMSO), 30 mL of 0.2% dexamethasone, and 30 mL of 12.3% oral trichlorfon solution (Miller, 1999). Multifocal lesions should be treated with systemic avermectins (Moore, 1992; Plummer, 2005). Intralesional corticosteroid injection (i.e., triamcinolone) and systemic corticosteroids can reduce the reactive inflammation and also the size of granulomas (Pusterla et al., 2003).

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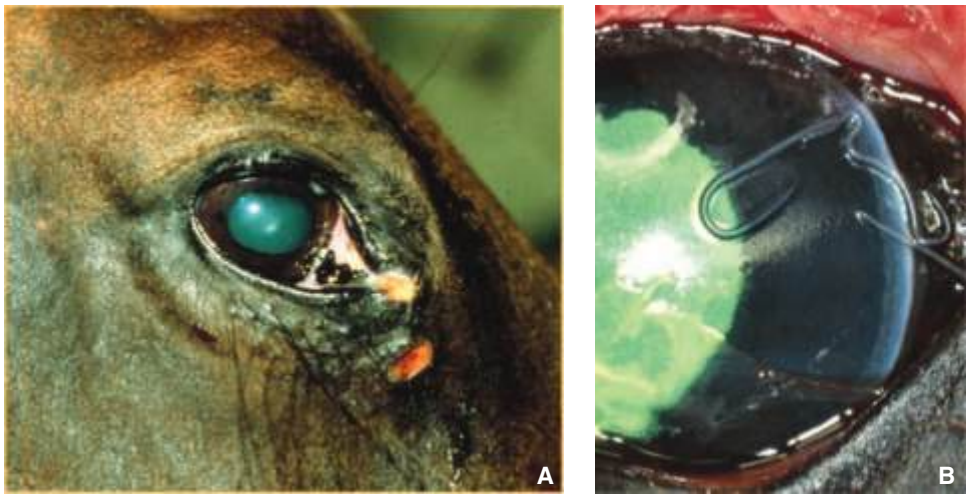


Figure 29.31 Parasitic blepharoconjunctivitis in horses occurs in horses not routinely wormed. **A.** *Habromena* blepharitis in the most common location at the medial canthus. **B.** *Thelazia* worms caused conjunctivitis and blepharitis in the horse.

The spiruroid nematode *Thelazia lacrimalis* is a commensal parasite that inhabits the conjunctival fornices and NLDs of the horse (Moore, 1992) (Fig. 29.31B). Most horses are asymptomatic, but signs can include mild lid swelling, conjunctivitis, superficial keratitis, and dacryocystitis. Demodex mites may cause meibomianitis, lid alopecia, and papulopustular dermatitis in the horse.

Acute and chronic allergic blepharitis, eosinophilic granuloma with collagen degeneration, pemphigus foliaceous and bullous pemphigoid, solar blepharitis of nonpigmented skin, and St. John's wort photosensitization of the lids have also been reported in the horse (Moore, 1992).

Eyelid Neoplasia

Neoplasia of the equine eyelids is very common and can be one of the most challenging periocular diseases to manage. SCC is the most common neoplasm, followed by sarcoids, but a variety of other neoplasms have been reported in the horse eyelid. Clinically, cutaneous or subcutaneous masses, proliferative conjunctiva, nonhealing eyelid ulcerations, or an elevated third eyelid are typical of adnexal neoplasia. In some cases, the only observed clinical sign is mucopurulent ocular discharge. Periocular neoplasia, in general, should always be confirmed with histopathology, and treated early and aggressively. Recurrent disease is always more resistant to treatment, is more likely to result in poor cosmesis and compromise of the globe. In some cases, especially in untreated chronic SCC, local and distant metastasis can occur, resulting in mortality.

Squamous Cell Carcinoma

SCC is the most common neoplasm of the eye and adnexa in the horse (Giuliano, 2011; Lavach & Severin, 1977). Horses with a lack of periocular pigmentation are at increased risk for development of SCC (Dugan et al., 1991a; Schwink, 1987). An increased prevalence of ocular SCC may occur with age, and a breed predilection for draft breeds and Appaloosas has been reported (Dugan et al., 1991a; Schwink, 1987). Animals with white, gray-white, and palomino hair coats have an increased incidence of SCC, whereas horses having bay, brown, and black hair coats are less commonly affected. Development of SCC is associated with various environmental factors including geographic influences of increased longitude, decreased latitude, increased altitude, and increased mean annual solar radiation exposure (Dugan et al., 1991a; Giuliano, 2011; Hendrix, 2005). Ultraviolet radiation is strongly correlated with SCC because it targets the tumor-suppressor gene *p53*, which is altered in equine SCC (Sironi et al., 1999; Teifke & Lohr, 1996). Cycloxygenase (COX) derived prostaglandins (COX-2) may also be responsible for for tumor growth, metastasis, and angiogenesis (Moore et al., 2003).

The eyelids, nictitans, conjunctiva, and corneoscleral limbus are commonly affected (Dugan et al., 1991a; Hendrix, 2005; Giuliano, 2011). The most common ocular locations for SCC are the nictitating membrane or medial canthus (approximately 28%) (Fig. 32A, B), limbus (approximately 28%), and lower eyelid (approximately 23%) (Fig. 29.32C, D). Other locations such as the cornea, conjunctiva, and orbit represent approximately 21% (Lavach & Severin, 1977; Schwink, 1987). The appearance of adnexal SCC can vary from erosive lesions resembling wounds to proliferative lesions which can be raised and expansive. Actinic solar keratitis may transform to carcinoma *in situ* SCC that often appears as hyperemic eyelid erosive plaques with dark-staining crusts, to eventually become papillomatous SCC or, alternatively, SCC may appear as a raised mass with a pink, cobblestone appearance (Fig. 29.33A), to ultimately develop into large, fleshy masses with variable degrees of ulceration,

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Figure 29.32 Squamous cell carcinoma (SCC) is the most frequent ophthalmic neoplasm in the adult horse. **A.** SCC of the nictitating membrane. **B.** SCC of the skin at the medial canthus. **C.** SCC originating at the temporal limbus extending into the paraxial cornea. **D.** Extensive SCC that has effaced the entire lower eyelid.

necrosis, and inflammation (Fig. 29.33B) (Giuliano, 2011; Lavach & Severin, 1977; Schwink, 1987). Ocular SCC must be differentiated from tumors, parasitic granulomas (such as habronema, onchocerca, and thelazia) and inflammatory lesions such as abscesses, granulation tissue, and foreign-body reactions (King et al., 1991). Urinalysis test strips placed in the ventral conjunctival fornix of horses with corneal and conjunctival SCC may detect occult blood in the tears and aid differentiation of SCC from granulation tissue.

Treatment for SCC is highly variable, and commonly reported therapies are summarized in Table 29.1. In one large retrospective study of equine ocular SCC, a main key to long-term success of management was found to be the owner's willingness to return horses for re-examination (Dugan et al., 1991b). Treatment depends on tumor location, tumor size, extent of invasion, vision status, the animal's purpose, available equipment, and the owner's financial constraints. Untreated ocular SCC can invade local soft tissues, the bony orbit, sinuses, and brain, and it can metastasize to the regional lymph nodes, salivary glands, and thorax (Hendrix, 2005; Kaps et al., 2005; King et al., 1991).

The need for adjunctive therapy, which may need to be repeated and is expensive, the adverse effects from these adjunctive therapies, and the frequent recurrence of SCC contributes to clinical frustration in the treatment of SCC. Tumor recurrence is highest with lesions of the eyelid or nictitans (King et al., 1991). In general, the ocular or periocular location of the SCC directs the type of treatment that is indicated. For example, corneal–scleral SCC generally responds to excision and adjunctive therapy of beta-irradiation, topical chemotherapeutics (e.g., mitomycin C), or possibly cryotherapy. Eyelid SCC is treated with excision and adjunctive therapy using cryotherapy, intralesional chemotherapy (i.e., cisplatin), immunotherapy, brachytherapy, or photodynamic therapy (PDT) (among others) (Fig. 29.34). Third eyelid/medial canthal SCC generally is treated with excision of the third eyelid with adjunctive treatment such as cryotherapy, brachytherapy, and possibly (depending on the extent of the

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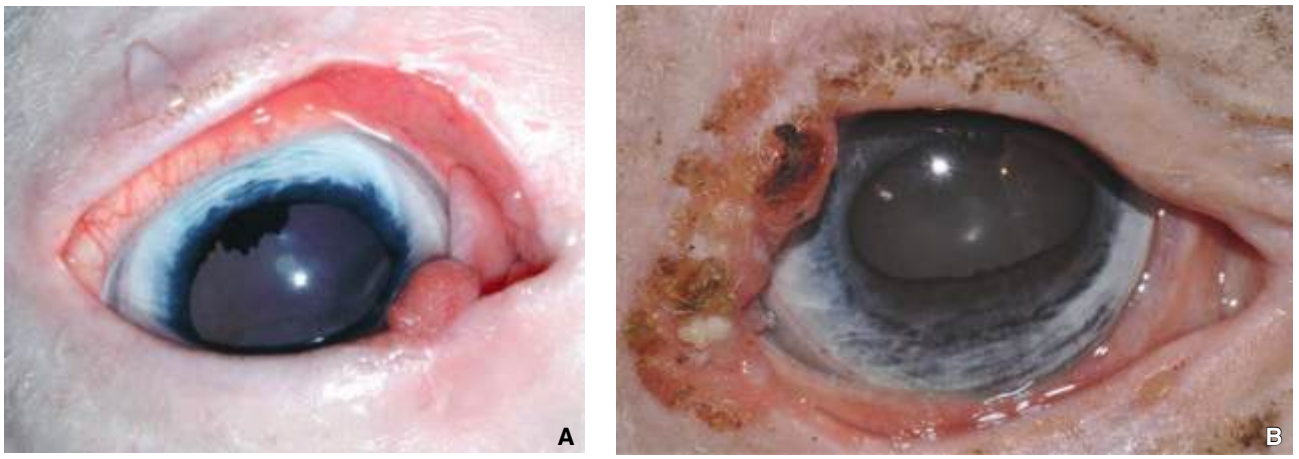


Figure 29.33 Squamous cell carcinoma (SCC) presents as either a mass or an ulcerated area. **A.** SCC may appear as a raised mass with a pink, cobblestone appearance, as seen in this horse with an eyelid squamous cell carcinoma. **B.** SCC may appear as erosive or ulcerative lesions with variable degrees of necrosis and inflammation.

Table 29.1 Treatment for periocular squamous cell carcinoma.

Type of therapy	Treatment	Therapy	Reported % non-recurrence
Intralesional immunotherapy	Bacille Calmette-Guérin	1 mL/cm^2 of tumor surface. Repeat every 2–4 weeks	100% (1 of 1 case)
Intralesional chemotherapy	Cisplatin	1 mg/cm^3 every 2 weeks for 4 treatments	71%
Surgical excision	Excision	Once	56%
Excision and cryotherapy	Cryotherapy	Double or triple freeze—thaw	33%–100%
Excision and photodynamic therapy (PDT)	PDT	1 mg/cm^2 of tumor bed area followed by application of appropriate light source 10 J/cm^2 and 200 mW/cm^2	80%–100%
Hyperthermia	Hyperthermia	Tissue temperatures between 41°C and 45°C	75%–100%
CO_2 laser	Laser ablation	Ablate tissues	100%
Brachytherapy	Radon, cobalt, gold, iridium, strontium	5000–25,000 cGy	74%–100%

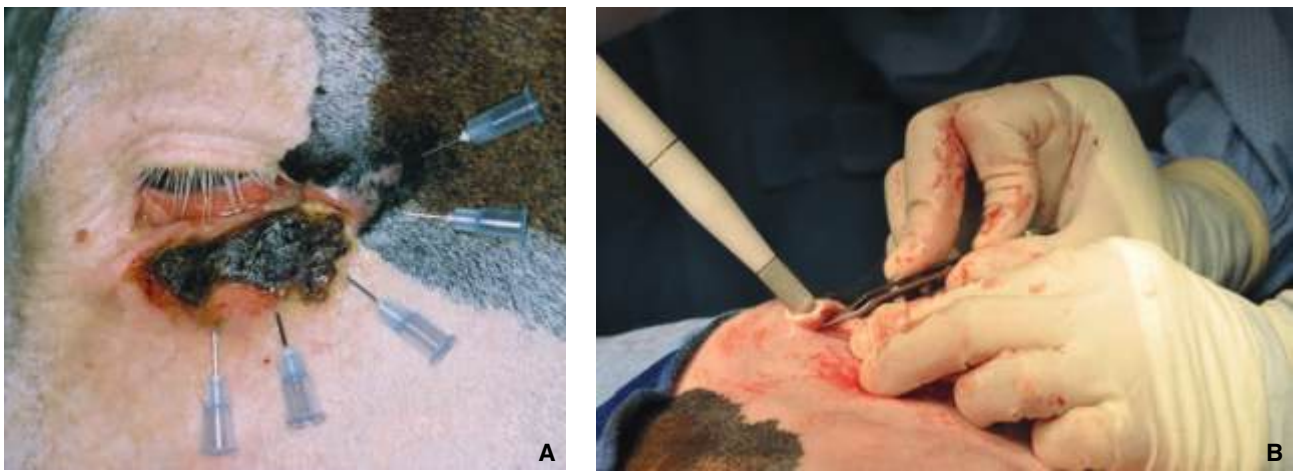


Figure 29.34 There are many therapeutic options for squamous cell carcinoma (SCC). Early and aggressive therapy is associated with the highest rates of success. **A.** Lower eyelid SCC with pre-placed needles prior to the administration of local chemotherapy. **B.** Cryotherapy applied to an eyelid SCC.

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lesion) intralesional chemotherapy, PDT, or immunotherapy (Giuliano, 2011). Recurrence rates of periocular SCC when treated with both surgical excision and an adjunctive therapy range from 25% to 67% (Giuliano, 2011). Rechecks for recurrence should continue for 3–5 years after treatment. Recurrence may develop distal to the primary location, such as the NLD (Elce et al., 2011).

Appropriate treatment of equine ocular SCC usually involves surgical excision combined with adjunctive therapy selected as appropriate for the anatomic site of the lesion. The horse owner should be carefully educated to understand that for best long-term results of the treatment of periocular SCC, they must be diligent in observing signs of recurrence or metastasis and be willing to have the horse examined as soon as adverse signs are observed (Dugan et al., 1991b).

Surgery can vary from local excision of small focal lesions to exenteration of the globe with removal of large amounts of surrounding periocular skin and partial orbital rim resection for large SCC lesions (Beard et al., 2002). Treatment may be surgical resection alone if adequate margins can be attained, though combinations of surgical debulking and adjunct therapy are best for large SCC (Plummer, 2005). Cryosurgery with liquid nitrogen or nitrous oxide will achieve optimal cryonecrosis of malignant cells between -20 °C and -40 °C using a double freeze–thaw technique (Hendrix, 2005; Plummer, 2005; Schoster, 1992). Radiation therapy has the best outcomes of all primary or adjunctive therapies for SCC, but its utility may be limited by cost, availability, or the need for general anesthesia. Beta-irradiation (i.e., strontium-90) is most beneficial in superficial SCC of the cornea and limbus after keratectomy because it has limited tissue penetration and therefore less damage to normal adjacent tissue (Hendrix, 2005). Brachytherapy with cesium-137, radon-222, gold-198, cobalt-60, and iridium-192 implants is effective after surgical debulking. However, concerns for personnel safety limits the availability of this modality (Hendrix, 2005; Mosunic et al., 2004). Interstitial radiation therapy provides the advantage of continuous tumor exposure to high levels of radiation over a period of time. Hyperthermia (50 °C for 30 seconds at 3–4 mm in and beyond the tumor margin) of small, superficial conjunctival and lid SCC and carbon dioxide (CO_2) laser ablation of superficial SCC may also be effective (English et al., 1990; Hendrix, 2005; Plummer, 2005; Wilkie & Burt, 1990). CO_2 lasers are generally set at 3–8 W and the tumor lasered until it is covered with a brown char.

Immunotherapy with bacille Calmette-Guérin (BCG) cell wall extract has been used with some success for SCC in the horse (1 mLextract/cm^3 tumor) (McCalla et al., 1992). Chemotherapy with intralesional, slow-release cisplatin may be effective, with or without surgical debulking. However, diligent monitoring and re-biopsy to determine if the site is tumor-free is critical. The 1-year relapse-free rates for SCC treated with cisplatin approach 90% (Théon et al., 1993, 1994, 1997). Four sessions at 2-week intervals with 1 mg cisplatin/cm^3 for tumors 10–20 cm^3 in size are necessary, and cisplatin, 3.3 mg/mL (10 mg of cisplatin in 1 mL of water and 2 mL of purified, medical-grade sesame oil), is also used. Five-fluorouracil (5-FU) (50 mg/mL 5-FU with 3 mL 1:1000 epinephrine per 10 mL 5-FU) can be used for intralesional treatment of periocular SCC (Yeats et al., 1995). Intralesional bleomycin has been used for ocular SCC. Lid tattooing may make the owners feel better but does not decrease SCC incidence and recurrence as the ink is subepithelial, thus providing no protection to the epithelial cells from UV light (Lavach, 1987; Lavach & Severin, 1977). Piroxicam (80 mg PO q24h) has been reported to have some palliative effects for periocular SCC in the horse (Moore et al., 2003).

PDT is the most recently described and promising new therapy for adnexal SCC in the horse. PDT entails the use of light and light-sensitive compounds in an oxygen-rich environment to cause localized tissue necrosis. This modality typically follows debulking (incomplete excision) of the SCC lesion and involves injecting a photosensitive dye into the resultant wound bed (Giuliano et al., 2008). This agent is then excited by a wavelength of light specific to the agent. Oxygen free radicals are elaborated that destroy rapidly dividing cells (tumor). Tumor selectivity during treatment results from a combination of selective retention of the photoactive chemical by neoplastic cells and targeted delivery of light to the specific area of interest. In a recent study comparing recurrence rates between adnexal SCC treated with cryotherapy or PDT after surgery, the likelihood of tumor recurrence was significantly reduced with local PDT compared with cryotherapy (11/14 cases recurred with cryotherapy; 0/10 recurred with PDT) (Giuliano et al., 2014).

The key to success in the treatment of adnexal SCC in the horse is early recognition and aggressive treatment combined with diligent and continued long-term monitoring for recurrence.

Sarcoids

Sarcoids are solitary or multiple cutaneous tumors of fibroblastic origin and have proliferative and hyperplastic epithelial components, and although metastasis is rare, recurrence is common, especially with the more invasive lesions (Dugan, 1992; Knottenbelt & Kelly, 2000; Plummer, 2005). Periocular/eyelid sarcoids are common and may result in significant pathology to the eye either by disrupting normal eyelid function or by directly rubbing on the eye. Sarcoids usually develop in young horses under 7 years of age, although they have been reported in animals of all ages (Knottenbelt & Kelly, 2000). Nearly all breeds have been reported to develop sarcoids, but Quarter Horses, Appaloosas, Thoroughbreds, and Arabians may be at increased risk, whereas Standardbreds and Lippizaners may be at decreased risk (Angelos et al., 1988; Knottenbelt & Kelly, 2000; Mohammed et al., 1992). There are a variety of clinical types

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and appearances including occult, hyperkeratotic fibropapilloma (i.e., verrucous), nodular types A and B, fibroblastic types A and B, and mixed forms (Bertone & McClure, 1990; Knottenbelt & Kelly, 2000; Martens et al., 2000) (Fig. 29.35). Periocular sarcoids are most commonly nodular, fibroblastic, or mixed (Knottenbelt & Kelly, 2000).The fibroblastic



Figure 29.35 Sarcoids are the second most frequent ophthalmic neoplasm in adult horses. **A.** Nodular type B periocular sarcoid. **B.** Fibroblastic sarcoid. **C.** Verrucous sarcoid. **D.** Medial canthal sarcoid at presentation. **E.** Following a series of intralesional bacille Calmette-Guérin treatments, the sarcoid resolved with some scar formation. **F.** Intralesional injection of bacille Calmette-Guérin for an eyelid sarcoid.

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form is very locally aggressive, and intervention can convert the verrucous to the fibroblastic form. A variety of etiologies have been proposed or suspected including retroviruses and bovine papilloma viruses (Bertone & McClure, 1990; Bogaert et al., 2005; Knottenbelt & Kelly, 2000). Flies may also initiate sarcoid formation by translocating sarcoid cells into open wounds of horses. An association between sarcoid susceptibility and the major histocompatibility complex (MHC)-encoded class II allele equine leukocyte antigen W13 has been found in several breeds (Gerber et al., 1998). Histopathologically, sarcoids are characterized by epidermal hyperplasia and dermal fibroplasia, with pegs of hyperkeratotic epithelium extending into the depths of the dermal lesions.

A surgical biopsy is always required for definitive diagnosis, but treatment needs to be performed concurrently or soon after the biopsy because the mass usually is stimulated to proliferate after the surgical trauma of the biopsy. Due to the close proximity of periocular structures to the globe, some treatments reported for use on sarcoids elsewhere on the body cannot be used on eyelids without risking significant damage to the globe (Knottenbelt & Kelly, 2000). Various treatments have been reported for the treatment of equine periocular sarcoids (Table 29.2).

Immunotherapy with the immunostimulant, BCG-attenuated *Mycobacterium bovis* cell wall in oil has been used with some success for periocular sarcoids (Bertone & McClure, 1990; Knottenbelt & Kelly, 2000; Plummer, 2005) (Fig. 29.67). Surgical debulking alone has a high recurrence rate, but success rates approach 100% if debulking is combined with BCG (Knottenbelt & Kelly, 2000). Using a 25-gauge needle, 1 mL of BCG for each cm^3 of tumor is injected into the lesion (Komaromy et al., 2004; Plummer, 2005) (Fig. 29.35F). The sarcoid should be saturated, especially around the tumor's borders. Therapy is repeated every 2–4 weeks for as many injections as necessary to achieve remission, and it may cause a mild-to-severe inflammatory tissue reaction. Anaphylaxis may occur but can be minimized with pretreatment of flunixin meglumine, 1.1 mg/kg intravenously, and systemic corticosteroids (Knottenbelt & Kelly, 2000).

Cryotherapy, hyperthermia, carbon dioxide laser excision, and radiation therapy can also be effective treatment (Knottenbelt & Kelly, 2000). Interstitial brachytherapy with iridium-192 has an 87%–94% success rate for sarcoids (Walker et al., 1991). Intralesional cisplatin (1 mg/cm^3 tumor), or 5-FU (50 mg/mL with 1:1 sesame oil; 1 mL/cm^3 lesion) can be effective in approximately 80% of sarcoids and there is anecdotal evidence that autogenous vaccines have been effective as well (Bertone & McClure, 1990; Knottenbelt & Kelly, 2000; Théon et al., 1993). Intralesional injections of bovine papilloma virus vaccine have been successful in horses with sarcoids, but systemic side-effects can be severe in a few horses. We have had success in recent years using PDT for periocular sarcoids using the same parameters as those for SCC.

Topical 5-FU and oil of rosemary ointments can benefit some superficial and verrucous sarcoids (Knottenbelt & Kelly, 2000). Herbal pastes of blood root extracts can be used topically in some sarcoids and ocular SCC (XXTERRA™, Larson Labs, Ft Collins, CO, USA), although studies into the efficacy and rates of recurrence are lacking.

Melanoma

Melanoma is a relatively uncommon tumor of the horse and usually is observed in horses with gray or white hair (Giuliano, 2011). Arabians and Percherons have an increased risk. A slowly progressive, cutaneous, partially alopecic, pigmented mass of the eyelids is the typical clinical appearance of most equine adnexal melanoma (Fig. 29.36). Caruncular and conjunctival melanomas may appear as just a flat or nodular firm pigmented lesion. The size and location of the mass will dictate the clinical signs, which may include mild blepharospasm and corneal irritation. Older horses are

Table 29.2 Treatment for periocular sarcoids.

Type of therapy	Treatment	Therapy	Reported % non-recurrence
Topical therapy	5% 5-fluorouracil	BID × 5 days, then qd for 5 days, the QOD for 5 applications	67%
Intralesional immunotherapy	Bacille Calmette-Guérin	1 mL/cm^2 of tumor surface. Repeat every 2–4 weeks	0%–100%
Intralesional chemotherapy	Cisplatin	1 mg/cm^3 every 2 weeks for 4 treatments	33%–95%
Surgical excision	Excision	Once	50%
Excision and cryotherapy	Cryotherapy	Double or triple freeze—thaw	8%–18%
Hyperthermia	Hyperthermia	Tissue temperatures between 41°C and 45°C	0%
Brachytherapy	Radon, gold, iridium	6000–9000 cGy	87%–100%

Modified from Giuliano (2011).

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Figure 29.36 Multiple melanomas of the eyelids, caruncle, and conjunctiva in a grey horse. Adnexal melanomas are usually slowly progressive, cutaneous, partially alopecic, pigmented masses.

predisposed to the development of melanoma, possibly because proliferation of melanocytes is a manifestation of aging (Fleury et al., 2000). Oral cimetidine (dose 2.5 mg/kg of body weight orally every 8 hours) has been used to shrink non-ocular melanomas in horses, but no studies have been published on this treatment modality for adnexal melanomas (Dugan, 1992; Giuliano, 2011). Surgical excision, CO_2 laser ablation, cryotherapy, and local PDT have been recommended. Excision of an eyelid melanoma is usually curative because most of the masses are benign.

Lymphosarcoma

Lymphosarcoma is a relatively uncommon neoplasm in the horse. Infiltration of the eyelids and conjunctiva are the most common ocular manifestation of lymphosarcoma, but orbital and/ or third eyelid involvement can also occur (Fig. 29.37) (Rebhun & Del Piero, 1997). Adnexal lymphosarcoma must be differentiated from other causes of eyelid tumors or swelling such as sarcoid, habronemiasis, SCC, papilloma, melanoma, conjunctival pseudotumors or nodular lymphocytic conjunctivitis, and orbital fat prolapse. Biopsy and histopathology are required for definitive diagnosis. Lymphosarcoma should be differentiated from conjunctival pseudotumors or nodular lymphocytic conjunctivitis, which can be unilateral or bilateral, nodular or smooth, pink, nonulcerated conjunctival masses (Stoppini, 2005). A recent retrospective looked at a series of cases of extraocular lymphoma and determined that the prognosis for clinical remission in horses with solitary extraocular lymphoma is generally fair to good, as long as the affected tissues are completely excised, and



Figure 29.37 Nodular conjunctival lymphoma in a horse.

there is no eyelid, cutaneous, or systemic involvement (Schnoke et al., 2013). Horses diagnosed with the nodular form of extraocular lymphoma seem to have the best prognosis with complete excision. Surgical resection of the extraocular lesions as part of the treatment produced a statistically higher chance of a positive outcome when compared with horses where resection was not performed. Surgical debulking and local administration of anti-inflammatory agents (i.e., intralesional corticosteroid ± topical corticosteroids) are recommended.

Other Lid Tumors

Mast cell tumor is not common in horses. It generally occurs as a solitary nodule involving the conjunctiva that is cured by excision (Flores et al., 2017; Halse et al., 2014). Congenital hemangioma of the lid, nasal cavity, and gums has been diagnosed in a foal. Intralesion corticosteroids, cryosurgery, and leeches may be used to resolve the condition (Fig. 29.38). Equine papillomas resulting from a papovavirus are common among immature horses, and they may either regress spontaneously or require surgery, cryotherapy, or autogenous vaccination (Moore, 1992).

Eyelash Disorders

Distichiasis resulting in corneal irritation or ulceration and blepharospasm has been reported in the Fresian horse (Hermans & Ensink, 2014). This condition in rarely reported and although possible in any individual or any breed, the Fresian horse appears to be predisposed (Fig. 29.39). Electrocautery of the offending hair follicle performed in the standing, sedated animal is reported to have good success and a low rate of recurrence if there are only a few distichiae.

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Figure 29.38 Congenital hemangioma of the lids and conjunctiva also involved the ipsilateral nasal and oral mucosas.

Ectopic cilia have been rarely reported in the horse (Hurn et al., 2005). Corneal ulceration was not reported to occur as a sequela; instead blepharospasm, epiphora and keratitis were the presenting complaints. Conjunctivectomy to remove the follicle is generally successful.

Diseases of the Conjunctiva

Conjunctivitis is a nonspecific indicator of ocular inflammation. The conjunctiva becomes inflamed during infectious and noninfectious diseases of the lids, cornea, sclera, anterior uvea, nasolacrimal system, and orbit. Conjunctivitis is found in the neonatal-onset systemic diseases of neonatal maladjustment syndrome, neonatal septicemia, and immune-mediated hemolytic anemia (Lavach, 1992). Adult-onset diseases associated with conjunctivitis include keratoconjunctivitis sicca, lymphosarcoma, multiple myeloma, infection with *Moraxella equi* or *Streptococcus equi*, leptospirosis, EHV-4, adenovirus, equine infectious anemia, equine viral arteritis, influenza type A_2, polyneuritis equi, equine protozoal myeloencephalitis, vestibular disease syndrome, African Horse sickness, and epizootic lymphangitis (Barnett et al., 1995; Lavach, 1992). Allergic reactions to dust and environmental pollutants, conjunctival foreign bodies and debris, and chemical sprays can also cause conjunctivitis in the horse. A nodular lymphocytic conjunctivitis has been reported in horses (Stoppini, 2005). When conjunctivitis is noted, a complete and thorough ophthalmic examination should be performed to rule out the presence of intraocular disease. Unfortunately, a large number of horses with the insidious form of equine recurrent uveitis receive diagnoses of allergic conjunctivitis without recognition and diagnosis of their intraocular disease and the chronically untreated uveitis leads to vision loss and long-term discomfort.



Figure 29.39 Multiple lower eyelid distichia in a Fresian horse.

Onchocerciasis is associated with temporolimbal conjunctival thickening and depigmentation as well as with corneal edema, vascularization, and stromal cellular infiltration in adult horses (Barnett et al., 1995). Keratitis, conjunctivitis, and keratouveitis may also be present. The causative organism is *Onchocerca cervicalis,* and the vector is the female *Culicoides* sp. midge. Conjunctival biopsy specimens placed in saline may show free microfilaria. Large numbers of eosinophils and lymphocytes, with or without microfilaria, are found in conjunctival histopathologic specimens. This disease does not appear to be common at present in the United States. Treatment is systemic ivermectin and topical anti-inflammatory agents.

Conjunctival Neoplasms

SCC is the most common neoplasm of the equine conjunctiva. Treatment typically involves excision and some adjunctive therapy such as cryotherapy, beta-irradiation, or topical chemotherapy (see Eyelid Neoplasia). Lymphoma (Fig. 29.37), papilloma, hemangioma, and hemangiosarcomas of the conjunctiva have been diagnosed in the horse (Barnett et al., 1995). Benign vascular lesions and limbal pseudotumors of the conjunctiva have been reported (Herrera et al., 2003; Saroglu et al., 2005). Jaundice and anemia may change the conjunctival color to yellow and pale pink, respectively (Barnett et al., 1995) (Fig. 29.40).

Diseases of the Nictitating Membrane

Protrusion of the nictitans is usually a sign of pain. The eye should be examined for conjunctivitis, corneal ulcers, or anterior uveitis. Tetanus, inflammation because of bacteria, trauma, or parasites, enophthalmos because of pain, decreased globe size (microphthalmos or phthisis bulbi), protrusion of orbital fat, Horner's syndrome, hyperkalemic periodic paralysis, foreign bodies behind the nictitans or in

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Figure 29.40 Icterus can be manifest in the conjunctiva and sclera.

the conjunctival fornices, and neoplasia can all cause protrusion of the third eyelid (Bedford et al., 1990; Bacon et al., 1996; Lavach, 1992; Barnett 1995; Spier et al., 1990; Sweeney & Sweeney, 1984). A congenital lack of pigmentation on the leading margin of the nictitans can cause a false impression of nictitans protrusion.

Horner's syndrome is oculosympathetic paralysis, and it manifests with ptosis, nictitans protrusion, slight miosis, hyperemia of nasal and conjunctival mucosa, and increased temperature and sweating of the base of the ear, side of the face, and neck on the affected side (Bacon et al., 1996; Sweeney & Sweeney, 1984). Jugular vein and carotid artery injections, cervical abscesses, guttural pouch infections, neoplasia of the neck and thoracic inlet, and trauma to the neck and thorax are common causes in the horse (Bacon et al., 1996; Sweeney & Sweeney, 1984). Depending on the cause, the condition may, or may not, be reversible.

The most common neoplasm of the equine nictitans is SCC (Hendrix, 2005; Lavach, 1977, 1987). The diagnosis is confirmed on the basis of biopsy results, and treatment is surgical resection of the nictitans combined with cryotherapy, chemotherapy or irradiation. Haflinger and Belgian horses have a genetic risk factor, a missense variant in the gene damage specific DNA binding protein 2 (DDB2) on equine chromosome 12 (the same recessive risk factor that influences the development of limbal SCC in this breed), that predisposes them to SCC of the nictitans (Singer-Berk et al., 2018).

Nasolacrimal Disease

Congenital nasolacrimal atresia is one of the most common congenital ocular diseases in horses and is described earlier in this chapter. Acquired nasolacrimal disorders include obstructions from inflammation (dacryocystitis), strictures, foreign bodies, diseases of the paranasal sinuses, diseases of the upper dental arcade, neoplasia (especially SCC), and external trauma (Cassotis & Schiffman, 2006). Endoscopy of the NLD has been described in horses (Spadari, 2011).

Obstruction of the NLD occurs most commonly from accumulation of foreign material followed by bacterial growth and inflammation (i.e., dacryocystitis) in the NLD. Obstructions can occur from environmental debris accumulating in the NLD most commonly at a location immediately prior to the NLD exit from the lacrimal canal of the maxilla bone (Latimer et al., 1984). Clinical signs of NLD obstruction include epiphora, conjunctivitis, and usually mucopurulent discharge (Fig. 29.10A). Initial diagnosis is made after a complete normal ophthalmic examination (no cause of ocular discomfort found) and the inability of topical fluorescein dye to exit the ventral nasolacrimal puncta (a negative Jones test). If mucopurulent discharge is present, bacterial culture and sensitivity, and cytology of the discharge should be performed prior to administering additional medications. Following these tests, retrograde and normograde nasolacrimal irrigation should be attempted with the horse tranquilized. If irrigation is successful at clearing an obstruction, copious irrigation of the NLD should then be performed to ensure all debris has been cleared. Excessive force when irrigating the NLD should be avoided so as to prevent damage to the NLD. Unsuccessful NLD irrigation attempts with the horse under standing sedation warrant additional diagnostic testing such as dacryocystorhinography (DCR) via radiology or CT (Fig. 29.10B) to locate the site of obstruction and assess the surrounding structures. Having the horse anesthetized may assist in removing an obstruction via irrigation, from relaxation of facial muscles.

Initially, NLD obstructions can be treated with antibiotic solutions (ideally selected based on culture sensitivity results – but commonly triple antibiotic is used) that contain a topical corticosteroid, which may be beneficial to decrease swelling in the NLD, provided there are no ocular surface contraindications (e.g., a corneal ulcer). If the NLD obstruction is chronic, recurrent, or does not respond to treatment after 2 weeks, DCR or other imaging modalities as mentioned earlier should be performed. A 5-French male silastic or plastic canine urinary or ureteral catheter can be threaded either normograde (from proximal to distal) or retrograde with an attempt to pass through or break up the obstructions. It helps to gently irrigate with eyewash or saline through the catheter as it is passed to help remove debris and to expand the NLD. The catheter should not be forced if resistance is encountered, because severe hemorrhage may develop (Latimer & Wyman, 1984). Once passed, the silastic tubing is sutured in place for 4–6 weeks (Fig. 29.10C). Use of oral anti-inflammatory and oral antibiotic medication may be considered in these cases. Correction of primary sinus or

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dental disease should be performed to minimize pressure on the NLD. Creating a new pathway from the canaliculi to the nasal cavity (canaliculorhinostomy) (McIlnay et al., 2001) or from the ventral medial conjunctival surface to the maxillary sinus (conjunctivosinostomy) can be done as a last resort but have not been extensively studied in the horse (Brink & Schumacher, 2016; Giuliano, 2011).

Lacrimal gland infections and tumors are rare, but have been reported (Greenberg et al., 2011; Mathes et al., 2011). Dacryoadenitis in the horse may present with severe eyelid swelling and eyelid abscessation. Ultrasonography of the affected orbit may reveal marked swelling of the orbital lacrimal gland which may protrude from beneath the orbital rim (Reimer & Latimer, 2011). Dacryops, or a lacrimal cyst, resulting in a periocular swelling adjacent to the NLD has been reported in the horse (Dawson et al., 2016).

Diseases of the Equine Cornea

Clinically, the most common ophthalmic disease of the horse is corneal ulceration. Ulcerative keratitis is a major problem in horses because of the propensity for horses to develop bacterial and fungal infections. Horses also are afflicted with various other inflammatory and noninflammatory, nonulcerative keratopathies, including the common group of diseases termed immune-mediated keratitis. Furthermore, horses tend to heal corneal lesions with a higher amount of fibrosis and scarring, compared with other species. These features make treatment of corneal disease in horses frustrating, and prognosis, in many cases, is poor for normal vision.

Corneal Anatomy

Corneal disease is, unfortunately, a common complaint in our equine patients. Injuries and infections of the cornea are often caused by a combination of factors, including the lateral position of the globes, the prominence of the corneas, the environment in which patients reside, the opportunistic nature of the ocular flora, and the quick-to-react behavior of this prey species.

The cornea is the transparent, anterior-most part of the fibrous tunic of the globe. It is protected mechanically by the palpebrae and nictitating membrane and is nourished anteriorly by the precorneal tear film (PTF) and posteriorly by the aqueous humor. The anterior-most layer of the PTF is the lipid or oily layer derived from secretions of the meibomian glands located in the eyelid and caruncle. The aqueous tear portion is produces by the lacrimal glands located in the superiotemporal margin of the orbit. The posterior mucous layer is derived from secretions of conjunctival goblet cells. The hydrophilic nature of mucus substantially reduces surface tension and provides a smooth surface for the aqueous tear layer. The separation between the middle lacrimal tear layer and the posterior mucous layer is actually indistinct, making definitive thickness measurements of the two components difficult. It is highly likely that these two components form a graded mixture, with the posterior mucous component gradually blending into the anterior aqueous lacrimal tear component (Duane et al., 1995).

In healthy animals, the cornea is avascular and is the major contributor to light refraction or focusing capacity. The horse cornea ranges in thickness from 0.770 to 0.893 mm, with the peripheral cornea being relatively thicker than the central regions (Andrew et al., 2001; Neaderland, 1987). The cornea is comprised of three main layers, an outer epithelium, a middle stroma, and an internal endothelium. The epithelium consists of stratified squamous epithelium in 8–12 cell layers and is anchored to its basement membrane by hemidesmosomes (Duane et al., 1995; Neaderland, 1987). The epithelium provides the outermost protective barrier for the eye and when intact is very effective at preventing invasion of the deeper corneal structures by pathogens. The corneal epithelium itself can be divided into several regions. Two to three layers of nonkeratinized squamous cells make up the outer-most part of the epithelium which is in contact with the environment. Deep to this lies a transitional zone consisting of two to three layers of polyhedral wing cells, which rest upon a single layer of columnar basal cells. The basal cell layer is attached to a basement membrane, which represents the caudal boundary of the corneal epithelium. Analogous to the epithelia of other organs, the corneal epithelium undergoes continuous desquamation as the outermost cells are replaced by those beneath them, which are continuously produced at the level of the basal cell layer.

The stroma makes up 90% of the corneal thickness and is poorly cellular. It consists of very regularly arranged collagen fibers and a matrix of proteoglycans (Komai & Ushiki, 1991). The stroma is made up of thick bands of parallel collagen lamellae which are uniformly 25 nm in diameter, and extend across the entire cornea. The lamellae are formed from parallel bundles of collagen fibrils and are arranged in repeating orthogonal layers, with each layer extending at right angles to the bundles positioned above and below. Each fibril's small, uniform diameter, combined with the overall organized lamellar arrangement and carefully controlled fibril volume fraction, provide an optimal structure for light transmission in the healthy cornea (Komai & Ushiki, 1991; Meek et al., 2001, 2003; Takahashi et al., 1993). Taken together, these attributes make the stroma an extremely important layer for maintaining corneal transparency, allowing up to 99% of light to pass through unimpeded. The stroma is comprised mainly of type I collagen with trace amounts of type III collagen and proteoglycans, mainly keratin sulfate and chondroitin/dermatin sulfate. Collagen types IV, V, VI, and VII also play a role in corneal structure and repair. The horse stroma has regional biochemical

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differences of the proteoglycans chondroitin 6 sulfate (C6S) and chondroitin 4 sulfate (C4S) with higher levels of C6S in the superficial and superficial central layers, and more C4S in the deeper areas and deeper peripheral layers (Biros et al., 2002). The C4S has less water-holding capacity than the C6S indicating that corneal edema tends to become more prominent in the superficial horse cornea. Throughout the stroma, specialized cells known as keratocytes are fixed between the lamellae. These cells have characteristically narrow nuclei, thin cell membranes, and contain crystallins, which are thought to aid in light transmission. Keratocytes produce the majority of the extracellular matrix (ECM), both the collagen and the proteoglycans. In the normal cornea, keratocytes contribute to the maintenance of the stromal lamellae, and in the wounded cornea keratocytes undergo apoptosis or transformation into myofibroblasts, which are integral to the healing process (Duane et al., 1995). Also present in the stroma are migratory leukocytes, responsible for immune surveillance and response.

Deep to the stroma is the basement membrane of the innermost endothelium, known as Descemet's membrane. This structure is much more easily appreciable than the epithelial basement membrane and thickens with age because of continued secretion. Descemet's membrane is composed of many types of collagen. Collagen types III and IV comprise the posterior banded zone, types IV and VIII comprise the anterior banded zone, and types V and VI comprise the anterior unbanded zone (Duane et al., 1995; Meek et al., 2001). Type VIII is interesting in that it is found in the iridocorneal angle only, and is not present anywhere else in the cornea (Duane et al., 1995).

The endothelium is the innermost monolayer of interdigitating hexagonal cells which function via a Na+/K+-ATPase to keep water and solutes out of the cornea. They constantly pump fluid out of the stroma to maintain that tissue in a relative state of deturgescence which is necessary for stromal collagen fibril organization and optical clarity. Following experimental removal of the endothelium in otherwise normal eyes, cornea edema results in a 500% increase in corneal thickness (Andrew et al., 2001). These cells exhibit much less regenerative potential than other corneal cells throughout life, as evidenced by decreased cell density over time. The density of horse endothelial cells is 3,155 cells/mm^2. The mitotic potential of the horse corneal endothelium is probably limited but is not known. The number of equine endothelial cells decreases with age.

The regular arrangement of fibers and relatively dehydrated status of the cornea allow for its clarity. To maintain the degree of sensation necessary for avoidance behavior and protection, it is innervated diffusely by the long ciliary nerves, which arise from the ophthalmic division of the trigeminal nerve (cranial nerve V) and terminate in naked nerve endings in the anterior stroma and among the wing cells of the corneal epithelium. The cornea of the adult horse is very sensitive with the central cornea the most sensitive region and the dorsal region the least sensitive. Corneal sensitivity determined by evaluating the corneal touch threshold with a Cochet-Bonnet esthesiometer was 2.12 ± 0.62 cm (central) in one study and 4.82 ± 0.87 cm in a second study (Brooks et al., 2000a; Kaps et al., 2003). The corneal touch threshold of sick foals was less than healthy foals and adults being 3.21 ± 0.24 and 5.01 ± 0.61 cm respectively (Brooks et al., 2000a).

Corneal Wound Healing

When the cornea sustains injury, the subsequent steps necessary for wound healing depend upon the extent, location, and type of the injury. A complex orchestration of cytokine and growth factor activity, cellular migration, transformation, and tissue remodeling is triggered, much of which is still only partially understood. The sequence of events begins with stabilization of the wound, followed by tissue reaction to produce cells and ECM and finally tissue remodeling. Cell death is necessary for initiation of a response from uninjured surrounding cells (Wilson et al., 2007; Zieske et al., 2001). This death may be accomplished by either necrosis, in which there is damage to the cell's membrane accompanied by cell swelling, rupture and release of cytoplasmic contents which can be damaging to adjacent cells and induce inflammation, or by apoptosis. Apoptosis is induced either by the loss of trophic factors (survival signals) or by the action of killing factors. Apoptosis results in cell shrinkage with maintenance of the cell membrane until late in the process and allows removal of the cell without inducing injury to surrounding tissues (Wilson et al., 2007).

The basic response to injury occurs with little variation, regardless of whether the stromal wound was created by trauma, infectious disease, surgical intervention, or other etiologies. Epithelial defects will generally heal rapidly (as much as 0.6 mm/day in the uncomplicated wound) via centripetal migration of basal epithelial cells surrounding the wound into the defect and mitotic replication of limbal stem cells to reform the normal epithelial structure (Neaderland, 1987). When a stromal defect is present, the edges of the wound are initially debrided by PMNs and then keratocytes adjacent to the wound transform into fibroblasts and begin to synthesize collagen and proteoglycans to replace that missing from injury or infectious destruction (Gan et al., 1999; Wilson, 2001). Since the process of stromal regeneration is more complex than that of reepithelialization, it can be considerably more time consuming. An epithelial defect might heal in a matter of days while a stromal wound might take weeks or longer. The stroma that is initially laid down is disorganized and results in a scar. Over time, this hastily produced collagen will be reorganized which is how scars fade and become less dense. However, the injured cornea does not return to normal and never achieves the tensile strength and transparency of native cornea.

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When the endothelium is damaged, its ability to regenerate is quite limited. Cells that die are not replaced by new cells, instead the adjacent cells spread out and hypertrophy. Once the endothelial cell density or function declines below a certain threshold (generally regarded to be 400–700 cells/mm^2), persistent corneal edema will result.

Epithelial Wound Healing

Replacement of damaged and destroyed epithelial cells is nearly immediate. The first priority is to bridge the wounded area and re-establish a continuous cellular barrier across the defect. Signals generated by the damaged cells or from exposure of the epithelial basement membrane to tear fluid or the circulation are sent to surrounding intact epithelial cells. There is a short latent phase of approximately one hour during which the cell cytoskeleton and intracellular junctions are modified. Flattening, retraction, and release of hemidesmosomal attachments to the epithelial basement membrane by the basal epithelial cells nearest the wound edge occurs (Adler, 1992). These cells begin to extend actin-rich pseudopodia via their microfilament structure over the denuded wound surface. Cell membrane receptors, such as those for integrin, bind to extracellular proteins such as fibronectin, collagen and laminin, which initiates migration of the basal cells onto the wound surface at a rate of 0.75 μm/minute (Wang et al., 1994). Fibronectin, which appears immediately after injury and is produced by adjacent cells or is delivered through tears, aqueous or plasma, creates a temporary matrix for epithelial cell migration on the wound surface. A variety of endogenous growth factors and their receptors, cytokines, ECM proteins, and proteases are also important in the regulation of epithelial wound healing.

New epithelial cells are formed by mitosis to replace those that are leading the advance forward. The healing epithelium draws upon a pool of rapidly dividing stem cells at the limbus, the junction between the cornea and the sclera and overlying conjunctiva. Limbal stem cells have an almost unlimited proliferative capacity and lifespan (Plummer, 2017). Their division by mitosis gives rise to daughter cells that either replenish the stem cell pool or give rise to transiently amplifying cells that in turn give rise to terminally differentiated epithelial cells. The cells in the basal layer of the epithelium have some mitotic capability, but as they migrate more superficially, they lose their ability to multiply. The normal corneal epithelium undergoes constant self-renewal with complete epithelial turnover occurring in 10–12 days in the horse (Neaderland, 1987). In the wounded state, this process is accelerated.

Depending upon the size of the epithelial defect, the cells may have to migrate over several millimeters, which requires the simultaneous formation and destruction of attachments between the cells and the underlying ECM (Plummer, 2017). The destruction of those attachments is accomplished by the action of proteases, such as the serine proteases (tissue plasminogen activator, urokinase-plasminogen activator, plasmin, neutrophil elastase) and matrix metalloproteinases (MMPs) (Ollivier, 2004; Ollivier et al., 2003). Migrating epithelial cells move forward in a sheet-like formation until contact inhibition occurs by physical contact with adjacent cells. Once the epithelial defect is closed, the basal epithelial cells reform their adhesion complexes, the epithelium thickens with basal cells moving superficially when they are replaced by new basal cells incoming from the limbus, and the superficial epithelial cells terminally differentiate (Plummer, 2017). Re-formation of an injured epithelial basement membrane by the basal epithelial cells may take several weeks after injury (Cameron, 2005; Neaderland, 1987).

Stromal Wound Healing

Even as the epithelium begins to proliferate and migrate in earnest, there are important changes taking place within the wounded corneal stroma. The stimulus that initiates corneal stroma reaction is keratocyte death. The degree of the response depends upon the number of keratocytes that expire as a result of apoptosis or necrosis. Apoptosis of keratocytes plays a central role in initiating corneal wound healing cascades. If only a small number of keratocytes undergo apoptosis, the stromal response may be negligible or minimal (Wilson et al., 2007). Even when the original insult is only to the overlying epithelium, but the basement membrane or some denuded stroma is exposed, keratocytes in the superficial stroma undergo apoptosis as a secondary effect. With more significant or stromal wounds, a larger number of keratocytes die, resulting in a more profound stromal reaction. Keratocytes within a few hundred microns of the wound undergo apoptosis and die and those beyond that zone become "activated" and enlarge in size and alter their biochemical apparatus. They become migratory and transform into a fibroblast-like phenotype in order to be capable of replacing damaged stromal collagen fibrils, synthesizing ECM material, and restoring natural curvature to the cornea (Myrna et al., 2009, 2012).

Once the site of the injury has been cleared of damaged tissue and debris by the action of inflammatory cells, the activated keratocytes start to produce replacement collagen. These new collagen fibers, although made of type I collagen, are generally larger and more variable in caliber than native corneal collagen and the new proteoglycans also differ in character and proportion. These differences contribute to corneal opacity. A stromal scar is characterized by an increased number and haphazard arrangement of collagen fibers and keratocytes (Cameron, 2005).

Some of the activated keratocytes and other recruited keratocyte-like fibroblasts, derived from circulating monocytes and cells of bone-marrow origin or from epithelial to mesenchymal cell transformation of corneal epithelial or endothelial cells, differentiate into myofibroblasts that have large amounts of α-smooth muscle actin (α-SMA) which

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enables the cells to contract the surrounding matrix in the wound bed. Myofibroblasts are crucial to the survival and repair of the wounded cornea because of their unique ability to secrete ECM, produce adhesions in the surrounding stroma by crosslinking the ECM, and contract wound edges (Myrna et al., 2009, 2012). In addition, myofibroblasts produce MMPs, which are very active in collagen remodeling (Brown et al., 1991). However, with prolonged myofibroblast activity there is an increase in corneal haze. Myofibroblasts express greater quantities of vimentin, α-SMA, and desmin as they mature which has been associated with the formation of corneal haze (Jester et al., 1995). In addition, activated keratocytes and myofibroblasts decrease production of their internal crystalline proteins which are responsible for helping the cells maintain transparency. Crystallins are water-soluble proteins which control optical clarity in the lens and cornea and are normally abundantly expressed in corneal cells. In the face of this change, there is an increased reflectance of the cells and a corresponding increase in corneal haze.

Endothelial Wound Healing

Because of the limited capacity of endothelial cells to undergo mitosis, defects of the endothelium are covered by spreading and hypertrophy of adjacent cells, followed by the formation of a new Descemet's membrane (Andrew et al., 2001). If the total number and density of cells drops below a critical threshold, the capacity of those cells to remove ions from the stroma drops precipitously and corneal hydration results. The highly ordered orthogonal arrangement of the corneal lamellae becomes distorted and corneal opacity results. Persistent and severe corneal edema may result in focal accumulations of fluid or microbullae in the superficial stroma and epithelium that are subject to rupture which may result in corneal ulceration.

Inflammation (Keratitis)

The most obvious evidence of inflammation in most tissues is the appearance, proliferation, and dilation of blood vessels. Blood vessels dramatically facilitate delivery of immune and inflammatory cells to the site of injury and may prevent perforation. Since the cornea is normally devoid of blood vessels, the delivery of cells and protein factors (coagulation factors, growth-stimulating factors, and oxygen ion-regulating factors) necessary for initial clearing of debris and subsequent restoration of structure in a corneal ulcer is accomplished through the tear fluid externally and the aqueous humor internally. Within the first 12–24 hours of injury, inflammatory cells such as neutrophils, lymphocytes, macrophages, and monocytes enter the stroma via the PTF and conjunctival blood vessels at the limbus (O'Brien et al., 1998). Limbal blood vessels dilate and their endothelial cell walls become increasingly permeable and adhesive for intraluminal inflammatory cells. Adherent leukocytes migrate through the vessel walls via diapedesis and are drawn toward the wound between the corneal lamellae by variable gradients of cytokines. Once present, the inflammatory cells work to scavenge the remnants of necrotic and apoptotic cells and remove any invasive microorganisms in the vicinity. They do so by liberating proteolytic enzymes and phagocytizing cellular and noncellular debris. If upregulated or produced in excessive amounts, these proteolytic enzymes, which include the serine proteases and MMPs, can contribute to progression of the original injury (Mulholland et al., 2005; Ollivier et al., 2004). Tear film proteases are elevated by 2–4 times normal levels in horse eyes with corneal ulcers, and must be reduced to baseline levels before healing is complete (Ollivier et al., 2003, 2004).

If the stimulus for inflammation persists, episcleral vascular endothelial cells at the limbus will proliferate and migrate forming capillary tufts that sprout into the cornea between the stromal lamellae towards the injury or stimulus (Dupps & Wilson, 2006). The cells then form a lumen for an incipient vessel. The ECM surrounding the new blood vessel is degraded by enzymes such as MMPs and a basal lamina forms around the vessel as it matures. Significant vascular invasion and the transitional tissues surrounding it lead to the development of granulation tissue. Vascularization is an expected healing response and can provide a range of cells and growth factors that encourage healing and structural integrity. However, blood vessels have the unwanted consequence of increasing corneal opacity. Corneal vascularization may occur at a rate of ~1 mm/day in the horse if unimpeded by pharmacotherapy or host or pathogen response.

While inflammation is an essential response to injury and infection, it can be a significant source of additional injury to host tissues and can initiate or exacerbate tissue scarring. Judicious modulation of corneal inflammation is a therapeutic goal in many instances of corneal disease.

Perforating Corneal Injury

If a wound results in a full-thickness rent in the cornea, the exposed hydrophilic stroma swells when exposed to tears and aqueous humor (Cameron, 2005). This swelling may seal the wound if there is not a large gap or a large degree of tissue loss. Alternatively, acute-phase inflammatory proteins, particularly fibrin, which are generated from the aqueous humor and from transudation of factors from surrounding blood vessels, will arrive to form a temporary plug. If the wound is too expansive to be supported by this fibrin plug, surgical stabilization is indicated to replace missing tissue. The anterior and posterior aspects of the wound gape and retract with subsequent curling of the epithelial basement membrane and Descemet's membrane. Biochemical signals then recruit distant cells toward the

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wound center with the epithelial cells being first to act. Epithelia cells at the leading edge of the wound loosen their attachments and migrate along a layer of newly accumulated fibronectin across the surface of the wound (Cameron, 2005; Plummer, 2017; Wang et al., 1994). Activated keratocytes react much more slowly and in some instances may not begin their migration until the epithelial cells have covered the wound surface. Once they migrate to the wound edges, these fibroblasts and fibroblast-like cells begin producing collagen and proteoglycans to replace the tissue missing as a result of the injury and clean up processes (Cameron, 2005; Wilson, 2012). The endothelial cell response occurs between those of the epithelium and the stroma. These cells thin and flatten and migrate over a provisional matrix of fibronectin toward the center of the wound. The epithelium and endothelium reform their respective basement membranes much later in the course of healing. Basement membrane and cellular adhesion sites may take up to 6 weeks after the insult to become well established. The formation of a stromal scar is a dynamic process and may continue for months or years after the initiating event. The wounded site will never regain the degree of tensile strength it originally had. Estimates range from 25% to 70% of normal depending upon the extent and orientation of the wound (Cameron, 2005).

Corneal Infection

Infection of the cornea requires four steps: (1) access of the microbe to the ocular surface, (2) attachment of the microbe to the ocular surface, (3) penetration of the microbe through the epithelium, and (4) subsequent growth and expansion of the organism. In instances when the physical, innate, and active immune responses of the ocular surface do not prevent infection of the cornea, a robust inflammatory and immune reaction will be triggered in the attempt to maintain ocular integrity (O'Brien et al., 1998).

Fortunately, the corneal immune system is robust and corneal infections are rare. In fact, most cases of corneal infection with bacteria or fungi require some sort of antecedent trauma or preexisting disease process. However, opportunistic pathogens are very adept at evolving ways around host defenses. Bacteria and fungi have several important virulence factors that can improve their ability to cause disease in immunocompetent hosts. Many bacteria express a thick capsule to minimize the ability of the immune system to recognize and respond to them. A variety of surface proteins and factors such as pili and flagella that permit pathogens to bind to epithelium, collagen, or fibronectin can facilitate adhesion to and migration through the ocular surface. Some pathogens are capable of secreting a slime layer, or glycocalyx, that increases adhesion as well. The production of enzymes such as hyaluronidase, alkaline protease, and elastase allow for the destruction of ECM which creates space for migration and invasion (Ollivier et al., 2003, 2004). Some pathogens secrete proteins such as coagulase, catalase, and leukocidin that increase resistance to phagocytosis. Others produce exotoxins that directly damage host tissue (Norlund & Pepose, 2005).

Once a pathogen has eluded the passive adaptations of the innate immune system, the corneal response to infection is a combination of innate and active immune responses and inflammation. The nonspecific responses include the production and upregulation of antimicrobial proteins that either prevent adhesion, inactivate bacterial proteases, impair microbial growth, or physically degrade the cell walls of pathogens, and the recruitment of phagocytic cells that kill and remove microbes. Inflammation results in increased blood flow and leukocyte delivery and recruitment from the conjunctiva, tear film, and areas of corneal vascularization. While the profound response to infection is necessary for elimination of the offending organism, it may contribute to further damage of host tissue and the formation of fibrosis and corneal opacity.

Leucocytes in the stroma appear clinically as white infiltrates. Ulcers are relatively clear without leucocyte infiltration, and turbid white if present. They eliminate bacteria by phagocytosis but release massive quantities of degradative enzymes which can cause the bystander injury of stromal "melting." Neutrophils can migrate into the cornea at ~8 mm/day and release lysosomal enzymes, superoxide radicals, and peroxides to damage the predominantly cell-free stroma as the defense mechanisms are intracellular (Miyahara et al., 2004; Reim et al., 1997). In the era of very effective antibiotics, microbes are rapidly eliminated leaving the leucocytes to destroy the cornea. This is generally followed by extensive fibroblastic collagen deposition and corneal scarring. Ulcers can, however, continue to deteriorate despite sterilization of the ulcer site caused by excessive activity of proteases elaborated by the host immune response and constitutive tissues (Ollivier et al., 2004). The horse cornea does have the often unrecognized amazing ability to slowly remodel itself to diminish the size of large corneal scars, however.

The environment of the horse is such that the conjunctiva and cornea are constantly exposed to bacteria and fungi. The conjunctival microbial flora of the horse varies, however, depending on the age of the horse, season, and the geographic area (Andrew et al., 2003; Rosa et al., 2003; Samuelson et al., 1984). Many bacterial and fungal organisms normally found in the equine conjunctival flora are potential ocular pathogens. *Fusarium* and *Aspergillus* sp. are both common causes of ulcerative fungal keratitis among horses in the United States (McLaughlin et al., 1983; Moore et al., 1983b). Young horses appear at risk of Gram-negative and fungal infections (Andrew et al., 2003). Gram-negative bacteria known to be associated with equine corneal ulcers include *Pseudomonas* sp. and assorted coliform bacteria (Gemensky-Metzler et al., 2005). *Staphylococcus*, *Listeria*,

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and *Streptococcus* sp. and other Gram-positive bacteria can cause infectious equine keratitis. Mixed bacterial and fungal infections can also be present.

The pathogenicity of a bacterial or fungal species for the cornea may relate to its ability to adhere to injured corneal epithelium (Dong et al., 2005). *Pseudomonas aeruginosa* and *Staphylococcus aureus* exhibit a greater degree of adherence to corneal epithelium than do bacteria that are not common corneal pathogens (Panjwani et al., 1990; Reichert & Stern, 1984). The intrastromal spread of the pathogen is facilitated by production of serine proteases, elastase and alkaline protease, and the MMPs. All of these proteases are increased in the tears of horses with ulcers. Fungi in horses appear to be able to adhere to healthy corneal epithelial cells in the absence of a normal PTF layer (Brooks et al., 2000b). Pathogenic fungi are better able to adhere to the cornea and PTF, chemotactically attract more leukocytes, are associated with higher levels of MMP-9, and penetrate deeper vertically into the cornea (Dong et al., 2005). Fungal organisms have a unique propensity to move or "tunnel" deep in the stroma towards Descemet's membrane of horses (Brooks, 2004). Pathogenicity may also be influenced by the host's ability to recognize and respond to a potential pathogen. Recently, it has been shown that the equine cornea cells express a variety of Toll-like receptors which are critical to the recognition of pathogens. By activating immune cells, Toll-like receptors are key factors in initiating the inflammatory cascade during infection (Gornik, 2011).

Ulcerative Keratitis

A corneal ulcer is present when there is a break in the corneal epithelium, most commonly caused by trauma. Ulcers can range from simple, superficial ulcers or erosions, to full-thickness corneal perforations with iris prolapse (Fig. 29.41). Abrasions are superficial and often subtle ulcerative injuries generally involving only the superficial epithelium. Some or all of the layers of the surface epithelium are lost, but the anterior stroma and the epithelial basement membrane generally remains intact in abrasions. Clinically, the healed superficial abrasion with no stromal involvement is transparent. Ulcers can exhibit hyperproteinase activity and be infected or sterile. Equine corneal ulceration is a potentially sight-threatening disease requiring early clinical diagnosis, laboratory confirmation, and appropriate medical and sometimes surgical therapy. Corneal infection, iridocyclitis, and excessive tear film protease activity are always major concerns in even the slightest corneal ulcerations in horses.

Diagnosis

The casual observer of a horse with a corneal ulcer will note lacrimation, blepharospasm, photophobia, conjunctival hyperemia, and ocular cloudiness. When a veterinarian is evaluating a horse with a possible corneal ulcer, it is important to look carefully for any abnormality that may prevent the ulcer from healing and to eliminate this abnormality. Infection should be considered possible in every equine corneal ulcer. Infectious keratitis in the horse develops in eyes with traumatic corneal abrasions and in eyes with epithelial defects resulting from chronic edema, keratoconjunctivitis sicca, exposure keratitis, neurotrophic keratitis from equine protozoal myeloencephalitis, and neuroparalytic keratitis.

Prior to instilling any medication, the palpebral conjunctiva and bulbar surface of the third eyelid are examined for the presence of a foreign body, the palpebral reflex and corneal reflex are evaluated, and the tear film is examined. A corneal ulcer should be characterized with regard to size, depth, and the presence or absence of cellular infiltration (white or yellow stromal infiltrate). It is important to approach each case of ulcerative corneal disease in the horse in a systematic manner. If the ulcer is chronic (e.g., greater than 5–7 days in duration) or if there is cellular infiltrate or significant uveitis present, then culture (bacterial and fungal culture and sensitivities) should be collected, followed by a Schirmer tear test, then application of fluorescein dye. Corneal cultures should be obtained first, then followed by corneal scrapings for cytology (Massa, 1999). Cytology of the corneal lesion is particularly helpful in the initial treatment of the ulcer. Sampling the edge and base of the lesion to detect bacteria and hyphal elements can be obtained with the blunt handle end of a sterile scalpel blade, Kimura spatula, or a cytology brush after application of topical anesthesia (Fig. 29.20C). While all techniques for collection are acceptable, the highest quality specimens are collected via the scalpel blade technique (Proietto et al., 2016a). A variety of topical and subconjunctival agents may be used to achieve corneal anesthesia including lidocaine (injected subconjunctivally or applied as a topical gel), bupivacaine, mepivacaine, tetracaine, and proparacaine, with durations of action ranging from 25 minutes to 2 hours (Jinks et al., 2018; Monclin et al., 2011a; Pucket et al., 2013; Regnier et al., 2018). Superficial swabbing may not yield the organism (or organisms) in a high percentage of cases as the organisms are deep within the ulcer. Following scraping of the equine cornea, cells are transferred to a glass slide and stained (Gram, Giemsa, and Diff-quik stains) to examine for bacteria, fungal hyphae, and predominate cell type that is present (Dwyer, 2011). The presence of Gram-negative rods may indicate an infection with *Pseudomonas* sp. The presence of fungal hyphae is pathognomonic for mycotic keratitis, with *Aspergillus* sp. and *Fusarium* sp. being the most frequent corneal pathogens. Fungal involvement should be suspected if there is a history of corneal injury with vegetative material or if a corneal ulcer has received prolonged antibiotic or corticosteroid therapy (or both) with either slight or no improvement. Mixed bacterial and fungal infections are not uncommon.

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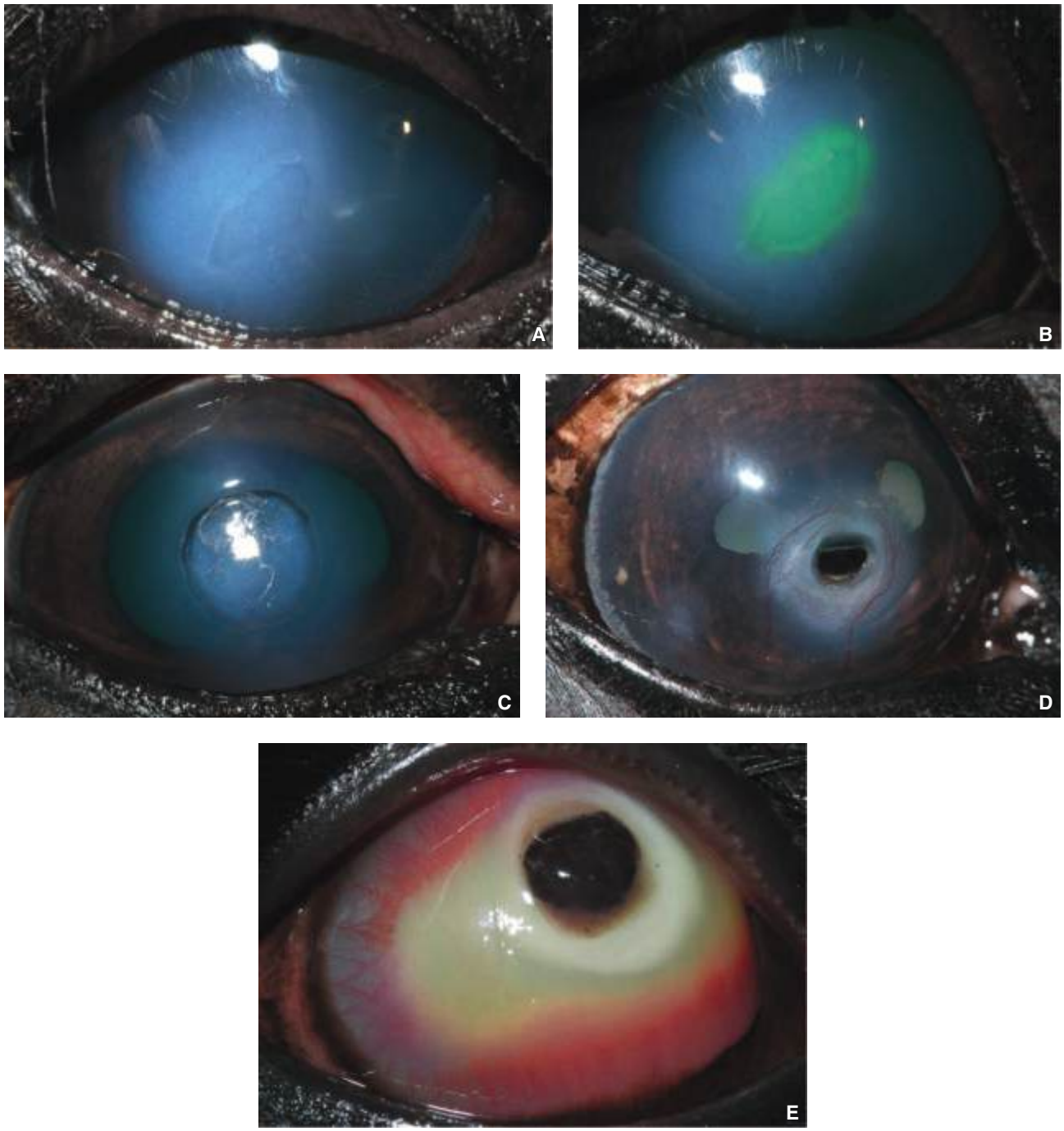


Figure 29.41 Corneal ulcers are characterized by the loss of epithelium and retention of topical fluorescein. **A.** Superficial ulcer exhibiting loss of only epithelium. Corneal edema surrounds the wound. **B.** Fluorescein retention in the stroma of the wound bed. **C.** The deeper stromal ulcer exhibiting loss of epithelium and anterior stroma. **D.** Descemetocele. All stroma is missing which exposes Descemet's membrane. This lesion is chronic, as evidenced by the ring of vascularization and fibrosis surrounding the ulcer. **E.** Full thickness corneal wound. Perforation of the cornea was followed by prolapse of the iris. There is severe infiltration of the cornea with inflammatory infiltrate and a robust vascular response.

Staining with fluorescein dye for detection of epithelial defects followed by staining with Rose Bengal dye to evaluate the stability of the PTF is critical in the horse. Absence of the mucin dominated PTF will result in Rose Bengal retention of erosions and ulcers.

Rose Bengal retention occurs in early stages of fungal keratitis, keratoconjunctivitis sicca, and viral keratitis in the horse likely because of disruption of the PTF (Brooks, 2004; Brooks et al., 2000b). Tear film stability is critical for the rapid healing of corneal ulcers in horses (Fig. 29.42). Tear

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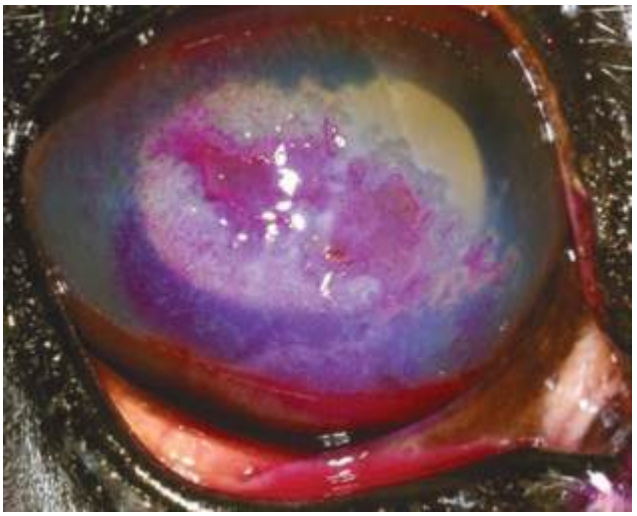


Figure 29.42 Corneal ulcer retaining Rose Bengal. The pink staining areas indicate foci absent of normal tear film.

film break up times are also important to assessing tear film health in the horse. Tear film break up times of 10 seconds or less are associated with delayed healing in many cases.

Principles of Therapy for Ulcerative Keratitis

Regardless of the stage or condition of the corneal ulcer, the goals of therapy are identical and include:

- Address any primary underlying etiology if one can be identified
- Treat or prevent infection
- Slow the breakdown/dissolution of corneal collagen
- Address secondary uveitis
- Provide structural support, if necessary
- Prevent self-trauma
- Analgesia.

The specific drugs chosen and the frequency of administration will vary, however. Horses with corneal ulcers are often in pain, and topical treatment is usually difficult. In a fractious horse or one with a painful eye needing frequent therapy, subpalpebral or nasolacrimal lavage treatment systems are recommended. Various techniques have been described, but we prefer to use a length of silicone tubing with a single hole and footplate positioned in the superior palpebral fornix (Fig. 29.43). Subpalpebral kits are are manufactured and distributed commercially (Mila International, USA) or can be made in-house if silastic tubing can be acquired. The ventral palpebral fornix can also be used (Giuliano et al., 2000). Using conventional eye drops beneath the upper lid, increased absorption into the anterior chamber was observed when compared with lower-lid administration (Wong et al., 1994). Minimal equipment is required and the tubing can be removed without sedation. Sedation, eyelid akinesia, sensory eyelid blocks, and topical anesthesia are generally sufficient to place this tubing system.



Figure 29.43 Subpalpebral lavage treatment system placed in the upper conjunctival fornix.

Medical Therapy

Medical therapy always comprises the major thrust of ulcer control, even when judicious surgical approaches are required. This intensive pharmacologic attack should satisfy the therapeutic objectives of ulcer sterilization, reduction in tear film protease activity, uveitis control, and be modified according to need and response to therapy. Treatment frequently needs to be sustained for weeks or, occasionally, even months. Once the cause of a corneal ulcer is presumptively diagnosed on the basis of cytology or is conclusively proved on the basis of culture, the objectives of medical therapy must be carefully considered to ensure comprehensive treatment. First, bacterial and fungal growth must be halted and the microbes rendered non-viable. Secondary tear film protease activity must be inhibited. Third, anterior uveitis must then be controlled to prevent blinding sequelae.

Antimicrobials

The ulcer must be sterilized although sterility does not necessarily equate with rapid or complete healing (Reim et al., 1997). In fact, antimicrobials may actually hinder corneal healing (although so does infection). Infection initiates and complicates ulcerative disease processes, but the increased proteinase activity in the PTF and stroma perpetuate it. The killing of microbes is not that difficult in most cases. However, the appropriate agent for the microbe must be selected. There are many considerations when choosing a topical antibiotic for ophthalmic use, including spectrum of action, bacteriostatic vs. bacteriocidal nature, relative toxicity, formulation,

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and the condition of the eye. In general, the more severe (infected, deep) the ulcer, the use of a bacteriocidal drug that has a more targeted spectrum is desired and a solution or suspension is preferred over an ointment. It will usually be administered very frequently until improvement is noted. A noninfected, uncomplicated ulcer benefits from a broad-spectrum, minimally toxic antibiotic of either formulation. It is best delivered less frequently (3–4 times a day; frequently enough to sterilize the wound and prevent infection, but not frequently enough to damage healing host cells). The aminoglycosides, fluoroquinolones, and drugs such as polymyxin B may be appropriate to treat Gram-negative bacterial infections (McLaughlin et al., 1992a). Cephalosporins, macrolides, tetracyclines, second-generation and higher fluoroquinolones, and drugs such as chloramphenicol and gramicidin have good action against Gram-positive bacteria.

Miconazole, natamycin, fluconazole, voriconazole, clotrimazole, itraconazole, and dilute betadine solution have been used successfully topically to treat fungal ulcers in the horse (Ledbetter, 2017). Newer antifungal agents including posaconazole and caspofungin have been used with success in a few instances. Antifungals may need to be used for several weeks because the offending agents are relatively long-lived and large compared with bacteria and because most antifungals are fungistatic rather than fungicidal. Systemic antifungals may be beneficial but their true efficacy and impact is not known. Intravenous miconazole is associated with severe anaphylactic reactions in the horse, and it should be used with caution. Oral itraconazole does not reach therapeutic levels inside the normal horse eye, although it may have improved penetration when the blood–aqueous barrier is compromised (as it is with uveitis), whereas oral fluconazole and voriconazole do reach therapeutic antifungal levels in the horse eye (Clode et al., 2005; Latimer et al., 2001).

Antimicrobial medications must be handled and stored with care. Each agent has different requirements to ensure efficacy, including temperature and composition of the vials used for storage and delivery. It was recently discovered that when voriconazole is stored in plastic vials or in constant-rate infusion pumps, the drug will crystalize out of solution or bind to the material and be unavailable for delivery to the eye (Smith et al., 2014a). New formulations that improve the delivery of antimicrobial drugs to target tissues or to create deposits of drug that can reduce the frequency of dosing are in development, such as a sustained-release voriconazole-containing thermogel for subconjunctival injection (Cuming et al., 2017).

Control of Uveitis

In the horse, as in other species, iridocyclitis is the usual and expected sequela to ulcerative keratitis. Uveal inflammation is incited through an axon reflex mediated by the ophthalmic branch of the trigeminal nerve, which is sensory for the cornea, conjunctiva, and uvea (Brooks, 2002). The sensory nerve endings release substances that induce the uveitic response. The horse is particularly sensitive to this corneal ulcer-associated axon reflex uveitis. Miosis, aqueous flare, hypopyon, and hypotony are present to some degree in eyes with ulcers. Controlling the uveitis may be as difficult as healing the cornea.

Anterior uveitis in horses with corneal ulcers should be treated by both the topical and the systemic route. Phenylbutazone (2 mg/kg PO q12h) or flunixin meglumine (1 mg/kg PO, IV, IM q12h BID) can be used orally or parenterally at anti-inflammatory dosages, although flunixin has the better clinical effect of the two agents. Firocoxib has been proven able to penetrate the blood–aqueous barrier of normal horses, but its clinical effect in uveitis has not been studied (Hilton et al., 2011). Topically applied anticholinergics (e.g., 1% atropine) are effective in causing pupillary dilation and stabilizing the blood–aqueous barrier. Pupillary dilatation protects the visual axis from occlusion, and it may minimize development of synechiae. Relaxation of the ciliary muscles also eliminates ciliary spasm, which is a factor in ocular discomfort. Horses on topical atropine should be watched closely for symptoms of reduced gut motility and in rare cases, colic. The frequency of administration will vary with the degree of uveitis present (q4–24h).

Collagenolysis Prevention

Severe corneal inflammation secondary to bacterial or fungal infection may result in sudden, rapid corneal liquefaction and perforation. Activation or production of proteolytic enzymes (or both) by corneal epithelial cells, leukocytes, and microbial organisms are responsible for stromal collagenolysis. MMPs and serine proteases are elevated in the tears of both eyes of horses with an ulcer in one eye (Ollivier, 2004; Ollivier et al., 2004; Strubbe et al., 2000). The ulcerated eye has higher tear protease levels. MMP-2 increased 83%, MMP-9 increased 232%, and neutrophil elastase increased by 172% in the PTF of equine eyes with ulcers (Strubbe et al., 2000). MMP tear levels decrease with treatment (Ollivier et al., 2004). MMP tear levels decline as an ulcer resolves/heals. Infected ulcer tear MMP levels must decline more to heal (Ollivier et al., 2004). Serine proteases (neutrophil elastase) are inhibited by serum and alpha-1-protease (A1P; pre-albumin inhibitor in the horse). Serum contains alpha-2-macroglobulins and platelet-derived growth factors. MMPs are inhibited by tissue inhibitors of metalloproteinases (TIMPS), serum, EDTA, tetracyclines, ilomostat, and acetylcysteine. Neutrophil elastase inhibits the activity of TIMPS. MMP inhibits pre-albumin inhibitors. Large amounts of neutrophil elastase may cause indirect breakdown of collagen by increasing the MMP activity.

Autologous serum and plasma have been successfully used in the treatment of severe dry eye, persistent epithelial defects, and other severe ocular surface disorders (Brooks, 2004; Geerling et al., 2004; Ollivier et al., 2003). It is supposed that growth factors, fibronectin, and vitamins in

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serum support the proliferation of corneal epithelial cells (Hartwig et al., 2005). Serum eye drops may be produced as an unpreserved blood preparation. For many years, we have routinely and successfully used topically administered autogenous serum in equine ulcers with evidence of collagenolysis, infection, or chronicity (Berman et al., 1975; Ollivier et al., 2003). This serum can be administered topically as often as possible, and it is replaced by new serum every 8 days. It can be stored frozen, at room temperature, or in a refrigerator. Acetylcysteine (5% or 10%) or 0.17% dipotassium EDTA can also be administered until stromal liquefaction diminishes. In some eyes, multiple anticollagenase products may be needed to arrest melting. We tend to minimize the use of acetylcysteine in our cases as it can disturb the stability of the tear film. In instances of gross keratomalacia, anticollagenase agents should be employed as often as hourly; if the goal is to prevent malacia and support healing with growth factors, administration every 4–6 hours is recommended. Recent studies suggest that platelet-rich plasma may also have a positive impact on corneal wound healing (Rushton et al., 2018) (Table 29.3).

Inappropriate Therapy

Topical corticosteroids are contraindicated in treatment of equine corneal infections. Even topical corticosteroid instillation to reduce the size of a corneal scar or reduce blood vessel perfusion may be disastrous if pathogens remain indolent in the corneal stroma or on the ocular surface.

Superficial, Uncomplicated Corneal Ulcers

Simple, uncomplicated corneal ulcers have the characteristics of having corneal epithelial cell loss with exposed corneal stroma, are acute in onset, do not have characteristics typical of infection (stromal malacia, cellular infiltrate, stromal defects), and a foreign body is not present. Diagnosis of a superficial, uncomplicated corneal ulcer is based on the history of an acute-onset painful eye and findings on a complete ophthalmic examination of possible focal corneal edema and fluorescein dye retention. Usually, the fluorescein dye retention is intense and uniform across the ulcerated area (Fig. 29.20B and Fig. 29.41B). It is always recommended to collect bacterial and fungal cultures and examine corneal cytology, even in these suspected uncomplicated ulcers. A superficial uncomplicated corneal ulcer should have no microorganisms (on culture or cytology), no cellular infiltrate, no foreign body, and no secondary uveitis. Treatment for an uncomplicated superficial ulcer should consist of a topical broad-spectrum antibiotic every 6 hours (e.g., neomycin, bacitracin, gramicidin, ofloxacin), topical 1% atropine once daily or as needed to keep the pupil dilated, and treatment of any secondary uveitis, if present (e.g., systemic NSAIDs). Topical corticosteroids are contraindicated in equine ulcerative keratitis, and topical NSAIDs may delay reepithelialization of the cornea and therefore are also contraindicated.

Complicated Corneal Ulcers

Complicated corneal ulcers are those that do not heal within 72 hours, have a collagenase component (i.e., melting corneal ulcers), have a mechanical obstruction to healing (i.e., foreign body, indolent), are infected (either with bacteria or fungus), and/or are in danger of perforation.

Indolent Corneal Ulcers

Indolent corneal ulcers in horses are similar to small animal indolent ulcers. They are chronic, superficial corneal ulcers

Table 29.3 Anticollagenase medications and their actions.

Equine serum*	Alpha-2 macroglobulin and alpha-1 protease inhibitor; MMP, serine protease inhibitor; entrapment of protease
EDTA (0.17% in sterile water)*	Chelating agent (Ca and Zn); MMP inhibitor
N-acetylcystene (5% in artificial tears)*	Chelating agent (Ca and Zn); MMP inhibitor
Ilomostat (Galardin)	Competitive inhibition of MMP; direct inhibition of MMP; inhibits release of TNF-alpha
Doxycycline*	Competitive inhibition of MMP
Minocycline*	Competitive inhibition of MMP
Alpha-1 proteinase inhibitor	Serine protease inhibitor; entrapment of protease
Aprotinin	Serine protease inhibitor; entrapment of protease
Tissue inhibitor of metalloproteinase (TIMP)	Direct inhibition of MMPs
Amniotic membrane (tissue and homogenate)*	Direct inhibition of MMP; inhibits release of TNF-alpha
Tetanus antitoxin*	Competitive inhibition of MMP
Platelet-rich plasma	Alpha-2 macroglobulin and alpha-1 protease inhibitor; MMP, serine protease inhibitor

* Available commercially or easily compounded. EDTA, ethylenediaminetetraacetic acid; MMP, matrix metalloproteinases.

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where the corneal epithelium will not adhere to the underlying corneal stroma. The characteristic appearance is a superficial ulcer with a redundant epithelial border (Fig. 29.44). Other signs include minimal corneal neovascularization, focal edema, and moderate discomfort. There is no age predilection, and foals may be affected. However, geriatric animals and those with pars pituitary intermedia dysfunction (also referred to as Equine Cushing's) have a harder time with corneal ulcer healing (Michau, 2003). Treatment of indolent ulcers requires searching for an underlying cause (foreign bodies, ectopic cilia, eyelid abnormality, repeated trauma). Cytology and bacterial and fungal cultures should be carried out to eliminate an infectious etiology. Typically, the lesions are sterile and there is no contributing abnormality of the eyelids or palpebral conjunctiva. If an underlying or contributing factor is not identified, the ulcer is then designated as indolent, suggesting a hyaline membrane has formed that is preventing epithelial adhesion (Håkanson & Dubielzig, 1994; Michau, 2003; Rebhun, 1983). However, a recent histopathologic study of indolent ulcers in the horse consistently failed to identify an anterior stromal acellular hyaline zone such as that observed in canine spontaneous chronic corneal epithelial defects (Hempstead et al., 2014). The most consistent histopathological characteristics of equine chronic, nonhealing, superficial, corneal ulcers in that study included epithelial nonadherence, epithelial dysmaturity and mild to moderate stromal inflammation (Hempstead et al., 2014). The etiology is poorly understood in all species but is likely to involve a complex process of failure of normal basement membrane regeneration and absent or delayed hemidesmosome attachment after minor superficial insult. Overexpression of MMPs by abnormal basal epithelial cells in combination with anomalous expression of adhesion macromolecules, fibronectin, and laminin may be contributing factors. In one study, six of 23 affected eyes had a past history of corneal ulceration and a further five had a history of corneal or periocular trauma (Michau, 2003). In some cases, the disease may represent a primary epithelial basement membrane disease.

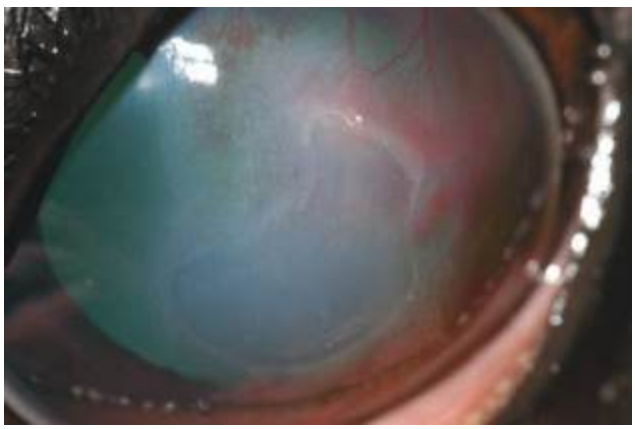


Figure 29.44 Indolent ulcer with characteristic hyperplastic and nonadherent "lip" of epithelium along its margins. Blood vessel advancement indicates the subacute to chronic nature.

Indolent ulcer treatment is similar to that for small animals except that grid keratotomy was shown, in one study, not to speed healing of these ulcers in horses (Michau et al., 2003). Debridement of the redundant epithelial margins and base is the initial treatment of choice (Michau, 2003). A diamond burr is an effective and safe tool for debridement of indolent corneal ulcer in the horse (Lassaline-Utter et al., 2014a). This may be used in conjunction with a therapeutic soft contact lens to physically protect regenerating basal epithelium. A temporary tarsorrhaphy may facilitate retention of the contact lens. Where initial debridement fails, superficial lamellar keratectomy and conjunctival grafting are further treatment options. If indolent ulcers persist, or develop a plaque-like area in the superficial stroma, then a superficial keratectomy must be performed. Thermal cautery has been used successfully in two horses with nonhealing erosions where epithelial debridement had failed (Bentley & Murphy, 2004). The use of topical oxytetracycline antibiotic ointment has been anecdotally associated with improvement of these ulcers. The prognosis in all cases is guarded because nonhealing erosions are potentially recurrent, and continued dehiscence of the poorly adherent repair epithelium by the mechanical action of the eyelids and/or poor tear film stability may be difficult to overcome.

Chemical Keratitis

Chemical keratitis is rarely reported in the horse and is likely to be either malicious or caused by inadvertant exposure to agricultural sprays, insecticidal preparations, or shampoos (Rebhun, 1980b). Immediate treatment is usually not the province of the veterinary surgeon, but owners should be instructed to carry out immediate, prolonged, and copious lavage of the eye with clean tap water as a primary first aid measure.

The distribution of the lesions over the corneal surface is very variable and depends upon the route by which the eye is exposed to the chemical. Spray injuries commonly cause focal punctate lesions whose distribution may match the palpebral fissure. This is particularly the case in acidic spray injuries. Where possible, the chemical involved should be identified and its pH established, or the pH of the conjunctival sac checked prior to lavage. The pH of the chemical involved is a primary determinant of the extent of the corneal injury to be expected.

Acid injuries are more common in the horse and are less threatening than alkali injuries. Acid exposure results in rapid coagulative necrosis and precipitation of epithelial proteins, and this superficial coagulum of cells and ground substance act as a barrier to further penetration (Cameron, 2005). Acid injuries can be extremely painful and may cause

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the horse to be fractious and difficult to manage. They present typically as well-defined, often extensive areas of epithelial denuding. Acid injuries can usually be managed in the same way as abrasions or superficial ulceration.

Alkali exposure disrupts the lipid component of the cell membrane, causing epithelial cell and keratocyte necrosis, along with hydration and fragmentation of collagen fibrils and subsequent interference with collagen synthesis. Ischemic injury arising from coagulation of conjunctival and episcleral blood vessels will further compromise the eye (Cameron, 2005). The cornea becomes susceptible to enzymic degradation by MMPs and serine proteases from native cells and polymorphonuclear leucocytes, resulting in corneal "melting" similar to that encountered in some forms of bacterial keratitis, most notably *Pseudomonas* keratitis. Treatment is the same as for "melting" ulceration and is based upon the aggressive topical use of protease inhibitor preparations along with a topical broad spectrum antibiotic. The prognosis is always guarded and depends upon the extent and depth of the injury, which are determined by the quantity, duration, and hydroxyl ion concentration in the chemical involved. Extensive fibrosis of the globe and adnexa are likely in most cases.

Corneal Foreign Bodies

Corneal foreign bodies may be made of various materials, and may be superficial, deep, or even perforate the cornea. Superficial foreign bodies will leave an ulcer that requires medical therapy once removed, whereas full thickness foreign bodies will require suturing of the corneal wound. Infection is always a worry with corneal foreign bodies, especially if the foreign material is organic in nature (Fig. 29.45).

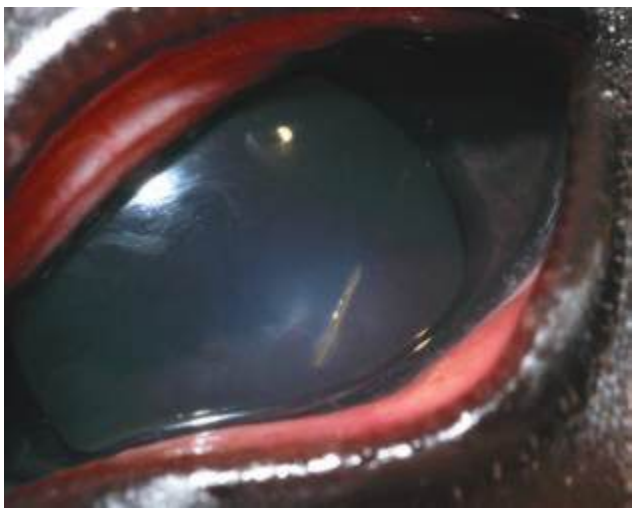


Figure 29.45 Corneal foreign body consisting of organic material in the anterior stroma.

In cases in which it is difficult to determine the depth of the foreign body or if it is unclear if it has perforated the cornea, look for evidence of fibrin accumulation in the anterior chamber, which would suggest a full-thickness rent.

Persistent corneal ulceration caused by burdock pappus bristle foreign bodies embedded in the conjunctiva are common among horses in the northeastern United States (Rebhun et al., 1991). Conjunctivalectomy of the bristle foreign body and surrounding tissue is recommended.

Fungal/Mycotic Keratitis

Fungi are normal inhabitants of the equine conjunctival microflora, but they can become opportunistically pathogenic in the face of corneal injury. Treatment of corneal ulceration with topical antimicrobials or corticosteroids (or both) may predispose the equine cornea to fungal infection. Exposure to vegetative material (e.g., hay, grasses, shavings, straw) and dust in the environment may influence exposure to fungi, and horses may be more susceptible to fungal corneal invasion and infection because of the large surface area and prominence of the equine eye (Scotty, 2005b). Tear film instability may predispose to fungal attachment and infection (Brooks et al., 2000b). Fungal organisms are ubiquitous in the equine environment, but geographic differences undoubtedly exist to account for variation among particular fungal species in specific regions. Fungal or mycotic keratitis is particularly common in the southeastern United States or in other areas in which the climate is warm and humid, although it has been reported worldwide. Previous reports have indicated a propensity for fungal keratitis in the summer and fall months, but other reports do not find this (Andrew et al., 2003; Grahn et al., 1993). This may result from temperature and humidity factors favoring fungal replication, or it may result from an increase in the amount of time that horses spend in their stalls (Moore et al., 1988). The seasonality of infection in the southern United States shows that ulcerative keratomycosis occurs throughout the year, with most cases occurring in the late fall to winter months (i.e., October through January) (Andrew et al., 1998).

Infections most commonly involve *Aspergillus* spp. or *Fusarium* spp. of fungi, but other fungal organisms have been reported. A recent study comparing the impact of fungal species identified with outcomes failed to reveal a difference in clinical outcomes between *Aspergillus*-associated keratomycosis and *Fusarium*-associated keratomycosis (Sherman et al., 2017). A variety of clinical appearances and behaviors are possible with fungal ulcers. Most commonly, fungal keratitis appears clinically as a worsening, subacute keratitis that generally appears very painful, with severe secondary uveitis. A typical history includes the use of previous topical corticosteroids and/or an ulcer present for 7–14 days.

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The four most common clinical presentations of fungal keratitis are: superficial ulcerative, stromal ulcerative, stromal nonulcerative, and deep stromal-endothelial nonulcerative (Fig. 29.46) (Brooks, 2013; Gaarder et al., 1998). Ulcerative keratitis refers to a disruption of the corneal epithelium, with varying amounts of stromal loss. They have a variety of clinical appearances ranging from superficial plaques that in some instances are pigmented, to melting ulcers or stromal wounds surrounded by a furrow or groove (Fig. 29.47A, B, C). Superficial, nonulcerative keratomycosis occurs occasionally and may be a precursor to ulcerative disease (Fig. 29.47D). Subepithelial forms of keratomycosis exist as well (Fig. 29.47E). The most common nonulcerative form of fungal keratitis is stromal abscess which results from stromal inoculation with bacteria or fungi through a small or large corneal epithelial defect. The organisms become encapsulated in the corneal stroma after reepithelialization of the corneal ulcer over the infection site. Diagnosis of fungal keratitis is made by history, clinical appearance, and demonstration of the organisms on cytology, culture, or histopathology of a keratectomy specimen (Fig. 29.47F). Because of the propensity for invasion into the deeper layer of the cornea by fungal organisms, however, negative cytologic or culture results may be obtained from superficial specimens (Bistner & Riis, 1979; Brooks, 2002) (Fig. 29.47G). It is often not possible to predict the outcome of a case of keratomycosis based upon the clinical appearance of the eye at presentation (Fig. 29.47H, I, J)

The pathogenesis of ulcerative fungal keratitis commonly begins with corneal trauma that results in an epithelial defect and stromal invasion by the commensal fungal organism, or seeding of fungi from a foreign body of plant origin (Scotty, 2005b). Abnormal tear film stability may also predispose to fungal keratitis (Brooks et al., 2000b). Stromal destruction results from the release of proteases and other enzymes from the fungi, chemoattracted leukocytes, and keratocytes (Ollivier, 2005; Strubbe et al., 2000). Fungi with high pathologic potential have the ability to adhere strongly

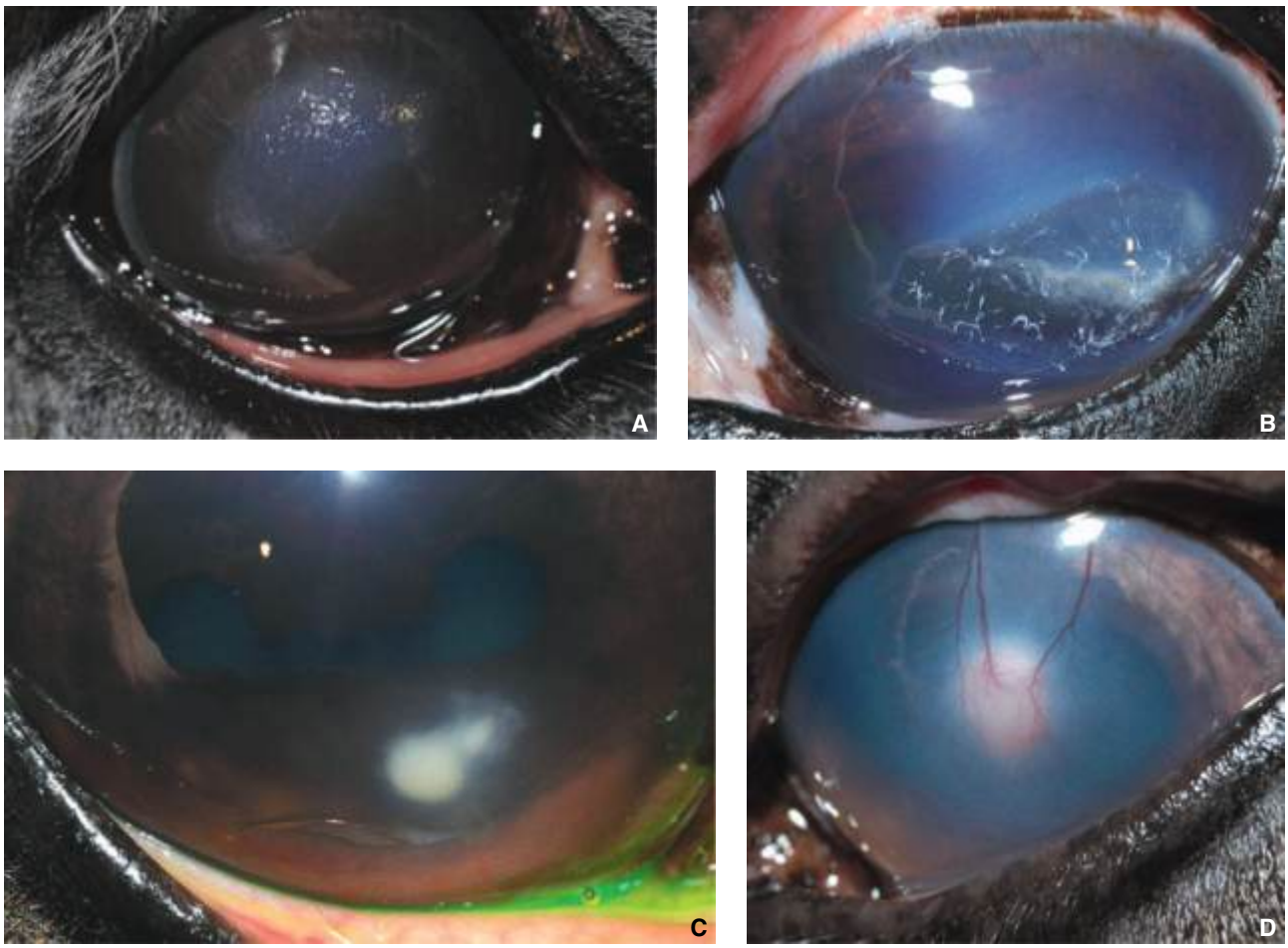


Figure 29.46 Fungal infections are common in the horse, especially in the southeastern United States. **A.** Superficial ulcerative fungal keratitis. The gritty, "cake frosting" appearance often signals a potentially aggressive and progressive behavior. **B.** Stromal ulcerative fungal keratitis. **C.** Stromal nonulcerative fungal keratitis manifests generally as a mid-to-posterior stromal abscess. **D.** Deep stromal to endothelial forms of fungal keratitis are deep stromal abscesses.

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to the epithelial or stromal tissue and attract large numbers of PMNs that release large quantities of MMPs that allow vertical deep movement in the cornea. Fungi of low pathogenicity adhere poorly, do not attract PMNs, are associated with small quantities of MMPs, and move laterally or horizontally in the corneal stroma (Dong et al., 2005). Fungi appear to have an affinity for Descemet's membrane, with hyphae frequently being found deep in the equine cornea (Bistner & Riis,1979; Brooks, 2002; Scotty, 2005b). Deeper corneal invasion can lead to a persistent endophthalmitis (Brooks, 2002; Hendrix et al., 1995).

Ulcerative keratomycosis is a serious, sight-threatening disease in the horse, and the veterinary literature is replete with cases of poor visual outcome in the various types of equine keratomycosis (Beech & Sweeney, 1983; Grahn et al., 1993; Sansom et al., 2005). Vision after keratomycosis in the horse may be retained in as few as 50% of eyes, with nearly half the eyes with ulcerative keratomycosis reported to become blind, require enucleation, or both. In general, the diagnosis of fungal keratitis carries a poor prognosis and requires long-term aggressive therapy.

Medical Treatment

Treatment must be directed at killing the fungus, killing secondary bacteria, and controlling secondary uveitis. Treatment must address the corneal and intraocular inflammatory responses that occur after fungal replication and hyphal death. Dead fungi incite keratitis and attract leukocytes. The primary leukocyte attracted is the PMN which is too small to phagocytize fungal hyphae. PMNs release large amounts of proteases that can be detrimental to the horse cornea. Macrophages are large enough to remove hyphae but are present in insufficient numbers. Because most fungal ulcers also have a bacterial component, treatment is initially similar to severe midstromal ulcers (frequent topical antibiotics, atropine, and anticollagenases). Antifungal therapy needs to be initiated early and aggressively. The levels of ophthalmic antifungal drugs in the cornea needed to achieve fungicidal effects are so difficult to obtain that many such agents are generally considered to exhibit fungistatic activity only, even though loss of corneal epithelium results in increased corneal and aqueous concentrations (Johns & O'Day, 1988; Ledbetter, 2017). Long duration of antifungal drug exposure is required for complete fungal destruction and resolution of clinical signs (Andrew et al., 1998; Johns & O'Day, 1988). The specific topical antifungal chosen will reflect the identity of the organism (if it is known) and the susceptibility of the agent based upon the common organisms seen in that geographic area. Antifungal susceptibility testing on fungal isolates from horses is recommended, but it can take several weeks to obtain results, and is not always consistent with clinical outcomes.

Voriconazole 1% (VFend®, Pfizer, New York, NY, USA) is a relatively broad spectrum antifungal agent that has a reasonable ability to penetrate corneal barriers. Natamycin (Pimaricin®, Alcon Laboratories, Ft Worth, TX, USA) is the only commercially available ophthalmic antifungal agent. It is very effective against *Fusarium* and *Aspergillus* sp., but it tends to be less effective against yeasts (Ledbetter, 2017). Miconazole (1%) has been used successfully and frequently as a topical antifungal agent (Andrew et al., 1998; Brooks et al., 1998). The 1% solution does not retard corneal healing or cause pathologic changes during corneal epithelial regeneration and is well tolerated (Foster, 1981). The gynecologic version of miconazole may be used topically, however, as it can be very irritating to the eye. Silver sulfadiazine is a topical antimicrobial agent with both antifungal and antibacterial activity that is believed to be fungicidal and is used in equine eyes (Betbeze et al., 2006; Ledbetter, 2017). Dilute (1 : 50) povidone-iodine is effective against bacteria, fungi, viruses, and protozoa, and it has also been used therapeutically for fungal corneal ulcers (Bates et al., 1996). It may have particular efficacy against *Fusarium* isolates (Hale, 1969). Itraconazole has been used in some cases of equine keratomycosis (Ball et al., 1997). Frequency of therapy can range from four times a day to hourly depending upon the severity and fragility of the lesion. There are anecdotal reports of exacerbation of uveitis after the initiation of therapy with an antifungal agent from a reaction to the death of stromal fungi, so some recommend starting therapy at a lower frequency and then increasing frequency after a few days. Combination therapy with a topical agent such as 1% voriconazole and an oral agent such as fluconazole (14 mg/kg starting dose on day 1, followed by 5 mg/kg/day each subsequent day) may be used in some instances. In resistant cases, subconjunctival injections of amphotericin B (0.2 mL of a 5 mg/mL solution administered subconjunctivally every 48 hours, generally for three doses) has also been used, but it can be irritating and the effectiveness is unknown. Client education is also very important because most cases of fungal keratitis will require 4–8 weeks to heal by corneal vascularization with scar formation.

Iridocyclitis is a frequent finding in horses with ulcerative keratomycosis, and it must be aggressively treated and controlled. Iridocyclitis is present any time a horse has a corneal ulcer and can escalate in intensity after hyphal death once antifungal therapy is initiated (Brooks, 2002; Ollivier, 2005). Flunixin meglumine, which is a prostaglandin synthetase inhibitor, is the most frequently used and efficacious NSAID for systemic treatment among horses. Unfortunately, it also reduces the speed of vascularization of corneal ulcers. One percent atropine sulfate, which is a parasympatholytic agent, is used in all cases for its mydriatic and cycloplegic effects (i.e., to dilate the pupil, stabilize uveal blood vessels, and diminish ciliary body muscle spasms associated with the axon reflex uveitis occurring with equine corneal ulcera-

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tion). Topical phenylephrine may be necessary in conjunction with atropine to achieve adequate mydriasis.

Surgical Treatment

Surgical treatment of fungal keratitis is generally indicated in most cases, but especially when there is no response to medical management, if a corneal furrow or groove develops, or if the lesion is very deep in the cornea (Table 29.4). The development of a corneal furrow surrounding the area of keratitis (Fig. 29.47C) in a superficial or stromal type of fungal keratitis generally indicates a particularly poor prognosis and suggests that rapid necrosis of the cornea is developing. When a furrow is observed, emergency surgery is needed to remove the infected cornea and place a corneal or conjunctival graft or both. Surgeries for keratomycosis include conjunctival grafts or corneal grafts after keratectomy of necrotic and infected cornea. Surgical treatments may leave the horse with a larger scar, but is a safer, more predictable outcome than medical therapy alone. Conjunctival grafts have the advantages of providing physical support, a regional blood supply, and a supply of endogenous antiproteases to the ulcer site (Brooks, 2002; Collins et al., 1994) (Fig. 29.47J). Amniotic membrane transplantation is not recommended for reconstruction of the ocular surface in cases of keratomycosis. Deep fungal lesions are best managed with penetrating keratoplasty, lamellar keratoplasty, or a deep lamellar endothelial keratoplasty. *In vivo* confocal microscopy, although limited in availability, may be extremely helpful in characterizing fungal keratitis and for the development of treatment strategies and monitoring (Ledbetter et al., 2011, 2019).

Bacterial Keratitis

Bacterial keratitis commonly induces blepharospasm, epiphora, ocular discharge, photophobia, and corneal opacification. However, unlike uncomplicated corneal ulcers, bacterial ulcers generally have stromal involvement that produces marked edema, cellular infiltration, and deepening of the ulcer bed, potentially accompanied by keratomalacia, or "melting" (Fig. 29.48). Anterior uveitis may be severe, manifesting as miosis, flare, hypopyon, and hypotony. Microbiologic culture should be performed in every case in which there is concern for the presence of a bacterial pathogen. *Streptococcus* sp. was the most common bacterial isolate from horses with ulcerative keratitis in one report from Florida (Chmielewski et al., 1997). In a separate study of horses in Missouri, however, Gram-negative bacteria, especially *Pseudomonas* and *Enterobacter* sp., were found to be responsible for most cases of ulcerative keratitis (Moore et al., 1983b).

Treatment should be aggressive with frequent use of broad-spectrum topical antibiotics every 1–2 hours, topical atropine, systemic NSAIDs, and anticollagenase medication to counteract the keratomalacia. Antimicrobial therapy may need to be altered based upon the results of the culture and susceptibility testing. Commonly used anticollagenase medications include autogenous serum (q1–2 hours), EDTA, and tetracycline-type medications (topical oxytetracyline, oral doxycycline). Rapidly progressing lesions should be managed surgically with use of a superficial keratectomy followed by a conjunctival graft or amniotic membrane graft (Lassaline et al., 2005).

Corneal Perforation/Laceration

Iris prolapse in the horse most frequently occurs after acute ocular trauma, particularly sharp and perforating corneal injuries or blunt injuries causing rupture of the cornea, limbus, or sclera. Corneal perforation can also occur secondary to rapid enzymatic degradation of stromal collagen and ground substance caused by infectious and noninfectious ulcerative keratitis. Once the cornea perforates, either as a result of a progressive corneal ulcer or penetrating trauma, the prognosis for vision and saving the globe in general is guarded to poor. Perforating lacerations caused by sharp injuries are generally associated with a better prognosis than those caused by blunt or missile injuries (Esmaeli et al., 1995; Lavach et al., 1984). High-energy, blunt ocular trauma may result in hyphema or globe rupture (or both), most often occurring at the limbus or equator, where the sclera is thinnest (Lavach, 1987;). Traumatic hyphema and iridocyclitis can be devastating conditions to the equine eye because of the labile nature of the equine blood–aqueous barrier (Turner et al., 1986). If uncontrolled, iridocyclitis may predispose to fibropupillary membrane formation, with subsequent posterior synechiae and cataract. The prognosis for eyes with cor-

Table 29.4 When is surgical intervention indicated?

1) Corneal rupture or impending loss of integrity of the globe
2) Progression of the condition of the cornea despite appropriate medical therapy
3) Lack of response or progression of anterior uveitis despite appropriate medical therapy
4) Targeted removal of diseased or infected tissue (remove offending organism, antigen, inflammatory products, cellular and extracellular matrix debris, and cytokine signals)

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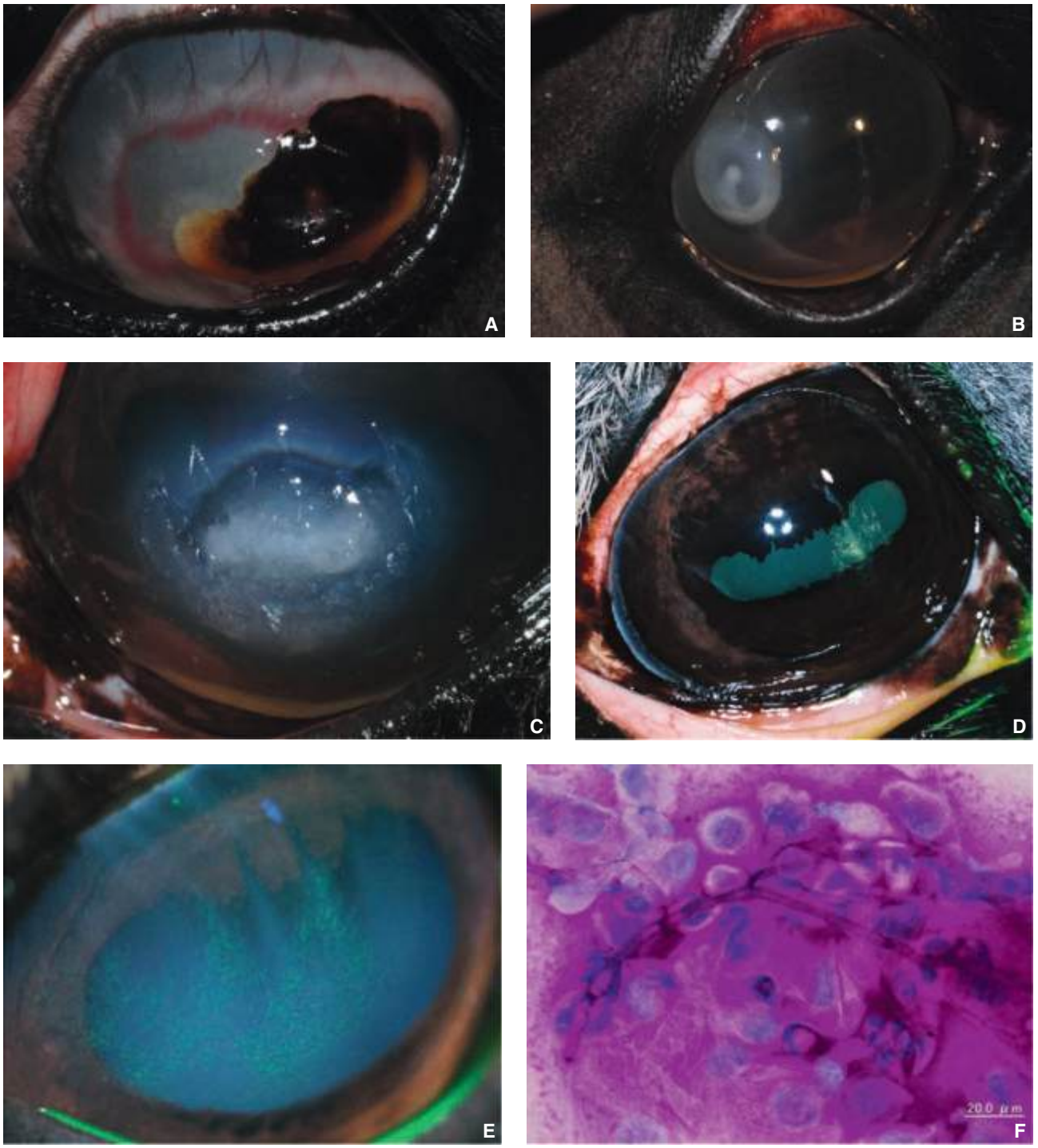


Figure 29.47 Fungal keratitis can present with multiple forms of keratitis. **A.** The plaque form of ulcerative fungal keratitis. **B.** Fungal keratitis in this eye manifesting as a melting ulcer. **C.** Fungal keratitis in this eye exhibits a central focus of necrotic cornea surrounded by a furrow or groove. The deep surrounding margins are areas of increased enzymatic activity, a function of both the pathogens and the host's inflammatory reaction. **D.** Superficial keratomycosis that is not yet ulcerated appears often as multiple punctate opacities in the epithelium. **E.** Superficial epithelial to subepithelial form of keratomycosis often retains fluorescein in a punctate pattern. **F.** Septate, branching fungal hyphae from a cytology specimen of a corneal ulcer; **G.** Keratectomy specimen after excision of a deep stromal abscess. The arrow indicates a fungal hyphal element in Descemet's membrane. ×40. **H.** It can be difficult to predict the behavior of a fungal ulcer at initial presentation. Superficial fungal keratitis at initial presentation. **I.** Despite appropriate and aggressive medical therapy, this ulcer progressed and required surgical stabilization. **J.** Postoperative appearance after keratectomy and conjunctival graft placement.

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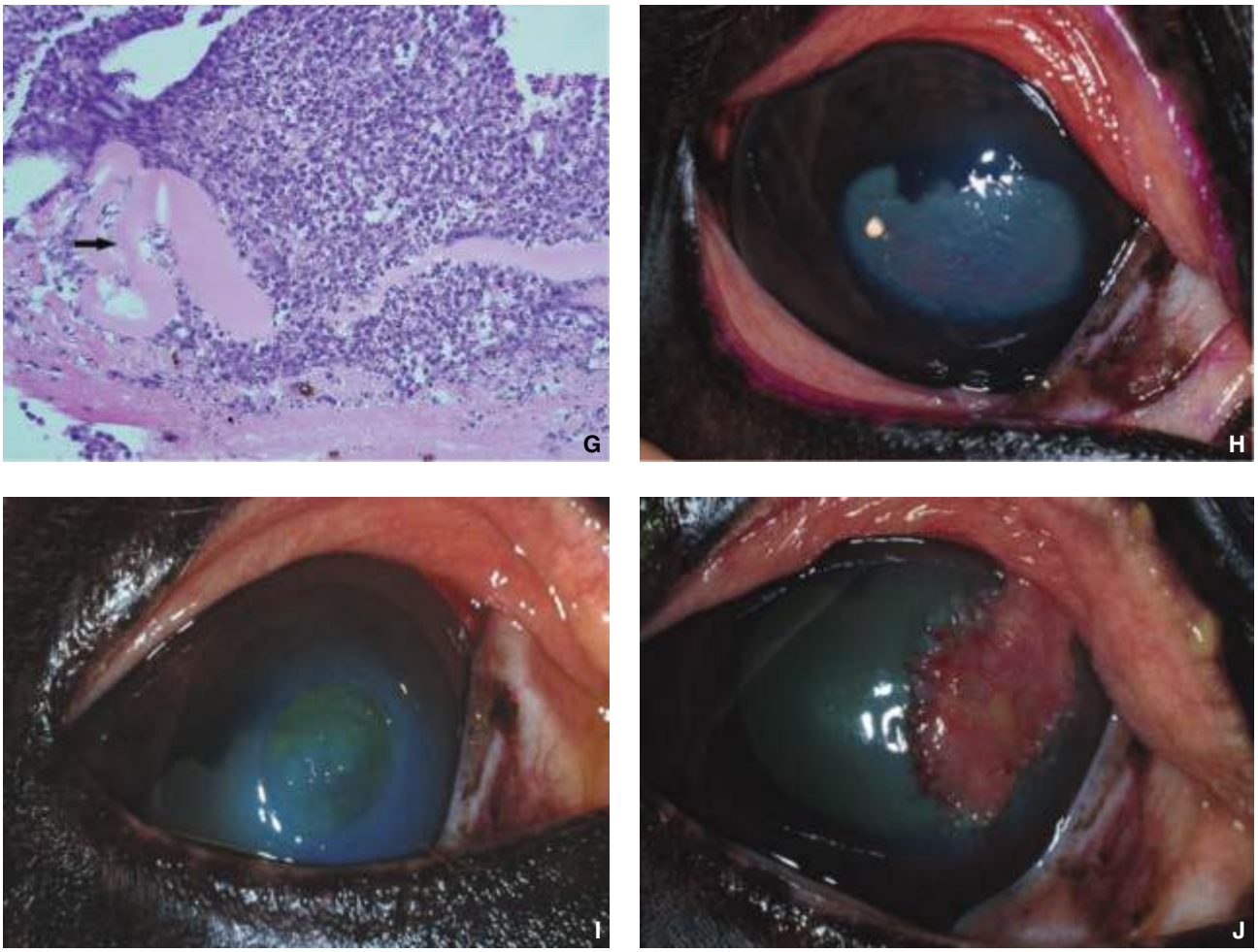


Figure 29.47 (Continued)

neal lacerations and mild hyphema is slightly more favorable, albeit still guarded, compared with that for horses having corneal lacerations and total hyphema (Lavach et al., 1984; Turner et al., 1986). In one study in horses, iris prolapse and hyphema comprising greater than an estimated 10% of the anterior chamber resulted in blindness, phthisis bulbi, or enucleation (Chmielewski et al., 1997). In horses with traumatic iris prolapse, corneal wound lengths of 15 mm or less were associated with a positive visual outcome, whereas wound lengths of greater than 15 mm resulted in either blindness, phthisis bulbi, or enucleation (Chmielewski et al., 1997). The prognosis is worse if the corneal laceration involves the limbus, significant hyphema is present, the lens is perforated, if a large uveal prolapse through the incision is present, or if a dazzle and consensual PLRs are absent. Examination of perforated eyes should include complete ophthalmic examination (including evaluation of dazzle and consensual PLRs) with the horse adequately tranquilized and eyelid nerve blocks performed to ensure that no further damage is done as a result of the examination. If the posterior segment (vitreous and retina) of the eye cannot be visualized on the ophthalmic examination, then an ultrasound should be performed. If the vitreous is hyperechoic (i.e., blood or cellular infiltrate) or a retinal detachment is observed on the ultrasound, then the prognosis for return to vision is very poor. Repair of the laceration or correction of the perforation is recommended if the lens and posterior segment are normal. Enucleation should be performed if there is no consensual PLR, a large uveal prolapse is present, or if ultrasound shows significant blood in the vitreous or retinal detachment.

If treatment for an iris prolapse is pursued, surgical stabilization and reconstruction are recommended. Medical therapy should continue as it would for any complicated corneal ulcer with the addition of systemic antibiotic therapy because the globe has been compromised and exposed to the outside world.

Surgical Therapy for Corneal Ulcers

Not infrequently during clinical treatment of corneal ulcers in the horse, surgery is necessary to augment the medical treatments.

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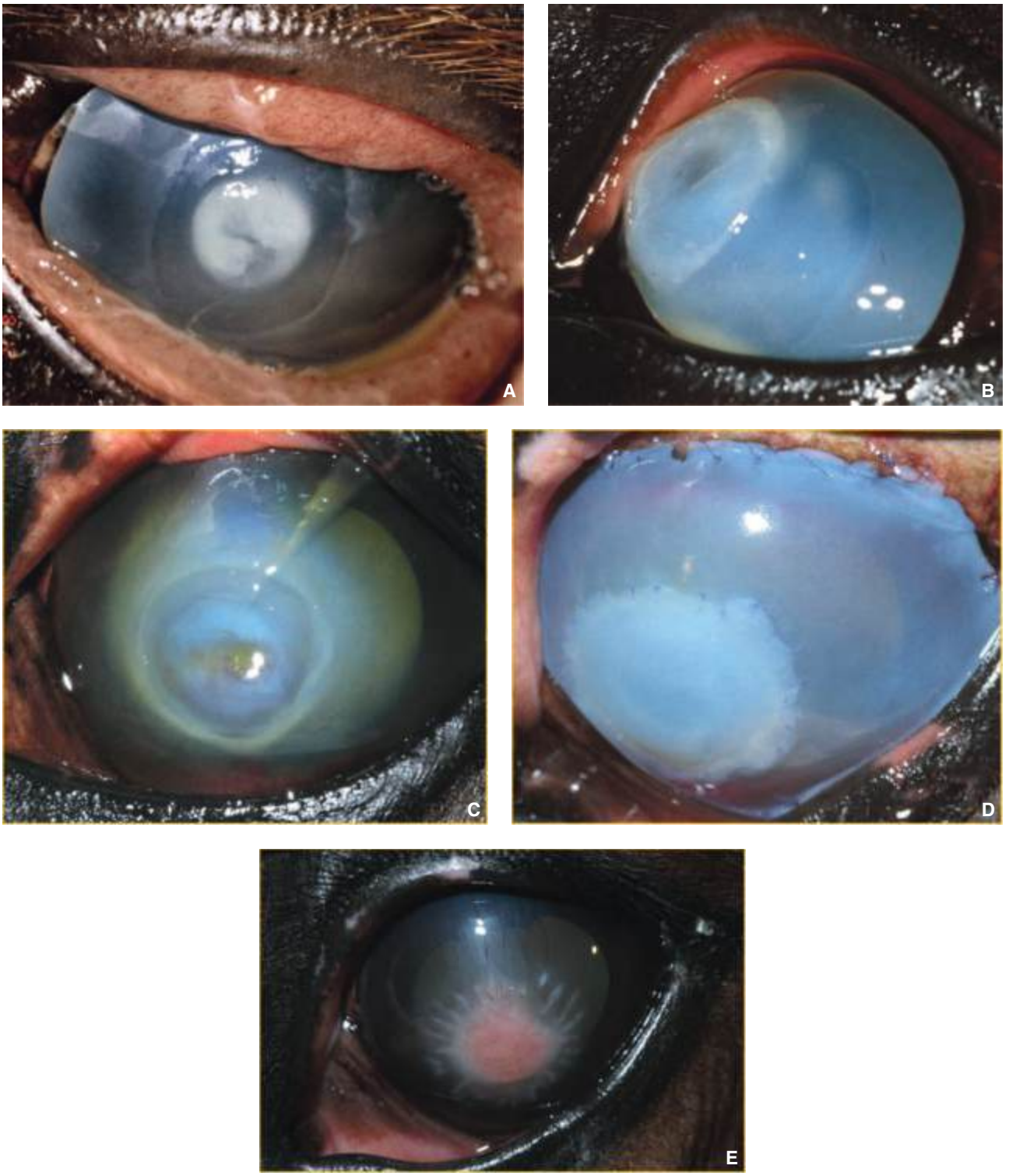


Figure 29.48 Bacterial keratitis and ulceration is also a common corneal disease. **A.** An infected stromal ulcer with central cellular infiltrate, a response to an infection with a *Staphyloccocus* spp. **B.** A melting ulcer caused by infection with *Pseudomonas aeruginosa*. **C.** A progressive, melting ulcer in a horse. **D.** Application of a double layer of amniotic membrane after keratectomy to remove necrotic tissue. **E.** Clinical appearance 5 weeks after surgery.

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Keratectomy

Keratectomy may prove to be useful during the early stages of ulcerative keratitis, when infection is confined to the corneal epithelium and anterior third or half of the cornea stroma. Removing necrotic tissue by keratectomy speeds healing, minimizes scarring, and decreases the stimulus for iridocyclitis. Deep anterior lamellar keratectomy to remove the diseased anterior cornea while leaving Descemet's membrane intact has been described in the horse (Martins et al., 2013).

Chemical Cautery

There is anecdotal evidence that chemical cautery of superficial ulcers with small amounts of topically applied phenol, trichloroacetic acid, or concentrated betadine is effective in treating superficial, refractory ulcers. It should not be performed on descemetoceles or rapidly progressive ulcers displaying evidence of collagenolysis, because the chemical agent will cause corneal rupture.

Corneal Cross-Linking

Corneal cross-linking, a procedure in which a photosensitive agent (usually riboflavin) is applied onto or injected into the cornea and then the tissue is treated with UVA radiation to activate the agent to cause structural changes in the constituent tissue collagen by increasing the covalent bonding between and amongst fibers, has been described in the standing, sedated horse for the treatment of ulcerative keratitis (Hellander-Edman et al., 2013, 2019). The study protocol for routine use of this modality has yet to be optimized (Gallhoefer et al., 2016).

Conjunctival Grafts

Conjunctival grafts or flaps are frequently used in equine ophthalmology for clinical treatment of deep, melting, and large corneal ulcers, descemetoceles, and perforated corneal ulcers both with and without iris prolapse. Conjunctival flaps are best mobilized from the bulbar conjunctiva. It is recommended that the conjunctiva near the nictitans be avoided, however, because postoperative nictitans movement can place tension on the graft and, thereby, result in premature graft release. Conjunctival flaps can be transposed and sutured onto the cornea to provide sufficient tissue to strengthen most weakened corneas, but they are not as strong as corneal grafts. Conjunctival autografts contain limbal stem cells, blood vessels, and lymphatics, thus offering significant antibacterial, antifungal, antiviral, antiprotease, and anticollagenase effects. With conjunctival grafts, PMNs, fibroblasts, antibodies, serum, and alpha-2-macroglobulins are immediately placed in the corneal ulcer bed. The fibrovascular, or deeper, layer of the conjunctival transplant offers immediate fibroblasts and collagen with which to begin rebuilding the corneal stroma. Conjunctival grafts will result in various sizes and degrees of corneal scars. Scarring can be minimized, however, by removal of necrotic cornea with keratectomy before graft placement.

Conjunctival autografts are simpler than corneoconjunctival and corneoscleral transpositions and penetrating keratoplasty surgeries. They are also easier to perform in the horse than in other species because the horse has a great deal of very mobile bulbar conjunctiva. Conjunctival autografts should be thin, and they should not include Tenon's capsule or the bulbar fascia. Tenon's capsule should be stripped or cut from the graft so that the graft lies over the corneal defect before suture placement. The inclusion of Tenon's capsule may contribute to surgical failure by increasing traction on the transplanted conjunctival graft. Debridement of the corneal epithelium over and adjacent to the wound bed will encourage adhesion of the conjunctival flap to the cornea. Melting ulcers should always be stabilized with medical therapy, if possible, before graft placement to prevent protease digestion of any absorbable sutures holding the conjunctival graft in place and premature graft release.

A conjunctival pedicle flap is made by incising the conjunctiva (excluding Tenon's capsule) 1 mm posterior to and parallel to the limbus with tenotomy scissors. The distance of the limbus to the corneal lesion determines the length of this incision. The flap is undermined posteriorly toward the fornix. A perpendicular incision is made at the distal end of the flap, and an incision parallel to the first incision and limbus is made as wide as is necessary to cover the corneal lesion. The flap is rotated over the corneal defect and sutured in place with absorbable 7-0 to 10-0 suture in a simple interrupted pattern. The degree of rotation of the pedicle should be less than 45 degrees. Conjunctival flaps should have tension-relieving sutures placed at the limbus to prevent the graft pulling away from the ulcer bed prematurely. Temporary tarsorrhaphies are performed concurrently with conjunctival grafts to minimize blinking movements to the corneal sutures and to allow quick graft adherence to the stroma.

Ocular Surface Reconstruction with Amniotic Membrane

Amniotic membrane transplantation (AMT) is an effective clinical therapy for reconstruction of the ocular surface in equine patients. Amnion is avascular and strong, contains antiangiogenic and anti-inflammatory properties and growth factors, and has properties that prevent or decrease

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fibrosis in healing tissue. Indications for its use are steadily growing and include grafting to replace diseased, missing or excised tissue, patching to support diseased tissue during the healing process and as a substrate for the expansion of epithelial cells for transplantation to the cornea. AMT, through a combination of mechanical and biologic factors, can preserve the integrity of the globe, optimize the visual outcome, and minimize scarring in severely diseased corneas (Plummer et al., 2009). AMT can be used to restore stroma and provide a healthy basement membrane for renewed epithelial proliferation and differentiation after keratectomy for ulcerative disease and resection of neoplastic lesions (Lassaline et al., 2005; Ollivier et al., 2006). It can be especially useful if a corneal wound is so large or severe that the traditional therapy of placing a conjunctival graft upon a corneal wound or defect would render a sighted or a potentially sighted globe blind. AMT may be the preferred method of ocular reconstruction in cases of keratomalacia, whether sterile or secondary to a bacterial infection (Fig. 29.48 C, D, E). It is not recommended, however, when a fungal infection is present.

Several protocols exist for processing amnion, but all include washing the placenta with a balanced salt solution and a cocktail of antimicrobial drugs (usually 50 μg/mL penicillin, 50 μg/mL streptomycin, 100 μg/mL neomycin, and 2.5 μg/mL amphotericin B) under sterile conditions. The fetal component of the placenta, which consists of the amnion and the chorion, forms the limits of the sac that encloses the fetus with the amnion forming the innermost layer of the sac. The amniotic epithelial monolayer is adjacent to the fetus whereas the spongy stromal matrix sits adjacent to the chorion. The amnion is separated from the chorion by blunt dissection, which is usually relatively easy because the amniotic stroma is only loosely connected to the chorion. The amnion is recognized as the avascular portion. It is then cut to a manageable size and placed epithelial side up on nitrocellulose paper. The amnion may then be placed in media, usually a mixture of glycerol and Dulbecco Eagle's Medium and frozen at −80° until further use. Amnion may also be freeze-dried or lyophilized for storage.

There are three surgical techniques for the application of AMT and the choice for which is based on the specifics of the case. In the inlay or graft technique, the amnion is tailored to the size of the defect and is meant to act as a scaffold for epithelial cell migration. This graft then becomes integrated into the host tissue. The amnion is secured with its basement membrane up to allow migration of surrounding epithelial cells onto the membrane. In the overlay or patch technique, the amnion is used as a sort of biologic contact lens in order to protect the healing surface of the defect below it. The patch may also reduce inflammation by its barrier effect against the chemical mediators in the tear fluid. When used as a patch, the amnion is either secured to the cornea with its basement membrane side up and it either falls off or is removed or it may be secured with the basement membrane side down which presents adhesion and incorporation of the patch. In the filling-in or layering technique, multiple pieces of amnion are trimmed to the size of the defect and placed within the depth of the ulcer crater. A larger graft is secured to the edges of the defect in an inlay fashion. An additional and larger patch may be placed atop the graft to help preserve the deeper layers for a longer duration. Regardless of technique for application, the amnion is most often sutured in place with 8-0 to 10-0 absorbable suture in a simple interrupted or, more commonly, simple continuous pattern. Chemically defined bioadhesives may be useful for attaching AM to the ocular surface, although further studies are needed to identify an ideal product and technique (Tsujita et al., 2012). Traditional medical therapy continues in the postoperative period until healing is complete.

Other alternative materials for reconstruction of the ocular surface that have been used with success include porcine urinary bladder ECM grafts (ACell Vet® Corneal Discs, Columbia, MD, USA), porcine small intestinal submucosa, donor cornea, conjunctiva, pericardium, renal capsule, peritoneum, and split-thickness dermal grafts (Bussieres et al., 2004; Mancuso et al., 2016; Ollivier et al., 2006).

Penetrating Keratoplasty

Penetrating keratoplasty (PK) involves full thickness removal and replacement of a portion of the cornea. PK is a rather confusing term. The reference point of the incision is the globe; therefore, when a full-thickness graft is performed, the incision penetrates the globe but perforates the cornea. Corneal sutures are necessarily utilized to heal a vertical stromal incision with an associated disruption of the corneal surface and topography. Corneal transplantation is performed to restore vision (i.e., optical), to control medically refractory corneal disease (i.e., therapeutic), and to reestablish structural integrity of the eye (i.e., tectonic) (Brooks, 2002, 2005b, c; Denis, 2004; Whittaker et al., 1997). Partial-thickness lamellar corneal transplantations in the horse have been reported for cosmetic and for tectonic/therapeutic reasons (Hekmati & Schels, 1976; McLaughlin et al., 1985). Full-thickness therapeutic PKs have been reported in the horse (Brooks, 2002, 2005b,c; Denis, 2004; Whittaker et al., 1997).

The surgical approach in horses with a corneal perforation and iris prolapse involves replacement or amputation of the exposed iris followed by placement of a corneal donor button at the site of the defect. If an iris prolapse is fresh, an attempt is made to replace the protruding iris. If the iris tissue is damaged or necrotic, the protruding iris is excised with electrocautery. Hemorrhage is a risk if the iris is transected. Necrotic tissue from the wound edges should be judiciously removed. Once the size of the recipient button

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needed to remove all grossly affected tissue adequately is determined with calipers, a donor button is harvested from fresh or frozen equine cadaver eyes that is 1 mm larger than the recipient bed. If corneal trephines are not available for this purpose, dermal biopsy punches may be employed. The button is grasped with fine-tooth forceps while paying particular attention to the orientation of the epithelium/endothelium, keeping it moistened with balanced salt solution. Bulging of the iris and the corpora nigra into the incision site or the presence of anterior synechiae necessitate injection of viscoelastic solution to move the iris posteriorly or to break down adhesions. Direct contact with the lens capsule is also avoided with the use of viscoelastics. The donor cornea is placed in the recipient bed, and four cardinal sutures of 8-0 or 9-0 Vicryl® (Ethicon) are placed at the 12-, 6-, 9-, and 3-o'clock positions. Partial thickness sutures (2/3 depth) are used in the cornea; full thickness penetrating sutures are never used. If a simple interrupted suture pattern is used throughout, each quadrant is progressively bisected into smaller sectors with sutures placed 1 mm apart; alternatively, three to four simple continuous sutures are placed in each graft. After partial closure of the wound, blood and fibrin clots in the anterior chamber are carefully removed by gentle lavage, or more appropriately digested with tissue plasminogen activator (50–150 µg in 0.1–0.3 ml). TPA can successfully digest blood clots in the anterior chamber that have been present for 2 weeks in horses. Once the donor cornea is sutured into place, viscoelastic solution may again be injected via a limbal approach to reform the anterior chamber. In many cases, however, this is not necessary, because the anterior chamber refills with aqueous humor during suture placement. A conjunctival pedicle graft may then be sutured over the graft site in those eyes with evidence of infection or vascularization to achieve more rapid assimilation into the cornea (Fig. 29.49). A temporary lateral tarsorrhaphy is performed to minimize eyelid trauma to the PK. Autogenous serum to decrease tear film proteinases attacking the graft and sutures, and cyclosporine A (CsA) to reduced graft rejection are added to the other medications postoperatively. Postoperative medications are maintained

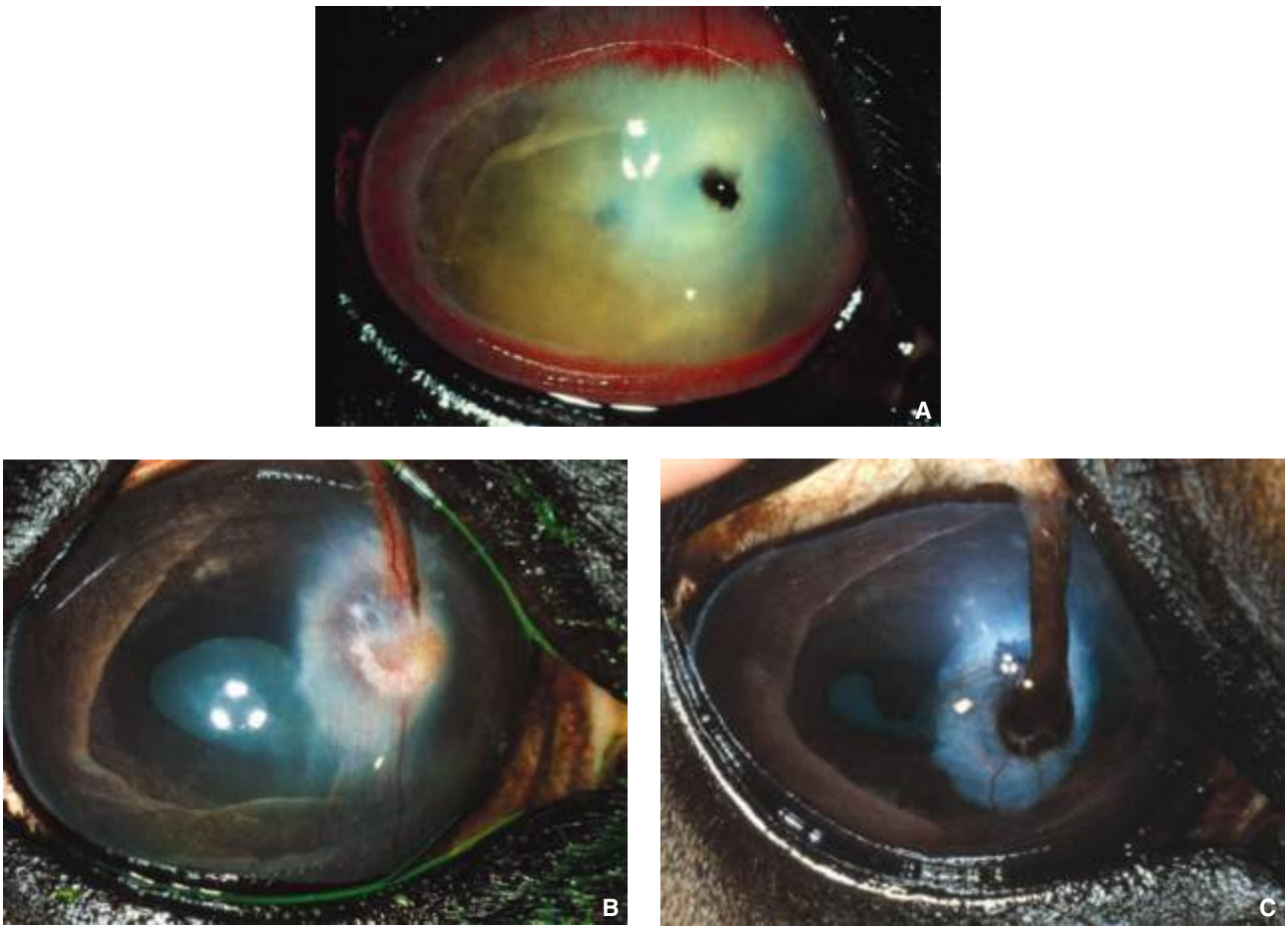


Figure 29.49 **A.** Iris prolapse in a horse accompanied by severe anterior uveitis. **B.** Postoperative appearance after replacement of missing tissue with a corneal graft covered by a conjunctival graft 5 weeks later. Note the anterior synechia resulting in dyscoria. **C.** One-year postoperative appearance.

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for an average of 57.2 ± 14.2 days in horses after PK (Brooks, 2005b; Denis, 2004; Whittaker et al., 1997).

Non-Ulcerative Corneal Diseases

This is a heterogeneous group of corneal diseases, many of which appear to be unique to the horse. There are four general categories of non-ulcerative corneal diseases in the horse: corneal edema, pigmentation, scarring, and inflammation. Geographic ulceration is not a feature of these diseases, although local epithelial sloughing associated with bullae formation may give rise to shallow erosions.

Superficial Punctate Keratitis

Superficial punctate keratitis is characterized by multifocal, lace-like epithelial to subepithelial corneal opacities some of which may be fluorescein positive with mild corneal edema (Fig. 29.50). Blepharospasm may be noted, but many horses are asymptomatic. The cause is unknown, but viral agents, specifically EHV-2 and EHV-5, and immune-mediated causes have been proposed (Borchers et al., 2006; Clode, 2011; Hollingsworth et al., 2015; Rushton et al., 2013). Treatment recommendations vary and include topical antibiotic-corticosteroid, topical CsA, and/or topical antiviral therapy. Although the condition responds well to topical corticosteroids, recurrence is common.

Corneal Stromal Abscesses

Corneal stromal abscess is recognized in the horse far more often than in other species. This lesion in the horse can be a vision-threatening sequela to apparently minor superficial corneal ulceration, or from an inoculation of organisms or foreign material via micropuncture through the epithelium into the stroma. After epithelial cells adjacent to a small epithelial defect or puncture divide and migrate over the puncture wound to seal infectious agents or foreign bodies in the stroma, an abscess forms in the stroma, usually 1–3 weeks later (Brooks, 2004; Brooks et al., 2004; Rebhun, 1982, 1992b). This reepithelialization forms a barrier that protects the bacteria or fungi from topically administered antimicrobial medications. A recent retrospective study that looked at environmental conditions at the time of initiation of deep stromal abscesses (DSA) discovered an association between wind speed and the prevalence of DSA (Proietto et al., 2016b). Wind speed is the first significant atmospheric risk factor to be identified for DSA formation in the horse. The importance of environmental variance in the incidence of DSA indicates that the pathogenesis of DSA formation may be multifactorial and provides support for the micropuncture hypothesis of DSA formation related to environmental conditions causing PTF and epithelial damage (Proietto et al., 2016b). Diagnosis of corneal stromal abscess is usually made based upon clinical appearance and history (Fig. 29.46C, D and Fig. 29.51A). The clinical appearance of stromal abscess may vary greatly depending on severity. However, all have a creamy-yellow cellular corneal infiltrate (Brooks, 2004; Hendrix et al., 1995; Henriksen et al., 2014; Rebhun, 1982, 1992b). Single or multiple abscesses may be present. A mild-to-fulminating iridocyclitis occurs secondary to what initially appears to be a relatively benign corneal disease, thus causing severe pain and, possibly, blindness (Hendrix et al., 1995; Henriksen et al., 2014; Rebhun, 1982). Corneal vascularization is variable at presentation and may obscure observation of the precise location of the abscess. Surrounding most abscesses is a variable amount of corneal edema. Some cases have initial clinical signs suggestive of minor corneal trauma. Recurrent stromal abscesses may be orange in color, suggestive of a more chronic and mature fibrovascular response.

A culture and cytology would be helpful, but unfortunately, this frequently requires surgery to get below the intact corneal epithelium. Reepithelialization of stromal abscesses interferes with both routine diagnosis and treatment. A stimulus for epithelialization or absence of an inhibitor of epithelialization, which is not found in other types of equine ulcerative keratitis, may be present in cases of stromal abscess (Brooks et al., 2004; Hendrix et al., 1995; Whittaker et al., 1997). Reepithelialization after corneal scrapings in medically treated horses is rapid and quite dramatic. Representative preoperative cultures are difficult, if not impossible, to obtain because of both the intact, epithelialized surface of the abscess and the deep location of the lesions in the cornea (Hendrix et al., 1995). The epithelium and stroma over DSA may be difficult to remove and it is no



Figure 29.50 Superficial punctate keratitis characterized by multifocal, lacelike epithelial to subepithelial corneal opacities.

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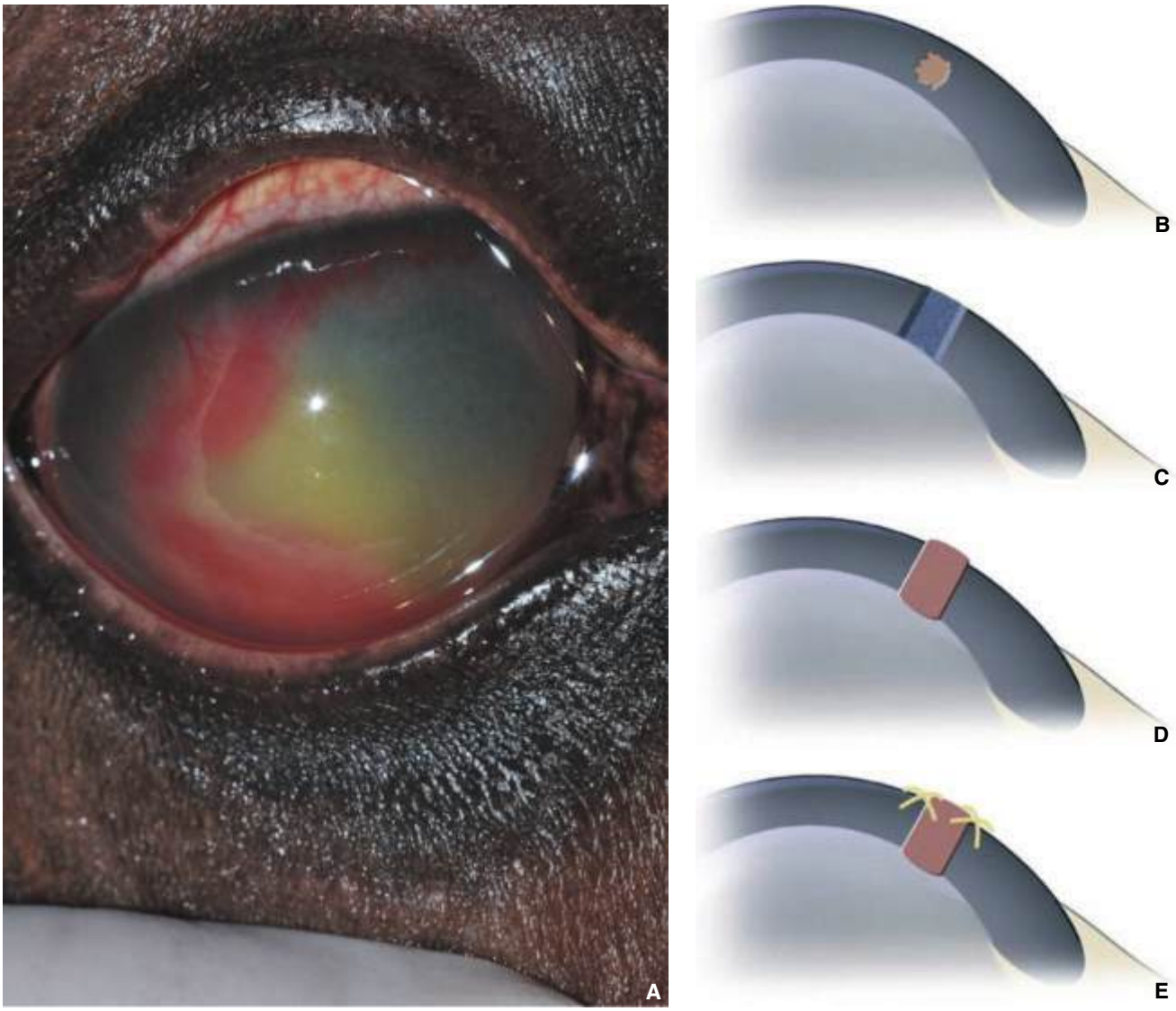


Figure 29.51 Corneal abscessation in horse. **A.** Large stromal abscess with surrounding vascularization and edema accompanied by severe anterior uveitis. **B.** A mid-stromal corneal abscess. **C.** The abscess is removed along with a full-thickness focus of corneal tissue. **D.** The defect is repaired with a piece of donor cornea that is approximately 1 mm in diameter wider than the section previously removed. **E.** The donor button is sutured in place, taking care that the sutures are not placed full-thickness through the cornea. In many instances, the donor graft is then covered by a conjunctival flap.

longer recommended to attempt removal of the epithelium over an abscess to improve drug penetration.

Most stromal abscesses are caused by fungal infections. Treatment depends on the depth of the lesion and the degree of secondary uveitis present. Superficial stromal abscesses may respond positively to topical mydriatic/cycloplegics, to topical and systemic antibiotic and antifungal therapy, and systemic NSAID therapy. Deep stromal abscesses are more frustrating and refractory to medical treatment. The same medical protocol is begun, however, if significant improvement in the signs associated with a stromal abscess does not occur within the first 48–72 hours of intense medical therapy, surgery should be considered. Surgery can improve results and reduce the duration of medical therapy. Deep endothelial plaques that are usually fungal in origin do best with PK. Horses that undergo early surgery in the course of this disease tend to have a more rapid recovery than those in which surgery is delayed (Hendrix et al., 1995; Whittaker et al., 1997). If a positive response to medical therapy is not seen quickly, especially when the stromal abscesses are deep or severe uveitis is present, surgery should be considered.

Equine patients with stromal abscesses do not completely heal until they become vascularized from corneal vascular ingrowth either into the abscess itself or any replacement grafting material that has been placed after surgical removal of the abscess. Vascularization can heal most abscesses but

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the process may take months. If medical therapy alone is used, systemic NSAID therapy should be carefully adjusted to allow control of the anterior uveitis without significantly inhibiting the corneal vascularization necessary to heal the corneal stromal abscess. The cyclooxygenase and lipoxygenase inflammatory pathways are instrumental in corneal angiogenesis, and use of flunixin meglumine, which is an inhibitor of the cyclooxygenase pathway, for anterior uveitis will at higher doses decrease the speed of corneal vascularization. However, if signs of anterior uveitis are not controlled, devastating, vision-threatening sequelae can occur inside the eye. A balance must be struck and if it cannot, surgery is indicated.

Corneal abscesses vascularize at a slow rate (much slower than the 1 mm per day reported to be possible in the horse), however, and waiting for the cornea to heal may result in loss of vision from complications of the severe endophthalmitis found with this disease (Rebhun, 1992b). In some cases of abscesses deep in the posterior stroma or along Descemet's membrane, vascularization of the cornea may occur atop the abscess but not within it. Deep lamellar and penetrating keratoplasties are used in eyes with abscesses near Descemet's membrane and in eyes with rupture of the abscess into the anterior chamber (Brooks, 2004). Abscess material projecting into the anterior chamber stimulates profound iridocyclitis and may be a reason for acute worsening in an eye previously controlled with medical therapy. In these instances, surgery should be performed to remove the offending nidus and to prevent intraocular invasion of corneal pathogens. Abscess material protruding into the anterior chamber will not vascularize. Surgical therapy can be very successful and is performed both to eliminate antigenic stimulation from the sequestered organisms and to remove the necrotic debris, metabolites, and toxins from the degenerating leukocytes and microbes in the abscess. Keratectomy specimens may also be the only way to obtain a definitive etiologic diagnosis via culture, histology, or polymerase chain reaction (PCR) to institute proper antimicrobial therapy (Henriksen et al., 2014).

Some stromal abscesses fail to initiate corneal vascularization at all. This may suggest that factors are being released from the abscess or the host that influence the vascular response (Welch et al., 2000). In fact, it has been reported that in some cases of DSA that have delayed or incomplete vascularization there is decreased expression of vascular endothelial growth factor-A (VEGF-A), a factor known to stimulate vascular proliferation (Henriksen et al., 2014). These cases benefit from surgical therapy.

Recently, there have been reports of successful resolution of corneal stromal abscesses after injections of antifungal medications, especially 1% or 5% voriconazole, into the corneal stroma above and surrounding the abscess (Smith et al., 2014b; Tsujita et al., 2013). This procedure dramatically increases the tissue concentration of the antifungal drug. Consistent and high stromal levels of drug are difficult to achieve with many drugs in the face of an intact epithelial barrier.

Penetrating Keratoplasty for Deep Corneal Stromal Abscesses

Corneal transplantation is performed to restore vision (i.e., optical), to control medically refractory corneal disease (i.e., therapeutic), and to reestablish structural integrity of the eye (i.e., tectonic) (Brooks et al., 2008, 2004; Brooks, 2004; Whittaker et al., 1997). PK involves full thickness removal and replacement of a portion of the cornea. Full-thickness therapeutic PKs have been reported in the horse (Brooks, 2004; Brooks et al., 2008; Whittaker et al., 1997) (Fig. 29.51B–E).

The recipient globe is stabilized with fixation sutures of 4-0 silk or 5-0 nylon. A corneal trephine of appropriate size (dependent upon the size of the abscess) is centered over the diseased area and then rotated with minimal downward pressure to obtain a partial thickness, clear-cut, round incision with vertical sides. The size of excision site should include the entire abscess and, ideally, at least 1 mm margin of clear, grossly normal cornea surrounding the abscess. The anterior chamber is entered vertically with a #65 Beaver blade, taking care to avoid the iris and corpora nigra when the deepest stromal layers are breached. The remaining deep part of the host button is then removed with corneal section scissors. Bulging of the iris and the corpora nigra into the incision site or the presence of anterior synechiae necessitate injection of viscoelastic solution to move the iris posteriorly or to break down adhesions. Direct contact with the lens capsule is also avoided with the use of viscoelastics.

Once the size of the recipient button needed to remove all grossly affected tissue adequately is determined with calipers, a full-thickness donor button, which is 1 mm larger than the recipient bed, is trephined from the endothelial side. The button is grasped with fine-tooth forceps while paying particular attention to the orientation of the epithelium/endothelium, and it is placed on a gauze swab moistened with balanced salt solution. The donor cornea is removed from the moistened gauze swab and placed in the recipient bed, and four cardinal sutures of 8-0 or 9-0 Vicryl® (Ethicon) are placed at the 12-, 6-, 9-, and 3-o'clock positions. If a simple interrupted suture pattern is used throughout, each quadrant is progressively bisected into smaller sectors until ultimately the sutures are space 1 mm apart from each other; alternatively, three to four sections of simple continuous sutures are placed in each graft. A conjunctival pedicle graft may then be sutured over the keratectomy/graft site to protect and prevent secondary infection and encourage assimilation of the graft into the host cornea.

Alternatively, two-step PK can be performed to permit placement of a partial thickness donor button, which may subjectively result in less postoperative swelling of the graft

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site as immunological rejection occurs. The procedure begins as for the traditional PK procedure. The corneal trephine or dermal punch which is at least 2 mm great in diameter than the abscess is centered over the diseased area and then rotated with minimal downward pressure to obtain a partial-thickness incision to a depth of approximately 50% of the corneal thickness. A Martinez corneal dissector is then used to remove the anterior corneal stroma. A second corneal trephine smaller in diameter than the first is used to incise the deeper tissues. The abscess is removed as above. The donor button used to repair the defect is split thickness (the posterior half) and sutured into the interior defect. There will remain then a partial thickness defect atop the donor graft that is wider than the graft site. A conjunctival graft is then sutured to the walls of the anterior defect.

The decision to perform surgery is made on the basis of continued progression by the anterior uveitis despite intense medical therapy, imminent or preexistent rupture of the abscess into the anterior chamber, severe and unrelenting endophthalmitis, or anticipated poor visual outcome resulting from a lack of vascularization of the stromal abscess (Brooks et al., 2008; Denis, 2004). The results indicate that PK for treatment of deep corneal stromal abscesses, with or without conjunctival pedicle grafts, is an effective treatment for this condition (Brooks et al., 2004; Denis, 2004; Whittaker et al., 1997). Generally, 5–10 days after placement of a donor graft, there will be swelling of the graft, an indication of the immunological response of graft rejection. This swelling may place additional strain on the sutures holding the graft in place.

Both the presence and degree of corneal vascularization influence the risk of corneal graft rejection in humans (Boisjoly et al., 1993; Völker-Dieben 1982; Wilson & Kaufman, 1990). This results, in part, from the unique immune privilege ordinarily enjoyed by the cornea. Lymphatic vessels infiltrate the diseased cornea with invading corneal blood vessels, thereby giving corneal antigens direct access to the afferent arm of the immune system (Collin, 1966, 1970). Corneal graft rejection in animals has not been studied as it has in humans (Williams et al., 1992). However, we assume the corneal graft opacification noted in the final status of the horse may actually be a clinical manifestation of partial graft rejection. The presence and degree of corneal vascularization seen preoperatively may also be associated with the degree of corneal opacification after PK. In humans, preoperative corneal vascularization is associated with a twofold increase in graft rejection rates in humans (Boisjoly et al., 1993).

Postoperative medications are maintained for an average of nearly 50 days post PK surgery until the graft is completely incorporated and healing is complete (Whittaker et al., 1997). The reported visual outcome for horse eyes after PK for DSA approaches 80% (Blackwood et al., 2007; Brooks et al., 2004; Brooks et al., 2008).

Lamellar Keratoplasty

Partial-thickness lamellar corneal transplantations in the horse have been reported for cosmetic and for tectonic/therapeutic reasons (Hekmati & Schels, 1976; McLaughlin et al., 1985). The superficial cornea may be vascularized but is otherwise normal in DSA. For horses with DSA and anterior chamber fungal invasion that persist, or even progress, with severe pain and vision-threatening uveitis in the face of aggressive medical therapy, surgical removal of the posterior stroma and endothelium containing the abscess by corneal transplantation is warranted. The anterior corneal tissues including epithelium and most of the stroma may be left intact.

The purpose of split thickness or lamellar surgery is to replace only the diseased portion of the cornea, leaving the normal overlying tissue intact. In other words, to do the least amount of resection for the greatest amount of benefit (Brooks, 2008, 2010; Brooks et al., 2004, 2008; Terry, 2003; Terry & Ousely, 2003). Both the posterior lamellar keratoplasty (PLK) and deep lamellar keratoplasty (DLEK) surgical methods are forms of split thickness PK. They avoid removal of superficial normal tissue but do surgically enter the anterior chamber (Terry, 2003). These surgical methods are important methods in resolving DSA in horses. These procedures should be performed under general anesthesia by an experienced ophthalmic surgeon. There are reports, however, of successful outcomes with modifications of these techniques in the standing, sedated horse (McMullen et al., 2015).

Posterior Lamellar Keratoplasty. PLK (Fig. 29.52) is recommended for DSA in the central cornea that have a clear overlying anterior stroma (Andrew et al., 2000; Baker et al., 2007; Brooks et al., 2004, 2008).

First a rectangular or rounded anterior lamellar corneal flap, hinged on one side, is constructed by hand dissection to two-thirds stromal thickness over the stromal abscess (Brooks, 2008; Brooks et al., 2008; Culbertson, 2003). The anterior PLK flap should be at least 1 mm wider than the donor tissue on all sides of the lesion. A Martinez corneal dissector is then used to undermine and elevate the superficial corneal layers to expose the abscess. The flap is gently raised, and a trephine, #65 Beaver blade and corneal scissors are used to remove the posterior stromal abscess, Descemet's membrane, and endothelium. The anterior chamber is reformed with viscoelastic solution. A circular graft of posterior stroma, Descemet's membrane and endothelium 1 mm larger than the defect is cut from donor tissue using a trephine. The graft is placed in the corneal defect and sutured every 1 mm using 8-0 or 9-0 absorbable suture material in a simple interrupted pattern. The three-sided superficial flap is then sutured in place using 8-0 or 9-0 absorbable suture material. Partial temporary tarsorrhaphies are placed in all eyes to protect the graft during recovery. Medical therapy for

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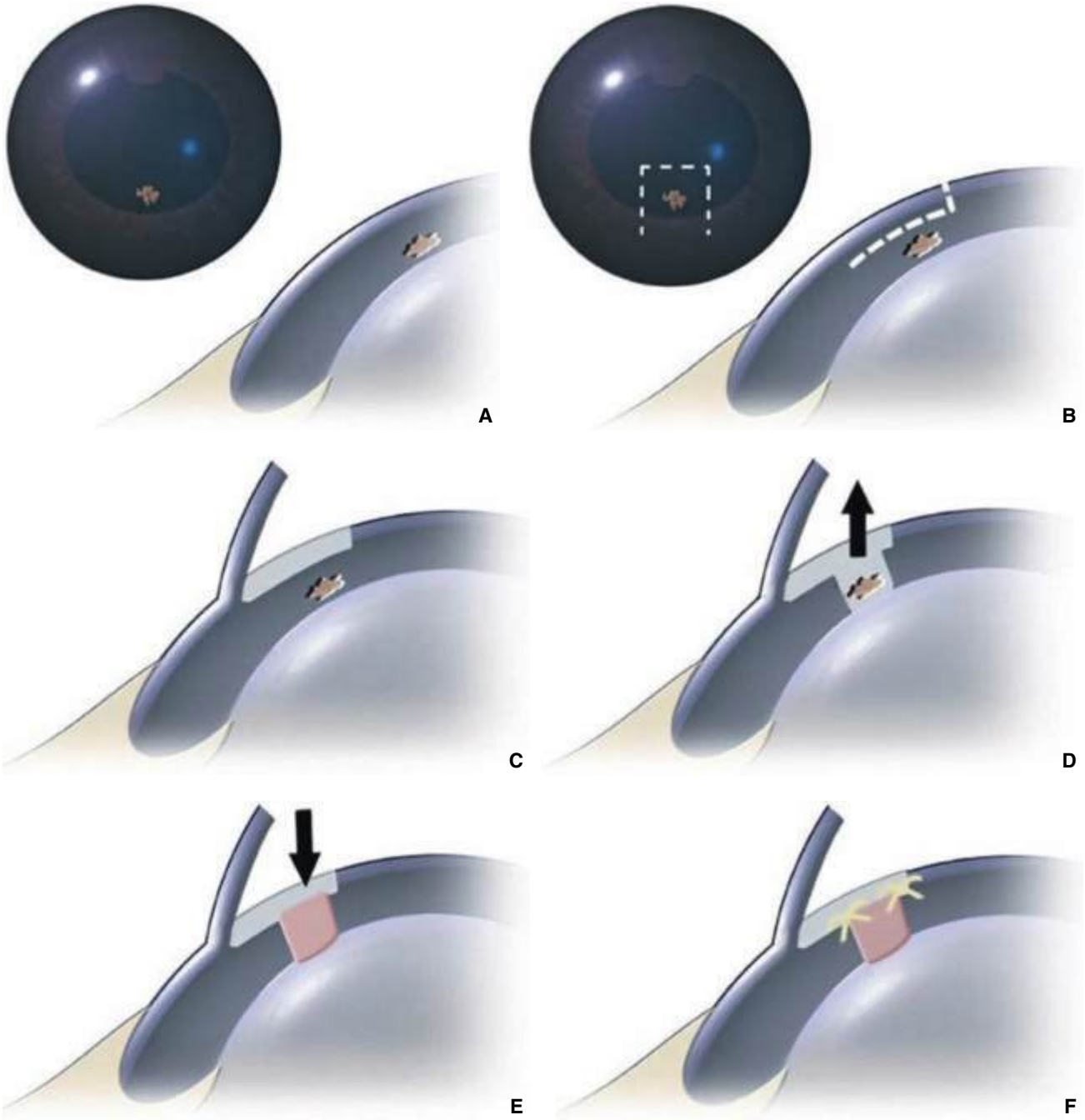


Figure 29.52 **A.** Illustration of a corneal abscess in the posterior stroma. **B.** For posterior lamellar keratoplasty, a hinged flap of anterior stroma is created over the defect. **C, D.** The flap is elevated and the abscess removed. **E**, **F**, **G.** A partial thickness graft of donor cornea replaces the removed tissue and is sutured in place. **H.** The anterior flap is then repositioned over the donor graft and sutured in place. **I.** Deep stromal abscess preoperative appearance. **J.** Postoperative appearance 3 days after posterior lamellar keratoplasty.

DSA is continued as before surgery with the addition of autologous serum or another anticollagenase agent to minimize tear proteinase activity that could result in ulceration of the anterior flap.

The PLK is associated with a shorter surgery and treatment time than the PK. Complications of PLK include superficial suture abscesses, suture incision leaks, flap ulcers, and flap edema. The donor graft remains transparent for up to 7 days and then opacifies. Median time to the completion of postoperative medical treatment is 24 days (Andrew et al., 2000). Partial graft rejection and scar formation are unavoidable for both the PK and PLK procedures. The resulting scar, which is typically vascularized and eventually opaque, is similar between PLK and PK. The visual

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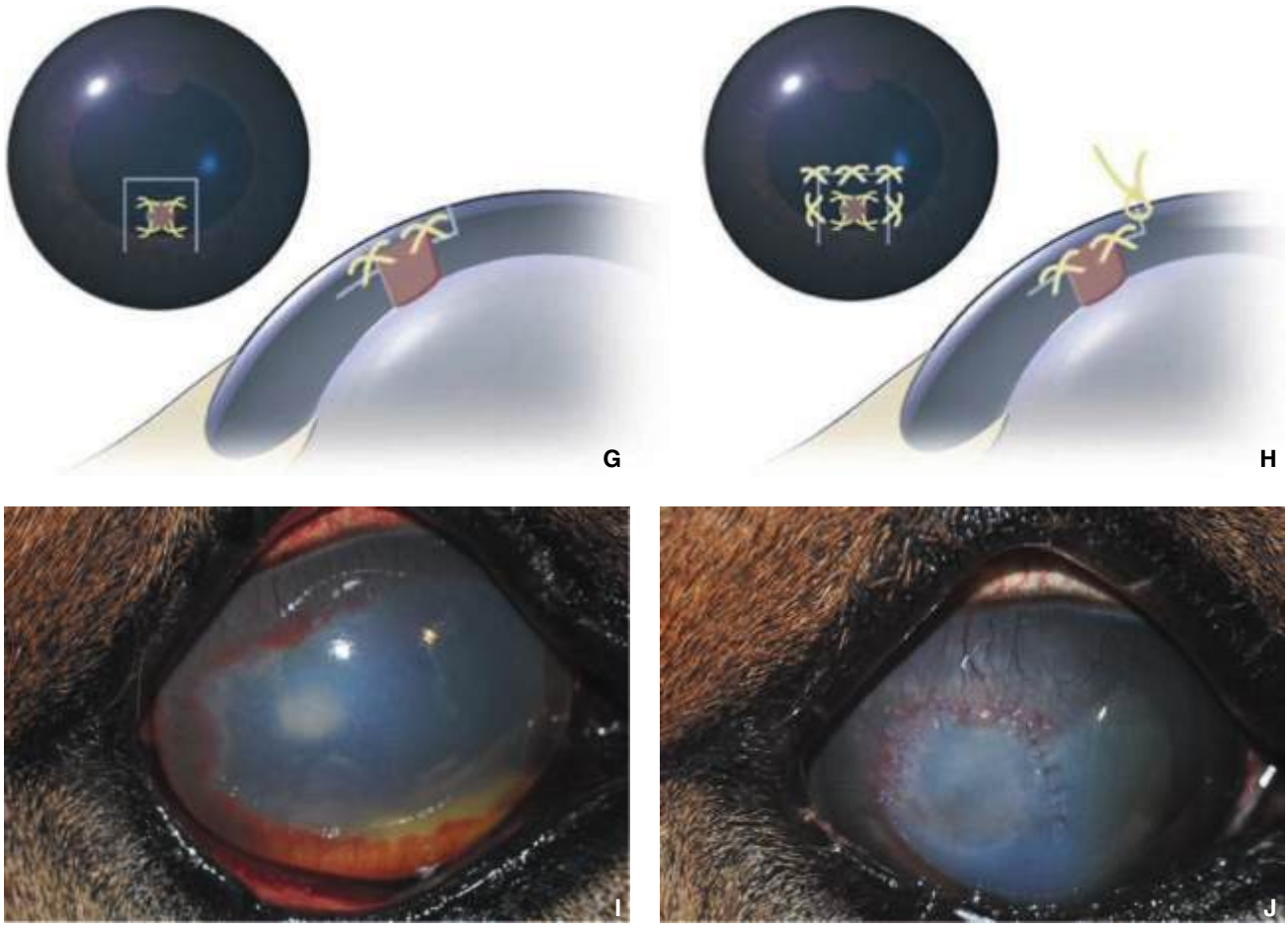


Figure 29.52 (Continued)

outcome approaches 98% for the eyes that have had the PLK procedure (Baker et al., 2007; Brooks et al., 2008).

Deep Lamellar Endothelial Keratoplasty. DLEK (Fig. 29.53) is recommended for DSA in the peripheral cornea that have a clear overlying anterior stroma. It avoids the superficial incisions and suturing of the central cornea. The DLEK transfers healthy endothelium while preserving the corneal surface integrity. A fully intact epithelium with no corneal sutures is present postoperatively (Plummer et al., 2008; Terry, 2003).

First, a two-thirds depth, limbal incision is made with a #64 or #69 Beaver blade adjacent to the abscess and extending to a length that will permit elevation and retraction of the anterior stroma to expose the DSA. A stromal pocket is formed over the DSA with a Martinez corneal dissector. Bleeding from the vascularized cornea is controlled with electrocautery. The superficial corneal flap is gently retracted and the abscess removed with a trephine, #65 Beaver blade, and corneal scissors. The anterior chamber is reformed with viscoelastic. The anterior one-half to two-thirds of the donor cornea is removed by hand dissection, and a trephine 1 mm larger in diameter than the recipient site used to obtain the circular donor graft from the remaining split-thickness cornea. The donor graft is then placed within the defect created by excision of the abscessed tissue and sutured in place with simple interrupted cardinal sutures or 8-0 or 9-0 absorbable material. Some surgeons opt not to suture the graft in place and instead, slide the graft between the dissected lamellar planes and employ the anterior chamber pressure to keep the graft in place. The superficial corneal flap is then replaced at the limbus and sutured in place with 8-0 absorbable material in a simple interrupted pattern. Partial temporary tarsorrhaphies are placed in all eyes to protect the surgical site during recovery.

The DLEK is associated with a shorter surgery and treatment time than the PK. Medical therapy postoperatively is as before surgery with the addition of an anticollagenase agent topically. Complications include suture abscesses, suture incision leaks, incision edema, and graft misalignment. Median time to end of postoperative medical therapy is 22 days

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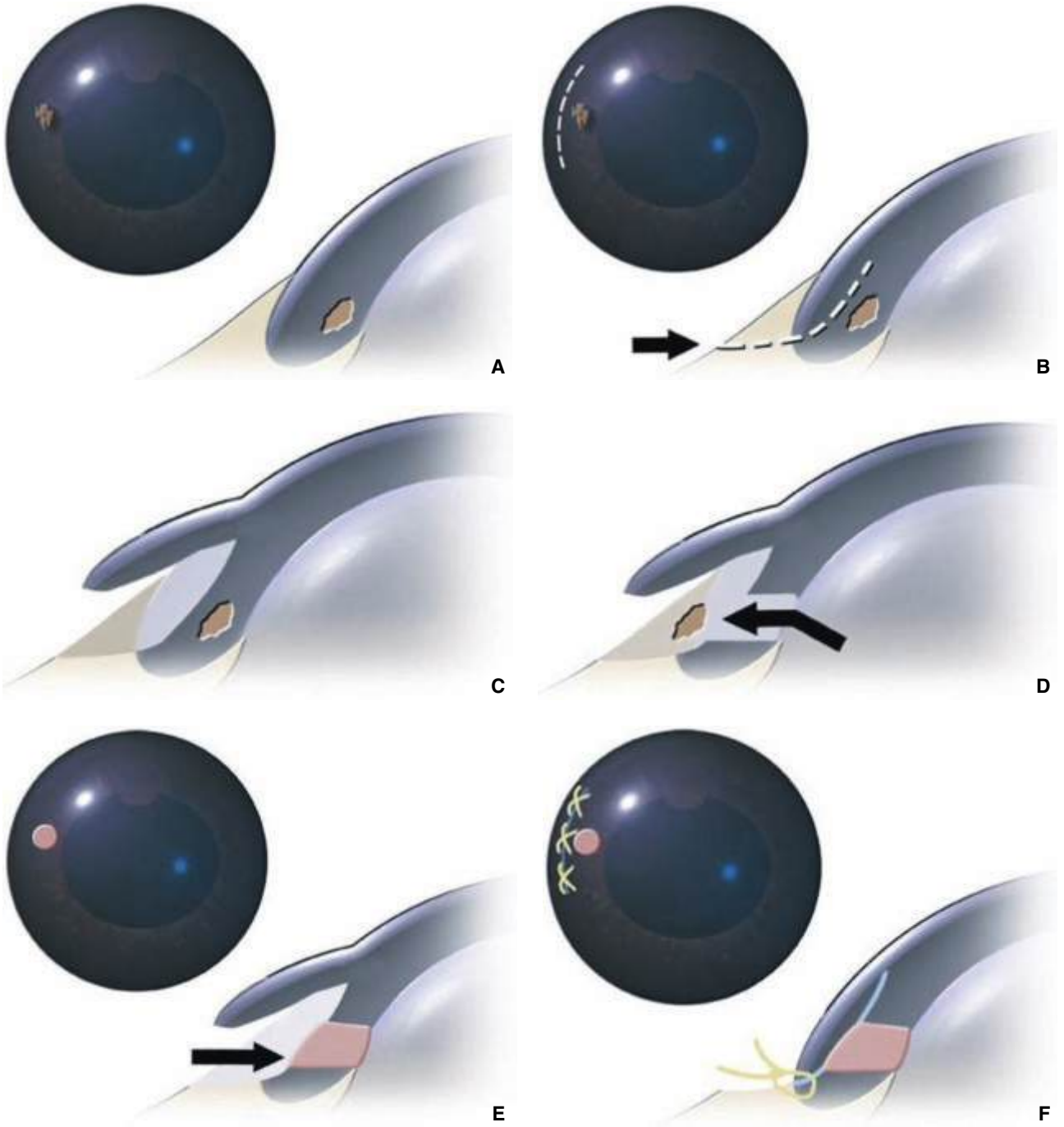


Figure 29.53 **A.** Illustration of a corneal abscess in the posterior stroma. **B**, **C.** For deep lamellar keratoplasty, a partial thickness incision is made in the perilimbal cornea and retracted to expose the abscess. **D**, **E.** The abscess is removed with the posterior stroma and replaced with a partial thickness donor button which may be sutured in place. **F.** The anterior cornea is repositioned over the graft and sutured in place along the limbus.

(Brooks et al., 2004). The resulting scar, which is typically vascularized and eventually opaque, is similar between PLK and DLEK. The visual outcome is greater than 90% for the eyes that have had the DLEK procedure (Brooks et al., 2008; Plummer et al., 2008).

Viral Keratitis

Initial reports of an etiological role for a virus in keratoconjunctivitis in the horse came in 1976 when EHV-2 was isolated from corneal biopsies taken from 3–6-week-old foals involved in a herd outbreak of focal superficial keratitis and

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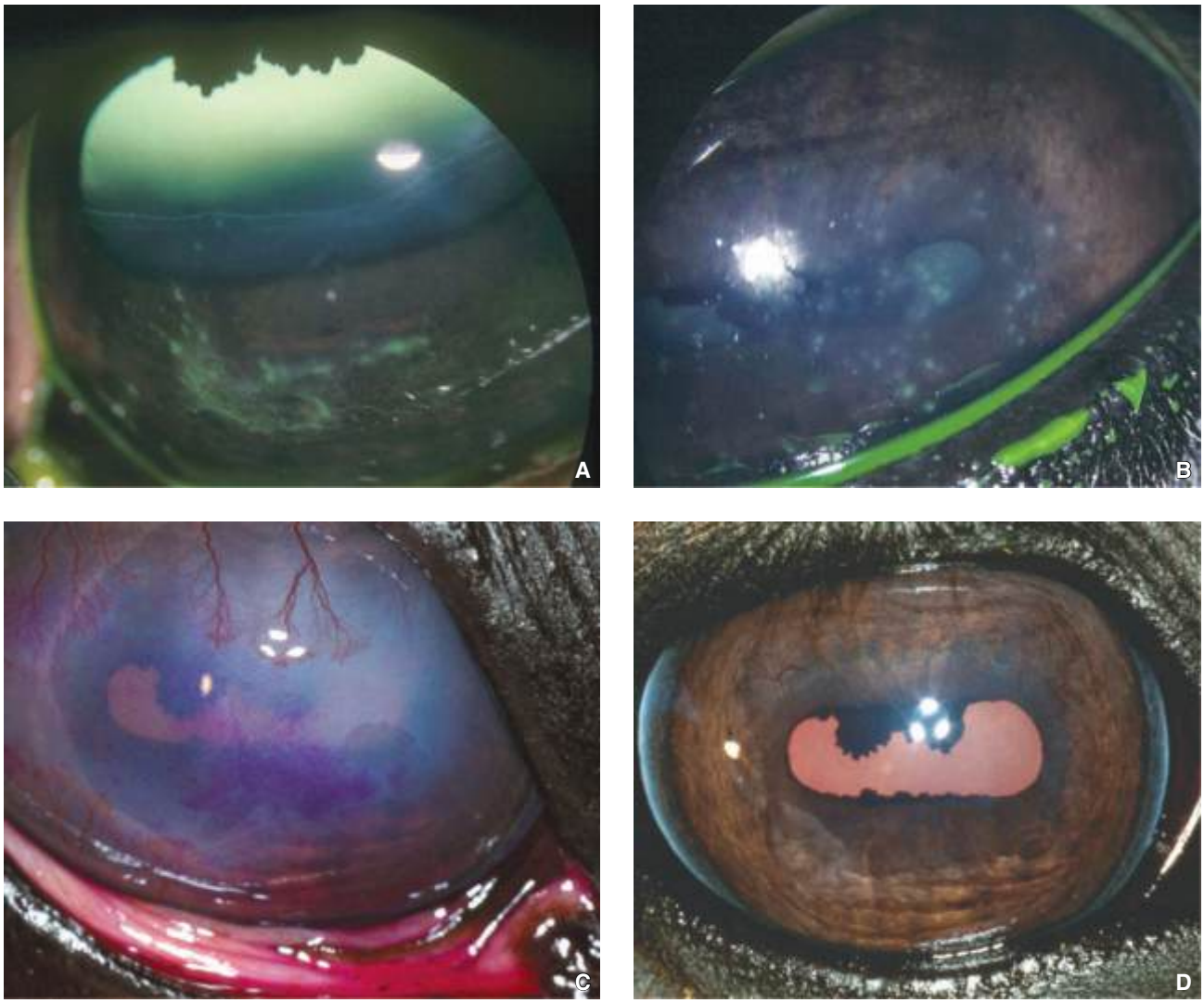


Figure 29.54 Suspected viral keratitis in the horse. **A.** Slight fluorescein retention adjacent to white opacities in this case of type 1 viral keratitis in the UK. A linear band opacity is also present. **B.** Multifocal stromal and epithelial opacities in a horse with type 2 viral keratitis in the UK. **C.** Rose Bengal retention and superficial vascularization with capillary tufts in a Warmblood stallion with suspected viral keratitis. **D.** The condition waxed and waned for several years.

conjunctivitis in Europe (Thein & Bohm, 1976). Subsequently, EHV-2 and EHV-5 have been isolated from animals with and without ocular surface disease, making the association between the virus and ocular signs loose if not tenuous (Borchers et al., 1997; Collinson et al., 1994; Hollingsworth et al., 2015; Kershaw, 2001; Matthews & Handscombe, 1984; Miller et al., 1990b; Rushton et al., 2013). The high seroprevalence of EHV-2 antibodies in the general horse population indicates exposure is widespread, particularly in young animals, although association of clinical disease with viral exposure is difficult to establish (Blakeslee, 1975; Borchers et al., 1997; Murray et al., 1996).

However, in some cases of superficial keratitis, particularly those with a punctate appearance, a viral etiology can be presumed from the rapid clinical response to topically applied antiviral drugs. Affected horses present with acute onset, usually unilateral ocular pain and an intense reflex miosis. Chemosis and conjunctival hyperemia are usually present. The disease is sporadic and is not contagious to in-contact horses. Two types of corneal lesion are recognized (Matthews, 2004b) (Fig. 29.54). In type one, the lesions appear as fine, irregular, fluorescein-positive epithelial fissures with contiguous anterior stromal edema. Rarely, these fissures may coalesce, resulting in a dendritic-like lesion, and in some instances may form a shallow geographic ulcer. In the type two form, the lesions appear as multiple focal fluorescein positive superficial ulcers, less than 0.5 mm in diameter, with perilesional anterior stromal edema. Some ulcers will heal spontaneously, leaving a combination of ulcerated and nonulcerated anterior stromal opacities. Vascularization does not occur in either case.

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Both presentations respond rapidly to topical 0.5%–1% idoxuridine solution applied every 2 hours until the eye is pain free and reepithelialization is evident. Topical diclofenac has weak antiviral properties and is beneficial in some horses with suspected viral keratitis. Topical corticosteroids should not be used during the acute stages of the disease, although they will provide some symptomatic relief. Alternative anti-DNA virus agents are commercially available for topical ophthalmic use, including trifluridine, acyclovir, and cidofovir. Their efficacy in equine keratitis has not been evaluated. Clinical experience indicates that 1% trifluridine solution is generally effective in treating equine viral keratitis, and that 3% acyclovir ointment is unreliable in its therapeutic effective. Anecdotal reports indicate that both topical human recombinant interferon alpha (3000 IU/mL in artificial tears) and CsA may be useful in managing some cases of the disease. Oral lysine (20 g SID PO) can reduce viral shedding in the horse (Cutler, 2004).

By analogy with viral disease of the ocular surface in other species, the acute epithelial disease in the horse may result from replication and cytopathic effects of the presumptive epitheliotropic virus in basal cells. By analogy with ocular herpesviruses in other species, EHV-2 in the horse may have the potential to act as a keratopathogen *via* immune mechanisms rather than direct virus-induced damage (Dix, 2002). This may derive from retention of antigenic determinants from some viral strains by host corneal tissues and their acting as a chronic source of heteroantigen, particularly in immunosuppressed individuals. Less likely, incorporation of viral epitopes into host cell membranes may impart immunogenicity to affected cells, potentially triggering an autoimmune inflammatory response (Dix, 2002). These or similar mechanisms may be responsible for nonulcerative keratopathies in the horse from which EHV-2 can be isolated. Alternatively, EHV-2 may have a role in deranging the immune privilege mechanisms in the cornea, facilitating induction of an inflammatory response by an unrelated infectious agent or mechanism.

The most common manifestation of EHV-2 keratitis in adult horses is reported to be sporadic multifocal subepithelial punctate opacities (Brooks, 2002). These stain variably with fluorescein but stain positive with Rose Bengal (Fig. 29.54C). Superficial vascularization is associated with the opacities. Affected horses exhibit persistent moderate ocular pain, and although uveitis is not a common feature of the disease, similar corneal lesions have been associated with aggressive and refractory anterior uveitis in a small number of cases. A primary and important differential diagnosis in these cases is early fungal keratitis, which may manifest as Rose Bengal-positive epithelial microerosions, and cytology and culture performed to rule out fungal involvement in areas where keratomycosis is a significant clinical threat (Brooks et al., 2000b). Topical 0.5% idoxuridine and 1% trifluridine are conventionally used in treating affected eyes with varying success. This may reflect the limited stromal bioavailability of these drugs in the presence of an intact epithelium, or that the lesions themselves are not the result of direct viral-induced injury. Immunosuppressive therapy using topical CsA appears to be of significant benefit in most cases but may require to be continued for protracted periods. Topical corticosteroid use is controversial and is not recommended where keratomycosis cannot be ruled out. However, topical corticosteroids used with caution and in conjunction with CsA can lead to rapid resolution of the corneal lesions. Topical NSAIDs (e.g., diclofenac) and serum have been used with varying success. Systemic NSAIDs and topical atropine sulphate may be used to manage concurrent uveitis where this is present. The prognosis is guarded as recurrence may occur.

Keratoconjunctivitis Sicca

There are two categories of keratoconjunctivitis sicca (KCS) or 'dry eye' syndrome that are recognized in horses, although there is some overlap between the two (Crispin, 2000). Quantitative KCS results when there is a decrease in aqueous tear production. Qualitative or evaporative KCS occurs when adequate amounts of aqueous tears are produced but the lipid or mucin fractions are decreased which results in premature evaporation or dissipation of the ocular tear film. Both generally take the form of a superficial keratitis of varying severity, often complicated by intermittent shallow ulceration or epithelial sloughing, vascularization, and pigmentation, and arise as a consequence of abnormal production, distribution, break up, or loss of the preocular tear film (Crispin, 2000). Fortunately, neither condition is common in the horse.

KCS, caused by a deficiency in the aqueous portion of the preocular tear film, occurs relatively rarely in the horse and is most frequently neurogenic, associated with traumatic injury to the parasympathetic nerve supply to the lacrimal gland. These fibers arise in the lacrimal nucleus and combine with sensory fibers from the facial nucleus as far as the geniculate ganglion. The parasympathetic fibers within the superficial petrosal nerve and the facial nerve leave the skull via the petrosal and stylomastoid foramena, respectively. Because of the anatomic location of these nerves in the temporal part of the skull, disruption of the parasympathetic supply to the lacrimal gland and KCS is reported in fractures of the stylohyoid bone, the proximal part of the vertical ramus of the mandible, and some cases of temporohyoid osteoarthropathy (middle ear disease) (Blythe & Watrous, 1997; Joyce & Bratton, 1973; Spurlock et al., 1989; Verdegaal et al., 2003). In these instances, concurrent facial palsy may be present because of the proximity of the nerves. KCS may also be present in vestibular disease with facial paralysis if the lesion of the facial nerve is proximal to the geniculate ganglion (Crispin, 2000). Bilateral KCS has been reported associated with suspected basilar skull fracture (Reilly &

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Beech, 1994). A less frequent cause of KCS is direct injury to the lacrimal gland caused by plant toxins, in particular locoweed (Spiess et al., 1989). Putatively immune-mediated dacryoadenitis causing bilateral KCS has been reported in young horses, in one case *Thelazia lacrimalis* migration being suspected as a cause (Collins et al., 1994; Spiess et al., 1989). Dacryoadenitis and KCS are recorded in association with eosinophilic keratitis (Yamagata et al. 1996). Congenital KCS does occur, although the cause is unknown, and idiopathic KCS is reported (Collins et al., 1994; Matthews, 2004b; Wolf & Meredith, 1981). Oral trimethoprim sulfa (30 mg/kg SID) does not reduce tear production in the horse (Rothschild et al., 2004).

Diagnosis is based upon clinical signs and is confirmed by Schirmer tear testing (STT). STT1 (basal and reflex tear production) results in normal horses vary widely and mean values from 12.7 mm/min to 24.8 mm/min are reported albeit using different test paper types (Beech et al., 2003; Williams et al., 1979). No horses with STT1 results of less than 10 mm/min were found in a population of normal horses, and, in general, STT1 results of 0–10 mm/min or less are considered confirmatory of KCS (Beech et al., 2003; Matthews, 2004b). There were no differences between STT1 (22 ± 6 mm wetting/min) and STT2 (20 ± 5 mm wetting/min; after topical anesthesia) in the horse in one study (Beech et al., 2003). The auriculopalpebral nerve block has no effect on tear production in the horse (Visser et al., 2017). Comparison with tear production in the contralateral eye may be useful. However, caution should be exercised because some normal horses show significant variation in STT1 results between both eyes.

Treatment generally involves the long-term use of corneal lubricants and tear replacement products every 2–6 hours. Surgical transpositioning of the parotid salivary duct to the medial canthus is possible in the horse and has been used with some success in treating a few cases of KCS. However, complications including fistula formation and avascular necrosis of the transposed duct have been reported (Montgomery et al., 2013; Wolf & Meredith, 1981). CsA appears to have some lacrimomimetic effect in the horse, although its use in the long-term management KCS has not been reported (Collins et al., 1994; Reilly & Beech, 1994).

In the horse, evaporative keratopathies are synonymous with exposure keratopathies, and they are most commonly associated with lagophthalmos and lid margin incongruities caused by primary adnexal diseases, such as coloboma, neoplasia, unrepaired injury, chronic conjunctivitis, chronic blepharitis, parasitic granuloma, meibomianitis, and chalazion. In these latter instances the resulting loss or disruption of the lipid layer of the tear film is likely to exacerbate evaporative loss of the aqueous component (Crispin, 2000). Less frequently, evaporative dry eye is a secondary complication of exophthalmos resulting from retrobulbar pathology, including neoplasia, or in buphthalmic foals. Ptosis, arising from facial nerve paresis or in cases of Horner's Syndrome, Grass Sickness or botulism, must cause significant compromise of the normal blink mechanism, but only rarely is associated with evaporative dry eye. Protracted general anesthesia is a potential and common cause of evaporative dry eye, and topical ocular lubricants are routinely recommended as a means of protecting the ocular surface. Similarly, the normal corneal hypoanesthesia occurring in neonatal foals may lead to evaporative dry eye complications in sick or hospitalized foals (Brooks et al., 2000a). Early cases of qualitative tear deficiency may show persistent mild blepharospasm in the absence of any overt clinical abnormality of the ocular surface. STT1 times are normal. However, tear break up times may be increased and the corneal surface retains Rose Bengal stain in an irregular or geographic pattern. The cause of the tear film abnormality is usually difficult to establish. In some cases, primary structural compromise of the mucin layer, or poor physical adhesion of the tear film to the corneal surface caused by primary abnormality of epithelial mucin receptors or from inadequate reestablishment of mucin receptors in repair epithelium, may be involved.

Treatment in these cases involves the regular application of ocular lubricants or artificial tears. Temporary tarsorrhaphy or bandage contact lenses may be used to protect the cornea in selected cases. In all cases the primary cause should be identified and where possible corrected.

Immune-Mediated Keratitis (IMMK)

With few exceptions, the corneal inflammatory pathology evident clinically in equine nonulcerative keratitis is nonspecific. However, it is possible to group some of these diseases according to the clinical presentation and progress of disease, the depth at which the inflammatory changes are occurring, and the response to anti-inflammatory or immunomodulatory therapy (Gilger et al., 2005; Matthews, 2000a, 2004b). As a group they may be referred to as immune-mediated keratitis (IMMK) (Gilger et al., 2005; Matthews, 2000a; Matthews & Gilger, 2009, 2010). A diagnosis of IMMK is made if there is a progressive or chronic (>3 months in duration) nonulcerative or recurring corneal opacity with mild to moderate signs of cellular infiltrate, corneal vascularization, and corneal edema (Gilger et al., 2005; Matthews, 2000a). IMMK is characterized by having only mild signs of ocular discomfort (i.e., only mild epiphora and/or slight blepharospasm). Other characteristic features include absence of secondary uveitis, absence of microorganisms on culture, cytology, or histopathology, and clinical improvement with anti-inflammatory medications (Gilger et al., 2005; Matthews, 2000a). In most instances where IMMK is suspected, ocular cytology and culture collection should be attempted to rule out an infectious cause of the lesions. If the diagnosis is still in doubt, a superficial keratectomy/biopsy should be considered for routine histopathology,

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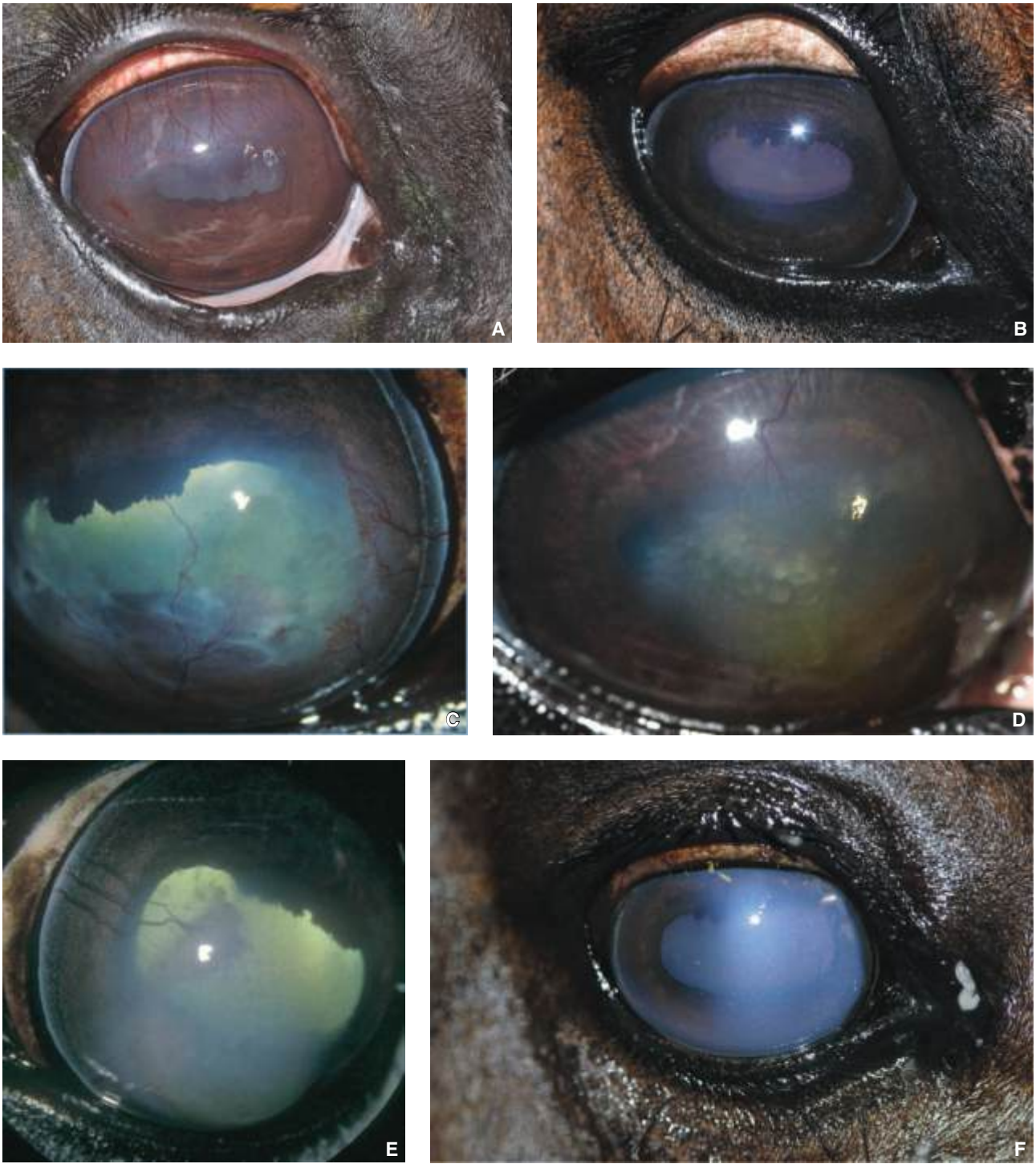


Figure 29.55 The immune-mediated keratitis (IMMK) complex is divided by the depth of cornea affected. **A.** Horse with superficial IMMK, characterized by superficial, branching corneal vascularization. **B.** Subepithelial, superficial, white-to-yellow stromal cellular infiltrate may be present. **C**, **D.** Diffuse midstromal cellular infiltrate, bullae formation, and peripheral corneal vascularization characteristic of a horse with mid-stromal IMMK. **E.** Horse with diffuse corneal edema associated with endothelial IMMK or endothelitiis. Focal areas of endothelial cellular infiltrate are also visible. This disease is characterized by a chronic, slowly progressive, nonpainful, diffuse ventrolateral or ventral full-thickness area of corneal edema. **F.** Central to ventral edema in a vertical orientation may be noted with endotheliitis. **G.** Edema has coalesced into bullae and microulcers in this endotheliitis eye. **H.** Multifocal punctate epithelial lesions in the ventral and ventral-paracentral corneal epithelium characteristic of superficial or epithelial IMMK. **I.** Multifocal punctate epithelial lesions present in epithelial IMMK.

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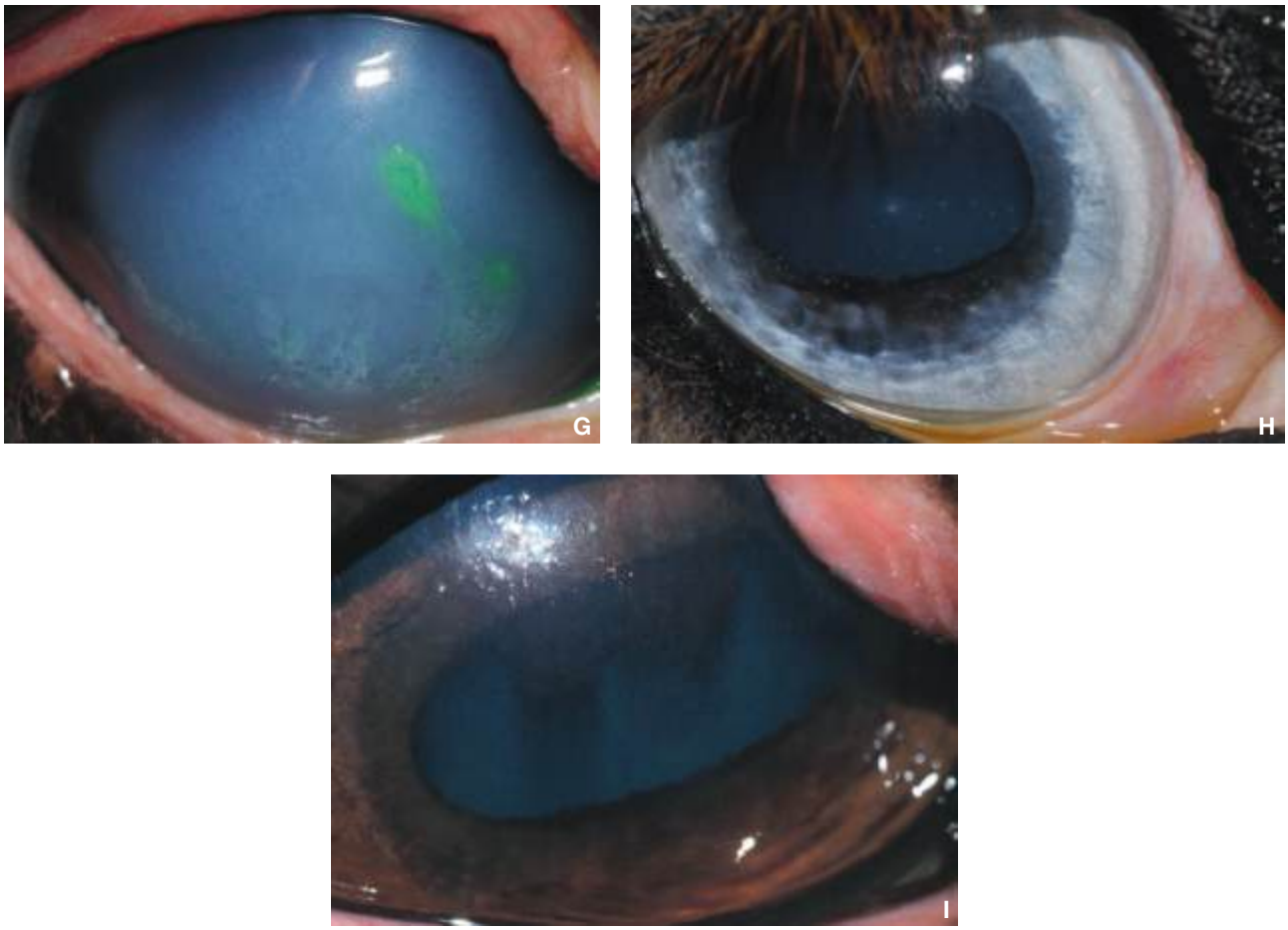


Figure 29.55 (Continued)

special organism staining, and if possible, immunostaining and PCR testing for presence of microbial or viral DNA.

There is considerable variation in the clinical appearance and response to therapy and subsets of disease are usually classified based on the depth of the lesions within the cornea (Fig. 29.55). In all types of IMMK, signs of significant discomfort are not usually observed. The most common clinical presentation of IMMK is superficial stromal disease (45% of cases), with midstromal (27% of cases) and endothelial disease being less common (23% of cases), and epithelial disease being much less common. Unilateral presentation of IMMK is most common although bilateral cases do occur. There is no breed or gender predilection, and the average age of diagnosis of all clinical manifestations in the United States was approximately 12 years (Gilger et al., 2005).

Superficial IMMK is characterized by a nonpainful subepithelial, superficial, white to yellow infiltrate surrounded by superficial branching corneal vascularization that follows a waxing and waning course. This form can usually be controlled with topical steroids or CsA. Superficial keratectomy appears to be useful to decrease antigen or autoantigen load and decrease recurrence.

The stromal form appears as mid-stromal cellular infiltrate with surrounding corneal edema and vascularization. The cellular infiltrate is deeper and denser than the superficial form and the cornea is generally more opaque. Occasionally, pockets or lacunae of green-tinged fluid and infiltrate are appreciated. Medical therapy is the same as for superficial IMMK. However, the stromal forms tend to be less responsive.

Deep or endothelial disease is also referred to as endotheliitis. This form is characterized by a chronic, slowly progressive, nonpainful focus of dense corneal edema with cellular infiltrate that accumulates at the level of the endothelium. Disruption of the function of the endothelium results in the accumulation of fluid in the stroma. Bullous keratopathy may also occur and result in secondary superficial focal or multifocal ulcerations. This form of IMMK may emerge as a precursor to a form of refractory anterior uveitis and secondary glaucoma. Endothelial disease is the least amenable to therapy, but some response may be seen with topical steroids and NSAIDs such as bromfenac and systemic flunixin. Topical hypertonic saline may help decrease the accumulation of microbullae.

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Differences in the clinical appearance and response to therapy may vary depending upon the geographic location of the affected patient. This suggests different populations have different genetic predispositions or that different environmental factors influence or precipitate the disease process. The underlying etiology of IMMK in any form is unknown. However, the clinical signs suggest the natural healing process is attempting to respond to what the body presumes is a focus of disease or infection. IMMK may be the manifestation of an aberrant or deviant response to insult. Evidence for involvement of a pathogen is lacking to date. However, it may be that such a pathogen has just yet to be identified.

The immune responsiveness of the normal mammalian cornea differs within the individual anatomic layers (Hori et al., 2000). However, overall the cornea is an immunologically privileged structure. Immune privilege (IP) is an evolutionary adaptation which downregulates the immunogenic inflammatory response of the eye as a means of protecting vulnerable ocular structures and preserving vision. However, IP exists in counterbalance with the threat of unchecked infection because of inadequate immunoresponsiveness. Although corneal IP is governed by normal endothelial cell function, it is determined by a number of factors (Dana, 2004; Hori et al., 2000). These include the absence of blood and lymphatic vessels, the expression of complement regulatory proteins in the aqueous humor and on corneal cells, the expression of Fas ligand on corneal cells, and the relative paucity of professional antigen-presenting cells constitutively expressing MHC class II antigen (e.g., dendritic cells and Langerhans cells). Activation and recruitment of these antigen-presenting cells into the cornea, along with inductive expression of MHCII antigen on native corneal cells, including a small population of MHCII-negative resident lymphoreticular cells, by proinflammatory cytokines, in particular IL-1 and TNF-alpha, appears to be central to the loss of corneal IP. This, along with corneal lymphangiogenesis under inflammatory stimulation permitting lymphocyte trafficking into afferent lymphatics, creates an effectively 'normal' adaptive immune responsiveness in the inflamed or injured cornea, which in part will underscore the immunopathogenesis of conditions such as corneal allograft rejection and exacerbation of herpetic keratitis in humans (Dana, 2004). In the horse, compromise of corneal IP, creating opportunistic immune-driven responses to putative heteroantigen or unmasked autoantigens in the corneal microenvironment, may be responsible for some of the nonulcerative keratides recognized in this species. Clinical expression of these diseases is likely to depend upon the extent and specificity of the derangement of IP, the nature and presentation of the antigen implicated, and the duration of the inflammatory insult.

Histopathology of non-eosinophilic, superficial, or midstromal IMMK reveals stromal fibrosis, vascularization, and infiltration of predominantly lymphocytes and plasma cells (Gilger et al., 2005). In a more recent study of histopathology of keratectomy specimens of eyes with superficial or midstromal IMMK (Pate et al., 2012), the predominant type of cellular infiltrate was lymphocytic-plasmacytic inflammation with variable degrees of histiocytic and PMN inflammation. Other histological changes found in most of the corneas included stromal necrosis, hyperplastic epithelium, and neovascularization. Immunohistochemical evaluation of superficial IMMK showed a predominantly T-cell-driven response, with both cytotoxic and helper T-cell involvement (Pate et al., 2012).

Epithelial IMMK

Epithelial IMMK is a unilateral disease affecting horses of any age. It is characterized by multifocal punctate areas in the ventral and ventral-paracentral corneal epithelium (Fig. 29.54H, I). These lesions are not ulcerated but may have very faint surrounding cellular infiltrate. Most commonly, there is no corneal vascularization, and the horse has minimal to no signs of discomfort. There may be some associated conjunctival hyperemia or chemosis. The superficial opacity represents irregular coalescing clumps or islands of thickened epithelium, with no underlying stromal edema. The unaffected areas of cornea appear normal. Fluorescein may be retained in the interstices between the islands of abnormal epithelium. A viral etiology needs to be ruled out, in particular EHV-2 or EHV-5. Topical dexamethasone results in rapid corneal clearing in most cases, and the disease has not been observed to recur after successful treatment.

Superficial IMMK

Horses with superficial stromal IMMK are characterized by an insidious onset, with affected eyes showing only slight to mild discomfort with a waxing and waning chronic corneal opacity. The opacity consists of a subepithelial, superficial, white to yellow stromal cellular infiltrate that is surrounded by prominent superficial, branching corneal vascularization (Fig. 29.55A, B) and perivascular epithelial edema. Tear production is normal and no fluorescein uptake occurs. The opposing palpebral conjunctiva is moderately hyperemic. Superficial IMMK is most commonly located in the ventral paracentral cornea, followed by ventral perilimbal corneal location, then a central location. The disease is initially unilateral but the contralateral eye may become affected with time. Superficial IMMK can usually be controlled with topical corticosteroids and CsA. Typically, the steroids are tapered after clinical resolution of the corneal cloudiness with topical CsA continued once a day to help prevent recurrence (Gilger et al., 2005). Superficial keratectomy, however, may prevent recurrence, as seen in 13 eyes of 12 patients in a recent study (Pate et al., 2012). Episcleral CsA implants have been shown to be effective for superficial IMMK if placed early in the course of the disease (Gilger et al., 2014).

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Midstromal IMMK

Midstromal IMMK is an episodic keratitis recurring at irregular intervals of up to several years. There is frequently history of initiating ocular trauma and the disease may derive from a local adaptive response to autoantigen in an immunocompetent cornea (Matthews, 2000a; Matthews & Gilger, 2009, 2010). It is clinically similar to superficial IMMK except that the location of the vascularization and cellular infiltrate is in the central layers of the corneal stroma. Also, the cellular infiltrate is denser, resulting in a more opaque cornea than superficial IMMK (Fig. 29.55C, D). Because of the deeper corneal location, vascularization is typically less branching and straighter than that observed in superficial IMMK. Most commonly, midstromal IMMK is located in the lateral paracentral, ventral, or central cornea.

In the acute or active phase of the disease there is an extensive and dense deep stromal edema and fibrovascular response, with isolated blood vessels encroaching on the affected stroma at various levels. The intensity of the stromal changes varies between cases and between episodes. Despite the dramatic appearance of affected eyes, the disease is associated with no ocular pain. However, subepithelial bullae may form and rupture to create superficial erosions, causing transient ocular discomfort. In some eyes lacunae of greenish tinged fluid may collect within the midstromal central and paracentral cornea. Subepithelial calcium deposition may occur in some eyes. Acute episodes of the disease will eventually subside without treatment in most cases. In the quiescent or inactive phase of the disease there is a modest diffuse stromal fibrosis with some superficial vascularization.

Treatment is similar to superficial IMMK but it is generally less responsive to therapy. The therapeutic benefit of topical corticosteroids is very limited, although they may accelerate clearing of the cornea in some cases. Topical CsA twice daily results in significant suppression of the acute corneal reaction and clearing of the cornea within 10–14 days in most cases. However, treatment may need to be maintained at a reduced frequency for a protracted period to prevent recrudescence of the disease until such times as corneal reactivity subsides spontaneously. For midstromal IMMK in horses, a superficial keratectomy may be beneficial for the long-term control of the disease. It is possible that this therapy is beneficial because of the surgical removal of the autoantigen(s) in the cornea, and thus eliminating the source of inflammation (Gilger et al., 2005; Pate et al., 2012).

Endothelial IMMK

Endothelial IMMK, or endotheliitis, is characterized by a chronic, slowly progressive, initially nonpainful, diffuse ventrolateral or ventral full-thickness area of corneal edema (Matthews, 2004b; Matthews & Gilger, 2009) (Fig. 29.55E, F, G). The disease is usually of sudden onset, and affected eyes are nonpainful. There is a deep, diffuse fibrocellular opacity and stromal edema in the central cornea, which may evolve rapidly into corneal hydrops. Isolated arborizing blood vessels encroach upon the affected area at the level of the posterior stroma or endothelium. In some cases, dense clumps of cells may be evident adherent to the endothelium in the region of the terminal vessel. In long-standing cases stromal mineralization can occur. When examined with a slit lamp biomicroscope, dark cellular infiltrate can usually be observed at the edge of the corneal edema at the level of the endothelial cells. Occasionally, with chronic disease, bullous keratopathy may develop, resulting in focal or multifocal superficial corneal ulcers. Horses with endothelial IMMK have normal IOP and no aqueous flare or miosis, so glaucoma and uveitis are not likely primary causes. Deep corneal abscesses may appear similar, but these horses are generally painful and have secondary uveitis. Endothelial IMMK in horses is slowly progressive and, in general, is poorly responsive to medication (Gilger et al., 2005). Topical steroids and CsA therapy are not generally effective; however, there are rare reports of rapid clearing of the cornea and regression of the blood vessels using topical dexamethasone (Matthews, 2000a). Recently, there have been anecdotal reports of response of endothelial IMMK to potent topical NSAIDs (e.g., bromfenac) (Clode, 2011). Episcleral CsA implants have been helpful in some cases of endothelial IMMK if placed early in the course of the disease (Gilger et al., 2014).

Eosinophillic Keratitis

Eosinophillic keratitis (EK) is a condition that has been seen more frequently in the past 20 years (Brooks, 2004; Ramsey et al., 1994; Yamagata et al., 1996). The clinical appearance of this condition is either a unilateral or bilateral white plaque on the surface of the cornea with surrounding corneal edema (Fig. 29.56) or a superficial stromal, perilimbal yellow infiltrate. Cytology of corneal scrapings show an intense eosinophil response with some plasma cells, mast cells, and PMNs (Dwyer, 2011). Often single or multiple shallow ulcers which are covered by dense white or gelatinous necrotic plaques loosely attached to the underlying stroma are identified (Brooks, 2005c; Matthews, 2004b; Ramsey et al., 1994; Yamagata et al. 1996). Typically, the ulcers appear initially in the perilimbal cornea and extend peripherally, although the geographic appearance of the lesions is highly variable. The most common location is the cornea located under the third eyelid, followed by the ventral-medial and ventral-lateral cornea. Vascularization of the anterior stroma accompanies the focal ulceration and may be very intense. Moderate to severe ocular pain accompanies disease, although more chronic proliferative nonulcerated lesions associated with minimal pain have been described. Conjunctival hyperemia, chemosis and a yellow or white caseous mucoid discharge are common. Dacryoadenitis and KCS in association with the corneal lesions can occur. The cause is unknown but may involve a hypersensitivity reaction.

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Figure 29.56 **A.** Eosinophilic keratitis which appears as a white plaque at a common location under the third eyelid adjacent to the medial limbus. **B.** Horses with eosinophilic keratitis present with chronic corneal pathology (± corneal ulcers) with moderate discomfort.

Eosinophilic keratitis seems to occur most commonly in the early or late summer months and develops in well-managed horses given appropriate vaccinations and deworming protocols. Several animals in a barn may be affected, some with only conjunctivitis characterized by a white, cheesy exudate. Eosinophilic keratitis is generally self-limiting and will resolve over 8–12 weeks. However, several treatments have been suggested to enhance or speed healing. Topical corticosteroids are generally effective, but their use may need to be continued for 9–10 weeks or longer to achieve resolution of the lesions. Topical NSAIDs may exacerbate the signs of the disease and should be avoided. Topical mast cell stabilizers and histamine receptor antagonists have been advocated in instances where corticosteroids are considered high risk therapy. Debridement of the necrotic plaques and superficial keratectomy will shorten the treatment period in most cases. Increasing the frequency of deworming treatments is also recommended.

Parasitic Keratitis

Onchocerca cervicalis can infect the ocular tissues in the horse. Adult nematodes live in the nuchal ligament of the horse and produce microfilaria which migrate through subcutaneous tissues and are ingested by flies and midges that act as intermediate hosts and then transmit the microfilaria to other horse with their bites (Cello, 1971; Schmidt et al., 1982). Aberrant migration of the noninfective form of the microfilaria to ocular tissues results in clinical signs which may include conjunctivitis, focal vitiligo, nodules along the limbus and stromal keratitis with superficial stromal opacities adjacent to the limbus, corneal edema, and vascularization. Anterior uveitis may accompany the keratitis. Treatment consists of the administration of an avermectin parasiticide and symptomatic anti-inflammatory therapy for the keratitis and uveitis.

Peripheral Ulceration (Limbal Keratopathy)

Peripheral ulceration (limbal keratopathy) is a rare progressive perilimbal ulceration, possibly of immunogenic origin (Dice & Cooley, 1990). The disease may be unilateral or bilateral, and is associated with moderate to severe ocular pain and a seromucoid ocular discharge. Perilimbal ulceration, involving up to half the stromal depth, is present and extends both circumferentially and centripetally, becoming confluent in some cases. Corneal vascularization may be evident. The lesions are sterile, and plasma cells and lymphocytes are prominent in corneal scrapings and perilimbal conjunctival biopsies. Eosinophils may also be present. Similar lesions have been noted in horses with systemic immune-mediated diseases such as pemphigus.

Topical 1% prednisolone acetate 4–6 times daily results in rapid resolution. However, careful monitoring of the eyes for secondary infection is necessary. Surgical debridement, topical antibiotics, and therapeutic soft contact lenses may be used in combination with steroid therapy, but are usually not necessary.

Corneal Dystrophy

Corneal dystrophies are primary biochemical abnormalities, typically presented as bilateral, symmetrical, and progressive opacities, and which are frequently inherited (Matthews, 2004b). There is no associated inflammation or vascularization.

Dystrophic corneal disease comparable with that recognized in human and dog corneas has not been reported in the horse. However, unilateral and bilateral progressive dystrophic-like stromal opacities are encountered sporadically in the horse. They occur only rarely, and there is no treatment (Matthews, 2004b).

Progressive, often bilateral and geographically symmetrical focal thinning of the stroma in Fresian horses has been

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reported (Lassaline-Utter et al., 2014b). The lesions appear as well-defined circular defects, usually in the inferiotemporal quadrant of the cornea. They may be shallow initially, but can progress to a descemetocele. Treatment to minimize the risk for perforation should be promptly initiated. In some cases, surgical reconstruction is necessary. The mechanisms of this progressive stromal loss have not been identified. However, there is some similarity to pellucid marginal degeneration in humans, a rare, adult-onset, non-inflammatory cause of corneal ectasia. Most cases respond well to surgical treatment.

Hereditary Equine Regional Dermal Asthenia

Hereditary equine regional dermal asthenia (HERDA), also called hyperelastosis cutis, is an autosomal recessive condition observed in American Quarter Horses that affects collagen synthesis. Affected individuals are normal at birth but develop a skin fragility syndrome by 2 years of age and exhibit dermal seromas, hematomas, ulcerations, and impaired wound healing. These animals also show decreased corneal thickness in several regions of the cornea, increased corneal curvature, increased corneal diameter, and mild corneal opacity (Badial et al., 2015). Disrupted collagen alignment is noted in the corneal stroma which manifests as haze and an increased susceptibility to ulceration (Mochal et al., 2010). It is not known whether the increased corneal curvature significantly impacts the vision of horses with HERDA.

Radiation-Induced Keratopathy

Progressive stromal edema with bullous keratopathy and nonresponsive geographic and punctate ulceration have been recorded as delayed sequelae of beta and high-dose gamma irradiation therapy respectively of limbal SCC and periorbital fibrosarcoma (Moore et al., 1983a; Slatter et al., 1983). In the latter case iris swelling and focal retinal atrophy were also noted. Such cases are rare and may in part reflect problems with computed radiation dosage and corneal exposure resulting from postoperative lid fibrosis and decreased corneal sensitivity (Slatter et al., 1983). Treatment is symptomatic, and these cases generally carry a guarded prognosis for return of corneal transparency.

Corneal Sequestrum

Corneal sequestrum is a very rarely reported complication of chronic keratitis. One report described refractory chronic superficial erosions in three horses associated with sequestrum formation (Håkanson & Dubielzig, 1994). The presenting shallow erosive lesions were fluorescein negative, had an opalescent surface appearance, and were variably vascularized with peripheral foci of mineralization. Histology of keratectomy sections typically showed an intensely eosinophilic, thin, wavy membrane comprising an acellular matrix which overlay or lay within the superficial stroma, and which overlay or fragmented within underrun peripheral epithelium. The staining characteristics of this nonpigmented membrane showed significant similarity to corneal sequestrum in the cat, but, unlike the cat, the lesions were periodic acid–Schiff positive and stained for elastin using Verhoeff's stain, although that this latter observation may have been artifactual. The second report described ulceration and corneal sequestrum associated with KCS in a Shetland pony, describing an extensive pigmented lesion involving much of the corneal thickness, clinically more like the feline lesion (McLellan, 2004). In this report, histology showed the sequestrum to be periodic acid–Schiff negative and to fail to stain for elastin.

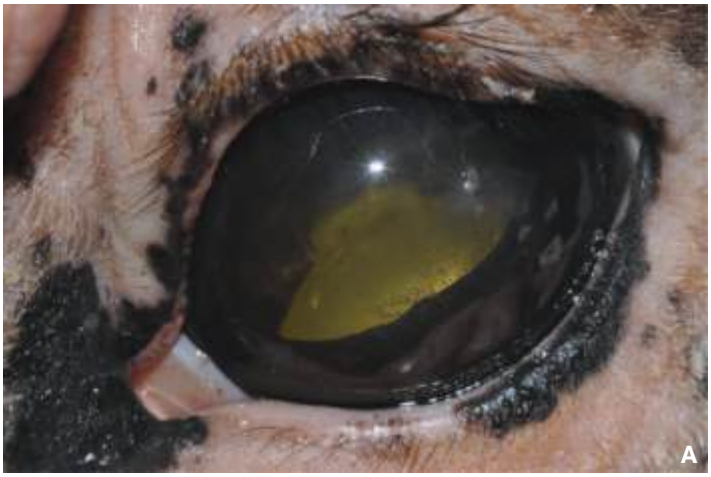
Management of such cases involves keratectomy to remove the sequestrum and subsequent treatment of the resulting corneal defect. Prognosis is likely to depend upon the nature, duration, and severity of the primary pathology giving rise to the lesion.

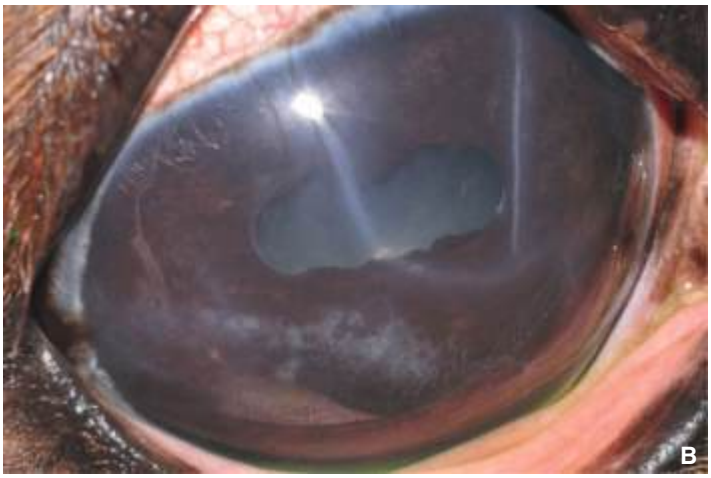
Corneal Mineralization and Calcific Band Keratopathy

Subepithelial mineralization is occasionally observed in association with keratitis and uveitis (Rebhun, 1992d; Rebhun et al., 1993). Calcific band keratopathy refers specifically to the deposition calcium salts at the level of the epithelial basement membrane and anterior stroma that is an occasional finding in chronic equine recurrent uveitis. The mineralized area typically adopts an oblate or linear configuration, geographically defined by the palpebral aperture, the peripheral cornea remaining clear (Fig. 29.57). The deposits are variably dense and small lucent areas may be present within the lesion, possibly corresponding to the points of penetration of corneal nerves through the basement membrane (Rebhun et al., 1993). Thicker deposits may elevate the corneal surface, resulting in excoriation of the epithelium and shallow ulceration, and the lesions may provoke their own inflammatory response. The specific cause of the mineralization is unknown. Spontaneous resolution may be promoted by topical instillation of EDTA to decrease calcium levels in the tear film, although epithelial dehiscence and ulceration are a possible disadvantage to chronic application of EDTA. In long-standing lesions or in cases of dense mineralization, superficial keratectomy may be required, although significant corneal scarring is likely to result. Topical 0.4%–7% EDTA in a neutral solution may promote dispersal of any remaining calcium salts after removal of the overlying epithelium.

Local mineralization of superficial ulceration is occasionally seen in the horse, and in most cases will resolve as the lesion heals (Håkanson & Dubielzig, 1994). Mineralization of the central or anterior stroma can occur as an uncommon sequel to chronic or recurrent keratitis arising from various causes (Matthews, 2004b; Rebhun, 1992c,d). These are nonprogressive dense, semirefractile opacities, geographically related to the site of the inflammatory insult. These lesions are usually prominently vascularized. There is no specific

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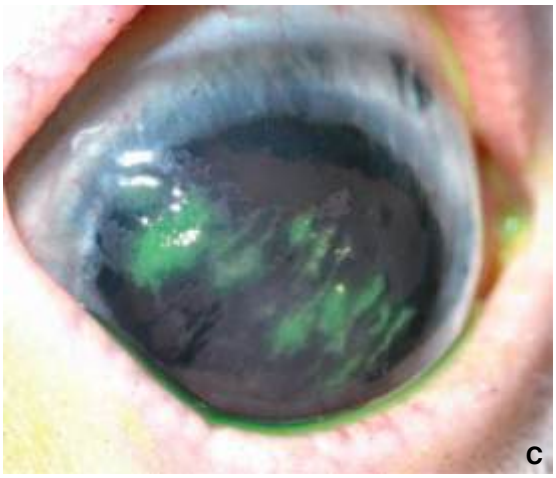


Figure 29.57 **A.** Calcific band keratopathy in a chronic equine recurrent uveitis eye with an associated superficial corneal ulceration. Note also the posterior lens luxation and the green discoloration to the ocular media. **B.** The white calcium deposits in band keratopathy are usually localized within the opening of the palpebral fissure in the central and ventral paraxial cornea. This chronic equine recurrent uveitis eye also exhibits linear striate keratopathy (Haab's striae) associated with glaucoma. **C.** This chronically inflamed eye has band keratopathy and associated corneal ulceration.

treatment and the cornea may clear spontaneously after resolution of the primary problem. Excision by lamellar keratectomy may be attempted.

Idiopathic Primary Edema (Bullous Keratopathy)

This is a rare, usually unilateral, condition believed to arise from a functional abnormality in the endothelium, resulting in the net ingress of water from the anterior chamber and consequent stromal overhydration (Matthews, 2000a; Millichamp et al., 1990; Rebhun, 1992d). A specific etiology has not been identified in the horse, although primary dystrophic-like disease or immune-mediated degeneration has been suggested. Clinically there is dense and nonpainful stromal edema and turgidity, generally of rapid onset and typically beginning in the mid-ventral cornea and progressing to involve the entire cornea. Subepithelial bullae (bullous keratopathy) may form and may rupture or be abraided by lid action, resulting in shallow erosions which cause low grade ocular discomfort (Matthews, 2000a) (Fig. 29.58). Perilimbal neovascularization may develop in rare instances. IOP is not elevated and no other ocular abnormality is evident. Histological examination in one case has shown disruption and cell loss in the endothelial cell monolayer (Millichamp et al., 1990).

Conventional treatment is based upon the use of topical hyperosmotic preparations such as 7.5% saline, 10% glycerine, or 5% hypertonic saline ointment. These, at best, achieve temporary clearing of the cornea, but may minimize the formation of microbullae. Hydrophillic soft contact lenses may be tried, but difficulties in placement and retention along with possible epithelial hypoxia are drawbacks to their use. Topical 0.2% CsA is reported anecdotally to have been of clinical benefit in some cases, and a nictitans membrane flap in other cases. Topical corticosteroids are conventionally

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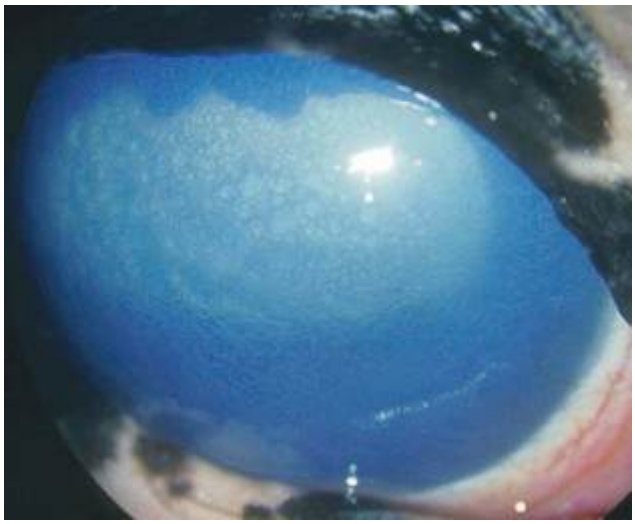


Figure 29.58 Generalized bullous keratopathy in an older mare. The stromal edema is so pronounced that water is trapped in the epithelium causing epithelial bullae to form.

used and may have some rationale, along with CsA, where an immunogenic etiology is suspected. Corticosteroids should be avoided where epithelial erosions are present. Thermokeratoplasty may be considered in cases refractory to medical treatment. The prognosis in all cases is guarded. Treatment is frequently ineffective and even where corneal clearing begins, it may not continue to completion.

Linear Keratopathy

Non-edematous striate lesions with well-defined, parallel refractile margins are occasionally observed traversing the cornea at the level of Descemet's membrane in normotensive and otherwise clinically normal eyes (Matthews, 2000a; Rebhun, 1992d; Walde, 1983; Wouters & De Moor, 1979). Typically, these striae are single and nonbranching, although multiple branching lesions may be observed. Usually the striae traverse the horizontal meridian of the eye, although oblique and vertical transcorneal lesions may be encountered, and rarely the lesion may fail to bridge the cornea. The striae are uniformly 1–2 mm in width throughout their length, and histologically have been shown to be thinning of Descemet's membrane with a normal endothelial overlay (Brooks, 2005c).

Clinically similar striate lesions are seen in chronically hypertensive eyes and in corneas after blunt trauma. In these cases, the striae are more typically multiple, branching, and may show significant variation in width. In glaucomatous eyes there is commonly contiguous deep stromal edema, and local fibrosis may develop with chronicity. In eyes with a history of blunt trauma there are typically other accompanying intraocular pathologies such as iridocyclitis, anterior capsular cataract, and vitreoretinal degenerations. Histologically, the lesions present in glaucomatous eyes are similar to those in normotensive and otherwise normal eyes (Brooks, 2005c; Wilcock et al., 1991). However, the striae present in the equine eye do not show the typical curling recoiled margins of the ruptured Descemet's membrane found in the deep striate corneal opacities occurring in both glaucoma (Haab's striae) and birth trauma in humans. This difference may reflect some unique elastic properties of Descemet's membrane in the horse.

The cause of the lesions in otherwise normal eyes is unknown, but some have proposed congenital, possibly dysplastic, etiologies (Hausser, 1921; Walde, 1983a, 2004). However, the histological similarity with lesions present in hypertensive eyes both in horses and in man indicates that acquired injury and subsequent partial repair of Descemet's membrane is likely to be in some way involved. It has been suggested that equine cornea may be particularly sensitive to transient rises in IOP, and that the linear lesions may be indicative of previous, possibly periparturient, IOP elevation (Matthews, 2000a). The lesions appear to be nonprogressive and have no detrimental effect on vision.

Linear keratopathy is significantly dissimilar to the dense, grey, and irregular fibrous retrocorneal membranes resulting from abrupt and major discontinuity in Descemet's membrane after surgical trauma and severe direct blunt trauma to the equine cornea (Matthews, 2004b).

Pectinate Ligament Avulsion

This is an occasional sequel to blunt trauma to the globe. Typically, a sector of overt disruption of the normal anatomy of the pectinate ligaments is evident in the medial or lateral perilimbal cornea, often accompanied by contiguous corneal vascularization and fibrosis. Intraocular postinflammatory pathologies may be present. There is no treatment.

Descemet's Membrane Detachment

Descemet's membrane detachment (DMD) is a disinsertion of Descemet's membrane and the attached corneal endothelium from the corneal stroma. Reports in the human literature have associated DMD with a wide range of conditions including PK, intraocular surgery, chemical injury to the eye or blunt trauma, use of obstetric forceps, and airbag deployment (Matas-Riera et al., 2015). DMD in humans is classified in three ways: separation (planar: <1 mm separation between Descemet's membrane and stroma and nonplanar >1 mm separation), conformation (scrolled edge or nonscrolled edge) and area (peripheral or peripheral with axial involvement). Planar DMD has a better prognosis than nonplanar DMD, and unscrolled DMD a better prognosis than scrolled DMD. Recent reports have described the disassociation of Descemet's membrane with the posterior stroma in two series of five horses each. All eyes experienced profound corneal edema. The first report discussed five eyes (four equine patients) with DMD in association with phacoemulsification surgery, either intraoperatively, postoperatively, or at postmortem examination (Matas-Riera et al., 2015). In this

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series, three of five eyes went on to resolve clinically with posterior stromal fibrosis. The second report described five eyes enucleated because of glaucoma and/or chronic ulceration (Henriksen et al., 2017). All five horses presented with unilateral severe diffuse corneal edema that had developed between 2 and 16 weeks prior to enucleation. Intraocular pressures for the affected eyes were between 9 and 87 mmHg prior to enucleation. DMD and an avascular spindle cell proliferation filling the space between the displaced peripheral Descemet's membrane and the corneal stroma was identified histopathologically in all five globes (Henriksen et al., 2017). It has been proposed that the relatively shallow anterior chamber of the equine eye may predispose to development of DMD during intraocular surgery and, once detached, may contribute to its clinical progression (Matas-Riera et al., 2015). An association between glaucoma and DMD in the horse has also been suggested, although a causal relationship has not been established (Henriksen et al., 2017). Another recent report of seven horses with DMD described similar clinical and histopathologic features (Slenter et al., 2020). In each of those patients, ultrasonography was considered an adequate antemortem diagnostic tool.

Corneal Neoplasia

SCC is the most common tumor of the equine cornea and is most commonly, but not exclusively, observed in horses with minimal ocular and periocular pigmentation such as Appaloosas, Quarter Horses, Paints, Haflingers, and draft horses (Belgians, Shires, Clydesdales). A genetic basis for the development of limbal SCC has been detected in the Haflinger, the Rocky Mountain Horse and the Belgian with simple autosomal recessive mode of inheritance of a missense mutation in the gene that codes for damage-specific DNA binding protein 2 (DDB2) (Bellone et al., 2017; Knickelbein et al., 2019, 2020; Lassaline et al., 2015). DDB2 binds to ultraviolet light damaged DNA and recruits other proteins to perform global genome nucleotide excision repair. This mutation has also been identified in the Belgian and the Percheron, suggesting that it may be a risk factor for SCC in other breeds as well (Bellone et al., 2017). The disease most commonly develops between 9 and 13 years, has no gender predilection, and can be bilateral. Other factors associated with increased prevalence include heredity, high levels of solar radiation and UV light exposure, increasing longitude and altitude, and decreasing latitude (Dugan et al., 1991a).

Corneal SCC originates from the cornea, conjunctiva, or limbus, with the lateral limbus the most common location. Corneal SCC most commonly appears nodular, elevated, white-pink, and fleshy, but may resemble a flat vascular keratitis that does not resolve with the application of a topical steroid (Fig. 29.32C and Fig. 29.59). Affected horses generally show minimal discomfort (i.e., blepharospasm, epiphora), no uveitis, but commonly high amounts of mucopurulent ocular discharge.



Figure 29.59 Raised, fleshy corneal squamous cell carcinoma (SCC). Corneal SCC usually arise from the limbus where it is most exposed.

Treatment involves surgical excision of the mass (e.g., superficial keratectomy) followed by an adjunctive therapy. The most commonly used corneal adjunctive modalities include strontium-90 beta irradiation, carbon dioxide laser, cryotherapy, and topical chemotherapy (5-FU or mitomycin-C). With the addition of strontium-90 adjunctive therapy, recurrence rates for corneal SCC decreases from 50% within 18 months for keratectomy alone to 20% for keratectomy with strontium-90 (Plummer et al., 2007). Nonrecurrence rates are similar with the use of either topical mitomycin-C or CO_2 laser ablation as the adjunctive modality (Clode et al., 2012; Michau et al., 2012). Twice yearly follow-up examinations for 3–5 years are recommended after any therapy for corneal SCC.

Other neoplasms involving the cornea are rare but include mast cell tumors, melanoma, lymphoma, and vascular neoplasms, such as hemangioma, hemangiosarcoma, lymphangioma, and lymphangiosarcoma (Allbaugh et al., 2016; Bolton et al., 1990; Clode, 2011; Flores et al., 2107; Gerding et al., 2015; Halse et al., 2014; Pinn et al., 2011; Rebhun & Del Piero, 1997; Vallone et al., 2016).

Diseases of the Equine Uvea

Diseases of the equine uvea are among the most common ocular problems in horses – especially equine recurrent uveitis (ERU). Congenital uveal defects, primary uveitis, uveal cysts, and neoplasia are also common in the horse eye. Some, but not all, of these defects may result in vision or globe loss.

Uveal Cysts

The corpora nigra, or granula iridica, which are vacuolated extensions of the posterior iris epithelium, normally extend from the dorsal and ventral pupillary margin into the ante-

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rior chamber. When the corpora nigra becomes cystic, its normally roughened appearance becomes smooth and spherical (Fig. 29.60). These uveal cysts are hollow structures that transilluminate with focal light sources, contain a viscous, opaque fluid, and may be more prominent after mydriasis. Uveal cysts may be free floating. Most cysts are small and do not cause significant interference with vision. Large corpora nigra and iridal cysts, depending upon their location, may interfere with vision and cause erratic behavior, especially when the horse is in bright light and the pupil is miotic. Uveal cysts must be differentiated from inflammatory or neoplastic changes to the iris. Although ultrasonography could be used to differentiate cystic corpora nigra from inflammatory or neoplastic infiltrates, this is rarely necessary because the clinical appearance is usually sufficiently characteristic (Hollingsworth, 2011).

Treatment is not usually necessary because corpora nigra cysts rarely obstruct vision. If the clinician is presented with a horse that has a corpora nigra cyst along with head shaking, poor jumping performance, or behavioral change, for example, prior to treatment, the clinician must warn the owners that these behaviors are unlikely to change after treatment of the cyst. The most effective and noninvasive treatment is deflation of the cystic corpora nigra with a laser, either a diode laser or an ophthalmic neodymium-yttrium aluminum garnet (Nd:YAG) (Gelatt, 1993; Gemensky-Metzler et al., 2004; Gilger et al., 1997) (Fig. 29.60C).

Iridal and ciliary body cysts are believed to originate from failure of the two layers of the neuroectoderm to fuse in the area of the iris and ciliary body, respectively. These translucent cysts may enlarge but rarely obstruct vision and can be associated with the MCOA syndrome of Rocky Mountain Horses (Ramsey et al., 1999a).

Uveal Neoplasia

Melanoma

Although melanoma is relatively rare in horses, it usually occurs in gray or partially gray horses between 5 and 10 years of age. The most common site of origin is the iris, but mela-

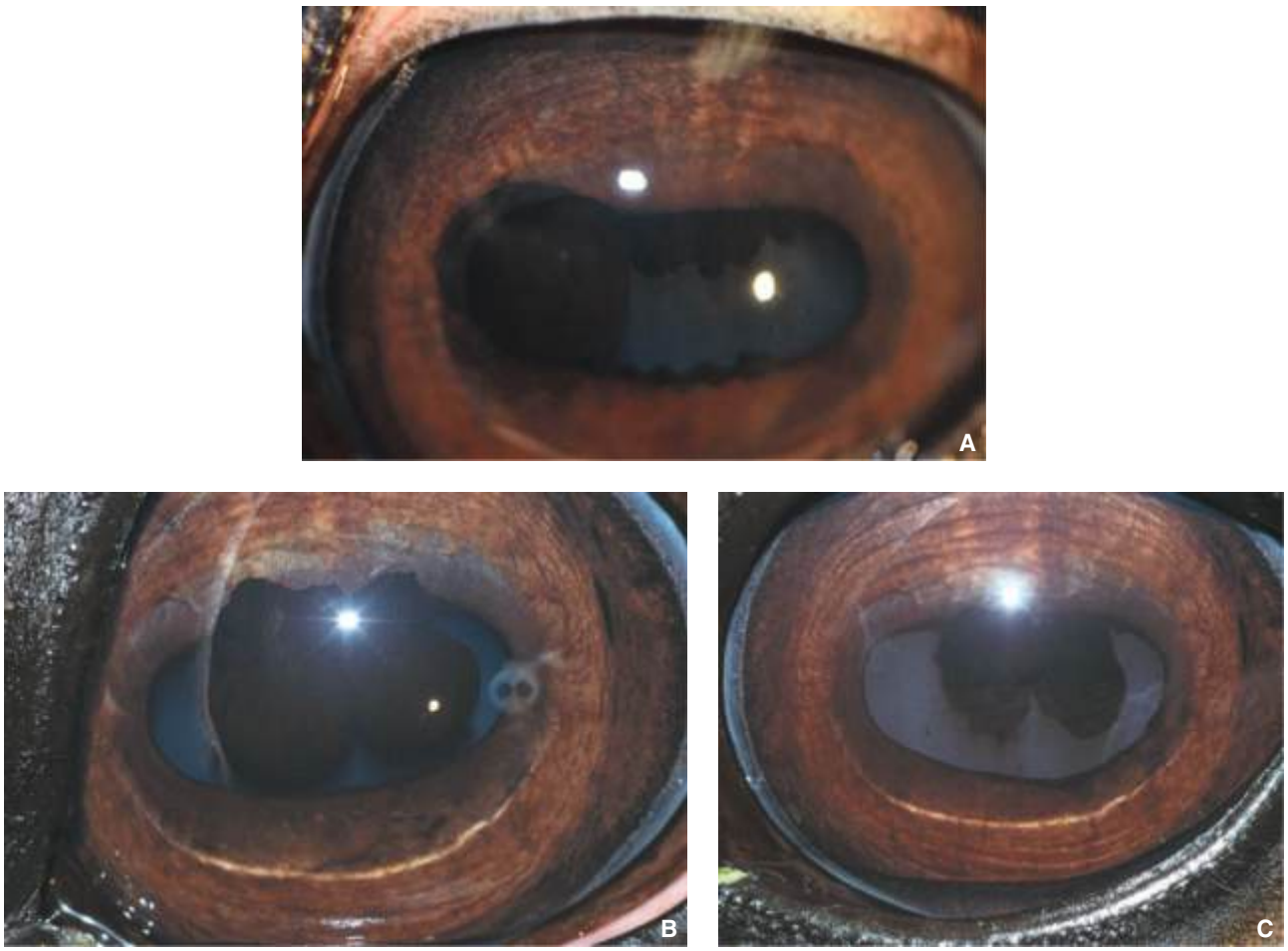


Figure 29.60 Corpora nigra cysts, if large or within the pupil, can affect vision and the horse's performance. **A.** Corpora nigra cyst along the dorsal pupil margin. Note the shadow it casts on the iris. **B.** Two corpora nigra cysts. **C.** Corpora nigra cysts immediately after laser ablation.

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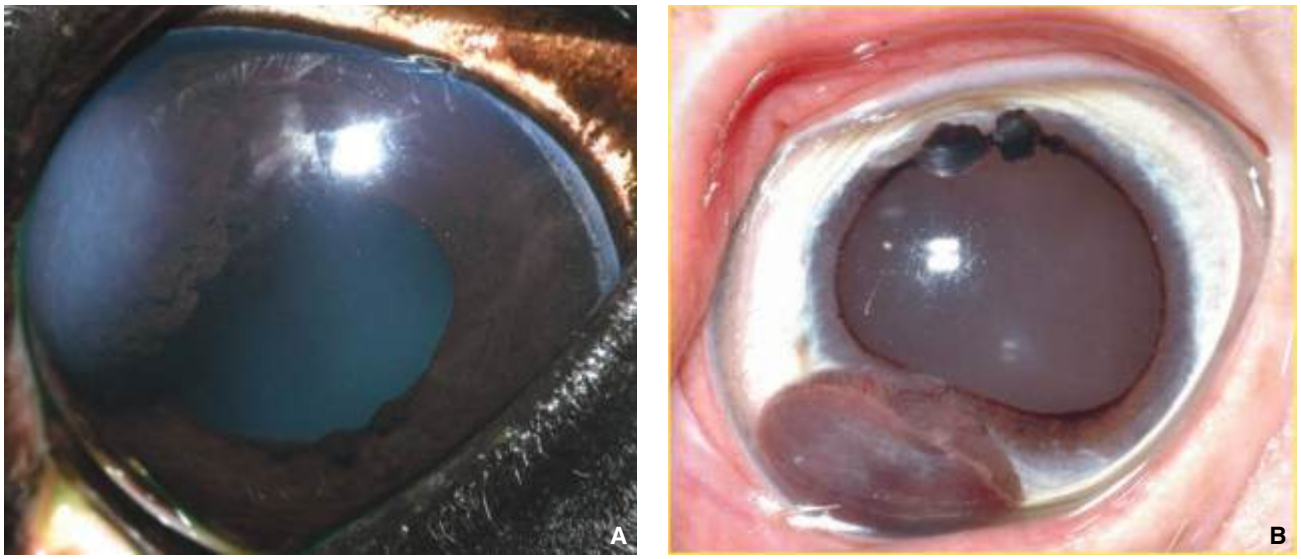


Figure 29.61 **A.** Pigmented iris mass extending into the anterior chamber and contacting the cornea resulting in edema. **B.** Iris melanoma in a blue iris.

nomas arising from the ciliary body have been reported. Common clinical signs include appearance of a dark mass extending from the iris into the anterior chamber (Fig. 29.61), or if advanced, a dark mass filling the anterior chamber with focal corneal edema associated with contact with the posterior surface of the cornea. Masses may also appear pink and fleshy in horses with lightly colored irises. Early in the course of the disease, there are no signs of discomfort; however, as the neoplasm gets larger, common clinical signs include blindness, blepharospasm, epiphora, diffuse corneal edema, and buphthalmos (Hollingsworth, 2011).

Treatment options are limited, and the prognosis for saving the eye is generally poor, but better if the lesion is small. Treatments include a sector iridectomy, diode or surgical Nd:YAG laser therapy, or use of cimetidine. Oral cimetidine (2.5 mg/kg PO q8h) has been used to shrink non-ocular melanomas in horses, but no studies have been done to determine the effect of cimetidine on uveal masses (Goetz et al., 1990). Corneal edema and secondary uveitis are common adverse effects of laser therapy. Generally, intraocular melanoma in horses has been treated by enucleation or exenteration.

Lymphoma

Lymphoma commonly involves the eye and adnexa, and in one study, 27% of horses with confirmed systemic lymphoma had ocular disease. In these horses, eyelid swelling and inflammation were the most common ocular signs followed by involvement of the anterior uvea (Rebhun & Del Piero, 1997). Signs associated with anterior uveal manifestation of systemic lymphoma are nonspecific uveal inflammation and include blepharospasm, episcleral injection, corneal edema and vascularization, aqueous flare, hypopyon, hyphema, iridal congestion, and swelling. Frequently, these nonspecific signs are accompanied by a history of chronicity, poor response to anti-inflammatory medication, and signs of systemic disease such as fever, respiratory disorders, weight loss, peripheral lymphadenopathy, and anemia (Germann et al., 2008b; Rebhun & Bertone, 1984). Solitary uveal lymphoma without systemic involvement has been described in the horse (Trope et al., 2014).

Intraocular lymphoma cannot usually be differentiated from other causes of primary uveitis based on ocular signs. The diagnosis of systemic lymphoma should be considered in any horse with anterior uveitis, especially when it is accompanied by systemic signs of illness such as fever, weight loss, lethargy, and swollen lymph nodes (Hollingsworth, 2011). The diagnosis of lymphoma can be confirmed by identification of neoplastic lymphocytes from samples (i.e., aspirates/ biopsy) of lymph nodes or skin nodules; however, definitive diagnosis can be challenging and prognosis is poor (Hollingsworth, 2011).

Uveitis

The term uveitis broadly describes inflammatory disease of the iris, ciliary body, and choroid, in isolation or in combination. The primary pathophysiological event in uveitis is pro-inflammatory cytokine-driven breakdown of the blood–ocular barrier resulting in the accumulation of proteinaceous and cellular debris in the anterior chamber, or in the vitreal chamber and intraretinal space.

Uveitis in the horse may arise from a variety of known or unknown causes and may be because of primary ophthalmic disease or related to an underlying systemic condition. Blunt or perforating trauma, including surgical trauma, to the

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globe will result in a uveitis of varying severity depending upon the severity of the initiating insult. Uveitis commonly accompanies corneal trauma, corneal ulceration, and some nonulcerative keratopathies, such as stromal abscesses. In some cases, the uveitis may be sufficiently severe or intractable as to become a major determinant of unsuccessful resolution of the primary corneal disease. Some systemic bacterial infections are recognized as uveitogenic in the horse, including *Salmonella*, *Streptococcus equi* var. *equi*, *Borrelia burgdorferi* and *Rhodococcus equi* (Blogg et al., 1983; Parker & White, 1992; Reuss et al., 2009; Smythe & Lundvall, 1963). These organisms may cause direct damage to the eye, but most often result in a systemic inflammatory reaction that affects the eye and the integrity of the blood–ocular barriers. Uveitis is a complication of Gram-negative septicemia in neonatal foals, and the organism may be recovered from the affected eyes (Whitley et al., 1981). *Mycobacterium avium* has been recorded as a cause of bilateral granulomatous uveitis in a horse (Leifsson et al., 1997). Iritis has been described in foals during the course of a field outbreak of EHV-1 (Greenwood & Simson, 1980; Platt et al., 1980). A mild bilateral iritis or iridocyclitis has been reported in association with equine influenza virus infection (Jones, 1942). Uveitis has been reported in cases of malignant lymphoma and in metastatic thyroid carcinoma (Bradley et al., 2000; Traub-Dargatz et al., 1985). Congenital uveitis, possibly caused by *in utero* infection, is a rare occurrence and may be associated with cataract development in the neonatal foal.

Horses commonly present with an apparently endogenous uveitis, generally referred to as ERU. Endogenous uveitis encompasses a heterogeneous group of presumptively immune-mediated, nongranulomatous diseases, and may present as anterior uveitis, panuveitis, or chorioditis. It is very important that the clinician does not assume that every case of uveitis in the horse is ERU. As the name suggests, ERU is characterized by multiple, recurrent episodes of uveitis, whereas acute uveitis is limited to a single event. There is no age, breed, or sex predisposition for acute anterior uveitis. Typical clinical signs associated with acute anterior uveitis are all caused by damage of the anterior uvea and subsequent compromise of the blood–aqueous barrier and include photophobia, blepharospasm, corneal edema, aqueous flare, hypopyon, miosis, vitreous haze, and chorioretinitis (Fig. 29.62) (Hollingsworth, 2011).

Diagnostic testing for primary equine uveitis may help determine the underlying cause of a specific episode of acute anterior uveitis. These would include complete blood count, serum chemistry profiles, serologic tests for specific infectious causes such as leptospirosis, and conjunctival biopsies for detection of *Onchocerca* microfilaria, although detection of *Onchocerca* microfilaria does not necessarily indicate a causal relationship (Attenburrow et al., 1983). For Leptospira, concurrent aqueous humor and serum serology is recommended to determine if there is intraocular production of antileptospiral antibodies (Gilger et al., 2008). Results of serology can be difficult to interpret, because many horses have "positive" titers without evidence of ocular or systemic disease. Leptospiral titers for *pomona*, *bratislava*, and *autumnalis* should be requested in the United States; a positive titer for serovars at dilutions of 1:400 or greater are of clinical importance. A higher titer in the aqueous humor than in the serum (positive C-value) is indicative of antibody production and supports a leptospiral cause for the uveitis (Davidson et al., 1987). Analysis of intraocular organism DNA by PCR may also be performed when possible. A positive C value and detection of organism DNA within the eye is strongly suggestive that the organism is playing a causative role in the uveitis (Gilger et al., 2008).

Treatment of primary uveitis is a combination of specific treatment of the underlying cause of the inflammation and nonspecific treatment of the uveitis with topical corticosteroids and atropine and systemic NSAIDs.

Equine Recurrent Uveitis

ERU (also known as moon blindness, iridocyclitis, and periodic ophthalmia) is a major ophthalmic disease of the horse and is the most common cause of blindness in this species (Gilger & Deeg, 2011; Jones, 1942). It is likely that ERU is a blanket diagnosis, encompassing various subsets of distinct endogenous uveitides that are pathophysiologically similar yet distinct, but are responsible for nonspecific clinical signs. This immune-mediated condition may present with clinical signs that are predominate in either the anterior segment or the posterior segment. However, it is truly a panuveitis affecting the entire uveal tract and by extension, the entire globe. The rate of prevalence for this disease varies from 2% to 30% with significant geographic differences, with a prevalence of 8%–25% among horses in the United States and up to 30% among horses in Central Europe (Cross, 1966; Dwyer & Gilger 2005; Gilger & Deeg, 2011). The disease is relatively uncommon in the UK, with a prevalence of 0.09% reported in 1963 (British Equine Veterinary Association, 1965). It is probable that the etiology of the disease varies in different localities, which may explain in part the significant geographic differences in prevalence of the disease. However, the etiology is likely to involve a series of complex immunopathological events culminating in derangement of the normal immunologically tolerant state of the uveal tract, leaving the eye vulnerable to injury resulting from mixed hypersensitivity responses to a presumptive local autoantigen or heteroantigen.

ERU is characterized by episodes of intraocular inflammation that develop weeks to months after an initial uveitis episode subsides. However, not every case of primary equine uveitis will develop into ERU. Horses can develop ERU at any age, but the peak time of the initial uveitis episode is 4–6 years, a time when most horses are at or nearing their prime performance years.

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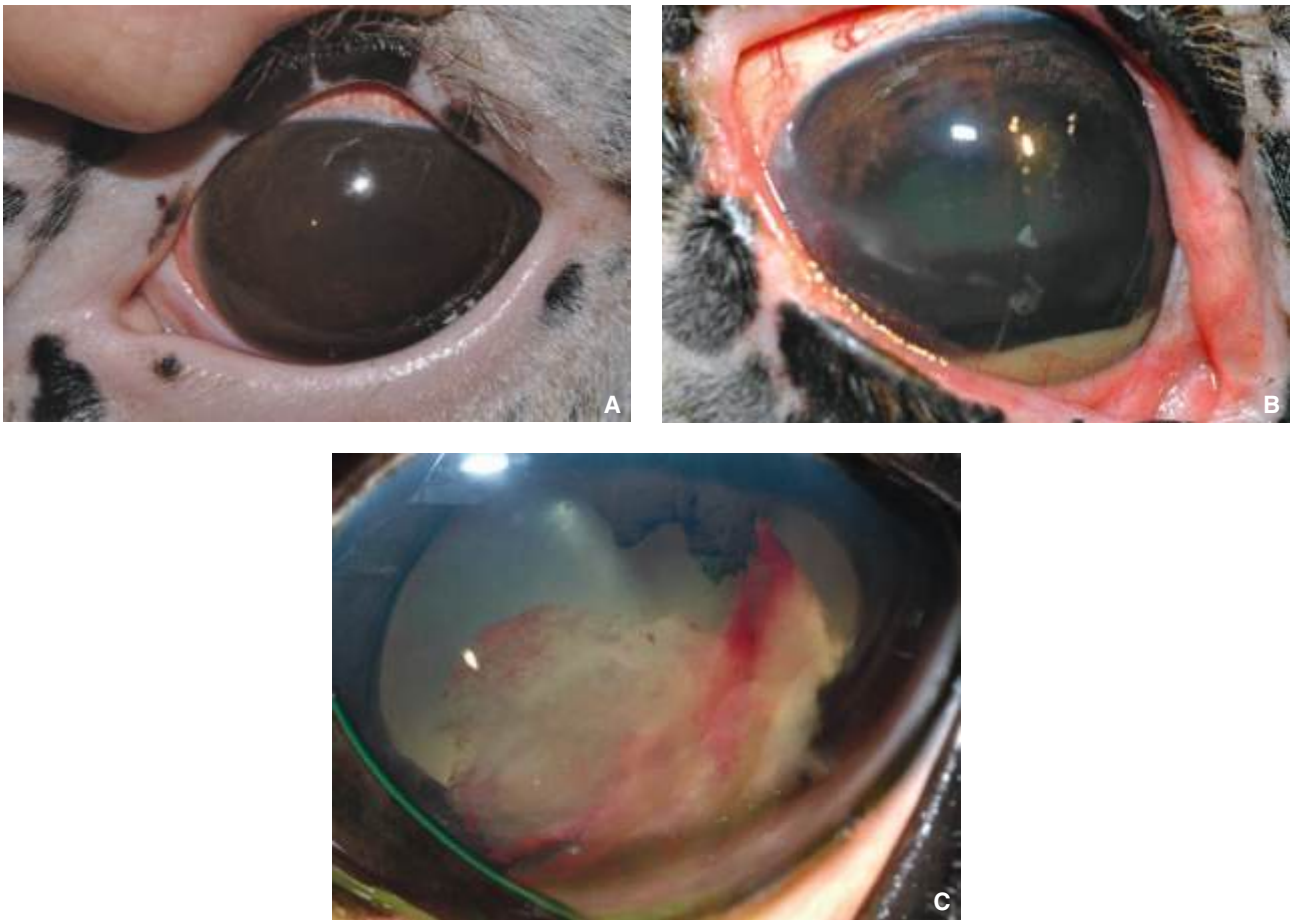


Figure 29.62 Anterior uveitis is usually divided into acute and chronic which show different clinical signs. **A.** Acute, active uveitis episode of anterior uveitis. There is episcleral injection, miosis, aqueous flare, fibrin in the anterior chamber, and mild corneal edema present. **B.** Horse with acute anterior uveitis with clinical signs of photophobia, blepharospasm, corneal edema, aqueous flare, hypopyon, and miosis. **C.** Fibrin and hyphema in an acute phase of equine recurrent uveitis eye.

In some instances, but not all, the uveitis associated with these systemic infections may develop into immune-mediated uveitis or ERU. One of the most commonly associated systemic diseases associated with uveitis is leptospirosis (Dwyer et al., 1995; Faber et al., 2000; Sillerud et al., 1987). Roberts showed that ERU could develop after primary infection (and acute uveitis) of leptospirosis; however, ERU typically did not develop until 1 year after the systemic infection (Roberts, 1963; Roberts et al., 1952). Onchocerciasis is another systemic disease associated with equine uveitis. This disease is much less common now with the widespread use of ivermectin; however, it is still a common initiator of uveitis (Hollingsworth, 2011). The inciting cause for the uveitis is the inflammatory reaction associated with dead and dying onchocerca larvae in the cornea after treatment with an anthelmintic. Other systemic infectious causes of uveitis and, perhaps its perpetuation as ERU, include *Streptococcus equi* infection, *Rhodococcus equi* infection, *Borrelia burgdorferi (Lyme disease),* brucellosis, toxoplasmosis, EHV-1, EHV-2, equine viral arteritis, parainfluenza type 3, equine influenza, equine infectious anemia, the parasite *Halicephalobus gingivalis (deletrix)*, and generalized septicemia, endotoxemia, neoplasia, tooth root abscess, or trauma (Blogg et al., 1983; Kinde et al., 2000; McCartan et al., 1995; Rames, 1995; Reuss et al., 2009; Parker & White, 1992; Schwink, 1992; Smythe & Lundvall, 1963).

Clinical Signs of Equine Recurrent Uveitis

Typical clinical signs of active ERU are similar to signs of acute primary uveitis including lacrimation, photophobia, blepharospasm, corneal edema, aqueous flare, hypopyon, miosis, vitreous haze, and chorioretinitis (Brooks, 2002; Dwyer & Gilger, 2005) (Fig. 29.62 and Fig. 29.63). Miosis is a hallmark clinical sign in horses with ERU and can result in a misshapen pupil and posterior synechiae. Delayed or failed pharmacologic mydriasis is common when uveitis is active. Aqueous flare may be the most sensitive indicator of uveitis activity. Flare occurs early in the disease and is one of the last signs to abate. The degree of pain exhibited by the animal may vary significantly. Some animals appear to be in

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Figure 29.63 Significant destructive effects of inflammation are seen with chronicity. **A.** Chronic low-grade anterior uveitis has resulted in iris hyperpigmentation and corpora nigra atrophy. **B.** Chronic equine recurrent uveitis has resulted in cataract and posterior synechia. There is fibrin in the anterior chamber. **C.** Vitreous cellular infiltrate and vitreal strands in a horse with predominantly posterior uveitis. **D.** Chronic equine recurrent uveitis has resulted in cataract formation and lens subluxation in this eye. Note that the equator of the lens is visible at the temporal pupil margin. **E.** Chronicity of inflammation has resulted in secondary glaucoma (multiple, linear branching Haab's striae). **F.** This eye has become hypotensive and is shrinking (phthisis bulbi). **G.** Cataract and iris atrophy are prominent in this very active, but chronically inflamed eye. Hyphema and fibrin are present in the anterior chamber.

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severe pain whereas others seem to be relatively untroubled. These differences are reflected in the different subsets or syndromes that are recognized as ERU. Clinical signs of chronic ERU include corneal edema, iris fibrosis and hyperpigmentation, posterior synechia, corpora nigra degeneration (smooth edges), miosis, cataract formation, vitreous degeneration and discoloration, and peripapillary retinal degeneration and optic nerve atrophy. Secondary glaucoma may result from chronic uveitis and phthisis bulbi may develop either directly from uveitis or as a consequence of end-stage secondary glaucoma.

Three main clinical syndromes are observed in ERU:

1) *Classic ERU* is the most common form and is characterized by active inflammatory episodes in the eye followed by periods of minimal ocular inflammation. The acute, *active phase of ERU* predominantly involves inflammation of the iris, ciliary body, and choroid, with concurrent involvement of the cornea, anterior chamber, lens, retina, and vitreous. After several weeks, typical (shorter with appropriate therapy) signs of active, acute uveitis can recede, and the disease enters a *quiescent* or *chronic* phase. After variable periods of time, the quiescent phase is generally followed by further and increasingly severe episodes of uveitis. It is the recurrent, progressive nature of the disease that is responsible for the development of cataract, intraocular adhesions, and phthisis bulbi.
2) *Insidious ERU* is characterized by inflammation that never completely resolves, even with appropriate anti-inflammatory therapy. A low-grade inflammatory response continues that leads to progression to chronic clinical signs of ERU. Frequently, these horses do not show overt ocular pain and owners of these horses may not recognize the presence of disease until a cataract forms or the eye becomes blind. They are often misdiagnosed as having allergies and conjunctivitis. This type of uveitis is most commonly seen in Appaloosa and draft breed horses.
3) *Posterior ERU*. The clinical signs exist entirely in the vitreous and retina, with little or no anterior signs of uveitis. In this syndrome, there are vitreal opacities, retinal inflammation, and in some cases retinal detachment and subsequent degeneration. This is the least common type of uveitis in the United States (Gilger & Deeg, 2011) (Fig. 29.63C).

Classic or insidious ERU can have either predominantly anterior (cornea, iris, lens, and ciliary body inflammation) or posterior (ciliary body, vitreous, and chorioretinal inflammation) segment involvement. Ultimately, even with aggressive treatment, many horses develop a chronically painful eye and blindness as a result of secondary cataract, synechia, scarring, glaucoma, and development of phthisis bulbi (Fig. 29.63F).

The clinical diagnosis of ERU is based on the presence of characteristic clinical signs (corneal edema, aqueous flare, posterior synechia, corpora nigra atrophy, cataract formation, vitreous degeneration, retinal edema or degeneration with or without signs of associated ocular discomfort such as epiphora, periocular swelling, and blepharospasm) *and* the history of documented recurrent or persistent episodes of uveitis. Both features are required to make this clinical diagnosis, especially to differentiate from non-ERU uveitis and other causes of recurrent or persistent ocular inflammation, such as herpesvirus keratitis or IMMK.

Pathogenesis of Recurrent Uveitis

ERU is a nonspecific immune-mediated disease that results in recurrent or persistent inflammatory episodes in the eye. To diagnose the syndrome of ERU, the clinician must differentiate it from non-ERU primary uveitis. As mentioned above, there is a long list of infectious and noninfectious agents responsible for causing primary uveitis in the horse (Matthews Handscombe, 1983b). Although any of these causes of uveitis may allow horses to develop ERU, not all of these acute uveitis cases will develop into ERU.

Since relatively minor intraocular inflammation has potentially devastating consequences for vision, the mammalian eye has evolved the means to limit the intensity and extent of the local response to antigen challenge. This immunological tolerance is fundamental to the integrity of the healthy eye and is generally referred to as immune privilege (Streilein & Wegmann, 1987). Privilege is determined by a number of mechanisms, including anterior chamber associated immune deviation, which represent a series of immunological responses to intraocular antigen challenge, resulting both in locally impaired expression of delayed type hypersensitivity and suppression of C3-fixing antibody production, but without affecting antigen specific cytotoxic T-cell activity. Thus, intraocular tissues are spared the collateral effects of uncontrolled T-cell driven inflammation. Recurrence of disease may be explained by persistence of the inciting antigen in ocular tissue resulting in periodic inflammation or by delayed-type hypersensitivity (Verma et al., 2012).

Impairment of anterior chamber associated immune deviation exposes the uvea to the possibility of immune-mediated insult. The means by which immune tolerance is broken down and immune-generated inflammatory disease arises are not known. However, the well-documented association of the onset of ERU with initial exposure to certain *Leptospira* serovariants, notably *L. interrogans* var. *pomona*, suggests these organisms may be implicated in at least some instances of the disease (Kalsow et al., 1997). The association of ERU with leptospires and, possibly, other microbial pathogens, may be based upon antigenic homology between microbial peptides, potentially uveitogenic intraocular autoantigens,

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and MHCI+ peptides. Antileptospiral antibodies produced in horses and present in the aqueous humor and tear film have been shown to bind to corneal endothelium, and a 90-kd protein common to several *L. interrogans* serovars has been shown to share epitopes with an equine corneal peptide (Lucchesi & Parma, 1999; Lucchesi et al., 2002; Parma et al., 1985, 1987). Infection, injury, or stress may result in a cytokine-driven increased turnover of MHC molecules, possibly stimulating the elaboration of normally suppressed T-cell clones recognizing these cross-reactive peptides and precipitating an autoimmune inflammatory crisis (Deschenes et al., 1997). This is supported by the observation of the predominance of Th-1 cells in ERU affected eyes (Gilger et al., 1999). Following an initial episode of uveitis, inflammatory upregulation of intraocular antigen-presenting cells and further loss of suppressor influences may overcome the residual mechanisms conveying immune tolerance resulting in episodic or recurrent inflammation driven by associated or unassociated heteroantigens, or by unmasked tissue autoantigens. It has been reported that MHCII+ cells are present in the post-ERU nonpigmented ciliary epithelium and retina, and MHCII+ specificity is reported on RPE and pigmented ciliary epithelial cells in ERU affected eyes (Romeike et al., 1998). Also, the incidence of serum and aqueous antibodies to retinal proteins is greater in horses with ERU than in normal horses and autoantibodies directed against retinal S-antigen and interphotoreceptor retinoid-binding protein (IRBP) along with CD4+ T cells specific for these antigens are found in over 70% of vitreous samples taken from ERU cases (Deeg et al., 2001; Hines & Halliwell, 1991; Maxwell et al., 1991). Subcutaneous injection of IRPB results in uveitis similar to the spontaneous disease in experimental horses, suggesting that it may be the major autoantigen in ERU (Deeg et al., 2002). A response to S antigen-derived peptide is present in horses with experimental uveitis induced by repeated injection of IRBP antigen (Deeg et al., 2002). It is possible that retinal autoantigens are unmasked during an inflammatory event of unrelated origin and the presence of autoantibodies may be coincidental to, rather than instrumental in, the genesis of ERU. However, experimental observations to date support the hypothesis that autoimmunity is probably fundamental to the genesis of ERU.

The origin and perpetuation of autoimmune diseases may be explained by the concepts of molecular mimicry, bystander activation, and epitope spreading (Deeg et al., 2006a, 2006b; Gilger & Deeg, 2011). These mechanisms may interact and appear together. *Epitope spreading* is defined as the diversification of epitope specificity from the initial focused, dominant, epitope-specific immune response, directed against a self or foreign protein to cryptic epitopes on that protein (intramolecular spreading) or other proteins (intermolecular spreading) (Deeg et al., 2006a; Gilger & Deeg, 2011). In most autoimmune diseases, several autoantigens participate in the pathogenesis (Deeg et al., 2006b), and epitope spreading is accountable for disease induction, progression, and inflammatory relapses (Deeg et al., 2006a). The shifts in immunoreactivity could account for the remitting/relapsing character of ERU. Genetic background and antigens encountered influence the direction and extent of epitope reactivity and probably play an important role in the heterogeneous clinical manifestations of ERU (Gilger & Deeg, 2011).

Epitope spreading in autoimmune diseases results in the detection of an increasing array of autoantibodies against various target antigens. Initial studies have confirmed epitope spreading in a high percentage of cases of ERU (Deeg et al., 2006a). An immune response to cellular retinaldehyde-binding protein (CRALBP) (Deeg et al., 2006b) was detectable in a large percentage of ERU cases. CRALBP was detected as a novel uveitis autoantigen. CRALBP and IRBP showed 100% uveitogenicity in the horse, and both autoantigens were capable of causing recurrent uveitis in the horse (Deeg et al., 2006b), closely resembling the clinical course of spontaneous ERU. Whatever the mechanisms involved, it is clear that a complex immunological environment must exist in ERU affected eyes, and that in each case an individual series of immunological events lead to a final pathway resulting in the typical clinical signs of ERU.

A variety of recent studies has attempted to characterize different features of ERU to improve understanding of the underlying pathophysiology. A few snippets of insight are included below. However, they do not yet provide a coherent big picture of the story of ERU. A recent study discovered strong immunoreactivity for IL-6, IL-17, and IL-23 in ERU cases. This, in conjunction with the fact that T lymphocytes are the predominating inflammatory cells present in ERU, suggests that IL-17-secreting helper T cells play a role in the pathogenesis of ERU (Regan et al., 2012). Additionally, the anti-inflammatory cytokine IL-10 and the pro-inflammatory cytokine IP-10 appear to play an important role in ERU because of elevations in their levels in the aqueous humor and serum of ERU patients (Curto et al., 2016). A recent study detected seven differentially abundant lymphocyte proteins in ERU patients. One of these proteins, lactotransferrin, showed higher expression levels in lymphocytes of ERU cases, whereas six of the identified candidates showed lower expression in ERU cases. Among the latter were glyceraldehyde-3-phosphate dehydrogenase, protein tyrosine phosphatase nonreceptor type 6, voltage-dependent anion-selective channel protein 2, programmed cell death 6-interacting protein, ezrin and septin 7. In blood-derived T lymphocytes from ERU cases, expression of septin 7, a potent inhibitor of cell proliferation, decreased to 62% of expression level in controls and its decrease in expression level may support inflammatory events in pathogenesis (Degroote et al., 2014).

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Decreased talin-1 expression in blood-derived granulocytes of ERU cases has been noted which serves as evidence to link the innate immune system to ERU. Changes in leukocyte protein expression pattern may play a role in pathological abnormalities leading to migration ability. CD90 (Thy1) is a novel interactor of talin-1 that is highly abundant in normal animals and significantly reduced in ERU, especially in effector cells (DeGroote et al., 2012; DeGroote et al., 2013).

Analysis of synaptotagmin-1 (SYT1) was recently identified as the first cell membrane associated autoantigen in ERU. Its expression in ERU retinas is downregulated to 24% of normal which suggests dysregulation of retinal neurotransmitter release in ERU (Swadzba, 2012b).

The expression of the ECM molecules fibronectin and osteopontin in vitreous and retina samples is markedly decreased. Severe ECM remodeling occurs in autoimmune uveitis which may affect the adhesive function of fibronectin and thus the anchoring of Müller cell endfeet to the internal limiting membrane. The absence of osteopontin in gliotic Müller cells may represent reduced neuroprotection, an attribute of osteopontin (Deeg et al., 2011).

It has been determined that there are significant intraocular immunoglobulin M (IgM) reactivities to the retinal proteome which shows an ongoing immune response that might contribute to the remitting relapsing character of ERU (Zipplies et al., 2012). IgM autoantibodies in vitreous specimens of ERU-affected horses show reactivity to the peptide neurofilament medium (NF-M), although there is not a corresponding IgG response. A persistent IgM response may play a role in the chronicity of ERU. NF-M expression in ERU-affected retinas decreases considerably (Swadzba, 2012a).

There is a significant upregulation of complement and coagulation cascades and downregulation of negative paracrine regulators of canonical Wnt signaling including the Wnt signaling inhibitors DKK3 and SFRP2 at the retinal Müller glial cells, which are prime responders to autoimmune triggers. Retinal expression levels and patterns of DKK3 change in response to ERU (Hauck et al., 2012). Aquaporin 11, a regulator of water efflux at the retinal Müller glial cell surface, was found to be decreased in retinas of affected horses (Deeg et al., 2016). This may explain the finding of retinal edema in ERU. A decrease in the plasma cell membrane proteins SYT1, basigin, and collectrin, which play important roles in cell adhesion, transport, and cell communication, and the photoreceptor-specific retinal degeneration slow protein peripherin-2 were recently identified in the RPE of ERU eyes (Uhl et al., 2104, 2015). Further study will be critical to the understanding of this very complex disease process.

Leptospirosis and Equine Recurrent Uveitis

The association between anterior uveitis and leptospirosis was first made in Germany in 1947, to be followed by several similar reports from various parts of the world (Rimpau, 1947). Subsequent observations on a field outbreak of *Leptospirosis interrogans* var. *pomona* in the United States described the occurrence of uveitis in five of six horses 12–24 months after their being affected with the acute disease (Roberts, 1958). Later experimental studies confirmed an association of *L. pomona* infection and equine uveitis, demonstrating the ocular lesions in subject ponies 12–14 months after experimentally induced leptospiremia (Morter et al., 1969). In the United States, serological linkage of leptospirosis and equine uveitis remains most consistently demonstrable for *L. interrogans* var. *pomona*, and it has been reported that the severity of ERU, measured by loss of vision, was greatest in *L. pomona* seropositive horses (Dwyer et al., 1995). In a more recent study in the United States, leptospirosis titers of serum and/or aqueous humour were obtained in 88 horses and were positive in 40 horses (45.5%), with *L. pomona* being the most frequently isolated serovar (Gerding & Gilger, 2016).

In the United States, UK, and Europe, several studies have shown serological linkage of *L. interrogans* serovariants other than *pomona* with some cases of equine uveitis, including *australis* var. *bratislava, autumnalis* var. *autumnalis,* and *sejroe* var. *sejroe* and *saxkoebing*. Serology is limited in its ability to detect local intraocular immunoreactivity to microbial pathogens, and in Germany Wollanke showed no difference in Leptospira seroprevalence between ERU affected and unaffected horses, but in these same horses, 60% of the ERU affected animals had significant intravitreal Leptospira antibody titers compared with the unaffected group (Wollanke, 1998). Brem and colleagues showed leptospires in the vitreous of four out of 42 horses undergoing surgical vitrectomy for the treatment of ERU, although 34 of these horses had intravitreal antibody titers (Brem et al., 1998). Faber detected leptospiral DNA using PCR techniques in the aqueous of 21 out of 30 cases of ERU in California, although the organism was cultured in only six cases (var. *pomona* in 4/6), and in Germany *L. interrogans* was isolated from the vitreous in more than 50% of eyes with ERU (Faber et al., 2000; Wollanke et al., 2002). In Germany, where *L. interrogans* has been identified in vitrectomy material, the *grippotyphosa* serovar has been predominant (Wollanke et al., 2002). A recent study from Germany reported serum and vitreous humor antibodies against *Leptospira* spp. in 225 horses presenting for pars plana vitrectomy for ERU (Dorrego-Keiter et al., 2016). In that study, a total of 127 of 221 (57.5%) horses had serum antibodies (≥1:100), most frequently antibodies against *L. interrogans* serovar *Grippotyphosa* (79/127), followed by *L. interrogans* serovar *Icterohaemorrhagiae* (34/127) and *L. interrogans* serovar *Bratislava* (29/127). Only 79/225 horses (35.1%) had leptospiral antibodies in vitreous humor, in which *L. interrogans* serovar *Grippotyphosa* (67/79) was identified most frequently followed by *L. interrogans* serovar *Pomona* (18/79) and *L. interrogans* serovar *lcterohaemorrhagiae* (8/79) (Dorrego-Keiter et al., 2016).

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Kalsow and Dwyer reported retinal degeneration in some ponies with experimental leptospira-induced uveitis (Kalsow & Dwyer, 1998). Immunohistochemistry showed MHCII antigen positive round and dendritiform cells in the retinal lesions, but no significant immunoreactivity associated with either RPE cells or with Muller cells. The MHCII+ cells in the postuveitic retinas were not identified. Similar observations were made on the retinas from naturally occurring uveitis. These findings prompted these authors to suggest that the retinopathy may be a primary immunological event in equine uveitis, and that leptospira-associated uveitis may be a distinct subset of the equine uveitides. Chorioretinal degeneration and lymphocytic infiltration is a consistent finding in ERU cases in Germany (Deeg et al., 2002). There is clearly a causal linkage between leptospiral infection and some cases of ERU. However, the exact nature of the link remains to be elucidated.

Inconsistencies in culture results and serology for the numerous implicated infectious agents support the theory that these agents may actually only activate the intense inflammatory reaction of ERU. Not all horses that are positive for *L. interrogans* serovar *pomona* have uveitis and the serologic evidence of *pomona* infection is more frequent than the incidence of ERU (Halliwell et al., 1985; Sillerud et al., 1987).

Recently, a novel protein, LruC, found in the outer membrane of *Leptospira* spp. organisms was identified that may play a role in equine leptospiral uveitis (Verma et al., 2012). The *LruC* gene was detected in all tested pathogenic *L. interrogans* strains and antibodies to this protein are significantly higher in both the sera and ocular fluids of uveitic horses. LruC joins the previously identified leptospiral proteins LruA and LruB, which are associated with very strong IgG and IgA responses in affected equine eyes.

Histologic Features of Equine Recurrent Uveitis

In chronic ERU, infiltration of the uveal tract with lymphocytes and macrophages is most evident in the ciliary body and base of the iris. Lymphoid follicles are occasionally present in the base of the iris. Loss of tissue structure/destruction was evident in the ciliary processes. Dubielzig and colleagues (Dubielzig et al., 1997) noted several histologic distinguishing features of ERU globes: a noncellular hyaline membrane adhered to the inner surface of the nonpigmented ciliary epithelium, linear intracytoplasmic inclusions in the nonpigmented ciliary epithelium (Cooley et al., 1990), and an influx of lymphocytes and plasma cells into the ciliary body. The choroid also revealed infiltration of mononuclear cells, with overlying retinal degeneration. Previous study of ERU eyes has revealed infiltration of the uveal tract with lymphocytes, plasma cells, and macrophages. Infiltration is most evident in the ciliary body and base of the iris. Loss of tissue structure (destruction) is most evident in the ciliary processes. Infiltrating lymphocytes are predominantly CD4+ T cells (e.g., 48% CD4+ and 18% CD8+ in the ciliary body stroma) (Gilger et al., 1999).

Breed Susceptibility to Equine Recurrent Uveitis

ERU susceptibility has long been suspected to have some heritability. This may be linked to equine leukocyte antigen (ELA) haplotypes influencing the occurrence and expression of, but not directly causing, autoimmune intraocular inflammatory disease. A strong association with the MHCI haplotype ELA-A9 with ERU in German Warmblood horses has been identified (Deeg et al., 2004). Similarly, non-ELA genes may be involved in creating the permissive genetic background necessary for developing the disease.

In the United States, a breed predilection to the development of the disease and to the severity of clinical expression of the disease is recognized in Appaloosa horses (Dwyer & Gilger, 2005). Even in the UK, where the prevalence of recurrent uveitis is low compared to other geographic regions, the relative frequency of disease in Appaloosas and Warmbloods is high (Malalan et al., 2020). There is an 80% chance that ERU will develop in both eyes in susceptible Appaloosas, whereas only a 20% bilateral potential in non-Appaloosas with ERU (Dwyer et al., 1995). A susceptibility allele for ERU exists in the Appaloosa with ERU in the MHC region. The UM011 microsatellite had a higher frequency of the 182 allele, and the microsatellite EqMHCI had a higher frequency of the 206 allele in Appaloosas with ERU (Kaese et al., 2005). A single dominant allele, LP (Leopard complex), is responsible for the color dilute white spotting patterns of coat color in Appaloosas and other horse breeds. The LP gene is located on equine chromosome 1. Heterozygotes with LP/lp have white base coat colors with darkly pigmented spots, whereas homozygotes (either LP/LP or lp/lp) often will have less pronounced spotting and darker base coat colors. In order to differentiate homozygous lp from homozygous LP, genotyping must be performed; phenotyping alone is not reliable. The distinction is important because heterozygotes and LP homozygotes have a significantly increased risk for the development of ERU. A theory exists that melanin may be more important for immunity than solar protection (Bukhardt et al., 2005). The lack of melanin in the coat and eyes of spotted Appaloosas may predispose these animals to develop ocular immunologic problems such as ERU.

Recently, three markers were identified in horses that are significantly associated with ERU in the horse: a single nucleotide polymorphism (SNP) within intron 11 of the *TRPM1* gene on ECA1, an ELA class I microsatellite located near the boundary of the ELA class III and class II regions and an ELA class II microsatellite located in intron 1 of the *DRA* gene (Fritz et al., 2014).

A recent genome-wide association study (GWAS) was performed to identify loci conferring risk for ERU in German Warmblood horses. A significant SNP on horse chromosome

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(ECA) 20 at 49.3 Mb was identified. *IL-17A* and *IL-17F* are the closest genes to this locus, suggesting a genetic component may be responsible for regulating the possible critical role of *IL-17A* and *IL-17F* in the pathogenesis of ERU. Another SNP on ECA18 near the crystalline gene cluster *CRYGA-CRYGF* was identified as well. This SNP may be indicative for cataract formation in the course of ERU (Kulbrock et al., 2013).

Treatment of Equine Recurrent Uveitis

The main goals of therapy for ERU are to preserve vision, to decrease pain, and to reduce and control ocular inflammation in an attempt to limit permanent damage to the eye and pain. In horses where a definite inciting cause has been identified, treatment is directed at eliminating the primary problem while symptomatically treating the ocular inflammation. However, because of the likely immune-mediated pathogenesis of ERU, an inciting cause is rarely identified. In these instances, therapy is necessarily directed at the alleviation of clinical signs by reducing ocular inflammation.

Medical Therapy for Equine Recurrent Uveitis

Treatment should be aggressive and prompt to maintain transparency of the ocular structures to prevent vision loss. Therapy can last for weeks or months and should not be stopped abruptly in order to prevent acute relapse. In some cases, the clinical signs may be decreased, but not altogether eliminated. Once improvement is noted, medications should be slowly reduced in frequency over a 30-day period once the clinical signs abate. In acute cases, treatment in the form of systemic and local therapy with anti-inflammatory drugs and cycloplegic/mydriatic agents is used. In severe cases, local subconjunctival, suprachoroidal, or intravitreal injections of corticosteroids may be indicated as an adjunct to therapy (Gilger, 2016; Yi et al., 2008). These injections must be used with the understanding that they will predispose the horse to infectious keratitis, especially fungal keratitis. Injection of triamcinolone into the suprachorioidal space with microneedles may be associated with fewer side effects than the other injection options (Gilger, 2016). In many instances, a subpalpebral lavage catheter is placed to facilitate delivery of topical medications. Most horses respond well to intermittent topical and/or systemic therapy of their active episodes of ERU and in many cases observant owners can minimize an active episode by initiating therapy at the onset of clinical signs. Some horses, however, do not respond to traditional therapy and may experience frequent recurrences of uveitis.

Corticosteroids

Anti-inflammatory medications, specifically corticosteroids and NSAIDs, are used to control the generally intense intraocular inflammation that can lead to blindness. Topically administered medications are initially administered every 2–6 hours depending on the severity of disease and tapered as the problem resolves. Topical corticosteroids are most commonly used to decrease inflammation. Prednisolone acetate 1% and dexamethasone HCl 0.1% are the most commonly used topical corticosteroids. Prednisolone has superior penetration, although it is not as potent and is considerably more expensive that preparations of dexamethasone. Topical corticosteroids have side effects, including the ability to potentiate infections and collagenase enzymes (melting of the cornea), delaying epithelialization of corneal ulcers, and possibly the potentiation of calcific band keratopathy. The presence of a corneal ulcer precludes use of topical corticosteroids, however, but not that of topical NSAIDs.

NSAIDs inhibit the enzyme cyclooxygenase, which is responsible for prostaglandin synthesis. Topical NSAIDs (e.g., 0.03% flurbiprofen, 0.09% bromfenac sodium, or 0.1% diclofenac sodium) offer as their main advantage that they can be administered without concern for potentiating infections. They will, however, delay epithelialization of corneal ulcers. Although bromfenac is a very potent NSAID compared to the others, in general, the anti-inflammatory effect of topical NSAIDs is much less than topical dexamethasone and prednisolone. When used in conjunction with corticosteroids, topically administered NSAIDs can provide additive anti-inflammatory effects.

Systemic therapy is the most potent therapy for management of ERU. Oral, intramuscular, or IV flunixin meglumine is one of the most potent anti-inflammatory medications for the eye. Phenylbutazone and aspirin are much less effective. Systemic dexamethasone or prednisolone are also effective but generally are only recommended in severe cases that will not respond to other anti-inflammatory medication (Gilger & Michau, 2004).

Mydriatics

Mydriatic/cycloplegic medications minimize the formation of synechiae by inducing mydriasis, and they alleviate some of the pain of ERU by relieving ciliary body muscle spasms (i.e., cycloplegia). These drugs also narrow the capillary interendothelial cell junctions to reduce capillary plasma leakage (Van Alphen & Macri, 1966). The two most commonly used, topically administered drugs that cause mydriasis and cycloplegia are atropine and tropicamide, both of which are parasympatholytic drugs that competitively inhibit the action of acetylcholine on ocular muscarinic receptors. Topically administered atropine can last several days in the normal equine eye, but its effect may be of only a few hours' duration in the inflamed eye with ERU. Gut motility should be strictly monitored by abdominal auscultation and observing signs of abdominal pain when using topically administered atropine in both adult horses and foals, because gut motility can be markedly reduced by atropine (Williams et al., 2000). This reaction appears to be an

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idiosyncratic reaction in a few adult horses, but topically administered atropine may be associated with a reduction in gut motility severe enough to cause clinical signs of colic. The causal effect of atropine on gastrointestinal motility disorders is still a matter of contention, however, as a recent study failed to detect any ileus or serum levels of the drug in normal horses administered topical atropine at clinically appropriate doses (Wehrman et al., 2017). The potential impacts of pain and the stress of hospitalization and their potential additive effects with atropine or gastrointestinal mobility have not been investigated. Should gut motility decrease during treatment with topical atropine, either discontinue the drug or change to the shorter-acting tropicamide. A combination of topically administered phenylephrine (2.5%) and atropine (1%) can also be used to obtain maximum dilation in the inflamed eye with ERU. Topically administered phenylephrine does not achieve mydriasis when used alone in the horse, however, and it does not cause cycloplegia (Hacker et al., 1987). The ease with which mydriasis can be achieved through intermittent use of atropine is an important indication as to the intensity of the ERU. Failure to achieve mydriasis with atropine indicates the ERU stimulus is quite prominent or the presence of synechiation (or both).

Intravitreal gentamicin has been advocated in ERU. In a recent study, it decreased intraocular inflammation and prevented recurrent episodes of uveitic attacks (Pinard et al., 2005). The mechanism behind its efficacy is not understood. A majority (17/18) of eyes had no episodes of uveitis and vision was maintained in 30% of those eyes. One dose of 4 mg was injected into the vitreous at the 12-o'clock position 8 mm from the limbus. In another study, 94% of ERU horses were reported to have improvement in their clinical signs after injection of 4 mg of preservative-free gentamicin intravitreally (Fischer et al., 2016).

Traditional treatments used for ERU (i.e., corticosteroids and NSAIDs) are aimed at reducing inflammation and minimizing permanent ocular damage at each active episode. They are not effective in preventing recurrence of disease. Other medications used to prevent or decrease severity of recurrent episodes, such as aspirin, phenylbutazone, and various herbal treatments have limited efficacy and potential detrimental effects on the gastrointestinal and hematologic systems when used chronically in the horse.

Immunosuppressive Drugs

Cyclosporine (CsA) is a 1.2-kD cyclic peptide that blocks the transcription of IL-2 production through the inhibition of calcineurin, a protein of the transcription factor NFATc (nuclear factor of activated T cell, cytoplasmic). Decreasing IL-2 minimizes T-lymphocyte activation, causing immunosuppression (Gilger et al., 1999). As the severe CD4+ T-lymphocyte infiltrate in the ciliary body and nonpigmented epithelium is the source of the elevated cytokines, CsA is a logical choice for treatment to prevent the activation of T lymphocytes and, therefore, the recurrence of uveitis (Deeg et al., 2004; Gilger et al., 2002; Romeike et al., 1998). However, CsA is hydrophobic and does not penetrate into the eye when applied topically, and the pharmacokinetics, toxicology, and cost of preventative systemic treatment in horses has not been evaluated.

Ocular sustained-release medication devices or implants have many advantages over more traditional methods of drug administration to the eye because they can deliver constant therapeutic levels of drug directly to the site of action, bypassing some of the blood–ocular barriers, and they can eliminate the need to rely on owners to treat their horse. Release rates are typically well below toxic levels of the drug; therefore, higher concentrations of the drug are achieved in the eye without any systemic side effects. Devices also have the benefit of being more convenient for the patient and reducing the risk involved with frequent intravitreal injections (Davis et al., 2004).

Cyclosporine-Releasing Devices

CsA-releasing devices, placed in or near the suprachoroidal space, are used routinely in horses with chronic ERU (Fig. 29.64) (Gilger et al., 2000a, 2000b, 2001, 2006). Horses with ERU (186 eyes of 156 horse) from six centers in the United States and two in Europe had the CsA device implanted and were followed for a mean of 29 months (1–7 years) (Gilger et al., 2010b). Horses with implants had significantly fewer flares after surgery (mean 0.05 flares/month) than prior to implantation. Overall, 79.9% were visual at the last follow-up time. Only three eyes required a repeat implant, all 4 years or longer after the first implant. These results suggested that the suprachoroidal placement of the CsA device resulted in good long-term control of ERU (Gilger et al., 2010b). Because recurrences of inflammation

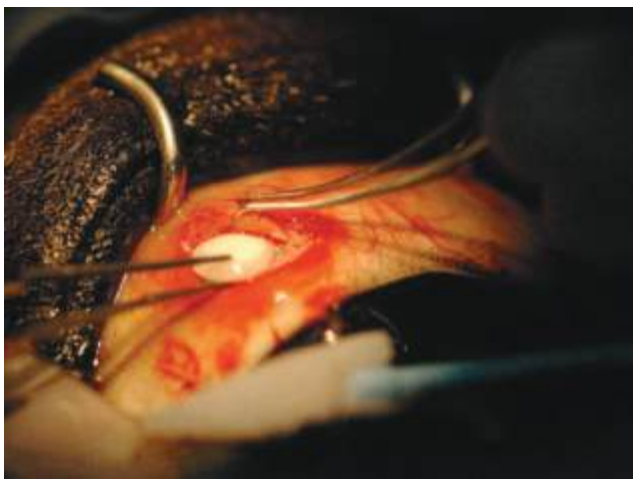


Figure 29.64 Placement of a cyclosporine-releasing device under a scleral flap adjacent to the suprachoroidal space, for long-term treatment of equine recurrent uveitis.

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did not increase after the theoretical depletion of the CsA (approximately 3 years), it is possible that autoreactive T cells may undergo anergy after a period of time in the presence of CsA, after which recurrence of disease will not occur.

The CsA delivery device preparation for use in the horse theoretically delivers 4 μg/day of CsA to the vitreous (Gilger et al., 2001). For surgical implantation, general anesthesia is recommended to minimize intraoperative complications, although placement of the implants in standing, sedated horses has been described. The surgical technique for placement of a suprachroidal implant has been described (Gilger & Michau, 2004). After sterile preparation of the eye, the dorsolateral quadrant of the globe is identified and a 10 mm long conjunctival incision is made parallel to, and approximately 8 mm caudal to the limbus just lateral to the insertion of the dorsal rectus muscle. A 7 mm scleral flap exposing the underlying uvea is created through the conjunctival incision. The CsA device is placed under the scleral flap in contact with the uveal tissue. Care is taken to minimize handling of the implant itself. The scleral flap is closed, followed by closure of the conjunctiva overlying the sclerotomy using 6-0 or 7-0 polyglactin 910 (Vicryl®, Ethicon). Horses are treated with systemic NSAIDs, as well as topical mydriatic and antibiotic therapy for 10–14 days. Systemic broad-spectrum antibiotics may be indicated for 5–10 days postoperatively.

Case selection for the CsA implant procedure is critical to the successful outcome. As CsA is immunosuppressive but not anti-inflammatory, horses that do not respond well to traditional therapies are not considered good candidates for this procedure. Only those horses who have little or no active inflammation but experience frequent relapses of ERU are considered ideal for long-term visual outcome.

Rapamycin

Rapamycin (RAPA) is a carbocyclic lactonelactam microlide antibiotic immunosuppressive drug that is similar in structure to CsA but is not a calcineurin inhibitor. RAPA causes the suppression of T-lymphocyte activation and proliferation by preventing the cell cycle from progressing from G1 to the S phase (Sehgal, 1998). Intravitreal injection of RAPA in normal horses was well tolerated without signs of toxicity (Douglas et al., 2008). The lack of ocular toxicity, potency, and positive effect on experimental and clinical uveitis suggests that RAPA may be a good candidate for local treatment of ERU. In a preliminary study, 10 mg of RAPA in PEG-400 was injected intravitreally into advanced stage, chronic ERU eyes. With a mean follow-up of over 14 months, it was found that 10 of 13 (77%) RAPA-injected eyes were comfortable and only three eyes had frequent or persistent uveitis flares (Gilger et al., 2010a). Availability of this medication may be an issue preventing its routine use for ERU and further study is needed to determine the effectiveness of intravitreal RAPA for long-term treatment of ERU.

Surgical Treatment: Vitrectomy

Pars plana vitrectomy (PPV) has been used in the management of chronic endogenous uveitis in humans and horses (Fruhauf et al., 1998; Gilger & Spiess, 2006), with the goal to improve vision by clearing the media or removing membranes and decreasing recurrent episodes of inflammation. PPV for ERU is used commonly in central Europe. Long-term follow-up reports describe either a decrease in recurrences or complete cessation of the uveitis episodes. In a study by Fruhauf and colleagues, 85% of eyes had no additional recurrence of disease and stable vision (Fruhauf et al., 1998). Of the remaining 15%, only a single recurrent uveitis attack was noted, often occurring within 5–7 weeks postoperatively. Serious complications in the postoperative period include severe vitreal hemorrhage, hyphema, retinal detachment, and cataract development or progression. The long-term clinical outcome results reported in the Frauhauf study are difficult to interpret as the findings were documented via communications from the clients or referring veterinarians, making the possibility of subclinical or low grade uveitic episodes that may have gone unnoticed a possibility for confounding the results.

While PPV is reported to be a successful treatment for ERU in Europe, less favorable results have been noted in the United States. In a study of 24 eyes, vision was noted to be reduced but still present in only four horses and cataract formation developed in 46% of eyes (Brooks et al., 2001). Thirty-seven percent of horses were noted to have decreased pain postoperatively. The variation in the results may be multifactorial. There is some suggestion that the clinical manifestations of ERU in Europe are different from those seen in the United States and that the successful use of vitrectomy may not be universal.

PPV may have a beneficial effect on the clinical course of chronic endogenous posterior uveitis by physically removing antigen and resident inflammatory cells with the vitreous (Fruhauf et al., 1998; Gilger & Spiess, 2006; Werry & Gerhards, 1992). Success has been reported in leptospiral-induced ERU, although complications (i.e., vitreal hemorrhage, cataract formation, retinal detachment) can occur.

The single port PPV procedure described is performed under general anesthesia with the horse in lateral recumbency. Dual port systems are utilized. After sterile preparation of the eyelids and ocular surface, the dorsonasal quadrant of the globe is stabilized with stay sutures, then a limbal-based conjunctival flap 10–15 mm in length is performed to expose the sclera. A penetrating sclerotomy is made approximately 10 mm caudal to the limbus with a double-edged blade aimed at the center of the globe. Subjectively, scleral thickening has been noted in horses chronically affected with ERU. At this position, the blade should enter through the pars plana ciliaris in an attempt to avoid trauma to the retina and ciliary body. The sclerotomy incision is enlarged to approximately 3 mm in length. Anterior vitrec-

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tomy is performed as the vitrectomy probe is inserted through the sclerotomy incision. Some surgeons prefer to perform the surgery by visualizing the vitrector probe via binocular indirect ophthalmoscopy whereas others choose to use the operating microscope in an orientation similar to phacoemulsification. Care is taken not to contact the posterior lens capsule or retina during the procedure. The vitreal cavity is irrigated with a balanced salt solution with 0.2 mg/mL of gentamicin added to the fluid. The same fluid is often used to replace the aspirated volume postoperatively. Aspirated vitreal material is often collected for diagnostic evaluation. Closure of the sclerotomy is performed via apposition of the cut edges in a continuous pattern with 6-0–7-0 polyglactin 910 (Vicryl®, Ethicon), followed by closure of the bulbar conjunctival flap. Postoperatively, the patient may receive subconjunctival dexamethasone and/or gentamicin in addition to topical neomycin, polymixin, dexamethasone, and mydriatic therapy.

Long-Term Equine Recurrent Uveitis Management

Reducing exposure to potential antigens through appropriate parasite control programs, eliminating environmental contact with cattle and wildlife, excluding horses from ponds and swampy areas, limiting rodent access to horse feed, decreasing the incidence of bacterial and viral respiratory and systemic infections, and maintaining a quality feed supply can all be beneficial in reducing ERU. Multivalent bovine and porcine leptospiral vaccines have also been used to treat intractable cases of ERU and to suppress herd outbreaks of leptospiral ERU, but their routine use as a preventive for ERU is controversial. Leptospiral vaccines increased the time to recurrence in one study (Rohrbach et al., 2005). The progression of the disease, however, was not halted by vaccination. A recently developed, equine-specific *L. Pomona* bacterin is available. However, its effects in ERU affected animals is yet to be described (Boggs et al., 2017).

Prognosis for Equine Recurrent Uveitis

Recurrence of uveitis caused by immunologic mechanisms is the hallmark of ERU (Matthews & Handscombe, 1983b; Schwink, 1992). The continued presence of inciting organisms or antigens in the eye or repeated exposure to inciting antigens may be responsible for repeat attacks. Sensitized lymphocytes or other immune-competent cells or specific antibodies may also remain in the uveal tract to cause repeat attacks of uveitis. Antigen–antibody complexes with complement can lead to corneal, endothelial, and lens damage. In addition, autoimmune complexes may form against antigens similar to ocular tissue antigens.

Serology for *L. pomona* can be predictive of developing blindness in horses (Dwyer et al., 1995). Appaloosas with ERU positive to Leptospirosis became blind in all affected eyes whereas Appaloosas with ERU negative to Leptopirosis became blind in 72% of eyes. Non-Appaloosas with ERU positive to Leptospirosis became blind in 51% of affected eyes whereas non-Appaloosas with ERU negative to Leptopirosis became blind in 34% of eyes.

A recent study that looked at the overall impact of ERU on affected horses' utility found that although a majority of ERU horses (70.6%) returned to the same job/role they had prior to the first bout of uveitis, only 38.7% performed this role at the same level compared with prior to the first bout of uveitis, whereas the remaining performed "worse" or "much worse" (Gerding & Gilger, 2016). Of the horses who did not return to their previous role, 35.1% adjusted poorly to vision impairment (i.e., not safe to ride per owner, 'spooky' behaviour, or unable to see jumps), 22.8% were euthanized shortly after diagnosis of ERU, 17.5% had a change of ownership after diagnosis (likely related to the diagnosis), and 14.0% were completely retired from their previous role by their owners (Gerding & Gilger, 2016). Owners reported that the monetary value of ERU horses decreased significantly in 84.5% of cases (Gerding & Gilger, 2016). Similarly, a recent study from western Canada evaluated breed, age, severity, blindness, and final outcome in ERU cases (Sandmeyer et al., 2017). Appaloosas represented 62.5% of cases and mean age at presentation was 12.13 ± 4.6 years. ERU was bilateral in 93.6% of horses and was severe in 59.4% of eyes at presentation. Bilateral blindness was present in 59.4% of horses at last follow-up; 63% were euthanized because of ERU. No significant differences in age, severity, blindness, or rate of euthanasia were noted between Appaloosas and other breeds (Sandmeyer et al., 2017).

Overall, the prognosis for a horse with ERU is usually poor. Treatment can be both time-consuming and expensive, but it is worth attempting to save the horse's vision as long as possible. The owner should be educated immediately about the potentially blinding nature of this disease and the possibility of enucleation to remove a painful eye if vision is lost.

Heterochromic Iridocyclitis

Heterochromic iridocyclitis with secondary keratitis (HIK) is a recently described ocular disease in which affected horses present with clinical signs of pigmented keratic precipitates (KPs), variable degrees of corneal edema, and in some cases, focal or multifocal iridal depigmentation and formation of a membrane in the anterior chamber that is attached to the corneal endothelium. Initially, these horses generally show minimal, if any, signs of discomfort and mild signs of intraocular inflammation characterized by miosis. Corneal edema may progress and become severe, accompanied by bulla formation and corneal ulcers. Five of 16 horses in a recent study had bilateral disease on initial presentation (Pinto et al., 2015). Response to anti-inflammatory treatment was generally unpredictable and variable with 11 of 21 eyes requiring enucleation because of progression of disease or the development of complicated corneal ulceration. These

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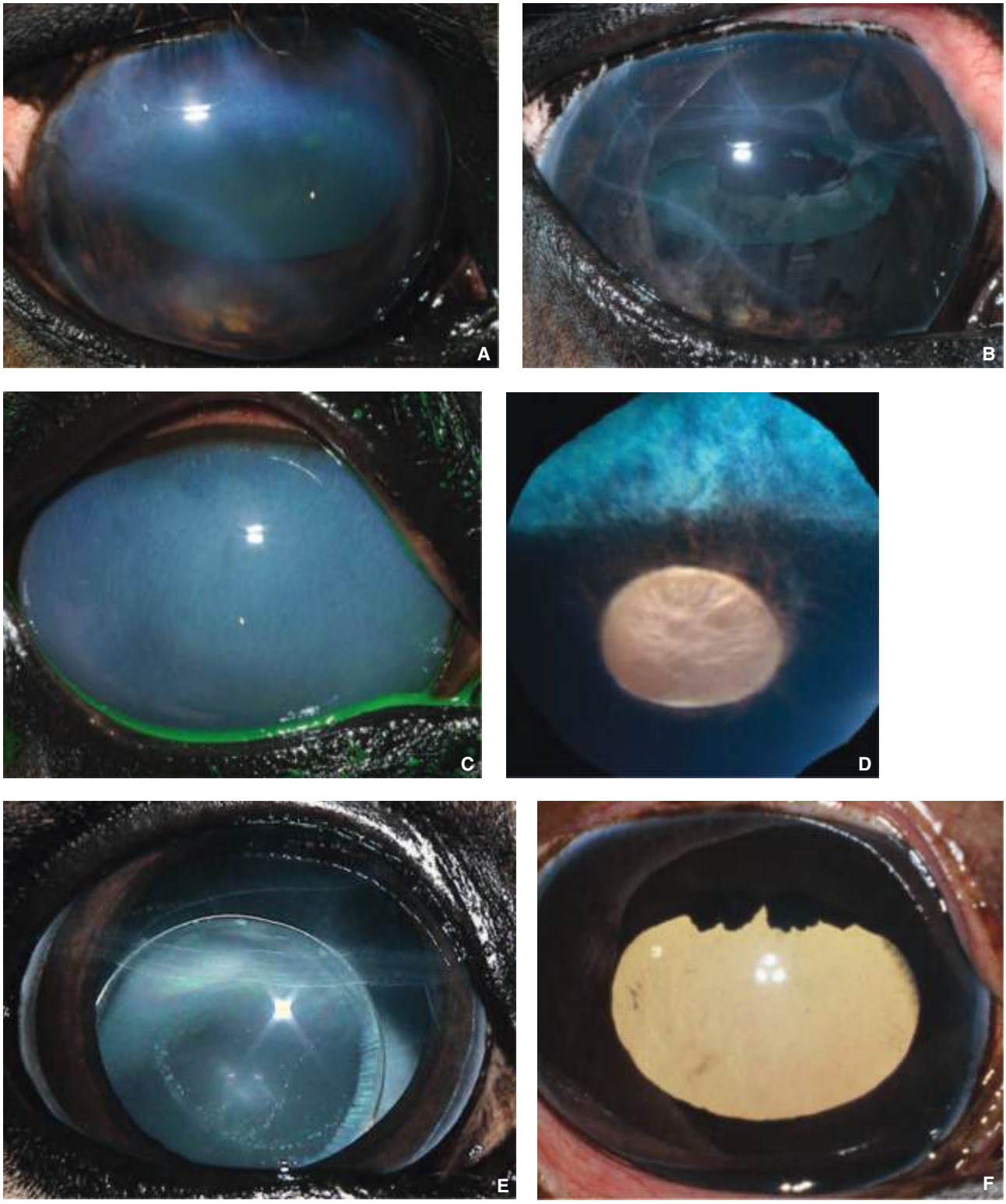


Figure 29.65 Glaucoma in the horse associated with age, previous uveitis, and the Appaloosa breed. **A.** Heterochromic iridocyclitis in this eye that has developed secondary glaucoma (mydriasis and corneal striae). Note the depigmentation of the ventral iris. Pigmented keratic precipitates are present as well (intraocular pressure [IOP] = 60 mmHg). **B.** The same eye after therapy was initiated for the glaucoma (IOP = 19 mmHg). Posterior synechia is prominent as are fibrinous retrocorneal membranes. **C.** The main initial clinical sign of glaucoma in this horse was diffuse corneal edema. **D.** Atrophy of the optic nerve head caused by glaucoma. The reticular pattern in the central cup region of the optic disc is the lamina cribrosa. The lamina is exposed with optic nerve axons are lost. **E.** Subluxated lens and corneal striae in a horse with chronic glaucoma. (*Source:* Photograph courtesy of Dr. Riccardo Stoppini.) **F.** Mydriasis and mild diffuse corneal edema are present in this eye that has an IOP of 65 mmHg. **G.** Open iridocorneal angle in a normal horse eye. **H.** Closed iridocorneal angle in a horse eye with glaucoma. **I.** Transcleral cyclophotocoagulation for glaucoma.

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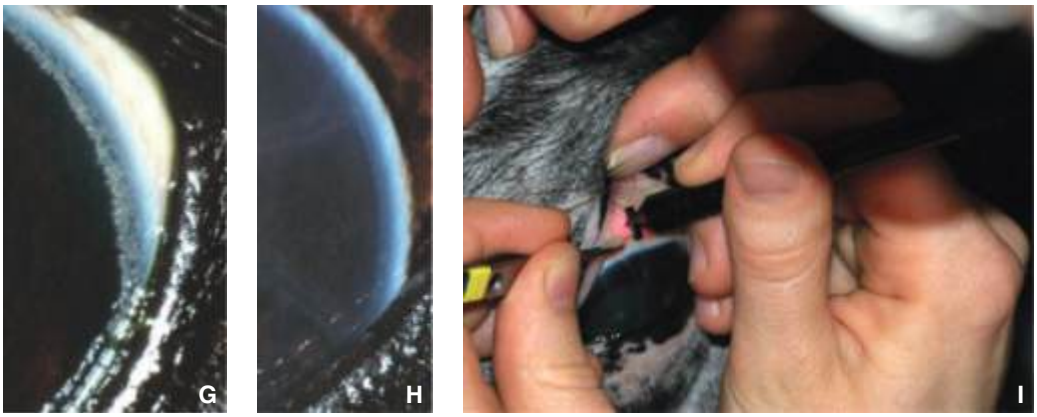


Figure 29.65 (Continued)

eyes exhibited moderate to severe lymphoplasmacytic panuveitis involving primarily the iris and iridocorneal angle, and to a much less extent the ciliary body and choroid, on histopathologic examination. The predominant infiltrating cells were T cells, and there was a variable degree of pigment loss from uveal tissue. The presence of individual macrophages did not constitute true granulomatous inflammation. The most pronounced lesions on histopathology were identified at the level of the corneal endothelium and included the formation of a retrocorneal fibrous membrane. The histopathologic findings support the hypothesis that pigment dispersion and resultant iridal depigmentation occurred as sequelae to a uveal inflammatory process, possibly a result of immune-recognition of melanosome-related self-antigen. HIK appears not to develop a quiescence period, a hallmark clinical feature of ERU, and pigmented KPs, focal corneal edema, iris depigmentation, and retrocorneal membranes observed in HIK horses are not clinical signs commonly associated with ERU (Pinto et al., 2015) (Fig. 29.65A, B).

Aqueous Humor Dynamics and Glaucoma

Aqueous humor provides nutrition to the avascular cornea, trabecular meshwork, and lens. Knowledge of aqueous humor formation and the morphology of the aqueous humor drainage apparatus is critical to understanding glaucoma of horses. Aqueous humor is formed primarily by active secretion through the ciliary body epithelia into the posterior chamber, utilizing energy and the enzyme carbonic anhydrase. A small portion of aqueous humor production arises from ultrafiltration of blood in the ciliary body circulation. Aqueous humor then percolates through the pupil into the anterior chamber, and finally exits through the highly specialized tissues of the iridocorneal angle (conventional outflow pathway), or through the more primitive pathways of the iris, ciliary body, and sclera (unconventional outflow pathway) (Brooks, 2005d; De Geest et al., 1990; Samuelson et al., 1989; Smith et al., 1986).

The iridocorneal angle (ICA) or ciliary cleft is bordered anteriorly by the peripheral cornea and perilimbal sclera, and posteriorly by the peripheral iris and ciliary body. Stout pectinate ligaments separate the anterior chamber from the ICA in the horse eye, and are visible at the limbus in many horses (De Geest et al., 1990; Samuelson et al., 1989; Smith et al., 1986). Aqueous humor moves between the pectinate ligaments into and through the cell-lined trabecular beams of the uveal trabecular meshwork (UTM), the corneoscleral trabecular meshwork (CSTM), the angular aqueous plexus (AAP), and then the intrascleral plexus (ISP) in the conventional outflow pathway (De Geest et al., 1990; Samuelson et al., 1989; Smith et al., 1986). The aqueous humor then drains from the ISP into the vortex veins that empty into the choroid. The UTM, CSTM, and AAP comprise 74.3%, 21.5%, and 4.2% of the equine ICA area respectively (Samuelson et al., 1989). The intertrabecular spaces of the UTM are very wide, and the spaces of the CSTM very narrow. The AAP is a plexus of radially oriented, narrow-diameter vessels (De Geest et al., 1990; Samuelson et al., 1989; Smith et al., 1986). The ISP consists of an extensive network of anastomosing circumferential channels that drain aqueous humor to the vortex venous system. There is a rich collateralization of the ISP and vortex systems. Aqueous humor thus follows a path of low resistance in the UTM and CSTM, high resistance to outflow in the narrow tributaries of the AAP and ISP, and low resistance to outflow again in the vortex systems. Resistance to outflow is focused at the AAP and ISP in the conventional outflow system of the horse. The CSTM acts as a sieve or filter to large particles, but it may or may not restrict aqueous flow directly (Samuelson et al., 1989; Smith et al., 1986). Tonography shows a very high facility of conventional aqueous outflow compared with other species ($0.88 \pm 0.65\,\mu L$ in the horse; $0.32 \pm 0.16\,\mu L$ in dogs; $0.28 \pm 0.01\,\mu L$ in humans) (Smith et al., 1990), but its unconventional outflow (uveoscleral outflow) may be even higher.

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Morphologic studies indicate an extensive unconventional aqueous humor outflow pathway in the horse (De Geest et al., 1990; Samuelson et al., 1989; Smith et al., 1986). The large ICA provides a large trabecular contact area with the iris and ciliary body. Aqueous humor enters the anterior iris face to drain into the vortex veins, and leaves the UTM through the interstitial spaces of the ciliary body musculature to drain into the supraciliary and suprachoroidal spaces, and choroid. Microsphere perfusion studies have shown the suprachoroidal and supraciliary spaces to provide an extensive unconventional outflow pathway to the sclera and choroid in the horse.

Obstruction of aqueous humor outflow can be the result of an abnormally developed drain (i.e., primary glaucoma) or through damage to the drain from scarring, vascularization, or accumulation of debris (i.e., secondary glaucoma). The result of this obstruction is retention of aqueous humor and subsequent increase in the pressure within the eye, referred to as glaucoma. Since horses have a greater percentage of aqueous humor outflow through the uveoscleral outflow compared to dogs and humans (Samuelson et al., 1989), the causes, clinical findings, and treatments are different for horses with glaucoma. Because of these differences and the fact that few veterinarians have a suitable tonometer for horses, glaucoma is not commonly recognized and therefore frequently not treated appropriately or effectively. Equine glaucoma is not easily recognized in the early stages of the disease because of the subtle nature of the early clinical signs and the potential for large diurnal variations in IOP in diseased eyes (Miller, 2017).

When IOP is elevated, ultimately the retina and optic nerve suffer insult which leads to a decline in vision. Normally, the horse has a very large retinal sensory surface area, vast numbers of photoreceptors, a massive population of retinal ganglion cells with large cell bodies, a large optic disc area and optic nerve cross-sectional area (15.7 mm^2 vs. 5.17 mm^2 in humans), high total optic nerve axon counts ($0.441–1.076 \times 10^6$ vs. 1.159×10^6 in humans), large mean individual optic nerve axon cross-sectional areas (3.11 vs. 1.75 μm^2 in humans), and 4.4 times the percent of optic nerve axons larger than 2 μm in diameter compared with humans (35.5% in horses vs. 8.0% in humans. The comparatively low density of axons in the horse optic nerve (62,800 axons/mm^2 in horses vs. 175,000 axons/mm^2 in humans) undoubtedly reflects a low tissue density of retinal ganglion cells, as the ratio of ganglion cells to optic nerve axons is one to one [7].

The optic disc is surrounded by the white, peripapillary scleral ring of Elschnig noted at the 6-o'clock position in the horse optic nerve head (ONH) (Brooks & Matthews, 2004). Myelin extends anterior to the equine lamina cribrosa to cover the surface of the optic disc. The myelinated axons generally stop at the edge of the scleral canal, although myelinated axons in the retinal nerve fiber layer are noted in the horizontal retinal quadrants of some horses. The horse ONH is oval with the horizontal axis longer. Scanning laser ophthalmoscopy of the horse ONH indicates that the neuroretinal rim area is most narrow at the superior and inferior rims of the horse optic disc, and widest at the nasal and temporal rims. The intrapapillary region of the ONH is the area inside Bruch's membrane at the scleral canal, and consists of the neuroretinal rim and the optic cup. The optic cup is defined on the basis of contour. ONH cup enlargement or "cupping" is associated with advanced glaucoma in the horse. Optic nerve "cupping" occurs because of axonal loss, laminar plate compression, rotation of the scleral insertion zone posteriorly, outward bowing of the lamina cribrosa, and a widening of the scleral canal behind Bruch's membrane. The associated enlargement of the ONH cup with these laminar and axonal changes is unique to glaucoma, and not found in other optic neuropathies. The neuroretinal rim is the intrapapillary equivalent to the nerve fiber layer. The neuroretinal rim becomes narrowed as retinal ganglion cells and axons are lost in glaucoma. The ratio of the cup to disc area is used to evaluate progression of glaucomatous optic nerve damage in humans. Enlargement of the cup to disc ratio indicates optic nerve axonal loss and is associated with deterioration in vision.

Large retinal ganglion cells have large diameter optic nerve axons, overlapping retinal receptive fields, and provide rapid transfer of visual input for detection of moving objects, an advantage for the horse (Brooks et al., 1995). The marked proportion of large diameter ganglion cells in the horse retina may be an adaptation to cover a large retinal sensory surface area with a relatively low population density of ganglion cells (Brooks et al., 1995). Retinal ganglion cell axons of the retinal nerve fiber layer become arranged into optic nerve fiber bundles by astrocytes in the choroidal lamina cribrosa. The scleral lamina cribrosa is a specialized ECM that spans the scleral canal as a complex, multilayered set of collagenous plates (Brooks et al., 2000c). The multiple plates of the scleral lamina cribrosa contain a hydrodynamic ECM of elastic and collagen fibers (types I, III, and VI), astrocytes, and capillaries. The optic nerve axons are insulated from the surrounding ECM by tubes of astrocytes through the entire length of the scleral lamina cribrosa.

The intralaminar optic nerve of glaucomatous horses contains a significantly larger total number of laminar pores, pores of significantly smaller individual area, and pores of rounder shape than the intralaminar optic nerve of normal horses (Brooks et al., 2000c). The intralaminar optic nerves of glaucomatous horses contain a higher percentage of connective tissue (74%) than the optic nerves of normal horses (67%) (Brooks et al., 1995, 2000c). These differences may represent an anatomic variation in horses predisposed to develop glaucoma, as well as changes resulting from IOP-induced radial stress forces causing stretching of the scleral lamina cribrosa. The scleral lamina cribrosa is a transition

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zone of high to low hydrostatic tissue pressure because of the prominent pressure gradient formed by the IOP and intraorbital pressure. The lamina cribrosa is an active and compliant structure in the horse whose movement during normal and abnormal fluctuations in IOP can both protect and obstruct optic nerve axoplasmic flow (Brooks et al., 2000c). IOP-induced, compressive conformational distortion within the scleral lamina cribrosa in glaucoma results in rotation, misalignment, and collapse of the laminar pores and laminar channels such that optic nerve axoplasmic flow is reduced and eventually blocked to cause retinal ganglion cell death. Glaucoma in the horse results in extensive and diffuse optic nerve damage with the optic nerve axon density in glaucoma horses reduced by 65% (Brooks et al., 1995).

Risk Factors for Equine Glaucoma

Horses with active or quiescent uveitis, aged horses (>15 years old), and Appaloosas are at increased risk for the development of glaucoma (Brooks et al., 1995; Curto et al., 2014; Miller, 2017; Smith et al., 1990. Glaucoma has also been reported in the American Paint, Standardbred, Morgan, Trakehner, Percheron, Mule, Paso Fino, Quarter Horse, Tennessee Walking Horse, Thoroughbred, Arabian, pony (Americas, Connemara, Shetland), American Saddlebred, and Warmbloods (Brooks, 2002). Congenital glaucoma is reported in Thoroughbred, Arabian, and Standardbred foals (Barnett et al., 1988; Gelatt, 1973; Halenda et al., 1997).

The glaucomas in horses are generally slowly progressive with little evidence of pain initially, and insidious loss of vision. Elevated IOP is clearly the primary risk factor for rapid progression of optic nerve damage and blindness in the horse, but iridocyclitis is the primary risk factor for development of glaucoma (Miller, 2017; Pickett & Ryan, 1993).

Clinical Features of Equine Glaucoma

Primary Glaucoma

Primary glaucomas have a bilateral and heritable potential, and possess no overt ocular abnormality to account for the increase in IOP. Horses with primary glaucoma most commonly present with partial or diffuse corneal edema. These eyes may or may not be painful. Early in the disease process, vision and the pupil size may be normal. IOP can range from 35 to 80 mmHg. With chronic primary glaucoma, vision decreases, the cornea becomes diffusely edematous, and other signs of chronic glaucoma may become evident (e.g., diffuse corneal edema, corneal striae, retinal and optic nerve degeneration) (Fig. 29.65). In general, however, the horse tends to lose vision much later in the disease process compared with dogs and humans (Utter & Brooks, 2011; Wilkie, 2010; Wilkie & Gilger, 2004). An increased size of the eye (>40– 45 mm anterior to posterior) and lens subluxation can also occur late in the disease.

Secondary Glaucoma

The secondary glaucomas in horses have an identifiable cause such as iridocyclitis, lens luxation, or intraocular neoplasia. Iris and ciliary body neoplasms can obstruct aqueous humor outflow to cause secondary glaucoma (Wilcock et al., 1991). The most common cause of glaucoma in horses is chronic or recurrent uveitis (a type of secondary glaucoma) (Gilger & Deeg, 2011; Utter & Brooks, 2011). Historically, these horses have multiple episodes of intraocular inflammation followed by a severe unrelenting bout of ocular cloudiness and discomfort that does not respond to traditional uveitis therapy. These eyes have high IOPs (40–80 mmHg), diffusely edematous corneas, and signs of chronic intraocular inflammation, such as posterior synechia, miosis, and cataract formation. These eyes may appear mildly enlarged or normal sized.

Diagnosis of Equine Glaucoma

The diagnosis of equine glaucoma is made with the documentation of elevated IOP and the presence of clinical signs specific to glaucoma. A tonometer is essential for the diagnosis of equine glaucoma. Indentation tonometers, such as the Schiotz tonometer cannot be used in horses because of the horse's thick cornea and because the horse's cornea cannot be positioned horizontally. Therefore, applanation or rebound tonometers must be used. The most practical and portable tonometers for use in horses are the Tonopen (Tonopen Tonometer, Medtronic, Jacksonville, FL, USA) or TonoVet (ICare, Espoo, Finland) tonometers (Knollinger et al., 2005; Komaromy et al., 2006; Miller et al., 1990a; Van Der Woerdt et al., 1995). The IOP in the normal horse is generally 21–23 mmHg with a range of 15–30 mmHg (Miller, 2017; Plummer et al., 2003). Both eyes of an individual should be between 5 and 8 mmHg of each other. The mean IOP in normal miniature donkeys ranges from 20.69 to 25.75 mmHg (Hibbs et al., 2018). Use of an auriculopalpebral nerve block prior to tonometry is recommended to avoid overestimation of IOP caused by pressure on the globes from active eyelid musculature (van der Woerdt et al., 1995). Sedation, particularly with alpha-2 agonists, will result in a decrease of measured IOP of up to 27% (Stine et al., 2014; van der Woerdt et al., 1995). While this may not be clinically significant, it should be recognized, especially when comparing trends or in the diseased state. Head and body position can have a significant effect on measured IOP. Tonometry in the horse should always be performed with the head raised above the heart to avoid artifactual elevations of up to 87% (Komaromy et al., 2006). In horses anesthetized and "tipped" in the Trendelenberg position while insufflated with CO_2 for laparoscopic surgery, the IOP can remain at over 70 mmHg for over one hour with no apparent effects on vision. Normal, anesthetized horses placed in a hoist for positioning on a surgical table have a significant

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increase in IOP relative to body weight, with heavier horses having a greater relative and absolute increase (Monk et al., 2017). The pressure measurement should be taken from the most normal, least edematous location of the cornea if possible.

A thorough and complete ophthalmic examination should also be performed to help differentiate the cause of the glaucoma and to rule out other causes of corneal edema, such as keratitis. With glaucoma, the cornea is edematous, but rarely is there yellow or creamy cellular infiltrate, epithelial loss (i.e., corneal ulceration), or diffuse vascularization. These findings are more common with primary corneal disease. The complete ophthalmic examination will also determine if the glaucoma is primary or secondary. Glaucoma secondary to intraocular disease other than uveitis is rare but is possible with intraocular tumors and luxation of the lens. Finally, glaucoma also needs to be differentiated from endothelial IMMK, which also commonly presents with the primary clinical sign of diffuse corneal edema.

Equine glaucoma may not be easily recognized in the early stages of the disease because of the subtle nature of the clinical signs. The pupils are often only slightly dilated, and overt discomfort is uncommon unless severe uveitis or corneal ulceration is present concurrently (Fig. 29.65F). An IOP greater than 32–35 mmHg is usually diagnostic, or at least suspicious of glaucoma (Miller, 2017). A fixed and dilated pupil occurs in horses with advanced glaucoma. However, the pupil may be mid-range if concurrent uveitis is present and may be miotic if posterior synechia and iris bombe have developed. Linear band opacities, corneal edema, iridocyclitis, cataracts and lens luxations, and optic nerve atrophy/cupping may be found in eyes of horses with glaucoma. Linear "band opacities" are thinned areas of Descemet's membrane that resemble Haab's stria, but do not histologically display the typical curling of the ruptured elastic basement membrane (Heusser, 1921; Wilcock et al., 1991). Fibrosis and collapse of the visible ICA may be evident at ophthalmoscopic examination (Fig. 29.65G, H). Buphthalmos will develop with chronicity and may predispose the horse to exposure keratitis.

Glaucoma in the horse results in early peripheral retinal and optic nerve damage with progression to generalized retinal and optic nerve atrophy. The horse eye seems to tolerate elevations in IOP that would quickly blind a dog; however, blindness is the end result. The marked number of axons in the optic nerve of the horse may act as an anatomic reservoir of axons that provides some early protection against total loss of vision despite very high IOP. Horses with glaucoma also appear to lose optic nerve axons of large individual area more rapidly than medium and small axons. Large retinal ganglion cells are involved with motion detection, stereopsis, and sensitivity to dim light. The consequences of the loss of such axons to the visual capabilities of the horse in early glaucoma are not known. The progressive, sustained elevation in IOP found in glaucoma in the horse is associated with optic nerve cupping, atrophy, and blindness.

The clinical features of glaucoma in the horse are mirrored on histopathologic examination. In a recent histopathologic retrospective of equine glaucoma cases, the most common histopathologic changes included hypercellularity of the optic nerve, retinal atrophy, corneal vascularization, descemetization of pectinate ligaments, hypercellularity of the anterior corneal stroma, posterior bowing of the iris base, ciliary body atrophy, corneal striae, pars plana elongation, cataract, and collapsed ciliary cleft/trabecular meshwork (Curto et al., 2104). Evidence of uveitis (cataract, lymphoplasmacytic infiltration of the uvea, and synechiae) was present in 87% of examined eyes. Posterior bowing of the iris base and relative sparing of the superior retina from atrophy associated with elevated IOP had not previously been reported in equine glaucoma (Curto et al., 2104).

Treatment of Equine Glaucoma

Usually, treatment of equine glaucoma aims to decrease the underlying inflammation and decrease the production of aqueous humor. Various combinations of drugs and surgery may be necessary to reduce the IOP to target levels that are compatible with preservation of vision. A target IOP of less than 20 mmHg is a reasonable goal in the glaucomatous horse eye. Control of IOP can improve vision in horses with decreased vision because of resolution of marked corneal edema and improvement of vascular perfusion. Because the outflow pathways of aqueous humor from the equine eye is primarily through the uveoscleral pathway, traditional medications to increase outflow through the ICA, such as miotic medications, are not useful in horses (van der Woerdt et al., 1998). Because the uveo-scleral outflow pathway is not well characterized and treatment modalities have not been developed specifically for horses, medications designed to increase the uveo-scleral outflow in humans and dogs (i.e., prostaglandin analogs) have not proven beneficial in horses and may be associated with inflammatory side effects (Davidson et al., 2002; Willis et al., 2001a). However, concurrent use of topical diclofenac 0.1% with the prostaglandin analogue latanaprost 0.005% in normal horses in a recent study resulted in modest decreases in IOP (1.64–2.06 mmHg) with fewer inflammatory side effects than when latanaprost was administered alone (Tofflemire et al., 2017). Brimonidine 0.2% has not been shown to lower IOP in normal horses, but its effects in glaucomatous animals has not been studied (Von Zup et al., 2017).

The beta-blocker timolol maleate (0.5%) can decrease the IOP in the horse's normal eye by 17% (4.2 mmHg) if administered topically BID (van der Woerdt et al., 2000). Beta-blockers interfere with the production of cAMP by the enzyme adenyl cyclase to reduce aqueous humor production. The maximum effect is in the afternoon and occurs

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4.5 days post-administration. There was also a decrease in pupil size but there were no other side effects.

Aqueous humor production can also be reduced if 99% of the carbonic anhydrase enzyme in the ciliary body is inhibited. The carbonic anhydrase inhibitor dorzolamide 2% alone or in combination with timolol maleate is effective in lowering IOP if administered topically BID-TID in horses (Tofflemire et al., 2015; Willis et al., 2001b). Once a day use was ineffective and actually increased IOP in horses. Topical carbonic anhydrase inhibitors, including brinzolamide, appear to be most beneficial in the medical treatment of equine glaucoma (Germann et al., 2008a; Wilkie, 2010).

Anti-inflammatory therapy consisting of topically administered corticosteroids such as prednisolone acetate, and systemically administered NSAIDs such as flunixin meglumine, are critical to the control of the iridocyclitis when it is inducing elevation in IOP.

When medical therapy is inadequate, surgery should be utilized to control IOP and preserve vision in the horse with glaucoma. The most common surgical option for a visual eye is laser cyclophotoablation (Wilkie, 2010). Surgical methods to increase outflow (i.e., glaucoma shunts or valves, drainage surgeries such as sclerostomies or iridectomies) are usually not successful because of the horse's high inflammatory response to intraocular surgery; however, glaucoma shunts may be attempted in cases unresponsive to other therapies.

Laser Cycloablation

If there is poor or no response to medical therapy, the laser cycloablation may be considered. Prior to laser therapy, existing uveitis must be controlled to minimize complications. Ideally, other ocular disease, such as corneal ulceration, should be resolved, and diseases such as intraocular neoplasia should be ruled out. Laser surgery is most indicated if there are signs that the eye has vision – for example, a consensual pupillary light response or dazzle reflex. Blind, painful globes should be removed. Laser surgery can be performed to help control the pressures in these chronic eyes but with poorer response than less chronic cases. When the IOP cannot be controlled with medical therapy, neodymium:yttrium-aluminum-garnet (Nd:YAG) or diode laser cyclophotoablation may be a viable alternative for long-term IOP control.

Transscleral cyclophotocoagulation (TSCPC) may be performed either under general anesthesia or in the standing sedated horse as long at sedation is adequate and the horse is not overly reactive (Fig. 29.65I). Topical proparacaine is given immediately prior to laser application and the diode laser is set at 1500 mW power and 1500–5000 ms duration (visual eye – 40 laser sites; blind eye 40–50 laser spots). The settings for a Nd:YAG laser are 10 W, 0.4 seconds at 40–60 sites (Miller et al., 2001; Whigham et al., 1999). The laser energy is delivered through the sclera by placing the laser probe at 5–7-o'clock (ventrally) 4 mm posterior to the limbus and 10–1-o'clock (dorsally) 4–6 mm posterior to the limbus (Annear et al., 2010; Miller et al., 2001). In buphthalmic globes, the recommended sites for TSCPC are located too far anterior to effectively deliver laser energy. These eyes should have TSCPC performed 6–8 mm posterior dorsally, 5–6 mm dorsotemporally, 4–5 mm ventrotemporally, and 4–5 mm ventrally (Gemensky-Metzler et al., 2014). The nasal quadrant should be avoided. Aqueocentesis is usually performed, either before or after laser applications, and 0.25–0.5 mL of aqueous humor is removed through the limbus with a 25–27-gauge needle. Tissue plasminogen activator may be delivered intracamerally after the procedure, especially if aqueocentesis is indicated to lower IOP. Insufficient laser application may not be effective in controlling the glaucoma.

Too high energy use or too many treatment spots may result in ocular hemorrhage or subsequent hypotony resulting in decreased vision in the eye. Therefore, the amount of laser therapy applied should be adjusted for each case. The IOP should be checked immediately after, 3, and 24 hours after surgery. The pressure should be measured again 1 week later, then monthly if pressures are low. Antiglaucoma medications are generally required after surgery (usually indefinitely). Systemic anti-inflammatory medications should be continued as needed after laser therapy.

A mean drop of 17 mmHg can be expected the first few days after Nd:YAG laser TSCPC in the glaucomatous horse eye. The IOP was 2 mmHg less at 20 weeks post-laser (Whigham et al., 1999). The target IOP lowering effects occur 2–4 weeks after diode lasering. A recent review of the efficacy of transscleral diode laser therapy in horses revealed at a mean follow-up of 49 months that 59% of the eyes treated with the laser remained sighted, but 64% required continued topical antiglaucoma medication (Annear et al., 2010).

Endoscopic cyclophotocoagulation (ECP), a procedure utilizing a small endoscope to visualize and deliver the laser energy directly to the ciliary body, has been investigated in normal horses and parameters developed (Harrington et al., 2011). However, no studies of the use of this modality has been reported in horses, and the high risks of development of cataracts and inflammation in phakic horses likely makes this modality unsuitable currently for treatment of equine glaucoma. Further study is needed before routine use of ECP is recommended for client horses.

Gonioimplants

Gonioimplant filtration surgeries to bypass the obstructed ICA and direct the outflow of aqueous humor to the subconjunctival spaces are experimental in the horse, but have been successful (Kellner, 1994). They have a short-lived lifespan because of fibrosis of the drainage tube and/or filtration bleb. A recent study in normal horses investigated the feasibility of shunts for the reduction in IOP in horses (Townsend et al., 2014). A significant reduction in IOP was noted in

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study animals immediately after placement of the shunt that was sustained until 1 month postoperatively despite the fibrosis surrounding the bleb that was identified. The conclusion of the study was that shunts may represent a feasible therapeutic option for equine glaucoma. The equine eye is large and can accommodate two gonioimplants.

Salvage Procedures

Eyes with glaucoma secondary to infection or intraocular tumors, and eyes with painful lens luxations, should be enucleated. Chronically painful and blind eyes, and severely buphthalmic globes should be enucleated.

Ciliary Body Ablation

Intravitreal injection of intravenous gentamicin (25–100 mg with or without 1 mg dexamethasone) or cidofivir can induce phthisis in a blind eye. A single injection is typically sufficient for pain reduction but a second may be necessary in some cases. Following sedation, auriculopalpebral and frontal nerve blocks, instillation of topical anesthetic and phenylephrine (2.5% to vasoconstrict conjunctival vessels), the ciliary body ablation is performed with a 22-gauge needle positioned dorsolaterally approximately 7 mm posterior to the limbus at a 45-degree angle (toward the optic nerve, and away from the lens). Prior to injecting the drug, an equal volume (or greater) of vitreous is aspirated. If no vitreous can be aspirated, an aqueous paracentesis can be used to decrease the intraocular volume and thereby temporarily decrease IOP.

Disease of The Horse Lens

The horse lens measures 17–22 mm in diameter, has an axial length of 12–15 mm, a volume of 2.5–3.0 ml, and a power of 14.88 Diopters (D). The anterior, posterior, and equatorial capsules measure 91, 14, and 20 µm thick respectively (Prince, 1956; Samuelson, 1999). The horse lens consists of ~6000 layers of perfectly clear living cells or fibers. These lens fibers are ~8–10 µm in diameter (Samuelson, 1999). Cataracts, or opacities of the lens of the eye, are the most common abnormality of the equine lens, and a leading cause of blindness in horses. It is conservatively estimated that some form of lens opacity, ranging from small epicapsular remnants of the fetal vasculature to dense and extensive cataract, is present in 5%–7% of horses with otherwise clinically normal eyes (Matthews, 2000b). In the horse, cataracts rarely involve the entire lens structure (i.e., complete or mature cataracts), and are more usually localized to one or other anatomic landmarks or sector of the lens. Complete cataracts are invariably associated with overt and significant visual disability. However, focal or incomplete cataracts alone seldom cause any apparent visual dysfunction in affected horses (Hurn & Turner, 2006).

Nuclear Sclerosis

Nuclear sclerosis describes the altered refractivity of the central lens occurring in older animals, caused by progressive compression of the nucleus by enveloping secondary fibers as part of normal lens growth. In ungulates, lens growth slows markedly with increasing age, which may restrict the development of true nuclear sclerosis in these species. However, increased definition of the nuclear-cortical junction on retroillumination is a common observation in horses over 18 years old. The nucleus remains largely optically clear in these animals, although in very old animals central brunescence of the nucleus may be an occasional finding. The typical blueish appearance of the central lens in diffuse illumination described in nuclear sclerosis in dogs is an inconsistent finding in the horse. These nuclear changes in older horses are frequently accompanied by senile cataract. The appearance can be brown.

Concentric Cortical Lamination

The optically clear lens cortex in mature horses may have a pronounced concentric laminar structure, the resulting refractive anomaly having an ‘onion ring’ appearance on distant direct ophthalmoscopy. The cause is related to the multifocal lens of the horse (Kroger et al., 1999). It is of no apparent clinical significance and is not a precursor of cataract.

Lens Luxation/Subluxation

Primary luxation of the lenses in adult horses has not been documented. However, acquired anterior or posterior luxation and subluxation of the lens occur relatively frequently in the horse as a sequela to ocular trauma and chronic uveitis, and, less frequently, in cases of glaucoma (Fig. 29.65E and Fig. 29.66H). Congenital anomalies of the zonules are unusual (Matthews & Handscombe, 1983a; Colitz & McMullen, 2011). A luxated lens, a lens that has either moved into the anterior or posterior chamber, will invariably become cataractous immediately or within a few weeks after the inciting incident. Intracapsular or phacoemulsification lens extraction may be possible in cases of lens luxation. However, a recent retrospective long-term evaluation in such cases has revealed that surgical intervention is coupled with a poor prognosis for both retention of vision and the globe (Brooks et al., 2009). Intraoperative and postoperative complications included suture dehiscence, ulcerative keratitis, glaucoma, hyphema, explusive choroidal hemorrhage, retinal detachment, and endophthalmitis (Brooks et al., 2014a). The poor prognosis is likely because of the fact that lens luxation in horses is accompanied by advanced disease processes, such as ERU, glaucoma, and severe trauma, that by themselves carry a poor long-term prognosis. Usually, medical management of the underlying cause of the lens

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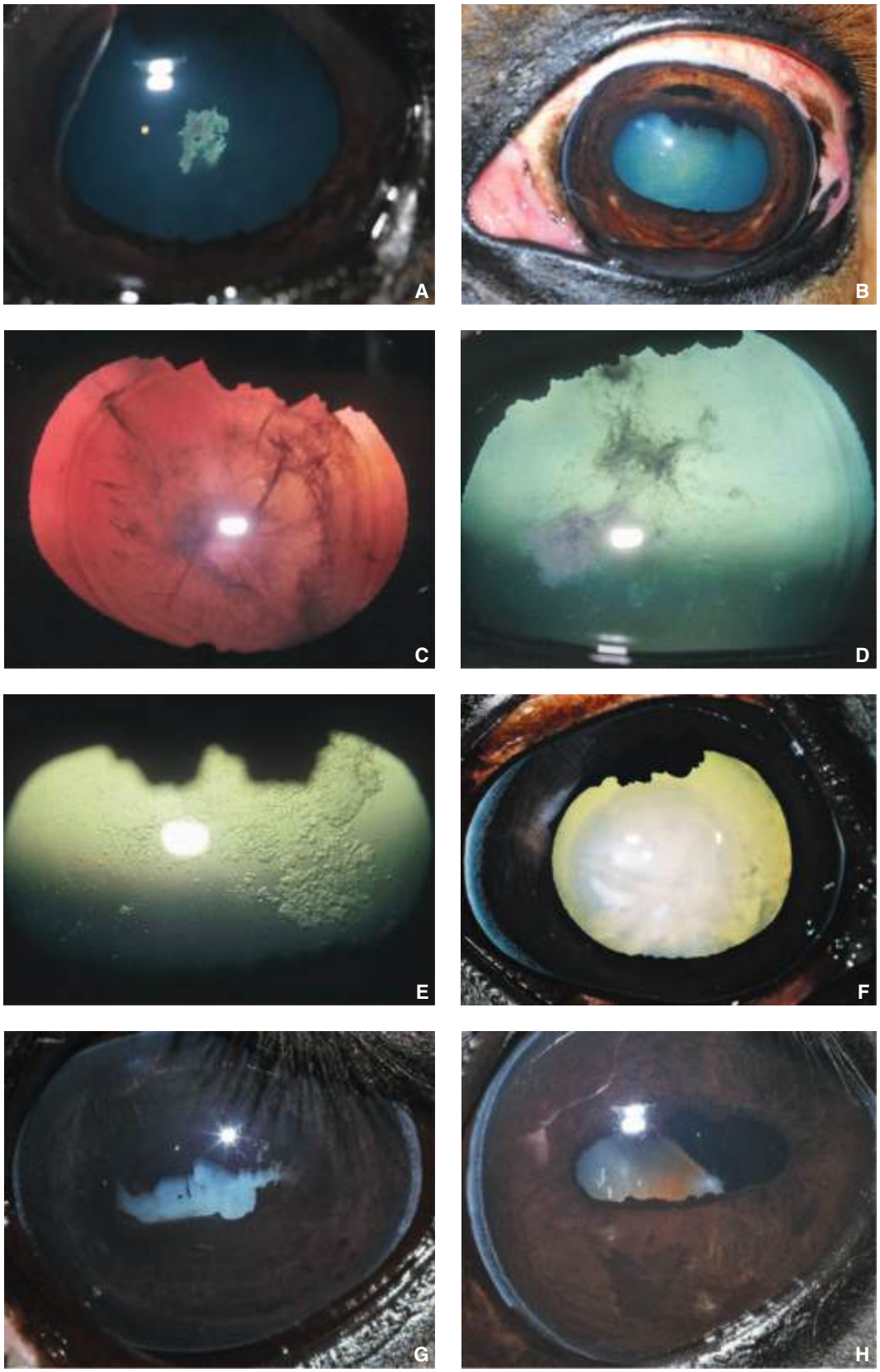


Figure 29.66 Cataracts, like other species, present in different areas, shapes, and sizes in the lens. **A.** Anterior suture and granular polar cataract. **B.** Nuclear, spiculated cataract in an adult horse. **C.** Lamellar cortical cataract in a horse. **D.** Anterior and posterior cortical lamellar lens opacities suspected to be caused by a toxin or metabolic problem. **E.** Posterior cortical vesicles in the lens of an ERU patient. **F.** Immature anterior and posterior cortical cataract. **G.** Mature cortical cataract in a chronic ERU patient with multifocal anterior synechia. **H.** Hypermature cataract with posterior luxation. Note the aphakic crescent and the lenticular brunscense.

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luxation and the accompanying uveitis is preferable to surgical removal of the lens. Enucleation of blind and painful eyes is recommended.

Cataracts

Loss of optical homogeneity of the lens results from derangement of its metabolic status and subsequently the fibers responsible for its make-up. The result is an opacity, or cataract, of the lens. A variety of etiologies and initiating factors have been proposed. However, the most common cause of cataracts (and lens luxation) in horses is chronic uveitis, or ERU. Cataracts also may occur in horses from inherited causes (these can be congenital or juvenile) or occur spontaneously after trauma to the eye. Although the pathways leading to postinflammatory cataract formation involve a complex and interdependent cascade of biochemical events, it is likely that oxidative injury and inorganic ion imbalance after disruption of the intraepithelial Na-K ATPase dependent pump are primary factors. Further injury to membrane permeability will result from subsequent aberrant transmembrane calcium transfer and accelerated activation of acid proteases. The former may also result in intracellular accumulation of calcium and induction of high MW protein aggregates, and the latter in increasing levels of low MW protein degradation products and a rise the colloid osmotic pressure of the cytosol.

Equine cataracts may be variously classified according to their anatomic location within the lens, their physical appearance, their presumptive etiology, or stage of progression or maturity (Matthews, 2000b). Classification of cataracts in the horse is similar to the description in other species and includes age of onset (i.e., congenital, juvenile, or senile/geriatric), location within the lens (i.e., anterior capsular, anterior cortical, perinuclear, nuclear, equatorial, posterior cortical, posterior capsular), and stage of maturity (i.e., incipient, immature, mature, and hypermature) (Fig. 29.66). Cataracts can also be classified based on their cause (e.g., hereditary, uveitis, trauma, toxin, nutritional, or metabolic disease), although in many cases the cause is not known at the time of clinical examination.

A fundamental and practical division of equine cataracts by etiology can be made: acquired or secondary cataracts, and developmental cataracts. Acquired or secondary cataracts occur as a result of influences arising from outside the lens, and in the horse these most commonly arise as a consequence of intraocular disease. Developmental cataracts result from disrupted evolution and accretion of the crystalline lens both *in utero* and postnatally, and have been elegantly described as aberrations rather than arrests (Mann, 1937). They include all congenital cataracts, with the exception of very rare congenital uveitic cataracts in foals. Their origins lie in interrupted or abnormal differentiation and growth of embryonic ectodermal derivatives, or in disruption of the normal maturation and laying down of secondary fibers in the fetal and postnatal lens. Most developmental cataracts can be morphologically related to a specific stage or event in lens embryogenesis and growth. More than one form of developmental cataract may be present in any one eye.

Whether or not a small cataract, which may not affect vision, will progress to a larger, visually inhibiting cataract is often a concern in horses, especially on prepurchase examinations. Certainly, in juvenile horses, the presence of any cataract, especially those that are bilateral, suggests that the defect may be hereditary, especially in Thoroughbreds, Quarter Horses, and Morgan horses (Beech & Irby, 1985; Beech et al., 1984; Eriksson, 1955; Joyce, 1990; Munroe & Barnett, 1984). Because ERU is the most common cause of cataracts in adult horses, the presence of other signs typical of ERU (e.g., corpora nigra atrophy, iris hyperpigmentation, posterior synechia, vitreal degeneration) suggests that the cataracts will progress as the ERU recurs. A cataract's location and cause may help give some clue to the rate of progression (Table 29.5) (Matthews, 2000b). Other cataractous changes observed in horses include anterior lens capsule/anterior cortex cystic lesions (Fig. 29.24) likely associated with anterior uveitis and age-related nuclear sclerosis, which is a relatively common finding among aged horses (Colitz & McMullen, 2011). Most non-uveitic cataracts in the horse are nonprogressive (Matthews, 2000b).

Developmental Cataracts

Capsulolenticular cataracts may be unilateral or bilateral and are nonprogressive. They are seldom, if ever, associated with compromised vision in the horse (Matthews, 2000b; Munroe & Barnett, 1984; Roberts, 1992).

Anterior capsular cataracts appear as small irregular focal opacities on the anterior capsule. They may be single or multiple and show no gross evidence of epithelial reactivity or fibrosis. Posterior capsular cataracts are morphologically very similar to anterior capsular cataracts and may be associated with minor anomalies such as adherent vitreal fibrils (Matthews, 2000b).

Anterior polar cataracts are congenital cataracts and have two distinct forms in the horse. The more common is a focal circular or elliptical cataract associated with minor aberrations in refraction in the anterior cortex. The second is a dense reactive epithelial opacity, often with radial subcapsular extensions. Anterior polar cataracts can occur in combination with embryonic nuclear cataract and focal posterior axial corneal opacities. Rarely a fine strand of tissue may bridge the anterior chamber connecting the corneal and anterior lenticular opacities (Matthews, 2000b).

Posterior polar cataract is a relatively rare congenital cataract, typically having a stellate configuration associated with radial extensions into the subcapsular cortex (Matthews, 2000b).

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Table 29.5 Clinical classification of cataracts (Matthews, 2000b).

Acquired (secondary cataracts)	Intraocular disease	Uveitis	Anterior	Progressive
			Posterior	
			Panuveitis	
			Recurrent	
		Glaucoma		
		Retinal detachment		
		Neoplasia		
	Trauma/injury			Progressive
	Systemic toxic or metabolic			
	Age-related senile			
Developmental cataracts	Extralenticular	Retrolenticular fibroplasia		Nonprogressive
		Mittendorf's dot		
		Persistent pupillary membranes		
		Pigmentation		
	Capsulolenticular	Anterior capsular		Nonprogressive
		Posterior capsular		
		Anterior polar		
		Posterior polar		
	Lenticular	Zonal cataracts	Embryonic nuclear	Nonprogressive
			Fetal nuclear	Nonprogressive
			Perinuclear (lamellar)	± progressive
			Equatorial	Nonprogressive
		Sutural cataracts	Posterior suture cataract	Progressive (slow)
			Anterior suture cataract	?
		Axial cataracts	Floriform cataract	Nonprogressive
			Elliptical cataract	Nonprogressive
	Complete cataract			NA

Lenticular cataracts, affecting the cortex and/or nucleus, with the exception of embryonic nuclear cataracts, are usually bilateral but are not necessarily symmetrical (Matthews, 2000b). They may be grouped into four types:

1) Zonal cataracts probably arise largely because of transient disruption of embryogenesis and growth. Normal development precedes and follows this disruption and is reflected in the optically clear lens adjacent to the cataract. Their geographic location in the lens is determined by the timing of the cataractogenic insult.
2) Embryonic nuclear cataracts are dense and central congenital opacities, caused by interrupted condensation of the primary lens fibers. These cataracts may decrease relatively in size as the animal ages and the cataract is compressed by succeeding secondary fibers.
3) Fetal nuclear cataracts are spherical or oblate congenital opacities with an optically clear center and are located within the zone of the adult nucleus. The nucleus and cortex peripheral to the cataract is generally optically clear but may contain small and irregular opalescent opacities. These cataracts are nonprogressive and may decrease in relative size as the animal ages.
4) Perinuclear or lamellar cataracts are the most commonly encountered developmental cataracts (Roberts, 1992). They appear as spherical or oblate opacities located on the periphery of the adult nucleus. The nucleus and surrounding cortex are usually optically clear. However, focal opalescent opacities are commonly found in the anterior cortex, and within the cataract the suture pattern is usually accentuated. These cataracts develop in early

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postnatal life, and in general are nonprogressive, although significant cortical and nuclear opacification may arise with senility.

Equatorial cataracts are nonprogressive disruptions in the optical homogeneity of the periequatorial cortex, and are associated with crenellation or irregularity of the lens surface (Walde, 1983). The shape of the equine pupil renders these opacities more prominent nasally and temporally. This type of cataract may arise from a primary abnormality of the zonular insertion.

Suture line cataracts may be congenital or appear postnatally (Matthews, 2000b). They are potentially progressive, but any progression is likely to be very slow. Anterior sutural cataracts are very rare in the horse and may adopt various configurations. Posterior sutural cataracts are relatively common and invariably have a 'Y' configuration. Dendritiform or staghorn extensions may be present near the abaxial extremities of the 'Y'.

Axial cataracts evolve in a relatively precise geometric configuration around the axis of the lens and are identified using descriptive terminology. Floriform cataracts are nonprogressive, discrete 'petal-shaped' cataracts within the posterior perinuclear cortex. These usually have a triradiate distribution, suggesting some developmental association with the posterior sutures. Elliptical cataract describes nonprogressive extensive ellipsoid encircling perinuclear opacities (Walde, 1983). The nucleus may be cataractous and vision is usually compromised in affected eyes. Coralliform or crystalline cataract is a nonprogressive, irregularly triradiate, and highly refractile cataract located in the posterior nucleus.

Complete congenital cataracts present as dense and uniform opacifications of the nucleus and cortex (Matthews, 2000b). In some lenses a narrow zone of clear periequatorial cortex may be evident. Vision is severely compromised. These cataracts are frequently associated with other ocular abnormalities, most commonly microphthalmos. Care should be taken in differentiating complete congenital cataracts from the very rare cases of complete cataracts in young foals caused by congenital uveitis. In the latter case there are usually very obvious postinflammatory changes on the iris.

Heritability of Equine Cataracts

The heritability of developmental cataracts in horses has not been widely studied. Some, mainly nuclear cataracts, have been described as having a sporadic familial occurrence in Arabs and Thoroughbreds. However, these reports are vague, and although a dominant mode of inheritance is most commonly suggested, recessive inheritance is reported (Weber, 1947). In Morgan horses, bilateral nonprogressive nuclear or perinuclear cataracts, inherited in an autosomal dominant fashion, have been described (Beech & Irby, 1985). However, similar, noninherited, nuclear cataracts also occur in this breed. Nuclear cataracts have been reported in association with complex and heritable ocular dysgeneses in the horse, including aniridia (iris hypoplasia) in Belgian Horses and Quarterhorses, and ASD syndrome in Rocky Mountain horses (Eriksson, 1955; Joyce, 1983; Ramsey et al., 1999a).

Senile Cataract

Slowly progressive cataracts are very commonly observed in horses older than 18 years (Matthews, 2000b). These are generally accepted to be age-dependent 'senile' cataracts. It is unclear how the aging process affects the mammalian lens, and the cataracts may derive from an age-determined susceptibility of the lens to autocrine injury, or from subclinical oxidative insult associated with deterioration of the antioxidative defence mechanisms in the ageing lens.

Typically, early senile cataract in the horse appears as microvesicles along the posterior sutures. More overt, optically dense condensations around the posterior sutures, along with perinuclear and focal cortical cataracts are observed in older animals. These cataracts are usually bilateral but are not necessarily symmetrical. Less commonly, extensive nuclear and cortical opacification may become apparent in extreme old age.

Senile cataracts are reported to be associated with visual impediment in more extensively affected horses, particularly in dim lighting conditions (Cutler, 2002). However, as senile retinopathy is almost invariably present in these eyes, any visual disability is probably a cumulative effect.

Acquired or Secondary Cataracts

Ocular or systemic disease, and well-documented extrinsic factors such as UV light, ionizing and microwave radiation, and ingested toxins have been implicated in the development of acquired cataract (Matthews, 2000b). In most cases, these cataracts are potentially progressive depending upon the persistence or recurrence of the primary insult.

The major cause of secondary cataracts in the horse is unquestionably uveitis, encompassing traumatic and infectious uveitis, and the heterogeneous group of presumptively immunogenic diseases described as ERU (McLaughlin et al., 1992b). Several different morphological forms of cataract are typically associated with intraocular inflammatory disease, and more than one form may be recognized in any one eye, depending on the extent and severity of the inflammatory disease (Matthews, 2000b).

Typically in cases of anterior uveitis or iridocyclitis there are focal anterior capsular and subcapsular cataracts, occasionally associated with posterior synechiae (Matthews, 2000b). These cataracts may have a plaque-like appearance in the axial lens because of fibrous metaplasia and proliferation of epithelial cells, and radial cleft-like extensions into

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the subcapsular cortex may be present. In some eyes, more generalized cleft formation, vacuolation and degradation of the lens fiber framework within the anterior subcapsular cortex may be present. In some cases of uveitis arising from blunt trauma, anterior capsular cataracts may be accompanied by posterior capsular opacification. Although rare, nonprogressive perinuclear cataract with optically clear nucleus and peripheral cortex has been observed after blunt ocular trauma (Matthews, 2000b).

'Whiplash' injury can result in a nonprogressive, dense, posterior axial 'Y' configured capsular cataract, which may arise from dehiscence of the cortical vitreous attachments from the posterior capsule (Matthews, 2000b).

Posterior uveitis or chorioretinitis may occasionally be associated with extensive diffuse and irregular posterior capsular and subcapsular cataracts (Matthews, 2000b).

Uveitic cataracts vary from a combination of the anterior and posterior subcapsular cataracts to complete cataracts. The latter are most frequently associated with ERU, and may rapidly progress from incipient to immature, mature, and hypermature cataracts. With maturity these cataracts develop a typical yellow–green coloration (Matthews, 2000b). Vacuolation of the periequatorial cortex is observed in cases of ERU. Circumferential periequatorial vacuolation is also seen in cases of nonrhegmatogenous complete retinal detachment, possibly reflecting ciliary body insult at the level of the ora serrata. Progressive cataract development is a recognized sequela of the anterior core vitrectomy procedure currently being used by some surgeons to manage ERU (Fruhauf et al., 1998; Matthews, 2000b; Werry & Gerhards, 1992). In Europe the incidence of this complication has been reported to be 34%, whereas in Florida an incidence of 46% has been reported (Brooks et al., 2001; Fruhauf et al., 1998). This may reflect differences in the basic ocular pathologies in the two populations being treated.

Rupture of the lens capsule and leakage of cortical material into the anterior chamber in cases of severe ocular trauma results in phacoclastic uveitis and complete cataract formation (Grahn & Cullen, 2000). One report details a traumatic phacocele in an American Minature Horse in which the lens was dislocated through a rent in the sclera at the limbus and entrapped in the subconjunctival space (Knickelbein et al., 2019).

Intraocular neoplasms, most commonly iridociliary melanomas, may impinge on the lens, distorting the lens shape and causing diffuse or localized cataract (Matthews, 2000b).

Toxic or metabolic cataracts appear to be very rare in the horse (Fig. 29.66D). No specific mechanisms of toxic cataractogenesis have been identified in this species and a presumptive diagnosis is made by exclusion. In general, these cataracts present as diffuse, usually bilateral, opacities which may progress to complete cataract. Diabetes mellitus rarely occurs in the horse, and diabetic cataractogenesis has not been reported (Corke, 1986).

Treatment: Cataract Surgery

Therapy for cataracts is necessarily surgical, but some degree of spontaneous cataract resorption may occur with hypermature cataracts. Most veterinary ophthalmologists recommend surgical removal of cataracts in foals younger than 6 months if the foal is healthy, has no grossly appreciable uveitis or other ocular problems and has a temperament that will tolerate aggressive topical therapy. Adults with visual impairment because of cataracts may also be candidates for surgery. However, because the etiology of acquired cataract in adults is often uveitis, the prognosis may be less favorable (Brooks, 2002; Brooks, 2005a; Brooks et al. 2014a; Dziezyc et al., 1991; Whitley et al., 1983, 1990). Surgery in foals is easier because the globe size is small enough that standard cataract surgical equipment may be used and because general anesthesia is easier and associated with less morbidity and mortality compared with adults. In general, foals heal very quickly after cataract surgery. Early return of vision is paramount in foals for development of the higher visual centers.

Patient Selection

To be considered for lens extraction, the horse should be in good physical condition. Complete ophthalmic and general physical examinations should be performed as well as preoperative complete blood count, serum biochemical profile and urinalysis to evaluate systemic organ function (Colitz & McMullen, 2011). Foals should have thoracic radiographs performed preoperatively to look for evidence of subclinical pneumonia which can contribute to serious postanesthetic complications and exacerbate postoperative uveitis. Slow or absent PLRs may indicate active iridocyclitis, with or without posterior synechiation, retinal disease, optic nerve disease, or iris sphincter muscle atrophy. Afferent pupillary defects in a cataractous eye cannot be attributed to the cataract alone, and normal PLRs do not exclude some degree of retinal or optic nerve disease. Any signs of anterior uveitis should delay cataract surgery until the cause of the inflammation has been diagnosed and successfully treated. Cataract surgery should also be delayed in the presence of active eyelid, conjunctival, or corneal disease. Examination of the fundus may be difficult because of the cataract. Preoperative electroretinography and B-mode ultrasonography are necessary to evaluate outer retinal function and integrity of intraocular structures, respectively.

Cataract surgery is indicated if the loss of vision is such that the horse cannot perform its regular activities (Brooks, 2005a; Edelmann et al., 2014). If the horse is healthy, has controlled uveitis, and the personality and temperament to tolerate aggressive postoperative topical therapy and repeat postoperative ophthalmic examinations, the horse may be a

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good candidate for unilateral or bilateral cataract surgery. An intractable horse is an unsuitable candidate. Horses with cataracts associated with ERU may be candidates for surgery if their uveitis is well controlled, their retinal function is normal, and there is minimal pre-existing ocular damage. These cases, however, have a higher risk of postoperative complications than non-uveitic cataract patients. Thorough client education about risks and potential complications is critical.

Types of Surgical Technique

The large equine eyes restrict the number of surgical options available. The anterior chamber is very shallow near the base of the iris as well. Thus, it is hard to make the corneal incision without touching the iris, and there is little room for placing and manipulating instrumentation inside the peripheral anterior chamber. The lens is also quite large, thereby necessitating very large corneal incisions for extracapsular or intracapsular techniques, and often more than one incision for phacoemulsification. In addition, the cataracts are generally very soft, with most of the cortex and often the nucleus being easily aspirated on completion of the capsular tear. The equine eye actually tolerates intraocular surgery surprisingly well, however, compared with those of most domestic animals. Postoperative uveitis is minimal in the horse after phacoemulsification compared with other mammals. Several surgical techniques for cataract removal have been described in the horse, but most veterinary ophthalmologists perform phacoemulsification preferentially.

Phacoemulsification Cataract Surgery

Phacoemulsification is the preferred extracapsular cataract extraction technique for the horse. Immature, mature, and hypermature equine cataracts have been successfully removed with this technique (Brooks, 2002, 2005a; Brooks et al., 2014b; Dziezyc et al., 1991; Hardman et al., 2001; Whitley et al., 1983, 1990). Subluxated, or partially luxated lenses may also be successfully removed in horses using phacoemulsification. Phacoemulsification through a small corneal or limbal incision utilizes a piezoelectric handpiece with a titanium needle in a silicone sleeve to ultrasonically fragment and emulsify the lens nucleus and cortex after continuous curvilinear capsulorrhexis (removal of a circular portion of the anterior capsule). The phacoemulsification needle moves at ~45 Hz in an anterior–posterior direction. The emulsified lens is then aspirated from the eye while IOP is maintained by infusion of heparinized lactated Ringer's solution.

Preoperative Preparation

Topical and systemic antibiotics are administered both preoperatively and postoperatively to reduce the chance of development of bacterial contamination, infection, and endophthalmitis. Topical and systemically administered NSAIDs are also used preoperatively and postoperatively to minimize inflammation. Topical steroids are employed starting at least 3 days prior to surgery to minimize any pre-existing low-grade lens-induced uveitis to decrease the likelihood of fulminant postoperative inflammation. Intravenous antibiotics are generally also recommended for the 24-hour perisurgical time period followed by 10–14 days of oral antibiotics. Topical atropine is used at least a day prior to surgery. Systemic NSAIDs, preferably flunixin meglumine, is given starting at least 1 hour prior to surgery and continued in a decreasing dosage for up to 3 weeks after surgery. It is generally recommended that both eyes be done under one anesthetic event in foals, and only one eye be done in adult horses. In most adult cases, if both eyes are candidates for cataract surgery, then only one eye should be operated on at a time. This is because of the risks of prolonged general anesthesia, including ventilation/perfusion concerns as well as those for endophthalmitis and the requisite frequent, aggressive, and longstanding aftercare.

Patient Positioning

Correct positioning of the horse is critical for success for any type of intraocular surgery. For cataract surgery, the horse is placed in lateral recumbency. The down eye is protected from pressure or exposure trauma, either by pillows or an inflatable ring. Lubricating the down eye and, if possible, performing a temporary tarsorrhaphy is recommended to ensure the down eye remains uninjured. The horse's nose is elevated using foam pillows or sandbags so that the cornea of the eye to be operated is parallel to the floor. The head and pillows must be taped into place with strong elastic tape, such as elasticon, to secure it firmly. To prevent facial nerve paralysis after surgery, care must be taken to prevent pressure on the facial nerve from pillows or tape. The halter must be removed prior to surgery. The surgeon is generally positioned at the 12-o'clock position of the eye; therefore, the head should be positioned at the outside of the surgery table. If surgery is to be performed on both eyes (usually only foals), the animal is placed in dorsal recumbency and the head turned right or left to position the surgical eye so that the cornea is parallel to the floor.

An operating microscope with coaxial illumination is essential to performing cataract surgery in the horse. Adequate visualization and lighting cannot be accomplished with any other system. The microscope base is placed opposite the surgeon, with the microscope arm extending over the horse's body to position above the eye. The foot pedal is placed under the operating table so that the surgeon can reach it comfortably. Whenever possible, the light from the operating microscope should be turned off or blocked so that thermal or photic injury to the cornea or retina is avoided.

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Surgical Preparation

After the horse is in a stable plane of general anesthesia, it should either be paralyzed with a neuromuscular blocking agent or have a retrobulbar block (Gilger & Stoppini, 2011) to prevent ocular movement and pressure on the eyes from tension of the extraocular muscles. Intraoperative complications from retrobulbar injections have not been observed during equine intraocular surgery. An auriculopalpebral nerve block is performed. The periocular skin, ocular surface, and fornices are cleaned with 1:50 povidone-iodine solution. A topical anesthetic and 2.5% phenylephrine are applied to the ocular surface.

Surgical Approach

A Castroviejo eyelid speculum is used to retract the lids. The nictitans may need to be sutured to the medial canthus, but a lateral canthotomy is rarely performed (Brooks, 2005a). The globe is entered dorsally with a 3.2 mm keratome blade through either three-step, hinged clear corneal incision (foals) or a scleral tunnel under a limbal-based conjunctival flap (adults) using a #64 or #69 microsurgical blade (Colitz & McMullen, 2011; McMullen & Utter, 2010). The peripheral anterior chamber of the horse is quite narrow, so care is necessary to avoid touching the iris and the corpora nigrum. The keratome blade is entered to one side of the corpora nigrum, as the corpora nigra can hemorrhage quite severely if touched, especially in adults. The corpora nigra should be cauterized if they slowly hemorrhage (Brooks, 2005a). Angling the blade parallel to the iris will help prevent iris trauma and allow complete entry with the blade. Remove the blade slowly to avoid iris trauma and minimize the rapid loss of aqueous humor which can result in an abrupt drop in IOP which may cause the iris or ciliary body to hemorrhage. If hemorrhage occurs, either during iris trauma or rapid pressure drop, or if the pupil becomes miotic, use of approximately 0.5 mL of 1:10,000 epinephrine (diluted in balanced salt solution [BSS]) injected intracamerally may minimize the hemorrhage. If the iris appears to be in the path of the triangular blade during ocular entry, place a small bleb of viscoelastic to deepen the anterior chamber near the incision. Use of higher concentration 2.0% hyaluronic acid viscoelastic (BioVisc®, AcriVet, Berlin, Germany) is particularly effective for this maneuver.

Capsulorhexis

The use of trypan blue to stain the anterior lens capsule will greatly facilitate visualization of the capsule prior to and during capsulotomy. Prior to injection of this dye, 2 mL of air is injected into the anterior chamber to minimize the potential for staining of the endothelium and Descemet's membrane. Viscoelastic is then injected into the anterior chamber to remove the trypan blue dye and maintain anterior chamber depth. To perform a continuous curvilinear capsulotomy (CCC), the anterior chamber is vaulted with viscoelastic and an incision is made in the peripheral lens capsule with a 25-g needle, cystotome, or a blade. Due to the large equine eye, shallow anterior chamber, and relatively small corneal incision, standard or elongated Utrata forceps are difficult to open and use. A much better instrument to use is the AcriVet equine capsulorhexis forceps (AcriVet, Berlin, Germany). Using this instrument to apply controlled shearing forces to the capsule will permit completion of a 10 mm capsulorhexis. Another, and perhaps more accurate, method of equine CCC is using a radiofrequency CCC unit (Spiess et al., 1996). This instrument eliminates the need to decide what type of initial incision is made and nearly always makes a perfect, central CCC. This central CCC facilitates intraocular lens placement and allows a clear central visual axis postoperatively.

Hydrodissection

Hydrodissection is a method to separate the lens cortex from the lens capsule using BSS. This is usually performed after the CCC, but can precede it, depending on surgeon preference. The hydrodissection should always be performed with a 27–30-g cannula and BSS. If viscoelastic is used for hydrodissection, extreme care should be taken because the fragile equine posterior lens capsule may rupture with viscoelastic use.

Phacoemulsification and Aspiration

Although phacoemulsification and aspiration (PA) can be accomplished successfully with a standard human or canine cataract system, use of a dedicated equine-specific PA system (e.g., ALEXOS, AcriVet, Berlin, Germany) is highly recommended. The long needle (23 mm), power, and irrigation and aspiration system designed for the horse eliminates the need to make multiple ocular incisions and allows the surgeon to be able to "reach across" the eye. A 30°, 0.9 mm diameter phacoemulsification needle is used for phacoemulsification to achieve needle tip occlusion better, and to minimize the chance of creating tears in the posterior capsule. Irrigation/aspiration with lactated Ringer's solution containing epinephrine (1:10,000) and heparin (2 IU/mL) is utilized to maintain the anterior chamber during phacoemulsification, and to remove any remaining cortex after most of the lens has been removed (Brooks, 2005). The phacoemulsification needle tip is kept parallel to the iris in the anterior chamber and only carefully angled posteriorly.

Use of an either one- or two-handed (using a second incision and a lens manipulator) PA technique can be performed depending on the density of the lens. If the horse is older than 8–10 years of age, it is recommended to perform the two-handed PA technique (Fig. 29.67A). The posterior capsule in the horse is especially fragile, even in older horses, so much care is needed to prevent posterior capsular rupture. The "conquer and divide" PA method works well in horses

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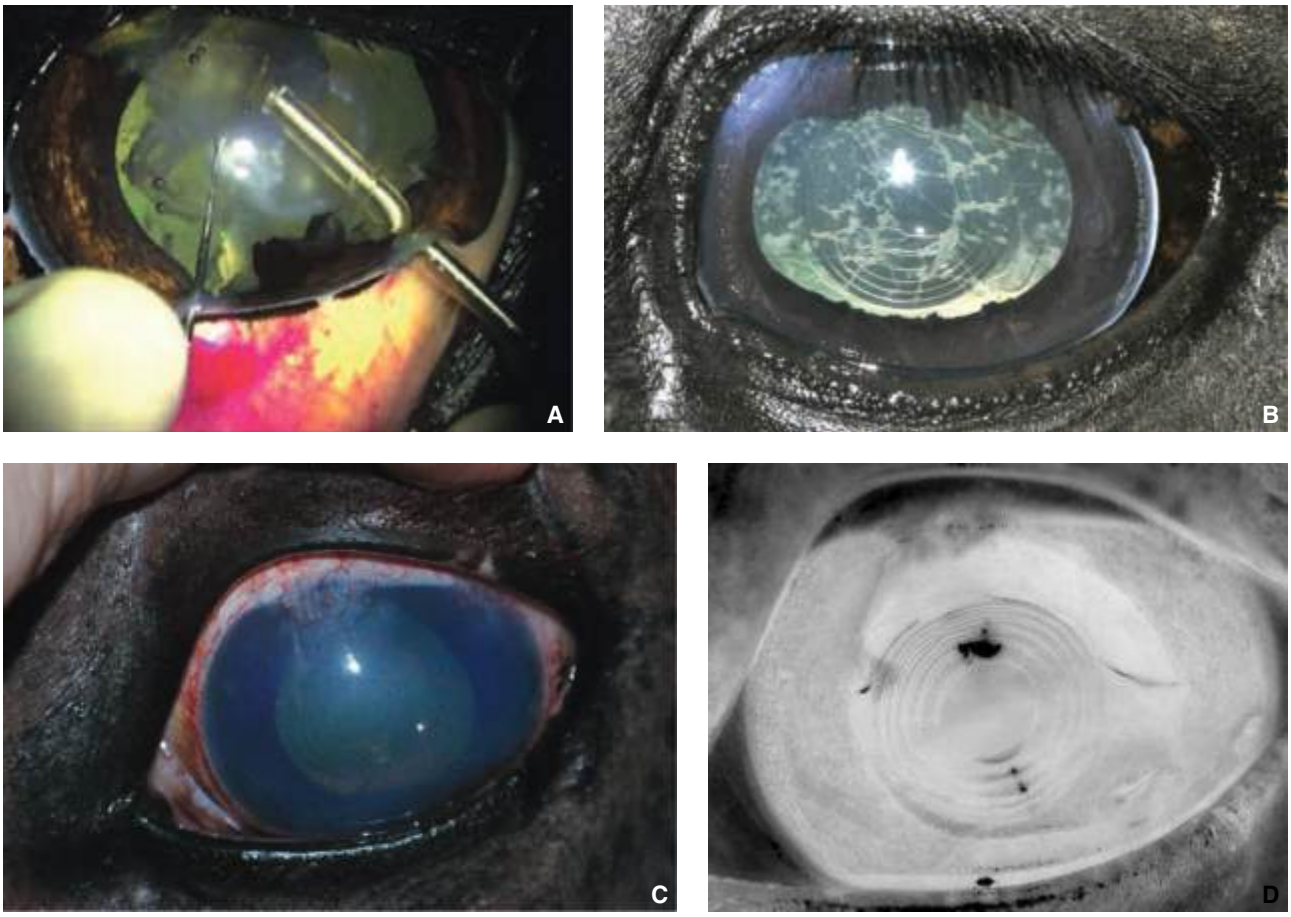


Figure 29.67 Two-handed surgical technique for phacofragmentation of an equine cataract. **A.** The right-handed surgeon generally approaches the eye from the approximately 4-o'clock position to avoid the corpora nigra. **B.** Mild lens capsule fibrosis surrounding the intraocular lens 6 months after cataract surgery in an adult horse. **C.** Glaucoma has developed in this globe after phacoemulsification removal of a uveitis cataract in an adult horse. **D.** Infrared photograph of same eye improves visualization of the globe interior.

and entails splitting the lens with a central groove, then splitting the halves and removing lens quadrants. Lens cortex that remains attached to the posterior capsule after removal of the cortex and nucleus can be aspirated through a 0.4 mm aspiration needle on an irrigation-aspiration handpiece.

Posterior Capsulotomy

Capsular fibrosis, especially the posterior capsule, is less common in horses than in small animals, except in those horses that have developed cataracts secondary to chronic uveitis. If the posterior capsule has an opacity or is fibrotic, a 6–10 mm central posterior capsulotomy can be performed. Using Vannas or capsulotomy scissors, the posterior capsule is carefully cut in a complete circle or nearly in a circle, and capsulotomy forceps are used to remove the capsule. Because of fibrosis and fragility of the surrounding posterior lens capsule, a CCC-type posterior capsulotomy is not recommended. If the capsule is not cut well, the resulting posterior capsulotomy will end up much larger than intended, vitreous will prolapse, and the intraocular lens will not be able to be placed. Use of higher concentration 2% hyaluronic acid viscoelastic (BioVisc®, AcriVet, Berlin, Germany) is effective to push vitreous posteriorly.

Intraocular Lens Placement

Although the appropriate equine intraocular lens (IOL) power has yet to be determined, studies indicate that the correct IOL power will ultimately be approximately 14–18 D. Use of the commercially available 18 D equine IOL (AcriVet, Berlin, Germany) is recommended in adult horses and the 14 D equine IOL in horses younger than 6 months. Although these lenses may not have the correct power, horses that have received it have done well and have had excellent visual outcomes. Studies are ongoing evaluating the long-term outcome in refraction in horses receiving the 14 D and 18 D equine IOL (McMullen & Gilger, 2006; McMullen et al., 2010; Townsend et al., 2011). A recent study that calculated the IOP power for the equine eye suggests that 18.5 D may be the appropriate strength to achieve emmetropia (Meister et al., 2018).

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To place the equine IOL, the lens capsular bag and anterior chamber are filled with viscoelastic. The cornea is opened along the original groove to a width of 5 mm using standard size right and left corneal section scissors. The IOL is folded in half with custom lens folding forceps and coated with viscoelastic. The leading haptic of the IOL is placed into the distal lens capsular bag, and the IOL forceps are removed leaving the IOL partially in the anterior chamber. The second IOL haptic is manipulated using a buttonhook lens manipulator so that the haptics are in the ventral capsule. A diagonal or horizontal placement of the haptics is recommended for a 24 mm diameter IOL (Fig. 29.67B, C, D).

Surgical Closure

The corneal or scleral incision is closed with simple interrupted, simple continuous, or a sawtooth continuous pattern of 8-0 absorbable suture, such as polyglactin 910 (Vicryl®, Ethicon). Removal of the viscoelastic by irrigation and aspiration is recommended prior to final tightening of the incision. The incisions are carefully checked for leakage with microsponges and a Seidel test. Because of postoperative inflammation, low incidence of postoperative pressure spikes, and lack of safety data, use of an intraocular miotic is not recommended in horses.

If concerned about the integrity of the corneal incision, a fornix-based micro-hood conjunctival graft over the incision to safeguard the eye further for any type of dehiscence can be performed. An incision through the conjunctiva is made at the limbus adjacent to the corneal wound. The conjunctiva is undermined and advanced over the incision. Generally, three to four simple interrupted sutures of 8-0 polyglactin 910 (Vicryl®, Ethicon) are used to tack the conjunctiva in place. A subpalpebral lavage treatment system should be placed while the patient is still anesthetized before recovery to facilitate postoperative administration of topical medications. To minimize ocular trauma on recovery, a lateral temporary tarsorrhaphy is placed.

Postoperative Considerations

Slight corneal edema is usually noted 24–72 hours postoperatively. One week after surgery, the pupil should be functional, any fibrin in the anterior chamber resorbing, and the fundus visible. Three weeks after surgery, the eye should be nonpainful, the patient should be visual, pupillary movement should be normal, and the ocular media should appear clear (Brooks, 2005a). Edema may persist in cases in which severe uveitis was present prior to surgery and if the phacoemulsification time is prolonged (>15 minutes).

Intraoperative complications of cataract surgery in the horse include miosis, hyphema or vitreal hemorrhage, vitreous presentation into the anterior chamber, posterior capsular tears, choroidal hemorrhage, and retinal detachment. Complications after equine cataract surgery are higher than in canine surgery (Brooks, 2008; Colitz & McMullen, 2011; Edelmann et al., 2014; Fife et al., 2006; Gelatt et al., 1974; McMullen & Utter, 2010; Whitley et al., 1990). Common short-term (<14 days) ocular complications include uveitis, corneal edema, hyphema, corneal dehiscence, and retinal detachment. Long-term complications (>14 days) include glaucoma, uveitis, corneal edema, capsular fibrosis, and retinal detachment. Other potential complications include persistent iridocyclitis and plasmoid aqueous, fibropupillary membranes, synechiae, iris bombé, corneal ulceration, corneal edema, corneal fibrovascular infiltrates, posterior capsular opacification, cortical regrowth, and infectious endophthalmitis. Most horses need anti-inflammatory medical therapy for up to 3 months, in decreasing frequency. Some, if not all, horses require a baseline level of anti-inflammatory medications lifelong to keep the eyes quiet.

Colic, cecal impactions, colitis, and laminitis are common, and sometimes fatal, complications in hospitalized horses. Owners should be advised of these risks (including other anesthetic-related risks such as orthopedic injury) prior to surgery. Careful monitoring of stool production, gut sounds, and digital pulses may catch the diseases in the early stages.

Long-Term Results

Little is known about the long-term prognosis for equine cataract surgery patients. The amount of lens capsular fibrosis and the incidence of glaucoma, as examples, are relatively unknown. In one study of the long-term results after implantation of a 14 D IOL in a foal, the IOL remained centrally positioned, and only mild fibrosis of the lens capsule was observed (Harrington et al., 2013). Furthermore, with this IOL, the net refractive error was +0.50 D (Harrington et al., 2013). Another study showed good visual results 6 months after surgery in five of six eyes receiving a 14 D IOL with one eye lost to glaucoma. The most common complication in this study was postoperative hypertension that occurred in five of six eyes (Townsend et al., 2011). In a recent retrospective that examined the visual outcome of 111 eyes of 95 horses that underwent cataract surgery (combined data from all ages, stages of cataract, and etiologies) found that 83 (87.3%) horses were visual for 1 month or less postoperatively, 47 (49.4%) horses were visual for more than 1–6 months postoperatively, 33 (34.7%) horses were visual from more than 6–12 months postoperatively, and 25 horses (26.3%) were visual for more than 24 months postoperatively (Brooks et al., 2014b). ERU horses had a similar prognosis to non-uveitis adult horses in this study.

Posterior Segment

The posterior segment consists of the structures viewed with the ophthalmoscope and includes the vitreous, retina and

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choroid, and optic nerve head. The Standardbred horse retina has been described in detail (Ehrenhofer et al., 2002). The horse retina differs in the number and type of glial cells and neurons, and in the pattern of vascularity compared with other species. The horse retina varies in thickness from 80 µm at the ora serrata to 250 µm at the nasal optic disc. Approximately 90% of the horse retina is thin enough that oxygen can diffuse to the entire thickness (<130 µm). Retinal ganglion cells form a single layer in the horse retina. Most retinal ganglion cells are large and Nissl positive with the highest density of ganglion cells in the central retina, and near the optic disc. Vascularization is only present in the retina adjacent to the optic disc. Astrocytes are only found in vascularized retinal regions.

There is much variation in the normal appearance of the equine fundus. Most lesions of the fundus are identified near and below the ONH, and typically involve hyperpigmentation or depigmentation (Cutler, 2002; Cutler et al., 2000). Examination in a dark area with mydriasis using tropicamide is recommended for the best examination. The direct ophthalmoscope provides the most magnified view of the fundus in the horse, with a lateral magnification of ×7.9 and an axial magnification of ×8.4. Indirect ophthalmoscopy with a 14 D lens provides a magnified view of ×1.18 lateral magnification and ×1.86 axial magnification, whereas a 20 D lens minifies the fundic view with ×0.79 and ×0.84 magnification laterally and axially, respectively (Murphy & Howland, 1987). The 20 D lens provides a nice panoramic, screening view of the equine fundus, but it is not satisfactory for detailed, highly magnified observations.

The retinal vasculature is classified as paurangiotic with 50–80, small-diameter retinal arterioles and venules arising from the edge of the disc and extending only a short distance from the ONH. A pyramid-shaped area at the 6-o'clock position of the equine optic disc does not receive a retinal blood supply as noticed at fluorescein angiography (Ehrenhofer et al., 2002; Slater et al., 1995). The ventral avascular retina of the horse is thin compared with the vascular peripapillary areas. The equine retina primarily depends on the choroid for its blood supply. Vascularized remnants of the hyaloid artery may be seen in the central area of the optic disc, and the retina is divided into dorsal tapetal and ventral non-tapetal regions (Barnett et al., 1995, 2004). The non-tapetal region is usually brown to dark brown in color because of melanin in the RPE, but this pigment may be absent depending on the coat and iris coloration. The tapetal fundus is usually yellow to blue to blue–green in brown horses, but variation can occur, again, with the horse's coat or iris color (Cutler, 2002). Palomino and chestnuts have a paler yellow tapetum and less pigment in the non-tapetum. Color diluents, subalbinotic, or albinotic coat-colored horses, or horses with heterochromia iridis or blue irides may have no tapetum, areas of tapetal thinning, or lack of pigment in the non-tapetal retina such that choroidal vessel patterns can be observed. Small dots ("Stars of Winslow") distributed in a uniform pattern throughout the tapetal fundus represent end-on views of choroidal capillaries penetrating the tapetum (Cutler, 2002). They may appear dark or red. Light-gray-colored linear striations may be seen extending horizontally from the optic disc and are myelinated axons in the nerve fiber layer.

The ONH, or optic disc, is oval to round in the horse, and it is located slightly temporal, in the inferior quadrant of the non-tapetal fundus. It is somewhat pink to orange in color. The equine optic disc is easily differentiated into the optic cup and neuroretinal rim regions, with visible fenestrations in the central region of the optic disc being the lamina cribrosa (Cutler, 2002). The cup-to-disc ratio in the horse is quite large, averaging 0.6 L. Exposure of the lamina cribrosa increases with age.

Vitreal Changes

During ophthalmoscopic examination, poor cohesion of the vitreal gel structure, giving the clinical impression of vitreous liquification, is a commonly observed phenomenon in otherwise equine normal eyes and may be seen in as many as 85% of normal horses (Matthews, 2004a). In each case they are nonprogressive and have no pathological association. This may derive from progressive dilution of the uniformly low-density vitreous hydrogel as part of normal postnatal development. Liquification of the equine vitreous is usually recognized by the presence of inclusions of varying configuration and optical density whose movement is provoked by ocular saccades. The effect on vision of these intravitreal inclusions is not known, and although very few affected horses exhibit any overt visual deficit, highly mobile peripheral 'floaters' may affect behavior in some horses (Matthews, 2004a; Miller & Murphy, 2011). In a small number of horses, pathological liquification of the vitreous and accumulation of fibrinous and cellular detritus is associated with posterior segment disease.

Vitreal alterations are commonly of developmental, degenerative, age-related, traumatic, or inflammatory origin; however, only hyalitis (inflammation) and degeneration are common in horses, and only hyalitis has clinical significance (Nell & Walde, 2010; Wilkie, 2011). Hyalitis or inflammation of the vitreous is most commonly observed in horses with posterior ERU and appears as yellow strands in the vitreous with vitreal cellular infiltrate (Fig. 29.68 and Fig. 29.69). Vitreal degeneration, or syneresis, which is a common finding in older horses, is seen as cobweb-like white strands in the vitreous (Fig. 29.70). Vitreal degeneration is rarely associated with other ocular pathology in horses.

Disorders of the Vitreous

Posterior uveitis may result from ocular trauma, endophthalmitis, optic neuritis, or may be associated with ERU (Matthews, 2004a). Post-traumatic ischemia of the poste-

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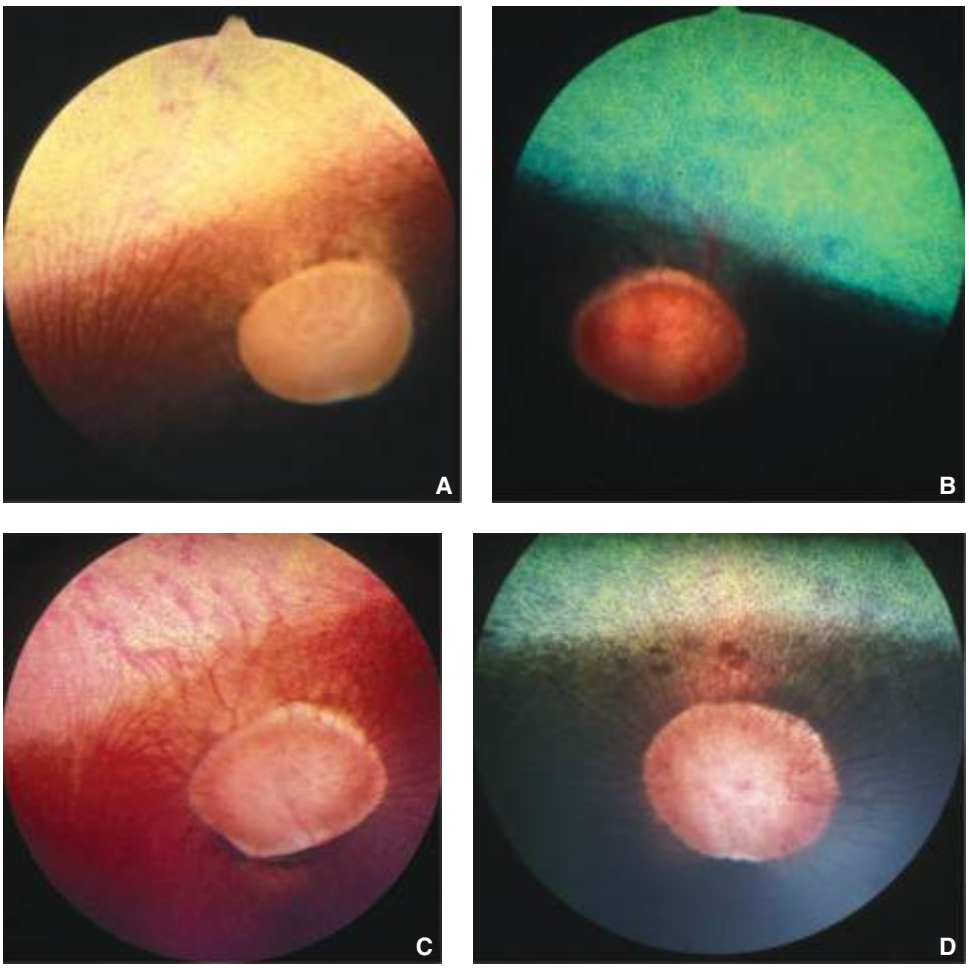


Figure 29.68 The different ophthalmoscopic appearances of the normal equine ocular fundus. **A.** Subalbinotic normal fundus in a Paint horse. **B.** Normal fundus appearance of horse that is blind from unknown reasons. **C.** Tapetal thinning and little pigment in the non-tapetum can be normal in light colored horses. **D.** Normal fundic appearance of a dark colored horse. Small spots in the tapetal fundus are capillaries called the "Stars of Winslow." Some choroidal nevi are present dorsal to the optic disc.

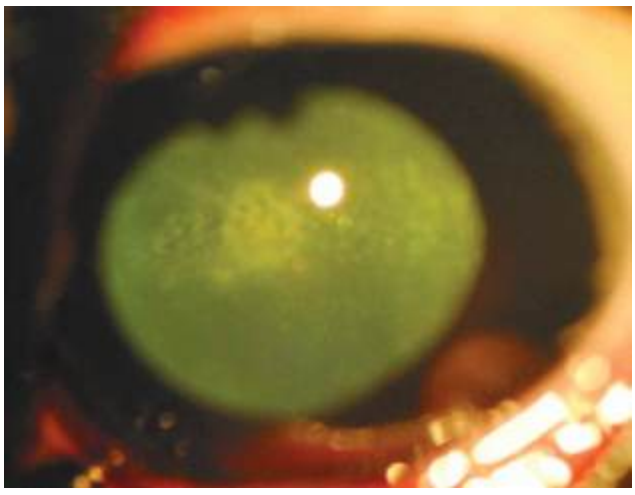


Figure 29.69 Horse with posterior equine recurrent uveitis with yellow cellular infiltrate in the anterior vitreous.



Figure 29.70 Horse with advanced vitreal degeneration, or syneresis, which is a common finding in older horses, and appears as cobweb-like white strands in the vitreous.

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rior segment can result in significant shedding of cell and glial debris into the vitreous body. Inflammatory detritus, hemorrhage, or vitreoretinal detachments within a liquified vitreal body may be apparent. These will vary in extent and configuration and may be accompanied by signs of more generalized intraocular disease, e.g., cortical or posterior capsular cataract, peripapillary chorioretinopathy, or optic atrophy.

Inflammatory change typically presents as a generalized and diffuse yellowing of the vitreal body, probably reflecting the presence of inflammatory proteins, and is a common finding in ERU (Matthews, 2004a). Clumped cellular debris scattered throughout the anterior vitreous may be present in pars planitis or in more generalized posterior uveitis or ERU. Inflammatory debris may become adherent to the vitreal tracts giving an impression of dense membranous detritus, and these can be difficult to differentiate from vitreoretinal detachments both clinically and on B-mode ultrasonography.

Discrete areas of opacity, usually within the posterior vitreous, are occasionally observed in association with peripapillary chorioretinopathy. Postinflammatory opacities in the vitreous generally resolve over a protracted period once the primary disease is controlled. However, in some cases the vitreal opacification may be permanent (Matthews, 2004a).

Intravitreal hemorrhage originates from the retinal, choroidal, or ciliary vasculature and will usually be the result of direct trauma to the globe or posterior uveitis, or rarely posterior segment neoplasms. Blood appears to be removed very slowly from the equine vitreous and organizing hemorrhage can be the cause of vitreoretinal detachments (Matthews, 2004a).

Postinflammatory adhesions within the vitreal cortex or cyclitic membranes in the anterior vitreous create traction and dehiscence of the underlying retina along the plane of the subretinal space. This results in dense, white infolding membranes of cortical vitreous and retina floating freely within the apparently liquified vitreal body. Occasionally, organized intravitreal hemorrhage or neovascularization of the detached retina is present (Matthews, 2004a).

Most horses older than 6 years have vitreal degeneration manifested by vitreal floaters and strands. Asteroid hyalosis is an incidental finding of older horses and appears as relatively large and regular whitish or refractile focal inclusions enmeshed in the vitreous gel structure (Cutler, 2002; Cutler et al., 2000). Typically, these inclusions remain suspended in the intermediate vitreous and do not settle out, although some movement is provoked by ocular saccades (Matthews, 2004a). Synchesis scintillans is an uncommon condition of older horses. Small highly refractile crystals float freely within the apparently liquefied vitreous, rapidly settling out under the influence of gravity. Some crystals may be adherent to intravitreal membranes or tracts (Matthews, 2004a).

Chorioretinitis

The retina and choroid are intimately related anatomically and an insult to one necessarily affects the other (Altunay, 2000). Chorioretinitis, inflammation of the choroid and retina, may be the result of ERU or may be a manifestation of systemic disease. Active lesions are characterized by edema, cellular infiltrate, and hemorrhage or retinal detachment and they often appear gray, white, or hazy (Fig. 29.71). The retina may be elevated by subretinal fluid and inflammatory cells. Inactive lesions, or chorioretinal scars, appear as hyperreflective or hyperpigmented in the tapetal fundus and may appear to be depigmented or to have pigment clumping in the non-tapetal fundus (Fig. 29.72). If the retina was elevated during the active phase of the disease, it may reattach in a wrinkled or folded fashion, appearing as gray linear folds. These folds are most commonly seen radiating from the optic nerve. Chorioretinitis lesions can be focal or diffuse and unilateral or bilateral, and are most commonly seen in the peripapillary region.

Chorioretinitis manifests in equine eyes as focal "bullet-hole lesions", diffuse chorioretinal lesions, non-tapetal "horizontal band" lesions, and peripapillary chorioretinal scars (Rebhun, 1992a; Slater et al., 1995). Active peripapillary chorioretinitis is not usually documented in ophthalmoscopy. It is far more common to recognize what appears to be an inactive scar. Active lesions may be associated with optic neuritis and can develop into secondary retinal detachments because of vitreoretinal adhesions (Cutler et al., 2000; Rebhun, 1992a). The "classic" inactive chorioretinal scar is seen circumpapillary and is referred to as a butterfly lesion (Fig. 29.72). This is an area of depigmentation and pigment clumping that radiates nasally and temporally from the optic nerve. This lesion has been associated with ERU, blunt

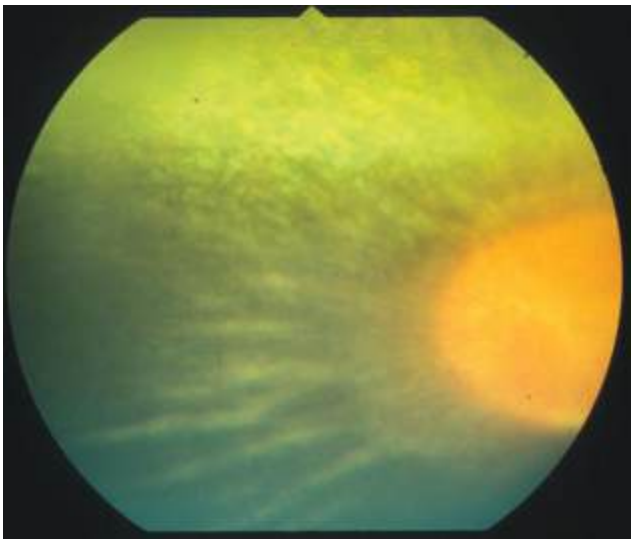


Figure 29.71 Peripapillary chorioretinitis and focal retinal detachment in a horse with equine recurrent uveitis.

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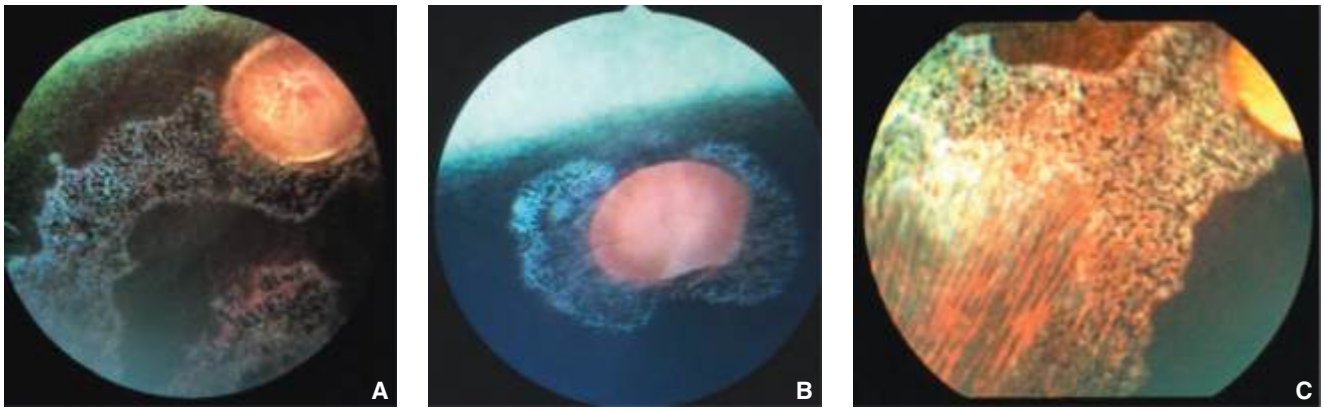


Figure 29.72 **A.** Large scars from ERU-induced chorioretinitis. **B.** Peripapillary chorioretinopathy in a horse eye can increase the size of the horse's blind spot or scotoma. **C.** Non-tapetal chorioretinal scar showing sector retinal pigmented epithelial loss, pigment clumping, and exposure of choroidal blood vessels and sclera.

trauma, and other causes of chorioretinitis (Matthews et al., 1990; Nell & Walde, 2010; Wilkie, 2011). Chorioretinitis or panuveitis may also be a manifestation of systemic disease and has been documented with EHV-1, equine infectious anemia (EIA), adenovirus, West Nile virus, neonatal septicemia, *Rhodococcus equi*, *Streptococcus equi* var. *equi*, Lyme disease, brucellosis, *L. interrogans pomona*, equine granulocytic ehrlichiosis, toxoplasmosis, *Halicephalobus gingivalis* (*Halicephalobus deletrix*), and onchocerciasis (Wilkie, 2011). Treatment is directed at the underlying cause.

Chorioretinopathy

Focal chorioretinopathy, termed bullet-hole chorioretinitis, is a generally multifocal, depigmented lesion that appears most commonly ventral to the optic disc in the non-tapetal fundus (Fig. 29.73). They typically have a hyperpigmented center surrounded by a white, depigmented zone. Acute lesions show foci of gray–white retinal edema. The etiology of these lesions is as yet unknown. However, EHV-1 has been implicated in their pathogenesis. In fact, experimental infection with EHV-1 has been observed to induce chorioretinal lesions (Hussey et al., 2013). Viral-mediated infarction of the choroid could result in RPE depigmentation at the periphery of the infarct and RPE hypertrophy at the central region has been implicated as a cause. On histologic examination, a loss of normal retinal architecture with RPE hyperplasia and migration of RPE cells into the retina can be observed. It has been suggested that these lesions may be the result of previous chorioretinitis, but these lesions are often seen, as incidental findings, in many horses (Wilkie, 2011). A few "bullet-hole" lesions probably have little impact on functional vision, but 20 or more focal lesions in one eye may produce subtle to obvious visual loss. Lesions near the optic disc affect a larger number of ganglion cells and more axons in the nerve fiber layer and thus may have more significant effects on vision (Cutler et al., 2000). However, a recent report of two horses with extensive "bullet-hole" retinopathy in which electroretinography was performed did not reveal any compromise to outer retinal function (Allbaugh et al., 2014).

Diffuse chorioretinal lesions are less common, and they manifest as circular, band-shaped, or vermiform lesions in the tapetum or non-tapetum. Tapetal lesions are rare and associated with tapetal hyperreflectivity, and the more common non-tapetal lesions are associated with RPE depigmentation and hyperpigmentation. Widespread retinal or choroidal inflammation (or both), choroidal infarction, massive blood loss, or severe head trauma may induce these lesions. Varying degrees of optic nerve degeneration and atrophy may be present as well. Toxoplasmosis, leptospiro-

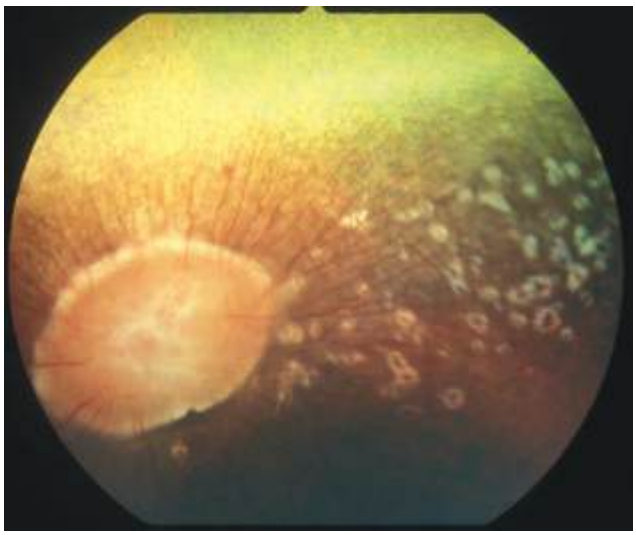


Figure 29.73 Focal chorioretinopathy, or bullet-hole chorioretinitis, are multifocal, depigmented lesions that appear most commonly ventral to the optic disc in the non-tapetal fundus.

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sis, and the Eastern, Western, and Venezualan equine encephalitides may cause chorioretinitis (Cutler et al., 2000).

"Horizontal band" lesions in the non-tapetum occur one to two optic disc diameters ventral to the ONH, where they radiate across the posterior pole from the nasal ora ciliaris retinae to the temporal ora (Rebhun, 1992a). They are associated with visual deficits or complete blindness, and they may be a result of vascular infarction. There is no treatment.

Congenital Stationary Night Blindness

Congenital stationary night blindness (CSNB) has been reported in the Appaloosa, Quarter Horse, Thoroughbred, Paso Fino, Standardbred, and Miniature Horse (Nunnery et al., 2005; Sandmeyer et al., 2007, 2012; Witzel, 1978). CSNB may have an incidence of up to 33% of the Appaloosa horses studied, and a significant association has been shown between CSNB and homozygosity of the leopard complex gene (*Lp*) (Bellone et al., 2008). Affected horses may show abnormal behavior (unease and unpredictability, especially at night) or vision loss in low-light conditions (nyctalopia), and some may also have decreased vision in normal light (Sandmeyer et al., 2007; Witzel, 1978). Ophthalmic examination is normal, although some horses may also have microphthalmia, dorsomedial strabismus, nystagmus, and an unusual dorsal ocular deviation and head elevation, which has been termed *star-gazing* (Wilkie, 2011). Foals may also appear to be disoriented and stare off into space (Rebhun 1984; Sandmeyer et al., 2007; Witzel et al., 1977; Witzel, 1978). Diagnosis of CSNB can be confirmed by electroretinography that has a normal a-wave but a decreased photopic and absent scotopic b-wave, sometimes referred to as an a-wave dominant pattern (Nunnery et al., 2005; Sandmeyer et al., 2007; Witzel, 1978). Cone flickers are normal but rod flickers are reduced in amplitude and reversed in polarity (Sandmeyer et al., 2007). Histopathologic examination of affected retinas is normal, thereby suggesting the possibility of a middle retinal neurotransmission problem (Rebhun 1984; Sandmeyer et al., 2007; Witzel et al., 1977; Witzel, 1978). There is no treatment for CSNB and affected horses should not be used for breeding.

Equine Motor Neuron Disease

Equine motor neuron disease (EMND) is a neurodegenerative disease that occurs as a result of a chronic dietary deficiency of the antioxidant, vitamin E (Bellone et al., 2008). RPE accumulation of a substance with characteristics of ceroid lipofuscin is found associated with EMND (Jackson, 1995). A mosaic, reticulated, or honeycomb pattern of dark to yellow brown pigmentation in the tapetal and non-tapetal retina of affected horses is noted sometimes associated with a horizontal band of pigmentation at the tapetal–non-tapetal junction (Fig. 29.74). Consistent evidence of vitamin E deficiency (<1.799 μg/mL) in horses with EMND suggests that the RPE, retinal, and spinal lesions are a result of oxidative injury associated with a deficiency of nutritionally derived antioxidants (Jackson, 1995). Clinically, horses affected with EMND may exhibit weight loss, weakness, muscle atrophy, trembling, low head carriage, and an abnormal stance (Bellone et al., 2008). While visual deficits may not be consistent, flash electroretinograms with 50% reductions in b-wave amplitude and normal appearing a-waves have been noted associated with retinal degeneration (Jackson, 1995).

Whether or not vitamin E deficiency has an impact on neuronal health of a particular individual depends upon genetic factors, the temporal occurrence of deficiency during development, or duration of deficiency during adulthood. In the horse, neuroaxonal dystrophy/equine degenerative myeloencephalopathy (NAD/EDM) is a neurodegenerative disease characterized by a general proprioceptive ataxia that affects genetically susceptible foals if they are deficient in α-tocopherol during the first year of life. EMND results in clinical signs of lower motor neuron weakness in older horses that have been α-tocopherol deficient for at least18 months and with no genetic predisposition. A recent report describes a pigment retinopathy in a family of α-tocopherol-deficient Warmbloods with clinically apparent NAD/EDM or EMND (Finno et al., 2017). Retinal pigmentation appears to be not only a feature of EMND but can also be present in NAD/EDM Warmblood horses with α-tocopherol deficiency. Therefore, an ophthalmologic

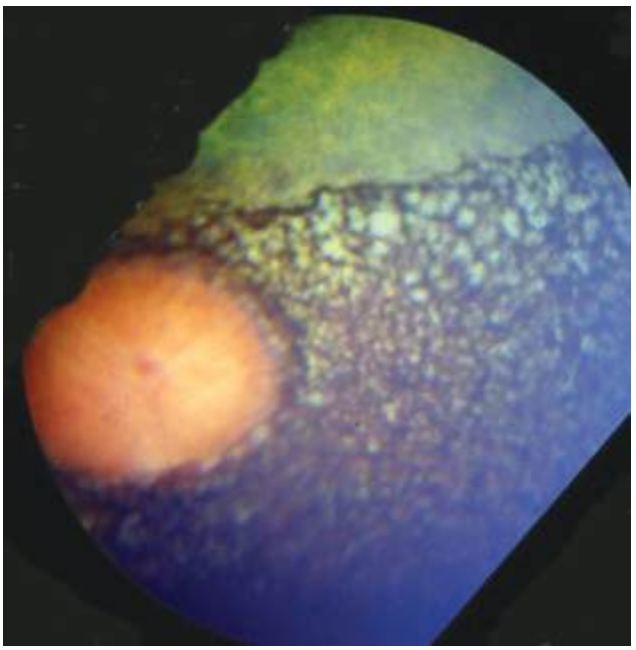


Figure 29.74 Reticulated or honeycomb pattern of accumulations of yellow–brown to black pigment in the tapetal and non-tapetal retina in a horse with equine lower motor neuron disease.

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examination is indicated in young horses with proprioceptive ataxia. The presence of pigment within the retina is a useful indicator of an underlying α-tocopherol deficiency, even if there are no associated neurologic abnormalities noted initially.

Retinal Detachment

A retinal detachment is the separation of the neurosensory retina from the outer retinal pigmented epithelium (Brooks, 2002; Mätz-Rensing et al., 1996; Rebhun, 1992a). The retina can detach as a result of fluid accumulation, a retinal tear, blunt force trauma, or traction toward the vitreous secondary to resolution of vitreal hemorrhage (Fig. 29.75). A focal bullous detachment appears as an elevated, hazy area of retina with subretinal fluid. This bullous detachment may reattach with folds or wrinkles, most commonly radiating outward from the optic nerve. With a complete detachment, the retina appears as a gray, free-floating, undulating veil of tissue extending into the vitreous toward the lens. If torn or disinserted dorsally, the retina will hang over and obscure visualization of the optic disc. The tapetum will appear hyperreflective. Complete detachments with tears or disinsertions will not resolve with therapy resulting in blindness (Wilkie, 2011). Progressive degeneration and atrophy of the sensory retina (beginning with the photoreceptors), hypertrophy of Müller cells, and hypertrophy of the RPE cells with transformation of the apical microvilli are consistent histopathologic findings of chronically detached equine retinas. In a retrospective study of 40 horses (46 eyes) with retinal detachment, the etiology was diagnosed to be ERU in 27 horses (33 eyes, 67.5%) and trauma (to the head or the globe)

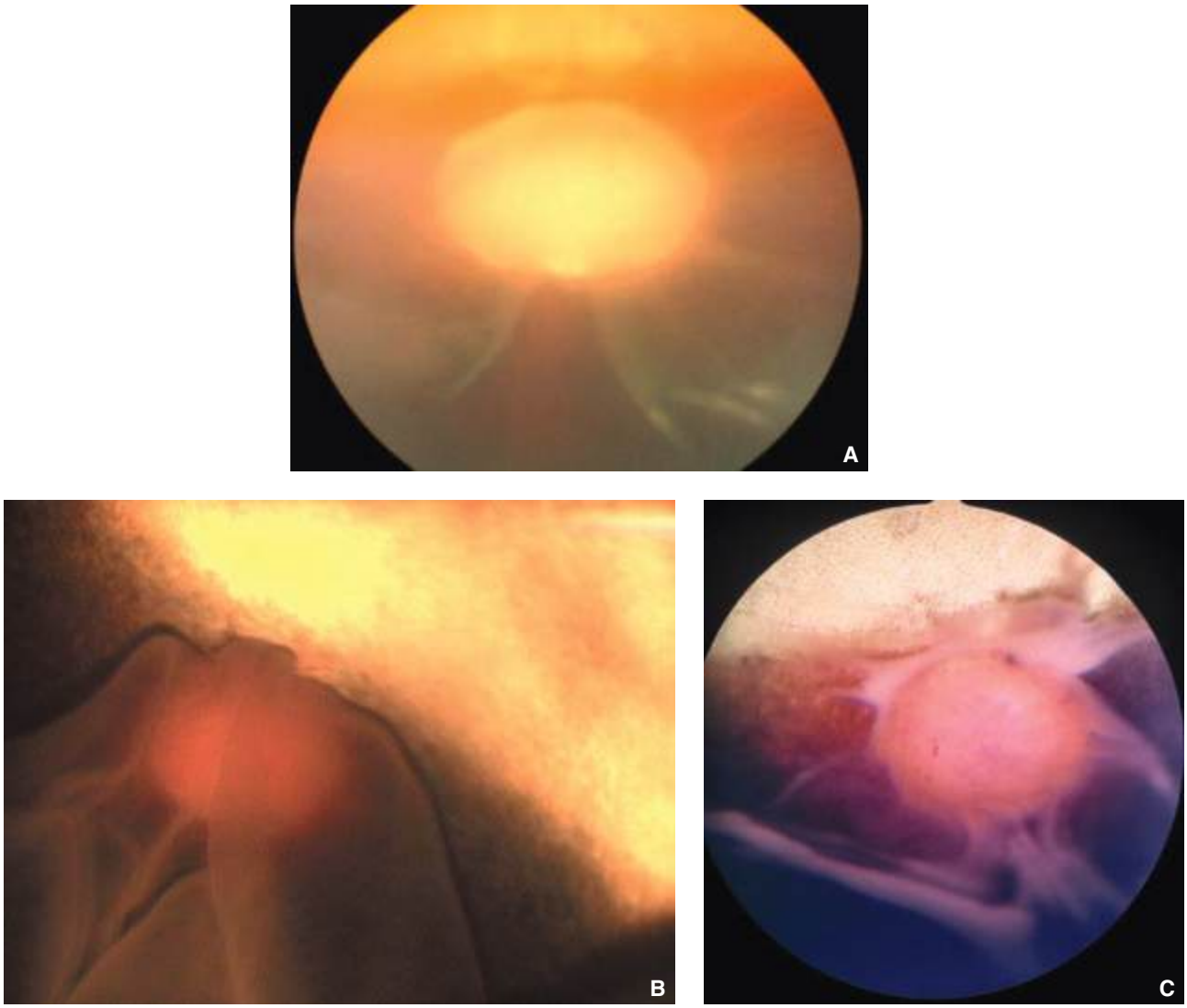


Figure 29.75 **A.** Diffuse retinal detachment in the non-tapetal ocular fundus in a horse. **B.** Complete retinal detachment and disinsertion in a foal with EHV-1. **C.** The retina has detached and appears as white folds and sheets in this eye.

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in 10 horses (10 eyes, 25%) (Strobel et al., 2007). Intraocular tumors may also contribute to retinal detachment. The prognosis for a retinal detachment depends on the severity, underlying cause, and chronicity of the lesions, but in general, it is poor for return of vision (Strobel et al., 2007).

Retinal Degeneration

Primary retinal degeneration or progressive retinal atrophy is uncommon in horses, but when present will be bilateral and progressive, and Thoroughbreds may be predisposed (Matthews et al., 1990; Nell & Walde, 2010; Wilkie, 2011). Affected horses show progressive vision loss. Retinal degeneration appears as hyperreflective changes in the tapetal retina and as multifocal depigmentation and hyperpigmentation in the non-tapetal retina. The optic nerve becomes pale, and the peripapillary retinal vessels are attenuated. Vision loss may begin with nyctalopia (night blindness) and progress to day vision loss (Matthews et al., 1990; Nell & Walde, 2010; Wilkie, 2011). Unilateral retinal degeneration can be associated with glaucoma, trauma, or vascular ischemia (Wilkie, 2011).

Electroretinography in Horses

Electroretinography can be performed with the horse standing. The horse should be sedated (detomidine hydrochloride 0.015 mg/kg IV) prior to performing electroretinography (Church & Norman, 2012). The pupil is dilated with tropicamide or another short-acting mydriatic agent and an auriculopalpebral nerve block is performed. The cornea should be anesthetized with a topical anesthetic agent. The electroretinographs are recorded with the active electrode on the cornea (DTL or contact lens electrode), the reference electrode near the lateral canthus, and the ground electrode over the occipital bone. The light intensities of the white strobe light are $0.03\,cd \times s/m^2$ (scotopic) and $3\,cd \times s/m^2$ (scotopic and photopic). Photopic and scotopic single flash and flicker responses to Ganzfeld stimulation are recorded. During the 20 minute dark adaptation period the retina is stimulated every 5 minutes with the $0.03\,cd \times s/m^2$ single flash (Ben-Shlomo et al., 2012). The median b-wave amplitudes and implicit times are 38 microV and 33 ms (photopic cone-dominated response), 43 microV and 63 ms (5 minute dark adaptation), 72 microV and 89 ms (10 minutes), 147 microV and 103 ms (15 minutes), 188 microV and 109 ms (20 minutes, $0.03\,cd \times s/m^2$, rod response), and 186 microV and 77 ms (20 minutes, $3\,cd \times s/m^2$, maximal combined rod-cone response). A steady increase in amplitude and implicit time is noted during dark adaptation. No oscillatory potentials could be isolated with this technique (Komaromy et al., 2003).

Diseases of the Optic Nerve

Pathologic changes to the optic nerve are commonly observed, especially in older horses, but rarely are these changes associated with vision loss. The most common abnormality is a condition called proliferative optic neuropathy, which appears as a focal growth on typically one edge of the optic nerve (Fig. 29.76). Proliferative optic neuropathy must be differentiated from exudative or ischemic optic neuropathy, which are acute lesions associated with complete vision loss in the affected eye (Hardy et al., 1990; Wilkie, 2011).

Optic Nerve Atrophy

Optic nerve atrophy in the horse occurs secondary to inflammation in optic neuritis and ERU, and from noninflammatory causes such as trauma, glaucoma, toxicity, and blood loss. Optic nerve degeneration appears as a pale, often recessed, ONH with absent or decreased vascularity (Fig. 29.77). Degeneration most commonly occurs after head trauma and if severe can result in complete and permanent blindness (Wilkie, 2011).

Traumatic Optic Neuropathy

The optic nerve is contained within a dural sheath that at the orbital apex is continuous with the periosteum of the optic canal. Traumatic optic neuropathy occurs in the optic canal, where the dural sheaths and the periosteum are fused.

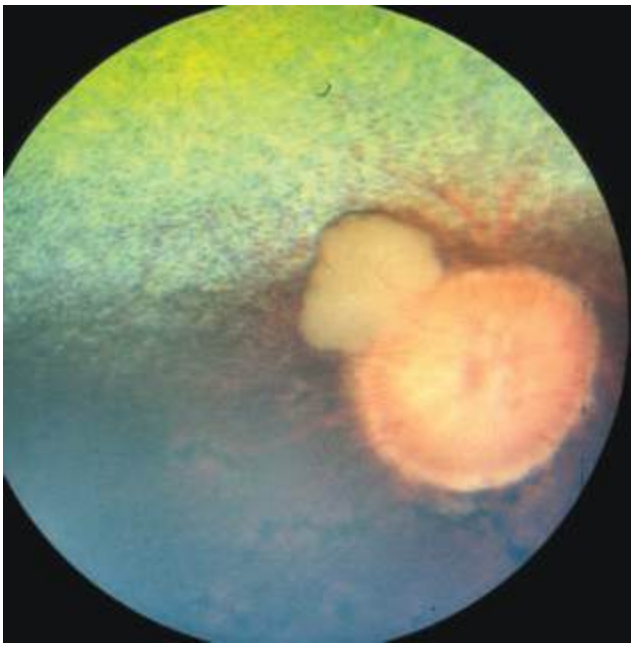


Figure 29.76 Proliferative optic neuropathy in a 20-year-old Thoroughbred mare.

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Concussive shock waves focused on the optic canal can result in optic nerve damage, because the nerve is fixed and experiences the same force as the surrounding bone. Stretching, shearing, or avulsion of the equine optic nerve or chiasm (or some combination thereof) can result in optic nerve atrophy and blindness from concussive cranial injuries (Krohne et al., 1988; Martin et al., 1986). Stretching of the optic nerve from blunt head trauma can cause blindness in horses. The atrophic optic disc becomes pale and the pupils dilated. There is no therapy (Cutler et al., 2000).

Proliferative Optic Neuropathy

Proliferative optic neuropathy is a condition found primarily in older horses. It is characterized by a slowly enlarging, white mass protruding from the optic disc and into the vitreous, with minimal effect on vision (Fig. 29.76). This lesion is unilateral and, histopathologically, resembles a schwannoma with proliferating lipid laden glial cells (Cutler et al., 2000; Matthews et al., 1990; Riis & Rebhun, 1990). There is no therapy for proliferative optic neuropathy. These are seen commonly in elderly horses, are rarely associated with vision deficits, and may be benign neoplasms (e.g., glioma) (Cutler, 2002; Wilkie, 2011).

Exudative Optic Neuritis

Exudative optic neuritis is found in older horses (Riis, 1981). It manifests as sudden onset of total blindness, and it is a bilateral condition. The optic discs are swollen, and retinal as well as optic disc hemorrhages may be present. The cause is not known but may be infectious in nature (Cutler et al., 2000).

Optic neuritis may also occur along with posterior uveitis or in cases of chorioretinitis from systemic disease, but this disease entity is uncommon.

Ischemic Optic Neuropathy

Chorioretinal degeneration, that tends to follow the choroidal blood vessels and optic nerve atrophy secondary to acute blood loss caused by trauma or surgery, has been reported in the horse (Gelatt, 1979). The chorioretinal degeneration with resultant pigmentation occurs as irregular linear streaks through the ocular fundus. The severe blood loss and thromboembolic disease may cause bilateral blindness in horses, although the exact mechanism for this is not understood (Gelatt, 1979).

Surgery to eliminate equine epistaxis because of guttural pouch mycosis by ligation of the internal and external carotid and greater palatine arteries is also associated with ischemic optic neuropathy and sudden, irreversible blindness (Hardy et al., 1990). Most of the ischemic damage is isolated to the ONH. Ligation of only the maxillary artery on each side of the lesion may decrease the likelihood of the development of ischemic optic neuropathy, but the risk of ischemia to the optic nerve remains. ONH congestion occurs initially and is followed within a few days by disc pallor and extrusion of axon contents into the nerve fiber layer (Hardy et al., 1990) (Fig. 29.78). Optic nerve atrophy occurs in 2–4

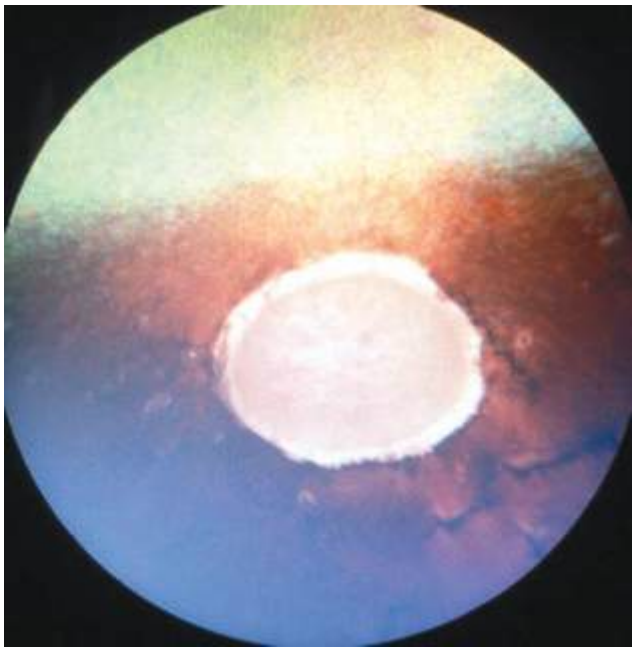


Figure 29.77 Pale optic nerve and decreased retinal vascularity associated with optic nerve degeneration.

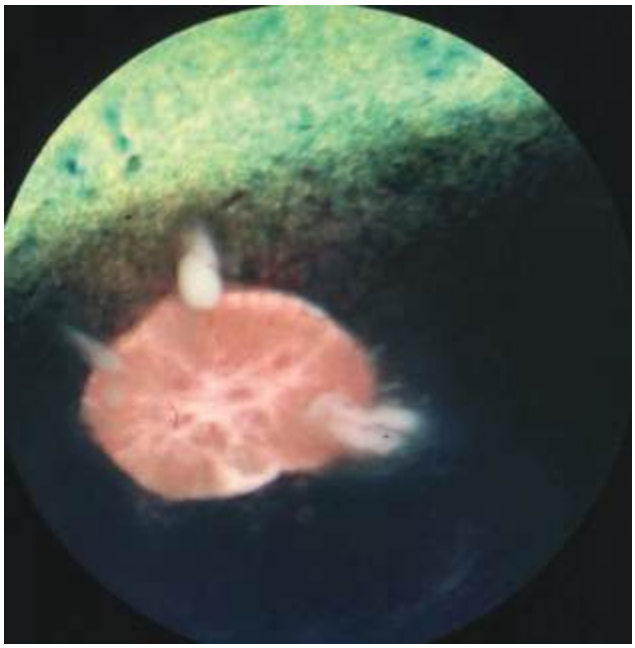


Figure 29.78 Ischemic optic neuropathy. The lamina cribrosa is easily seen indicating axonal loss.

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weeks. Severe blood loss and thromboembolic disease may cause bilateral blindness in horses, though the exact mechanism for this is not understood (Gelatt, 1979).

Photic Headshaking

Idiopathic headshaking, or head-tossing, behavior in horses is recognized as uncontrollable, persistent or intermittent, seasonal or nonseasonal, spontaneous and frequently repetitive vertical, horizontal, or rotatory movements of the head (Madigan et al., 1995; Mair et al., 1999; Newton, 2005). These signs occur with such violence that the horses are dangerous to themselves and riders. Rubbing of the face, head pressing, and holding the head low are also seen (Newton, 2005). It is not a vice, neurosis, or behavioral problem. Clinical signs suggest that there are areas of the face, nose, or nasal cavity acting as sensory trigger zones. The role of light in this behavior in some horses was assessed by blindfolding the horses, placing them in darkened environments, or placing eye masks over their eyes. Photic headshaking behavior improved significantly when the amount of light striking their eyes in some horses was diminished. A nasal occlusal mask was used to reduce clinical signs in other horses with idiopathic headshaking behavior. Most horses were asymptomatic in the winter months, and the headshaking behavior was commonly initiated with the onset of summer and with strenuous exercise. A condition in these horses similar to the photic sneeze of humans is suggested as the causative mechanism for the photic behavior. Otitis media/interna from mites, premaxillary bone cysts, maxillary osteomas, guttural pouch disease, upper respiratory tract disease, bit and tack problems, and dental as well as ocular diseases such as iris cysts must also be ruled out as a cause (Stephenson, 2005). The mechanism for photic headshaking in the horse may be a form of optic–trigeminal nerve summation, in which optic nerve stimulation produces referred sensation to the nasal cavity. Sunlight may stimulate parasympathetic activity in the infraorbital nerve (maxillary branch of the trigeminal nerve), or the facial sensory branch of the trigeminal nerve, thereby resulting in irritating nasal sensations to the horse that explain the rubbing, sneezing, and flipping of the nose and head as seen in photic headshaking behavior (Madigan et al., 1995; Wilkins, 1997). A trigeminal neuritis or neuralgia may be the basis of the underlying etiopathology of other types of equine headshaking. Selective nerve blocking may be helpful in ameliorating this condition. Infraorbital nerve blocks relieved clinical signs in three of 19 horses (Mair et al., 1999). Posterior ethmoidal nerve (caudal nasal branch of the maxillary division of the trigeminal nerve) blocks were more effective in abolishing clinical signs (Newton, 2005). A favorable response to oral cyproheptadine, which is an antihistamine serotonin antagonist given at a dose of 0.3 mg/kg twice daily, occurs in most horses, and melatonin therapy may also be beneficial (Madigan et al., 1995; Wilkins, 1997). The antiepileptic drug carbamazepine can help others (10 mg/kg PO q6h, or 29 mg/kg PO q12h). Tinted contact lenses can help some horses (Newton, 2005). Bilateral infraorbital neurectomy can be used for medically refractory cases if infraorbital nerve blocks ameliorate the behavior but is nearly as effective as caudal nasal nerve sclerosis (Madigan et al., 1995; Mair et al., 1999; Newton, 2005; Wilkins, 1997).

Geriatric Eye Problems

Ophthalmic disease increases with age in horses and ponies (Chandler et al., 2003). A variety of ocular conditions can affect the eyes of the aged horse (Cutler, 2002). In one study, 81% of horses older than 15 years had ocular lesions (Chandler et al., 2003). Geriatric horses often present with degenerative or age-related conditions of the eyes (Cutler, 2002; Dwyer, 2011). In one study of 83 horses over the age of 15 years, 49% had retinal lesions (e.g., senile retinopathy, retinal degeneration, peripapillary chorioretinopathy, optic nerve atrophy, or proliferative optic neuropathy), 46% had vitreal degeneration, and 19% had cataracts. However, only seven (8%) had vision loss (Chandler et al., 2003). However, older horses will develop some reduction in visual acuity and loss of color vision from lenticular sclerosis. Visual problems were noted in 8.4% (Chandler et al., 2003). Another study of geriatric horses in the UK noted that ophthalmic lesions frequently were identified and included vitreous degeneration (66.0%), cataracts (58.5%), and senile retinopathy (33.7%) (Ireland, 2012).

Proliferative optic neuropathy and exudative optic neuropathy are found in horses older than 15 years. Iris atrophy (Fig. 29.76), iris cysts, persistent superficial corneal ulcers, corneal thickening caused by endothelial cell loss, senile cataracts, lenticular sclerosis, vitreal degeneration, and increased exposure of the scleral lamina cribrosa caused by axonal demyelination are found in the older horse. Glaucoma and ERU are also more common in the aging horse. Asteroid hyalosis is present in some aged horses. Senile retinopathy with symmetrical non-tapetal depigmentation in linear or diffuse patterns near the optic disc may be progressive and is reported in geriatric horses and ponies (Cutler, 2002; Chandler et al., 2003; Ireland, 2012). Tapetal areas may be hyperreflective. Peripheral cystoid retinal degeneration and loss of retinal cell layer organization in the peripheral retina also occurs in the older horse (Ehrenhofer et al., 2002).

Horses over the age of 15 years are also at increased risk for many kinds of neoplasia, including intraocular neoplasia (such as melanoma in aged gray horses) and adnexal SCC. Geriatric horses commonly develop chronic conditions that may have ocular manifestations including dental disease, sinus infections, and Cushing's syndrome (Dwyer, 2011). Cushing's syndrome can cause supraorbital fat protrusion and compress the optic chiasm to cause blindness in older

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ponies and can predispose the animal to infections and delayed healing (Rendle, 2005). Temporohyoid osteopathy in older Quarter Horses can cause KCS. Cauda equina neuritis is associated with facial nerve paralysis. See Chapter Chapter 37, Part 3 for more details regarding these systemic diseases.

Ophthalmic Manifestations of Systemic Disease

See Chapter 37, Part 3 for a discussion of the systemic conditions in the horse that may affect the health, comfort, or function of the eyes.

Breed-Related Eye Conditions

Several horse breeds are predisposed to various ocular conditions (Table 29.6).

Prepurchase Ophthalmic Examination

A complete ocular examination of both eyes using a focal light source such as a transilluminator and a direct ophthalmoscope should be part of every examination of the performance horse. The eye examination before purchase is performed by a veterinarian representing the buyer, and it is designed to detect congenital or hereditary ocular abnormalities as well as any active disease that may lead to decreased vision (e.g., cataracts, uveitis). Minor signs of eye disease overlooked at this examination may lead to vision loss, rider injury, and lawsuits. The purpose for which the horse is to be used determines the emphasis to be placed on any ocular problems noticed. For example, a horse with a large corneal scar may be unsuitable for young children but satisfactory for more mature riders. Some horses may need to be re-examined before they are determined to be suitable.

Epiphora, eyelid abnormalities, corneal scarring, conjunctival and adnexal tumors, cataracts, evidence of active or inactive uveitis, and retinal scarring are common problems noted during prepurchase examinations. Some of these lesions may be acquired or breed-associated.

The source of any epiphora should be determined by placing fluorescein dye in the eye. After several minutes, the dye should appear in the nasal passages if the NLDs are patent. Use of fluorescein dye will also allow for detection of small corneal ulcers that might also be associated with tearing.

Eyelid defects may also be associated with exposure keratitis. The nictitans should be carefully examined to see if it can protect the cornea in the presence of a lid defect. The most common adnexal tumors in the horse are SCCs. Identification of any type of ocular neoplasia is of serious concern.

The cornea should be clear, smooth, and shiny. Corneas that appear dull and rough may be ulcerated, edematous, or scarred. Corneal scars from previous injuries or ulcerations may pose no problem for the horse's vision if they are small or located near the limbus. Large scars in the central cornea, however, may be associated with less-than-satisfactory vision and should be evaluated carefully. The presence of corneal striae or corneal endothelial "band opacities" in non-buphthalmic equine eyes warrants a high degree of suspicion for equine glaucoma. The IOP should be carefully measured with applanation or rebound tonometry to determine if it is elevated. Linear corneal opacities may be found in eyes that are normotensive at examination. Serial IOP measurements over a 12- to 24-hour period may be necessary to detect transient, but significant, elevations in IOP.

Cataracts or lens opacities are always important because they may be progressive and associated with visual impairment. Lens opacities are best seen with the pupil dilated and the examination being performed in complete darkness. They can be staged according to their degree of maturity as incipient (i.e., focal), immature (i.e., partial lens opacity and the horse still visual), and mature (i.e., complete lens opacity and blindness). Normal aging of the equine lens will result in cloudiness of the lens nucleus (i.e., nuclear sclerosis) beginning at 7–8 years of age, but this is not a true cataract and does not impair functional vision. Cataracts of the posterior lens sutures and those associated with persistence of the hyaloid artery are found in the horse. Most equine cataracts are secondary to previous bouts of uveitis.

ERU is the most common cause of blindness in the horse. Buyers should be made aware of any evidence for previous episodes of active ERU, because clinical signs may recur. Corneal scarring, iris synechiae and depigmentation, cataracts, aqueous flare, vitreal floaters, and chorioretinal degeneration manifesting as "butterfly lesions" are common signs of uveitis. The non-tapetal region ventral to the optic disc should be carefully examined with a direct ophthalmoscope, because this is where focal retinal scars are seen. Large areas of retinal depigmentation and degeneration are suggestive that the animal has a blind spot at least the size of the scar and, therefore, may have reduced vision.

Retinal detachments may be congenital, traumatic, or secondary to ERU, and these are serious faults because of their association with loss of vision. Vitreal floaters can develop with age or be sequelae to ERU, may cause some headshaking in a few horses, and generally are benign in nature. Optic nerve atrophy can be related to ERU, glaucoma, or trauma, and it is associated with blindness. Proliferative lesions of the optic nerve may be noted in older horses but generally are not sight- or life-threatening.

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Table 29.6 Breed-related eye disease in the horse.

Appaloosa
Congenital stationary night blindness
Congenital cataracts
Glaucoma
Equine recurrent uveitis
Optic disc colobomas
Squamous cell carcinoma
Arabian
Congenital cataracts
Vitiligo
Belgian Draft Horse
Aniridia and secondary cataracts
Squamous cell carcinoma
Morgan
Cataracts: nuclear, bilateral, symmetrical, and nonprogressive
Quarter Horse
Congenital cataracts
Entropion
Thoroughbred
Congenital cataracts
Microphthalmia associated with multiple ocular defects
Retinal dysplasia associated with retinal detachments in some cases
Entropion
Color-dilute breeds
Iridal hypoplasia (photophobia)
Squamous cell carcinoma
Standardbred
Retinal detachments
Congenital stationary night blindness
Paso Fino
Congenital stationary night blindness
Glaucoma
Fresian
Corneal dystrophy
Distichia
American Saddlebred
Cataracts
Esotropia
Warmbloods
Glaucoma
Equine recurrent uveitis
Rocky Mountain Horse
Anterior segment dysgenesis: collectively the cornea, iris, and ciliary body lesions are termed anterior segment dysgenesis (ASD).
Congenital miosis, corpora nigra, and iris hypoplasia
Macrocornea
Ciliary body cysts (temporal)
Cataract, lens luxation
Retinal dysplasia, retinal detachment
Miniature Horses
Upper eyelid entropion
Connemara Pony
Anterior segment dysgenesis
Mules
Strabismus
Aggressive sarcoid
Misplaced nasolacrimal puncta
Haflinger
Squamous cell carcinoma

Vision should be assessed during the examination by ophthalmoscopy and by the dazzle and menace reflexes. Appaloosas should be examined in both the light and the dark to detect evidence of night blindness. Maze testing with blinkers alternatively covering each eye may also provide information regarding subtle or unilateral visual deficits.

To avoid litigation, inform the potential buyer of what was and was not done during the examination because of the limitations of the equipment available. In legal thinking, the veterinarian must show that all aspects of the ocular examination were considered, even if sophisticated equipment (i.e., a slit lamp) for a detailed study of the eye was not available.

In most cases, the veterinarian is examining an eye without overt clinical signs. The findings of the ocular examination should be related to the intended use of the animal, and an assessment should be made concerning the possibility that any lesion noted could progress to interfere with vision. The intended functions of the horse must be considered in the determination of whether any ocular lesions present are unimportant or "safe" for the horse and its rider and whether the horse can satisfactorily perform its intended functions. Some eye problems might not preclude use of a horse in certain circumstances, in which unexpected visual stimuli are unlikely to be present and the rider is experienced and aware of any shortcomings in the horse's vision. There are many examples of horses with varying degrees of blindness that can perform at a high level in various types of equestrian competitions, so horses with "suspicious" or subtle signs of ocular disease should not necessarily be excluded. The impor-

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tance of ocular lesions with an uncertain significance may be determined if they are re-examined over several months. If the horse being examined is a brood mare, the genetic nature of any ocular lesion should also be considered.

The veterinarian performing the prepurchase examination must recognize and acknowledge that it is their responsibility to discover and document existing medical problems for the buyer so that the buyer may make an informed decision. When there is an abnormality or disease which is damaging eye function and a visual deficit is present in the horse, it is either a major problem, and is likely to affect behavior and safety of horse and rider, or it is a minor problem and is, on balance of probability, likely to be of little consequence. It is ultimately the buyer's responsibility to determine if the horse is suitable. Horses do not pass or fail prepurchase examinations. According to the American Association of Equine Practitioners: "The veterinarian should make no determination and express no opinions as to the suitability of the animal for the purpose intended. This issue is a business judgment that is solely the responsibility of the buyer that he or she should make on the basis of a variety of factors, only one of which is the report provided by the veterinarian."

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Food and Fiber Animal Ophthalmology

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Food and fiber producing animals include cattle, sheep, goats, and pigs. Large, well-controlled studies of ocular abnormalities in food producing animals are not commonly found in the literature, and most ophthalmic alteration reports are of random cases with limited work-up. This chapter covers the available literature by species. For each species, specific anatomical and physiological characteristics, ocular parameters, and congenital and acquired abnormalities of each ocular region are discussed.

Bovine

Ocular Examination and Ophthalmic Parameters

Proper restraint is critical when examining any food-producing animal to ensure a complete and detailed examination, and provide safety for the examiner. An experienced handler is helpful for this task. Dairy cattle patients can be restrained in headlocks, whereas beef cattle are better restrained in a squeeze chute. A halter or lead rope should be used to pull the head laterally and secure it elevated at examiner eye level. Sedation may be required for fractious animals, and α_2-adrenergic agonists are the most common agents used. It is important to remember that these drugs may lead to pregnancy loss in ruminants, especially in late pregnancy. An auriculopalpebral block may be useful to facilitate opening of the eyelids. The auriculopalpebral nerve can be palpated as it crosses the zygomatic arch, and 1 mL of lidocaine hydrochloride can then be injected subcutaneously in the area. A meat and milk withdraw period of 24 hours is recommended when local anesthetics are used (Craigmill et al., 1997).

The ruminant eyes are laterally located and provide for a wide field of vision. Vision can be accessed by the examiner by moving his/her hand toward the eye, which should elicit a blink response. Care should be taken to avoid touching the eyelashes or vibrissae, and to minimize air movement towards the eye, culminating in a false-positive response. It is also important to ensure that the animal is able to blink, by eliciting a palpebral reflex (Townsend, 2010). Facial nerve paralysis caused by trauma to the side of the head is not rare, and cranial nerve paralysis may also result from infectious diseases, such as listeriosis.

The tear production in adult cattle has been reported to be between 25 and 35 mm/min (Whitley & Moore, 1984; Wieser et al., 2013). Calves exhibit lower STT1 values, with an average of 20 mm/min (Tofflemire et al., 2015). The intraocular pressure in normal dairy cows was determined to be around 28 ± 4 mmHg with the Mackay-Marg tonometer and 26 ± 6 mmHg with the TonoPen-XL (Reichart, Buffalo, NY, USA) (Gum et al., 1998). The intraocular pressure obtained using the Perkins applanation tonometer (Haag-Streit, Koeniz, Switzerland) is lower than previously reported. With this tonometer, results of 18.8 ± 1.7 mmHg were obtained which correlated strongly with manometry values (Andrade et al., 2011). When rebound tonometry (TonoVet, Icare TonoVet, Vantaa, Finland) is used, values obtained vary from 15.2 mmHg in calves (Tofflemire et al., 2015) to 23 mmHg in adult cattle (Peche & Eule, 2016). The corneal sensitivity has been measured, using a Cochet–Bonnet aesthesiometer, in healthy bovine calves. Values of 1.33 ± 1.1 g/mm^2, corresponding to a filament length of 34.56 ± 8.02 mm, were obtained (Tofflemire et al., 2014). Cattle possess a small corpora nigra (granula iridica) compared with camelids and horses, and an oval pupil on the horizontal axis (Fig. 30.1).

The Orbit and Globe

Congenital Globe Abnormalities and Blindness

The occurrence of congenital abnormalities in food and fiber-producing animals has increased over the years, likely because of a larger number of animals being raised. Most of those cases present as single occurrences in livestock, and

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Figure 30.1 Normal extraocular photograph of a Holstein cow showing a small corpora nigra and a horizontally oriented oval pupil.



Figure 30.2 Microphthalmia in a calf. (*Source*: Courtesy of University of Missouri Comparative Ophthalmology Service.)

most affected individuals are euthanized and disposed of without having a complete ophthalmic evaluation to characterize the findings. Therefore, the true incidence of congenital ocular abnormalities is not known. It is important to recognize, though, that congenital globe abnormalities are often linked genetically with abnormalities in other body systems (Leipold, 1984).

True anophthalmos is rare. Most animals with suspected anophthalmos actually have microphthalmia with vestigial remnants of ocular tissues (Fig. 30.2). Congenital anophthalmia/microphthalmia syndrome with malformations of the posterior vertebral column was reported in 26 dairy and beef cattle (Leipold & Huston, 1968). The exact etiology was not known, but some cases were speculated to have a hereditary basis. The condition has been reported in a Japanese brown cow, in association with various caudal vertebral abnormalities, such as wedge vertebra, hemivertebra, and sagittal cleft



Figure 30.3 Microphthalmia of the left eye in a calf. The right eye is normal in size. (*Source*: Courtesy of University of Missouri Comparative Ophthalmology Service.)

vertebra (Moritomo et al., 1995). Vestiges of ocular remnants were reported, albeit dysplastic or hypoplastic (or both), implying that these cattle actually had microphthalmia rather than true anophthalmia. It was speculated that these calves were exposed to some unknown teratogen at the critical time of optic organogenesis and notochordal formation. Microphthalmia is usually combined with other ocular defects, including corneal opacities, cataracts, aniridia, corectopia, persistent pupillary membranes, thickening or ossification of the choroid, and various retinal abnormalities, such as gliosis, folds, and rosette formation, as well as retinal nonattachment and detachment (Fig. 30.3). The orbit in anophthalmic/microphthalmic animals also fails to develop because the enlarging globe dictates the development of the surrounding bony structures. For that reason, anophthalmic/microphthalmic animals usually will present with small orbits.

Congenital blindness with multiple ocular anomalies, including dysplasia of the lens, retinal detachment, persistence of the hyaloid artery, retinal dysplasia, and microphthalmia, has also been reported in cattle, with both recessive (Saunders & Fincher, 1951) and dominant (Kaswan et al., 1987) inheritance patterns being postulated. The locus responsible for this syndrome has been mapped to the proximal region of bovine chromosome 18 as a mutation in the *WFDC1* gene, which plays an essential role in mammalian eye development (Abbasi et al., 2009).

Congenital ophthalmic anomalies in food animal have also been associated with several infectious organisms. The most common maternal infection causing multiple ophthalmic defects in cattle is bovine viral diarrhea. Ocular lesions associated with bovine viral diarrhea include cataract, persistent pupillary membranes, retinal dysplasia, retinal

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degeneration, optic neuritis, and microphthalmia (see Chapter 37, Part 4 for additional information). Bluetongue virus has also been associated with blindness and so-called "dummy" calves, which are affected with hydranencephaly and are blind with normal pupillary light responses (Vercauteren et al., 2008). Profound corneal edema has also been reported in some calves infected *in utero* with bluetongue virus (Holzhauer & Vos, 2009).

Abnormalities of Globe Position and Movement

Abnormalities in globe position in cattle are usually bilateral and convergent (i.e., esotropia) (Distl et al., 1991; Gelatt, 1976), but they can also be unilateral and divergent (i.e., exotropia) (Distl & Scheider, 1994; Julian, 1975). Two castrated male full siblings were reported to have divergent unilateral strabismus, associated with other anatomic abnormalities. The reason for the eye defect was a displacement of the lateral rectus muscle 40 degrees ventrally (Distl & Scheider, 1994). Conclusions regarding inheritance of the condition could not be drawn.

Divergent bilateral strabismus in association with hydrocephalus has also been reported (Julian, 1975). Bilateral convergent strabismus with exophthalmia (BCSE) is an eye disorder affecting many cattle breeds worldwide (Fig. 30.4). The condition is of significant importance, because it is progressive and often leads to complete blindness caused by anterior–medial rotation of both globes, and the disappearance of the pupils beneath the nasal orbital rim (Momke & Distl, 2007). The globes are fixed in this undesirable position and unable to move. The disease occurs as an autosomal recessive defect in Jersey cattle (Regan, 1944; Willoughby, 1968). In two studies of German Brown Swiss cattle, a dominant autosomal gene model with 70% incomplete penetrance gave the best fit as the inheritance pattern for the condition (Distl, 1993; Distl & Gerst, 2000). A whole-genome scan for BCSE loci revealed one locus mapped to the centromeric region on bovine chromosome 5 (BTA5) and another locus mapped to the telomeric region of chromosome 18 (BTA18) (Momke et al., 2008). These reports suggest that two genes may be responsible for the disease, or that one gene causes the disease and the other could affect progression or severity. Environmental effects may also be important (Distl et al., 1991). On the basis of histopathologic results, a defect in the motor nucleus of the abducent nerve may be responsible for the symptoms of BCSE (Schutz-Hanke et al., 1979). Esotropia also occurs in Holstein and Ayrshire cattle. Exophthalmia and esotropia progress until the animal reaches maturity. Nystagmus may be present, and vision is compromised (Rebhun, 1979).

In some cases, strabismus may be associated with a generalized systemic infection (Rebhun, 1984). Bilateral dorsomedial strabismus may be associated with polioencephalomalacia. Affected calves are usually blind and exhibit opisthotonus. Ipsilateral neurologic signs in association with a medial strabismus are suggestive of listeriosis (Fig. 30.5). Inflammation of the brainstem impinges on the abducens nucleus, resulting in medial strabismus through loss of function of the lateral rectus muscle (Rebhun, 1984).

Retrobulbar Space-Occupying Lesions

Unilateral strabismus or exophthalmia (or both) usually results from space-occupying orbital lesions caused by inflammation or neoplasia. However, other anatomic defects have been implicated (Distl & Scheider, 1994; Lamb & Naylor, 1985). An Ayrshire calf was described with exophthalmos and an orbital arteriovenous fistula (Lamb & Naylor, 1985). Calves administered daily dexamethasone injections develop exophthalmos caused by increased deposition of retrobulbar adipose tissue (Fig. 30.6) (Townsend et al., 2003).

The prognosis for exophthalmos depends on its etiology. Most forms of retrobulbar neoplasia in cattle carry a guarded prognosis, whereas inflammatory disease (e.g., sinusitis) is



Figure 30.4 A Holstein calf with convergent strabismus and exophthalmos. (*Source*: Courtesy of Cecil Moore.)



Figure 30.5 Drooping of the left upper lip and ear in a Jersey cow with systemic listeriosis. (*Source*: Courtesy of Lawrence Horstman.)

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Figure 30.6 Marked bilateral exophthalmos caused by retrobulbar fat deposition in a 1-month-old Holstein bull calf treated with dexamethasone as part of a metabolic study. (*Source*: Courtesy of Wendy Townsend.)



Figure 30.7 Exophthalmos with marked hyperemia and thickening of both the palpebral and bulbar conjunctiva in a cow with systemic lymphosarcoma involving the orbit. (*Source*: Courtesy of Lawrence Horstman.)

usually more amenable to treatment (Ward & Rebhun, 1992). Fine-needle aspirates of the orbital tissue, particularly guided by B-mode ultrasonography, may be helpful. A 3-in (7 cm), 18-gauge needle can be used for this procedure, which is similar to that described for the Peterson nerve block (Whitley & Moore, 1984).

A single case of unilateral exophthalmia secondary to cavernous sinus syndrome was reported in a Holstein bull, which had a history of a resolved abscess at the base of his right ear. Postmortem magnetic resonance imaging (MRI) and necropsy evaluation revealed several masses, including a space-occupying lesion extending through the region of the round foramina, where cranial nerves III, IV, V, and VI are present, into the area of the cavernous sinus and into the thalamus. Overall, findings were consistent with multiple abscesses affecting intra- and extracranial areas. Although cavernous sinus syndrome in small animals are frequently associated with neoplastic processes, the condition in large animals may be related to infectious organisms and abscesses (Jacob et al., 2015).

Orbital Neoplasia

Lymphosarcoma in cattle affects the retrobulbar tissues and is the most frequent cause of exophthalmos with and without strabismus (Fig. 30.7) (Rebhun, 1979). The complete physical examination may reveal lymphadenopathy, cardiac arrhythmia, and melena, as well as uterine and renal masses. Cases of primary ocular lymphoma have been reported without retrobulbar extension (Ruggles et al., 1992). Bovine leukemia virus is the cause of lymphoma/lymphosarcoma in cattle (Miller, 1980). Serologic tests and polymerase chain reaction (PCR) are available to determine presence of bovine leukemia virus, but it is important to remember that animals remain seropositive throughout life. A positive test will not confirm the diagnosis of lymphoma, but a negative test for bovine leukemia virus rules out the possibility of lymphoma. The only definitive diagnostic for bovine lymphoma is a biopsy. Treatment is usually palliative, because most cattle with orbital lymphosarcoma die within 6 months. In those cases, exenteration may be performed to relieve the pain associated with exposure and subsequent keratitis/panophthalmitis (Rebhun, 1979).

Other reported retrobulbar orbital neoplasms include metastatic squamous cell carcinoma and adenocarcinoma (Guard et al., 1984). These tumors appeared to originate from the nasopharynx and extended into the nasal cavity. In both cases, Horner's syndrome was present. Although these tumors typically carry an extremely guarded prognosis (Rebhun, 1979), animals may still live for months to years (Guard et al., 1984).

A Holstein cow with a nonpainful swelling of the forehead and exophthalmos of the right eye was diagnosed with an extracranial meningioma after histopathologic examination of a biopsy specimen (Yamada et al., 2005). The animal was subsequently euthanized. A retrobulbar meningioma has also been reported in a Simmental cow (Reis et al., 2007).

Ocular lymphangiosarcoma has been reported in an 8-year-old Holstein cow (Ruggles et al., 1992). The light tan

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mass was attached to the perilimbal sclera, and both cytologic and histopathologic examinations confirmed lymphangiosarcoma. Orbital recurrence was not observed 2 years after exenteration.

A retrobulbar malignant histiocytoma was diagnosed in a one-year-old Holstein heifer (Yaygingul et al., 2017). The animal presented with exophthalmia, ventral strabismus and vision loss. Recurrence was not observed during the 6-month follow-up period.

Orbital Inflammation

Inflammatory orbital disease is common in cattle and involves orbital and periorbital tissue. Trauma, puncture wounds of the eyelids or conjunctiva, foreign-body migration from the mouth to the retrobulbar space, actinobacillosis, and panophthalmitis are potential causes. Associated systemic signs may include pyrexia, anorexia, temporomandibular pain, exophthalmos and associated sequelae, and leukocytosis. Treatment involves identifying the underlying cause, hot packing the area, drainage and lavage of any nidi of infection, possibly topical and systemic antibiotics, and if panophthalmitis is present, enucleation (Rebhun, 1979).

Exophthalmos and orbital inflammation may be sequelae to chronic frontal sinusitis in cattle. In one study of 12 cattle (Ward & Rebhun, 1992), the sinusitis in 67% of animals resulted from dehorning, whereas the sinusitis in 25% was associated with respiratory tract disease. In the former group, the most common organism isolated was *Actinomyces pyogenes*; in the latter, it was *Pasteurella multocida*. Clinical signs included anorexia, pyrexia, frontal bone distortion, exophthalmos, nasal discharge, and neurologic abnormalities. Treatment consisted of trephination, drainage, and lavage of the sinus cavity. Eight of the 12 cattle responded well to this treatment, whereas the other four animals with central nervous system (CNS) signs died or were euthanized.

Nystagmus

In cattle, nystagmus may be either congenital or acquired. A congenital rapid pendular nystagmus, which is usually horizontal, is observed in Holstein-Friesians especially and also in other breeds (McConnon et al., 1983). Vision does not seem to be significantly compromised, and the animals are affected for life. A possible genetic relationship may exist. Other causes include brain tumors and abscesses, intoxication by chemicals, plants, and heavy metals, cerebral anemia and vascular disease, and congenital or early postnatal blindness.

Other Orbital Diseases

Bilateral episcleral prolapse of orbital fat has been reported in a 10-month-old Santa Gertrudis bull (Gilger et al., 1992). The masses were located in the dorsomedial episcleral space, were slightly lobulated in appearance, and were freely movable under the bulbar conjunctiva. No treatment was performed. The inheritance pattern of this condition in cattle is not known.

Bilateral exophthalmos, epiphora, third-eyelid prolapse, and bulbar subconjunctival emphysema developed after tracheostomy in a 3-month-old Simmental bull calf (Fig. 30.8) (Grahn & Wolfer, 1995). Crepitation was detected during palpation of the eyelids and retropulsion of the globes. Treatment was symptomatic and the calf recovered completely. It was postulated that the orbital and subcutaneous emphysema were complications of the tracheostomy.

The Eyelids

Entropion and Eyelid Defects

Entropion is relatively rare in cattle, but it has been reported in the Simmental breed (Leipold et al., 1972; Thier & Bay, 1965). Spastic and cicatricial entropion are more common than congenital entropion. Surgical intervention in an affected Gelbvieh bull using a modified Hotz–Celsus procedure was successful after a second surgery (Brown et al., 1995). No offspring from this bull were affected.

Ectropion

Although ectropion may pose less danger to the eye, it can produce chronic exposure keratitis, conjunctivitis, keratoconjunctivitis, epiphora, and tear staining, as well as scalding of the eyelids. Ectropion may result from developmental, cicatricial, trauma, neurologic, and postoperative causes (Gelatt & Gelatt, 2011).

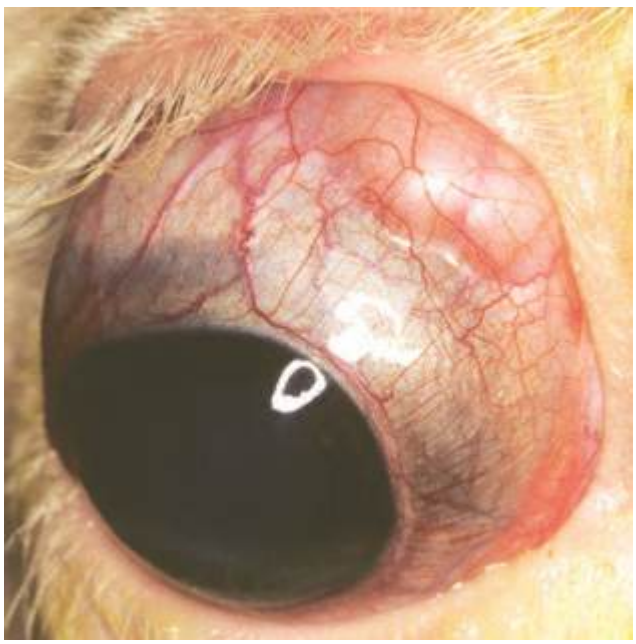


Figure 30.8 Left eye of a 3-month-old Simmental calf with orbital and subconjunctival emphysema. (*Source*: Courtesy of Bruce Grahn.)

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Eyelid Trauma

Lacerations are the most common traumatic injury to the eyelids, but they are infrequent among food animals (Fig. 30.9). The basic principles of eyelid repair apply when such lacerations occur.

Blepharitis

Bacterial

Dermatophilosis (i.e., rain scald) is caused by *Dermatophilus congolensis*, a Gram-positive, aerobic, filamentous bacterium. The infective stage is a motile, coccoid zoospore that is released from scabs by wetting. The zoospores then invade deeper layers of the dermis to incite an inflammatory response. The distal extremities, muzzle, and dorsum are usually involved initially, but it may spread over the entire face (Smith, 2009). Treatment consists of providing a dry environment and bathing with iodine or chlorhexidine shampoos. In severe cases, penicillin (20,000 IU/kg) with or without streptomycin (10 mg/kg) intramuscularly for 3–5 days or one intramuscular injection of long-acting oxytetracycline (20 mg/kg) may be necessary. A case series has described nine dairy cows with ulcerative blepharitis and conjunctivitis where *Moraxella bovoculi* (an agent more commonly associated with infectious bovine keratoconjunctivitis [IBK]) was isolated. Isolation of this organism came from a cow that also had concurrent corneal ulceration so a true etiologic relationship cannot be confirmed (Galvao & Angelos, 2010). Nonetheless, it is appropriate to consider culture and evaluation in cases of cattle with ulcerative blepharitis and concurrent ulcerative conjunctivitis and/or keratitis.

Mycotic

Trichophyton spp. can affect all food-producing animals (Radostits et al., 2007). Despite the self-limiting nature of dermatophytosis, treatment is recommended to limit any further infection of unaffected animals and humans (Kielstein, 1990). Topical and systemic fungicidal agents, iodine shampoos, improved nutrition, and dry environs all may assist in eliminating the disease. Vaccination of newly infected herds shows potential as a prophylactic measure (Radostits et al., 2007).



Figure 30.9 Extensive traumatic eyelid laceration in a cow.

Ectoparasites

Sarcoptic mange is caused by *Sarcoptes scabiei*, with a subspecies specific for each host species. This host specificity is not complete, however, and transference from one host species to another can occur (Radostits et al., 2007). The disease is characterized by intense pruritus, papules, and general erythema. The first clinical signs may include facial dermatitis, with thick, crusty, wrinkled, and denuded areas around the face and eyelids. The lesions may become widespread. The disease is uncommon in the United States. At the time of publication, it is not considered to be a reportable disease. However, sarcoptic mange in cattle has been cited as a reportable disease in the past; readers are referred to online documentation for current status of this disease. Treatment of all affected and contact animals is indicated. For many years, the most common way to treat infected animals was using dip vats, but the efficacy of new compounds that may be applied topically as sprays, drenches, and pour-ons has reduced the cost and time needed to treat this disease (Cortinas & Jones, 2006).

Demodex spp. are host specific (*Demodex bovis* affects cattle). The adult mites invade hair follicles and sebaceous glands of the face, limbs, and back, which then become distended with mites and inflammatory material. Secondary bacterial invasion of these lesions will result in formation of pustules and abscesses. Pustules may be seen around the eyes and pruritus may be present. The disease tends to be generalized in cattle (Radostits et al., 2007). Chronic granulomatous eosinophilic blepharitis has been reported in a cow (Gearhart et al., 1981). Acaricidal treatments may be used; however, self-resolution has been reported.

Photosensitization

Direct solar irritation (i.e., sunburn) may occur in food animals with little periocular pigmentation, but acute periocular dermatitis is more likely the result of photosensitization. If photosensitizing substances are present in sufficient concentration in the skin, dermatitis occurs when that skin is exposed to light. The causative photodynamic agents may be ingested preformed (i.e., primary photosensitization), be products of abnormal metabolism, or be normal metabolic products that accumulate in tissues because of faulty excretion through the liver (Radostits et al., 2007). Photodynamic agents include hypericin in *Hypericum perforatum* (St. John's wort), fagopyrin in *Polygonum fagopyrum* (buckwheat), and perloline from *Lolium perenne* (perennial ryegrass); miscellaneous agents include phenothiazine sulfoxide from phenothiazine, Rose Bengal, and acridine dyes (Kako et al., 1993; Radostits et al., 2007). In all cases of secondary photosensitization, phylloerythrin, which is a normal end-product of

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chlorophyll metabolism, is the photodynamic agent. When biliary secretion is obstructed by hepatitis or biliary duct obstruction, phylloerythrin accumulates in the body. The progressive clinical manifestation of both primary and secondary photosensitization consists of lacrimation, photophobia, erythema, cutaneous edema, fissuring of the epithelium, exudation and crusting of serum and necrosis, and sloughing of nonpigmented exposed skin (Casteel et al., 1986). Corneal edema is also evident in many cases (Casteel et al., 1991). Treatment involves removing the affected animal from sunlight, preventing ingestion of toxic material, and administering laxatives. In secondary photosensitization, treatment of the underlying disease is recommended, but death of the animal may still result (Radostits et al., 2007).

Neoplasia

Ocular squamous cell carcinoma (OSCC) is the most common tumor of the eye and eyelids in cattle. On the eyelid, lesions may initially appear as ulcerative areas (Fig. 30.10). Meibomian carcinoma of the eyelid has been reported in a Simmental cow in Turkey (Gokhan et al., 2010). Infection with bovine papillomavirus may cause neoplastic lesions to form on the periocular skin and eyelids. Manifestations include acanthosis (epidermal hyperplasia), papillomas (Fig. 30.11), and keratinized elongated proliferative lesions (Fig. 30.12) (keratoacanthoma, cutaneous horn). In most cases, the disease is self-limiting, and the lesions may resolve over time, but potential for malignant transformation into squamous cell carcinoma exists (Ford et al., 1982). Surgical excision has been shown to be successful if lesions are small and limited in number (Welker et al., 1991).

The Nasolacrimal System

The tear-producing glands in food animals rarely have any primary abnormality. Epiphora is the most common abnormality and is usually secondary to irritative ocular disease causing increased tear production rather than to defects in tear outflow.

Developmental Anomalies

Ectopic lacrimal gland tissue has been reported in the globes of cattle with variable infiltration into the surrounding structures. Adenomatous tissue may be found within the ectopic lacrimal gland as well (Hoffmann, 1979; van der Linde-Sipman & Klein, 1984).

Congenital anomalies of the nasolacrimal system are rare in food animals (Heider et al., 1975; Van der Woerdt et al., 1996; Wilkie & Rings, 1990). Focal intrauterine infections (i.e., resulting in dacryocystitis) have been suggested as a contributory cause (Duke-Elder, 1964). Dacryocystorhinography has been extremely useful in diagnosing anatomic defects in the nasolacrimal ducts (Van der Woerdt et al., 1996; Wilkie & Rings, 1990).



Figure 30.11 Papillomas of the left eyelid and periocular area in a steer. (*Source*: Courtesy of Cecil Moore.)



Figure 30.10 Erosive lesion on lower eyelid, presumptive of early OSCC change. Third eyelid papillomatous mass is also present.



Figure 30.12 Keratoacanthomas (keratinized elongated proliferative lesions) of the right eyelid of a cow. These are often associated with bovine papillomavirus infection. (*Source*: Courtesy of Cecil Moore.)

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Supranumerary openings of the nasolacrimal drainage apparatus occur in cattle (Fig. 30.13). In one report, 13 Brown Swiss calves and one Holstein-Friesian calf were affected (Heider et al., 1975). The gross appearance of affected calves was unremarkable. The openings on the face varied in distance from the medial canthus, but all the openings connected in the proximal third of the nasolacrimal duct. Some supranumerary openings were delineated by short hair around the anomalous orifices, but others were not clearly defined. Dacryocystorhinography performed on affected cattle revealed the nasolacrimal duct had dorsal and ventral branches proximally, with anomalous openings to the face from the dorsal branch (Heider et al., 1975).

A case of chronic unilateral epiphora was repaired successfully in a 1-year-old Holstein bull (Wilkie & Rings, 1990). Dacryocystorhinography revealed multiple, irregular filling defects, and distally, the nasolacrimal duct had multiple anomalous branches and emptied prematurely into the nasal passage. Surgical intervention included a conjunctivorhinostomy and marsupialization of an epithelial and hair-lined cystic lesion that communicated with the nasolacrimal duct.

Dysplastic lacrimal puncta were also treated surgically in a 6-week-old mixed-breed calf (Van der Woerdt et al., 1996). The puncta were in abnormal positions, only 2–3 mm from the medial canthus, and were small in diameter as well. Additionally, the caruncle appeared to inhibit tear movement to the puncta. The surgical procedures included a medial canthoplasty and widening of the puncta. There was no epiphora at follow-up 8 months later.



Figure 30.13 Supernumerary openings of the nasolacrimal duct and an associated dacryocystitis in a 4-year-old Holstein cow. (*Source*: Courtesy of Susan Jacobi.)

The Conjunctiva and Cornea

The conjunctiva and cornea are major sites for ophthalmic diseases in food-producing animals, with profound economic effects. In cattle, IBK and OSCC are the predominant conditions affecting the conjunctiva and cornea.

Congenital Anomalies

Dermoid

Dermoids occur principally in cattle, but they can occur in other food animal species as well (Fig. 30.14) (Brightman et al., 1985). Of 229 ocular defects in cattle reported in one study, dermoids accounted for four (Barkyoumb & Leipold, 1984). The defect in Herefords is genetically transferred, with characteristics of autosomal recessive and polygenic inheritance (Barkyoumb & Leipold, 1984). In cattle, the site predilection of ocular dermoids is, in decreasing order, the limbus, third eyelid (Fig. 30.15), canthi, eyelid, and conjunctiva. There is one case report of a dermoid cyst arising from the bony part of the nasolacrimal duct in a Scottish Highland heifer, which was successfully removed (Steinmetz et al., 2009). Dermoids rarely appear bilaterally except in certain lines of Hereford cattle (Barkyoumb & Leipold, 1984; Croshaw, 1959). The clinical manifestation varies from an unsightly blemish to various degrees of visual impairment, keratoconjunctivitis with epiphora, blepharospasm, and corneal ulceration (Fig. 30.16). In some cases, other congenital defects may exist concurrently. One report of bilateral corneoconjunctival dermoids, nasal choristomas, and ectopic glandular tissue in an Angus × Hereford calf exists (Brudenall et al., 2008). Surgical removal is recommended if vision is impaired or the eye is painful (Brudenall et al., 2008).



Figure 30.14 Hereford calf with a large dermoid involving the cornea and limbus. (*Source*: Courtesy of Cecil Moore.)

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Figure 30.15 A large dermoid involving the nictitating membrane in a Hereford calf.



Figure 30.16 A large dermoid involving the cornea, bulbar conjunctiva, and bulbar aspect of the nictitating membrane in a 4-month-old Angus cross calf. (*Source*: Courtesy of Wendy Townsend.)

Birth Trauma

Subconjunctival hemorrhage subsequent to birth trauma has been documented in a Shorthorn calf (Vestre et al., 1978). Resorption of the blood usually occurs without complications (Fig. 30.17).

Congenital Porphyria and Protoporphyria

Inherited defects of porphyrin metabolism in cattle and swine are characterized by excessive deposition of porphyrin isomers in the tissues (Wass & Hoyt, 1965). Congenital porphyria is similar to Gunther's porphyria in humans and is inherited as an autosomal recessive trait (Jorgensen & With, 1963). The incidence is higher in females than in males, but the disease is rare. Even so, it has been recorded in Shorthorn, Holstein, Black and White Danish, Jamaica Red and Black cattle, and Ayrshires (Jorgensen, 1961). Congenital erythropoietic porphyria in cattle is caused by an inherited deficiency

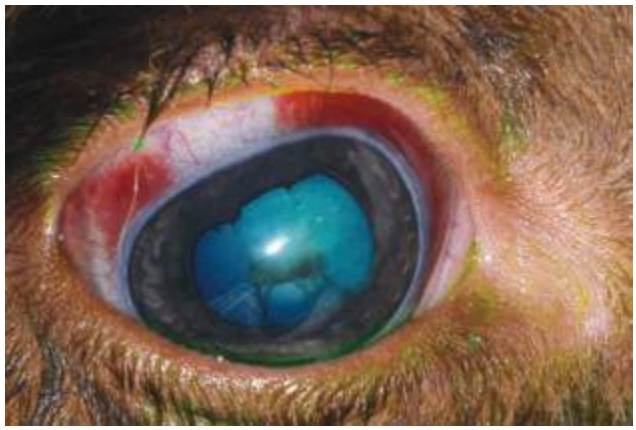


Figure 30.17 Subconjunctival hemorrhage in a calf. Persistent pupillary membrane (iris-to-lens) is also present.

of the enzyme uroporphyrinogen III synthase (Agerholm et al., 2011; Levin, 1968). Insufficient activity of this enzyme leads to the formation of the metabolites uroporphyrinogen I and coproporphyrinogen I. These porphyrinogens are oxidized to their end products uroporphyrin I and coproporphyrin I, which accumulate in the body. These high levels of porphyrins sensitize the skin and eyes to light (Jorgensen & With, 1963).

Protoporphyria is a less common, milder disease than porphyria and is thought to be inherited in cattle. In this disease, there is deficient activity of the enzyme ferrochalase, resulting in excessive synthesis of protoporphyrin (Radostits et al., 2007). Ocular clinical signs related to abnormal porphyrin metabolism result from photosensitization. These signs include photophobia, edema, inflammation, and necrosis of the eyelids and the periocular skin. Treatment consists of maintaining affected animals indoors. Genetic selection against lines of cattle with these inherited defects is recommended.

Inherited Corneal Disease

Most cases of corneal edema seen in food animals are secondary either to intraocular disease that affects endothelial cell function or extraocular disease that causes a defect in the overlying corneal epithelium. Primary endothelial disease is extremely rare in food animals, but an autosomal recessive corneal disease of Holsteins and other cattle has been reported (Deas, 1959). Affected animals show bilateral corneal edema either at or soon after birth. The condition is not amenable to treatment and affected animals should not be used for breeding.

Phenothiazine-Induced Corneal Disease

Phenothiazine is used as a prophylactic in the control of manure-breeding insects and as an anthelmintic in livestock (Radostits et al., 2007). Corneal edema and keratitis have been associated with phenothiazine toxicity, but this is a

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condition seen mainly in calves and, to a lesser extent, in pigs and goats (Bistner et al., 1981; Enzie & Whitmore, 1953; Vestre, 1984). Most ophthalmic cases result from a high dose of phenothiazine, but low daily doses may produce ophthalmic disease as well (Radostits et al., 2007).

The metabolism of orally administered phenothiazine varies by species. In calves and sheep, phenothiazine is absorbed from the rumen as the sulfoxide and conjugated in the liver to form leucophenothiazine ethereal sulphate, which is then excreted into the urine and the bile. Cattle are unable to detoxify all the phenothiazine sulfoxide, however, and a proportion enters the systemic circulation and aqueous humor of the eye, thereby causing photosensitization (Whitten et al., 1946).

Beginning with lacrimation, clinical signs of phenothiazine toxicity may occur unilaterally or bilaterally within 12–36 hours after treatment (Bistner et al., 1981). This is followed by edema in the parts of the cornea exposed to light (Bistner et al., 1981; Radostits et al., 2007). Photophobia, blepharospasm, and keratitis may subsequently occur, and eyelid edema has also been reported.

Treatment for the condition is symptomatic but affected animals may show no clinical signs or may even recover spontaneously if access to sunlight is restricted, especially for 12–36 hours after treatment (Whitten et al., 1946). Affected animals may recover within 5–7 days, but recovery may also be prolonged (60–90 days) (Bistner et al., 1981).

Parasitic Keratoconjunctivitis

Thelazia Species

The pathogenic significance of *Thelazia* spp. is not known, but some thelazial conjunctivitis may be mistakenly attributed to bacterial infection (Prange et al., 1968). In North America and Europe, *Thelazia* spp. are regarded as being nonpathogenic to mildly pathogenic (Arbuckle, 1977; Kennedy, 1993; Patton & Marbury, 1978). In contrast, more severe disease, and even blindness, has been reported in other countries (Patton & Marbury, 1978; Vohradsky, 1970). The variability in pathogenicity may result from host, parasite, livestock management, and climatic factors (Geden & Stoffolano, 1980).

Thelazia spp. nematodes are small, slender, white worms. The males are 7–13 mm in length and the females are 12–18 mm (Kennedy et al., 1990). They occur in the conjunctival sac and nasolacrimal ducts, and they move rapidly in the preocular tear film. *Thelazia rhodesi*, *Thelazia gulosa*, *Thelazia skrjabini*, and *Thelazia lacrymalis* affect cattle (Kennedy & Moraiko, 1987; Kennedy et al., 1990; Overend, 1983). Mixed infections of two or more genera of parasites have also been reported (Kennedy, 1993). The prevalence of the parasite may be in excess of 20%, and seasonal variations occur. The worms are more abundant in beef than in dairy breeds (Kennedy & MacKinnon, 1994). A study in 2005 showed marked reduction in the prevalence of *Thelazia* spp. recovered from the eyes of cattle in England compared with a similar population evaluated in 1978. The prevalence of *Thelazia* spp. was 41% in 1978 and 1.5% in 2005 (Tweedle et al., 2005). A possible factor explaining the reduced incidence is the widespread use of endectocides in the cattle industry since the late 1970s.

Unilateral chronic follicular or mucoid conjunctivitis is most common, with irregularities in the lining of the nictitans gland ducts (Patton & Marbury, 1978). Other clinical signs include profuse epiphora, photophobia, and ulcerative keratitis (Radostits et al., 2007). A subconjunctival cyst has been reported in a Simmental calf caused by *T. gulosa* (Miller & Campbell, 1992). Face flies, especially *Musca autumnalis*, act as biologic vectors (Moolenbeek et al., 1980) and transfer the larvae to the eyes while feeding. Hence, cases are more prevalent in the summer and fall months. The prevalence is lower among cattle grazing short and mid-size grass pastures than among those grazing transitional or aspen parkland pastures, rough fescue, or woodland-type pastures (Kennedy, 1993).

The diagnosis is usually made postmortem by identification of the parasite in the conjunctival sac or nasolacrimal duct. Antemortem diagnosis can be made by careful gross examination of the whole lacrimal apparatus or by demonstration of fully embryonated eggs, larvae, or immature worms using specialized techniques. Often, the clinical diagnosis is made when the eye is being manipulated for unrelated diagnostic or surgical procedures (Miller & Campbell, 1992). Treatment modalities include simple lavage, mechanical removal after topical anesthesia, administration of levamisole (5 mg/kg orally or 1% solution topically) or fenbendazole, and topical administration of ivermectin or echothiophate iodide (Kennedy, 1992, 1994). Subcutaneous ivermectin (0.2 mg/kg) has been reported to be 100% effective against *T. skrjabini* and more than 99% effective against *T. rhodesii* (Kennedy, 1992; Soll et al., 1992). A pour-on preparation of ivermectin (0.5 mg/kg) reduces the burden of *T. gulosa* by 100% and decreases the burden of *T. skrjabini* by 97%. Doramectin given subcutaneously was found to be 100% effective against *Thelazia* spp. in both experimental and naturally infected animals (Kennedy & Phillips, 1993). The incidence of disease can be reduced by adequate fly control.

Cystic nodules on the bulbar conjunctiva have also been observed in bovine affected by besnoitiosis, in Ireland, a protozoal disease caused by *Besnoitia besnoiti*. The parasite can be found in cystic lesions in mucosal tissues and skin. A histopathological examination of the conjunctival cysts of cows affected by besnoitiosis contained pockets of the bradyzoite stage of the parasite (Grimes et al., 2016).

Infectious Keratoconjunctivitides

Infectious keratoconjunctivitis in food animals represents an important group of diseases, not only from an economic standpoint but also for the well-being of affected animals.

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Keratomycosis

Fungal infection of the bovine cornea is quite uncommon. A confirmed case of *Aspergillus* and *Fusarium* keratitis was reported in a 5-year-old Holstein cow. Clinical signs included ocular discharge, periorbital swelling, an area of full-thickness corneal cellular infiltrate, fibrin, hypopyon, diffuse corneal edema, and miosis. The patient was diagnosed with a corneal stromal abscess and secondary anterior uveitis. Histopathology, mycotic culture, and PCR confirmed the presence of fungal infection with *Aspergillus* and *Fusarium* spp. Response to standard topical therapy was good; follow-up with the patient 1 year after diagnosis revealed a focal area of corneal fibrosis with maintenance of vision (Elligott et al., 2006).

Infectious Bovine Rhinotracheitis

Infectious bovine rhinotracheitis (IBR) may cause nonulcerative keratoconjunctivitis. Conjunctivitis is the most common manifestation of IBR and is characterized by raised, white plaques on the bulbar and palpebral conjunctival surfaces (Fig. 30.18). Chemosis is also often present. Variable degrees of nonulcerative keratitis can also develop with peripheral edema and vascularization initially. In severe cases, the corneal edema and cellular infiltrate can be quite extensive, resulting in blindness (Fig. 30.19) (Rebhun et al., 1978). Please see Chapter 37, Part 4 for additional information.

Listerial Keratoconjunctivitis

The etiologic agent is the rod-shaped, Gram-positive bacteria *Listeria monocytogenes*. This condition is also known as silage eye, because the etiologic agent is usually found in fermented hay silage. Ocular lesions are frequently observed in the meningoencephalitic form of the disease (also called listeriosis of the CNS). Neurologic signs include vestibular ataxia and unilateral cranial deficits, with reports of facial nerve paralysis and keratoconjunctivitis sicca (Oevermann et al., 2010). Lesions may be located unilaterally or bilaterally, but unilateral presentation is most common. Ocular surface signs include conjunctivitis with excessive lacrimation, and photophobia. Keratitis is manifested by punctate abscesses, peripheral clouding (corneal edema), ulceration and corneal vascularization (Fig. 30.20). Uveitis is also a classic manifestation of this condition with the presence of infiltrative uveal disease, hypopyon, and miosis (Erdogan, 2010). Further discussion of this condition can be found in Chapter 37, Part 4.

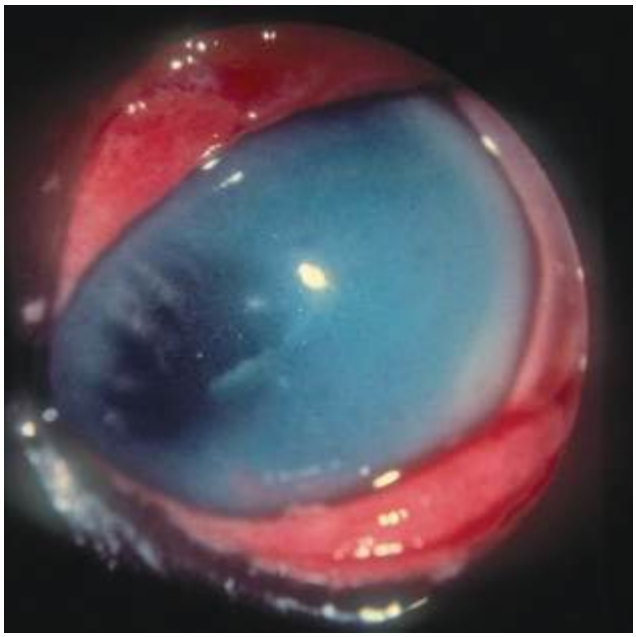


Figure 30.19 Extensive corneal edema and conjunctivitis in a cow associated with infectious bovine rhinotracheitis virus. (*Source*: Courtesy of Cecil Moore.)

Chlamydial Keratoconjunctivitis

Chlamydiae have been isolated from cattle with conjunctivitis (Storz, 1988). Two case reports describe incidents of recurrent bilateral keratoconjunctivitis in three different cat-

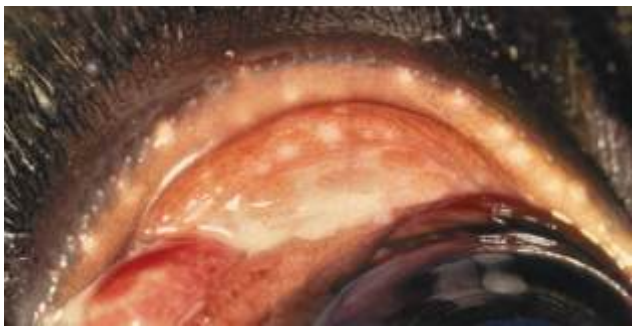


Figure 30.18 Conjunctivitis, chemosis and white, lymphocytic, conjunctival plaques associated with infectious bovine rhinotracheitis virus infection in a cow. (*Source*: Courtesy of Cecil Moore.)



Figure 30.20 Corneal ulceration, vascularization, cellular infiltrate, and uveitis in a cow with systemic listeriosis. (*Source*: Courtesy of David Williams.)

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tle herds (Otter et al., 2003; Twomey et al., 2003). The cases were quite persistent and responded poorly to antibiotic treatment. *Chlamydophila* spp. DNA was detected in conjunctival swabs by PCR. No other pathogens were detected. Two herdsman also developed concurrent eye disease, suggesting a possible zoonotic risk. A similar association has been recognized between the development of human conjunctivitis and contact with *Chlamydophila felis*-infected cats (Twomey et al., 2003).

Malignant Catarrhal Fever

Malignant catarrhal fever is a frequently fatal infectious disease that affects cattle, bison, buffalo, deer and other ruminants. It is caused by several rhabdoviruses belonging to the gamma herpes family. In cattle, it is often transmitted by ovine herpesvirus-2. Cattle usually do not spread the virus by contact transmission and are considered dead-end hosts. The "head and eye" form is considered the classical form of the disease, and is accompanied by high fever, inappetence, depression, lesions of the oral cavity and muzzle, profuse mucopurulent nasal discharge, dyspnea, stertor, and diarrhea. The most common ocular sign is corneal edema, which can vary from mild perilimbal to dense complete corneal edema. Other ocular symptoms include exophthalmos, blindness, nystagmus, photophobia, lacrimation and mucopurulent ocular discharge, eyelid edema, and other symptoms of conjunctivitis, keratitis and anterior uveitis. The degree of corneal edema on first examination does not correlate with prognosis. However, cases that exhibit improvement of the corneal edema may have a better prognosis. Deterioration of uveitis is associated with a poor prognosis; however, improvement of uveitis is not associated with a better prognosis (Zemljic et al., 2012).

Other Systemic Infections

Other systemic infections may cause nonulcerative keratoconjunctivitis. Please see Chapter 37, Part 4 for additional information.

Infectious Bovine Keratoconjunctivitis

History

IBK, also known as pink eye, contagious ophthalmia, and New Forest disease, has received considerable attention because of its worldwide distribution and economic impact. The first report of presumed IBK appeared in 1888 (Billings, 1889). Cattle with keratitis were shown to have bacilli on histopathologic sections of the cornea, yet at that time, experimental transmission of the disease was unsuccessful. In 1897, the term "contagious ophthalmia" was used subsequent to the successful transmission of keratitis from two affected to two noninfected cattle via conjunctival inoculation (Penberthy, 1897). In 1936, the primary pathologic nature of the causative organism was proposed, and in 1952, Barner concluded that the keratitis was caused by *Moraxella bovis* (Barner, 1952; Magens, 1936).

Economic Impact

Both regional and national surveys have documented the profound economic impact of IBK (Killinger et al., 1977; Simms et al., 1993; Slatter et al., 1982a). Financial losses resulting from decreased weight gain, decreased milk production, and treatment costs were estimated to be $150 million in the United States in 1993 (Simms et al., 1993). The decreases in weight gain can range from 8 to 18 kg (Snowder et al., 2005; Troutt, 1985). Less tangible economic losses can also occur, such as a loss of value in show or breeding stock, weight loss and injury from handling animals for treatment, condemnation at slaughter because of ocular lesion detection, and lost productivity during time devoted to treatment. In affected unweaned calves, it was thought that losses associated with IBK were temporary and would recover after weaning and resolution of the condition. However, a study showed that yearlings that had evidence of IBK at weaning had less body weight than cohorts without evidence of IBK, and associations between IBK at weaning and production variables persisted well into the postweaning period (Funk et al., 2014).

Incidence

IBK occurs worldwide. In a 1997 report of the US National Animal Health Monitoring System, IBK (1.1% infection rate) was the second-most prevalent condition affecting unweaned beef calves over 3 weeks of age (USDA, 1997). In the same report, IBK (1.3% infection rate) was the most prevalent condition affecting all beef heifers and cows. In studies at the University of California–Davis field station in Browns Valley, the yearly prevalence of IBK in yearling calves ranges from 57% to 98% (Allen et al., 1995; Eastman et al., 1998; George et al., 1988).

IBK occurs primarily during the summer months, though winter outbreaks occur (Hughes & Pugh, 1970; Pugh & Hughes, 1972; Webber & Selby, 1981). This seasonal fluctuation may result from the increased presence of hemolytic *M. bovis*, the fly population, and solar radiation during the summer months (Pugh & Hughes, 1975). The decline through the fall season may result from the lack of susceptible calves, fewer vectors, and decreased intensity of enhancing factors.

Etiology

Although *M. bovis*, a Gram-negative bacillus (Fig. 30.21), is considered to be the primary cause of IBK, other microbial agents have also been implicated (Angelos, 2010; Gourlay et al., 1974; Hughes et al., 1964; Pugh & Hughes, 1971, 1972; Pugh et al., 1976; Webber & Selby, 1981). However, *M. bovis* is the only organism for which Koch's postulates have been satisfied (Angelos et al., 2011). Keratitis in gnotobiotic calves may be induced by inoculation of *M. bovis* into the conjunctival cul-de-sac (Rogers et al., 1987). Other infective agents that may play a role in development of IBK include *Moraxella ovis* (formerly *Neisseria/Branhamella ovis*), *Moraxella*

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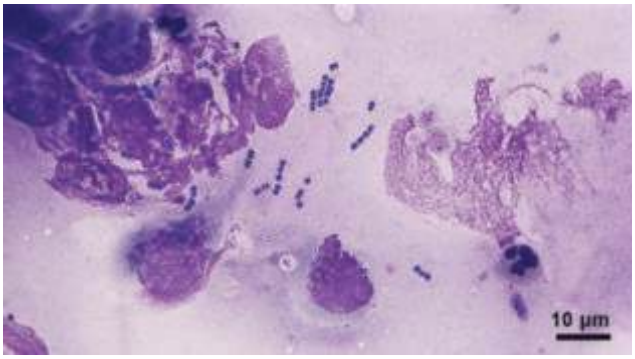


Figure 30.21 Wright–Giemsa stained photomicrograph of corneal cytology from a cow with infectious bovine keratoconjunctivitis demonstrating multiple short, plump, bacilli consistent with *Moraxella bovis*. (*Source*: Courtesy of Gia Klauss.)

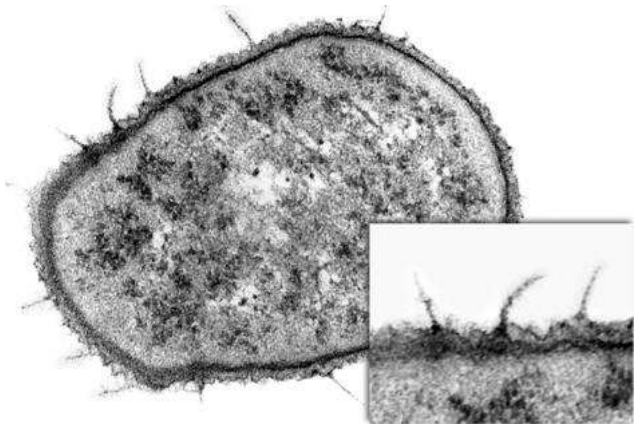


Figure 30.22 Cross-section of a *Moraxella bovis* bacterium harvested from rough colony showing peritrichous distribution of pilion the cell surface. Insert is a higher magnification of these pili. (*Source*: Courtesy of the late Charles F. Simpson.)

bovoculi, IBR virus, *Mycoplasma* spp., *Thelazia* spp., and *Listeria monocytogenes* (Angelos, 2010; Pugh & Hughes, 1971; Rosenbusch, 1983; Rosenbusch & Ostle, 1986). Concurrent infection with IBR causes more severe clinical signs than with IBK alone (Pugh & Hughes, 1971). Herds vaccinated with modified live IBR virus have an increased incidence of IBK (Webber & Selby, 1981), more severe clinical signs (Pugh & Hughes, 1971), and increased numbers of *M. bovis* isolates in the tear film (Pugh et al., 1984). *Mycoplasma* spp. have also been supposed to play an ancillary role in IBK (Pugh et al., 1976). In a study evaluating potential etiologic agents, IBK-affected eyes of dairy and beef calves were cultured and, in most calves, hemolytic Gram-negative cocci (but not *M. bovis*) were isolated (Angelos et al., 2007c). Biochemical and molecular data indicated that these isolates were distinct from *M. ovis* and *M. bovis* and warranted their classification as a novel species called *Moraxella bovoculi* (Angelos et al., 2007c). The new bacteria, *M. bovoculi*, can be differentiated from *M. bovis* and *M. ovis* using PCR and via a positive phenylalanine deaminase test, which is positive in *M. bovoculi* and negative in both *M. bovis* and *M. ovis*. Phenylalanine deaminase-negative *M. bovoculi* has been identified but can be differentiated from *M. ovis* and *M. bovis* using previously cited PCR methods (Angelos, 2010; Angelos et al., 2007a). A novel in-house multiplex real-time PCR assay has been developed for the detection and differentiation of *M. bovis*, *M. bovoculi*, and *M. ovis* directly from lacrimal swabs. The concordance between this real-time PCR from lacrimal swabs and conventional culture was 86.7% for *M. bovoculi* and 75.6% for *M. bovis* (Shen et al., 2011). In the period since *M. bovoculi* was identified and characterized, it has become clear that the vast majority of *M. ovis* recovered from bovine eyes would now be reclassified as *M. bovoculi*. However, the causal role of *M. bovoculi* and *M. ovis* in naturally occurring IBK is unclear. A study showed that *M. bovoculi* and *M. bovis* are both more frequently recovered from eyes with IBK lesions than unaffected eyes, which provides weak evidence for a causal role for *M. bovoculi* in IBK (O'Connor et al., 2011b). Another recent study evaluated the role of *M. bovis* and *M. bovoculi* on the etiology of IBK using a corneal scarification model in calves. Both organisms were topically inoculated after iatrogenic corneal scarification. Although 90% of the animals exhibited clinical signs consistent with IBK after *M. bovis* inoculation, none of the calves that received *M. bovoculi* developed clinical signs. The absence of symptomatology in *M. bovoculi* inoculated calves suggests it is not a causal organism for IBK in this specific model (Gould et al., 2013).

***Morphology of** Moraxella bovis*

The morphology of *M. bovis* colonies is either rough or smooth. Clinical cases of IBK are associated with the rough type, which have cell-surface pili, autoagglutinate in distilled water, stain with crystal violet, and hemagglutinate (Brown et al., 1998; Sandhu et al., 1974; Simpson et al., 1976). *M. bovis* colonies are easy to identify, do not require complex growth media, and may be identified by characteristic growth patterns (McMichael, 1992; Pugh et al., 1966; Riley, 1984). However, a semiselective media of brain–heart infusion agar with 5% bovine or ovine red blood cells and 2.5 µg/mL of cloxacillin will reduce overgrowth by other organisms and increase the yield of *M. bovis* isolates (Webber et al., 1982b). The beta-hemolytic variants are usually associated with clinical disease (Brown et al., 1998).

Electron microscopy has revealed that bacteria from rough colonies of *M. bovis* are piliated and able to cause disease, whereas those from smooth colonies are nonpiliated and nonpathogenic (Fig. 30.22 and Fig. 30.23) (Sandhu et al., 1974; Simpson et al., 1976). Spontaneous transformation of rough to smooth colony type also occurs (Sandhu et al., 1974). Therefore, different strains of *M. bovis*, as well as different isolates of the same strain, may vary in virulence

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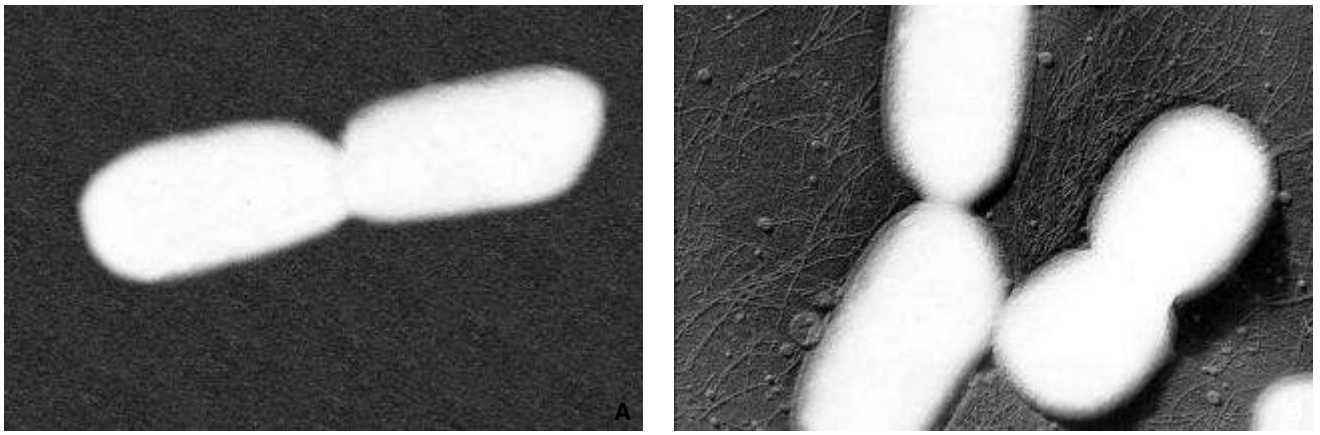


Figure 30.23 Cells from smooth (**A**) and rough (**B**) colonies of *Moraxella bovis*. Only the rough form of *M. bovis* shows the peritrichous distribution of pili, many of which have been fractured from the cell. (Chromium shadowed; original magnification, ×20,000.) (*Source*: Courtesy of the late Charles F. Simpson.)

(Lepper & Power, 1988; Pugh & Hughes, 1971). The capsular pili promote cellular adhesion and enhance the ability to overcome host defenses and maintain an established infection (Jayappa & Lehr, 1986; Lepper et al., 1992; Ruehl et al., 1993). As a general rule, the piliated, hemolytic form is found in acute cases of IBK (Jayappa & Lehr, 1986; Ostle & Rosenbusch, 1984), and proportionately more nonpiliated and nonhemolytic isolates are recovered from convalescent and clinically normal carrier cattle (Hughes et al., 1976; Wilcox, 1970). Pilus biotyping is possible through immunofluorescence and immunogold electron microscopy (Vandergaast & Rosenbusch, 1989). The pili are classified into seven groups, and isolates show little antigenic variation (Moore & Lepper, 1991). The emergence of a new pilus type may be associated with outbreaks of IBK (Vandergaast & Rosenbusch, 1989).

Transmission

The source of infection is usually a new animal or a carrier animal within the herd. *M. bovis* can typically be found on the conjunctivae and in the nasal secretions of cattle without any signs or history of infection (Pugh & McDonald, 1986). Nonhemolytic *M. bovis* may reside in a herd over the winter months and not cause clinical signs. However, with the onset of spring and increased ultraviolet (UV) radiation, there can be a reversion to the pathogenic, hemolytic form, with subsequent infection of susceptible calves (Bryan et al., 1973; Hughes & Pugh, 1970). The possibility that reservoirs of *M. bovis* exist in animals other than cattle (e.g., wild animals) has not been investigated (Pugh & Hughes, 1975).

M. bovis is transmitted by animal handlers, direct contact with infected animals, contact with fomites, and mechanical vectors, such as flies (Kopecky et al., 1986; Pugh & Hughes, 1972, Pugh et al., 1976). The face fly (*Musca autumnalis*) is considered to be the most important vector (Gerhardt et al., 1982; Steve & Lilly, 1965). However, the house fly (*Musca domestica*) and stable fly (*Stomoxys calcitrans*) have also been incriminated as mechanical vectors (Gerhardt et al., 1982). These flies may harbor the organism on their legs for as long as 3 days. Without flies, transmission of IBK throughout a herd may be slow. Spread of the disease over long distances is probably associated with the movement of carrier cattle (Alexander, 2010).

Predisposing Factors

The sex of an animal is not a significant factor in development of the disease (Powe et al., 1992). All breeds may be affected, but breed-related differences in susceptibility occur. *Bos indicus* breeds are more resistant than *Bos taurus* breeds, and Herefords as well as Hereford crossbreeds appear to have a much higher susceptibility, as do Murray Greys (Slatter et al., 1982b; Snowder et al., 2005). Because of the predilection for IBK in Herefords, the role of periocular pigmentation has been investigated. Some investigators have concluded that increased pigmentation has a protective effect, but others have not found a significant difference (Caspari et al., 1980; Clegg et al., 1982). One investigator noted that scleral color appeared to have a greater bearing on the incidence of infection than did periocular hair color (darker sclera appeared protective) (Wettemann et al., 2002). Other genetic variables may also be a factor, because significant familial differences in susceptibility have been reported in Herefords (Pugh et al., 1986a). A specific single nucleotide polymorphism (A/G in -26 Ex2 position of Intron 1 of Toll-like receptor 4) was found to be associated with significantly increased infection rates in animals in-season and at weaning (Kataria et al., 2011). This study and others suggest a possible relationship between the genotypes with specific polymorphisms and possibly other polymorphisms in other candidate genes that are yet to be identified may play a role in the rate of IBK infection in American Angus cattle (Kizilkaya et al., 2011).

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The age of cattle affects the persistence and severity of infection with *M. bovis*. Younger cattle, less than 2 years old, consistently have an increased risk and severity of clinical disease compared with older cattle, even though large numbers of older animals are infected (Brown et al., 1998). Developmental immunity is also suggested by observations that infected calves develop disease, whereas their infected dams fail to develop clinical signs (Hughes et al., 1976).

The mechanism of increased resistance among older cattle is unknown. Previous contact with *M. bovis* and subsequent development of antibodies may be responsible (Hughes & Pugh, 1970; Pugh & Hughes, 1976; Wilcox, 1970). Studies have shown that calves with increased antibody titers to *M. bovis* have significantly lower rates of infection and disease. However, increased serum antibody levels do not necessarily protect cattle from reinfection with *M. bovis (*Hughes et al., 1976). This apparent contradiction may be explained by the presence of varying strains of *M. bovis* (Pugh et al., 1978). Cattle usually possess greater resistance to reinfection by homologous rather than heterologous strains (George, 1984).

On the basis of long-term field studies, a good correlation exists between the annual peak incidence of IBK and annual peak levels of UV radiation. Nuclear fragmentation and loosening of bovine corneal epithelial cells occur with increased UV radiation, thereby increasing sites for bacterial adherence. UV radiation also causes degeneration of corneal epithelium (Vogelweid et al., 1986) and enhances *M. bovis*-induced keratitis in mice (Gerber & Frank, 1983). Increased UV radiation also assists in the transformation of *M. bovis* from nonhemolytic to hemolytic strains (Arora et al., 1976a). However, in one study of calves naturally infected with a nonhemolytic, nonpiliated strain of *M. bovis*, exposure to UV radiation and topically applied betamethasone failed to induce clinical signs of IBK. Ocular contact with ragweed pollen, both alone and in addition to UV light, enhances keratitis (Gerber & Frank, 1983).

The number of face flies present correlates well with the infection rate and the number of new isolates (Gerhardt et al., 1982). Once the number of flies exceeds 10 per animal, IBK spreads from one herd to another. Cattle housed indoors have a higher infection rate of longer duration, but milder clinical disease compared with those housed outdoors (Kopecky et al., 1981). Other environmental factors, such as mechanical irritants to the conjunctiva and cornea and ingestion of aflatoxin, have also been suggested as enhancing factors (Pugh et al., 1984).

Pathogenesis

In clinical outbreaks of IBK, *M. bovis* can be isolated from most affected cattle (Bryan et al., 1973; Gil-Turnes & Albuquerque, 1984). The initial corneal lesions probably result from bacterial cytotoxicity, whereas advanced lesions may be associated with bacterial/host inflammatory interaction. Although *M. bovis* does not produce collagenase, the pathophysiology of IBK is likely associated with collagenase release from damaged epithelial cells, fibroblasts, and neutrophils (Frank & Gerber, 1981). In addition, gelatinase and DNAase have been detected in whole cultures, whereas dermonecrotoxins and cytotoxins for BHK 21 cell line monolayers (Franco & Turnes, 1994) and soluble factors that cause reversible detachment of cultured corneal epithelial cells have been detected in *M. bovis* culture filtrates (Marrion & Riley, 2000).

Numerous neutrophils surround the corneal lesions and may contain phagocytosed organisms (Chandler et al., 1981). *M. bovis* has a marked cytotoxicity for bovine neutrophils and corneal epithelial cells (Kagonyera et al., 1989). A leukocidin has been identified that can damage neutrophils in a dose-dependent manner (Hoien-Dalen et al., 1990). Both hemolytic and cytotoxic activities are important in the pathogenesis of IBK and may be linked to a specific toxic protein of 110 kDa (Gray et al., 1995). Cytotoxic factors are calcium dependent and found only in whole cells and filtrates of hemolytic strains (Kagonyera et al., 1989). A positive correlation exists between the percentage of hemolytic strains isolated and the incidence of clinical disease (Brown et al., 1998). A hemolytic fraction of *M. bovis* is cytotoxic to calf corneal epithelial cells (Beard & Moore, 1994). Lipopolysaccharide of both rough and smooth *M. bovis* colonies induces production of tumor necrosis factor, which also may be important in the pathogenesis of IBK (Johansen et al., 1990).

Some studies have characterized the *M. bovis*–host relationship by using tear film analysis. Bovine lacrimal secretions contain secretory immunoglobulin (Ig) A, IgGa, IgGb, and IgM (Arora et al., 1976b). Bovine tears do not contain lysozyme, which may reduce their ability to control infection (Brightman et al., 1991; Gionfriddo et al., 2000). Lactoferrin, however, has been identified in bovine tears (Brown et al., 1996). In the absence of lysozyme, lactoferrin and secretory IgA are important to the defense of the host. Lactoferrin exerts a bacteriostatic effect by chelating iron, an essential growth element. Lactoferrin may also be a potential source of iron for pathogenic bacteria (Brown et al., 1998). *M. bovis* possesses receptors and siderophores (iron acquisition systems) that can compete with host lactoferrin for iron (Fenwick et al., 1996). It is currently unknown whether iron acquisition by *M. bovis* from lactoferrin in bovine tears enhances infection, but if so, immunologic recognition of iron-acquisition systems may provide an effective means of preventing IBK (Brown et al., 1998). Phospholipase B enzyme production is another potential virulence factor of *M. bovis* (Farn et al., 2001).

Pathogenic factors of *M. bovis* include pilin and cytotoxin (hemolysin, cytolysin) (Postma et al., 2008). Pilin facilitates attachment to the corneal surface. Cytotoxin lyses bovine neutrophils, erythrocytes, lymphocytes, and corneal epithelial cells (Angelos & Ball, 2007b). The cytotoxin is known to

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be an RTX (repeats in the structural ToXin) toxin (Angelos et al., 2001). The *M. bovis* cytotoxin is maintained within an operon composed of four genes (mbxCABD) that encode proteins for cytotoxin activation (*mbxC* gene product), cytotoxin (mbxA gene product), and secretion (*mbxB* and *mbxD* gene products). A closely linked gene involved in secretion (*tolC*) flanks the *mbxD* gene. When *M. bovoculi* was examined for the presence of similar RTX genes, a complete RTX operon (designated the mbvCABD operon) was identified. A high degree of nucleotide and deduced amino acid sequence similarity exists between the *M. bovoculi* and *M. bovis* RTX operon genes. These results suggest a possible role for *M. bovoculi* in the pathogenesis of IBK (Angelos et al., 2007a). The *M. bovis* cytotoxin (mbxA) appears to be conserved among geographically diverse isolates of *M. bovis* from the United States and appears to be a candidate target for vaccine (Angelos & Ball, 2007b).

Clinical Signs

The earliest clinical signs are varying degrees of epiphora, blepharospasm, and photophobia; conjunctival hyperemia and chemosis also occur. Often, this stage may be missed clinically because of an inability to observe affected animals carefully. Within 24–48 hours after the onset of clinical signs, the axial cornea may develop small epithelial defects. Small corneal vesicles may precede ulceration. A small, pale, yellow to white raised abscess may appear near the center of the cornea, and over the following 24–48 hours, the corneal opacity may increase in size or slough, leaving a shallow, round to oval, superficial ulcer with perilesional edema (Fig. 30.24 and Fig. 30.25). During the next few days, the corneal ulcer may expand and deepen (Fig. 30.26).

There is marked perilimbal conjunctival vascular hyperemia and initiation of superficial corneal vascularization. Blepharospasm, mild to moderate aqueous flare, and iridocyclitis are present. The conjunctival exudate becomes mucopurulent, with matting of the eyelashes. Vascularization of the cornea proceeds rapidly toward the primary central lesion. By 7–9 days postinfection, an area of inflammation and corneal vascularization surrounds the well-delineated corneal ulcer (Fig. 20.27). As the vascularization reaches the ulceration, the corneal opacity clears from the periphery toward the center. The ulcer epithelializes, and the facet gradually reduces by stromal regeneration, leaving a slightly raised, dense scar (Fig. 30.28). Corneal healing is well-advanced in 2–3 weeks and in 1–2 months only a faint localized central corneal opacity may remain.

The keratoconjunctivitis may result in secondary iridocyclitis, with hypopyon, synechiae, and even panophthalmitis. Occasionally, perforation of the corneal ulcer results in iris prolapse (Fig. 30.29), in which case blindness may result. The eye may also become hypotensive and phthisical or buphthalmic from secondary glaucoma (Fig. 30.30).



Figure 30.24 Early, faint fluorescein retention by a central cornea affected with infectious bovine keratoconjunctivitis. (*Source*: Courtesy of Kirk N. Gelatt.)

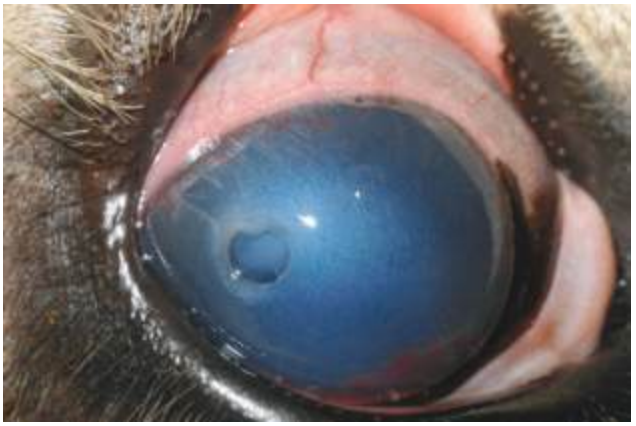


Figure 30.25 Mid-stromal corneal ulcer surrounded by corneal edema and early limbal corneal vascularization associated with infectious bovine keratoconjunctivitis. (*Source*: Courtesy of Jacqueline Pearce.)

In 75% of cases, ocular involvement is unilateral (Slatter et al., 1982a) but bilateral involvement may also occur. Affected animals are reluctant to compete for food, milk production is reduced, and weight gain is suppressed, usually in direct relation to the severity of the lesion. In young cattle, the disease process is usually more severe than in older animals.

Medical Treatment

A review of randomized clinical trials reporting antibiotic treatment of IBK in cattle was performed. The objective of

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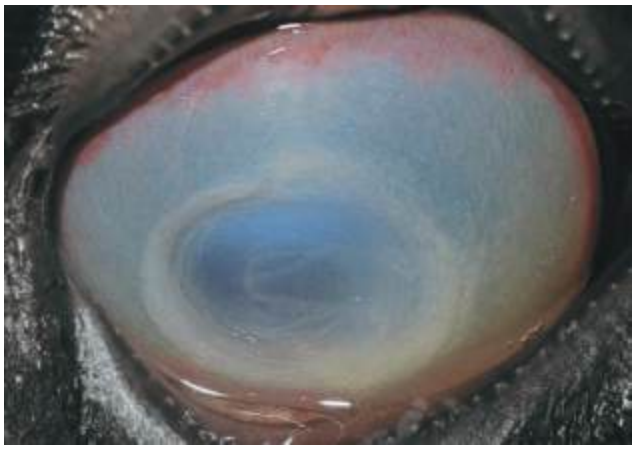


Figure 30.26 Large, deep-stromal corneal ulcer surrounded by cellular infiltrate, corneal edema, and ciliary flush associated with infectious bovine keratconjunctivitis. (*Source*: Courtesy of Jacqueline Pearce.)



Figure 30.27 Central, deep-stromal corneal ulcer with a dense cellular infiltrate and corneal vascularization associated with infectious bovine keratoconjunctivitis. (*Source*: Courtesy of Jacqueline Pearce.)



Figure 30.28 Central corneal granulation and fibrosis secondary to corneal ulceration during previous infectious bovine keratoconjunctivitis, now inactive. (*Source*: Courtesy of Jacqueline Pearce.)



Figure 30.29 Central corneal perforation with staphyloma formation associated with infectious bovine keratoconjunctivitis. There is mild corneal edema and vascular response in the surrounding cornea. (*Source*: Courtesy of Jacqueline Pearce.)



Figure 30.30 Secondary glaucoma with buphthalmos caused by infectious bovine keratoconjunctivitis. (*Source*: Courtesy of Cecil Moore.)

the study was to evaluate treatments for IBK, based on a systematic review of the published literature, which yielded 196 manuscripts. Overall, the study suggested that antibiotic treatment is successful in reducing healing times of IBK-associated corneal lesions. The review identified very few manuscripts that reported a direct comparison of different antibiotic classes, so it was not possible to evaluate comparative antibiotic efficacy. There is clearly a need for further randomized controlled trials that evaluate the efficacy of antibiotic treatment for IBK, including direct comparisons of two or more antibiotics (O'Connor et al., 2006).

Currently, oxytetracycline formulations such as Liquamycin/LA-200™ (Zoetis Animal Health, Parsippany, NJ, USA), Bio-Mycin 200™ (Boehringer Ingelheim Vetmedica Inc., St. Joseph, MO, USA), and Noromycin 300 LA™ (Norbrook Inc., Overland Park, KS, USA), and the tulathromycin formulation Draxxin™ (Zoetis Animal

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Health) are the only parenteral antibiotics labeled for IBK in cattle. Topical medications approved for IBK at the time of publication include the oxytetracycline formulation Terramycin™ (Zoetis Animal Health) and Vetericyn Pink Eye Spray™ (Innovacyn Inc., Rialto, CA, USA). Veterinarians are encouraged to consult current online publications for up to date information on IBK labeled drugs. Other treatment options require extralabel drug use in food animals, which is very carefully regulated by the U.S. Food and Drug Administration and by the American Veterinary Medical Association via the Animal Medicinal Drug Use Clarification Act. Therefore, other treatment options should only be used if currently labeled drugs have been shown to be ineffective, and as long as the *drugs are not prohibited for* extralabel *use in food animals* (American Veterinary Medical Association, 2007).

Therapy for IBK is recommended to relieve pain and maintain productivity. Combined parenteral (20 mg/kg) and oral (alfalfa pellets containing 1 g/0.45 kg of pellet administered daily for 10 days at a dosage of 2 g/calf/day) administration of oxytetracycline appears to be an effective method of reducing the severity of herd outbreaks of IBK (Eastman et al., 1998). Oxytetracycline therapy appears to be superior to penicillin G. Calves treated with oxytetracycline had fewer recurrences and less shedding of *M. bovis* compared with those treated with penicillin G (Eastman et al., 1998; George, 1990). Parenteral oxytetracycline is effective even with relatively low tear drug concentrations, because the concentrations are maintained above the minimal inhibitory concentration for a prolonged period of time (George et al., 1985; Smith & George, 1985). Oxytetracycline is selectively distributed to the conjunctiva and lacrimal gland (George et al., 1985). This treatment option is particularly appealing because long-acting oxytetracycline formulations (LA-200, LA-300, and Bio-Mycin 200) are currently approved for treatment of IBK in the United States. Although parenteral long-acting oxytetracycline formulations can be used in lactating dairy cattle, alfalfa pellets containing oxytetracycline cannot. The duration of the carrier stage (i.e., a normal eye with hemolytic *M. bovis*) is reduced by two injections of long-acting oxytetracycline at 20 mg/kg each. In addition to shortening the carrier stage, treatment reduces the progression of lesions and shortens healing times in affected animals (Brown et al., 1998).

Antibiotics demonstrating efficacy against *M. bovis* include tilmicosin (one dose of 5–10 mg/kg subcutaneously) (Zielinski et al., 2002), long-acting ceftiofur crystalline-free acid (one dose of 6.6 mg of ceftiofur equivalents/kg subcutaneously into the posterior aspect of the pinna) (Dueger et al., 2004), florfenicol (two injections of 20 mg/kg intramuscularly q 48 hours or a single dose of 40 mg/kg subcutaneously) (Angelos et al., 2000), tulathromycin (2.5 mg/kg, subcutaneously) (Lane et al., 2006), and clindamycin (150 mg subconjunctivally q 24 hours for 3 days) (Senturk et al., 2007). Other drugs recommended by various authors include penicillin, ampicillin, ormetoprim-sulfadimethoxine (prohibited for extralabel use in lactating dairy cattle in the United States), furazolidone (prohibited for use in food animals in the United States), gentamicin, and neomycin (Edmondson et al., 1989; George, 1990; George et al., 1984; Wilson et al., 1987).

M. bovis is usually resistant to tylosin, lincomycin, and erythromycin, and has variable susceptibility to cloxacillin (George, 1990; George et al., 1989; Webber et al., 1982a). Given intravenously (prohibited in lactating dairy cattle in the United States), sulfadimethoxine establishes effective levels in the tear film and eliminates both ocular and nasal infections with artificially induced IBK (Angelos et al., 2011; Wilson et al., 1987). Some *M. bovis* strains, however, may be sulfa-resistant. Although *M. bovis* is sensitive to many antibiotics, regional and strain differences may necessitate culture and sensitivity tests to select a specific antibiotic, especially during a severe outbreak (George, 1990; Webber et al., 1982a). The treatment selected is influenced by the management practice of the affected animals. Dairy operations usually have daily access to the animals, but milk withdrawal times become important issues. Dairy operations therefore may choose procaine penicillin because of the short milk-withdrawal times (Miller & Fales, 1984). Because beef cattle are infrequently handled, beef practitioners may opt for long-lasting parenteral medications such as oxytetracycline (Brown et al., 1998). As antibiotic drug residues vary according to the drug formulation, dose, frequency, route of administration, and weight of the animal, the Food Animal Residue Avoidance Database should be contacted to determine withdrawal times and legality of use of a particular drug in an extralabel fashion.

A study of minimum inhibitory concentrations of several antimicrobial agents has been published for *M. bovoculi* since it was identified. The low minimal inhibitory concentration (90) of *M. bovoculi* isolates suggests that commonly used antibiotics for treatment of IBK associated with *M. bovis* should also be effective against *M. bovoculi* (Angelos et al., 2011).

Other medical treatments for IBK include topical atropine and nonsteroidal anti-inflammatory drugs. These medications assist in relief of intraocular pain and decrease the incidence of inflammatory-induced ocular lesions. Some reports detail use of local corticosteroids in IBK-affected eyes without any detrimental effect (Allen et al., 1995). The lack of evidence-based medicine indicating corticosteroids are beneficial in IBK cases, and the possibility of potentiating collagenases and prolonging healing times must be considered. Therefore, corticosteroids are best avoided in IBK.

A novel nonchemotherapeutic treatment therapy using *Bdellovibrio bacteriovorus* has been investigated as a possible future therapeutic option for IBK. The predatory bacterium *B. bacteriovorus* is a bacteriolytic organism capable of attacking a

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living bacterium, attaching to its surface, and causing lysis of the infected cell. An *in vitro* study revealed that *B. bacteriovorus* decreased adherence of *M. bovis* to host cells, as well as decreased the number of unattached *M. bovis* cells, indicating that *B. bacteriovorus* has potential as an effective biological therapy against *M. bovis* (Boileau et al., 2011).

Regardless of the therapy chosen, additional treatment steps should be taken to control the herd infection and minimize the economic effects. Critical measures include use of insecticides to control face flies, segregation of affected animals, personal disinfection between treatments of affected and noninfected animals, and frequent mowing of pastures.

Surgical Treatment

The majority of cattle with IBK do not require surgical treatment of the corneal ulcer, but deep and perforated corneas require surgical intervention. Nictitating membrane flaps and complete temporary tarsorrhaphies have been used in the past for the treatment of deep and perforated corneal ulcers in IBK (Anderson et al., 1976). There are, however, no published, controlled studies assessing the benefits of those surgical treatments.

Vaccination

Several vaccines for *M. bovis*, including live or formalin-killed cells, ribosomes, pili, and cytolysin, have been tested. Early vaccines provided only limited protection, and unfortunately the recent vaccines appear to be only slightly more efficacious (Angelos, 2010; Angelos et al., 2007b; McConnel & House, 2005; Pugh et al., 1982). Passive immunity from vaccinated animals may occur. Calves of vaccinated cows or calves fed colostrum from vaccinated animals show reduced incidence of IBK, reduced severity of clinical signs, and delay in onset of clinical signs (Pugh et al., 1980, 1982, 1986b).

Vaccination with homologous strains reduces the incidence and severity of disease, whereas heterologous strain vaccines against IBK have limited success (Hughes & Pugh, 1975; Hughes et al., 1968; Pugh & Hughes, 1976; Pugh et al., 1977). In general, autogenous *M. bovis* vaccines are ineffective in controlling naturally occurring IBK (O'Connor et al., 2011a). Because endemics of IBK have been associated with *M. bovis* isolates possessing novel pili types (Vandergaast & Rosenbusch, 1989), multivalent vaccines should include pili from one representative strain of each serogroup to be effective (Lepper et al., 1992, 1995). Pilus-antigen vaccines have shown reduction of incidence and severity of IBK (Lepper, 1988); ribosomal vaccines are not effective (Pugh et al., 1981). Recombinant DNA technology has also been used to develop low-dose pili vaccines (Lepper et al., 1993). A recent cytolysin-enriched vaccine provided partial protection from IBK (George et al., 2005). A recombinant *M. bovis* cytotoxin–ISCOM matrix adjuvanted vaccine was slightly more effective than currently available vaccines in reducing IBK within vaccinated calves (Angelos et al., 2004). Angelos also recently tested a recombinant *M. bovis* pilin–*M. bovis* cytotoxin subunit vaccine that delivered a conserved pilin domain with a previously tested recombinant carboxy terminus of mbxA (Angelos et al., 2007b). He found a reduced cumulative proportion of IBK in the pilin-cytotoxin vaccinated calves compared with those given the cytotoxin vaccine alone. Concerns have arisen that the efficacy of *M. bovis* vaccines may be reduced in herds where IBK has been associated with *M. bovoculi*. Another study evaluated a recombinant *M. bovoculi* cytoxoxin–ISCOM matrix adjuvanted vaccine potential to prevent naturally occurring IBK in California. In this study, the use of *M. bovoculi* antigens alone in vaccines to prevent IBK did not appear to be beneficial, perhaps because IBK in the tested herds was associated with both *M. bovoculi* and *M. bovis* (Angelos et al., 2010). A following study evaluating the efficacy of a recombinant *M. bovis* pilin-cytotoxin-*M bovoculi* cytotoxin subunit vaccine was not effective and detected no difference between vaccinated and nonvaccinated groups (Angelos et al., 2012).

After vaccination, natural challenge, or experimental exposure, levels of lacrimal and serum antibodies to *M. bovis* vary. There is evidence for general immunity after exposure to *M. bovis* (Kopecky et al., 1983). The immunoglobulin content of the lacrimal secretion has been variably reported as IgG or IgA (Bishop et al., 1982; Hughes et al., 1977; Yancey, 1993). Initial immunity to infection with *M. bovis* is thought to be mediated by humoral IgG, with assistance 2 weeks later from secretory IgA (Miller & Fales, 1984). Protection against a second episode of IBK appears to relate more to lacrimal IgA, however, than to serum IgG (Rosenbusch, 1987). Vaccination causes a rise in anti-*M. bovis* IgG titers in the serum (Bishop et al., 1982; Miller & Fales, 1984). Unfortunately, the presence of anti-*M. bovis* IgM, IgG, and IgA does not preclude development of disease (Powe et al., 1992).

The protection provided by vaccination is also a function of the route of administration. The highest level of protection is provided when tear film antibodies (i.e., IgA) are induced by mucosal vaccination (Nayar & Saunders, 1975). However, subcutaneous bacterins afford protection as good as, or better than, that afforded by bacterins given subconjunctivally (Pugh et al., 1985). A study also evaluated the local ocular mucosal IgA response against *M. bovis*-purified pili, produced after intranasal inoculation of experimental vaccines by an indirect enzyme-linked immunosorbent assay (ELISA). Significantly higher anti-pili IgA response was detected in calves vaccinated intranasally with pili compared with control calves, although this specific immune response did not seem to be related to protection against *M. bovis* infection or typical IBK lesion development (Zbrun et al., 2011).

In herds severely affected by IBK, vaccination may be worthwhile. Recommendations are to vaccinate 6 weeks before onset of the expected disease season (Miller & Fales, 1984). Calves should be vaccinated at 21–30 days of age, with

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a second vaccination occurring 21 days later. Vaccine administration should be at least 21 days before the fly season. It is not known whether colostral antibodies will interfere with the vaccines. Adult cattle should receive two initial vaccinations, followed by yearly boosters near the beginning of the vector season. Vaccination programs work best if calving is performed at a time with decreased flies and UV-B radiation.

Neoplasia of the Conjunctiva and Cornea

Of the food animal species, cattle are most affected by ocular and periocular neoplasia. The most common neoplasia is OSCC. In one study of 95 ocular tumor types in cattle, 91 cases were either OSCC (84 cases) or papillomas (7 cases). The other conjunctival tumors were eyelid lymphomas (3 cases) and adenocarcinoma (1 case) (Blodi & Ramsey, 1967).

Ocular Squamous Cell Carcinoma

OSCC has considerable economic impact, particularly from the loss of older breeding animals and because of partial carcass condemnation at slaughter. In a study performed in 2009, OSCC/epithelioma was the fourth leading cause (9.15%) of carcass condemnation at postmortem examinations of animals sent to harvest for beef in the United States from 2003 to 2007 (White & Moore, 2009). Cattle with OSCC are condemned if the eye has been destroyed, if there is extensive infection, if the animal is in poor condition, or if there is evidence of spread to other parts of the body, including structures around the eye. Cattle with small, localized lesions may pass inspection after condemnation of affected parts such as the head. The presence of OSCC in slaughter animals is estimated to cause annual losses of $20 million in the United States alone. The National Cattlemen's Association has focused on ocular neoplasia as part of their Beef Quality Assurance program because a negative public perception results when cows with prominent, unsightly external lesions are seen at a livestock market or slaughterhouse (McKinnon, 1997; Roeber, 2003).

Incidence Actual incidence in the general cattle population of the United States is often difficult to assess. In herds of live cattle, the incidence of OSCC has shown to vary from 4.4% to 5.6%. However, many of these studies considered herds of Hereford or Hereford cross cattle only and hence it is difficult to extrapolate (Heeney & Valli, 1985). In the Netherlands, the incidence is 0.04%, as determined from examinations of 35,000 animals (Klein et al., 1984). In some breeds, the incidence may be much higher.

Geographic Distribution Bovine OSCC occurs worldwide, but there is an association between the occurrence of OSCC and an increased level of solar radiation (Anderson & Badzioch, 1991). Using disposal data for 4960 female Herefords born between 1926 and 1954 in nine herds, Anderson and Skinner showed that after adjusting for age, the incidence of OSCC increased significantly with decreases in latitude, increases in altitude, and mean annual hours of sunlight (Anderson & Skinner, 1961).

Signalment The onset of OSCC is age related, with older cattle having a significantly greater risk (Anderson & Skinner, 1961). The tumors are uncommon in cattle younger than 5 years, and rare in cattle younger than 3 years (Russell & Loquvam, 1951). The average age of cattle with OSCC is 8.1 years (Anderson & Badzioch, 1991).

In an experimental herd of 276 female cattle examined sequentially between 1979 and 1988, OSCC was first observed at 4.5 years of age (Bailey et al., 1990). In a herd of purebred Simmental cattle, 12% had OSCC at 3 years of age, and this percentage increased to 50% at 7 years (Anderson & Skinner, 1961). In another study involving five breeding herds of Simmental cattle, OSCC prevalence increased with age such that from 36% to 53% of cattle older than 7 years had one or more tumors (Russell & Loquvam, 1951). The odds ratios for age in a study of 595 affected animals indicated a 2% increase in the risk of affliction for each additional month of age (Anderson & Badzioch, 1991). It has been suggested that, in a herd of Simmental cattle, virtually all cattle without periorbital pigmentation will acquire OSCC (Anderson & Skinner, 1961).

The incidence of OSCC is significantly higher in *Bos taurus* than in *Bos indicus* breeds (Bailey et al., 1990). Although other cattle breeds are affected, the Hereford is overrepresented. This may result, in part, from the popularity of this breed in the United States; Herefords outnumber all other breeds of range cattle combined (Russell & Loquvam, 1951). This association is also partially related to the typical periocular depigmentation. Examinations of 2775 female Herefords from 34 herds located in the United States and Canada found that 595 (21%) had OSCC (Anderson & Badzioch, 1991). Logistic regression analysis indicated that age and lack of corneoconjunctival pigmentation were significant risk factors. In another study, significantly more Hereford × Shorthorn cattle than *Bos indicus*-based breeds were culled because of OSCC (Bailey et al., 1990). Finally, a reduced incidence of all types of OSCC was observed in F1 Brahman-cross dams versus F1 Red Poll × Herefords, F1 Hereford × Red Polls, or F1 Angus × Herefords. Ayrshires are the most susceptible dairy breed and have a corresponding predilection for SCC of the vulva (Radostits et al., 2007).

The sites of OSCC may be single or multiple, unilateral, or bilateral (Anderson & Skinner, 1961). Of 93 tumors recorded in the eyes of 46 adult Simmental cattle, 22 cattle had a single tumor, 15 had two tumors, four had three tumors, four had four tumors, and one had nine tumors. Both eyes were affected in 35% of cattle. This contrasts with a herd of 523 Friesians in which 1.4% were affected with OSCC and only single tumors were present.

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There is no true sex difference in the incidence of OSCC. The higher incidence observed in females results from the males having been marketed before the age of peak incidence (Heeney & Valli, 1985).

Genetic Predisposition There is considerable evidence suggestive of a genetic basis for OSCC, such as variable morbidity rates among various breeds of cattle, lines of sires, and increased rates in the progeny of affected compared with that of unaffected parents (Anderson, 1963; Cleaver et al., 1972; Dennis et al., 1984, 1985). Lesion development is not heritable directly, but the genetic effect on periocular pigmentation determines to a large extent the degree to which the eye is susceptible (Anderson & Badzioch, 1991). In Zimbabwe, OSCC has not been observed in breeds with fully pigmented heads, such as the Jersey, Brahman, and Mashona (Anderson & Skinner, 1961). When cattle were older than 7 years, 60% of eyes without periorbital pigmentation had OSCC, whereas only 24% of eyes with periorbital pigmentation had tumors.

A negative association exists between eyelid pigmentation and the occurrence of OSCC (Heeney & Valli, 1985). Average eyelid pigmentation has a heritability of 0.55 (Anderson, 1991; Vogt & Anderson, 1964). Eyelid margin pigmentation clearly has an inhibitory effect on eyelid lesions but seems to have little effect on development of the much more frequent, conjunctival OSCC. Because the lack of ambilateral circumocular pigmentation (ACOP) has been associated with increased risk for bovine OSCC, selecting animals with such a characteristic is desirable to decrease the incidence of the disease. Because the heritability of eye-area pigmentation appears to be higher than for the susceptibility to OSCC, selection for ACOP is expected to rapidly decrease the number of affected animals. The results of a genome-wide study support a polygenic inheritance pattern for ACOP and may be the initial steps for efficient genomic selection of animals with eye-area pigmentation (Pausch et al., 2012).

Corneoscleral (i.e., limbal) and bulbar conjunctival pigment have a local inhibitory effect on the development of OSCC. Eyelid and corneoscleral pigmentation are related both phenotypically and genetically (Anderson, 1991). Corneoconjunctival pigment has a heritability of 0.53 (Anderson, 1991). Some animals have OSCC in pigmented areas of the limbus, which would argue against the protective effect of pigment (Anderson, 1991). However, serial photographs and observations of 120 animals over 15 years indicate that pigment can develop in previously unpigmented areas in response to OSCC (Russell & Loquvam, 1951). Subsequent observations then reveal OSCC in a pigmented area. Although ocular pigmentation may not be discernible in Herefords younger than 1 year or be fully expressed until 5 years, the inhibitory effect on lesion frequency is significant when adjusted for age and compared with animals having little or no corneoconjunctival pigmentation. Hence, breed susceptibilities are predominantly a function of periocular pigmentation (Anderson et al., 1957).

Etiology of Ocular Squamous Cell Carcinoma A specific carcinogen has not been identified. A number of factors, including age, gender, breed, periocular and corneoscleral pigmentation, exposure to sunlight, viral infection, and nutrition, likely contribute to development of OSCC (Anderson, 1991; Anderson & Badzioch, 1991; Chapman et al., 1995; Den Otter et al., 1995a; Heeney & Valli, 1985; Kuchroo & Spradbrow, 1985; Rutten et al., 1992; Taylor & Hanks, 1969).

Exposure to sunlight plays a significant causal role in the development of OSCC (Den Otter et al., 1995a). In cattle, all measures of solar radiation indicate a significant association between increasing risks of OSCC and increasing levels of radiation (Anderson & Badzioch, 1991). Associations are evident whether affliction is defined as the occurrence of any type of tumor (i.e., plaque, papilloma, and carcinoma) or as the occurrence of only papilloma or carcinoma. Average ages of affected cattle are lower at high levels than at low levels of radiation. The total UV solar irradiance varies markedly with latitude and season (Chapman et al., 1995). UV-B affects all living organisms, and it damages DNA (Mayer, 1992).

Humans with xeroderma pigmentosum suffer an enzyme deficiency that prevents the repair of DNA defects (Cleaver et al., 1972) and exhibit a very high frequency of OSCC. They are the best example of a direct link between unrepaired DNA lesions and cancer induction (Arbault et al., 2004). A similar enzymatic defect has not been found in cattle with OSCC (Cleaver et al., 1972). Enzymatic assays for superoxide dismutase and catalase have shown no correlation with OSCC (Hamlet & Lavin, 1987). Although most solar-induced DNA lesions are repaired very efficiently in normal cells (Ley, 1984; Ley et al., 1988), UV radiation causes mutations in oncogenes and tumor-suppressor genes, and specific p53 mutations have been detected in UV light-induced cutaneous SCC of humans, cats, dogs, horses, and cattle (Coulter et al., 1995; Oram et al., 1994; Teifke & Lohr, 1996).

Viral cofactors have been suggested in the etiology of OSCC, but there is no definite evidence. IBR virus has been isolated from ocular carcinoma and one of its precursor lesions, and "IBR-type" inclusion bodies have been consistently observed in all types of OSCC lesions (Sykes et al., 1959; Taylor & Hanks, 1969). It is not known whether IBR virus has a predilection for the epithelial tissue in ocular tumors. In addition, because IBR virus can be frequently isolated from early plaque lesions, it apparently exists early in the course of the disease among many animals. Whether IBR has a part in initiating tumor growth is only speculative (Taylor & Hanks, 1969). Bovine herpesvirus-5 antigens have been detected in OSCC cell cultures (Anson et al., 1982).

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The role of bovine papilloma virus (BPV) in OSCC has also been examined. Neither the use of papilloma virus specific antibodies nor of DNA hybridization assays for all six known types of BPV could show a direct association with OSCC (Rutten et al., 1992; Sundberg et al., 1984). Although not needed for tumor maintenance, BPV may play a role initially in tumor formation (Rutten et al., 1992).

Nutritional status affects the development of OSCC from 6 to 9 years of age (Russell & Loquvam, 1951). Cattle with high nutritional levels have an occurrence of OSCC of 14%, whereas cattle on lower feed intakes have an occurrence of 1.5% (Radostits et al., 2007). Animals on a high nutritional plane also have increased severity and number of tumors and reduced 5-year survival rates compared with that in animals at a low level of nutrition. Similar results have been shown in laboratory animals (Anderson et al., 1970).

Clinical Signs Approximately 75% of OSCC and precursor lesions affect the bulbar conjunctiva and cornea, and of these, 90% involve the limbus and 10% the cornea. The remaining 25% of OSCC lesions are distributed in the palpebral conjunctiva, nictitating membrane, and eyelids (Russell et al., 1956). Limbal lesions occur more frequently in the horizontal than in the vertical meridian, which could result from greater exposure to irritation by foreign matter and sunlight. Bovine OSCC has a characteristic progression through a series of benign stages and then, possibly, to a malignant stage (Russell et al., 1956). On the globe and third eyelid, the initial lesion is a plaque. Plaques may progress to a papilloma, then to a noninvasive carcinoma (i.e., carcinoma *in situ*), and finally to an invasive carcinoma. In the eyelids, however, extensive keratosis (i.e., keratoma) may occur, particularly near the mucocutaneous junction. This keratosis may appear as a cutaneous horn and be the precursor to carcinoma formation (Moulton, 1961). The keratotic lesions are moistened by tears, collect debris, and become brown. They can be easily removed, leaving a bleeding surface.

A plaque is a small area of hyperplastic epithelium (Anderson et al., 1957). Plaques may be single or multiple, raised, of various shapes, and found in the conjunctiva following the curvature of the limbus. Their surfaces are smooth or irregular, and their consistency may be firm (because of keratinization). Plaques are opaque and grayish white (Fig. 30.31) (Taylor & Hanks, 1972). Papillomas are distributed similarly to plaques, and they may be thrown up into fronds. They have a connective tissue core with multiple hard, spine-like projections of variable size, and they may be sessile or pedunculated (Fig. 30.32) (Anderson et al., 1957). Papillomas often merge with underlying plaques.

Carcinoma *in situ* arises directly from plaques and is characterized microscopically as the stage before the neoplastic cells have penetrated the subepithelial lamina propria. Grossly, they resemble papillomas and exhibit no invasive tendencies (Fig. 30.33) (Anderson et al., 1957). Invasive carcinomas are generally large and protrude through the lamina propria (Fig. 30.34 and Fig. 30.35). They can invade the anterior chamber and eventually infiltrate the entire globe (Fig. 30.36). Carcinomas arising from the nictitating membrane are locally invasive, seldom invade the cartilage, but may infiltrate the medial orbit (Fig. 30.37). Secondary changes, such as necrosis, ulceration, hemorrhage, and inflammatory cell infiltration, appear in more than 40% of the invasive carcinomas (Anderson et al., 1957).



Figure 30.31 Limbal gray-white plaque in a Hereford cow.

Metastatic Potential Systemic metastases occur late in OSCC; however, local invasion may be particularly aggressive (French, 1959). As the carcinomas penetrate the lamina propria, they extend "fingers" of neoplastic cells into the surrounding tissues. To some extent, the consistency and nature of that tissue will determine the progression of the tumor. Limbal OSCC shows less inward invasion, resulting from resistance of the stroma, Descemet's membrane, and the sclera. However, the anterior chamber of the eye may still be involved, and in one series, intraocular extension was



Figure 30.32 Limbal papilloma in a cow.

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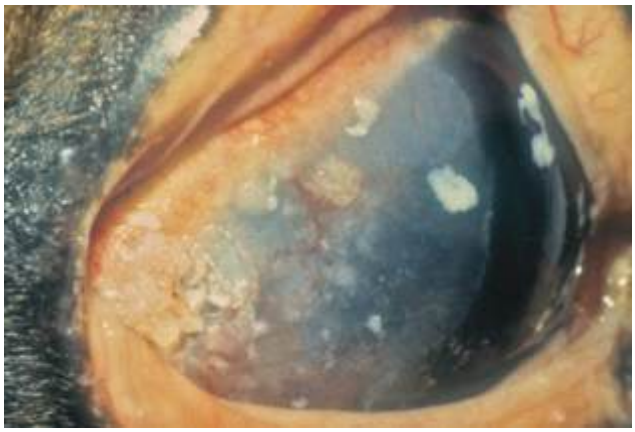


Figure 30.33 Limbal carcinoma *in situ*. (*Source*: Courtesy of Cecil Moore.)



Figure 30.35 Ulcerated squamous cell carcinoma lesion involving the lower eyelid in a Hereford cow. A local anesthetic block has been performed to prepare for subsequent surgical excision. (*Source*: Courtesy of Cecil Moore.)

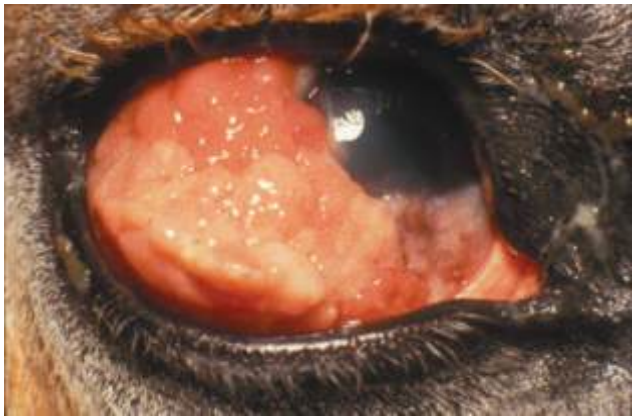


Figure 30.34 Extensive invasive limbal squamous cell carcinoma involving more than two-thirds of the cornea and protruding through the palpebral aperture. (*Source*: Courtesy of Lawrence Horstman.)



Figure 30.36 Squamous cell carcinoma of the nictitating membrane in a Holstein cow. (*Source*: Courtesy of Jacqueline Pearce.)

reported in 67 (14%) of 471 carcinomas (Anderson et al., 1957). The posterior segment is rarely affected.

A greater percentage of systemic metastases occur from tumors of the lid and nictitating membrane (Tsujita & Plummer, 2010). Metastases often involve the regional lymph nodes and orbital bones (McKinnon, 1997). Intracranial metastasis, probably by extension through the foramen orbitorotundum, has been reported (Zeman & Cho, 1986), and intracranial invasion via the cranial nerves (i.e., optic nerve and ophthalmic branch of trigeminal) has been documented (Samuel et al., 1987). Systemic metastasis usually occurs via the parotid lymph node to the regional lymph nodes, including the atlantal, retropharyngeal, submaxillary, mandibular, and cervical nodes. Once the metastatic cells gain access to the thoracic duct, they spread hematogenously via the venous circulation. Metastases can affect the lungs, heart, pleura, liver, kidney, and bronchial as well as mediastinal lymph nodes (Moulton, 1961).

Diagnosis: Cytologic Examination Cytology should not be used as an alternative to histopathology, although a strong correlation exists between cytologic and histopathologic diagnoses. High rates of agreement (86.5%) between the two diagnostic modalities have been reported (Hoffmann et al., 1978). Any time an equivocal cytologic decision occurs, a histopathologic specimen should be examined (Garma-Avina, 1994). With very anaplastic tumors, it may be impossible to decide if it is epithelial or mesenchymal in nature on the basis of cytology or histopathologic sections (Kadota et al., 1985). Immunohistochemical evaluation may assist in diagnosing these disputed cases. (Garma-Avina, 1994).

In a series of 40 OSCCs, the cytologic changes were compared with the histopathologic results (Garma-Avina, 1994). In this study, the well-differentiated OSCCs showed a marked predominance of large, markedly angular, nucleated squamous cells with nuclear features of malignancy, such as hyperchromatic chromatin and large multiple nucleoli of

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Figure 30.37 Invasion of the anterior chamber and glaucoma associated with squamous cell carcinoma in an aged Hereford cow. (*Source*: Courtesy of Kirk N. Gelatt.)

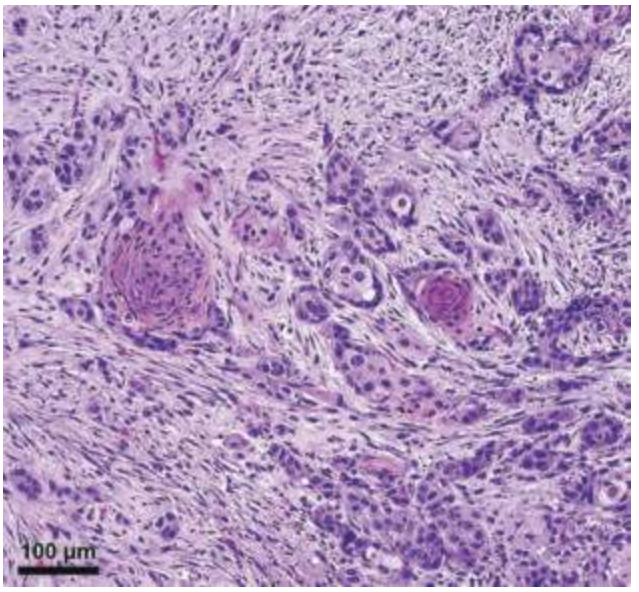


Figure 30.38 Hematoxylin and eosin stained photomicrograph demonstrating typical histological appearance of bovine squamous cell carcinoma with desmoplasia. The neoplastic cells have moderate amounts to abundant cytoplasm, distinct cell borders, and round to oval nuclei with a prominent nucleolus. Individual cell keratinization and a keratin pearl can be found in the center of the neoplasm. (*Source*: Courtesy of Kei Kuroki.)

various shapes. The predominance of medium-sized, round to oval cells with a high nucleus–cytoplasm ratio, malignant-looking nuclei, and clear-cut cytoplasmic evidence of squamous origin suggested a moderately differentiated OSCC. The predominance of small, round cells with a high nucleus–cytoplasm ratio and malignant-looking nuclei with a few keratohyaline granules in the cytoplasm suggests a poorly differentiated OSCC. Grading must be performed only after examination of the entire smear, because tumors often vary in their degree of differentiation at various areas.

Severe inflammatory reactions may cause a false diagnosis of OSCC. Inflammation can increase the number of cells in karyolysis or pyknosis, and it can also obscure the criteria for malignancy. Chronic inflammation may irritate the epithelial cells and induce dysplasia. The role of dysplastic cells in OSCC development is not known. Therefore, strict adherence to the criteria of malignancy is suggested (Garma-Avina, 1994). The basic difference between dysplasia and carcinoma *in situ* is that dysplastic cells have abnormal-looking nuclei but normal amounts of cytoplasm, whereas the cells of carcinoma *in situ* have malignant nuclei and less cytoplasm (Graham, 1972).

Diagnosis: Histopathology Most periocular and ocular neoplasia in cattle is OSCC, but other tumor types have also been reported (Blodi & Ramsey, 1967). Therefore, biopsies (often excisional) with adjunctive therapy are strongly recommended. Lesional characteristics and surgical margins may then be evaluated (Fig. 30.38).

The plaque is an area of hyperplastic conjunctival epithelium. It can involve any, or even all, layers of the epithelium. Varying amounts of hyperkeratosis occur, and rarely extreme keratosis forms a horny growth. As epithelial cell hyperplasia develops, the underlying connective tissue proliferates into the overlying epithelium. At this stage, the plaque becomes a papilloma.

When fully developed, the papilloma consists of multiple papillary projections (i.e., fronds), which are covered by proliferative epithelium and supported by vascular connective tissue stalks. The overlying epithelium exhibits varying extents of hyperkeratosis.

Carcinoma *in situ* exhibits malignant transformation of the epithelial cells in the basal layer or, less commonly, in the stratum spinosum. These cells display hyperchromatic nuclei, increased numbers of mitotic figures, pleomorphism, and loss of polarity. The neoplasm may show signs of early invasiveness, and infiltration of mononuclear cells is common at these sites.

Invasive carcinomas have been graded on the basis of the World Health Organization classification of tumors. The histopathologic gradations are well-differentiated, moderately differentiated, and poorly differentiated OSCC.

Treatment Before therapeutic intervention, the extent of the lesion should be evaluated. Topical anesthesia and a lubricated, gloved hand are usually sufficient to palpate the

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orbital rim. OSCC extends firm tendrils, which can be followed to their most invasive extent. A thorough physical examination concentrating on possible sites of metastasis is essential. Extensive systemic invasion may preclude further treatment because of financial and prognostic reasons. Examination at slaughter revealed that 5% of animals had metastatic lesions (Anderson et al., 1957). Animals with invasive OSCC have an even higher level of metastasis (11%) (Hamir et al., 1980). If indicated and finances allow, complete blood counts and serum biochemistry profiles are also suggested. Orbital radiography may be useful in determining bony involvement; dorsal oblique radiography provides the most useful information. Bony involvement carries a very guarded prognosis.

When deciding on treatment strategies, it is important to realize that not all precancerous lesions progress. In one herd study, 52% exhibited precursor lesions (e.g., plaque, papilloma, keratosis) of OSCC. Of these lesions, approximately one-third regressed spontaneously and disappeared (Taylor & Hanks, 1972). Other reports suggest spontaneous regression rates as high as 50% (French, 1959). Whether such lesions recur over a long period of time is not known.

If treatment is undertaken, the options include surgical excision with or without adjunctive therapy, cryotherapy, hyperthermia, immunotherapy, radiation therapy, and possibly chemotherapy. The most common method of treatment is surgery, and when combined with other treatment modalities, the success rates are quite good (Tsujita & Plummer, 2010).

Surgery: Salvage Procedures

Salvage procedures used together may either cure or prolong an animal's life, which may be desirable for pregnant cows or for bulls to allow semen collection. Enucleation may be performed via subconjunctival or transpalpebral approaches. The latter procedure is frequently used in cattle with extensive neoplasia of the globe, eyelids, nictitating membrane, or conjunctiva. Exenteration should be considered if any orbital involvement by the tumor is detected or suspected.

In animals with evidence of local lymph node metastasis only, which may be up to 33% of cases, block resection offers cure rates as high as 90%. Transpalpebral enucleation alone may show a recurrence rate of 37% (Klein et al., 1984). Block resection involves removal of the retropharyngeal lymph node, mandibular salivary gland, and parotid salivary gland/subparotid lymph node as well as a transpalpebral enucleation (Bier et al., 1979). Care must be taken not to damage the vagosympathetic trunk (Klein et al., 1984). This procedure is suggested for animals that are valuable and have local lymph node enlargement but no radiographic evidence of spread to the lungs.

Eyelid and orbital surgery are performed most frequently in standing cattle, and regional anesthesia for most ocular surgeries in food animals may be achieved with either a Peterson nerve block (Peterson, 1951) or a four-point retrobulbar block of the orbit. In a comparison of the retrobulbar and Peterson nerve block techniques in bovine cadavers (Pearce et al., 2003), the four-point technique was characterized by widespread distribution of contrast medium around the periorbital structures, along the optic nerve, and in the ethmoid turbinates and nasopharynx. The Peterson technique was characterized by contrast medium repeatedly located in the pterygopalatine fossa with minimal distribution to the surrounding structures. However, though rare, it is important to inform clients that apnea and occasionally death may occur 8–9 minutes after performing a Peterson nerve block (Ramakrishna, 1995). This may result from injection of the anesthetic agent directly into a blood vessel, which can be avoided by aspirating first, or injection into the dural sheath.

The Peterson nerve block is a retrobulbar injection that when performed appropriately and effectively blocks the optic (II), oculomotor (III), trochlear (IV), abducens (VI), and ophthalmic as well as maxillary branches of the trigeminal (V) nerve (Fig. 30.39). Lack of pupillary constriction indicates successful application of this block, in which a slightly curved, 10-cm, 18-gauge needle is inserted at the caudal angle between the supraorbital process and the zygomatic arch. The concavity of the curvature is directed posteriorly to allow passage of the needle anterior to the anterior border of the coronoid process of the mandible. The needle may need to be walked off the coronoid process anteriorly. The needle is advanced in a slightly ventral direction to the pterygopalatine fossa and the foramen orbitorotundum; complications may be avoided if the needle is not advanced to the bony floor of the pterygopalatine fossa. Aspiration is then performed, and approximately 15–20 mL of lidocaine (2%) is injected. Alternatively, a four-point block (Fig. 30.40)

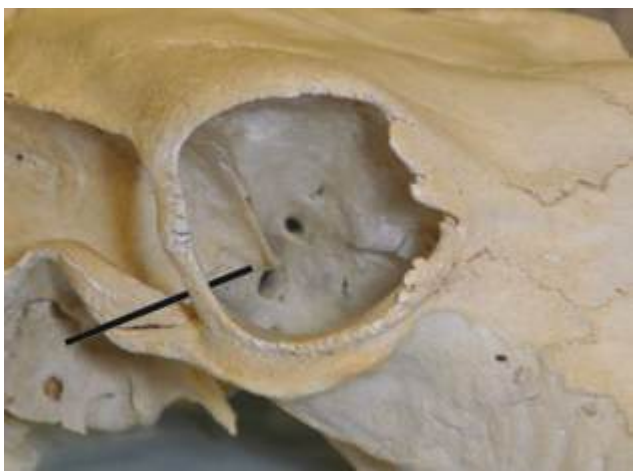


Figure 30.39 Lateral view of the Peterson nerve block for retrobulbar anesthesia in cattle. (*Source*: Courtesy of Jacqueline Pearce.)

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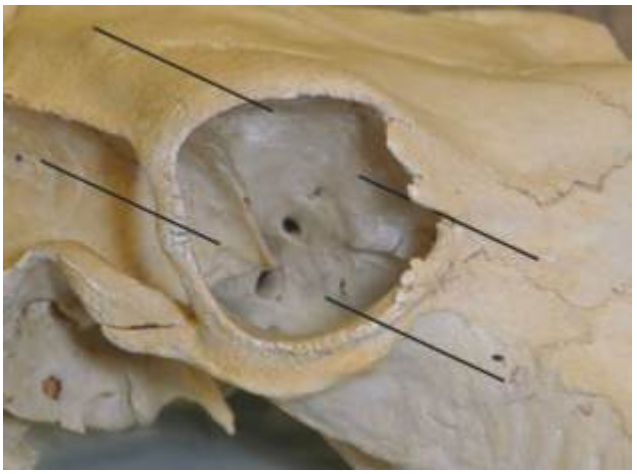


Figure 30.40 Lateral view of the four-point nerve block for retrobulbar anesthesia in cattle. (*Source*: Courtesy of Jacqueline Pearce.)

may achieve sufficient anesthesia. In this block, a 6-cm needle is inserted transconjunctivally adjacent to the globe at the 12-, 3-, 6-, and 9-o'clock positions, and 5–10 mL of lidocaine are injected at each site. A variation of this technique is to direct the needles through the eyelids rather than the conjunctiva. Possible complications of retrobulbar nerve block in cattle include orbital hemorrhage, penetration of the globe, damage to the optic nerve, and injection of local anesthetic into the optic nerve meninges (Edge & Nicoll, 1993; Rubin, 1995; Skarda, 1996).

Akinesia of the eyelids is obtained by an auriculopalpebral nerve block. Local anesthetic is injected subcutaneously 5–7 cm caudal to the supraorbital process, where the nerve crosses the zygomatic arch. Eyelid anesthesia is achieved with local anesthetic infiltration (line block).

A recent retrospective study about transpalpebral exenteration in cattle revealed that OSCC was the most prevalent indication for exenteration (80.9% of the cases), with Herefords having higher odds for undergoing exenteration because of OSCC compared with other breeds, and Holsteins having higher odds for undergoing exenteration for retrobulbar lymphoma compared with other breeds. Complications after exenteration were reported in 13% of the cases, including orbital abscesses, recurrence of OSCC, wound dehiscence, and excessive hemorrhage. There was no association between diagnosis and occurrence of postsurgical complications (Chigerwe et al., 2017).

After enucleation, most animals do not require systemic postoperative antibiotic treatment; however, an injection of flunixin meglumine, 1 mg/kg, will decrease postoperative pain and swelling. In the presence of marked sepsis, administration of appropriate systemic antibiotics for several days is indicated. Packing the orbit with sterile gauze after enucleation is not recommended unless uncontrollable hemorrhage occurs. If used, the gauze is gradually removed from between the sutures over a 3- to 4-day period. The opening for the gauze removal is usually sutured closed after removal to prevent fistula formation.

Surgery: Eyelid Neoplasia

If any doubt exists regarding the extent of an eyelid OSCC, then exenteration, with or without radical surgery, is advised. If, however, there is no evidence of lymph node metastasis, some form of blepharoplastic procedure by itself may cure the animal. Use of an H-plasty in cattle with OSCC affecting the lower lid provides excellent results (Welker et al., 1991). Tumors larger than 50 mm in diameter or with ill-defined margins are suitable candidates. In 14 animals treated in one study, 12 did not have recurrence at the 6-month follow-up (Welker et al., 1991). All wounds were cosmetically acceptable, and all wounds healed after primary intention. In addition, all but two animals had normal eyelid function postoperatively. These high success rates were attained because the large excisions can be achieved with this technique.

Surgery: Nictitating Membrane Neoplasia

Small OSCCs may be removed, leaving an intact nictitating membrane, but larger ones usually require total excision of the structure. OSCC in this area may frequently recur after surgical removal, and it may invade the orbit either hematogenously or by direct infiltration because of the difficulty in completely removing the gland surrounding the base of the cartilage.

Surgery: Conjunctival Neoplasia

Neoplasms may affect the fornix, palpebral, and bulbar conjunctivae. In the early stages, these tumors may be amenable to local excision with a scalpel, electrocautery, or carbon dioxide laser. Though not reported in cattle, the CO_2 laser has been used in other animals (English et al., 1990).

Surgery: Limbal and Corneal Neoplasia

Keratectomies may be used to remove corneal and limbal neoplasms limited to the outer layers of these tissues. Postoperative corneal scarring is not a significant problem in cattle. Limbal lesions affecting the cornea and adjacent bulbar conjunctiva are similarly removed.

Cryotherapy

Cryotherapy is a popular treatment of OSCC (Farris & Fraunfelder, 1976), and high success rates have been achieved. In one study using a double freeze–thaw technique, 97% of OSCC regressed, including 73% of those larger than 20 mm in diameter (Farris, 1980). The data must be interpreted carefully, however, because 76% of the samples were smaller than 10 mm, and it is not known what percentage would have spontaneously regressed. Joyce (Joyce, 1976) has reported an 86.6% success rate in treating limbal and corneal SCCs.

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All suspected premalignant lesions (e.g., focal ulceration or keratosis on eyelids, with or without epidermal plaques) and OSCCs smaller than 50 mm in diameter may be treated. Advantages of cryosurgery are its ease and rapidity, low cost, prolonged analgesia because of sensory nerve injury, minimal requirement for pre- and postoperative medications, minimal side effects, repeatability, and excellent success with suspect premalignant lesions. Disadvantages of cryotherapy include local hair depigmentation, lid necrosis, loss of function of normal structures, and cicatrix formation, which can cause entropion or ectropion. Lesions that are not successfully treated with cryotherapy are those that have metastasized, those larger than 50 mm in diameter and with poorly defined margins, and those with invasion of adjacent bones (Farris & Fraunfelder, 1976). Large OSCCs should be debulked surgically prior to performing cryotherapy.

Nitrous oxide and liquid nitrogen are most commonly used, and several cryosurgical units are available. Cryosurgical units designed to deliver liquid nitrogen are more effective than units designed to deliver nitrogen vapor (Farris, 1980). A closed-tip probe or spray gun is available as well. The former offers a more controlled freeze, whereas the latter is much quicker. With the spray gun there is the potential for damage because of "runoff" onto adjacent structures (Schoster, 1992).

The most important factor in the success or failure of cryosurgery is the extent of freezing. Surgical debulking of large tumors prior to cryotherapy is ideal, and a uniform freeze of −25°C should be sought to address the wound bed after debulking of the tumor. Polystyrene, surgical lubricant, or petrolatum-impregnated gauze may be used to protect surrounding normal tissue (Farris, 1980; Farris & Fraunfelder, 1976).

Hyperthermia/Electrothermal Therapy

Hyperthermia has been successful in treatment of bovine OSCC (Grier et al., 1980; Overgaard & Bichel, 1977). Often, hyperthermia is combined with some other treatment modality, such as surgical debulking or immunotherapy (Grier et al., 1980; Witt, 1984). In one study of 45 tumors, 80% regressed completely and 16% partially after a single treatment (Farris, 1980). Fifty percent of these tumors had been previously treated by some other modality. In another study with 3- to 12-month follow-ups and an average of 1.5 treatments, 96% of tumors either disappeared (53%) or were represented by suspicious scar tissue (43%), which was retreated (Grier et al., 1980). No permanent, functional eye impairment resulted from hyperthermia, but treated portions of the cornea were edematous for several weeks after therapy.

Neoplastic cells are selectively destroyed with hyperthermia (Cavaliere et al., 1967). Increased acidity, poor cell nutrition, and increased cell density all contribute to selective destruction of neoplastic cells. Of these, the pH may be the determining factor of lethality (Doss, 1977; Overgaard & Bichel, 1977).

Electrothermal treatment involves the passage of radiofrequency (i.e., 2 MHz) electric current between two electrodes. A small, handheld radiofrequency unit (Western Instrument Company, Denver, CO, USA) has been developed for the treatment of OSCC (Doss, 1977) and is powered by rechargeable batteries. Electrodes are placed directly on the tumor. Resistance of the tissue to the flow of electric current causes heat to be generated in that tissue. High-frequency current produces no sensation of electrical shock. The temperature of the tumor tissue is raised to approximately 50°C. Temperature control is monitored with a temperature-sensitive device (i.e., a thermistor) that is built into one electrode. Thirty seconds are allowed to elapse after the tissue temperature reaches 50°C (i.e., 122°F). The unit is small, and can be carried and used in the field.

Hyperthermia is not recommended for tumors that extend deeper than 3 mm or are larger than 4 cm in diameter (Grier et al., 1980). Surgical debulking may reduce the size of the tumor sufficiently to allow adequate results from treatment with hyperthermia. Follow-up evaluation at 30 days is generally recommended, with possible further treatment if needed.

Immunotherapy

In bovine OSCC, antibodies to tumor cells have been shown in sera (Atluru et al., 1982; Chung et al., 1977). Common antigens exist among cattle with OSCC. Sera from animals with plaque, papilloma, or carcinoma react best to cultured autologous tumor cells and, to a variable degree, to cultured allogenic cells (Atluru et al., 1982). IgG-containing cells accumulate in precancerous and neoplastic tissues (Hamir et al., 1980). The regional lymph nodes on the affected side have larger and more active follicles. This may account for the finding that as many as 30% of OSCC lesions regress spontaneously (Taylor & Hanks, 1972),

Successful use of immunotherapy has been reported in treatment of bovine OSCC (Den Otter et al., 1995b; Heck & England, 1977; Klein et al., 1982, 1986; Witt, 1984). Between 78% and 94% of cows with OSCC showed arrest and resolution of the tumor within 8 weeks after a single, intramuscular injection of a concentrated saline-phenol extract of fresh tumor tissue, which consisted primarily of tumor nucleoproteins (Hoffmann et al., 1981; Van Kampen et al., 1973). Subconjunctival inoculation of tumor cells has also been shown to cause regression of the primary tumor (Dennis et al., 1984). Use of peritumoral interleukin-2 (injected as close to the base of the tumor as possible) has also shown promise. Complete regression of OSCC was observed at 20 months in 67% of cases treated with 10 injections of 200,000 U of interleukin-2; lower doses were associated with higher rates of relapse (Den Otter et al., 1995b). Low peritumoral doses of interleukin-2 appeared to be as effective as high

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doses. Third eyelid tumors seem to be more sensitive to interleukin-2 therapy than tumors found in other periocular areas (Tsujita & Plummer, 2010).

Nonspecific immunotherapy includes use of Bacillus Calmette–Guérin (BCG) inoculations (Klein et al., 1982; Ribi et al., 1986). Ribi and colleagues gave two to four injections of BCG vaccine at 3-week intervals in cattle with OSCC (Ribi et al., 1986). Using a dose of 5 mL of vaccine per 2.5 cm of tumor diameter, regression occurred in 88% of tumors smaller than 2.5 cm and in 74% smaller than 7 cm. The recurrence rate was 5%. A single injection of BCG vaccine in 30 cases resulted in permanent regression of the neoplasm in 11 and temporary regression in eight (Klein et al., 1982, 1986).

Radiation

Ionizing radiation has been used to treat OSCC in food animals. The expense and legal requirements to possess such radioactive materials, however, limits its utility as a treatment modality. Disadvantages of brachytherapy include temporary corneal opacity, local necrosis, hair loss, damage to normal structures, and local depigmentation. Three types of radiation are used: beta emitters, gamma emitters, and roentgen rays. Beta radiation, such as Strontium-90, may be used after superficial keratectomy (i.e., to minimize the possibility of tumor recurrence), or it may be applied directly to the tumor (i.e., for corneal and limbal neoplasms) (Banks & England, 1973; Wheat et al., 1954). Use of beta radiation is often combined with surgical debulking, because 75% of the beta rays are absorbed within the first 2 mm with minimal penetration in deeper or surrounding tissues to the field. Therefore, a lesion should be less than 2 mm thick if beta radiation therapy is attempted. Furthermore, a 2 mm margin around the lesion should be treated as well, because the lesion often is surrounded by a precancerous plaque or is incompletely excised (Elkon & Constable, 1979).

Complications after beta radiation therapy are rare but have been reported in the veterinary literature (Moore et al., 1983). In humans, keratopathies resulting from radiation therapy include nonresponsive punctate ulcerations, corneal edema with bullous keratopathy, and neovascularization.

Interstitial brachytherapy has been used in various species, and implants have included radon, gold, iridium, cobalt, and cesium (Banks & England, 1973; Theon & Pascoe, 1995). These gamma emitters, as well as roentgen rays, are especially useful for eyelid masses. However, use of brachytherapy in cattle is often not feasible because of financial constraints. Even so, gamma emitters offer several advantages, including a high dose of radiation to the tumor and not to the surrounding tissue, placement of the needles under heavy sedation, possible increased effectiveness because of continuous low-dose irradiation (Bloedorn et al., 1977), a short therapy interval (7–10 days), and a good cosmetic result. Among the disadvantages, however, is that neoplastic cells may be forced into vascular and lymphatic channels during implantation. In addition, the implantation procedure may be harmful to those performing the procedure itself; however, this risk can be minimized with an after-loading technique (Gavin, 1997).

Radioactive gold seeds have been used successfully in treatment of OSCC (Banks & England, 1973). Because of their short half-life and lack of a foreign-body reaction, gold seeds do not need to be removed. Seeds are considered to be nonhazardous after 10 half-lives; after 27 days the radioactivity in the seeds is reduced to a noninjurious level (Lavach, 1987). The desired tumor dose is 5000 rads (Shalek et al., 1957). Accurate dosage requires that radioactive seeds be properly calibrated, and that measurement of the ocular mass is accurate to facilitate plotting dose curves and dosimetry calculations.

Prevention and Control

Past studies indicate that selective breeding can be employed toward control of OSCC (Anderson, 1991). Animals should be selected with increased amounts of lid and corneoconjunctival pigment, but the latter pigmentation is not fully expressed until 5 years of age (French, 1959). Selection on the basis of eyelid margin pigmentation alone leads to only a slight reduction in the incidence of OSCC because the eyelids are sites only for approximately 10% of these tumors (Russell et al., 1956; Vogt & Anderson, 1964).

In purebred herds, offspring of affected animals should be culled (Moulton, 1961). Bulls with a history of OSCC should not be used as herd sires (Woodward & Knapp, 1950). Introduction of animals into purebred herds should include consideration of phenotypes together with information on the resistance of parents, siblings, or progeny.

Glaucoma

Glaucoma is an optic neuropathy usually associated with elevated intraocular pressure (IOP). The incidence of glaucoma in cattle is less than 1% (Mertel et al., 1996; Sarma et al., 1990). In India, three cows (0.23%) in a herd of 1302 animals had glaucoma, and in Italy, one case was found among 500 Friesian dairy cows examined (Sarma et al., 1990). Congenital (Greene & Leipold, 1974; Rebhun, 1979; Schuh, 1989), hereditary (Carter, 1960; Gregory et al., 1943), and secondary glaucomas (from inflammatory or neoplastic processes) (Meek et al., 1987; Mertel et al., 1996; Miller & Fales, 1984) have been reported. Steroid-induced ocular hypertension has been consistently produced within 30 days by application of prednisolone acetate three times daily to the eyes of normal cows and sheep (Gerometta et al., 2004, 2009). Endogenous inflammatory episodes, such as those seen with neoplastic or granulomatous processes, may cause both peripheral anterior and posterior synechiae, which in turn may impede aqueous outflow sufficiently to elevate

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IOP. Perforated corneal ulcers, especially from IBK, may result in globe rupture, iris prolapse, and synechiae, which may also result in secondary glaucoma.

Clinical signs in cattle with glaucoma depend on the cause of the condition. Cattle with primary glaucoma show enlarged globes that are not overtly painful, little or no episcleral injection, mild corneal edema, corneal vascularization and striae, a pupil poorly responsive to light stimulation, lens subluxation, and fundus abnormalities (Fig. 30.41 and Fig. 30.42) (Mertel et al., 1996).

In one well-documented patient with glaucoma, lens-induced uveitis arising from the leakage of lens proteins through an intact lens capsule was the most likely cause (Mertel et al., 1996). Ophthalmic findings included retinal vascular attenuation, generalized tapetal hyperreflectivity, and optic disc atrophy. IOPs were greater than 39 mmHg for longer than 1 year. Electroretinography (ERG) confirmed the outer retinal damage suspected on ophthalmoscopy, because the b-wave amplitude recorded in the glaucomatous eye was less than half that in the normal eye.

On subsequent histopathologic and gross examinations, the globe in the affected left eye had an axial length of 4.5 cm compared with the normal right eye at 3.7 cm. Optic nerve histomorphometry showed severe reduction (98%) in the total number of optic nerve axons in the glaucomatous compared with the nonglaucomatous eye. The lamina cribrosa was also depressed (Fig. 30.43). The remaining axons were of small diameter and located in the central part of the optic nerve (Mertel et al., 1996). Successful treatment of glaucoma in cattle has not been reported.

The Uveal Tract

Congenital Disorders of the Anterior Uvea

Congenital disorders of the anterior uvea in food animals are not clinically significant, with a few notable exceptions. Such anomalies include persistent pupillary membranes (Fig. 30.44), heterochromia, aniridia and iris hypoplasia, polycoria, cysts, pigment nevi, and colobomas.

Heterochromia Iridis

In cattle, heterochromia iridis represented almost 10% of ocular anomalies in one study (Barkyoumb & Leipold, 1984). Heterochromia iridis may be unilateral or bilateral, complete or partial. Iridal pigmentation may vary between white, light pink, blue, gray, and brown (Fig. 30.45). Heterochromia iridis may be associated with other ocular anomalies (e.g., tapetal hypoplasia and colobomas of the fundus) (Gelatt et al., 1969). Dominant and recessive forms of inheritance have been reported (Leipold & Huston, 1966; Ojo, 1982).

Among cattle, heterochromia iridis has been reported in various breeds, including Ayrshires, Holsteins, Angus, Brown Swiss, and Guernseys (Barkyoumb & Leipold, 1984; Huston et al., 1968; Leipold & Huston, 1966; Leipold et al., 1968). In most cases, vision is unaffected; however, photophobia and nystagmus have been reported (Gelatt et al., 1969; Leipold et al., 1968). Among eight cattle examined in one study, fundic coloration varied from red to yellow-red in seven and from yellow-green to red-yellow in one (Gelatt et al., 1969). All cattle had typical optic nerve colobomas that were always bilateral but not always symmetrical.

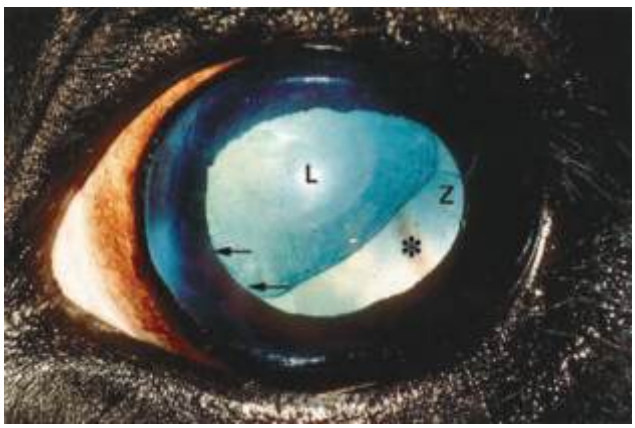


Figure 30.41 Buphthalmos in a 9-year-old Friesian cow that has perilimbal, localized corneal striae with branches (black arrows), subluxated hypermature cataract (L) with tearing of the zonules (Z), and a wide, aphakic crescent (*). (*Source*: Reprinted with permission from Mertel, L., Cammarata, G., Magni, R., Brooks, D. & Samuelson, D. (1996) Clinical and pathologic study of a cow with chronic glaucoma. *Veterinary & Comparative Ophthalmology*, **6**, 18–29.)



Figure 30.42 Funduscopic views through the aphakic crescent of a glaucomatous eye in a 9-year-old Friesian cow. Dull and nonhomogenous, hyperreflective tapetal fundus with retinal vascular attenuation. Reduced and hypovascular optic disc surrounded by a whitish border. (*Source*: Reprinted with permission from Mertel, L., Cammarata, G., Magni, R., Brooks, D. & Samuelson, D. (1996) Clinical and pathologic study of a cow with chronic glaucoma. *Veterinary & Comparative Ophthalmology*, **6**, 18–29.)

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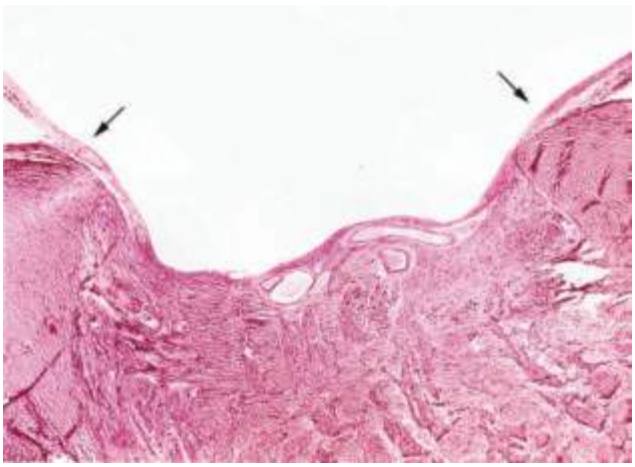


Figure 30.43 Histopathologic section showing optic nerve cupping in the buphthalmic eye of an 11-year-old Friesian cow. Note the cavitation of the optic papilla, thinning of the nerve fiber layer (arrows), and rarefaction of the optic nerve. (Hematoxylin and eosin; original magnification, ×40.) (*Source*: Reprinted with permission from Mertel, L., Cammarata, G., Magni, R., Brooks, D. & Samuelson, D. (1996) Clinical and pathologic study of a cow with chronic glaucoma. *Veterinary & Comparative Ophthalmology*, **6**, 18–29.)



Figure 30.45 Iridal heterochromia in an albino beef Shorthorn calf. Clinically, the central iris is pink and the peripheral iris is white. (*Source*: Courtesy of Kirk N. Gelatt.)

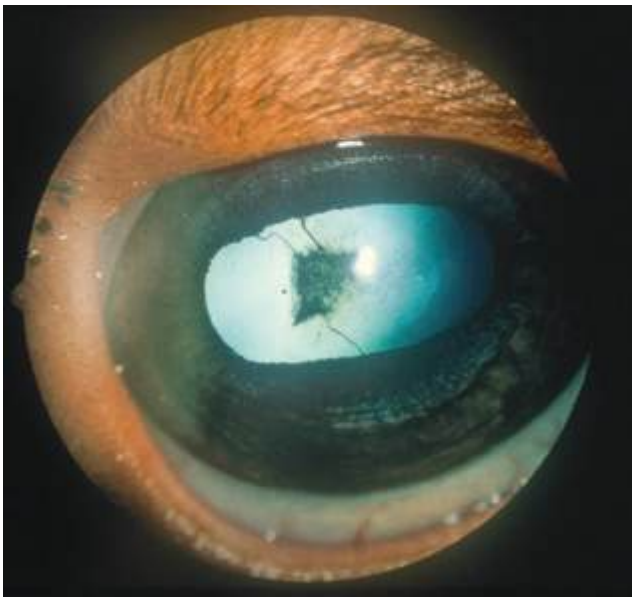


Figure 30.44 Iris-to-lens persistent pupillary membranes in a calf. (*Source*: Courtesy of Cecil Moore.)

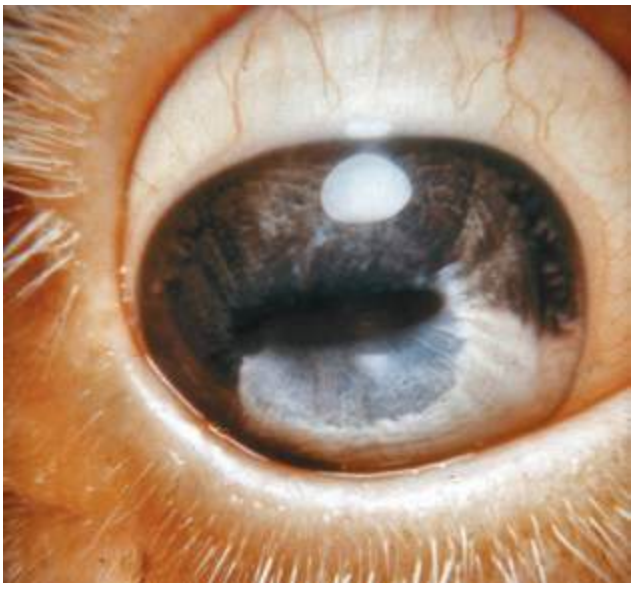


Figure 30.46 Tricolored heterochromic iris of a Hereford bull with dominant albinism. (*Source*: Courtesy of Kirk N. Gelatt.)

In 23 cases of heterochromia iridis reported in another study, Herefords and Ayrshires were overrepresented, but this may reflect the popularity of the breeds at the time (Barkyoumb & Leipold, 1984). In Guernseys, there is a suggestion that the condition is inherited recessively (Huston et al., 1968; Leipold et al., 1968). Heterochromia iridis with incomplete albinism are inherited as an autosomal dominant trait with variable expressivity in Herefords (Fig. 30.46) (Gelatt et al., 1969; Leipold & Huston, 1966). The cattle are usually totally white, though some have patches of pigmentation on the shoulder and hip. Most irides have a white periphery and a medium-blue center, but a few exhibit distinct zones of blue, white, and tan. Ocular fundus anomalies, including typical optic disc colobomas, are also present.

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Iris Abnormalities

An autosomal recessive, hereditary iridal defect has been observed in Jersey calves as part of multiple eye defects (Saunders & Fincher, 1951). Affected animals may show bilateral aniridia or iridal hypoplasia in association with microphakia, cataracts, and ectopia lentis. The calves exhibit visual impairment or blindness.

Inflammation of the Uvea

Uveitis does not suggest a causative diagnosis in and of itself but represents nonspecific ocular pathologic processes derived from inflammatory mediators. The associations of uveitis with systemic diseases are numerous (see Chapter 37, Part 4).

Specific etiologies of uveitis include neonatal infections, bacterial septicemia associated with severe mastitis, metritis, or traumatic reticuloperitonitis, malignant catarrhal fever, tuberculosis, IBK, thromboembolic meningoencephalitis, leptospirosis, toxoplasmosis, listeriosis, parasitic migration (*Setaria digitata*), toxins such as lead, poisonous plants such as *Dryopteris filix-mas*, and lymphoma (Bardsley, 1989; Hindson, 1989; Lavach, 1990; Mee & Rea, 1989; Rebhun, 1984; Rubin, 1974; Watson, 1989). In one outbreak of idiopathic uveitis in a herd of 44 milking Holsteins, 18% were affected with lesions that included aqueous flare, hyphema, iritis, anterior capsular cataracts, retinal hemorrhages, chorioretinitis, and papillitis (Davidson et al., 1992). In a subsequent examination of 30 adult cows, 47% were found to have chronic ocular abnormalities, including corneal vascularization, stromal scars, corneal edema, posterior synechia, cataracts, chorioretinal scars, optic nerve granulomas, and phthisis bulbi. An extensive diagnostic workup failed to identify a causative agent.

Uveal Tumors

Primary tumors of the anterior and posterior uvea in food animals are rare. Sarcomas and ciliary body epitheliomas do occur in cattle (Saunders & Barron, 1958). A congenital intraocular melanoma has also been reported in a Charolais cross-calf (Schuh, 1989). The tumor was well-differentiated, with rare mitotic figures and no evidence of extrascleral or vascular invasion.

Secondary intraocular tumors of the uveal tract can occur by extension from the orbit, conjunctiva, and cornea. The sclera is resistant to external invasion, but it may be breached by squamous cell carcinomas. One study reported penetration of the globe in 67 (14%) of 471 cases of OSCC in cattle (Tsujita & Plummer, 2010). Secondary intraocular tumors are also possible by hematogenous metastasis from other sites. Intraocular lymphosarcoma is rare but has been reported (Peiffer & Simons, 2002).

The Lens

Cataracts in food animals are rarely reported. However, the actual incidence may be much higher because careful inspection of the lens is not routinely performed unless the animal has visual impairment. Small, focal lens opacities do not usually result in visual impairment and are usually missed unless mydriasis is induced before the ophthalmic examination. Among food animals, cataracts have been classified on the basis of etiopathogenesis (Gelatt, 1971). Congenital cataracts (with or without associated ocular anomalies), secondary cataracts, and cataracts of unknown origin have been described (Lavach, 1990).

Congenital and Juvenile Cataracts

Congenital cataracts have been reported in cattle (Fig. 30.47) (Gelatt, 1971). Though not specifically designated as such in one study, cataracts, which were presumed to be congenital, were present in 31% of 72 calves as old as 22 weeks and in 18% of adults (Odorfer, 1995). The cataract was nuclear in 28% of calves and in 18% of adults. Congenital bilateral cataracts are autosomal recessively inherited in several breeds of cattle, including the Jersey, Hereford, and Holstein-Friesian (Gelatt, 1971; Gregory et al., 1943). The cataracts are usually mature when the calves are 4–11 months of age. Congenital, nuclear, nonprogressive cataracts have also been reported in cattle (Ashton et al., 1977; France & Shaw, 1990; Grahn et al., 2016). In the cases described by Ashton (Ashton et al., 1977), the nuclear opacity ranged from abnormal refractivity to a dense, white opacity. The incidence of cataracts was 31% in one herd and 34% in another, and no sex predilection was noted. Similar cataracts were seen among 3.73% of 830 calves examined in England and Wales (Clay, 1977). Environmental causes were suspected with cataracts that were more common in calves born during late summer months and were rarely seen in calves born to heifers (France & Shaw, 1990). Gelatt has also reported congenital cataracts, documenting a Hereford cow and its bull calf with complete, mature, cortical cataracts (Gelatt, 1971). In a study of congenital nuclear cataracts in a closed purebred Holstein dairy herd, 21% of



Figure 30.47 Complete congenital cataract of unknown cause in a calf. (*Source*: Courtesy of Cecil Moore.)

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the animals were affected. No environmental or infectious causes were detected, and the data and pedigree analysis supported a genetic basis for this condition (Grahn et al., 2016). In Romagnola cattle, juvenile-onset bilateral nuclear cataract has been reported. In this breed, the condition has been determined to be inherited as a monogenic autosomal recessive inheritance associated to a deletion in the *nidogen 1* (*NID1*) gene (Murgiano et al., 2014).

Other ocular abnormalities in association with cataracts have been described in the Hereford, Holstein-Friesian, Jersey, and Shorthorn breeds. Multiple ocular anomalies including cataracts have been attributed to a dominant inherited trait in a herd of cows bred with a Hereford bull (Kaswan et al., 1987). The ocular defects in Holstein-Friesian cattle are lens luxation, buphthalmia, retinal detachment, and occasional lens rupture (Carter, 1960). Aniridia, microphakia, lens luxation, and cataracts occurred in Jersey calves as an autosomal recessive trait in one study (Saunders & Fincher, 1951) and as a dominant gene in another (Carter, 1960). Hydrocephalus in association with ocular defects, including cataracts, occurred in Shorthorn calves with a suspected dominant inheritance (Greene & Leipold, 1974; Leipold et al., 1971). Microphthalmia and cataracts with retinal lesions may occur in calves exposed to bovine viral diarrhea *in utero* at days 76–150 of gestation (Bistner et al., 1970) (see Chapter 37, Part 4).

Acquired and Secondary Cataracts

Secondary cataracts occur as sequelae to an inflammatory episode. Examination typically reveals ocular changes compatible with previous inflammation, such as posterior synechiae and pigment deposition on the lens (Fig. 30.48 and Fig. 30.49). Most infectious systemic diseases have the potential to affect the uveal tract and cause secondary cataracts. Various infectious causes of bovine uveitis are listed previously in the "Inflammation of the Uvea" section. A hematogenously disseminated infection with *Rhizopus* spp. that resulted in endophthalmitis and cataracts has been reported (Vasconcelos & Grahn, 1995). Microscopic ocular lesions in this case included vasculitis, suppurative keratitis, anterior uveitis, chorioretinitis, and extensive subcapsular cataracts.

Cataracts, goiter, and infertility have been reported as a result of an exclusive diet of *Leucaena leucocephala* (commonly known as white leadtree, jumbay, river tamarind, subabul, or white popinac) (Holmes et al., 1981). The toxic component was suspected to be mimosine, which may lead to formation of insoluble protein aggregates within the lens. Radiation-induced cataracts have been seen in some cattle (Brown et al., 1972). The cataracts typically begin at the posterior pole and may subsequently involve the entire lens. Hereford cows exposed to between 200 and 600 rads of cobalt-60 gamma radiation at 15–20 months of age developed cataracts at a rate of 6.7%.



Figure 30.48 Anterior segment of a cow with cataract secondary to chronic uveitis. Posterior synechia, capsular pigment deposits, and cortical cataract are present. (*Source*: Courtesy of Ellison Bentley.)



Figure 30.49 Complete cataract secondary to uveitis. Note multiple areas of posterior synechia and pigment deposition on anterior lens capsule. (*Source*: Courtesy of Kirk N. Gelatt.)

In some cataract cases, the cause remains unknown (Fig. 30.50). Among five calves in one report, the idiopathic cataracts were bilateral and involved the axial anterior lens capsules and anterior cortices. In one older Hereford bull, punctate bilateral lens opacities were observed throughout the anterior and posterior lens cortex. The lens nucleus and capsules were normal, but the cortices were translucent. All other ocular structures were normal, and the cataracts were nonprogressive (Gelatt, 1971).

Treatment of Cataracts

Most incomplete or immature cataracts in cattle do not result in noticeable vision problems, and therefore are not usually examined by ophthalmologists. Cataract surgery has been successfully performed in food animals (Gelatt, 1971). The decision to perform surgery is governed by economic factors, general health of the animal, presence of coexisting ocular

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Figure 30.50 Immature cortical and nuclear cataract of unknown cause in an Angus cow. (*Source*: Courtesy of Kirk N. Gelatt.)

disease, technical expertise of the individual, and intended use of the animal. Ethical questions also arise. The suggested inherited nature of cataracts implies that breeding animals should not be operated on, or that if they are, they should not be bred subsequently. Previous reports are favorable regarding the success of cataract extraction in cattle (Gelatt, 1971).

The Ocular Fundi

Ophthalmoscopic Examination

Fundic examination is facilitated by administration of 0.5%–1.0% tropicamide topically, though incomplete mydriasis occurs in cattle (Gelatt et al., 1995). Maximum mydriasis within 1 hour resulted with 1% and 3% atropine and with 0.25% scopolamine. Phenylephrine (10%) caused either no or limited mydriasis. With adequate restraint of the animal's head and mydriasis, both direct and indirect ophthalmoscopy are easily performed in food animals, because eye movements are limited.

The clearest focus of the bovine fundus is obtained by setting the diopter reading on the direct ophthalmoscope in the range from 21 D to 25 D; most are in focus at 23 D or 24 D. The bovine retina is typical of mammalian retinas (Fig. 30.51) (Mason et al., 1973). Like most domestic ruminants, the retina of the cow is holangiotic. Three, and occasionally four, major venules drain the retina, and these are accompanied by paralleling arterioles. The superior arteriole and venule may twist about each other. Additional arterioles radiate from the optic disc; from the major vessels, secondary and tertiary branches may arise. The vessels also project far more vitread than in most other domestic species. Increased tortuosity of many, or all, retinal vessels may occur, and the tortuosity may be bilateral (McCormack, 1974). Inflammatory signs are usually absent.

The tapetal fundus varies from yellow to bluish purple, and it is uniformly stippled by end-on capillaries (i.e., stars

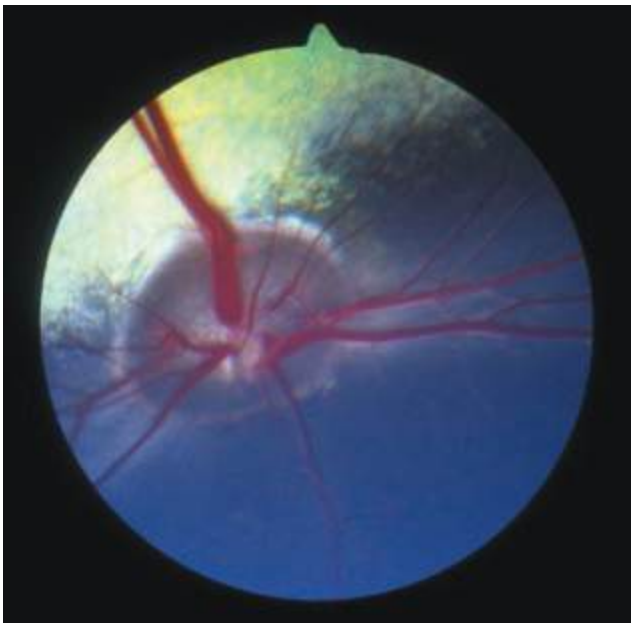


Figure 30.51 Normal bovine ocular fundus. The optic disc is predominantly in the non-tapetal fundus. The large, primary blood vessels emerge from the surface of the optic disc. (*Source*: Courtesy of Wendy Townsend.)

of Winslow). The reflective material of the bovine tapetum is a large array of extracellular collagen fibrils arranged in lamellae of varying thickness (Ollivier et al., 2004). Pigment occurs commonly in the tapetal fundus, especially in the dorsomedial quadrant. The average size of the bovine tapetal fundus is 55.8 × 32.2 × 39.6 mm (McCormack, 1974). It follows the general shape of a right triangle with a horizontal base that traverses just superior to the optic disc.

The non-tapetal fundus is generally a uniform shade of brown, and there is little variation with the coat color or breed. The optic disc is always located at the junctional area of the non-tapetal and the tapetal fundi, usually within the non-tapetal fundus just below the junction.

The optic disc is in the shape of a horizontally flattened oval. In most, the temporal portion is located nearer to the tapetal fundus than is the nasal portion. Myelinization of the optic nerve fibers normally stops at the lamina cribrosa. Myelin may occasionally continue onto the retina for a short distance and appear as white fiber bundles with featherlike margins protruding from the optic disc. These medullated fibers are not usually present at birth, but they may develop within the first months of life. A physiologic cup is present in older animals but not usually in the young. The average size of the optic disc in cattle is 4.2 mm horizontally and 2.9 mm vertically. The size of the disc, however, is directly proportional to the animal's size. The largest disc occurs in adult bulls and the smallest disc in newborn calves. The mature bull has a disc more circular in shape, with margins more indistinct than those in the cows.

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The optic disc varies in color. In general, the young animal (<6 months) has a white to salmon-pink disc with distinct margins. Older animals may have discs of orange, gray, tan, or various combinations. The most common disc coloration in adult animals is an orange center with a grayish brown periphery. The orange central zone contains the vessels, and the darker, grayish outer zone is the sheath of the optic nerve. Hyaloid remnants (specifically, Bergmeister's papilla) frequently protrude from the center of the optic disc into the vitreous body, appearing as gray, translucent protuberances (Fig. 30.52) (McCormack, 1974).

In addition to the primary pairs of vessels that emerge from the disc, 15–20 other vessels cross the margins of the disc. These small arterioles and venules emerge from the disc in a radiating fashion and disappear from view approximately 0.5- to 1.0-disc diameters from the optic disc. An "area striata," the bovine equivalent of the area centralis, consists of a band-shaped area running horizontally above the disc in the lower part of the tapetal fundus.

Congenital Disorders

Congenital fundic abnormalities are unusual, but they may mimic acquired lesions. The prognostic implications of an acquired versus a congenital lesion may be profound. Acquired lesions may affect the entire herd if caused by infectious diseases. Therefore, careful ophthalmic and systemic evaluations of affected animals should be performed.

Ocular Albinism

Complete albinism is rare, but it has been documented in cattle (Leipold & Huston, 1966; Leipold et al., 1968). More commonly, a partial albinism (i.e., subalbinism) is described (Gelatt et al., 1969; Ojo, 1982). In one study of congenital ocular defects in calves, complete albinism accounted for 5% of defects and incomplete albinism for 38% (Barkyoumb & Leipold, 1984). Albinism is an inherited disorder of melanin metabolism in which the ocular, cutaneous, or oculocutaneous melanocytes do not possess the normal amount of melanin. Albinism may relate to faulty tyrosine metabolism.

In cattle, complete albinism is characterized by pink skin and a lack of pigment in the muzzle, eyelids, iris, and choroid (Greene et al., 1973). Affected animals have clinically normal vision. However, they may have variable amounts of photophobia, and nystagmus may be present as well. Ophthalmoscopic examination reveals a normal, beige (albinotic), or yellow (subalbinotic) tapetal fundus, but no pigment in the non-tapetal fundus. Retinal blood vessels are superimposed on the underlying choroidal blood vessels (Fig. 30.53). Histopathologic examination reveals pigment only in the posterior layer of the iris and the ciliary body; the retinal pigment epithelium contains few melanin granules.

Colobomatous Malformations

Colobomas of the choroid are relatively common among cattle. Various estimates indicate a prevalence rate of 1%–2%. Typical colobomas of the optic disc occur in the dominant form of incomplete albinism among Hereford cattle

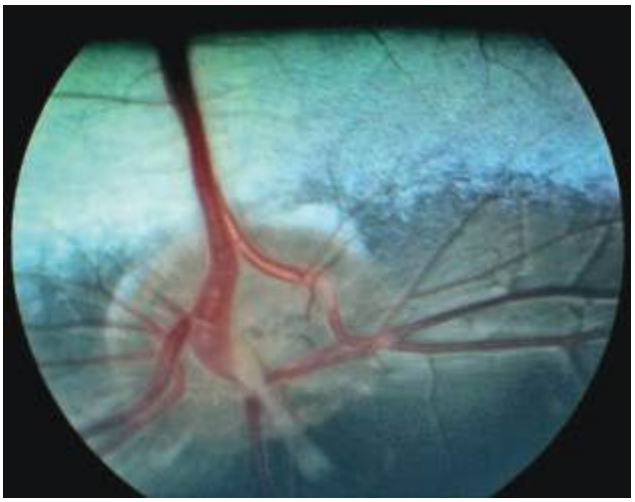


Figure 30.52 Bovine ocular fundus showing the presence of a hyaloid remnant (Bergmeister's papilla) protruding from the center of the optic disc. Also note intertwined dorsal retinal arteriole and venule characteristic of typical bovine fundus. (*Source*: Courtesy of Gia Klauss.)

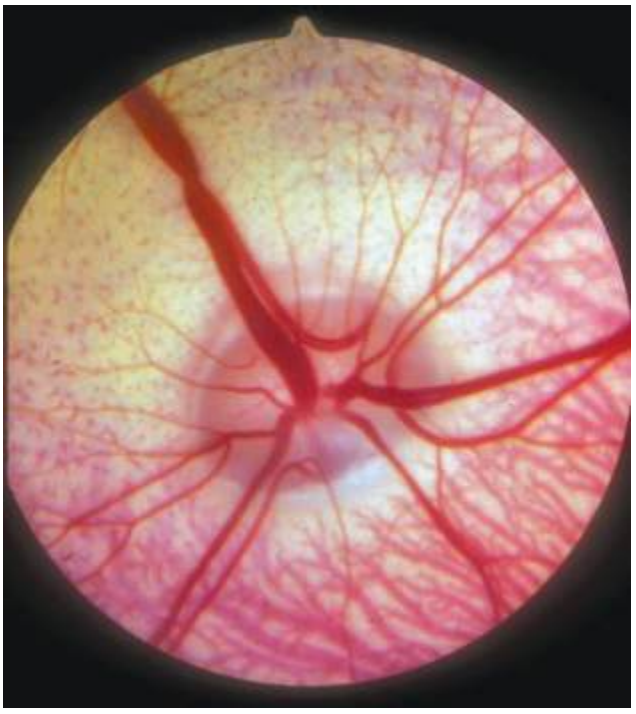


Figure 30.53 The ocular fundus of a subalbinotic Shorthorn calf. The tapetal fundus is light yellow clinically. The absence of pigmentation in the non-tapetal fundus allows underlying choroidal vasculature and white sclera to be observed. (*Source*: Courtesy of Kirk N. Gelatt.)

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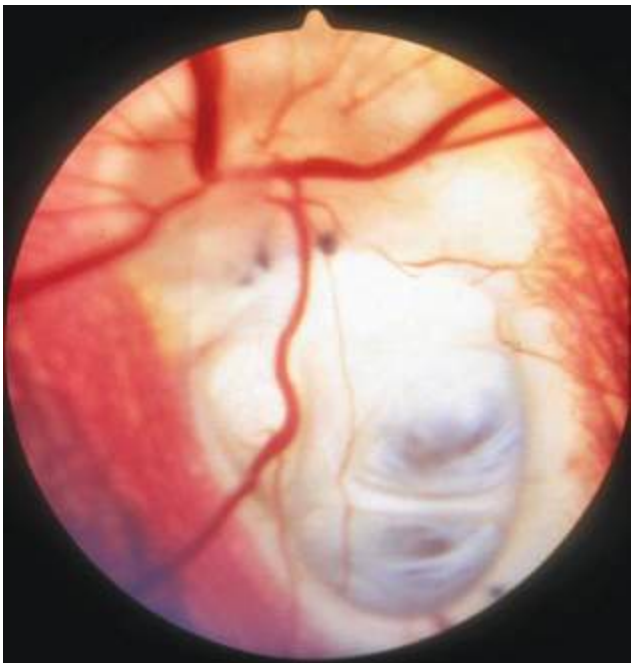


Figure 30.54 Typical coloboma of the optic disc and non-tapetal fundus. The multiple-depth defect is traversed by a large venule and a smaller arteriole. (*Source*: Courtesy of Kirk N. Gelatt.)

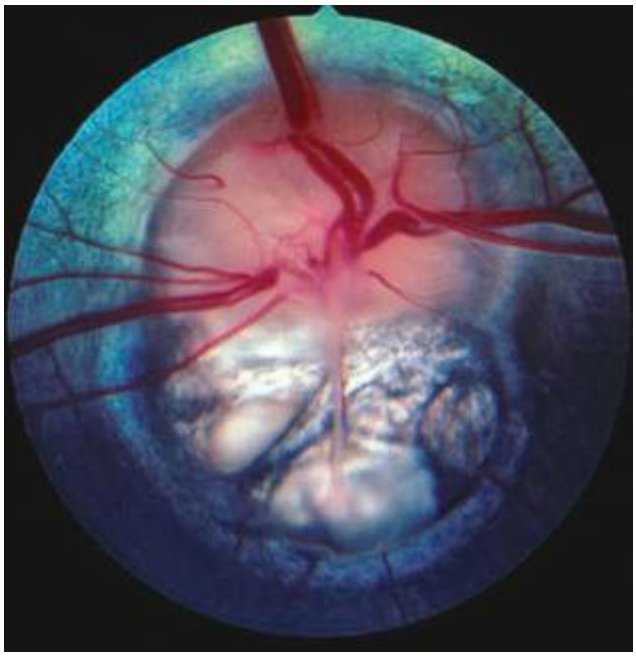


Figure 30.55 Typical coloboma in a Charolais cow. (*Source*: Courtesy of the University of California-Davis Comparative Ophthalmology Service.)

(Fig. 30.54 and Fig. 30.55) (Gelatt et al., 1969). In this syndrome, the colobomas are always bilateral, but they are not necessarily symmetrical. Both the clinical and histopathologic features of ocular anomalies, including colobomas, in such animals have been documented (Fig. 30.56) (Ojo, 1982). The colobomas vary markedly in size and depth (i.e., from one-quarter to five-disc diameters wide and 1–6 D deep).

Histopathologically, smaller colobomas show retinal thinning (primarily from photoreceptor loss and loss of the outer nuclear layer), choroidal hypoplasia, and normal sclera (Ojo, 1982). Occasional retinal rosettes occur as well. In larger colobomas, changes of the optic nerve head, retina, choroid, and sclera are pronounced. Retina within these large colobomas either is thickened and disorganized or is a thin glial membrane. The retinal pigment epithelium is incomplete, the choroid absent, and the sclera thinner than normal.

Typical colobomas of the optic disc occur in Charolais cattle; they are bilateral and often small, though not symmetrical, and are generally restricted to the posterior segment (Barnett & Ogien, 1972). Larger colobomas involve the entire optic disc and occasionally extend into the choroid and sclera in other areas of the ocular fundus. The effect of the ocular defect on vision ranges from slight to severe. In some extreme cases, calves have been born blind with grossly affected eyes. The pattern of inheritance for typical colobomas in Charolais cattle is suggestive of a dominant mode, but test breedings are indicative of a polygenic inheritance (Barnett & Ogien,1972).

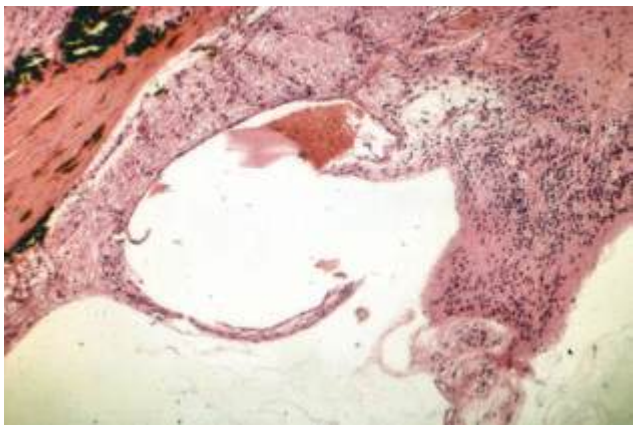


Figure 30.56 Hematoxylin and eosin stained photomicrograph of a colobomatous area adjacent to the optic disc in a Hereford calf with incomplete albinism. The disorganized retinal and glial tissues have formed a cyst filled with eosinophilic debris. (×100.) (*Source*: Courtesy of Kirk N. Gelatt.)

Congenital Vascular Anomalies

Remnants of the hyaloid vessel appear as a white, irregular tube extending from the optic disc to the posterior pole of the lens. If the vitreous body is fluid, small movements of these structures can occur. Normally, only a small, translucent structure (Bergmeister's papilla) projects from the optic disc into the posterior vitreous. Sometimes, these hyaloid remnants may terminate in a fine fiber. Histopathologically, the persistent hyaloid artery is surrounded by glial cells. The fine

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thread is made of those arterial remnants not surrounded by glial cells (Schebitz & Reike, 1953).

A persistent hyaloid artery has been found in 54% of calves younger than 6 weeks of age (Odorfer, 1995). Some hyaloid vestige can nearly always be found. In older cattle, 80% of animals may still have some remnant of the hyaloid.

Retinal Dysplasia

Inherited forms of dysplasia must be differentiated from those resulting from intrauterine infection with infectious agents, such as bovine virus diarrhea virus. On histopathologic sections, the retinal rosette is diagnostic of retinal dysplasia (Fig. 30.57). Multiple inherited ocular anomalies, including retinal dysplasia and internal hydrocephalus, have been reported in Shorthorn cattle (Fig. 30.58) (Greene & Leipold, 1974; Leipold et al., 1971). Data collected were consistent with either a recessive or incomplete penetrant dominant mode of inheritance. The retinas were not only dysplastic but were often detached. These detachments were believed to result from differences in the growth rate of the inner and outer layers of the embryonic eye.

Osteopetrosis-Induced Ocular Fundus Disease

Osteopetrosis in cattle is a generalized skeletal disease characterized by the absence of bone cavities because of defective bone remodeling (Greene et al., 1974). The disease is expressed as an autosomal recessive trait (Huston & Leipold, 1971). Clinical signs resulting from this condition include fragile bones, brachygnathia, hypoplastic foraminae, and various neurologic defects (e.g., blindness). Most animals are premature at birth and are stillborn. The disease has been described only among North American Black Angus cattle (Greene et al., 1974).

The ocular complications of osteopetrosis include defects in the retina and optic nerve. The optic nerves have prominent, thick interfascicular connective tissue septa and round to irregular basophilic bodies in surrounding areas of spongy nervous tissue. Retinal lesions are characterized by numerous vacuoles that result from necrotic ganglion layer cells (Greene et al., 1974).

Inflammations of the Ocular Fundus

Various infectious agents have been implicated as causing posterior segment inflammatory changes in food animals. Cattle have been reported to be affected by neonatal septicemic infections (*Escherichia* and *Pasteurella* spp.), thromboembolic meningoencephalitis (*Histophilus somni*, formerly *Hemophilus somnus*), rabies and other viral causes, toxoplasmosis, tuberculosis, and listeriosis (Bardsley, 1989; Crispin, 1989; Hindson, 1989; Mee & Rea, 1989; Rubin, 1974; Watson, 1989). See Chapter 37, Part 4 for additional details.

Degeneration of the Ocular Fundus

Most documented retinal degenerations in food animals are acquired and arise from ingestion of forage material. Ocular defects usually are only one of several systemic signs in such cases. Chronic inflammatory diseases may also result in degenerative retinal disease. Possible genetically based retinal degenerations have also been reported in cattle (Bradley et al., 1982; Stehman & Rebhun, 1987).

Abnormalities in outer retinal or visual cortex function may be assessed, when feasible, by electrodiagnostic means. Normal values for the ERG and visual-evoked potentials have been reported for cattle (Kotani et al., 1993; Strain et al., 1990). In Holstein-Friesian cattle, a significant difference in ERG amplitude and latencies was found between adults and calves, and the a- and b-wave ERG latencies in Japanese Black calves were significantly different from those in adult Japanese Black cattle (Kotani et al., 1993). Electrodiagnostic testing has been used in ruminants with thiamine responsive polioencephalomalacia or suspected listeriosis (Strain et al., 1990).

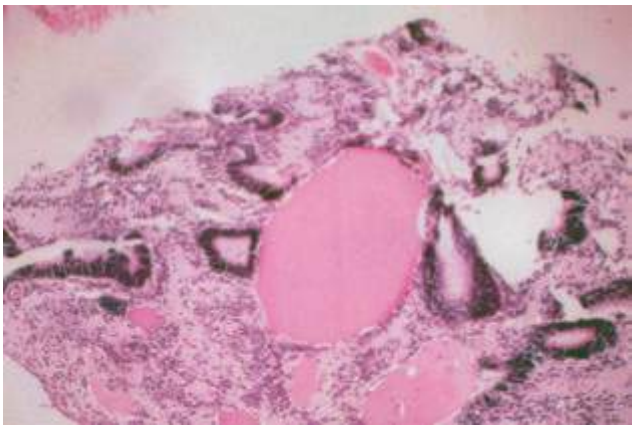


Figure 30.57 Hematoxylin and eosin stained photomicrograph of retinal rosettes typical of retinal dysplasia adjacent to a large retinal vein in a Shorthorn calf. (*Source*: Courtesy of Kirk N. Gelatt.)

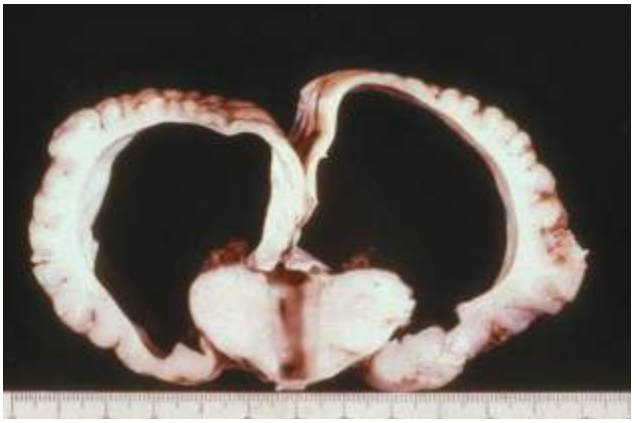


Figure 30.58 Marked internal hydrocephalus in a Shorthorn calf. (*Source*: Reprinted with permission from Gelatt, K.N. (1976) Congenital ophthalmic anomalies in cattle. *Modern Veterinary Practice*, **57**, 105–109.)

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Possible Hereditary Retinal Degeneration

A condition similar to canine progressive retinal atrophy occurs in cattle (Rubin, 1974). A familial occurrence, implying a possible genetic link, has been suggested but not proven (Bradley et al., 1982; Stehman & Rebhun, 1987). Clinical signs initially include pupils that are poorly responsive to light stimulation and nyctalopia with subsequent blindness. Fundic examination is typical of retinal degeneration. Tapetal hyperreflectivity, small vessel attenuation (but preservation of the larger vessels until late in disease), and minimal optic nerve abnormalities characterize the disease initially. Diffuse pigmentation of the tapetal fundus occurs in the end stages of the disease. There may be little difference in color between the tapetal and non-tapetal fundi. The optic disc appears a brownish gray (Fig. 30.59). Histopathologic examination cannot show normal rod photoreceptors. Lesions are limited to cell loss in the outer nuclear and photoreceptor layers, but the inner nuclear layer may also be thinned in severely affected areas (Fig. 30.60) (Bradley et al., 1982; Kotani et al., 1993).

A suspected inherited retinal degeneration caused by a mutation in the *retinitis pigmentosa* (*RP*) *1* gene has been documented in Normande dairy cattle. The majority of the cows homozygous for the *RP1* gene mutation show signs of bilateral retinal degeneration after 4 years of age, with hyperreflective tapeta and thinning of the retinal vasculature. Although the majority of the heterozygous animals had a normal fundic exams, a few heterozygous animals also presented with signs of retinal degeneration. Full field electroretinography showed a complete absence of response in homozygous cows (Chahory et al., 2015).

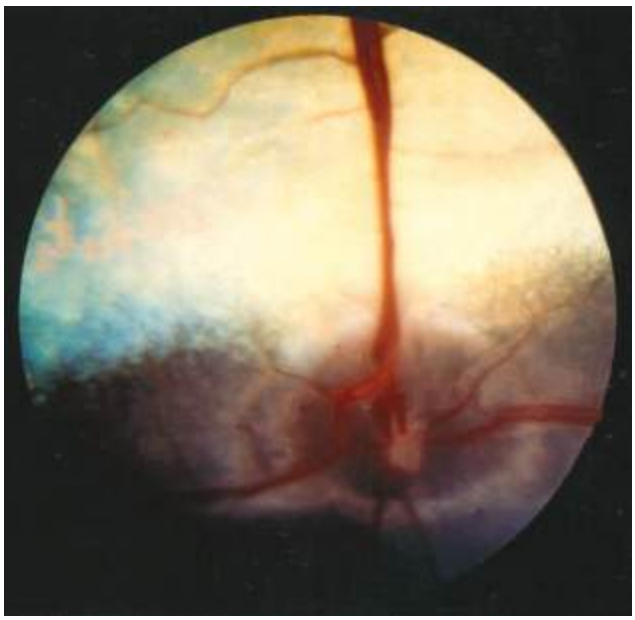


Figure 30.59 Funduscopic photograph of a congenitally blind Japanese Black calf showing thin retinal vessels. The optic discs in some of these calves appear slightly smaller than normal. (*Source*: Reprinted with permission from Kotani, T., Kurosawa, T., Numata, Y., et al. (1993) The normal electroretinogram in cattle and its clinical application in calves with visual defects. *Progress in Veterinary Comparative Ophthalmology*, **3**, 37–44.)

Vitamin A Deficiency

Serum vitamin A inhibits the differentiation of pre-adipose cells into adipose cells, affecting the beef marbling score. Therefore, some breeders try to maintain low serum vitamin A levels in their herds (approximately 30 IU/dL). However, vitamin A is essential for rhodopsin regeneration, normal bone maturation and remodeling, and normal epithelial function. Vitamin A deficiency may cause blindness, abnormal bone growth, abnormal epithelial function, and embryologic maldevelopment. In Japanese Black Cattle, serum vitamin A deficiency has been associated with bleaching of the tapetum, white mottling of the non-tapetal fundus and pale optic discs (Takahashi et al., 2011). This topic is covered in detail in Chapter 37, Part 4.

Retrobulbar Neuropathy and Retinal Degeneration

Ingestion of *Dryopteris filix-mas* (i.e., male fern) is associated with vision loss caused by retrobulbar optic nerve disease (Mitchell & Wain, 1983; Rosen et al., 1970). Bilateral blindness is the main presenting sign, but weakness, malaise, and constipation can also occur. In severely affected animals, optic nerve atrophy occurs with subsequent retinal degeneration. Fundoscopy reveals hemorrhage on or about the optic disc and various amounts of papilledema (Fig. 30.61). Chronically affected animals exhibit blindness, optic nerve atrophy, attenuated retinal vasculature, and tapetal degeneration.

Histopathologic findings reveal both death of retinal ganglion cells and loss of optic nerve fibers. Within the optic nerve, myelin and axons are widely destroyed, but axons per-

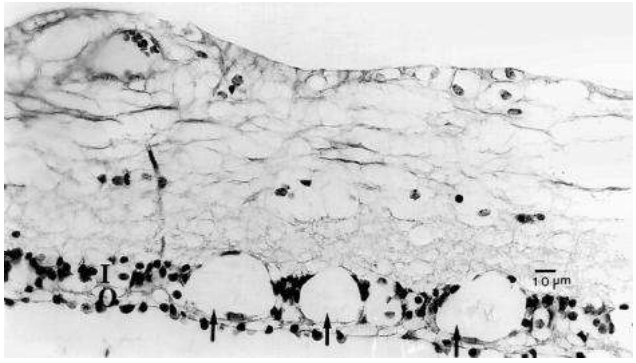


Figure 30.60 Retina from a congenitally blind Japanese Black calf. The nuclear layers are thin, with the inner nuclear layer showing vacuolar degeneration (arrows). Photoreceptors are absent. I, inner nuclear layer; O, outer nuclear layer. (*Source*: Reprinted with permission from Kotani, T., Kurosawa, T., Numata, Y., et al. (1993) The normal electroretinogram in cattle and its clinical application in calves with visual defects. *Progress in Veterinary and Comparative Ophthalmology*, **3**, 37–44.)

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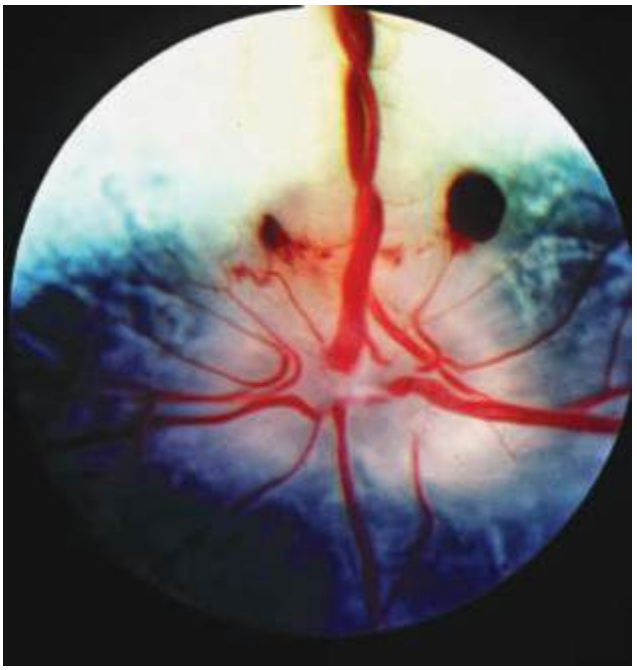


Figure 30.61 Fundus photograph of a cow after ingestion of male fern. Hemorrhage is evident on and adjacent to the optic disc and papilledema is present. (*Source*: Courtesy of the University of California-Davis Comparative Ophthalmology Service.)

sist in areas where myelin is absent. These findings suggest that the primary toxic action is on the medullary sheaths and their associated oligodendrocytes, which may be more vulnerable because of their lipoid nature.

Hypothiaminosis

Polioencephalomalacia (PEM), or cerebrocortical necrosis, is most often caused by thiamine deficiency (Edwin et al., 1968; Markson et al., 1972). The disease of PEM is most commonly seen in young feedlot cattle on low-fiber, high-concentrate rations. Under these dietary conditions, ruminal concentrations of thiamine are decreased (Smith, 2009). Ingestion of thiaminase-containing plants, such as bracken fern (*Pteris aquilina*), can also cause secondary thiamine deficiencies. PEM has also been caused by water deprivation and intake of high levels of sulfur, either through *ad libitum* ingestion of concentrates, mineral premixes, plants in the family *Brassicaceae*, or high sulfur content in the water (Gooneratne et al., 1989; Hamlen et al., 1993; Low et al., 1996; McKenzie et al., 2009; Padovan, 1980). Treatment with copper, as well as vitamin B_1, appears to be beneficial for the sulfur-induced cases (Hamlen et al., 1993).

The basic lesion of PEM is necrosis of the cerebrocortical neurons, with associated perineuronal and pericapillary edema (Markson et al., 1972). Neurologic signs are associated with increased cerebrospinal fluid pressure and neuronal necrosis; impaired vision may be an early sign. The blindness is cortical, but ocular signs of papilledema and decreased pupillary light reflexes may occur. ERGs remain normal, but visual-evoked potentials are abnormal (Strain et al., 1990). Bilateral dorsomedial strabismus also may be present (Rebhun, 1984).

Treatment consists of thiamine hydrochloride (6–10 mg/kg) either intramuscularly or intravenously every 8 hours (Daly, 1968). Corticosteroids may benefit cases early in the course of disease. Recovery may be slow and decreased vision or blindness may persist.

Locoweed Poisoning

Poisoning with locoweed (*Astragalus* and *Oxytropus* spp.) causes retinal degeneration in cattle, sheep, and other species (Smith, 2009; Van Kampen & James, 1970). Bipolar, ganglion, and ciliary body epithelial cells show vacuolation of the cytoplasm. Similar changes occur in brain neurons (Van Kampen & James, 1970, 1971). The lacrimal gland has marked cytoplasmic vacuolation of the secretory cells, and poisoned animals show vision disturbances and dry lackluster eyes.

Other Toxic Plants

Several other plant species may also cause neurologic disease with visual impairment, and in some cases, blindness precedes death. Water hemlock (*Cicuta* spp.) causes an acute syndrome associated with sudden death (Radostits et al., 2007). A fatal mycotoxicosis of cattle has been recognized in Australia and feeding trials have shown a previously unknown mycotoxic species of *Corallocytostroma* that grows on Mitchell grass (*Astrebla* spp.) (Jubb et al., 1996). The disease is colloquially called "black soil blindness." The onset of blindness and rapid progression to death are the main clinical features of this disease.

Kochia scoparia (Mexican fireweed, summer cypress, or burning bush) can produce blindness and nystagmus (Dickie & Berryman, 1979). Darling pea (*Swainsona galegifolia*) causes signs similar to those of locoweed in cattle and sheep (Hartley & Gibson, 1971).

Inherited Lysosomal Storage Diseases

A variety of inherited lysosomal storage diseases with ophthalmic implications have been reported, including GM1-gangliosidosis (i.e., leukodystrophy in Holstein cattle), GM2-gangliosidosis (i.e., lipodystrophy in Angus and Beefmaster cattle), and mannosidosis (Smith, 2009). The inherited lysosomal storage diseases are covered in Chapter 37, Part 4.

Optic Nerve Diseases

A primary demyelinating disorder of young Limousin crosscalves has been described (Palmer et al., 1991). Approximately 1 month after birth, affected animals showed signs of blindness, nystagmus, rotation of the eyes, opisthotonus, hyperprotraction of the forelegs, and in one case, seizures.

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Histopathologically, there was necrosis of the optic chiasm and focal areas of myelin sheath vacuolation or demyelination, particularly in the cerebellar peduncles. In one case that lived for 7 months, there was remyelination by Schwann cells of some axons, but there was no evidence of oligodendrocyte remyelination. A genetic association was considered to be likely.

Papilledema is a descriptive term for noninflammatory swelling of the optic disc caused by various conditions. It may signal increased intracranial pressure. In cattle and sheep, papilledema is commonly encountered. Causes may include vitamin A deficiency (Fig. 30.62) (Divers et al., 1986), acquired and congenital hydrocephalus (Leipold et al., 1971), space-occupying brain lesions (McCormack, 1973), meningitis, encephalitis, and hexachlorophene toxicity (Udall, 1972).

Papilledema is usually bilateral. The optic disc margins appear to be hazy, and the physiologic depression is lost. The disc becomes thickened and swollen and appears to be grayish white with striations. The retinal veins and arteries show a distinct bend as they pass down over the edge of the disc and onto the retina. The retinal venules may be dilated and engorged peripherally, and hidden centrally within the swollen disc. Many more fine veins are visible. The arterioles are a brighter red and more threadlike than the congested venules. If the cerebrospinal fluid pressure remains elevated, the optic nerve and disc will atrophy.

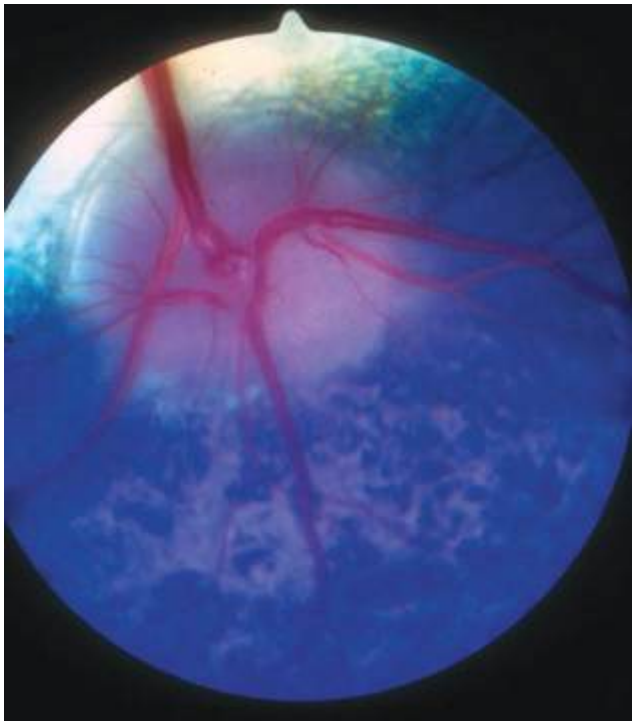


Figure 30.62 Papilledema and retinal degeneration secondary to Hypovitaminosis A in a yearling Angus steer. (*Source*: Courtesy of Kirk N. Gelatt.)

Sheep and Goats

Ocular Examination and Ophthalmic Parameters

For proper restraint, sheep and goats can be backed into a corner, with their head restrained by an assistant. A sheep shearing stand, or goat milking stand, may also be helpful. Sheep and goats have an oval-shaped, horizontally positioned pupil, with corpora nigra present on the dorsal and ventral pupil margin (Fig. 30.63).

In a study comparing the tear production and corneal sensitivity in several species, it was determined that sheep have a higher tear production and a more sensitive cornea, compared with goats. The tear production in sheep was determined to be 26.4 ± 17.7 mm/min, whereas in goats it was 14.5 ± 3.78 mm/min. Corneal sensitivity in sheep was 35.23 ± 8.09 mm, whereas in goats it was 30.50 ± 5.60 mm (Wieser et al., 2013). A study comparing IOP in sheep using TonoVet and TonoPen Avia revealed average pressure of 11 mmHg and 10 mmHg, respectively. In goats, average value obtained with the TonoVet was 23 mmHg, whereas the TonoPen Avia revealed average IOP of 13 mmHg (Peche & Eule, 2016). The tear production and IOP appear to increase as the animal grows, similar to other species. In Saanen goats, tear production is higher in older animals, compared with young ones (13.80 mm/min vs. 10.38 mm/min). The same is true of IOP, which was determined to be 9.79 mmHg in adult animals, and 8.03 mmHg in young goats (Ribeiro et al., 2010).

As in other species, anesthetic and sedative agents may have an effect on the IOP in sheep. For example, anesthesia induction with a ketamine-diazepam combination without premedication significantly decreases IOP immediately after induction of anesthesia, with subsequent return to baseline values after intubation. However, in sheep premedicated



Figure 30.63 Normal extraocular photograph of a goat showing well-developed corpora nigra and a horizontally oriented oval pupil.

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with sustained-release buprenorphine, the induction with the same combination of ketamine-diazepam does not alter the IOP immediately, and an increase in IOP can be observed after intubation (Gatson et al., 2015). On the other hand, when a combination of propofol-diazepam is used as the induction agent without premedication, no changes in IOP are observed at any time-point. In sheep premedicated with sustained-release buprenorphine, a small (but not significant) decrease in IOP is observed immediately after induction, followed by a significant increase 5 minutes after induction. Because both protocols using sustained-release buprenorphine as the preanesthetic agent lead to an increase in IOP after intubation, this regimen should be avoided in sheep when increases in IOP are undesirable (Gatson et al., 2015).

A study evaluating the echobiometric changes with age in goats determined that the sizes of axial globe length, central corneal thickness, anterior chamber depth, anterior-posterior lens size, and vitreous chamber size increased with age, and reached adult size at 1.5 years old (Ribeiro et al., 2009). Age also influence the corneal characteristics in sheep. The average central corneal thickness in lambs is $699 \pm 56\,\mu m$, whereas in adults it reaches $804 \pm 87\,\mu m$. Endothelial cell density (ECD) decreases with age, with average of $3532 \pm 259\,cells/mm^2$ in lambs, and $2204 \pm 261\,cells/mm^2$ in adults (Coyo et al., 2016).

The Orbit and Globe

Congenital Globe Abnormalities and Blindness

In a study of congenital malformations in the eyes of sheep, microphthalmia with multiple cysts was observed (Rosenfield & Beath, 1947). In histopathologic studies of the malformed eyes, both cellular and structural misplacement occurred during early embryonic development. The purported cause of these malformations was selenium toxicity, but this suggestion has been disputed (O'Toole et al., 1996). Through collaborative research in Switzerland, Germany, and Australia, microphthalmos in Texel sheep has been linked to a region on chromosome 23 (Tetens et al., 2007). The condition is an autosomal recessive trait and results from a missense mutation in the homeobox gene *PITX3* (Becker et al., 2010). The most common maternal infection causing multiple ophthalmic defects in offspring is bluetongue disease in sheep (see Chapter 37, Part 4).

Teratogenic Agents

Veratrum californicum

Among domestic animals, the best-documented teratogenic ocular defects have been those associated with ingestion of *Veratrum californicum* in sheep. Various globe abnormalities, such as anophthalmia, cyclopia (one central globe), and synophthalmia (two fused globes), may be induced in lambs by the maternal ingestion of *V. californicum* (Fig. 30.64)



Figure 30.64 Synophthalmos in a lamb. (*Source*: Courtesy of David Wilkie.)

(Binns et al., 1962, 1963). The common names of *V. californicum* include skunk cabbage, western helibore, false helibore, and wild corn. The plant varies widely in toxicity and teratogenic agent between the different range areas. Among affected flocks, the incidence of malformations may be 25%. Such malformations have been reproduced under controlled, experimental conditions by feeding sheep both fresh and dried *V. californicum*. The agents responsible are a group of alkaloids (e.g., jervine, pseudojervine, isorubijervine, and veratrosine) that occur throughout the plant but are concentrated in the roots (Keeler & Binns, 1966).

Sheep embryos are highly susceptible to the teratogenic agent cyclopamine, a steroidal alkaloid, from the plant *V. californicum* when the plant is eaten by the ewe on gestational day 14 (Binns et al., 1965). In cases of cyclopia, this timing corresponds to the period of gastrulation and formation of the neural plate, before separation of the optic fields. Ewes fed plants on gestational days 11, 12, 13, 15, and 16 had normally developed fetuses or normally developed embryos that died between the 18th and 23rd days of embryonic development. All embryonic deaths occurred in ewes with severe clinical signs of poisoning. The dose of *V. californicum* that had a teratogenic effect was less than that necessary to cause clinical signs of poisoning in the ewes. The elimination half-life of cyclopamine in ewes has been determined and is 1.1 ± 0.1 hours. The rapid clearance of cyclopamine confirms that ingestion of *V. californicum* must occur during a very narrow window for synophthalmia formation to occur (Welch et al., 2009).

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Other teratogenic effects arising from ingestion of *V. californicum* include distortion of the facial bones, fusion of the cerebral hemispheres, absence of the pituitary gland, hydrocephalus, and anophthalmia. Occasionally, the anomaly involves full-term twin lambs, one of which is malformed and the other normal. This discrepancy could result from a difference in the developmental rates of the respective embryos. Teratogenic effects of *V. californicum* have also been reported in cattle and goats (Binns et al., 1972).

Selenium

Selenium has been credited historically with causing "blind staggers" in livestock and being a teratogenic agent (Rosenfield & Beath, 1947, 1964). Reported necropsy findings attributed to ewes grazing on seleniferous pastures include: microphthalmia with multiple cysts; corneal, lens, and iris defects; and colobomas of various structures. However, examination of the original data (Draize & Beath, 1935; Rosenfield & Beath, 1946) reveals many inconsistencies and false conclusions (O'Toole et al., 1996). Furthermore, some of the reported selenium values are not compatible with current guidelines for acute toxicity (O'Toole et al., 1996). Thus, it has now been speculated that many field cases of blind staggers were in fact sulfur-related PEM. Plants that bioaccumulate selenium are often associated with waters high in sulfate, and high sulfate levels have been linked with PEM (Gooneratne et al., 1989; Hamlen et al., 1993; Jeffrey et al., 1994). A review of 40 years of data from the laboratory that proposed the original association revealed no substantiated cases of naturally occurring selenosis (Raisbeck et al., 1993).

Other possible causes of blind staggers include malignant catarrhal fever, the polyhydroxyindolizidine alkaloid swainsonine, chronic laminitis, parasitism, thromboembolic meningoencephalitis, lead poisoning, and starvation (O'Toole et al., 1996). The cause of the congenital ocular defects may actually have been maternal ingestion of *V. californicum* or some other teratogen.

The Eyelids

Entropion

Congenital entropion is relatively frequent in small domestic ruminants and usually affects the lower lid (Fig. 30.65) (Moore & Whitley, 1984). A combination of orbicularis oculi muscle spasticity and globe retraction by the retractor bulbi muscle encourages additional eyelid inversion. The incidence of congenital entropion in sheep varies markedly between flocks; documented reports range from 1.0% to 80.0% (Green et al., 1995; Wyman, 1983). Entropion in sheep is thought to be inherited as a polygenic trait (Green et al., 1995; Littlejohn, 1954; Taylor & Catchpole, 1986). In one study, a greater proportion of lambs suffered entropion if sired by Charolais or Texel rams compared with those sired by Suffolk rams (Green et al., 1995).

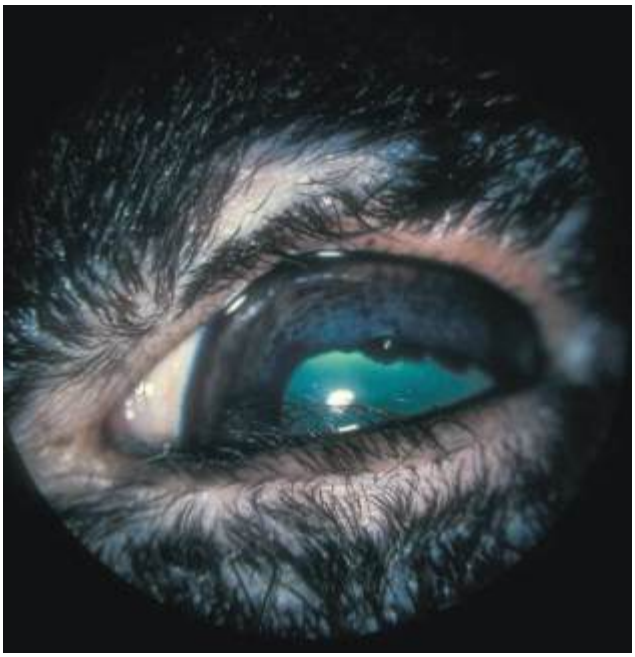


Figure 30.65 Inferior eyelid entropion and secondary keratitis in a lamb. (*Source*: Courtesy of Kirk N. Gelatt.)

Initial clinical signs are frequently bilateral and may be seen in lambs 2–3 days old (Moore & Whitley, 1984). With uncontrolled progression of the disease, an initial serous epiphora may become mucopurulent. Secondary corneal ulceration and vascularization, keratouveitis, and endophthalmitis may develop as well (Moore & Whitley, 1984). Treatment involves eversion of the affected eyelid, and a variety of techniques are possible. Mechanical eversion using two or three metal wound clips adjacent to the eyelid margin or vertical mattress sutures may be used (Rasmussen, 1980). Tissue glue has been used in other species to create an effect similar to that achieved using a vertical mattress suture, and subcutaneous injections of minor irritants (e.g., 1–2 mL of penicillin) have also been used. The tissue swelling thus created corrects the entropion, and subsequent fibrosis helps to prevent recurrence. If only a few lambs are affected by severe entropion and corneal disease that persists into adulthood, or if highly valuable individual animals are affected, a modified Hotz–Celsus technique is effective (Shams & Din, 1992). Affected lambs should not be retained for breeding.

Ectropion

Congenital ectropion is rare, but it has been recorded in Piebald sheep. Affected animals exhibit a gross deformity or notching of the upper eyelid with entropion at either side (Littlejohn, 1969).

Surgical intervention is recommended when secondary ophthalmic disease results. The surgical procedures primarily aim to shorten and strengthen the affected lid (Smith, 2009). Most ectropion procedures involve the lateral eyelid

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and lateral canthus so that the nasolacrimal system is preserved.

Eyelid Colobomas

Eyelid colobomas (Fig. 30.66) have been seen in goats and appear to be more frequent in rare sheep breeds, such as Hebridean, Manz Loaghtan, and Jacob (Hindson & Winter; Hosie, 2000). The defect can be found in association with the four-horn gene.

Blepharitis

Bacterial

Pyogranulomatous cutaneous nodules with associated draining tracts may occur on the face of sheep and goats after cutaneous punctures and secondary infection with *Actinobacillus lignieresii* (Moore & Whitley, 1984). Eyelid edema and facial swelling are observed with "bighead" disease in sheep, in which blepharoedema may develop secondary to anaerobic infection with *Clostridium novyi* (Wyman, 1983). Secondary keratitis and conjunctivitis may develop because of a resulting lagophthalmos. Dermatophilosis (rain scald or lumpy wool) occurs as in cattle. See the bovine section for more details.

Mycotic

Trichophyton spp. (usually *verrucosum*) can affect all food-producing animals (Smith, 2009). Sheep and goats may also be affected by *Microsporum* spp. (Radostits et al., 2007; Smith, 1983). Dermatomycoses occur most commonly in goats and may result in crusty areas of periocular and facial alopecia (Moore & Whitley, 1984). Owners should be informed of the zoonotic potential. The disease may resolve spontaneously within 4–5 weeks in an individual animal, but it may persist in a flock for some months. Despite the self-limiting nature of the disease, treatment is recommended to limit any further infection of unaffected animals and humans (Radostits et al., 2007). Topical and systemic fungicidal agents, iodine shampoos, improved nutrition, and dry environs may assist in eliminating the disease. Vaccination of newly infected herds shows potential as a prophylactic measure (Smith, 2009).



Figure 30.66 Superior eyelid coloboma in a goat. (*Source*: Courtesy of Gia Klauss.)

Viral

Viral diseases implicated in eyelid disease include pox viruses, orbivirus, and papilloma virus (Moore & Whitley, 1984). The pox viruses are species-specific under natural conditions; however, multiple antigens are shared by members of the same subgroup. Sheep and goat pox (*Capripoxviruses*) may have morbidity rates of up to 70%, and the mortality rate may reach 50% (Wyman, 1983). The first ocular signs are circular, hyperemic maculae of the eyelids, which then progress to firm papules elevated above the surrounding tissue. Serum exudate and blepharospasm may occur as well. Contagious viral pustular dermatitis (contagious ecthyma, sore mouth, and orf) is a *Parapoxvirus* causing a sequence of papules, vesicles, pustules, and scabs on the eyelids, lips, muzzles, and nostrils of sheep and goats, but it does not usually cause systemic illness. Ovine ulcerative dermatosis virus (lip and leg ulcer) is an unclassified pox virus similar to contagious ecthyma, but the former causes lesions that are ulcerative and destructive rather than proliferative, as with contagious ecthyma (Smith, 1983). Specific treatment is neither necessary nor effective in uncomplicated cases, but symptomatic treatment is advised. The potential for zoonotic infection does exist. Vaccinations are available for contagious ecthyma, sheep pox, and goat pox.

Bluetongue virus is an acute, noncontagious orbivirus spread by *Culicoides variipennis* midges. The virus may cause blepharitis and conjunctivitis in sheep, and it occasionally affects cattle. Hyperemia and eczema of the periocular skin may occur. The most notable change, however, is retinal dysplasia in lambs born to infected ewes (Moore & Whitley, 1984).

Papillomatosis is caused by a DNA virus that may affect the eyelids of sheep with a predilection for young animals up to 5 years of age (Wyman, 1983). Papillomas are usually benign, self-limiting, and may have an associated blepharitis. Surgical removal of the papillomas may potentiate the immune system to the virus (Moore & Whitley, 1984).

Ectoparasites

Sarcoptic mange is caused by *Sarcoptes scabiei*, with a subspecies specific for each host species (Smith, 2009). The lesions become widespread except in sheep, in which they are restricted to the haired skin of the face and eyelids (see the bovine section) (Moore & Whitley, 1984). Treatment with moxidectin at a dose of 0.2 mg/kg given twice at 10-day intervals or ivermectin injected subcutaneously at a dose of 0.2 mg/kg provide satisfactory results (Gnad & Mock, 2001).

Demodex caprae is a mite that can inhabit hair follicles in goats (Gnad & Mock, 2001). Pustules form around the mites, causing skin lumps on the head, neck, and shoulders. The

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diagnosis is made by microscopically identifying the cigar-shaped mite. Demodectic mange is generally not harmful, and treatment is usually not necessary (Loomis, 1986). *Psoroptes, Psorergates*, and *Chorioptes* spp. are cutaneous mites that may cause intense pruritus but infrequently involve the facial area (Lofstedt, 1983; Radostits et al., 2007).

Keds (*Melophagus ovinus*), lice (*Bovicola* and *Linognathus* spp.), and ticks may cause pruritus and self-trauma. Periocular involvement is secondary to self-trauma and results in mild conjunctivitis and blepharitis (Moore & Whitley, 1984). Drugs such as coumaphos, diazinon (do not use on goats), fenvalerate, malathion, methoxychlor, and permethrin may be used to control infestations (Gnad & Mock, 2001).

Endoparasites

Elaeophorosis (sore head) is a disease of sheep caused by *Elaeophora schneideri*, an intraarterial parasite of deer, elk, and domestic sheep (Abdelbaki & Davis, 1972; Smith, 2009). The horseflies *Hybomitra* and *Tabanus* spp. are the intermediate hosts (Pence & Gray, 1981; Wyman, 1983). Local inflammation because of migration of *Elaeophora* microfilaria may cause severe facial dermatitis, keratoconjunctivitis, uveitis, chorioretinitis, optic neuritis, and CNS disease. The skin lesions involve the face and are pruritic, alopecic, ulcerated, and encrusted. Adult animals are more often affected in the winter months. The demonstration of microfilariae in biopsy specimens is diagnostic (Moore & Whitley, 1984) and treatment is symptomatic for the secondary ocular lesions (Wyman, 1983). Treatment of the parasite may cause death by occlusion of the carotid arteries in heavily parasitized animals (Smith, 2009). Treatment options include piperazine, diethylcarbamazine, and stibophen.

Photosensitization

Direct solar irritation (i.e., sunburn) may occur in food animals with little periocular pigmentation, but acute periocular dermatitis is more likely the result of photosensitization (see the bovine section).

The Conjunctiva and Cornea

Similar to many other species, the normal conjunctival microflora of sheep has a preponderance of Gram-positive bacteria. Depending on the study, positive cultures for bacteria may be found in 40%–100% of individuals and for fungi in 86% of individuals (Bonelli et al., 2014). The most frequently isolated bacteria are *Bacillus subtilis*, *Enterococcus* sp., *Bacillus cereus*, *Escherichia coli* and *A. faecalis*. The most common reported fungi are *Aspergillus* sp., *Penicillium* sp., *Alternaria* sp., and *Cladosporium* sp. (Bonelli et al., 2014). Geographic location and environment also play a substantial role on ocular surface microflora. In a study evaluating the conjunctival bacterial flora of goats in the midwestern United States, *Staphylococcus* and *Streptococcus* were the most common bacterial genera isolated from adult (94%) and young (100%) animals. *Moraxella bovoculi* was the most common single isolate in adult animals, whereas it was *Staphylococcus equorum* in young goats. *Mycoplasma* sp. DNA was detected by PCR in fewer than 50% of the animals, and no DNA of *Chlamydia* sp. was identified (Meekins et al., 2017).

Infectious Keratoconjunctivitides

Decreased twinning rates in ewes, increased cases of pregnancy toxemia, starvation, weight loss, blind ewes trampling offspring, and decreased economic return have all been attributed to infectious keratoconjunctivitis (Egwu, 1991). Numerous infectious agents have been implicated, and the terms pink eye, heather blindness, or blight are therefore used somewhat broadly. The causative agents producing the clinical sign of keratoconjunctivitis in small ruminants are probably varied, with no one organism consistently being responsible.

Chlamydial Keratoconjunctivitis

Chlamydia pecorum (formerly a serotype of *Chlamydia psittaci*) is an important cause of keratoconjunctivitis in sheep and goats, and polyarthritis in sheep (Nietfeld, 2001). *C. pecorum* is introduced into a flock by affected animals often with mild infection (Hosie, 2000; Matthews, 1999). Transmission can occur between sheep and goats. Direct contact is the most important method of transmission.

Chlamydiae are obligate, intracellular bacteria (Everett, 2000). They have a unique development cycle involving two morphologic forms: the elementary body and the reticulate body. The elementary bodies are specialized for extracellular survival, insensitive to antibiotics, and infectious. The reticulate bodies are sensitive to antibiotics and are obligate, intracellular organisms engaged in active multiplication within eukaryotic host cells (Bogaard, 1984). They are found in cytoplasmic vesicles termed cytoplasmic inclusion bodies.

C. pecorum is associated with an infectious keratoconjunctivitis in sheep that occurs worldwide (Andrews et al., 1987; Surman, 1979). Outbreaks usually occur during the lambing season, when ewes and lambs are confined with maximal contact and stress. Carrier animals may be reservoirs for the disease. The pathogenesis is probably multifactorial, with the immune status of the animal, secondary infection, and other factors all playing a role (Bogaard, 1984). Experimental transmission has been successfully performed to naive animals through inoculation of infective lacrimal fluids into the lacrimal sac (Wilsmore et al., 1990). In the clinical setting, immunity appears to be of short duration because animals may be infected repeatedly. However, in experimental disease, not all lambs could subsequently be reinfected (Wilsmore et al., 1990). Those animals from which

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Chlamydia were recovered had less severe conjunctivitis, thereby implying at least a limited immunity to subsequent challenge.

In experimental conditions, clinical signs begin within 4 days of infection and initially include epiphora, chemosis, and conjunctival hyperemia. By 11 days post-infection, the serous conjunctival exudates become more purulent with associated blepharospasm. Lymphoid follicles begin to develop by 23 days postinfection (Wilsmore et al., 1990), but they can also develop as early as 6 days after inoculation with *C. pecorum* and *Branhamella ovis* (Dagnall, 1994b). The follicular reaction is not unique to this disease; many causes of conjunctivitis may result in follicular hyperplasia (Dagnall, 1994b). Approximately 10% of patients develop interstitial keratitis one week after the initial signs develop with deep vascularization and edema of the cornea (Cello, 1967). Because corneal ulceration is uncommon, permanent scarring of the cornea is infrequent (Egwu, 1991; Hosie, 2000).

A diagnosis is most easily obtained from scrapings of infected conjunctival epithelial cells early in the course of the disease (Bogaard, 1984; Wilsmore et al., 1990). New methylene blue, Wright's, or Giemsa stains show the typical cytoplasmic inclusions in infected cells. However, fluorescent antibody staining is preferable because Chlamydiae can be confused with melanin granules (Hosie, 2000). Failure to culture Chlamydiae in the latter part of the disease process does not necessarily preclude *Chlamydia* spp. as the initial causative agent. Culture in the latter stages of chlamydophila-induced ocular disease may show a variety of commensals, such as *Brucella ovis* (Wilsmore et al., 1990). Fourteen days after experimental inoculation, Chlamydiae could be isolated from 80% of lambs, but by 18 days postinfection, Chlamydiae usually could not be isolated. However, immunofluorescent antibody tests were able to detect chlamydial antigens 5 weeks postinfection. Therefore, fluorescent antibody tests may be more sensitive than culture in detecting Chlamydiae.

The currently available ELISA kits are manufactured for identification of *Chlamydia trachomatis* and have not been evaluated for diagnosis of *C. pecorum* (Nietfeld, 2001). Although identification with PCR is possible, false-negative results because of inhibitors in the samples could be a problem (Rodolakis et al., 1998).

In most clinical settings, testing is not economically viable and treatment is instituted empirically. The most effective treatment is a single intramuscular injection of long-lasting oxytetracycline (20 mg/kg) (Hosie, 2000). Daily feeding of 150–200 mg of tetracycline per head to lambs and kids reduces the incidence and severity of disease. Intramuscular injection of tylosin or topical application of tetracycline ophthalmic ointment provides satisfactory results (Hosie, 2000; Matthews, 1999; Smith & Sherman, 1994).

Mycoplasmal Keratoconjunctivitis

Although typically thought to be more common in goats, *Mycoplasma* spp. have been associated with conjunctivitis in sheep and goats both clinically (Egwu et al., 1989; McCauley et al., 1971; ter Laak et al., 1988b; Van Halderen et al., 1994) and experimentally (Egwu & Faull, 1991; ter Laak et al., 1988a). Subclinical carrier states of *Mycoplasma* spp. exist as well because, in some animals, the presence of *Mycoplasma conjunctivae* is not associated with clinical disease (Dagnall, 1994a, 1994c). The lack of association may result from differences in the pathogenicity between individual strains, or the samples may have been taken just before development of clinical signs. The respective conjunctival isolates for sheep and goats were *M. conjunctivae* var. *ovis* and *M. mycoides* var. *capri*. Concurrent presence of *Branhamella ovis*, *Escherichia coli* and *Staphylococcus aureus* may enhance the severity of keratoconjunctivitis (Dagnall, 1994a; Egwu et al., 1989).

There may be a slight variation in clinical signs between sheep and goats (Dagnall, 1993a; Egwu, 1991; Konig, 1983; ter Laak et al., 1988a, 1988b). There is an initial hyperemia of the palpebral and conjunctival vessels, serous lacrimation, and blepharospasm (Fig. 30.67). Keratitis with superficial and deep vascularization may also develop (Egwu, 1991). In more advanced cases in sheep, a mucopurulent conjunctivitis, occasional follicular conjunctivitis, iritis with hypopyon, and corneal ulceration occur (Fig. 30.68). Phthisis bulbi rarely results, and the disease usually lasts between 1 and 4 weeks. Older sheep are generally more affected (Egwu, 1991; Van Halderen et al., 1994). Goats do not usually develop cor-

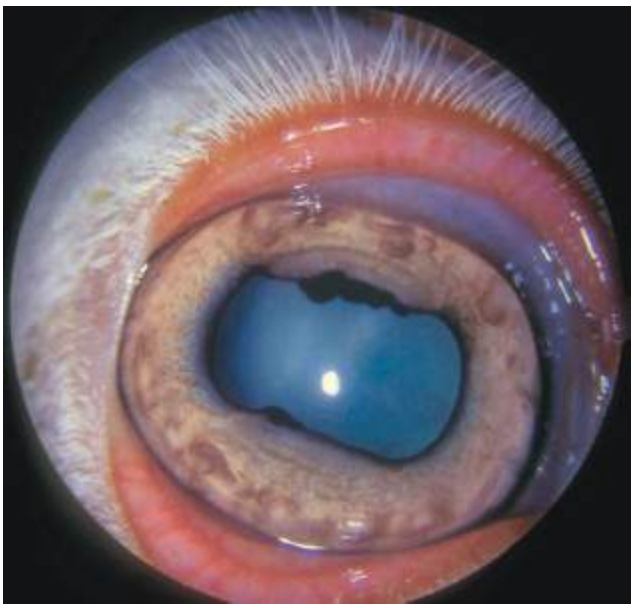


Figure 30.67 Early stage of keratoconjunctivitis associated with mycoplasma infection in a goat. Predominant early clinical signs are hyperemia of the palpebral and bulbar conjunctiva and epiphora. (*Source*: Courtesy of Kirk N. Gelatt.)

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Figure 30.68 Keratoconjunctivitis associated with *Mycoplasma* infection in a sheep approximately 7–10 days after the onset of clinical signs. Note the focal corneal opacities and vascularization. (*Source*: Courtesy of Kirk N. Gelatt.)



Figure 30.69 Keratoconjunctivitis associated with *Mycoplasma* infection in a goat. Extensive corneal abscessation, vascularization, and anterior uveitis are present. (*Source*: Courtesy of Cecil Moore.)

neal ulcers or hypopyon, but permanent corneal opacity and blindness may result (Fig. 30.69 and Fig. 30.70).

The diagnosis of infection with *Mycoplasma* spp. is made on the basis of clinical signs and results of conjunctival cytology, culture, and serology (Dagnall, 1994c; Levisohn et al., 1991; Wyman, 1983). Cytologic preparations can be



Figure 30.70 Advanced keratoconjunctivitis associated with *Mycoplasma* infection in a goat. In this case, the disease has progressed with axial consolidation of inflammatory cells and corneal abscessation. (*Source*: Courtesy of Cecil Moore.)

stained with Giemsa stain, carbol basic fuchsin stain of Gimenez, or Gram's stain. Cytologic specimens from healthy ovine eyes show predominantly epithelial cells, with occasional lymphocytes; neutrophils are rarely present (Dagnall, 1994c). In acute mycoplasmal keratoconjunctivitis, large numbers of neutrophils, but no plasma cells, can be found. Intracytoplasmic coccobacillary and ring-shaped bodies may be observed in epithelial cells with *Mycoplasma* spp. infection (Dagnall, 1994c). Bright-field as well as dark-ground examination of Giemsa-stained smears show *Mycoplasma* spp. in scrapes from the conjunctivae of affected and even healthy sheep. In some cases, the conjunctival epithelial cells contain phagocytosed neutrophils but no bacteria. The role of phagocytic conjunctival epithelial cells in the development of latent infections is uncertain.

The organism can also be cultured, provided that special nutrient requirements and incubation methods are used (Marmion, 1967; Van Halderen et al., 1994). Previous use of antibiotics can interfere with the growth of the organism in culture. Serology, including complement fixation, indirect hemagglutination, and ELISA tests, may be used in making the diagnosis. ELISA tests in goats may be used to detect subclinical mycoplasmal infection and individual carriers, which may assist in determining control measures (Levisohn et al., 1991). A fluorescent antibody test is available (Ruffin, 2001). A PCR assay based on the *16S rRMA* gene has also been described (Giacometti et al., 1999). In one report, a single PCR assay was shown to be robust, more rapid, and superior to culture in the face of known prior treatment with antibiotics (Baker et al., 2001). In most cases, testing for the organism is not economically viable and empirical treatment is pursued.

Mild infections are often self-limiting, but antibiotic therapy can shorten the course of disease and is indicated in severe cases (Hosie & Greig, 1995). Treatment may not elimi-

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nate *M. conjunctivae,* however, and it may promote a carrier state (Hosie & Greig, 1995). Oxytetracycline, applied either topically or intramuscularly (20 mg/kg), is the drug of choice. Minimal inhibitory concentrations and minimal mycoplasmacidal concentrations of various antibiotics suggest that tylosin, streptomycin, and chlortetracycline may be efficacious (Egwu, 1992). Topical 0.5% gentamycin has been reported to resolve the clinical signs in affected Lohi sheep (Shahzad et al., 2013). Florfenicol, a monofluorinated analogue to thiamphenicol, has a prolonged half-life of elimination after intramuscular and subcutaneous administration in sheep, and a large volume of distribution, which suggests good diffusion into body tissues (Jianzhong et al., 2004). In sheep, florfenicol readily penetrates the tear fluid after administration (20 mg/mL), with higher levels reached when injected or intramuscularly (0.7 μg/mL) compared to subcutaneous administration (0.22 μg/mL). However, the drug minimum inhibitory concentration for most strains of *Mycoplasma* range between 0.5 μg/mL and 8 μg/mL, indicating that doses higher than 20 mg/kg would be needed for treatment of most strains (Regnier et al., 2013).

Immunity to subsequent infection may be possible. Lambs experimentally infected with *M. conjunctivae* show evidence of both local and systemic antibody production (Egwu & Faull, 1991). Seroconversion occurs in adult ewes inoculated with *Mycoplasma* sp. (Egwu, 1991). Transient local and systemic antibody responses to *M. conjunctivae* occur among experimentally infected goats (Trotter et al., 1977) and in the serum of goats in spontaneous outbreaks (Baas et al., 1977). The role of local or systemic immunity is not known; they may be involved in the recovery from the disease (Egwu, 1991).

Diseases concurrent with mycoplasmal conjunctivitis include mastitis, pleuropneumonia, and arthritis in sheep and goats (Smith & Sherman, 1994). *M. agalactiae* has been associated with mastitis, arthritis, and conjunctivitis, with pregnant animals being more severely affected than nonpregnant animals (Hasso & Al-Aubaidi, 1993). A case of uveitis, pneumonia, and arthritis caused by infection with *Mycoplasma* spp. in the absence of keratoconjunctivitis has also been reported (Whitley & Albert, 1984). *Acholeplasma oculi* has been implicated as a cause of keratoconjunctivitis in sheep (Arbuckle & Bonson, 1980), with approximately 25% exhibiting blepharospasm, conjunctivitis, keratitis, and pannus. Subsequently, approximately half the flock was affected. Treatment with subconjunctival oxytetracycline was successful. *A. oculi* was also isolated from a group of goats with conjunctivitis and pneumonitis (al-Aubaidi et al., 1973).

Branhamella Keratoconjunctivitis

Cases of keratoconjunctivitis in sheep and goats have been attributed to *Branhamella ovis* (formerly known as *Neisseria ovis*), either alone or in combination with other microorganisms (Bankemper et al., 1990; Dagnall, 1994a, 1994b, 1994c; Fatimah et al., 1994). The role of *Branhamella* spp. as a primary pathogen is questioned by some authors, however, because it may be normal conjunctival flora (Bogaard, 1984; Fatimah et al., 1994). *B. ovis* occurs in conjunctival scrapings from affected as well as healthy sheep (Dagnall, 1994c). In one study of an infectious keratoconjunctivitis outbreak, *Branhamella* spp. were isolated in 40% of affected eyes, compared with 30% of unaffected eyes, but this difference was not statistically significant (Fatimah et al., 1994).

Both smooth and rough types of *B. ovis* have experimentally induced conjunctivitis, either alone or together with *M. conjunctivae* and *C. pecorum* (Dagnall, 1993b, 1994b). An isolate of *B. ovis* with smooth-colony morphology from a field case of follicular conjunctivitis could produce lesions similar to the field case when inoculated into the conjunctival sac of lambs. In association with *M. conjunctivae, B. ovis* contributes to the severity of the keratoconjunctivitis (Dagnall, 1994b).

Parasitic Keratoconjunctivitis

Oestrus Ovis

Oestrus ovis (also known as sheep nasal botfly) may cause conjunctivitis if larvae invade the ocular mucous membranes (Moore & Whitley, 1984). The condition is often referred to as external ophthalmomyiasis (Sucilathangam et al., 2013). The adult flies deposit eggs around the mucous membranes of the face. When the eggs hatch, the larvae migrate to the nasal cavity, turbinates, and the maxillary and frontal sinuses. Larvae may progress to the nasolacrimal duct and eye. The larvae are large (2.5 cm), spiny, and cause irritation. Secondary infection, epiphora, and conjunctivitis may result. The larvae mature within several weeks to months and then return to the nostril, where they drop or are sneezed onto the ground to pupate.

Treatment usually involves physical removal of larvae and systemic organophosphates. The only drug labeled for control of sheep nasal bots in the United States is Ivomec Sheep Drench (0.08% ivermectin), which may be administered only to sheep at 0.2 mg/kg (Gnad & Mock, 2001). Treatment is best performed in the fall months, when the larvae are small (Moore & Whitley, 1984). External ophthalmomyiasis caused by *O. ovis* has also been diagnosed in humans (Sucilathangam et al., 2013).

Thelazia Species

Thelazia californiensis occurs in sheep, deer, and other species (see the bovine section).

Other Parasites

Trypanosoma spp. are reported to cause blepharitis, conjunctivitis, and keratitis in sheep and goats (Moore & Whitley, 1984). Conjunctival cysts may be seen in the bulbar conjunctiva of sheep and goats infected with *Besnoitia* spp.

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Besnoitiosis, which is associated with alopecia, infertility, and abortion, is widespread in Africa and the Middle East (Bwangamoi et al., 1989).

Miscellaneous Conjunctival Abnormalities

Locoweed poisoning may cause keratoconjunctivitis sicca in sheep (Van Kampen & James, 1971). Drying of the eyes may result from chronic degenerative neurotoxicosis, causing failed neurogenic stimulation of tear secretion and an inadequate blink response.

Interestingly, the conjunctiva of sheep and goats is commonly used to detect anemic status of one individual or herd. With the increasing popularity of small ruminant farming and intensification of production systems, the control of gastrointestinal nematode parasites is an ongoing challenge (Kaplan et al., 2004). To add to the problem, many common pathogenic helminths have developed resistance to antihelmintics, requiring drastic measures to address the issue. The species of primary concern is *Haemonchus contortus*, a highly pathogenic blood-feeder that causes anemia, reduced productivity, and can lead to death in heavily infected animals (Burke et al., 2007). One of the major limitations to controlling the infections has been the lack of an efficient and economical means to identifying those animals requiring treatment. With that in mind, the FAMACHA© eye color chart system was developed (van Wyk & Bath, 2002). Originally developed in sheep, the test has also been validated for goat (Kaplan et al., 2004), bovines (Grace et al., 2007), and camelids (Storey et al., 2017). The test consists of a color chart that illustrates five colors of the palpebral conjunctiva: 1 (deep red; non-anemic), 2 (red-pink; non-anemic); 3 (pink; mild anemia), 4 (white-pink; anemic), and 5 (white; severely anemic). Several studies have shown that the FAMACHA eye score was strongly correlated with the degree of anemia (Kaplan et al., 2004; Burke et al., 2007; Storey et al., 2017), and the use of FAMACHA has successfully reduced the morbidity in the flock (van Wyk & Bath, 2002). The system has been deemed one of the most important advancements in small ruminant parasitology in the United States in recent years (Storey et al., 2017). The evaluator should remember, however, that other conditions may affect the pallor of the conjunctiva.

Phenothiazine-Associated Corneal Disease

Corneal edema and keratitis have been associated with phenothiazine toxicity, but this condition can be found mainly in calves and, to a lesser extent, in pigs and goats (see the bovine section) (Bistner et al., 1981; Enzie & Whitmore, 1953; Whitten et al., 1946).

Ocular Squamous Cell Carcinoma

Although uncommon, OSCC has been reported in sheep (Wilcock, 1993). In 2005, spontaneous OSCC in twin goats was reported (Mara et al., 2005). In both goats, Papillomavirus-like sequences were detected with PCR analysis, suggesting that, as in cattle, Papillomavirus may have played a role in the pathogenesis of the OSCC.

Glaucoma

Steroid-induced ocular hypertension is reported in sheep to occur after one week of prednisolone acetate topical treatment administered three times daily. After discontinuation of the corticosteroid instillation, IOP declined to baseline values over 1–3 weeks (Gerometta et al., 2009). A single dose of a gene therapy vector carrying an inducible metalloproteinase human gene is protective against the IOP increase produced by corticosteroid instillation in the sheep model and quickly reverses the IOP increase elicited by the corticosteroid (Gerometta et al., 2010).

The Uveal Tract

Iris Abnormalities

Defects in iris anatomy, termed "essential iris atrophy," have been described among purebred Shropshire sheep in Pennsylvania (Aguirre et al., 1981). Affected animals are normal at birth, but by 1.0–1.5 years of age may be affected with full-thickness holes in the iris stroma. The corpora nigra is rudimentary or absent, and animals are affected bilaterally but not symmetrically. Reported lesions have not been associated with any previous inflammatory episodes.

Inflammation of the Uvea

When treating uveitis, the use of iridocycloplegic drugs is often necessary to relieve the ciliary spasms and to allow ophthalmic examination of the ocular fundus. However, care should be taken when choosing a cycloplegic agent that will provide sufficient pupil dilation without increasing IOP. It is also important to remember that several cycloplegic agents may reduce ruminal and intestinal motility, and this parameter should be constantly monitored. In a study evaluating several mydriatic agents and administration routes, topical and subconjunctival 1% atropine, 0.5% tropicamide, and 1% homatropine induced pupil dilation, but resulted in significant reduction in ruminal and intestinal motility in healthy sheep. Topical 10% phenylephrine and 2% ibopamine did not result in pupil dilation. Changes in IOP were not observed with any of the administered drugs (Ribeiro et al., 2013.

In sheep and goats, neonatal pyosepticemia, listeriosis, mycoplasmal infections, toxoplasmosis, elaeophorosis, thiamine deficiency, trypanosomiasis, blunt trauma, retroviral, and toxic causes have been reported to have uveitis (Moore & Whitley, 1984; Radostits et al., 2007; Raoofi et al., 2004; Smith, 2009; Smith & Sherman, 1994). Additional information on such conditions may be found in Chapter 37, Part 4.

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Uveal Tumors

Although primary tumors of the anterior and posterior uvea are rare, a malignant melanoma has been reported in a sheep (Saunders & Barron, 1958). An iridociliary adenoma in a sheep has also been reported (Raoofi et al., 2004). One month after the affected globe had been enucleated, the ewe was doing well.

The Lens

Congenital Cataracts

Congenital cataracts have been reported in sheep, but they are rare in goats (Brooks et al., 1982a, 1982b; Smith & Sherman, 1994). Congenital nuclear cataracts have been observed in sheep and goats (Lavach, 1990). The cataracts did not progress to involve the cortex.

Acquired Cataracts

Inflammatory cataracts result from lenticular trauma or from severe uveitis. The nematode *Elaeophora schneideri* has induced cataracts among domestic sheep in the western United States (Abdelbaki & Davis, 1972). Diabetes mellitus has been implicated as the cause of cataracts in ram lambs (Mattheeuws et al., 1982).

The Ocular Fundi

Ophthalmoscopic Examination

The ocular fundi of cattle and sheep are quite similar ophthalmoscopically. The retina of the sheep is holangiotic (Fig. 30.71). Three, and occasionally four, major venules drain the retina, and these are accompanied by paralleling arterioles. Occasionally, in sheep, the superior arteriole and venule may twist about each other.

The tapetal fundus reflects a greenish-blue color and is a horizontal strip in shape with its lower edge just touching the point of entry of the optic nerve (Ollivier et al., 2004). The upper edge is not clearly defined. The optic disc is always located at the junctional area of the non-tapetal and the tapetal fundi, usually within the non-tapetal fundus just below the junction.

In sheep, the optic disc has a kidney shape. Myelinization of the optic nerve fibers normally stops at the lamina cribrosa. Small ruminants have stereoscopic vision, at least in middle-and long-distance vision but not in near vision (Moore & Whitley, 1984). Histopathologically, a high density of ganglion cell nuclei occurs in the retina (Nilsson et al., 1973). A study recently looked at the topography of ganglion cells and photoreceptors in the sheep retina. Retinal ganglion cells were distributed densely in the area centralis, horizontal visual streak, and anakatabatic (dorsotemporal) area. The highest density in the area centralis was approximately 18,000 retinal ganglion cells/mm^2. Cones showed high density in the horizontal area crossing the optic disc and dorsotemporal area, whereas rods showed high density in the horizontal area, which was greater in height than the horizontal area of high cone density. The rod/cone ratios were high horizontally in the retina dorsal to the optic disc, with a mean value of 11:1. This suggests that sheep have better visual acuity in horizontal and anteroinferior visual fields, which may be of ecologic benefit to them (Shinozaki et al., 2010).

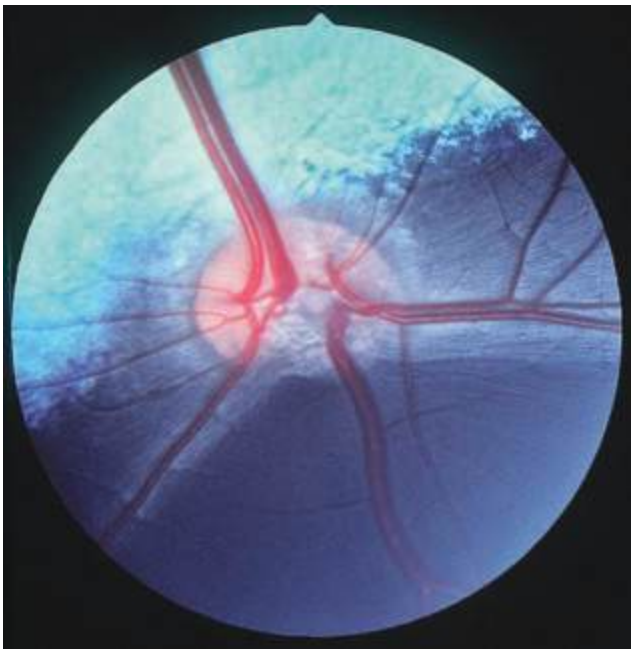


Figure 30.71 Normal ovine ocular fundus. The kidney-shaped optic disc is at the junction of the tapetal and non-tapetal fundi. (*Source*: Courtesy of the University of California-Davis Comparative Ophthalmology Service.)

The ocular fundus of the goat is somewhat different from that of cattle and sheep. The retinal blood vessels are more numerous, and five to eight primary venules often occur. The optic disc is rounder than in sheep and cattle, and it frequently is situated totally within the tapetal fundus. A pigment ring often surrounds the optic disc as well (Fig. 30.72) (Galan et al., 2006).

Fluorescein angiography without sedative or anesthetic agents has been evaluated in normal goats and sheep. All of the angiographic phases were observed using 20 mg/kg fluorescein IV in both species. Fundus fluorescein angiography results revealed wide stars of Winslow in the tapetal fundus, central or marginal flow during the first part of the arterial phase, delayed filling of the focal areas in the choroid near the optic disc that often coincided with others in the disc, and lack of evidence of the "striate area" in the tapetal fundi. In goats, the angiographic times were 6.54 ± 1.25 seconds for the arterial phase, 7.80 ± 1.37 seconds for the arteriovenous phase, and 14.13 ± 2.01 seconds for the venous phase. In

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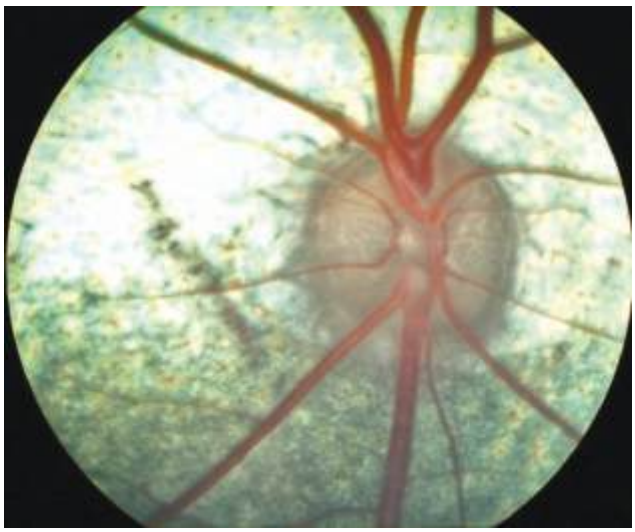


Figure 30.72 Normal caprine ocular fundus. The round optic disc is at the junction of the tapetal and non-tapetal fundus. (*Source*: Courtesy of Gia Klauss.)

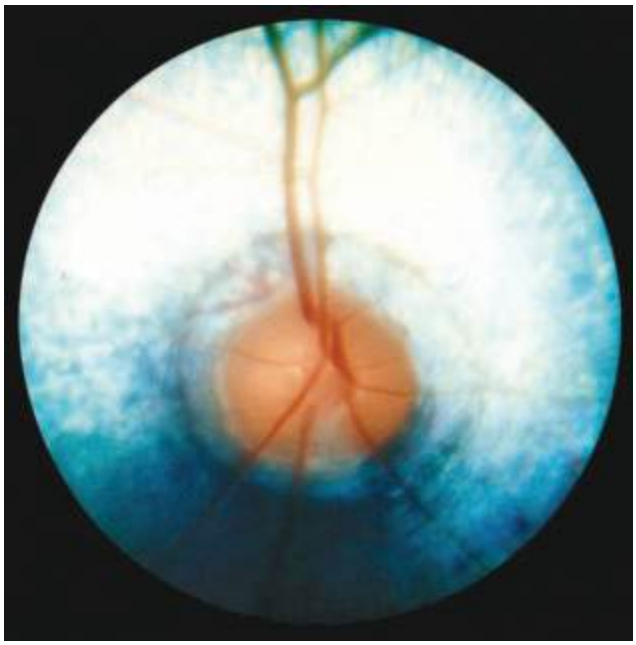


Figure 30.73 Fundus of a Toggenburg goat with retinal degeneration, generalized tapetal hyperreflectivity, and retinal vessel attenuation. (*Source*: Courtesy of Bruce Grahn.)

sheep, times were 9.54 ± 2.18 seconds, 11.73 ± 2.10 seconds, and 20.86 ± 2.74 seconds (Galan et al., 2006).

Ocular Albinism

Complete albinism is rare, but it has been documented in sheep (Adalsteinsson, 1977). In Icelandic sheep, albino animals have occurred among both white and nonwhite strains. Affected animals have visual deficits in bright light, and albino lambs with a normal twin are often deserted by the dam in open country. The albino condition in sheep totally inhibits the formation of both eumelanin and pheomelanin. The condition is autosomal recessive and is assumed to be a mutation at the C locus (Adalsteinsson, 1977). In Suffolk sheep, albinism is an autosomal recessive trait: the *cmar* (albino marrabel) gene on the C locus encodes a defective tyrosinase (Rowett & Fleet, 1993). This condition appears homologous to albinism in rodents (Adalsteinsson, 1977).

Retinal Dysplasia

Inherited retinal dysplasia must be differentiated from dysplastic changes resulting from intrauterine infection. Infectious agents, particularly bluetongue in sheep, have been implicated as causing retinal dysplasia (see Chapter 37, Part 4).

Inflammation of the Ocular Fundus

Various infectious agents have been implicated as causing posterior segment inflammatory changes in food animals. Small domestic ruminants have been reported to have posterior segment changes related to bacterial and parasitic causes (mycoplasmosis, listeriosis, elaeophorosis, trypanosomiasis, and toxoplasmosis) and viral causes (bluetongue and scrapie) (Barnett & Palmer, 1971; Moore & Whitley, 1984; Piper et al., 1970; Strain et al., 1990) (see Chapter 37, Part 4).

Degeneration of the Retina and Optic Nerve

Abnormalities in outer retinal or visual cortex function may be assessed, when feasible, by electrodiagnostic means. Normal values for the ERG and visual-evoked potentials have been reported for sheep (Strain et al., 1991).

Retinal Degeneration in Toggenburg Goats

Retinal degeneration has been reported in Toggenburg goats (Buyukmihci, 1980; Wolfer & Grahn, 1991). In the cases reported by Wolfer and Grahn, two kid goats born of half-sisters bred by the same buck were born blind. Clinically posterior segment abnormalities were the only significant lesions, and these consisted of generalized tapetal hyperreflectivity and retinal vascular attenuation (Fig. 30.73). Both kids had a searching nystagmus. Histopathology showed diffuse photoreceptor loss and the loss of virtually all the outer nuclear and outer plexiform layers. The inner nuclear layer was in an early stage of degeneration, but the ganglion cell layer and optic nerve were histopathologically normal (Fig. 30.74).

Stypandra glauca Intoxication

In sheep and goats, a syndrome of retrobulbar optic neuropathy and retinal degeneration occurs after ingestion of *Stypandra glauca* (i.e., blind grass) (Main et al., 1981; Whittington et al., 1988). Field evidence suggests that *S.*

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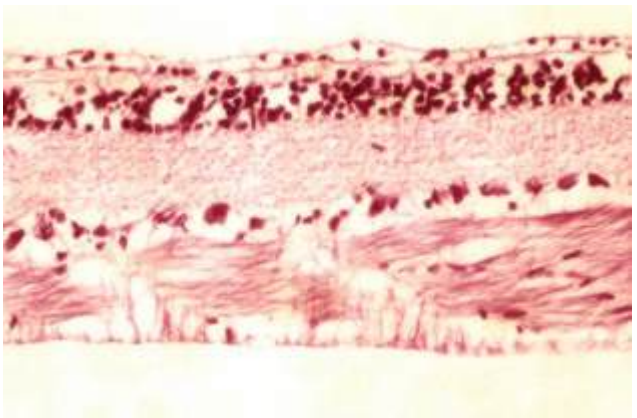


Figure 30.74 Histopathologic section with diffuse photoreceptor and outer nuclear layer retinal atrophy in a Toggenburg goat. (*Source*: Courtesy of Bruce Grahn.)

glauca is toxic in the flowering stage. Affected animals may die after an acute illness with signs of neurologic disturbances, or they may survive but remain permanently blind. Fundoscopy shows multifocal tapetal and peripapillary hyperpigmented foci interspersed with other areas of tapetal hyperreflectivity. Optic nerve atrophy may be present as well.

An ERG reveals a decreased b-wave amplitude (Whittington et al., 1988). Fluorescein angiography shows no leakage. Histopathology shows multifocal photoreceptor degeneration with accompanying hypertrophy of the retinal pigment epithelium. Optic nerve lesions are most evident in the intracanalicular and intracranial regions, with the orbital portion being relatively unaffected. Stypandrol, a binapthalene tetrol, is most likely the toxic principle. The pathogenesis of the optic neuropathy may relate to acute swelling of the optic nerve because of myelin edema, thereby resulting in compression and irreversible injury to the optic nerve within the bony optic canal. Stypandrol may also be directly retinotoxic.

Hypothiaminosis

PEM, or cerebrocortical necrosis, may be caused by thiamine deficiency (Edwin et al., 1982; Markson et al., 1972). The disease is especially common in goats fed a sudden excess of carbohydrates (Smith, 2009). Affected animals display blindness, ataxia, depression, opisthotonus, nystagmus, convulsions, coma, and can die of respiratory failure (see the bovine section) (Loew, 1975).

Pteris aquilinum-Induced Retinal Degeneration

Pteris aquilinum (i.e., bracken fern, brake fern, hog brake) has been associated with a progressive retinal degeneration (PRD) of the outer layers in sheep (Barnett & Watson, 1970; Watson et al., 1965, 1972a; Watson & Barnett, 1970). Affected animals have variously been called "bright blind," "moonlight blind," "clear blind," or simply "glass eyed"; this terminology has arisen on the basis of the abnormal shine of the affected eyes in semidarkness (Barnett & Watson, 1970). The disease has been seen clinically in sheep grazing bracken (*P. aquilinum*), and it has been reproduced experimentally by feeding a concentrate ration containing 50% dried bracken at 1 kg/day for up to 63 weeks (Watson & Barnett, 1970; Watson et al., 1972b). Ptaquiloside, which is a norsesquiterpine glucoside of the illudane type, is a bracken carcinogen and the principal causative agent of PRD (Hirono et al., 1993).

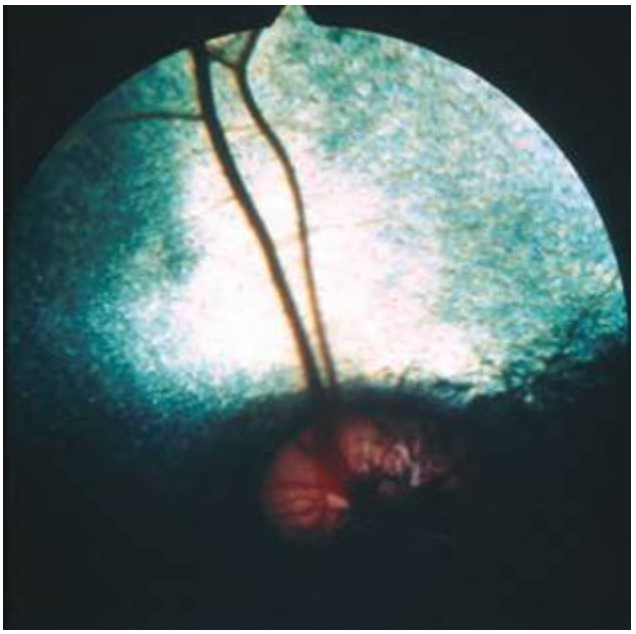


Figure 30.75 Advanced retinal degeneration (bright blindness) in an ewe secondary to toxic effects of bracken fern (*Pteris aquilina*). (*Source*: Courtesy of the University of California-Davis Comparative Ophthalmology Service.)

The disease is limited to certain areas, including northern England, Scotland, and possibly Wales. In flocks grazing bracken-laden fields, up to 25.6% of sheep may have PRD (Watson et al., 1972b). In any one flock, 37% of sheep may be affected. The incidence is highest among 3- to 4-year-old sheep. It is seldom seen in sheep younger than 2 years, but a 9-month-old ewe lamb has been affected. In field conditions, rams have never been affected (Watson et al., 1972a).

Clinically, the sheep are permanently blind. Affected animals have dilated pupils and sluggish pupillary responses. The earliest ophthalmoscopic sign is an increased tapetal reflection. The optic disc is normal. There is attenuation of the retinal blood vessels (Fig. 30.75). In advanced cases, the non-tapetal area is affected (Watson et al., 1965).

Biochemical and hematologic abnormalities also exist in PRD. Retinal lactate dehydrogenase isoenzyme activity decreases, and the ratio of H- to M-type monomers increases. Platelet and leukocyte counts are lowered as well.

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Histopathologic changes are confined to the retina. Initially, there is degeneration of the rod and cone outer segments, which fragment and break into fine, granular forms. As the disease progresses, there is loss of the rod, cone, and outer nuclear layers, as well as parts of the inner nuclear layer. As a result, the retinal pigment epithelium appears to abut directly onto the remains of the inner nuclear layer (Watson et al., 1965).

Locoweed Poisoning

As in cattle, poisoning with locoweed (*Astragalus* and *Oxytropus* spp.) causes retinal degeneration in sheep (see the bovine section) (James, 1972).

Other Toxic Plants

Sarcostemma spp. cause neurologic disease among sheep in Africa, and they may also be associated with visual impairment (Terblanche & VanStraten, 1966). Darling pea (*Swainsona galegifolia*) causes signs similar to those of locoweed in cattle and sheep (Watson et al., 1972a).

Other Ocular Toxins

Toxins other than those involving plants may cause retinal and optic nerve disease as well. Antiparasitic drugs, such as hexachlorophene and rafoxanide, may cause optic nerve pathology (Moore & Whitley, 1984). The toxic effects include degeneration and gliosis of the CNS, retina, and optic nerve, resulting in blindness and even death. In one flock of 168 sheep, 83 animals were affected, of which 25 (30%) died within 1 week of treatment (Prozesky et al., 1977). Histopathology of the optic nerves showed demyelination with Schwann cell proliferation, edema, and congestion. No structural abnormalities were seen in the retina.

Inherited Lysosomal Storage Diseases

Lysosomal storage diseases with ophthalmic implications include GM_1-gangliosidosis (i.e., leukodystrophy in Suffolk sheep), GM_2-gangliosidosis (i.e., lipodystrophy in sheep), mannosidosis in Anglo-Nubian goats, and ceroid lipofuscinosis in South Hampshire sheep in New Zealand (Smith, 2009). The inherited lysosomal storage diseases are covered in Chapter 37, Part 4.

Scrapie

Transmissible spongiform encephalopathies are fatal neurodegenerative diseases in which an abnormal isoform of a cellular prion protein accumulates in tissues of the CNS. In sheep affected with scrapie, prion proteins also accumulate in the inner and outer plexiform layers of the retina. Electroretinograms on scrapie-affected sheep show reduced b-waves in one study (Smith et al., 2009), and reduced a-waves and b-waves in another study (Regnier et al., 2011). Histopathology of affected retinas is variable. Reports of very few morphologic lesions exist, as do reports showing marked lengthening and disorganization of photoreceptor segments and substantial reduction in cellularity/thickness of the inner nuclear layer (Regnier et al., 2011; Smith et al., 2009). Another study evaluating scrapie-infected sheep has found evidences that *Spiroplasma* sp. has a role in the pathogenesis of transmissible spongiform encephalopathies (Bastian et al., 2011).

Central Blindness

Diseases that may cause central blindness include pregnancy toxemia, CNS abscesses, *Taenia multiceps* (*Coenurus cerebralis*) cysts (Vicary, 1979), PEM, listeriosis, and lead poisoning (Hindson & Winter, 2002). Additional information can be found in Chapter 37, Part 4.

Pigs

The Orbit and Globe

Pigs possess an open orbit which is continuous with the temporal fossa (Fig. 30.76). The field of vision is probably 260–275° with an estimated binocular field of 30–50° (Middleton, 2010). An orbital venous sinus in pigs has been described as a site for blood collection. The pig is placed in dorsal recumbency, and the fibrous conjunctival tissue is punctured using a glass pipette to rupture the venous sinus and the medial canthus just inside the nictitating membrane (Muirhead, 1981). However, this technique is not recommended as there are other preferred methods of blood collection in pigs. The corneal epithelium of pigs contains angiostatin, an inhibitor of angiogenesis, which may have a regulatory role in the maintenance of corneal clarity (Pearce et al., 2007).

The tear production (basal + reflex tears – STT-I) in normal pigs is 15.6 mm/min, whereas the basal tear production (STT-II) is 12.4 mm/min. As with other species, the tear production increases with age, with an average of 12.6 mm/min in pigs younger than 6 months of age, compared with



Figure 30.76 Normal extraocular photograph of pot-bellied pig.

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18.7 mm/min in adult pigs (Trbolova & Ghaffari, 2012). The IOP in pigs has been measured and found to be 15.2 mmHg using the Tono-Pen XL in adult pigs under general anesthesia with ketamine and xylazine (Ruiz-Ederra et al., 2005). Another study showed average IOPs of 27.3 mmHg OD and 26.3 mmHg OS in awake Gottingen minipigs using the Tono-Pen XL (Middleton, 2010). Compared with manometry, rebound tonometry (Icare TAO1, Vantaa, Finland, calibrated for humans) underestimates the IOP values by 17%–63% in porcine eyes, with higher deviations when IOP is higher than 30 mmHg. When such an instrument is used, a linear calibration function should be used to correct the readings to obtain "true" IOP values (Lobler et al., 2011). When compared with manometry, rebound tonometry (TonoVet) slightly underestimated IOP at lower pressures and slightly overestimated IOP at higher pressures. The applanation tonometer (TonoPen Vet) consistently underestimated IOP. In comparison, the TonoVet more closely approximated the true IOP obtained with manometry (Lewin & Miller, 2017).

Congenital Globe Abnormalities and Blindness

In a study of 319 congenitally malformed pigs, 653 distinct malformations occurred (Selby et al., 1971). Among these pigs, 16 had cyclopia, 13 anophthalmia, and seven microphthalmia. Genetic studies were not reported, but 92% of the anophthalmic defects were associated with other malformations. Holoprosencephaly with varying degrees of optic hypotelorism, including cyclopia, has also been reported in the pig (Fisher et al., 1989).

Maternal vitamin A deficiency has been linked with anophthalmia, microphthalmia, macrophthalmia, retinal dysplasia and other ocular abnormalities in piglets (Goodwin & Jennings, 1958; Huston, 1978; Palludan, 1976; Watt & Barlow, 1956). The severity varies between litters, between littermates, and even between eyes in the same animal (Palludan, 1976). Microphthalmia is the most common abnormality (Huston, 1978). Congenital microphthalmos can be found in Yorkshire pigs and is thought to be inherited as an autosomal recessive trait (Howard & Smith, 1999)

The Eyelids

Entropion

The popularity of the pot-bellied pig has resulted in an increased number of entropion cases presented to veterinary ophthalmologists. The large amount of subcutaneous fat in the forehead and periocular region of this breed, as well as the enophthalmos, contributes to the development of entropion (Fig. 30.77 and Fig. 30.78). Surgical intervention is usually required, and successful use of a modified Hotz–Celsus procedure has been reported (Linton & Collins, 1993). A modified brow sling (Elder, 1993; Kirschner, 1994), using either Mersilene (Ethicon, Bridgewater, NJ, USA) mesh or polyester suture coated with polybutilate, is effective in some cases. The large suture or mesh acts as a scaffold for the attachment of fibroblasts. A novel method for removal of redundant fat and skin can be used to alleviate clinical signs of entropion and vision loss secondary to periocular fat pad hypertrophy of pot-bellied pigs (Allbaugh & Davidson, 2009; Andrea & George, 1999). The procedure consists on the surgical excision of the subdermal periocular fat pads and redundant associated skin (Allbaugh & Davidson, 2009). A small percentage of Vietnamese Pot-Bellied Pigs are prone to abnormal fat accumulations in the facial region, particularly the periorbital region, that results in a mechanically narrowed palpebral fissure, entropion, and impaired vision. Postoperative control of the animal's weight is important for long-term success of surgery to correct entropion in pigs, but this is often a challenge.



Figure 30.77 Entropion in an obese pot-bellied pig. The large amount of subcutaneous fat in the forehead and periocular region of this breed, as well as the enophthalmos, contributes to the development of entropion. (*Source*: Courtesy of Ellison Bentley.)



Figure 30.78 Entropion in a pot-bellied pig, with secondary trichiasis.

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Blepharitis

Dermatophilosis is very rare in swine but affected pigs can have a generalized crusting dermatitis (Smith, 2009). Dermatophytosis is also rare in swine but can be caused by *Microsporum nanum*. Lesions are typically red–brown discolorations of skin and dry brown to orange crusts. See the earlier bovine section for more information.

Swine pox may cause lesions on the eyelids, conjunctiva, and third eyelid similar to those seen elsewhere on the body (Howard & Smith, 1999). Infection with *E. coli* may cause severe eyelid edema, chemosis, conjunctival inflammation, and exophthalmos.

Infectious Keratoconjunctivitis

Pseudorabies causes a mild conjunctivitis in affected swine. Hog cholera produces a severe conjunctivitis. These systemic diseases are covered in more detail in Chapter 37, Part 4.

Pigs with chlamydial keratoconjunctivitis (*Chlamydia suis*) showed a combination of conjunctivitis and keratoconjunctivitis, with or without mucopurulent rhinitis (Rogers et al., 1993). Histopathologically, the disease was characterized by mild to moderate, diffuse lymphoplasmacytic conjunctivitis, with mild lymphofollicular hyperplasia. Conjunctival swabs isolated chlamydiae in 50% of pigs. Other flora isolated included *Mycoplasma, Klebsiella*, and *Pasteurella* spp. in varying proportions. Ultrastructural examination of the conjunctival specimens from all pigs revealed all morphologic forms characteristic of chlamydial development. It was concluded that both chlamydiae and mycoplasma play a role in the pathogenesis of some cases of conjunctivitis and keratoconjunctivitis in swine (Rogers et al., 1993). It has been shown in swine with an outbreak of mucopurulent conjunctivitis that organisms identical to *Mycoplasma* spp. could remain intact within conjunctival epithelial cells (Rogers et al., 1991).

Acquired Corneal Diseases

Phenothiazine

Phenothiazine has caused corneal edema and keratitis in pigs (see the bovine sectionne) (Mathalone, 1968; McClanahan et al., 1966; Radostits et al., 2007; Wheeler et al., 1969).

Neoplasia of the Conjunctiva and Cornea

Primary tumors of any site, including the eye, are rare in swine (incidence, 0.64%) (Priester & Mantel, 1971).

The Uveal Tract

Congenital Disorders of the Anterior Uvea

Congenital disorders include PPMs, heterochromia, aniridia and iris hypoplasia, polycoria, cysts, pigment nevi, and colobomas. In one study, these defects, and specifically PPMs, were found in 66.1% of 7- to 12-month-old Yucatan Micropigs (Saint-Macary et al., 1994). By 19–33 months of age, however, there was a decreased incidence of PPMs. These data must be interpreted carefully, because the normal age for regression of PPMs is not known in this species.

Heterochromia iridis has an estimated incidence of 5%–7% in swine (Fig. 30.79) (Gelatt, 1973; Middleton, 2010). There is a higher incidence of heterochromia iridis in white miniature pigs (38.3%) than in miniature pigs with a variety of coat colors (15.8%). The abnormality is inherited as an autosomal recessive trait with variable expressivity. The frequency and bilateral involvement of heterochromia iridis depends on heterochromia in the parents. The histopathology of heterochromia iridis in these cases is characterized by reduced pigmentation of the iridal stroma and increased pigmentation of the posterior epithelial layers (Gelatt, 1973).

A strain of Miniature Sinclair swine has a high incidence (54%) of cutaneous malignant melanomas at birth, which increases to 85% of the population at 1 year of age. As tumors spontaneously regress, this is often followed by depigmentation of the skin, hair, eyes, and the presence of uveitis caused by autoimmune destruction of melanoyctes by macrophages (Feeney-Burns et al., 1988). The regression of tumors is associated with loss of telomerase activity and reduction of telomeric repeats in the melanoma, resulting in cell death (Pathak et al., 2000).

Inflammation of the Uvea

The associations of uveitis with systemic diseases are numerous (see Chapter 37, Part 4). Causes such as hog cholera, Glasser disease, and erysipelas have been reported (Vestre, 1984).

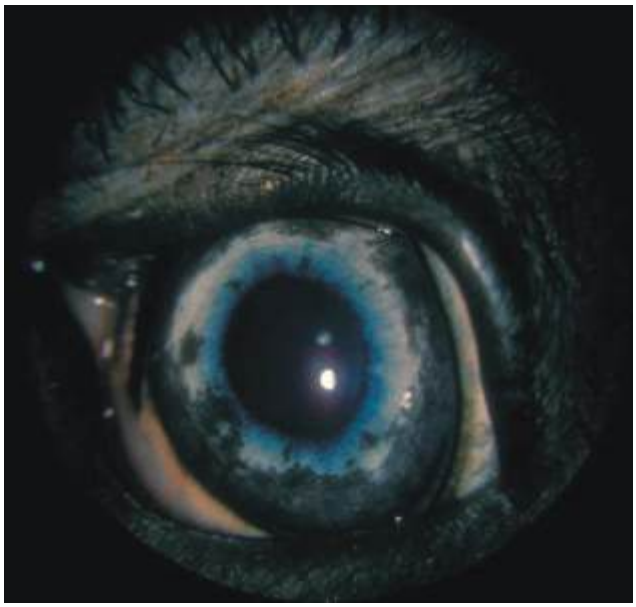


Figure 30.79 Heterochromia iridis (clinically blue and white) in a white Miniature Pig. (*Source*: Courtesy of Kirk N. Gelatt.)

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The Lens

Congenital Cataracts

Congenital cataracts have been reported (Saint-Macary et al., 1994). In Yucatan Micropigs, posterior cortical pinpoint opacities were seen in 20.5% of 7- to 12-month-old animals. Posterior capsular pinpoint opacities, nuclear opacities, and suture line abnormalities were seen.

Acquired and Secondary Cataracts

Bilateral cortical opacities have been described in mature sows fed hygromycin B (Cargill et al., 1983). Formation of cataracts caused by hygromycin B appears to be dose-dependent and potentially cumulative. The amount of cataract formation with hygromycin B varied from small posterior polar opacities to mature cataracts and may be asymmetric between eyes (Sanford & Dukes, 1978). Development of cataracts may have depended on the age of the pigs at the onset of supplementation. Approximately 30% of sows older than 2.5 years were affected. Sows treated with alloxan gave birth to piglets with nuclear cataracts (Cargill et al., 1983). The cataracts were most prominent at the nuclear cortical junction and did not progress or significantly affect vision.

Radiation-induced cataracts have also been seen in swine (see the bovine section) (Brown et al., 1972). Starvation and riboflavin deficiencies have been described as causing incomplete cataracts (Howard & Smith, 1999). Vietnamese Pot-Bellied Pigs have juvenile cataracts that are thought to be inherited.

The Ocular Fundi

Ophthalmoscopic Examination

The pig ocular fundus lacks a tapetum. The disc is horizontal and sharply defined, with 8–10 arterioles, 3–4 of which are more prominent. The vascular pattern is holangiotic and vessels branch dichotomously; a single artery and vein accompany each other. Vessels may bulge internally into the vitreous body. In white pigs, the fundus is pink; in heavily pigmented animals, the background is bluish-gray to brown (Fig. 30.80). More commonly, partial albinism (i.e., subalbinism) is described (Gelatt, 1973; Saint-Macary et al., 1994).

The photoreceptor mosaic of pigs and humans are similar and supports the use of the pig retina as a model for human/animal research (Samuelson et al., 1993; Severin et al., 1976). The pig retina is well endowed with cones, an extensive vascular tree, and an area sufficiently free of blood vessels to suggest an area centralis close to the posterior pole (Chandler et al., 1999).

Colobomatous Malformations

In swine, there are few reports of colobomas. In one report of 112 Yucatan Micropigs from 7 to 12 months of age, an optic disc abnormality suggestive of a coloboma was found in one female (Saint-Macary et al., 1994). In miniature swine, large colobomas of the optic nerve and choroid have been observed (Rubin, 1974). Optic nerve hypoplasia has been observed in piglets raised for research purposes (Rubin, 1974). The condition was bilateral, and direct pupillary responses to light were absent in both eyes. Families of swine have also been reported to have optic atrophy with multiple ocular anomalies, including scleral staphylomas, hydrophthalmos, retinal and choroidal atrophy, retinal calcification, and microphthalmia, all of which are possibly hereditary anomalies.

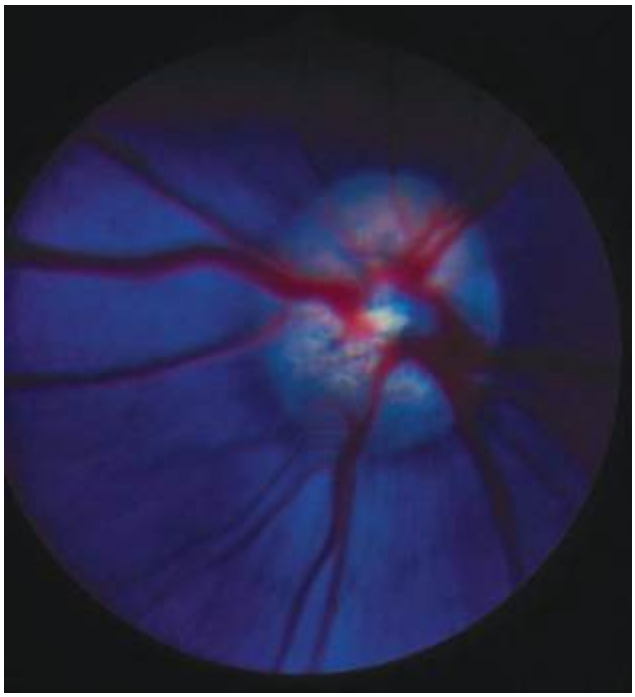


Figure 30.80 Normal ocular fundus of the pig. The swine fundus does not contain a tapetum lucidum. (*Source*: Courtesy of Kirk N. Gelatt.)

Congenital Vascular Anomalies

In Yucatan Micropigs, hyaloid remnants (82.1%) and pupillary membrane remnants (66.1%) were the most frequently reported ophthalmic findings. Persistence of the hyaloid remnants even occurs in some micropigs older than 33 months (Saint-Macary et al., 1994).

Inflammation of the Ocular Fundus

Most fundus abnormalities induced by systemic diseases are discussed in Chapter 37, Part 4. Chorioretinal lesions may result from pseudorabies, hog cholera, listeriosis, toxoplasmosis, Glasser disease, ocular cysticercosis, Teschen encephalitis, and swine erysipelas (Busch et al., 1971; Cardenas-Ramirez et al., 1984; Gordon & Luke, 1952;

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Howarth & De Paoli, 1968; Saunders et al., 1958; Schneider & Harvarth, 1973).

Degeneration of the Ocular Fundus

Amaranthus retroflexus (redroot pigweed) and *Chenopodium albuim* (lambsquarters) cause neurologic signs and decreased vision in pigs (Buck et al., 1966; Osweiler et al., 1969). Arsanilic acid toxicity may result in blindness among pigs (Menges et al., 1970; Vorhies et al., 1969; Witzel et al., 1976). Arsanilic acid is used therapeutically for swine dysentery and as a growth stimulant. Clinical signs appear when arsanilic acid is given in excess, for a prolonged period of time, or during times of restricted water intake (Menges et al., 1970; Vorhies et al., 1969). Affected swine show blindness, weakness, torticollis, and incoordination. The pupillary light reflexes are absent, and ophthalmoscopic examination reveals bilateral optic disc atrophy, which is characterized by pallor, well-defined margins and narrowed retinal arterioles. The ERG is normal in blind pigs, but visual-evoked potentials are not recordable or are abnormal compared with those in normal animals. The essential histopathologic lesion of arsanilic acid toxicity is a parenchymatous neuropathy, with demyelinization and axonal destruction of the optic nerves and tracts (Witzel et al., 1976). Lesions have not been detected in the outer layers of the retina (Vorhies et al., 1969). The optic nerve lesions are detected 4 or more days after the onset of blindness, and these lesions continue to develop even after the arsanilic acid has been withdrawn.

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Avian Ophthalmology

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Within the class Aves, approximately 9000 species are classified in two superorders: Neognathae containing 99% of extant species, and Palaeognathae that contains the remainder. They inhabit the land, sea, and air in a diverse array of ecologic niches. Only a few species have been truly domesticated as food or companion animals. Although their eyes present examination and therapeutic challenges to veterinarians charged with their medical and surgical ophthalmic care, these can be overcome by innovation and modifications of standard veterinary ophthalmic diagnostic tests, examination techniques, and medical and surgical interventions.

For purposes of clarity, general avian ocular anatomy and physiology and examination will be introduced first, followed by discussion of the ophthalmology of nonraptor species. Raptor ophthalmology will conclude this chapter.

Ophthalmic Anatomy

Upper and lower eyelids and membrana nictitans are present. The lower lid is more mobile than the upper and usually contains a fibroelastic tarsal plate. The nictitans is well developed, actively mobile, nearly transparent, thin, and covered by a papillary layer of epithelium. Drawn from the medial canthus, the nictitans is moved by contracture of the pyramidalis muscle that originates from the posterior pole sclera, where it loops through a sling formed by the quadratus muscle; both are innervated by cranial nerve VI. Both muscles may be derived from the crocodilian retractor bulbi muscles otherwise absent in birds. The oblique and rectus muscles are thin and relatively poorly developed. Meibomian glands are also absent. When present, the lacrimal gland is located inferotemporal to the globe, and a harderian gland is found adjacent to the posterior sclera near the base of the nictitans but not part of it. Two lacrimal puncta drain lacrimal secretions into a nasolacrimal duct and then to the nasal cavity (Wood, 1915) in some but not all birds. A supraorbital gland (nasal/salt gland) is present in aquatic species, poultry, and other birds (Schmidt-Nielsen & Sladan, 1958). The orbit is typically but not universally incomplete, large, and open; it can be evaluated radiographically (Paul-Murphy et al., 1990). Interspecies variation in the orbital bone structure of psittaciform birds has been described in detail. After 27 skulls from 14 species of psittacines were analyzed, they were classified into two groups. One group had a complete enclosed bony orbit formed by the junction of the orbital and postorbital processes, creating a suborbital arch. The second group lacked the suborbital arch and had an open incomplete bony orbit typical of most modern birds; even in this group, orbital and postorbital processes were present (Machado et al., 2006). Subcutaneous periocular and cervicothoracic sinuses that communicate with the respiratory system are present in psittacines and some other species (Kern, 1997). Paranasal sinus anatomy of 10 macaws representing four species was investigated using computed tomography, skeletal studies, histology, and deep-frozen tissue sections, and identified two unpaired rostral compartments and eight paired caudal compartments (Artmann & Henninger, 2001).

The globe is very large relative to body size (Fig. 31.1 and Fig. 31.2). The posterior segment is relatively much larger than the anterior segment. Three basic shapes are typical: (1) flat, with a short anteroposterior axis and a flat or partly concave ciliary region (intermediate segment) in the center of which the cornea protrudes, with a hemispheric posterior segment, the most common shape; (2) globose, in which the ciliary region protrudes further from the posterior segment while remaining somewhat concave, which is present in many diurnal birds needing high-resolution distance vision (e.g., crows, insectivorous wing-feeders, diurnal raptors); and (3) tubular (such as in owls), in which the concave intermediate segment is elongated anteroposteriorly, forming a tube before joining the posterior segment at a sharp angle (Duke-Elder, 1958; Walls, 1942). A fourth shape category, quasispherical, has been proposed to describe penguin eyes

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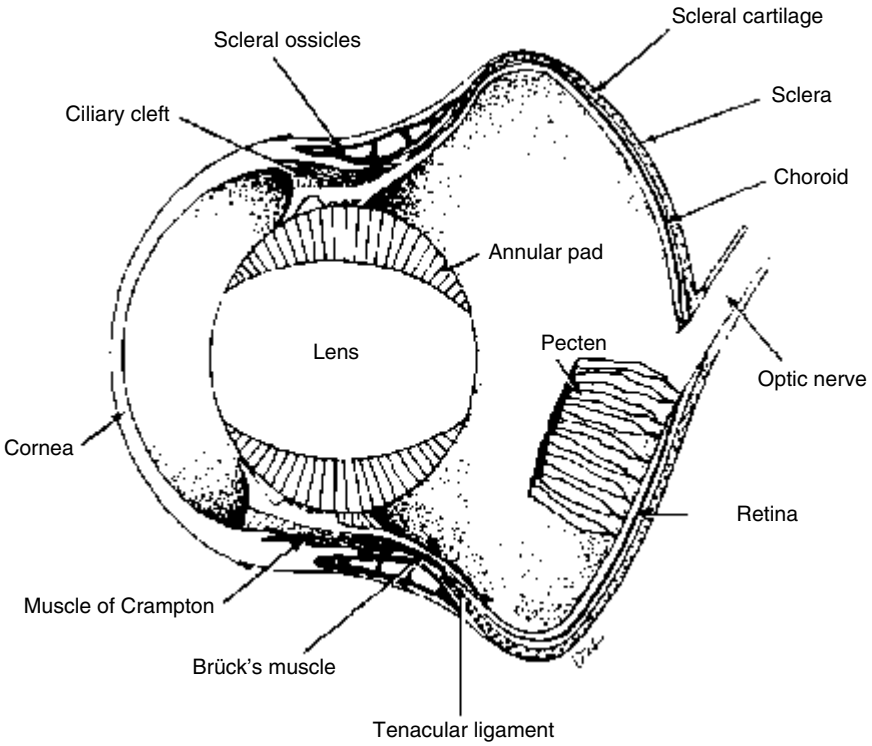


Figure 31.1 The owl eye. (Adapted from Duke-Elder, Stewart (1958) *System of Ophthalmology*, Vol. 1, *The Eye in Evolution*. London: Kimpton.)

(Suburo & Scolaro, 1990). The shape of the globe is formed and maintained by hyaline cartilage in the sclera of the posterior segment and by 10–18 scleral ossicles (sometimes pneumatic) in the sclera of the intermediate segment. The ultrasonographic anatomy and biometry of the eyes of the blue-fronted Amazon parrot (*Amazona aestiva*) have been described (Lehmkuhl et al., 2010).

The cornea has the same layers as in mammals. *In vivo* confocal microscopy of the corneas of five birds of different species confirmed this and identified a Bowman's-like layer (Kafarnik et al., 2007).

Conjunctiva-associated lymphoid tissue in poultry is important in mucosal immunity (Fix & Arp, 1989, 1991).

The iris contains striated sphincter and dilator muscles and myoepithelium and smooth muscle, and its stroma harbors several pigments responsible for variable iris coloration (Chiasson & Ferris, 1968; Chiasson et al., 1968; Randall & McLachlan, 1979). The circular pupil is subject to influence from retinal stimulation as well as voluntary control. Iris vascularization is similar to that in lizards. The iridocorneal angle is well developed and drained by two annular channels.

The lens is soft, pliable, and of variable shape: spherical in nocturnal species, flattened anteriorly in some diurnal species. An equatorial annular pad formed of modified lens fibers is present and may be very prominent. Between the central body of the lens and the annular pad is a fluid-filled cleft or lenticular space. Though not playing a direct optical role, the annular pad serves an important function in accommodation and may have a nutritive role in lens metabolism. Its size is generally related to the accommodative range of the lens, which varies with species. Except in diving birds, the pad is largest in birds with the widest range of accommodation (e.g., diurnal birds of prey, other fast-flying species). The smallest are present in nocturnal species with small accommodative ranges. Accommodation in birds involves changes in corneal curvature, anterior movement of the lens, and lens deformation. Lens power is increased by contraction of the striated meridional ciliary muscles: Brücke's muscle posteriorly and Crampton's muscle anteriorly (which inserts on the peripheral cornea) move the ciliary body axially, compressing the lens by exerting pressure on the annular pad. Crampton's muscle contraction may flatten the peripheral cornea (Murphy & Dubielzig, 1993). In the chicken and pigeon, changes in corneal curvature account for half or more of the 15–17 D accommodative range of the eye (Schaeffel & Howland, 1995). In one investigation of avian accommodation, the accommodative range of 15 species of owls was from 0.7 D to greater than 10 D (Murphy & Howland, 1983). Lower visual field myopia present in some birds (chickens, pigeons, quail) but absent in raptors allows them to keep the ground in focus while performing other tasks (Murphy et al., 1995). Aquatic birds, in which the corneal accommodative mechanisms are neutralized under water, have accommodative ranges up to 50 D

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Figure 31.2 Skull radiograph with dacryorhinocystogram of a screech owl depicting the very large tubular globes and the nasolacrimal duct opacified with radiopaque dye.

(Katzir & Howland, 2003). Penguins are emmetropic in both air and water (Howland & Sivak, 1984; Martin & Young, 1984; Sivak et al. 1987). In chickens, pigeons, and kestrels, the ciliary muscle fibers predominate in the anterior muscle fiber groups, suggesting an emphasis on corneal accommodation, whereas in the hooded merganser, the majority of fibers are in the internal and posterior muscle fiber groups, suggesting that lenticular accommodation predominates (Pardue & Sivak, 1997). The numerous ciliary processes are tightly fused to the equatorial lens capsule. In a study of the development of refractive state in the eyes of ostrich chicks, their eyes were 4.5 D myopic at hatching and by day 7 after hatching, six were slightly hyperopic and changed little after this time point (Ofri et al., 2001).

The retina is avascular and atapetal, but has a well-developed choroid and pecten (Bellhorn, 1997; Duke-Elder, 1958; Walls, 1942). The pecten is a highly vascular pigmented structure of greatly variable size extending into the vitreous from and obscuring examination of the optic nerve head. A vascular mesodermal core overlying neuroectodermal cells, as in reptiles, the avian pecten differs from the purely mesodermal falciform process of fish. The pecten probably has a primary nutritive function, but has been credited with over 30 possible functions. Considerable variation in photoreceptor type and density exists. Some species (most domestic species) are afoveate, others are monofoveate, and some are bifoveate (hummingbirds, some raptors, and passerines; Tucker, 2000). Both rods and cones are present (including double cones with oil droplets); proportions vary with the species' visual ecology. A protocol for electroretinography (ERG) and oscillatory potential recordings of Hispaniolan Amazon parrots (*Amazona ventralis*) showed that the latencies of a- and b-waves and amplitudes of dark-adapted b-waves of the parrots were similar to those of normal dogs. The light-adapted a- and b-waves of the parrots had greater amplitudes than the corresponding values of dogs. Oscillatory potentials were composed of three or four peaks (Hendrix & Sims, 2004). Some avian species possess ultraviolet (UV) vision, the function of which is uncertain. One hypothesis is that UV vision functions in orientation for foraging and signaling (Bennett & Cuthill, 1994). Pigment epithelial processes contain pigment granules and respond to light by elongation between rods. The fundus appearance *in vivo* is a gray or red background speckled with heterogeneous pigmentation through which choroidal vessels may be seen in some species. The choroid of the chicken contains a conspicuous system of thin-walled lacunae not seen in mammalian choroid, which may represent short lymphatic vessels (DeStefano & Mugnaini, 1997).

Ophthalmic Examination and Normative Values: Nonraptor Species

Clinical examination of avian eyes utilizes the same instrumentation and diagnostic techniques as in mammals, albeit with modification dictated by the size of the eye and physiologic characteristics of the iris. Basic instrumentation should include a bright focal light source (e.g., transilluminator); a low-power magnifying head loupe; from 28 D to 30, 40, or 60 D indirect condensing lenses (Volk Optical, Mentor, OH, USA); and a direct ophthalmoscope. Accessory diagnostic aids include fluorescein dye strips, Schirmer tear test (STT) strips (Iolab Pharmaceuticals, Claremont, CA, USA), phenol red threads (Zone-Quick, Menicon, Nagoya, Japan), culture swabs (Minitip Culturette, Becton-Dickinson, Cockeysville, MD, USA), microscope slides, sterile scalpel blades for conjunctival and corneal cytology collection, and an applanation and/or rebound tonometer (Tono-Pen® XL, Tono-Pen AVIA®, Reichert Technologies, Buffalo, NY, USA; TonoVet Plus® and Tonolab®, Icare, Finland). When available, slit-lamp biomicroscopy and ocular ultrasonography potentially enhance the diagnostic yield. Complete ocular evaluation of birds includes a history, functional examination, and morphologic examination. The history should

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include pursuit of management techniques, husbandry, prior health history, and current ocular and systemic signs. It should be revisited, expanded, or investigated further after functional and morphologic ocular assessment.

Avian responses to the eye-related reflexes differ from those of mammals in some respects. Palpebral response is present, with the lower lid covering the globe more extensively than the upper lid; membrana nictitans excursions are prominent. Menace responses seem inconsistent even in birds with evidently normal vision; thus, absent menace response has little diagnostic significance. Avoidance behavior is a more reliable indicator of vision than menace reflex. Because retractor bulbi muscles are absent in birds (replaced by the quadratus and pyramidalis muscles that subserve membrana nictitans motility), globe retraction is not a feature of eye-related reflex responses. The corneal reflex is present, manifested by blinking, nictitans excursion, and avoidance behavior. Direct pupillary light reflex is present. Its assessment is often problematic owing to presumptive voluntary control of the striated components of the iris musculature and the emotional state of the bird. Slight, intermittent, dynamic anisocoria may be normal. Because of complete decussation of optic nerve fibers, consensual pupillary light responses are not expected in birds (Levine, 1955); however, this theory has been challenged by experiments with unilateral optic nerve transection (Li & Howland, 1996). In operated chicks, pupillary constriction occurred in operated eyes when direct pupillary responses were stimulated in the normal fellow eye. Artifactual consensual responses may be induced by inadvertent stimulation of the retina of the fellow eye during elicitation of the direct pupillary response through the posterior pole of the stimulated eye and the thin interosseus septum separating the two orbits (Levine, 1955).

Posterior segment examination in birds is confounded by difficulty in achieving mydriasis. Parasympatholytic agents are ineffective because of the complex muscular arrangement of the iris. Predominantly striated in nature, the iris muscles may be partially paralyzed by neuromuscular paralyzing agents. Intracameral injection of d-tubocurarine, a nondepolarizing neuromuscular blocking agent, has been reported to cause consistent moderate to maximal mydriasis in pigeons and several raptor species (Murphy, 1987; Verschueren & Lumeij, 1991). Topical application of tubocurarine (3 mg of tubocurarine powder per mL of 0.025% benzalkonium chloride solution) instilled 3–4 times over 20 minutes resulted in partial mydriasis in some species but not others (Bellhorn, 1973). Three curariform (d-tubocurarine, pancuronium, and vecuronium bromide) and two autonomic drugs (atropine and phenylephrine) were evaluated for topical use with and without addition of surface-acting penetration agents (saponin or benzalkonium chloride) in three species of large psittacines (Ramer et al., 1996). One eye of each bird was tested. Vecuronium (0.8 mg/mL, 2 drops administered twice 2 minutes apart) without an enhanced penetration agent produced the most consistent and greatest mydriasis with the fewest systemic side effects in all three species. Amazon parrots treated with this protocol developed mild transient systemic side effects. Administration of vecuronium with 1% saponin was fatal to one cockatoo. Topical pancuronium caused mild to severe systemic effects in some cockatoos. *Note that the safety and efficacy of bilateral simultaneous administration were not evaluated in this study*. In juvenile double-crested cormorants (*Phalacrocorax auritus*), mydriasis was best achieved with a combination of 1% topical atropine, 2.5% phenylephrine, and 4 mg/mL of vecuronium (Loerzel et al., 2002). Mydriatic effects of 0.15 mg intramuscularly and 20 mL of a 10 mg/mL solution of rocuronium bromide applied to the eyes of Hispaniolan Amazon parrots (*Amazona ventralis*) resulted in up to 60 minutes of mydriasis (Baine et al., 2016; Petritz et al., 2016). Variable mydriasis can be fairly consistently achieved under general anesthesia. In raptors, short-acting anesthesia consists of 10–15 mg/kg ketamine hydrochloride (Vetamine®, Mallinckrodt Veterinary, Mundelein, IL, USA) and 1–2 mg/kg xylazine (Rompun®, Bayer Animal Health, Shawnee Mission, KS, USA; Greenwood & Barnett, 1981).

Tonometry poses certain difficulties in birds. The small size of the eye and cornea of most species of interest makes Schiøtz tonometry difficult to impossible. Conventional tonometers have not been validated for use in birds as they have for dogs and cats. High corneal and scleral rigidity compared with mammalian eyes no doubt affects the reliability and interpretive value of the measurements in birds. Intraocular pressure (IOP) of normal turkeys measured approximately 25 mmHg by applanation (Mackay-Marg tonometer®, Cooper Vision Systems, Biotronics, Irvine, CA, USA; Davis et al., 1986). In a series of tonometric examinations of 275 normal birds of 39 species and 8 orders using the Tono-Pen device, IOPs measured 9.2–16.3 mmHg (Korbel, 1993). Reproducible readings were obtained from eyes with a minimal corneal diameter of 9 mm (Amazon parrot eye). Reproducibility was limited to a corneal diameter of 5 mm (cockatiel eye), and below 5 mm (budgerigar eye) measurements were unreliable. Normal IOP values have been reported in several species of penguins using rebound tonometry (Bliss et al., 2015; Gonzalez-Alonso-Alegre et al., 2015; Mercado et al., 2010; Sheldon et al., 2017). IOP measurements using rebound tonometry were also reported for two additional species (Woodhouse et al., 2016a, 2016b). IOP determined by applanation tonometry was reported in penguins (*Spheniscus humboldti*; Swinger et al., 2009). IOP values measured in rebound tonometry and other diagnostic tests have been determined in American flamingos (*Phoenicopterus ruber ruber*; Meekins et al., 2015; Molter et al., 2014). Normal values and other diagnostic tests and findings have been determined in groups of American white and brown pelicans (*Pelecanus occidentalis*, *Pelecanus erythrorhynchos*; Kinney et al., 2017; O'Connell et al., 2017). Tonometry values for domestic ducks, geese, guinea fowl, and pigeons were profiled

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(Mood et al., 2017; Park et al., 2017; Rajaei & Ansari Mood, 2016). Reference values for IOP and STTs in ostriches (*Struthio camelus*) and domestic pigeons (*Columbia livia*) were also noted (Ghaffari et al., 2012; Mood et al., 2016).

STT values without (STT I) and with (STT II) topical anesthesia have been reported in 42 species of birds in seven orders. Values for psittacines (± standard deviation, SD) for STT I and II were approximately from 3 to 7 ± 2 mm/min and from 1.7 to 4.5 ± 2 mm/min, respectively. Normal values for the phenol red thread test (PRTT) were determined for two groups of large psittacines. Mean PRTT values for the two groups were approximately 20–25 mm/15 seconds, but repeatability was low (Holt et al., 2006). STT and PRTTs were performed before and after topical anesthesia in Amazon parrots. Topical anesthesia did not significantly affect PRTT values (mean 12.5 mm/15 seconds), but did affect STT values (mean 7.9 mm/min before and 5.1 mm/min after anesthesia; Storey et al., 2009). PRTT values in normal common mynahs (*Acridotheres tristis*) were approximately 18 mm/15 seconds (Rajaei et al., 2015). PRTT values determined in normal pigeons were approximately 23 mm/15 seconds (Hayat & Biricik, 2014). PRTT values in normal captive helmeted guinea fowl (*Numida meleagris*) were approximately 17 mm/15 seconds (Rajaei & Ansari Mood, 2016)

Ophthalmic Diseases: Nonraptor Species

The spontaneous clinical disorders of birds, especially cage birds, have been the subject of several excellent reviews (Kern & Colitz, 2013; Kern et al., 1996; Mustaffa-Babjee, 1969; Small & Burke, 1982; Williams, 1994). Avian ocular disorders may be generally albeit imperfectly categorized as malformations, inflammations, infections, degenerations, neoplasia, nutritional disorders, and traumatic injuries.

Developmental Malformations

Developmental malformations have been reported infrequently. Cryptophthalmos occurs sporadically in cockatiels, in which surgical correction has usually failed to reconstruct an anatomic eyelid margin and palpebral fissure (Buyukmihci et al., 1990). Congenital symblepharon was reported in a cockatiel chick (Buyukmihci et al., 1988). Corneal dermoids were reported in a goose in which feathers grew from the aberrant skin on the temporal cornea (Busch, 1985). A unilateral corneoconjunctival dermoid was successfully removed from a blue-fronted Amazon parrot (*Amazona aestiva*; Leber & Bürge, 1999). Impatent nasolacrimal ducts were suspected in a cockatoo with choanal atresia, and ectropion was diagnosed in cockatiels (Williams, 1994). Cataract and optic nerve hypoplasia of unknown cause in turkey poults was reported in a commercial flock (Barr et al., 1988). Iris colobomas were seen in a flock of rosecomb Bantam chickens (Cardona & Plumer, 2004). Photoreceptor dysplasia was diagnosed in two Tippler pigeons (Moore et al., 2004). Broiler chicks were presented blind due to panretinal dysplasia of possible genetic origin (Shivaprasad & Korbel, 2003). In albino Japanese quail (*Coturnix coturnix japonica*), optic nerve diameter is 25% smaller than in normal quail, with approximately the same number of (thinner) nerve fibers. Different from albinos of many other species, there was no reduction of ipsilateral retinofugal projections (Takatsuji & Nakamura, 1987). The same strain of quail was described with closed-angle glaucoma (Takatsuji et al., 1986). Evidently congenital or perinatal retinal detachment of uncertain cause was found in 3%–5% of captive-raised pheasants (VanderKop, 1993). The *rd* (retinal degenerate) chicken is behaviorally and electrophysiologically blind at hatching despite an apparently normal-appearing retina (Ulshafer & Allen, 1985; Ulshafer et al., 1984). Partial retinal dysplasia and subsequent retinal degeneration were investigated in a mutant strain of chicken (*rdd*; Randall et al., 1983). Chicks were blind and retinal detachment occurred in adults. Recessive mode of inheritance was suspected. A congenital or perinatal retinopathy purportedly different from the above two was reported in chickens in Britain (Curtis et al., 1987).

Experimental manipulation of environmental factors in growing chickens and turkeys has provided considerable information regarding normal eye growth and the ontogeny of emmetropization and refractive errors. Myopia and hyperopia have been induced in chick eyes of some strains with visual field occlusion, constant darkness, defocusing spectacle lenses, and constant light (Kinnear et al., 1974; Li et al., 1995), lid suturing (Lauber & Oishi, 1987), induction of thermal gradients within the eye (Hodos et al., 1987), and chemical retinal ablation (Wildsoet & Pettigrew, 1988). Astigmatism also develops with myopia and hyperopia (Kee & Deng, 2008). Raising chicks under constant light results initially in hyperopia (after 3 weeks) that subsequently becomes myopia (after 6 weeks; Li et al., 1995). Strain differences are important insofar as similar environmental manipulations cause variable refractive errors (Li et al., 1995; Troilo et al., 1995). Turkey poults exposed to constant light developed buphthalmos and heavier eyes, but retained normal IOPs (Davis et al., 1986). Poults exposed to a prolonged photoperiod showed normal IOP and astigmatism in reduced a- and b-wave ERG amplitudes with lower cone flicker responses than poults reared in reduced photoperiod conditions (Leis et al., 2017).

Ophthalmic Inflammations and Infections

Ocular inflammation in birds originates from infections, both primary ocular and systemic diseases; nonseptic inflammation, including presumptively immune-mediated processes; and traumatic injuries.

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Photosensitization in ducks and chickens occurred following ingestion of the methypsoralen-containing plants *Ammi majus* and *Cymopterus watsonii* (Egyed et al., 1975). Blepharoconjunctivitis, chemosis, keratitis, symblepharon, and dyscoria were prominent signs. Inflammation of the nasal salt gland in the superior orbit was noted in range-reared tom turkeys (Riddell & Roepke, 1991). The histologic changes were characterized by predominantly nonsuppurative inflammation and epithelial hyperplasia. Etiology was not determined. Granulomatous salt gland adenitis associated with intralesional *Pseudomonas aeromonas* and *Proteus* bacteria was diagnosed in ducklings (Klopfleisch et al., 2005). Gram-negative bacterial nasal gland adenitis was seen in blue penguins (*Eudyptula minor*; Suepaul et al., 2010). Chorioretinitis and buphthalmos were found in turkey poults in Britain apparently unassociated with the lighting conditions used on the original turkeys (Barnett et al., 1971). Secondary angle-closure glaucoma was investigated in Slate turkeys in which uveitis developed consistently by 1 day of age and progressed to iris bombé and increased IOP and buphthalmos (de Kater et al., 1986). A transient idiopathic, generally self-limiting punctate keratitis in Amazon parrots was described (Karpinski & Clubb, 1986). Topical antimicrobial therapy was ineffective. A small minority of birds developed deep corneal ulceration and anterior uveitis.

The normal external ocular microflora of captive cranes (Miller et al., 1995), psittacines (Zenoble et al., 1983), and a variety of exotic birds in public collections (Wolf et al., 1983) has been surveyed. In cranes, Gram-positive organisms predominated (58% of isolates), represented by *Corynebacterium* spp., *Staphylococcus* spp., "hemolytic" *Streptococcus* spp., and *Bacillus* spp. The balance (42%) of isolates were Gram-negative organisms, most commonly *Enterobacter* spp. and *Pseudomonas* spp. A tendency to multiple isolations (more than four) was noted in chicks. No age or species differences were evident. In healthy psittacines, no growth was found in 41% of cultured eyes (Zenoble et al., 1983). *Staphylococcus epidermidis* and "hemolytic" streptococci predominated. In the study of public collections, 83% of cultures yielded bacteria and 14% yielded fungi (Wolf et al., 1983); 70% of the bacterial isolates were Gram positive, with *Staphylococcus* and *Corynebacterium* predominating. *Mycoplasma* were not isolated despite special effort. A wide variety of Gram-negative organisms were isolated. The fungal isolates were not specified.

Bacteria, fungi, viruses, protozoa, microsporidia, trematodes, and nematodes cause ocular disease in birds (Abrams et al., 2002; Fig. 31.3 and Fig. 31.4). Acute severe fibrinopurulent blepharitis and conjunctivitis in chickens and turkeys were associated with infections with *Staphylococcus hyicus*, *E. coli*, and *Streptococcus* spp. (Cheville et al., 1988). *Pasteurella multocida* caused blepharoconjunctivitis and uveitis in turkeys (Olson, 1980). Panophthalmitis was a prominent feature of natural and experimental infection of broiler chickens with *Salmonella arizonae* (Silva et al., 1980). *Actinobacillus* spp. were recovered from native and exotic waterfowl with conjunctivitis (Hacking & Sileo, 1977; Maddux et al., 1987). Staphylococcal blepharokeratoconjunctivitis was diagnosed in a large group of newly imported Amazon parrots (Shimakura et al., 1981). In captive Siberian and whooping crane chicks, an outbreak of *Pseudomonas aeruginosa* keratitis resulted in melting corneal ulceration and perforations (Miller et al., 1994). Visceral and corneal mycobacterial infections were diagnosed in a Maximilian's parrot (*Pionus maximiliani*; Stanz et al., 1995). *Mycobacterium avium* was cultured from conjunctival granulomas on the third eyelid of an ostrich (Hood, 1978). Mycobacterial orbital infection was diagnosed in an Amazon parrot (Woerpel & Rosskopf, 1984) and the conjunctiva in two emus (*Dromaius novaehollandiae*; Pocknell et al., 1996). The extensive cervicocephalic air sac system of psittacines is commonly involved in respiratory infections, leading to ophthalmic complications (Kern, 1997). Magnetic resonance imaging proved an excellent diagnostic tool for evaluation of infraorbital sinuses in psittacines with chronic sinusitis (Pye et al., 2000). Infraorbital sinus nocardiosis and supraorbital extension of sinusitis due to *Pseudomonas aeruginosa* were found in Amazon parrots (Baumgartner et al., 1994; Tully & Carter, 1993). *Mycoplasma gallisepticum* has caused keratoconjunctivitis in layer chickens and has been implicated as the cause of an epizootic of conjunctivitis in house finches and other species (Dhondt et al., 1998; Farmer et al., 2002, 2005; Hartup et al., 1998, 2001; Kollias et al., 2004; Ley et al., 1996, 2006; Luttrell et al., 1998; Mashima et al., 1997; Nunoya et al., 1995; Sydenstricker et al., 2005; Wellehan et al., 2001; Fig. 31.5). In the house finches, treatment with topical ciprofloxacin (Ciloxan®, Alcon Laboratories, Fort Worth, TX, USA) and tylosin tartrate (Tylan®, Eli Lilly, Indianapolis, IN, USA) in drinking water resolved clinical signs. *Mycoplasma*



Figure 31.3 Cockatiel with blepharoconjunctivitis.

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Figure 31.4 Spice finch with periocular cellulitis.

has been suspected but not proven to cause conjunctivitis in cockatiels (Karpinski & Clubb, 1986). *Mycoplasma sturni* has been isolated from blue jays, mockingbirds, and European starlings with conjunctivitis (Forsyth et al., 1996; Frasca et al., 1997; Ley et al., 1998). House finches infected experimentally with *M. sturni* did not develop disease (Ley et al., 2010). Ocular chlamydiosis is often a prominent feature of avian infections, notably in cage birds and domestic ducks (Farmer et al., 1982; Gerbermann & Korbel, 1993; Surman et al., 1974). Conjunctivitis in passerine birds has also been associated with *Streptococcus* spp., *Erysipelothrix rhusiopathiae*, *Clostridium botulinum*, *Mycobacterium avium* serotype 2, *E. coli*, *Pseudomonas aeruginosa*, and *Bordetella avium* (Kern, 1997). Bilateral nocardial endophthalmitis was diagnosed in a captive prothonotary warbler (*Protonotaria citrea*; Reynolds et al., 2009).

Ocular candidiasis in ornamental ducks was characterized by small masses on the membrana nictitans, keratitis, and uveitis (Crispin & Barnett, 1978) and by conjunctival granulomas on the third eyelid (Kern et al., 1996). The ducks were successfully treated with specially compounded 4% amphotericin B ointment (from Fungizone®, Apothecon, Princeton, NJ, USA) and oral or parenteral 5-flucytosine (Ancobon®, Roche, Nutley, NJ, USA). Nodular conjunctival candidiasis was reported in a gull (Kern et al., 1996; Fig. 31.6). Disseminated aspergillosis has been associated with endophthalmitis in turkeys (Kern, 1997; Mustaffa-Babjee, 1969). Ocular candidiasis was found in a budgerigar (Tsai et al., 1993) and in chickens (Mustaffa-Babjee, 1969). Orbital involvement in disseminated cryptococcosis was seen in a cockatoo (Fenwick et al., 1985). *Rhinosporidium seeberi* caused nodular blepharoconjunctivitis in captive mute and black swans that was not treated (Kennedy, 1994). Mycotic keratitis was diagnosed in a blue-fronted Amazon parrot (Hoppes et al., 2000). Keratomycosis due to *Aspergillus* species was successfully treated with topical voriconazole in a Khaki Campbell duck (*Anas platyrhynchos domesticus*; Sadar et al., 2014). Keratoconjunctivitis caused by *Aspergillus* species in red-legged partridges (*Alectoris rufa*) and *Scedosporium apiospermum* has been diagnosed in layer pullets (Dalton & Ainsworth, 2011; McCowan et al., 2014). Cerebral and ocular infection with the fungus *Ochroconis gallopava* was fund in two elegant crested tinamou (*Eudromia elegans*; Ossiboff et al., 2015). Granulomatous dacryoadenitis of unknown cause in an ostrich resolved with surgical excision (Saroglu et al., 2003).

Avian poxvirus is responsible for the large majority of reported viral infections involving birds' eyes (Karstad, 1971; Tripathy & Hanson, 1975). A wide variety of species have been affected, including conures (Emanuelson et al., 1978), mynahs (Panigrahy & Senne, 1991), Amazon parrots



Figure 31.5 House finch with conjunctivitis due to *Mycoplasma gallisepticum* infection.



Figure 31.6 Nodular conjunctivitis in a cormorant due to candidiasis.

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(Karpinski & Clubb, 1986; McDonald et al., 1981), racing pigeons (Dodd, 1974), bobwhite quail (Davidson et al., 1980; Poonacha & Wilson, 1981), peacocks (Al Falluji et al., 1979), exotic pheasants (Ensley et al., 1978), a whistling swan (Montgomery et al., 1980), and canaries (Cavill, 1964; Giddens et al., 1971; Johnson & Castro, 1986). Proliferative multifocal keratoconjunctivitis is the characteristic lesion; secondary keratitis and lid deformity may be sequelae to resolution of the lesions (Karpinski & Clubb, 1986). Poxvirus may occur in either or both of two forms: (1) a mild form causing proliferative lesions of the skin of eyelids and beak; and (2) a severe, generalized form involving the skin of many body sites and fibrinonecrotic lesions of the mouth or upper respiratory tract and pneumonia (Karstad, 1971). In psittacines, lesions occur 10–14 days after infection. Blepharitis may be followed by ulcerative keratitis and even perforation. Within 2–3 weeks, scabs form on the eyelids. In one study, 46% of parrots with poxvirus infection had residual ocular disease, including lid deformities, loss of periocular pigmentation and filoplume lashes, corneal neovascularization, subepithelial corneal crystal deposition, conjunctivitis and symblepharon, corneal ulcers, uveitis, cataract, phthisis and enophthalmos, and chronic epiphora from punctal occlusion (Karpinski & Clubb, 1985). Diagnosis can be confirmed histologically by demonstration of eosinophilic intracytoplasmic inclusions, epidermal hyperplasia, and intraepithelial vesicles; pox virions can be seen on electron microscopy (Tripathy & Hanson, 1975). Therapy of pox lesions is directed toward prevention of secondary bacterial infection (by administration of topical and systemic antibiotics) and careful attention to hygiene (daily eyewash); vitamin A administration (10,000–25,000 IU per 300 g body weight weekly by intramuscular injection) has also been empirically recommended (Karpinski & Clubb, 1986). Proventricular dilatation disease (PVD) in an African grey parrot (*Psittacus erithacus erithacus*) associated with retinal degeneration with lymphoplasmacystic infiltrate has been reported. Avian bornaviruses have recently been implicated in the pathogenesis of PVD, but signs have not been reported before or since (Steinmetz et al., 2008).

In chickens, cataracts and iridocyclitis have been associated with avian encephalomyelitis infection (Barber & Blow, 1963; Bridges & Flowers, 1958). Marek's disease causes iridocyclitis and secondary cataract (Rigdon, 1959). Nodular proliferative blepharoconjunctivitis in an African grey parrot was associated with cutaneous infection with a papilloma-like virus demonstrated by electron microscopy (Jacobson et al., 1983). An epidemic of conjunctivitis with respiratory distress and high mortality investigated in a flock of Gouldian finches was ascribed to a cytomegalovirus-like infection (Desmidt et al., 1991). Intranuclear inclusions were found in conjunctival epithelium by electron microscopy. Conjunctivitis in passerine birds has been associated with Newcastle disease virus and paramyxovirus-2 (Kern, 1997). In domestic poultry, infectious laryngotracheitis, duck plague, Newcastle disease, influenza A, infectious bronchitis, quail bronchitis viruses, turkey and pigeon herpesviruses, adenovirus, and pneumovirus cause conjunctivitis (Calnek, 1991).

Endophthalmitis and encephalitis due to *Toxoplasma gondii* were confirmed histologically in two flocks of canaries (Vickers et al., 1992; Williams et al., 2001). Chorioretinitis due to toxoplasmosis was diagnosed in chickens (Mustaffa-Babjee, 1969). Eyelid swelling has been documented with malaria infection (*Plasmodium* spp.) in canaries and domestic poultry (Mustaffa-Babjee, 1969). Goose parvovirus causes blepharitis and enteritis (Kern, 1997). Papovavirus inclusions were reported from the eyelids of budgerigars (Tsai et al., 1993).

Severe conjunctivitis due to cryptosporidiosis has been reported in pheasants (Randall, 1986), a domestic duck (Mason, 1985), stone curlews (*Burhinus oedicnemus*; Zylan et al, 2008), and a peacock (Mason & Hartley, 1980). *Encephalitozoon bellem* was the cause of unilateral keratoconjunctivitis in a cockatoo (Phalen et al., 2006).

Parasitic diseases occasionally cause avian ocular disease (Greve, 1986). Parasites are sometimes found under the membrana nictitans, associated with no clinical signs or conjunctivitis. These include the spirurids *Ceratospira* and *Oxyspirura* species in psittacines, mynahs, and domestic and wild birds (Dunham et al., 2016; Greve, 1986; Murphy, 1987; Mustaffa-Babjee, 1969); the nematodes *Thelazia* species in a Senegal parrot (Brooks et al., 1983a), a captive oriental white stork (*Circonia boyciana*; Murata & Asakawa, 1999), and a *Setaria* in passerines (Kern, 1997); and the trematode *Philophthalmus gralli* in ostriches, waterfowl, rheas, tinamous, and other species (Church et al., 2013; Greve & Harrison, 1980; Nollen & Murray, 1978; Rojas et al., 2013; Schmidt & Toft, 1981; Verocai et al., 2009; Williams, 1994). Treatment of chickens experimentally infected with oxyspirurids from wood partridges with topical ivermectin (0.005–0.5 mg, one dose) was effective in eliminating the nematodes from the conjunctival sac; oral and parenteral ivermectin administration was ineffective (Thomas-Baker, 1986). The life cycle of the oxyspirurids involves ingestion by a bird of an infected cockroach; nematode larvae migrate from crop to esophagus, then into the nasolacrimal duct to the conjunctival sac, where they lay eggs that are swallowed by the host and are expelled in feces (Thomas-Baker, 1986).

In budgerigars and other aviary and pet birds, *Knemidokoptes pilae* infestation causes scaly proliferative lesions of the legs, cere, and eyelids; other species cause similar lesions in poultry and wild passerines (Kern, 1997; Williams, 1994). Diagnosis is confirmed by skin scraping that demonstrates the organism. Systemic ivermectin administration is usually curative (Ivomec®, Merck, West Point, PA,

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USA), diluted 1:8 in propylene glycol and given at 200 µm/kg subcutaneously or orally (Karpinski & Clubb, 1986). Periocular myiasis occasionally occurs in wild and aviary birds (Kern, 1997).

Degenerations

Crystalline corneal degeneration of unknown cause was found at necropsy in 8.7% of birds at a quarantine station, most commonly in cockatiels, budgerigars, ring-necked parakeets, Amazon parrots, and Gouldian finches (Tsai et al., 1993). Similar deposits have been found in Amazon parrots following poxvirus infection (Karpinski & Clubb, 1985).

Lenticular degeneration with cataract development has been commonly noted in domestic, captive, and wild birds (Kern, 1997; Keymer, 1977; Williams, 1994; Fig. 31.7 and Fig. 31.8). Retrospective investigation of avian cataract incidence and management in a large zoologic collection revealed 90 cataracts in 54 birds from 42 species; 12 of 54 affected birds underwent cataract removal by phacoemulsification or extracapsular lens extraction (Rainwater et al., 2015). Presumptively heritable cataract was reported in a small kindred of Yorkshire and Norwich canaries; autosomal recessive inheritance was postulated in the Yorkshires (Slatter et al., 1983). Spontaneous cataract of unknown cause was identified in a large flock of bobwhite quail, detectable after 3 months of age (Krehbiel, 1972). In Brahma chickens, focal polar cataracts that progressed to maturity by 6 months of age were associated with the concomitant development of crooked toes; inheritance pattern was undetermined (Chmielewski et al., 1993). Spontaneous cataract in chickens and turkeys has been reported (Critchley & Tham, 1983; Rigdon et al., 1959). Maternal vitamin E deficiency in turkeys and dinitrophenol fed to chicks caused cataract (Mustaffa-Babjee, 1969). At a quarantine station, the incidence of uncomplicated cataract was 15.4% (Tsai et al., 1993). Presumptive senile cataract has been documented in aging macaws, an Amazon parrot, and a Bali mynah (Clubb & Karpinski, 1993; Jähne, 1979; Schmidt, 1983). In the captive macaws, most birds over 35 years of age had at least unilateral cataract; many also had iris atrophy, typified by darkening of a normally light-colored iris from exposure of the posterior pigmented iris epithelium (Clubb & Karpinski, 1993). Risk factors associated with cataract development in captive macaroni (*Eudyptes chrysolophus*) and rockhopper penguins (*Eudyptes chrysocome*) included water quality, age, diet, exhibition lighting, increased population density, and increased photoperiod (Woodhouse et al., 2016a, 2016b). Cataract surgery has been described in multiple bird species. The extracapsular cataract extraction has been performed in a Mandarin duck (Schmidt, 1983) and phacoemulsification



Figure 31.7 An 18-year-old peregrine falcon with dense cataract.

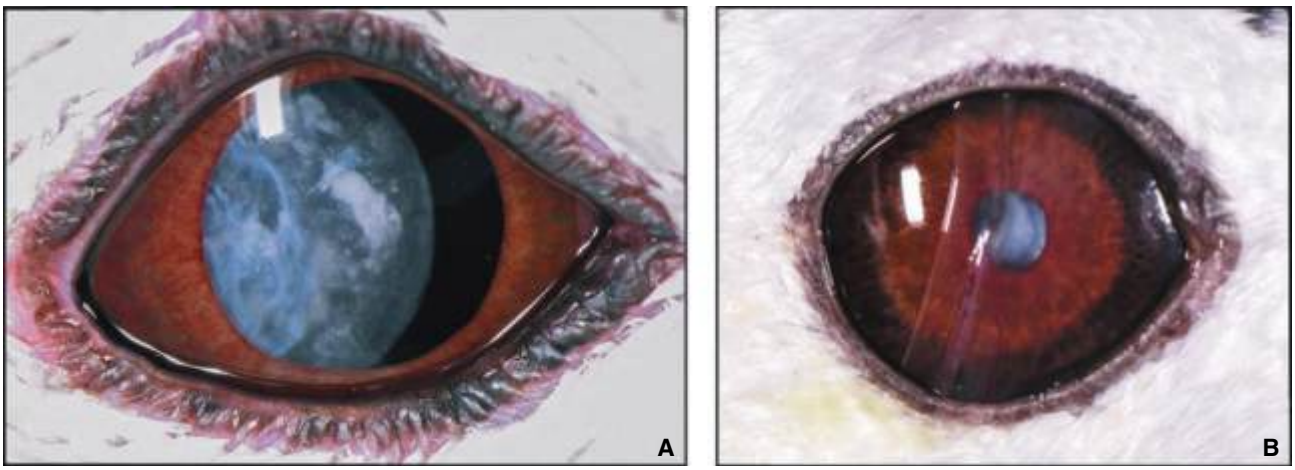


Figure 31.8 **A**. Right eye of a chinstrap penguin pharmacologically dilated with topical rocuronium bromide. Hypermature cataract and lens subluxation are present. **B**. Right eye of a nondilated chinstrap penguin with hypermature cataract. Note the clarity of the healthy nictitating membrane.

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has been described in macaws (Hacker & Shifrin, 1988). In most instances, intracameral injection of a curariform drug prior to surgery facilitated mydriasis. Injection of 0.1–0.3 mL of aqueous tubocurarine chloride (tubocurarine chloride injection, USP, E.R. Squibb, New York, USA), 3 mg/mL, has been effective (Kern et al., 1984).

Retinal degenerations in birds occur as inherited, postinflammatory, and posttraumatic conditions. Hereditary retinal degeneration in Rhode Island Red chickens appears to follow photoreceptor dysplasia (Ulshafer et al., 1984). Bilateral idiopathic generalized retinal degeneration was diagnosed in a budgerigar (Tudor & Yard, 1978). Retinal degenerations due to inflammation or trauma are focal to multifocal, sometimes extensive enough to cause blindness. Funduscopic appearance is characterized by pigmentary disturbance and asymmetric fundus pigmentation when both eyes are compared. Retinal and uveal calcifications of unknown cause were found in ring-necked parakeets at necropsy (Tsai et al., 1993). Spontaneous retinal detachment in young pheasants was unexplained (Randall et al., 1986).

Neoplasia

Neoplasia involving the avian eye and adnexa seem relatively uncommon (Dukes & Pettit, 1983; Kern, 1997; Williams, 1994). Marek's disease of chickens is the most common cause (Ball, 1945; Calnek, 1991; Dukes & Pettit, 1983). Marek's disease virus-associated ocular lymphoma was confirmed in Roulroul partridges (*Rollulus rouloul*; Haesendonck et al., 2015). Orbital lymphosarcoma associated with reticuloendotheliosis virus infection in a peafowl has been described (Miller et al., 1998). Intraocular and orbital and periorbital lymphoma had been diagnosed in several species of macaw (Alexander et al., 2017; Hausmann et al., 2016; Le et al., 2017). Eyelid and conjunctival neoplasia has been rarely reported. Neoplasms include a benign basiloid cell tumor in a budgerigar (Brightman & Burke, 1978), a mastocytoma of the lower eyelid of a chicken (Patnaik & Mohanty, 1970), a chondrosarcoma of the third eyelid of a great white heron (Spalding & Woodard, 1992), a periocular cystadenoma in an African grey parrot (Hochleithner, 1990), and neoplasms of the third eyelid (squamous cell carcinoma in a hawk, basal epithelioma in a parrot, xanthoma in a budgerigar; Kern et al., 1996). A mucinous adenocarcinoma of the globe was diagnosed in a 2-year-old male ostrich (*Struthio camelus*) and managed by local incision (Perrin et al., 2017). A subconjunctival hibernoma, a benign neoplasm of brown fat, was successfully excised from a domestic goose (Murphy et al., 1986). In addition to herpesvirus-induced ocular lymphomatosis (Marek's disease) in chickens, primary uveal neoplasia reports include iris melanoma, iris hemangioendothelioma, and anterior uveal rhabdomyosarcoma in chickens (Dukes & Pettit, 1983), medulloepithelioma in two cockatiels (Schmidt et al., 1986), adenocarcinoma in a budgerigar (Tripathy & Hanson, 1975), and uveal malignant melanoma in a duck with extrascleral extension (Gilger et al., 1995). Periocular swelling was caused by multicentric or metastatic malignant melanoma in an African grey parrot and a pigeon (Paul-Murphy et al., 1985; Rambow et al., 1981). Orbital neoplasia included optic nerve glioma and round cell sarcoma (Williams, 1994). Between 1982 and 2011, 284 avian ocular pathology cases were presented to the Comparative Ocular Pathology Laboratory of Wisconsin (COPLOW) that represented ocular neoplasia. Seven tumors were metastatic and six of those were diagnosed as lymphoma. Tumors were primary in eight cases, including two tumors of epithelial origin (a teratoid medulloepithelioma and a ganglioneuroma). A round cell tumor, squamous cell carcinoma, and teratoma were diagnosed as well (Fernandez & Dubielzig, 2015). Pituitary adenomas in budgerigars and cockatiels may cause tonic mydriasis and blindness due to optic neuropathy (Curtis-Velasco, 1992; Dezfoulian et al., 2011; Langohr et al., 2012; Schlumberger, 1954; Small & Burke, 1982; Spalding & Woodard, 1992; Suchy et al., 1999). Malignant intraocular teratoid medulloepitheliomas were identified in three cockatiels (Bras et al., 2005; Schmidt et al., 1986). Squamous cell carcinoma of the infraorbital sinus was diagnosed at necropsy in a Solomon eclectus parrot (*Eclectus roratus solomonensis*) with fungal tracheitis (Diaz-Figueroa et al., 2006). Surgical resection of a conjunctival xanthoma from a blue and gold macaw (*Ara ararauna*) was curative (Souza et al., 2009). Surgical removal of a retrobulbar adenoma suspected to be associated with hypovitaminosis A from an African grey parrot (*Psittacus erithacus*) was complete with preservation of the globe and vision (Simova-Curd et al., 2009). Intraocular osteosarcoma with orbital extension in an umbrella cockatoo (*Cacatua alba*) was treated with exenteration and radiation therapy, but the bird was euthanatized 2 months afterward for neurologic signs. Although axial and appendicular osteosarcoma have been reported in birds, this was believed to be the first report of intraocular osteosarcoma (Fordham et al., 2010). Bilateral liposarcoma was diagnosed in an African grey parrot (*Psittacus erithacus*; Graham et al., 2003).

Vitamin A Deficiency

Hypovitaminosis A, a common subclinical condition in cage birds, may predispose them to diseases of the mucous membranes (e.g., keratitis, conjunctivitis). Clinical deficiency may be manifest as swollen eyelids due to conjunctival hyperkeratosis, mimicking pox lesions. Cytologic and histologic examination of lesions may be used to differentiate the causes. Parenteral and dietary vitamin A supplementation is effective (Koschmann, 1986).

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Trauma

Traumatic ocular injury is most frequent in raptors, but also occurs commonly in wild passerine birds. Injuries are often not confined to the eye and ocular injuries may be complex, involving external eye, anterior, and/or posterior segments.

Presumptive Horner's syndrome following cervical trauma has been described in a red-bellied parrot (*Poicephalus rufiventris*). Ptosis without miosis and ipsilateral facial feather fluffing were the clinical signs, which improved over time (Gancz et al., 2005). Surgical excision of an infraorbital secretory epithelial cyst that developed following trauma was curative in a white cockatoo (*Cacatua alba*; Stiles & Greenacre, 2001). Surgical repair of bilateral acquired ankyloblepharon secondary to thermal injury was successful in a young cockatiel (Pinard et al., 2006). An ocular prosthesis was implanted in a grey parrot (Neumann & Kummerfield, 1983).

Newly imported mynahs developed corneal erosions associated with capture and cage trauma (Williams & Flach, 2003). In most birds, the keratitis resolved uneventfully. Some mynahs developed chronic keratoconjunctivitis with proliferative conjunctival masses, which required excision. Penetrating keratoplasty was performed on a California brown pelican to resolve axial corneal scarring (Lynch et al., 2007).

Raptors

Raptors, or birds of prey, are well known for numerous visual adaptations that allow them to successfully hunt prey worldwide, in a broad range of habitats. The comparative anatomy and physiology of the eyes of raptors have been studied extensively over the past 50 years and comprehensive reviews have been written on the subject of vision in raptors by several authors (Jones et al., 2007; Martin, 2012). The subject is unfortunately beyond the scope of this chapter.

In this section, the clinical aspects of raptor ophthalmology will be emphasized. Raptors will often be broadly divided and referred to as diurnal (hawks, falcons, condors, eagles) or nocturnal (all owls) species. The reader is encouraged to reference excellent reviews of this topic (Buyukmihci, 1985; Buyukmihci et al., 1988; Davidson, 1997; Greenwood & Barnett, 1981; Kern, 1997; Korbel, 2000; Murphy, 1987; Murphy et al., 1982a).

Restraint

The examination equipment and environment required for the ophthalmic examination of raptor species are similar to those needed for other bird species discussed earlier in this chapter. Handlers of these birds should have experience in avian restraint techniques to ensure the patient's safety and comfort. The talons of many raptor species are capable of inflicting serious harm to both handlers and examiners and should be specifically restrained or wrapped (Labelle et al., 2012; Murphy, 1987).

Bony Orbit

While the anatomic features of the raptor globe and bony orbit contribute to excellent visual acuity, the large size of the eye and relative lack of orbital protection predispose the eyes to environmental trauma. The bony orbit is made up of a number of individual elements, with contributions from the frontal, prefrontal, sphenoid, ethmoid, palatine, and quadrate bones as well as the bony components of the jugal arch. The two globes are separated from each other by the exceedingly thin interorbital septum. The osseous septum is complete in owls, while in diurnal birds of prey, an aperture is present that is covered by a tough fibrous membrane in life. The bony component of the posterior orbital wall is less than 1 mm thick in some locations. The posterior aspect of the eye fits snugly within the orbit, but the majority of the globe's temporal and dorsal aspects remains completely outside of its protection.

Many of the larger bony elements are pneumatized, which increases their susceptibility to environmental and surgical trauma (Murphy, 1987). Fractures of orbital bones are commonly caused by blunt trauma and may be readily apparent due to gross facial distortion. Fractures can be palpated directly, or detected with radiography (Davidson, 1997; Murphy, 1987) or computed tomography (Gumpenberger & Kolm, 2006). Orbital fractures can lead to secondary complications, such as septic contamination and periorbital abscessation (Bezjian & Kollias, 2014), and are often associated with other central nervous system injuries (Davidson, 1997). Disorders associated with the soft tissues of the orbit are rare, though retrobulbar neoplasia has been reported (Coello & Schaeffer, 2014).

Glands of the Raptor Orbit

The Harderian gland is the major source of tears in birds and is attached to the posterior aspect of the globe in raptors, ventral to the medial rectus muscle. A lacrimal gland is present and associated with the ventromedial orbital rim in most raptors (Murphy, 1987), but is absent in owl species (Duke-Elder, 1958), some of which instead possess a nasal salt gland in the dorsonasal aspect of the orbit (Murphy, 1987). This salt gland has also been observed in hawks and, in addition to providing an adaptive mechanism for living in dry habitats (Sabat, 2000), may represent an alternative source of tears (Beckwith-Cohen et al., 2015), or provide tear film stability.

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Eye

The eyes of raptors are very large relative to their body size and are directed forward in the skull, creating a large field of binocular vision (Waldvogel, 1990). These features are especially apparent in owls (Murphy, 1987). Torsional ocular mobility is limited to 2 degrees in owls and 8 degrees in hawks. Owls predominantly use head movements to direct their field of view. Hawks rely heavily on ocular movements for tracking prey and have larger extraocular muscles than owls (Plochocki et al., 2018). Because of the close fit of the globe within the orbit and the absence of a retractor bulbi muscle, raptors are unable to withdraw the globe into the orbit (Murphy, 1987). The shape of the eye is flat in some of the small diurnal raptors, such as the kestrel; globose in large diurnal raptors, such as the red-tailed hawk; and tubular in all owls (Duke-Elder, 1958; Walls, 1942).

Similar to those of other birds, the shape of the raptor globe is formed and maintained by hyaline cartilage within the posterior segment and by an average of 14–16 bony ossicles within the sclera of the intermediate segment (Curtis & Miller, 1938; Lima et al., 2009). Several species of owl possess a scleral sesamoid bone associated with the tendon of the pyramidalis muscle that may reduce the shearing forces of this tendon and control the trajectory of third eyelid excursions (Bohorquez Mahecha & de Oliveira, 1998). An additional scleral bone, known by several names – *os nervi optici* (Murphy, 1987), *os opticus* (Tiemeier, 1950), or Gemminger's ossicle (Evans, 1979) – is present in diurnal species, but is not present in owls. The function of this bone is uncertain, though it may protect the optic nerve from damage associated with IOP changes experienced during atmospheric pressure fluctuations associated with flight (Tusler et al., 2017), or possibly from the ocular trauma associated with predatory behaviors. Scleral ossicle fracture can occur secondary to trauma, and secondary infection and osteomyelitis have been known to occur (MacLaren et al., 1995). These fractures have been identifiable by palpation (Murphy, 1987) and are typically associated with a poor prognosis for the globe (Davidson, 1997; Lindley et al., 1988; Murphy et al., 1982b) and the bird (MacLaren et al., 1995).

Developmental malformations of the globe are uncommon, though microphthalmia has been reported in several raptors (Buyukmihci et al., 1988). Presumptive keratoglobus in a juvenile great horned owl (*Bubo virginianus*) was investigated and studied by postmortem ocular measurements and histopathology. It was determined that IOP was normal bilaterally and a keratoglobus was present bilaterally. The bird was sighted and posterior segment measurements were representative of the normal posterior segment of this species, but anterior segment measurements were larger than normal (Lau et al., 2017).

Ocular ultrasound is often used to assess the globe of normal and diseased raptors. Normal ocular biometric parameters have been published in numerous diurnal raptor and owl species (Gumpenberger & Kolm, 2006; Kuhn et al., 2015; Seruca et al., 2012; Squarzoni et al., 2010; Wills et al., 2016) and may be useful in providing more objective evaluation of ocular disorders and associated outcomes in free-living raptor species (Labelle et al., 2012).

Tonometry and Glaucoma

Several anatomic and physiologic variations of the raptor globe have been shown to influence IOP measurements obtained with applanation and rebound tonometry. Younger raptors have been shown to have slightly lower IOPs relative to adults (Labelle et al., 2012; Reuter et al., 2011), and species differences have been documented in numerous studies, with owls displaying lower IOPs relative to diurnal raptors in some studies (Labelle et al., 2012; Stiles et al., 1994), but not in others (Barsotti et al., 2013; Beckwith-Cohen et al., 2015). Species-specific deviations from manometry within the 5–60 mmHg range have been observed using the TonoVet, underestimating IOP in some species and overestimating IOP in others (Reuter et al., 2010). A direct relationship between corneal thickness and IOP has been observed when using the TonoVet in one study evaluating six raptor species (Bayón et al., 2006). Greater pressures and wider ranges were recorded in raptors with thicker corneas with the TonoVet, whereas applanation tonometry (Tono-Pen XL) produced more consistent readings across corneas of differing thicknesses. Differences between the two instruments were extreme in some species with relatively thick corneas, notably so in Bonelli's eagle (*Aquila fasciata*), with the TonoVet and Tono-Pen recording a mean IOP of 40.26 ± 7.14 mmHg and 19.61 ± 2.43 mmHg, respectively – greater than a 20 mmHg difference. Corneal diameter may also impact the accuracy of IOP measurements. Specifically, applanation tonometry (Tono-Pen XL) correlates well with manometry within the 10–25 mmHg range when the corneal diameter exceeds 9 mm (Braun, 1995; Korbel & Braun, 1995, 1999), and shows greater variability with smaller eyes (Bayón et al., 2006; Braun, 1995). Conversely, rebound tonometry has demonstrated greater variability in larger eyes relative to applanation tonometry, with the rebound tonometer producing a minor (i.e., a 1.1 mmHg difference between mean IOPs obtained between the two instruments), but statistically significant overestimation of IOP in Eurasian eagle owls (*Bubo bubo*) in one study (Jeong et al., 2007). The effects of an upright versus dorsally recumbent body position have been shown to subtly influence IOP in two of six raptor species evaluated by rebound tonometry (Reuter et al., 2011). Overall, these observations suggest that in general, rebound tonometry should be utilized for smaller eyes and applanation tonometry for larger eyes, and that species-specific reference values should be used rather than relying on interspecies

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extrapolation. Where possible, reference values should be extrapolated from studies that directly compare tonometric measurements (rebound or applanation techniques) with manometric readings (Braun, 1995; Korbel & Braun, 1995, 1999; Reuter et al., 2010). It remains unknown what specific influence scleral ossicles, corneal rigidity, nonspherical globe shapes (Kern, 1997), aqueous humor flow rates (Jones & Ward, 2012), and aqueous humor viscosity (Davis et al., 2015) may have on IOP measurements.

Rare cases of suspected primary glaucoma (Rayment & Williams, 1997) and medically responsive aqueous humor misdirection with ocular hypertension (Jayson et al., 2014) in raptors have been reported. Topical carbonic anhydrase inhibitors (Buyukmihci, 1985; Jayson et al., 2014) and intravenous mannitol (Jayson et al., 2014) have been well tolerated and effective in some cases. Secondary glaucoma following traumatic uveitis occurs more often (Bayón et al., 2007; Buyukmihci, 1985; Chitty, 1995; MacLaren et al., 1995; Murphy et al., 1982b; Williams et al., 2006). Prognosis for glaucoma in raptors appears to be poor, as birds are often reported to be euthanized (Buyukmihci, 1985; MacLaren et al., 1995; Rayment & Williams, 1997).

Tear Quantification

Quantification of the normal tear film of numerous owl and diurnal raptor species has been documented in recent studies (Barsotti et al., 2013; Beckwith-Cohen et al., 2015; Korbel & Leitenstorfer, 1996; Komnenou et al., 2013; Kuhn et al., 2013; Smith et al., 2015; Williams et al., 2006; Wills et al., 2016). Three methods of tear film evaluation in raptors have been reported. The STT is most commonly utilized; however, the PRTT (Beckwith-Cohen et al., 2015; Smith et al., 2015) and the longitudinally cut, or modified, STT (Korbel & Leitenstorfer, 1998; Williams et al., 2006) have also been described. In general, and in agreeance with anatomic descriptions of orbital glands, owls produce lower STT results relative to diurnal raptors, typically ranging between 1 and 3 mm/min, though there are some reported exceptions; specifically in two eagle owl species (Beckwith-Cohen et al., 2015), great gray owls, and snowy owls (Wills et al., 2016), which display mean STT measurements between approximately 10 and 15 mm/min. Despite higher average STT tendencies, diurnal raptors show significant variation in tear production, ranging between approximately 2 mm/min in the lesser kestrel (Beckwith-Cohen et al., 2015) and 14 mm/min in the bald eagle (Kuhn et al., 2013). STT and PRTT results do not correlate with one another and reference values should be considered independently for each test/species (Beckwith-Cohen et al., 2015). Primary disorders of the precorneal tear film have not been reported; however, lacrimal remnants capable of producing secretions following modified evisceration procedures are possible (Murray et al., 2013).

Eyelids

The palpebral reflex can be incomplete in normal raptors, owing to excitement (Murphy, 1987) and normal spontaneous blinking occurs less often in nocturnal species relative to diurnal species (Kirsten & Kirsten, 2008). The lower lid of most raptors contains a fibrous plate that is roughly semicircular in outline, with the flat edge facing the palpebral margin. The nasolacrimal puncta of raptors are well developed, especially in owls. The nasolacrimal duct empties into the nasal cavity dorsal to the choanal cleft (Wood, 1915).

Developmental eyelid malformations (Kern et al., 1985) and neoplastic eyelid disorders (Sacré et al., 1992; Swayne & Weisbrode, 1990) have not been commonly reported in raptors. Traumatic disorders of the eyelid such as laceration, gunshot wounds, or burns (Seruca et al., 2013; Wills et al., 2016) are occasionally noted in large surveys of traumatized birds (Murphy et al., 1982a). Surgical repair of eyelid defects has been described, noting that the eyelid is thin, making double-layered closure impractical (Murphy, 1987). Temporary partial tarsorrhaphy has been utilized for prevention of exposure keratitis (Murphy, 1987) and for protection of corneal (Gionfriddo & Powell, 2006) or intraocular surgical sites. Eyelid disease not amenable to surgical correction can lead to chronic exposure keratitis, necessitating modified evisceration (Murray et al., 2013).

Primary infectious blepharitis and dermatitis are exceptionally rare in owl species, but are sporadically reported in debilitated or immunocompromised diurnal raptors. Primary fungal blepharitis has been reported (Abrams et al., 2001); however, poxvirus infections and knemidokoptic mange are encountered more frequently (Fitzner et al., 1985; Graham & Halliwell, 1986; Sadar et al., 2015; Shrubsole-Cockwill et al., 2010). Poxvirus lesions are typically nodular, raised, and can develop scabs and crusts, most often affecting the nonfeathered skin of the eyelids and feet. The disease is confirmed with histologic demonstrations of large eosinophilic intracytoplasmic inclusion bodies (known as Bollinger bodies; Fitzner et al., 1985). Uncomplicated poxvirus infections are self-limiting, with irregular nodular lesions tending to regress after approximately 3 weeks (Graham & Halliwell, 1986), but fungal coinfection and subsequent death have been reported (Shrubsole-Cockwill et al., 2010). Knemidokoptic mange has a similar predilection for nonfeathered areas and causes scaling of the skin of the face and legs. Mite infestations can also affect feathered skin and can cause proliferation and inflammation of the beak (Pence, 2008; Schmidt & Lightfoot, 2006). Diagnosis of knemidokoptic mange can be achieved by demonstrating the mite cytologically through skin scrapings or acetate tape preparations (Miller et al., 2004; Schulz et al., 1989). Periocular knemidokoptic mange has been reported in a golden eagle (*Aquila chrysaetos*) treated successfully with a combination of ivermectin and selemectin (Sadar et al., 2015).

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Third eyelid excursions in raptors occur spontaneously as well as reflexively (to eyelid palpation) more so than of the eyelids themselves. This third eyelid reflex is reportedly one of the last to disappear under general anesthesia (Murphy, 1987). Disorders localized specifically to the third eyelid are uncommon and are limited to case reports and small case series. Specifically, nodular conjunctivitis, dystrophic plaque formation, trauma-induced restriction/denervation, porcupine quill injury, epidermoid carcinoma (Kern et al., 1996), and third eyelid symblepharon (Williams & Flach, 2003) have all been reported. Complete third eyelid excision has been described and did not appear to cause any deleterious effects to the ocular surface in two snowy owls (Williams & Flach, 2003).

Conjunctiva

The normal external ocular microflora of raptors has been surveyed (Beckwith-Cohen et al., 2015; Cousquer et al., 2010; Dupont et al., 1994; Harris et al., 2008; Wolf et al., 1983). Across all studies, Gram-positive bacteria, specifically *Staphylococcus* spp. and *Corynebacterium* spp. (Dupont et al., 1994; Wolf et al., 1983), predominate and have been isolated in various raptor populations at a frequency ranging at 52%–100% and 28%–33% of all cultured populations for *Staphylococcus* spp. and *Corynebacterium* spp., respectively. More virulent bacteria such as *Chlamydophila* spp. (Beckwith-Cohen et al., 2015) have been cultured uncommonly in normal raptor eyes. *Mycoplasma* spp. have been cultured or demonstrated by polymerase chain reaction (PCR) in captive and free-ranging birds of prey in Europe without signs of infection, leading some to believe that *Mycoplasma* spp. may be a commensal organism in some raptor populations (Lierz et al., 2000, 2008a, 2008b). Fungi are rarely cultured within the conjunctiva of normal raptors and have been detected in approximately 5% of cultured populations (Beckwith-Cohen et al., 2015; Dupont et al., 1994).

Infectious conjunctivitis is rare in raptors, but has been documented in association with avian cryptosporidiosis (Molina-Lopez et al., 2010; Rodriguez-Barbon & Forbes, 2007). Cryptosporidiosis is a protozoal disease of young and immunocompromised birds most common in chickens (Molina-Lopez et al., 2010; O'Donoghue, 1995). Conjunctivitis and respiratory disease (rhinitis and tracheitis) associated with this organism have been observed in several captive falcons (Rodriguez-Barbon & Forbes, 2007) and in a population of 16 scops owls (*Otus scops*) within a rehabilitation center (Molina-Lopez et al., 2010). Infected owls displayed blepharedema conjunctival hyperemia, mucopurulent ocular discharge, as well as corneal edema and uveitis (Fig. 31.9). Diagnosis can be confirmed by direct observation (cytology or histopathology) and by immunofluorescent assay or PCR (Zylan et al., 2008). Treatment with azithromycin is effective, resulting in disease resolution within 15 days (Molina-Lopez et al., 2010).



Figure 31.9 Blepharedema and conjunctivitis in a scops owl affected by ocular cryptosporidiosis. (Reproduced with permission from Molina-Lopez, R.A., Ramis, A., Martín-Vázquez, S., et al. (2010) *Cryptosporidium baileyi* infection associated with an outbreak of ocular and respiratory disease in otus owls (*Otus scops*) in a rehabilitation centre. *Avian Pathology*, **39**, 171–176.)

Cornea

The corneal diameter in diurnal birds of prey is much smaller and has a steeper curvature relative to owls of similar size, giving the illusion that the diurnal raptor eye is smaller than it actually is (Murphy, 1987). The corneal diameters of numerous nestling (Labelle et al., 2012) and adult raptor species (Beckwith-Cohen et al., 2015; Harris et al., 2008; Labelle et al., 2012; Wills et al., 2016) have been published recently and should be referenced clinically when establishing normal globe size and before measuring IOP, as mentioned previously. Corneal curvature assessed by keratometry has been measured in the bald eagle (Kuhn et al., 2015) and numerous owl species for the purposes of calculating the refractive state of the eye (Murphy & Howland, 1983) and for predicting theoretical intraocular lens (IOL) power for implantation following cataract surgery in the great horned owl (Carter et al., 2007) and bald eagle (*Haliaeetus leucocephalus*; Kuhn et al., 2015). The intraocular power of custom-made IOLs in the great horned owl was 13.8 D. Bald eagles were predicted to require an IOL power of 16.4–17.4 D (Kuhn et al., 2015).

The central cornea is exceptionally thin in several raptor species such as the little owl (*Athena noctua*; 141 µm) and common kestrel (*Falco tinnunculus*; 155 µm) and does not necessarily correlate directly with body size. For instance, the comparably sized Eurasian eagle owl (*Bubo bubo*) and Bonelli's eagle (*Aquila fasciata*) have a reported central corneal thickness of 240 µm and 627 µm, respectively (Bayón et al., 2006).

Corneal sensitivity measured by Cochet–Bonnet aesthesiometry has been reported for normal common kestrels (*Falco tinnunculus*) and three species of owl (Lacerda et al., 2014). Central and peripheral corneal sensitivities are similar in

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Figure 31.10 A conjunctival pedicle flap is well incorporated into the cornea of a great horned owl. (Reproduced with permission from Gionfriddo, J.R. & Powell, C.C. (2006) Primary closure of the corneas of two great horned owls after resection of nonhealing ulcers. *Veterinary Ophthalmology*, **9**, 251–254.)

these birds and corneal sensitivity was similar between all species studied, though fledgling birds of prey demonstrated greater sensitivity relative to adults (Lacerda et al., 2014). When comparing similarly designed studies, birds of prey possess a relatively high degree of corneal sensitivity, similar to that of humans (Millodot, 1977), and more sensitive than cats (Chan-Ling, 1989) and dogs (Barret et al., 1991).

Traumatic superficial corneal erosion/ulceration is the most commonly encountered corneal lesion in raptors, especially in owls (Harris et al., 2008; Murphy et al., 1982a; Murray et al., 2013; Seruca et al., 2012; Williams et al., 2006; Wills et al., 2016), and has been associated with blunt, penetrating, and thermal injuries. In a recent large survey of traumatic ocular lesions in nocturnal raptors, corneal ulceration was the most common clinical abnormality observed in Eurasian scops owls (*Otus scops*), representing 57% of ocular lesions observed in this species (Seruca et al., 2012). Interestingly, ulcers in raptors rarely become complicated by infection, nor do they develop significant corneal vascularization (Moore et al., 2017; Murphy, 1987). More often, ulcers are complicated by persistence or recurrence, which has been managed successfully with chronic (1–3 months) prophylactic topical antibiotic therapy (Seruca et al., 2012), subconjunctival antibiotic injection (Kern, 1997), or conjunctival pedicle flap (Gionfriddo & Powell, 2006; Fig. 31.10). Great horned owls have developed severe corneal edema (Fig. 31.11), similar in appearance to acute corneal hydrops of cats and humans (Andrew et al., 2002; Gionfriddo & Powell, 2006), which has been described specifically as keratoglobus in one report (Lau et al., 2017). Excision and primary closure of the diseased cornea were successful in two owls with this disorder (Gionfriddo & Powell, 2006). Penetrating keratoplasty and corneal transplantation failed in another report (Andrew et al., 2002).

An idiopathic corneal lipoidal degeneration has been observed in falcons (Fig. 31.12; Moore et al., 2018) and has been suspected in a barred owl (*Strix varia*; Murphy et al., 1981) and a common buzzard (*Buteo buteo*; Greenwood & Barnett, 1981). This rare condition has been observed most often in aged birds.

Anterior Uvea

Among raptor species, iris coloration is variable, with brown and yellow colors being predominant. The pigments of the great horned owl's (*Bubo virginianus*) iris have been described in detail (Oliphant, 1988). The color that is appreciated



Figure 31.11 Bullous corneal edema in a great horned owl, treated initially with a conjunctival pedicle flap. (Reproduced with permission from Gionfriddo, J.R. & Powell, C.C. (2006) Primary closure of the corneas of two great horned owls after resection of nonhealing ulcers. *Veterinary Ophthalmology*, **9**, 251–254.)

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Figure 31.12 Lipoidal corneal degeneration in a falcon.

grossly is a composite of various chromatophores, blood vessels, connective tissue, nerves, and muscles that bears greater anatomic similarity to poikilotherms (i.e., fish, reptiles, amphibians) than to other homeotherms (mammals; Oliphant, 1988). Iris coloration may provide information as to the relative age of an individual in certain species (Greenwood & Barnett, 1981; Murphy, 1987), especially the Accipitridae (hawks, eagles, and buzzards). The juvenile red-tailed hawk (*Buteo jamaicensis*) and bald eagle (*Haliaeetus leucocephalus*) have a yellow-gray iris, which becomes more darkly pigmented with increasing age (Kuhn et al., 2013; Labelle et al., 2012; Murphy, 1987). Alterations of iris coloration, synechiae, hemorrhage, and peripheral disinsertion have all been noted following traumatic uveitis.

The iris musculature of avian species shows variable presence of smooth muscle, myoepithelium, and skeletal muscle assigned to pupillary dilatation or constriction (Oehme, 1969). The rapid speed of the direct pupillary light reflex in raptors is attributed primarily to a striated constrictor muscle, while the much slower pupillary dilation is controlled by radial dilator myoepithelium, as demonstrated histologically in the great horned owl (Oliphant, 1983). A subtle and dynamic anisocoria can be normal in raptors; however, marked dilation in a well-lit environment is often suggestive of significant damage to the retina and/or optic nerve (Fig. 31.13 and Fig. 31.14; Harris et al., 2008; Kern, 1997).

Voluntary constriction of the avian pupil can limit posterior segment examination and surgery of the lens in birds. Parasympatholytic agents are ineffective in producing mydriasis, although dilation can be achieved through general anesthesia (Kern, 1997) or through the use of neuromuscular paralyzing agents (NMBAs), which paralyze the pupillary constrictor muscle. Intracameral injection of d-tubocurarine, a nondepolarizing NMBA, has been reported to cause consistent moderate to maximal mydriasis in several raptor species (Murphy, 1987). Mydriasis was consistently and safely achieved in European kestrels (*Falco tinnunculus*) by topical administration of vecuronium bromide (4 mg/mL; Norcuron, Organon Teknika, Paris, France), two drops every 15 minutes for three instillations applied to one eye only (Mikaelian et al., 1994). Maximal mydriasis occurred about 1 hour after treatment and was maintained for 4 hours. Alcuronium chloride (5 mg/mL; Alloferine®, Roche, La Rochelle, France) given 1 drop (0.05 mL) unilaterally twice at 15 minute intervals resulted in mydriasis for up to 3 hours, but most birds developed eyelid paralysis; one also developed neck and hind limb paralysis (Mikaelian et al., 1994). Pancuronium bromide (2 mg/mL; Pavulon®, Organon Teknika) administered unilaterally (2 drops twice, 15 minutes apart) had an inconsistent mydriatic effect; most birds did not achieve maximal mydriasis (Mikaelian et al., 1994). *Note that the safety of simultaneous bilateral topical ophthalmic administration of these drugs was not investigated in this study*. In several recent studies, Barsotti et al. (2010a, 2010b, 2012) have safely achieved sus-

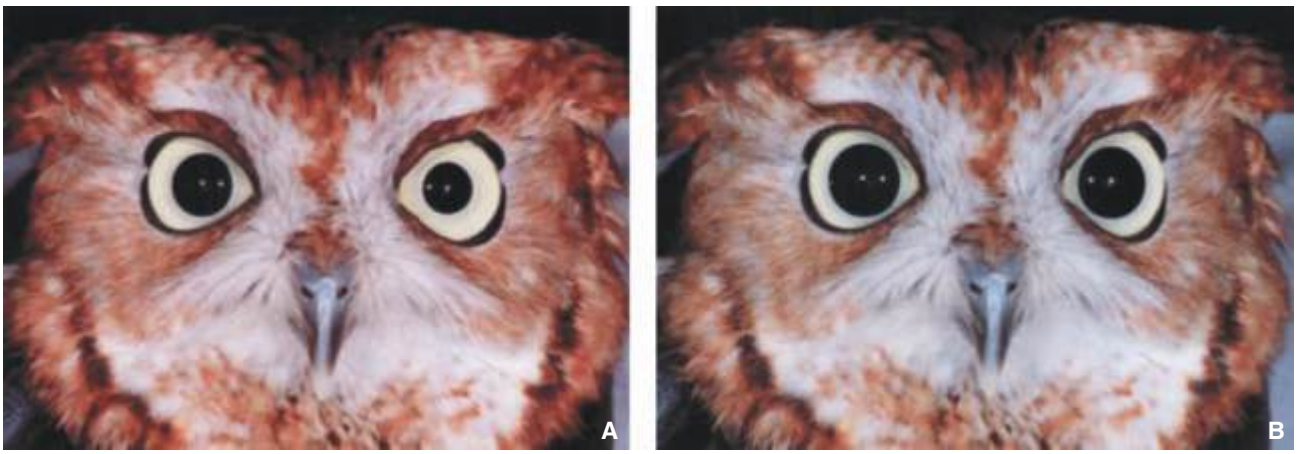


Figure 31.13 **A**. Normal iris in a healthy screech owl. **B**. Normal, dynamic anisocoria in the same bird. (Reproduced with permission from Harris, M.C., Schorling, J.J., Herring, I.P., et al. (2008) Ophthalmic examination findings in a colony of screech owls (*Megascops asio*). *Veterinary Ophthalmology*, **11**, 186–192.)

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Figure 31.14 Marked anisocoria and dilation of the left pupil in a great horned owl with complete retinal detachment. (Courtesy of Dr. Filipe Espinheira.)



Figure 31.15 Eurasian eagle owl with traumatic corneal perforation and secondary cataract of the right eye.

tained mydriasis (up to 4 hours) using topical rocuronium bromide (Esmeron®, Organon Italia, Rome, Italy) in several owl species, kestrels, and the common buzzard using multiple dosage protocols. Topical vecuronium bromide produced similar effects and was safe in European kestrels (Mikaelian et al., 1994); however, topical alcuronium chloride and pancuronium bromide have produced either unsafe or inconsistent results (Mikaelian et al., 1994). Body weight has been used to estimate the appropriate dosage of topical rocuronium bromide (Barsotti et al., 2012), and iris coloration (Barsotti et al., 2010a) has been suspected to influence the speed of onset and duration of mydriasis. As outlined above, it is important to note that several studies have only investigated unilateral application of NMBAs (Barsotti et al., 2010a; Mikaelian et al., 1994; Ramer et al., 1996) and safety has not been documented for bilateral administration. Because fatal complications can occur following application of intracameral (Murphy, 1987) or topical NMBAs (Ramer et al., 1996), avian practitioners should pay close attention to the exact protocol described when referencing previous studies.

Sharp and blunt trauma to the eye (see Fig. 31.9 and Fig. 31.15) are responsible for the majority of inflammatory pathologies observed in the anterior uvea. Anterior uveitis with hyphema, specifically, is one of the most common ocular examination findings following trauma (Labelle et al., 2012; Murphy et al., 1982b; Seruca et al., 2012). A recent histopathologic survey of traumatic ocular lesions in raptors also showed iridocyclodialysis to be a common lesion following acute or chronic blunt trauma (Moore et al., 2017). Endogenous/infectious uveitis is being increasingly recognized in raptors since the emergence of West Nile Virus in North America in 1999 (Campbell et al., 2002); hawks and owls appear to be especially predisposed (Pauli et al., 2007; Wünschmann et al., 2004, 2005). Supportive care involving systemic and topical anti-inflammatory medications is the mainstay of therapy for intraocular inflammation (Davidson, 1997; Murphy, 1987; Seruca et al., 2012).

Uveal neoplasms in raptors are exceptionally rare, though an iris melanoma has been identified in a great horned owl (*Bubo virginianus*; Fournier et al., 1983).

Pupilloplasty and synechiectomy have been described for restoring the visual axis in a great horned owl and a bald eagle with pupillary occlusion/synechia (Aguilar et al., 1993; Canton et al., 1992).

Lens

Cataracts are most often reported in raptors due to senility (Keymer, 1977; Kuhn et al., 2013; see Fig. 31.7) and as a result of blunt and/or penetrating trauma (Harris et al., 2008; Moore et al., 2017; Murphy et al., 1982a, 1982b). A case of electrocution-induced cataracts was reported in a great horned owl in which bilateral anterior cortical vacuoles were noted 5 days later and then resolved within 8 weeks (Dees & MacLaren, 2013). Juvenile cataracts have been reported in tawny, screech, and great horned owls (Murphy, 1987), though there is no evidence to indicate that juvenile or congenital cataracts in raptors are heritable.

Cataract extraction through intracapsular (Brooks et al., 1983) and extracapsular techniques (Moore et al., 1985; Van Niekerk & Petrick, 1990) and phacoemulsification (Kern et al., 1984) have been described in owls and diurnal raptors. Bilateral implantation of custom-made IOLs resulted in postoperative emmetropia in a great horned owl following phacoemulsification (Carter et al., 2007). The optic diameter was 10 mm and the haptic diameter was 17 mm.

Posterior Segment

Perhaps because of their relatively large eye size, fundus evaluation is relatively easy in many raptors without the assistance of pharmacologic mydriasis, especially if the room light and examination light are dimmed. The pecten is the most identifiable structure fundoscopically. The comparative anat-

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omy of the diurnal and nocturnal raptor pecten has been well characterized via histology, electron microscopy (Braekevelt, 1991, 1993; Gültiken et al., 2012; Kiama et al., 1994, 1998; Smith et al., 1996), and Doppler ultrasonography (de Moraes et al., 2017). The anangiotic retina is relatively nondescript. The retinal pigmented epithelium is strongly pigmented in diurnal raptors and less so in owls (Korbel, 2000). The single fovea of owls and the double fovea of numerous diurnal raptors can be challenging to discern with routine ophthalmoscopy, though the fovea has been described by this technique in C.A. Wood's impressive illustrated guide to the avian fundus (Wood, 1915). Rod and cone photoreceptors vary in density and distribution according to nocturnal or diurnal habitat and numerous flash ERG protocols have been described for assessing normal (Ault, 1984) and diseased raptors (Labelle et al., 2012; Seruca et al., 2012). Spectral-domain optical coherence tomography has recently been used to characterize the retinal structure of several diurnal and nocturnal raptor species (Fig. 31.16; Ruggeri et al., 2010).

The tightly encased raptor globe – especially the tubular-shaped globe of owls – is theorized (Buyukmihci, 1985; Davidson, 1997) to be particularly predisposed to contrecoup injury following blunt ocular trauma. Compressive forces may be easily distributed through the eye and transferred to the posterior segment, causing a high prevalence of posterior segment injuries, including retinal edema, tears, and detachment (Fig. 31.17); intravitreal hemorrhage, especially surrounding the pecten; and perforation of the posterior segment (Korbel, 2000; Murphy, 1987; Murphy et al., 1982b; Fig. 31.18). In a retrospective survey of tissues from 75 birds diagnosed with ocular trauma at the COPLOW, blunt trauma was the most common source of trauma and was most frequently associated with lesions of the retina, identified in 91% of eyes, causing retinal tears or detachments (71%) and chronic degenerative changes (46%; Moore et al., 2017). Sharp or penetrating ocular trauma to the eye (and posterior segment; see Fig. 31.9) is observed less often than blunt traumatic injuries and is most often associated with gunshot injuries in raptors (Murphy et al., 1982a).

Endogenous and/or exogenous bacterial, viral, and parasitic causes of chorioretinitis have been reported in raptors. Among these, West Nile virus has received the most significant attention in the scientific literature. Birds are the natural host for this virus and among raptor species, hawks and owls are the most frequently affected. Systemic clinical signs of West Nile virus are nonspecific and include lethargy, weight loss, and in some instances vision loss with other neurologic impairments. Antemortem diagnosis of this virus can be challenging; however, the presence of characteristic chorioretinitis lesions (Pauli et al., 2007) – especially when accompanied by other neurologic impairments during mosquito season – is supportive of this disease. Fundic lesions in

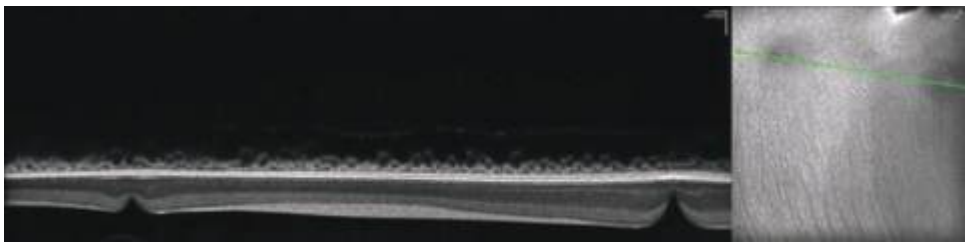


Figure 31.16 Bifoveate fundus spectral-domain optical coherence tomographic image of a red-tailed hawk. (Courtesy of Dr. Filipe Espinheira.)

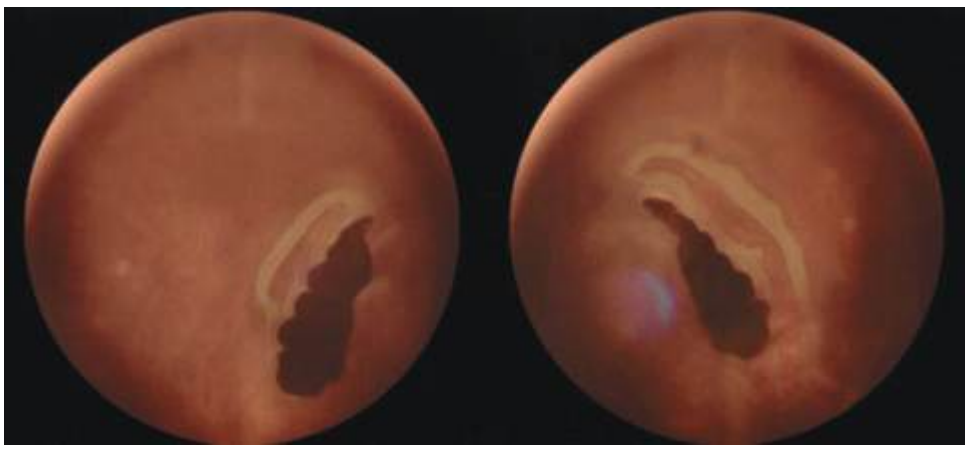


Figure 31.17 Bilateral retinal tears and detachment near the pecten in a screech owl that likely suffered blunt trauma and contrecoup injury to the posterior segment.

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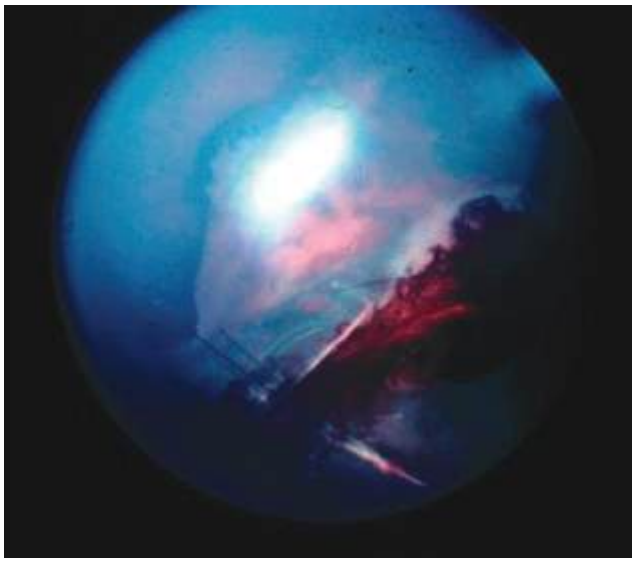


Figure 31.18 Great horned owl fundus with vitreal foreign body (feathers associated with traumatic posterior segment perforation of the globe).

red-tailed hawks and Cooper's hawks consist of linear or geographic areas of raised white exudates. Histologically, affected birds have displayed multifocal lymphoplasmacytic optic neuritis, pectenitis, choroiditis, and iridocyclitis, as well as heterophilic retinitis in some cases (Pauli et al., 2007; Wünschmann et al., 2004, 2005, 2017).

Disseminated mite infection with intraocular involvement was described in a juvenile bald eagle (*Haliaeetus leucocephalus*). Serpiginous retinal scars were noted in one eye and apparently viable mites of unknown species were found histologically in the retina and episcleral tissues, lungs, and liver (Bueno-Padilla et al., 2011).

Other infectious agents reported to be associated with chorioretinitis in raptors include *Salmonella typhimurium* var. Copenhagen, mycobacteria, herpesvirus, paramyxovirus, and *Toxoplasma* sp. (Korbel, 2000).

Lead toxicity is the most common toxicosis in raptors, with carrion-eating birds and scavengers being most commonly affected (Russell & Franson, 2014). The primary route of exposure is through ingestion of lead bullets from unretrieved carcasses of hunted game (Church et al., 2006). Histologic lesions of lead toxicosis involving the avian posterior segment were recently described in an affected bald eagle. A choroidal vasculopathy was observed that involved severe thickening, hyalinization, and fibrinoid necrosis of choroidal arterioles. Complete retinal detachment was also present (Eid et al., 2016).

An interesting retinal metaplasia has been sporadically reported in raptors and parrots. Histologically, spheroid clusters of cells bearing a lens-like phenotype are observed, suggesting extracapsular lentoid formation (Buyukmihci et al., 1988; Moore et al., 2017; Zeiss & Dubielzig, 2006). These lesions seem to appear commonly following chronic traumatic injury, occurring in approximately one-third of 75 traumatized avian eyes recently reviewed from the COPLOW collection (Moore et al., 2017). Inherited malformations of the avian retina are uncommon, although retinal dysplasia consisting of folds and unilayer rosettes has been reported to cause blindness in a prairie falcon (*Falco mexicanus*; Dukes & Fox, 1983).

Enucleation and Evisceration

Several enucleation and evisceration techniques have been described in raptors as a treatment for end-stage ocular disease or the chronically painful eye. Enucleation in birds may be performed by a lateral or transaural approach (Murphy et al., 1983). In owls specifically, their very large tubular eyes may be more easily enucleated if the auricular skin fold bordering the external ear is transected (Murphy et al., 1983). In some birds, incision and collapse of the globe facilitate its removal. During enucleation, special care must be taken to avoid traction on the optic nerve; the fellow optic nerve can be avulsed easily because of its close proximity. In addition, careful hemostasis is necessary to prevent hypovolemia, shock, and death, especially in small birds. Lethal oculocardiac reflex has been reported (Pipo et al., 1996). After removal of the globe, nictitans, conjunctiva, lacrimal and harderian glands, and marginal eyelid skin, closure is accomplished with one cutaneous layer of absorbable or nonabsorbable suture (Murphy et al., 1983). An alternative to enucleation is the modified evisceration technique, in which the eyelid margins, conjunctiva, cornea, and intraocular contents are removed. The eyelids are then closed in one or two layers of absorbable suture (Dees et al., 2011; Murray et al., 2013). This technique avoids many of the possible intraoperative complications associated with enucleation, is associated with decreased anesthetic time, and preserves the symmetry of the head. Evisceration with intrascleral prosthesis has been described in a great horned owl (Graham et al., 1999).

Release Recommendations

The release of free-living raptors with visual impairment is the subject of some debate. While it is generally accepted that the release of a bilaterally blind bird is inappropriate, there is less certainty regarding the release of raptors with partial or unilateral visual deficits. Anecdotal reports of hawks and owls that have presented to rehabilitation centers in good health and good body condition despite evidence of chronic unilateral visual impairment (Buyukmihci, 1985; Murphy, 1987) suggest that some birds may be capable of survival following release. Behavioral differences between diurnal and nocturnal raptors are significant factors that should be considered. For instance, diurnal raptors rely heavily on binocular vision and visual acuity for hunting, whereas owls are

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more dependent on auditory cues. It has thus been theorized that owls with unilateral visual impairment may be better candidates for release relative to diurnal raptors (Davidson, 1997; Murphy, 1987; Pauli et al., 2007). There is some evidence to support this theory based on postrelease assessment and tracking of western screech owls (*Otus kennecotti*; Allbritten & Jackson, 2002). In this study, owls with unilateral visual impairment survived as well as birds with normal vision bilaterally. A standardized examination protocol for raptors with ophthalmic disease has been utilized in a large survey of diurnal and nocturnal raptors (Labelle et al., 2012). This protocol (or similar) may provide a means of establishing more objective outcomes for the release of raptors with partial or unilateral visual impairment.

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Ophthalmology of New World Camelids

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Camelids evolved in North America 40–50 million years ago with a subsequent outward dispersion. Although the exact evolutionary sequence that led to the animals of today has not been completely elucidated, it is thought that three camelid tribes arose in North America: the Camelopini, the Camelini, and the Lamini. During the height of the Pleistocene epoch, these animals flourished with some migrating back and forth across the Bering Strait (Webb, 1974). The camel lines eventually settled within Asia, Europe, the Middle East, and North Africa, and the lamoids moved into South America 3 million years ago via the Isthmus of Panama. All wild camelids had become extinct in North America by 3000 BC, but they flourished in South America where some of the species became eventually domesticated.

Today the camelids are divided into two categories: Old World camelids, which contains the dromedary camel (*Camelus dromedaries*) and the Bactrian camel (*Camelus bactrianus*), and New World camelids, which contains llamas (*Lama glama*), alpacas (*Vicugna pacos*), guanacos (*Lama guanicoe*), and vicuñas (*Vicugna vicugna*). The scientific name of alpacas was recently changed from *Lama pacos* to *Vicugna pacos* based on DNA studies showing that alpacas are more closely related to vicugnas than llamas (http://eol.org/pages/7686/overview). New World camelid species have been divided further into subspecies based on morphologic and genetic studies (Lady Cano et al., 2012). The domestication of llamas and alpacas in the Andes started around 4000–5000 BC. The other two New World camelids remain wild in South America (Nowak, 1991). In the past 30 years, many domesticated South American camelids have been imported to and bred in North America (Fowler, 1998). The popularity of New World camelids in the United States and Canada reached its height in the 1990s, with a subsequent decline. As of 2017 there were thought to be 65,000 llamas, 7000 alpacas, and 200 guanacos in North America. Veterinary care, including the need to understand the anatomy, physiology, and diseases of the camelid eye, is important for these animals.

In order to better understand camelid ocular problems, several surveys investigating their ocular health and disease have been published. In 1997 a retrospective study using the Veterinary Medical Data Base (VMDB) was published. It identified the ocular diseases for which llamas were presented to veterinary hospitals in North America over a 13-year period (Gionfriddo et al., 1997). Not surprisingly, traumatic ocular disease was the most common presenting complaint, although other diseases were also seen, both congenital and acquired. Around this same time, Gelatt et al. (1995) published the results of ophthalmic examinations of 29 apparently healthy alpacas in South America. Although these animals had no reported clinical signs, 38% had at least one ocular abnormality, including conjunctivitis, corneal scars, posterior synechiae, cataracts, a subluxated lens, vitreous opacities, and/or an optic disk coloboma. Many lesions were thought to be secondary to trauma, but some may have been hereditary (Gelatt et al., 1995). In contrast, a study of camelid livestock in Sajama National Park in Peru (1424 llamas and 654 alpacas) identified conjunctivitis in only 0.67% of the animals and one animal (0.05%) had an orbital infection. These data suggest that the incidence of ocular disease in different populations can vary greatly (Zacari & Pacheco, 2005).

In 2006 and 2010, Webb and colleagues published reports of ophthalmic findings and auditory abilities in a group of llamas and alpacas living in eastern Canada (Webb & Cullen, 2010; Webb et al., 2006). These studies investigated the idea that the increased incidence of genetic problems in Canadian camelids was associated with the closure of the Canadian registry of llamas and alpacas to newly imported animals from South America. This may have led to increased inbreeding with subsequent expression of undesired phenotypic traits. Interestingly, they found that many of the 17 llamas and 23 alpacas that had ophthalmic examinations had

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potentially hereditary ocular abnormalities, including persistent pupillary membranes (PPMs; 14/17 llamas and 5/23 alpacas), cataracts (9/17 llamas and 5/23 alpacas), and corneal dystrophy (0/17 llamas and 2/23 alpacas). In the same study, 25 llamas and 38 alpacas were tested for deafness by brainstem auditory-evoked response (BAER). The results of the BAER tests were compared with coat and iris colors: 7 of 10 pure white-haired, blue-eyed animals were bilaterally deaf and 1 was unilaterally deaf. The authors concluded that there was an association between skin, iris hypopigmentation, and congenital sensorineural deafness in llamas and alpacas (Webb & Cullen, 2010; Webb et al., 2006).

The Cooperative Ophthalmic Pathology Laboratory of Wisconsin (COPLOW), housed at the University of Wisconsin, Madison, has a database of the histologic evaluations of enucleated eyes presented to the laboratory from 1990 to 2017. This includes both wild and domesticated camelid species. These diagnoses and those from the above studies will be discussed further in the following pages.

Vision

Until 2015, what was known about vision in South American camelids was either extracted from anecdotal reports (Beacham, 2003) or extrapolated from studies of camel retinas (Harman et al., 2001). In 2015 Wang et al. published about an extensive study on alpaca vision, which greatly expanded our knowledge about alpaca vision.

The position of the eye on the sides of the llama and alpaca head suggests that they principally have monocular vision (Beacham, 2003), and their ecologic role as prey animals tends to support this. However, a study of the retinal cells in dromedary camels, which are closely related to South American camelids, found that they have neither an *area centralis* (prominent in primates) nor a *visual streak* (which is prominent in horses, pigs, and cows; Harman et al., 2001). Instead, they have areas of high retinal ganglion cell (RGC) densities in the nasal retina and in the temporal retina, with low densities of RGCs between the two regions. Since regions of high RGC densities are those with corresponding high visual acuities, the authors speculate that dromedary camels have some degree of binocular vision due to their high densities of RGCs in the temporal retina. The purpose of high RGC density in the nasal retina is not clear. The authors suggest that the mobile, flexible necks in camels allow the animals to cover the visual field more fully than other species, and thus they need to have another area of acute vision outside the binocular field (Harman et al., 2001). Since South American camelids are closely related to camels, and they also have very flexible necks, it is possible that they have two areas of visual acuity as well. Interestingly, some of the dromedary camels that were examined had vertical retinal streaks that were highly dense with retinal cells, possibly amacrine cells (Harman et al., 2001). The function of this streak is unknown.

South American camelids do not have a vertical streak as reported in camels but, like many herbivores, have a horizontal streak across the median of the retina, superior to the optic disc (Wang et al., 2015; Fig. 32.1). The highest density of RGCs is in the temporal part of the visual streak. From these data combined with other ocular anatomic parameters, the authors estimated that the maximal acuity of the alpaca eye ranges from 12.5 to 13.4 cycles per degree. This indicates that the visual acuity of alpacas is better than that of camels, which has a maximum of 9.5–10 cycles per degree in the high RGC retinal regions (Harman et al., 2001). In comparison, the visual acuity of a domestic cat is 6–9 cycles per degree in the visual axis (Bloom & Berkeley, 1977; Jacobson et al., 1976) and in the horse it is 18–20 cycles per degree (Harman et al., 1999). On the basis of behavioral testing, the estimate of visual acuity in the dromedary camel was 10 cycles per degree (Harman et al., 2001).

In 1901, Johnson published a treatise describing the comparative ophthalmoscopy of many species including the llama. He suspected llamas to be slightly myopic (Johnson, 1901), and this was confirmed in 2000 using refractometry (Willis et al., 2000b). Willis and colleagues estimated the mean refractive error of llamas to be -0.6 diopters (D) horizontally and -1.11 D vertically. Females were slightly more myopic than intact or castrated males. In contrast, alpacas were almost emmetropic, measuring -0.12 D horizontally and -0.7 D vertically (Willis et al., 2000b).

Examination Techniques

Ocular examination is optimally undertaken with the llama or alpaca restrained in stocks, although some can be examined in a stall or in a "cushed" position. Most domestic camelids are amenable to examination; however, chemical sedation (butorphanol 0.02–0.04 mg/kg as a sole agent; for deeper sedation, butorphanol 0.07–0.1 mg/kg may be combined with 0.2–0.3 mg/kg ketamine and 0.2–0.3 mg/kg xylazine intravenously; or, alternatively, tiletamine-zolazepam 2 mg/kg with xylazine 0.2–0.4 mg/kg intramuscularly) may be necessary to control head movement (Gionfriddo 1994, 2010; Gionfriddo & Friedman, 1993; Seddighi, 2013; Wolff, 2009). A transilluminator or halogen pen light is recommended, as regular penlights are not bright enough to elicit pupillary light reflexes (PLRs) in camelids. Their menace reflex, however, is particularly pronounced, and they will often jump or throw their heads in response. It is very easy to trigger a false response by touching the very long vibrissae that are present above and below the eye. Direct and indirect PLRs of camelids are slow, and movement of the iris is

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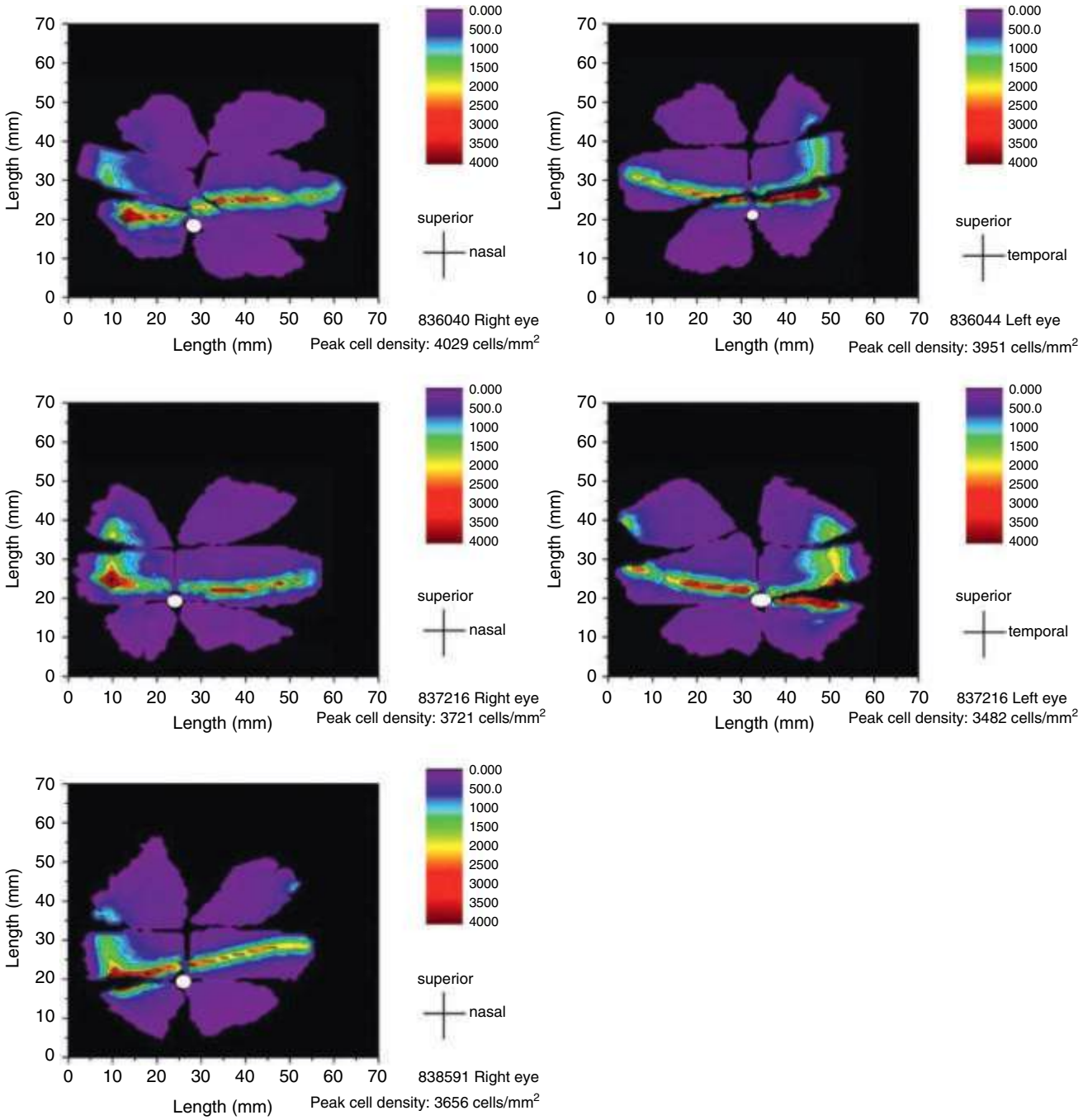


Figure 32.1 Retinal maps of five eyes of three alpacas showing all presumed neurons in the ganglion cell layers. The highest densities of cells are in a horizontal streak dorsal to the optic disc (white). Note the vertical streaks indicating the high densities of neurons at the lateral end of the horizontal streak. (Reproduced with permission from Wang, H.H., Gallagher, S.K., Byers, S.R., et al. (2015) Retinal ganglion cell distribution and visual acuity in alpacas (Vicugna pacos). *Veterinary Ophthalmology*, **18**, 35–42.)

minimal. Mydriasis is usually easily achieved by the application of 2–3 drops of 1% tropicamide, with maximum dilation typically occurring within 15–20 minutes and dilation lasting 2 hours.

Tear production in camelids is measured in the same manner as in dogs. The mean Schirmer tear test I (STT I) of llamas was found to be 17.3 (range of 15–19 mm/min), while the mean STT II of 14 eyes of 7 llamas was 15.4 mm/min (range 12.5–17.5 mm/min; Trbolova et al., 2012). Tear production is somewhat slow in a stressed animal, and to obtain an accurate measurement, it often requires having the tear test strip in place for the entire minute. Mean tear production

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in alpacas (STT I) was found to be 20.88 ± 4.04 mm/min (range 15–30 mm/min; McDonald et al., 2018). No significant differences were detected between eyes, breed, or gender. The STT I values significantly increased by 3.45 mm/min for every 10-year increase in age. These values are slightly higher than were found in normal alpacas in Europe (16.9 ± 4.1 mm/min; Pietro et al., 2016).

Tonometry with either a TonoPen® (Mentor Ophthalmics, Norwell, MA, USA; applanation tonometry) or TonoVet® (Icare, Finland; rebound tonometry) is the easiest and most accurate method of measuring intraocular pressures (IOP) in camelids. In one study, IOPs taken with a TonoPen showed that there were no differences between llamas and alpacas, and that the mean IOP was 16.5 mmHg, with a range of 14.89–18.21 mmHg (Nuhsbaum et al., 2000). However, in a 2006 survey of camelids in Canada, significant differences were found in IOP between the two species. In that study, llamas had significantly lower IOPs than alpacas (mean IOP in 33 llama eyes was 16 mmHg; mean IOP in 46 alpaca eyes was 19 mmHg; Webb et al., 2006). A study of normal llamas and alpacas also demonstrated that llamas had significantly lower IOPs than alpacas (Willis et al., 2000a). Mean IOP for llamas was 13.10 ± 0.35 mmHg and for alpacas was 14.85 ± 0.45 mmHg. Significant differences were not detected between eyes or due to sex, age, or time of measurement. The difference between species, although statistically significant, is probably clinically irrelevant. In a recent study, 40 normal alpacas were evaluated with both the TonoPen-XL and the TonoVet (McDonald et al., 2017). The mean IOP value for the TonoVet was 14.21 ± 2.73 mmHg and for the TonoPen-XL was 12.51 ± 2.78 mmHg. No significant differences were found between eyes or with age, sex, or breed. The TonoVet value was significantly higher than those of the TonoPen-XL, but this difference is likely not clinically important.

Imaging techniques, such as plain film radiographs, contrast radiographs, magnetic resonance imaging (MRI), computed tomography (CT), and ocular ultrasound, have been used to diagnose both ocular and periocular diseases in camelids. Dacryocystorhinography has been a particularly useful tool to diagnose the site of obstruction in alpacas with nasolacrimal disease (Fig. 32.2). For this procedure, about 5 mL of a mixture of sodium and meglumine diatrizoate is injected into the dorsal lacrimal punctum, and lateral and dorsoventral radiographs are then taken (Mangan et al., 2008; Sandemeyer et al., 2011; Sapienza et al., 1992). Alternatively, the contrast agent can be tracked with fluoroscopy as it moves through the nasolacrimal drainage pathway (Mangan et al., 2008; Sapienza et al., 1992). If a camelid with congenital or juvenile-onset cataracts is going to undergo cataract surgery, ocular ultrasonography should be used prior to the procedure to evaluate the posterior segment. This technique was essential for detecting the presence of a patent hyaloid artery in a young llama with bilateral cataracts (Gionfriddo, 2002; Gionfriddo & Blair, 2002; Fig. 32.3).



Figure 32.2 Dacryocystorhinogram of a cria with nasolacrimal disease showing the dye column in the nasolacrimal duct. The dye normally emerges at the nasal opening of the duct. Here the dye only reaches the central portion of the duct (distal arrow), which is a common site of atresia to camelids.

Orbital ultrasound, MRI, and CT have also proved useful to detect and characterize intraocular and retrobulbar masses in camelids (Hamor et al., 1999; Hendrix et al., 2000).

Spectral domain optical coherence tomography (SD-OCT) is an imaging method that has recently been used in veterinary ophthalmology (LoPinto et al., 2017b): "Owing to its high speed and superior sensitivity, SD-OCT has become indispensable in biomedical imaging applications." SD-OCT creates a better image of the eye than plain OCT (Yaqoob, 2005). LoPinto et al. (2017b) used SD-OCT to measure the corneal thickness in normal camelids. The technique shows great promise for further research and diagnostics in veterinary ophthalmology.

Angiography is another technique that has been used in camelid eyes with some success. LoPinto et al. (2017a) used this method to image the anterior-segment blood vessels in alpacas. Due to the dense pigment of many alpaca eyes, indocyanine green was superior to sodium fluorescein dye at outlining the blood vessels (LoPinto et al., 2017a).

Ocular Medications

Topical ocular medications that are used in other species are generally safe for camelids (J. Gionfriddo, personal

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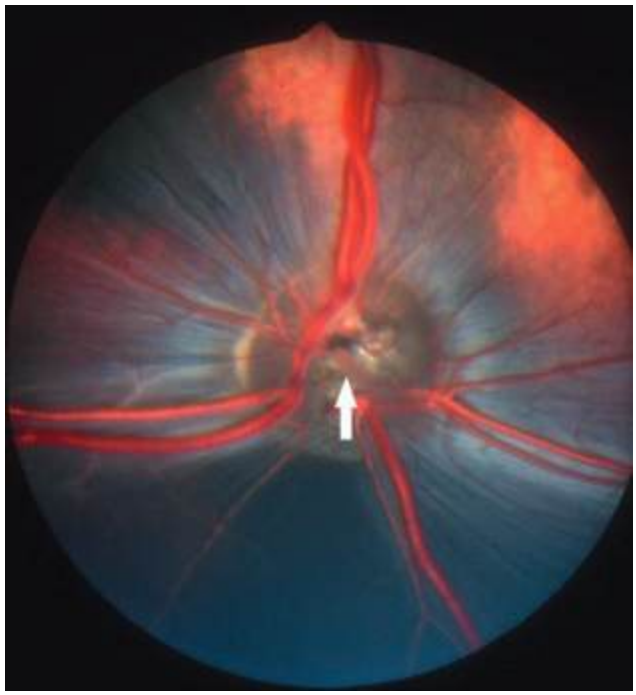


Figure 32.3 Fundic photograph of an alpaca. The hyaloid remnant extends from the surface of the optic disc.



Figure 32.4 The nasal punctum is the exit of the nasolacrimal duct into the nares. The ease of locating this structure facilitates cannulation with soft, flexible, small-gauge polyethylene tubing.

communication, 2010). The exception is topical corticosteroids in pregnant animals. In a study on llamas in the late stages of pregnancy, giving 1 drop 3 times daily of topical dexamethasone-containing ophthalmic preparation for 8 days caused them to abort their near-term fetuses (B. Graham, unpublished data, 2004).

Delivery of topical ocular medicines in camelids can be facilitated by a nasolacrimal lavage system (NLLS) or subpalpebral lavage system (SPLS). Since the nasal punctum of camelids is relatively easy to locate, an NLLS is not difficult to place, but may require that the animal be under sedation or general anesthesia (Fig. 32.4). The procedure is accomplished by threading soft tubing (such as 22-gauge polyethylene) into the nasal opening and up the nasolacrimal duct until it stops at the level of the nasolacrimal sac. The nasal end of the tubing can then exit the nostril, or may be threaded through a large-diameter needle puncture that is made in the alar fold of the nose, and fastened via tape tabs to the face. Medication can be injected through an injection port that has been placed into the end of the tubing. Although this method is effective, the tubing that exits the nose is vulnerable to damage and traction forces caused by the animal.

It was originally thought that the SPLS might cause corneal trauma in camelids because of the tight fit of the eyelids around the globe. However, an adaptation of a commercially available equine SPLS with a soft low-profile footplate was reported to deliver topical therapy to the eyes of two llamas with severe corneal ulcers (Borkowski et al., 2007). Initially the medication was manually injected to the llamas' eyes through the tubing, but when the ulcers failed to heal readily, the device was modified to connect with a balloon infusion system. This involved placing commercial balloon infuser and flow control to the tubing, which delivered medication at a constant rate of 1 mL/h. No corneal complications were associated with the devices in two animals, but mild swelling and irritation of one eyelid at the site of SPLS tubing penetration was reported (Borkowski et al., 2007). Others have reportedly used carefully placed nonmodified SPLS in camelids in both the upper and lower eyelids for pulse therapy of topical medications without incident (C. Plummer, personal communication, 2015).

General Features of the Eye and Orbit

Anatomically, the eyes of South American camelids are very similar to those of other ruminants (pseudoruminants), with some notable exceptions. The camelid eye is well adapted for the high-altitude regions of South America, where there is increased ultraviolet (UV) light and little shade. Structures important to preventing UV light damage include their long eyelashes, the robust corpora nigra, sometimes referred to as the "pupillary ruff" (Fig. 32.5), and the darkly pigmented scleral band around the limbus.

One interesting adaptation to high-altitude living in camelids may be extrapolated from the retinal vascular pattern of the dromedary camel (Harman et al., 2001). In that species, even though there are specific high-density areas of RGCs

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Figure 32.5 A normal camelid eye. This iris is heterochromic, containing shades of brown and blue. The pupillary ruff is distinct and the pupil is roughly a dumbbell-shaped oval.

within the retina, the major blood vessels do not avoid these regions as they do in other species. This could be a mechanism to improve oxygenation to these important retinal areas at high altitudes where partial pressure of oxygen is low (Harman et al., 2001).

The camelid globe is large in proportion to the head size and is only slightly smaller than the globe of cattle. The appearance of large eyes in these animals is accentuated by their prominent placement laterally in the skull and by the long upper and lower eyelashes present in most animals.

The bony orbit of camelids is complete (Fig. 32.6). It is made up of portions of the frontal, lacrimal, zygomatic, maxillary, palatine, temporal, and sphenoid bones. There is a large palpable dorsal notch in the frontal bone. Rostral to the medial aspect of the orbit is a 2 cm diameter opening into the nasal cavity, which is probably associated with a scent gland.

Eyelids and Nasolacrimal System

Camelid eyelids fit tightly to the globe, and conformational eyelid defects are rare. The eyelids cover much of the sclera so almost no "white" is showing, which makes their corneas appear very large. The sclera and exposed conjunctiva may be largely pigmented or nonpigmented, but there seems to always be a darkly pigmented, 2–3 mm band at the limbus. This may protect their eyes from solar radiation damage.

Unlike most other domestic mammals, New World camelids have no eyelid meibomian glands. This is similar to pinnipeds, who, as a consequence, have no lipid layer to their tear films (Colitz et al., 2010). Histologic evaluation of the canthal area in camelids, however, reveals abundant sebaceous glands that are similar to meibomian glands (Fig. 30.5; R. Dubielzig, unpublished data, 2009). Although confirmation of a lipid tear layer is lacking, it is unlikely to be missing in New World camelids and is probably produced by these sebaceous glands. Interestingly, the one-humped camel does have "tarsal glands," but they are only on the upper eyelid



Figure 32.6 The camelid orbit is complete and made up of portions of seven cranial bones. A large dorsal notch in the orbital rim (arrow) allows for the passage of nerves.

(Fahmy et al., 1971). These are tubular mucous glands with ducts that open onto the conjunctiva along the posterior margin of the lid.

The histologic, histochemical, and fine structure of the lacrimal gland and the gland of the third eyelid have recently been studied (Kleckowska-Nawrot et al., 2015). Both glands are situated within the orbit in locations similar to other mammals. Both glands are tubulo-acinar with mucoserous characteristics. The cartilage of the third eyelid is composed of hyaline tissue.

Because tears are one of the initial ocular defense mechanisms, differences in susceptibility of cattle and llamas to some ocular diseases could be related to differences in their tears. Thus, tear pH and protein content (e.g., enzymes) were compared using 40 llamas and 35 cattle (Gionfriddo et al., 2000b). The pH of llama tears was similar to that of cattle (8.05 ± 0.01 and 8.10 ± 0.01, respectively).

The camelid has both an upper and a lower punctum. Each is located 4–6 mm from the medial canthus and is large and slit-like, making it relatively easy to cannulate. The lacrimal sac is small, and the nasolacrimal duct exits from it, traversing through the lacrimal and maxillary bones and terminating in the nasal cavity (Sapienza et al., 1992). In most camelids the nasal opening can be seen fairly easily, as it is located laterally in the nasal cavity and 1.5–2 cm proximal to the wings of the nares (see Fig. 32.4). In the adult llama, the duct is 11–15 cm long and 2–4 mm in diameter (Sapienza et al., 1992). Lactoferrin, ceruloplasmin, transferrin, α1-antitrypsin, α1-amylase, α2-macroglobulin, and immunoglobulin (Ig) A are present in the tears of both llamas and cattle.

Because cattle tears are reported to lack lysozyme, an abundant enzyme in the tears of other animals (e.g., primates; Brightman et al., 1981), Gionfriddo et al. (2000a) analyzed camelid and sheep tears for the presence of this enzyme. A 13.6 kd protein band, identified as lysozyme, was

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detected using gel immunodiffusion in llama and sheep tears. Quantification of the amount of enzyme showed only a small amount (10 ± 14.1 U/mL) in cattle tears, but llama and sheep had high concentrations (2760 ± 29.3 U/mL and 2199 ± 26.9 U/mL, respectively). Lysozyme has specific activity against Gram-positive bacteria (Gillette & Allansmith, 1980). This may explain why llamas appear to be resistant to the invasion of ocular surface diseases such as *Moraxella* spp.

Diseases

Blepharitis is the most common eyelid problem in camelids. This is often present in conjunction with generalized dermatitis. Bacterial infections can lead to blepharitis and concurrent bacterial conjunctivitis (Gionfriddo et al., 1997). Reports of eyelid lacerations in camelids are rare, and in the VMDB study they were reported in only two llamas (Gionfriddo et al., 1997). Because the camelid eyelid fits so closely to the globe, there is a high potential for corneal injury with full-thickness eyelid lacerations due to concurrent trauma and subsequent increased exposure.

Blepharitis caused by chigger mites has been reported in Peruvian alpacas (Gomez-Puerta et al., 2012): 22 out of 130 animals were affected and had signs of periocular and facial blepharitis, pruritis, scaling, and alopecia.

No cases of entropion have yet been reported in South American camelids; however, one case of very severe bilateral upper eyelid entropion has been described in a female one-humped camel (Yeruham et al., 2002). The entropion was diagnosed when she was 18 years old but had been noted at 4 months of age. Clinical signs were severe blepharospasm, epiphora, conjunctival edema, and mucopurulent ocular discharge, and almost 360° inversion of the eyelid. Secondary corneal ulcers were present, as was extensive corneal neovascularization. This camel had given birth to two offspring who were similarly affected and so the owner was advised not to breed the camel again (Yeruham et al., 2002).

Periocular neoplasms are also rare in camelids. This is an interesting finding, as members of this family have evolved in areas of increased UV light exposure and little shade, which are predisposing factors for periocular neoplasia in horses and cows. A report on the prevalence of neoplasms in llamas and alpacas in Oregon from 2001 to 2006 documented the presence of squamous cell carcinomas on the nictitating membranes of one llama and one alpaca (Valentine & Martin, 2007). In a case report of a 4.5-year-old llama, a firm mass near the medial canthus of the left eye was diagnosed as an ossifying fibroma that had originated in the area of the second premolar tooth (McCauley et al., 2000). Nasal endoscopy revealed a mucosa-covered mass that was originating adjacent to the tooth and extending to the soft palate. Although this mass was close to the nasolacrimal system, no epiphora was seen (McCauley et al., 2000).

Congenital nasolacrimal duct disorders that have been reported in camelids include nasolacrimal duct atresia, conjunctival punctal atresia, nasal punctual atresia, or combinations of these (Boer & Schoon, 1984; Gionfriddo & Friedman, 1993; Mangan et al., 2008; Sapienza et al., 1992). Alpacas seem to be more commonly affected than llamas. Affected animals usually present with a "wet face" due to the tear overflow and mucopurulent ocular discharge due to secondary dacryocystitis. Most often, these animals are young when they present for treatment, but older animals may also present because of secondary periocular dermatitis and/or fly strike.

In the 1997 VMDB database study, it was reported that only two crias had been presented for nasolacrimal defects in a 10-year period, but the incidence appears to be increasing. In the early 1990s, four llamas had congenital conjunctival eyelid punctal atresia (G. Severin, personal communications, 1993). More recently, five alpaca crias were presented to Colorado State University for bilateral nasolacrimal duct obstructions (J. Gionfriddo, unpublished data, 2010). The abnormal puncta were surgically opened and catheterized using a procedure similar to that in horses (Lavach, 1990). Three of these crias were distantly related. Failure of nasal punctal formation was the cause of the obstruction in four of the five crias, and in the remaining cria the duct was not patent but blind-ended in the bony canal as it traversed the nasal cavity.

A case of severe epiphora due to bilateral atresia of the nasolacrimal ducts at the level of the nasal puncta was reported in a llama cria (Sapienza et al., 1992). Surgical opening of the ducts was successful. In a 2002 report, Arnold et al. described three cases of nasal punctal atresia in alpaca crias that were apparently unrelated, and in another publication four alpacas with congenital nasolacrimal atresia and their treatments are described (Sandemeyer et al., 2011). In each of these animals, the presenting complaints were chemosis, lacrimation, and mucopurulent ocular discharge that were not responsive to topical antibiotic therapy. In some of these crias, the problem was unilateral, and it was bilateral in the others. In all of these cases, the atresia was close to the site of the nasal punctae, and all animals responded well to surgical opening, similar to the method described below.

Dacryocystitis is relatively common in camelids, perhaps because their large conjunctival puncta are vulnerable to invasion by foreign bodies such as grass awns. Animals with this disorder are typically adults with a history of chronic mucopurulent ocular discharge, which can be profuse (Fig. 32.7). There can also be a history of blepharospasm and conjunctival hyperemia.

Treatment

Because of the potential for secondary corneal injury or exposure keratitis, all full-thickness eyelid lacerations should

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Figure 32.7 Flushing the nasolacrimal duct through the ventral punctum is an important step in the diagnosis and treatment of dacryocystitis. Material flushed from the duct should be cultured for identification of pathogenic organisms.

be sutured in a two-layer closure, with the first layer in the muscle or tarsal plate and the second in the skin. Since the camelid eyelids so closely appose the cornea, great care must be taken to avoid exposure of suture or knots to the corneal surface.

Initial treatment of camelids with clinical signs of nasolacrimal obstruction involves identifying and attempting to cannulate both the upper and lower nasolacrimal puncta. Imperforate puncta are relatively common, especially in alpaca crias. Correction of an imperforate punctum involves incising the mucous membrane covering the opening. If the puncta are present and patent, the nasolacrimal duct should be flushed orthograde through one of the conjunctival puncta (see Fig. 32.7). This can be performed with local anesthetic alone in some animals, but some individuals are head-shy and must be sedated or anesthetized for the procedure. If the fluid fails to pass through the ducts and into the nasal cavity, the animal should be placed under general anesthesia, and catheterization of the nasolacrimal ducts through the conjunctival puncta should be attempted. Catheterization is performed with large suture material or with polyethylene tubing. If the material will not pass, then imaging procedures such as dacryocystorhinography are indicated in order to localize the obstruction (see Fig. 32.2).

The above procedures were performed on four of five alpacas that presented to Colorado State University and subsequently diagnosed with nasolacrimal atresia. In the four crias, the puncta were present and patent, but attempted flushing of the ducts was unsuccessful. A piece of polyethylene tubing was subsequently threaded in an orthograde fashion through the nasolacrimal duct until it stopped at the point where the duct prematurely terminated. In three of the animals, the tip of the tubing could be palpated through the nasal mucosa where the nasal punctal opening should have been. An incision through the mucosa over the tubing was made and the tubing was passed into the nasal cavity, at which point it was anchored to the surrounding nasal mucosa with a Chinese finger-trap suture technique. It was then threaded through a large needle, which was used to pierce the skin of the nares, and attached to the skin with tape tabs. The tubing was left in place for 6 weeks to prevent closure of the punctum. This corrected the problem in each case. In the fifth cria, the tubing could not be palpated through the nasal mucosa. A dacryocystorhinogram showed that the blockage was at the level of the maxillary bones. This indicated that the obstructions were due to failure of formation of the distal one-third of the nasolacrimal duct (Mangan et al., 2008). A bilateral conjunctivosinusostomy (creation of a new opening from the conjunctiva into the sinus) was performed to allow for lacrimal drainage. This technique is relatively complicated (Mangan et al., 2008).

Treatment of dacryocystitis is aimed at clearing the nasolacrimal system of foreign material and addressing the associated secondary bacterial infection. Topical antibiotics can be attempted initially, but frequently do not lead to resolution. Flushing of the nasolacrimal duct through the upper or lower punctum will often remove foreign material, purulent exudate, and infectious agents (see Fig. 32.7). This can sometimes be performed on an awake animal after instillation of topical anesthetic drops. If the system does not flush easily, general anesthesia is required to allow for more aggressive flushing.

Conjunctiva

The conjunctival bacterial and mycoplasmal flora of 88 normal camelids (llamas, alpacas, guanacos, and llama–guanaco hybrids) were evaluated (Gionfriddo et al., 1991). The most common species of bacteria isolated were *Staphylococcus epedermidis* (52%), *Pseudomonas spp*. (41%), and *Bacillus spp*. (28%). Most of the *Pseudomonas* organisms isolated were not considered to be pathogens. No mycoplasmas were isolated from any of the 69 samples evaluated. More recently Storms and her colleagues (2016) cultured the conjunctiva of 46 alpacas residing in Belgium. The most common bacteria isolated were Gram positive and included *Staphylococcus xylosus* and viridans streptococci. In addition, two species of *Moraxella* were cultured, the first time *Moraxella* has been reported in the eyes of normal New World camelids. There was no significant effect of age or sex on the number of bacteria isolated, but alpacas with viridans streptococci and *Moraxella spp*. were significantly younger. The fungal flora of normal camelids (llamas, alpacas, guanacos, and llama–guanaco hybrids) was also evaluated, in both winter and summer (Gionfriddo et al., 1992). While fungal species of 10 different genera were found, *Aspergillus* was the most commonly isolated genus.

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Diseases

Congenital

Dermoids and cysts are congenital conjunctival abnormalities that have been reported in camelids (Fowler, 1989; Gionfriddo et al., 1997; Moore et al., 1999; Schuh et al., 1991). Large cysts have been reported infrequently in the conjunctiva of neonatal crias (Schuh et al., 1991). Schuh et al. reported on a case of a cria with a cyst-like structure on the bulbar conjunctiva. Aspiration of this structure yielded a clear fluid. Because the same eye had other defects, the cyst was thought to be part of a general ocular maldevelopment.

A very large conjunctival cyst was seen in a cria who had no other ocular abnormalities (L. Johnson, personal communication, 1999). After drainage of the cyst by aspiration, it refilled with clear fluid, but surgical excision proved curative.

Acquired

Conjunctivitis is common in camelids (Fig. 32.8 and Fig. 32.9). The clinical signs are similar to those seen in other ruminants and typically include mild blepharospasm, conjunctival hyperemia, epiphora, and occasionally chemosis. Irritation from dust or foreign bodies is a common cause for self-limiting mild conjunctivitis. Fischer and Hendrix (2012) reported on 21 alpacas from the same herd who concurrently were afflicted with conjunctivitis and ulcerative keratitis. Because of the multiple animals involved, an infectious cause was suspected, but upon thorough examination plant foreign material was found in the temporal conjunctival fornix in 7 eyes of 6 animals, and the other 15 animals had foreign bodies that were manually removed on the farm.

Since foreign bodies are common, careful inspection of the conjunctival sacs is important. In the VMDB study, however, 19 (10%) of the llamas with conjunctival disease had no definitive cause identified (Gionfriddo et al., 1997). Several cases of bacterial conjunctivitis were also documented in that study. In those cases, the clinical signs were more severe and included marked hyperemia, mucopurulent ocular discharge, and blepharospasm. In an unpublished study of five llamas with severe conjunctivitis, pathogenic bacterial species were isolated from the lower conjunctival fornix of each animal and were suspected to be the primary cause of the disease (J. Gionfriddo, unpublished data, 1990). In a case of keratoconjunctivitis in a llama, Brightman et al. (1981) reported that *Staphylococcus aureus* was isolated from the conjunctival sac, while *Moraxella liquifaciens* was isolated from the cornea. Williams et al. (2000) examined and took bacterial cultures from the superficially infected eyes of nondomestic animals in the London Zoo. This included one llama who had purulent conjunctivitis and a small corneal ulcer (Williams et al., 2000). Although the most common bacterial genus that was cultured from the eyes of the affected zoo population was *Staphylococcus*, the organism cultured from the llama was not specified.

Chlamydiae have also been isolated from camelids with conjunctivitis (Glenn Severin, personal communication, 1993). No herd outbreaks of *Moraxella bovis* keratoconjunctivitis ("pink eye" in cattle) have been reported in the literature in New World camelids, although a single case of



Figure 32.8 A mild, serous conjunctivitis in a llama. The conjunctiva is hyperemic and the nictitating membrane is protruding. This type of conjunctivitis is usually associated with ocular irritation (wind, blowing dust, or foreign body).



Figure 32.9 Severe chemosis with marked conjunctival hyperemia. This severity of conjunctivitis is most often found in bacterial conjunctival infections.

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ulcerative keratitis from which *M. liquifaciens* was cultured has been reported (Brightman et al., 1981). There is one report of two outbreaks of keratoconjunctivitis in a dromedary camel herd in Spain that was caused by *Moraxella canis*, but this has not been reported in llamas or alpacas (Tejedor-Junco et al., 2010). In general, cytologic evaluation of both a conjunctival scraping and a microbiologic culture (bacterial and fungal) and sensitivity testing are recommended in cases of conjunctivitis and keratoconjunctivitis.

In addition to bacterial conjunctivitis, parasites have been reported to induce moderately severe conjunctivitis in camelids. The larvae of the nematode parasite, *Thelazia californiensis*, can be present in the conjunctival sacs of many species, including llamas and alpacas. This disease seems to be particularly prevalent in the western United States (Fowler, 1989). Clinical signs of *Thelazia* infection range from mild epiphora and hyperemia to severe epiphora and blepharospasm. This larval nematode is transmitted between animals by face flies. It is small and may be seen moving across the surface of the eye or hiding beneath the third eyelid. Occasionally, its presence can cause enough irritation that the animal will self-traumatize and this can lead to a secondary corneal ulcer.

Toxoplasmosis was the suspected cause of a case of uveokeratoconjunctivitis in a 15-year-old male llama (D. Tinsley, unpublished data, 2011). This animal had neurologic signs plus marked blepharospasm, lacrimation, and mucopurulent periocular discharge. There was severe conjunctival hyperemia and chemosis and signs of uveitis consisting of iridial swelling, posterior synechiae, and debris on the anterior lens capsule. Based on the absence of other causes of these signs and the presence of a rising vitreal IgG titer to *Toxoplasma gondii*, a presumptive diagnosis of ocular toxoplasmosis was made.

Treatment

Infectious and irritative conjunctivitis should be treated according to the cause. A culture and sensitivity should be done on all cases of suspected bacterial conjunctivitis. Prior to receiving the results of culture, a broad-spectrum antibiotic, such as a triple antibiotic, should be applied 3–6 times daily. If a *Thelazia* larva is seen, mechanical removal of the worm under topical anesthetic is curative. Alternatively, topical diethylcarbamazine or a drop of injectable ivermectin instilled into the conjunctival sac will kill the parasite, and it will either be flushed out with the tears or may be removed manually (Fowler, 1989). Many types of flies feed on llama lacrimal secretions and can cause conjunctival irritation. Consequently, fly control is important for minimizing this form of conjunctivitis.

Large conjunctival wounds should be sutured with small-gauge (e.g., 6-0), absorbable suture material. Small wounds usually heal by second intention with medical therapy alone.

Cornea

Anatomy

The corneas of llamas and alpacas are large and semi-oval-shaped (see Fig. 32.5). Although the head size of the alpaca is smaller than that of the llama, the corneal diameters of the two species are very similar. In one study, the mean horizontal corneal diameter of llamas was 28.2 mm, while that of alpacas was 30.2 mm (Andrew et al., 2002). The mean vertical diameters were 24.2 mm in llamas and 22.2 mm in alpacas. The mean corneal thicknesses were also very similar. When measured by ultrasonographic pachymetry, they were 608 µm in llamas and 595 µm in alpacas. Both the thickness and diameter of their corneas increased significantly with the increasing ages of the animals (juvenile vs. adult animals; Andrew et al., 2002).

Because of the propensity of camelids to develop marked corneal edema secondary to intraocular surgeries, trauma, and uveitis, it was thought that these animals might have low numbers of corneal endothelial cells compared to species who do not have problems with excessive edema formation (Gionfriddo et al., 1997). The densities of endothelial cells in camelids (2673 cells/mm^2 in llamas, and 2275 cells/mm^2 in alpacas) are only slightly lower than those of other species that have been studied (Andrew et al., 2002). However, frequent polymegathism (variability in cell size) and pleomorphism (variability in shape) of the endothelial cells are observed in normal camelids (Andrew et al., 2002). This is a common finding in other species with pathologically decreased endothelial cell density, which suggests that clinically normal alpacas and llamas have potential corneal endothelial instability and increased vulnerability to the development of corneal edema (Andrew et al., 2002).

Corneal pachymetry by SD-OCT in the normal alpaca measured a total corneal thickness of 634.8 ± 6.2 µm (LoPinto et al., 2017b). The corneal epithelial thickness, corneal stromal thickness, and Descemet's membrane thickness were 147.4 ± 5.7 µm, 446.1 ± 7.4 µm, and 44.5 ± 5.0 µm, respectively. The total corneal thickness measurement (595 µm) was slightly higher than reported by Andrew et al. (2002) using ultrasonic pachymetry.

In order to determine the relative sensitivities of the different regions of the alpaca cornea, an esthesiometric study was done (Welihozkiy et al., 2011). As in other species, the center of the cornea was more sensitive than the peripheral areas. The next most sensitive area was the ventral region, followed in order by the medial, dorsal, and lateral regions. Similarly, a study using immature and adult alpacas confirmed that the central cornea is the most sensitive, with the dorsal and temporal regions the least sensitive (Rankin et al., 2012). In that study there were no differences between the eyes or between males and females, but cria were noted to have significantly greater corneal sensitivity in all areas compared to adult alpacas.

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Diseases

Corneal trauma is probably the most common ocular disease in New World camelids. In studies of apparently healthy camelids having no history of pain or squinting, many animals had corneal scars suggestive of prior trauma (Gelatt et al., 1995; Webb et al., 2006). Of llamas presented to veterinary teaching hospitals for all eye diseases, 41% had corneal disease and more than half of these had an active corneal ulcer (Gionfriddo et al., 1997). Most of these ulcers were of unknown cause but likely traumatic in origin.

The prominence and vulnerability of the camelid cornea predispose it to injury. Trauma may be caused by fighting, penetration, or scratching of the cornea by foreign bodies or from prolonged recumbency due to tick paralysis, meningeal worms, prolonged anesthesia, or lack of passive transfer in crias (Gionfriddo et al., 1997). Other trauma-associated corneal diseases reported in the 1997 study included lacerations, foreign bodies, and stromal abscesses (Gionfriddo et al., 1997). Histopathologic examination of two enucleated alpaca eyes having corneal perforations had severe panophthalmitis (R. Dubielzig, COPLOW unpublished data, 2017). One of the eyes also had an explosive choroidal hemorrhage, which was presumed to have occurred at the time of the perforation. Another enucleated llama eye also had an extensive corneal abscess initiated by trauma (R. Dubielzig, COPLOW unpublished data, 2009). A case of one llama with a corneal ulcer that was infected with *M. liquifaciens* was reported (Brightman et al., 1981), but no herd outbreaks of a "pink eye"-like disease have, to our knowledge, been seen.

Abscesses frequently develop in camelid corneas from trauma that perforates the epithelium and enters the stroma (Dubielzig, unpublished data, 2009; Gionfriddo, unpublished data, 2010). These appear as yellowish-white collections of purulent material at various depths within the corneal stroma; they are often very deep (Fig. 32.10). These abscesses are often infected by bacteria, and if treated aggressively they will often resolve quickly with medical support. Some may be fungal in origin, and mycotic keratitis has been seen in many camelids (Ledbetter et al., 2013). In the Ledbetter study, 9 of 11 cases of fungal keratitis were identified by culture and by cytology. The most common fungal isolates were the opportunistic *Aspergillus* spp. and *Fusarium* spp. These cases were treated similarly to fungal keratitis in horses, and 9 out of 10 cases having follow-up examinations retained vision in the affected eye.

A case of a 7-year-old llama with unilateral corneal abscesses, uveitis, and weight loss was described (Coster et al., 2010). The corneal lesions were multifocal and cream-colored. In addition, there was corneal edema and neovascularization, but no ulceration. Neither cytologic evaluations of deep scrapings nor cultures of an abscessed area revealed any organisms. Histopathologic evaluation of the globe after enucleation showed multiple granulomas containing spherules of *Coccidiodes posadasii* throughout the cornea, iris, and ciliary body. Ten months after enucleation, the llama was euthanized, and necropsy revealed disseminated coccidiodomycosis (Coster et al., 2010). Although camelids are susceptible to this disease, this was the first reported case of the organism causing ocular disease.

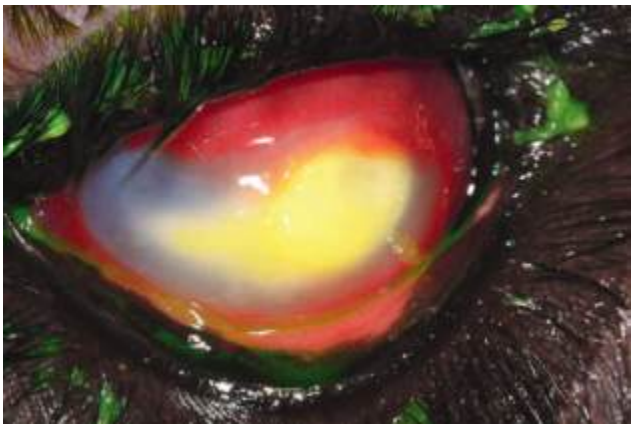


Figure 32.10 This animal had a traumatic ulcer in the central cornea that became infected. The bacterial and auto enzymes began to "melt" the cornea. The fluorescein stain placed in the eye to delineate the ulcer has been absorbed into exposed corneal stroma. The extensive, deep vascularization of the cornea is typical in camelids.

Ledbetter et al. (2008) evaluated the corneas of 16 alpacas that had ulcerative keratitis for the presence of obligate anaerobic bacteria. Three eyes (18%) had positive culture results that isolated one each of *Clostridium perfringens*, *Clostridium bifermentans*, a *Peptostreptococcus* sp., and a *Eubacterium* sp. All corneal ulcers from which anaerobic bacteria were isolated were stromal.

In a recent report of 56 sick neonatal camelids, the most commonly reported ophthalmic lesion was ulcerative keratitis (Bertin et al., 2015). Interestingly, none of the cases that were diagnosed with any ophthalmic lesion presented with an ophthalmic complaint. Corneal ulcers, often very deep, can arise in camelids with facial nerve paralysis (Sumner et al., 2012). The inability of the animal to blink its eyelids and keep the cornea moist leads to progressive exposure keratitis.

Spontaneous corneal epithelial defects (also called indolent or refractory ulcers) have been diagnosed in camelids (Jones et al., 2007). The cause for these is unknown, but could be the same as for dogs. They generally heal well with proper therapy (see below).

Cases of superficial, dendritic ulcers in camelids have been documented (U. Dietrich, personal communication, 2009; M. Blair, personal communication, 2009; J. Gionfriddo, unpublished data, 2009). These ulcers appear to be very similar to herpesvirus-induced ulcers in cats, but as of yet the causative organism has not been positively identified.

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The fact that these corneal ulcers generally heal well if the animal is placed on topical cidofovir suggests that they may be indeed viral in origin (Fig. 32.11).

Nonulcerative corneal degeneration is rarely reported in camelids; however, dystrophies and degenerations have been seen in clinical practice (Glenn Severin, personal communication, 1993) and have been reported in surveys of ocular diseases of camelids (Webb et al., 2006). A survey was conducted to examine the incidence of genetic problems in Canadian camelids (Webb et al., 2006). Potentially hereditary ocular defects were present in 23 of the 40 animals, with anterior stromal corneal dystrophy present in 2 of the 23 alpacas. Bilateral calcific band keratopathy has also been reported in an alpaca (Pucket et al., 2014).

While many of the corneal degenerations/dystrophies seen in camelids may be hereditary, acquired corneal degeneration has also been reported. A lipid keratopathy was described in an 8-year-old castrated male alpaca (Richter et al., 2006). The alpaca had a history of cloudy corneas and fluorescein-positive erosions. The erosions were surrounded by areas of neovascularization and dense-white crystalline deposits. A diagnosis of bilateral lipid keratopathy was made based on the results of a histopathologic examination of keratectomy samples. The source of the lipid was most likely due to the very high serum cholesterol concentrations of unknown origin that led to corneal lipid deposition as well as atherosclerosis (Richter et al., 2006).

Other corneal lesions have been infrequently reported in camelids. A limbal-based corneal epithelial inclusion cyst was reported by Pirie (2008). This cyst in a 13-year-old female llama may have been secondary to trauma or a previous corneal biopsy that had been done to aid in the diagnosis of a spontaneous chronic corneal epithelial defect. Mass excision followed by a conjunctival advancement flap graft was curative. Miller (unpublished data, 2017) examined a llama that had a large, pedunculated, axial, corneal mass that had been removed by the referring veterinarian and recurred quickly. After being removed by a veterinary ophthalmologist via a superficial keratectomy, it was found to be polypoid granulation tissue that did not reoccur after surgery.

Other corneal diseases reported in camelids include dermoids, a mass, and spontaneous edema (Barrie et al., 1978; Gionfriddo et al., 1997; Kilic et al., 2010; G. Severin, personal communication, 1993). Bilateral, spontaneous, corneal edema was reported in a captive guanaco and her offspring (Barrie et al., 1978). The cause was not found, but corneal endothelial dystrophy was suspected. An interesting case of a corneal papilloma in a dromedary camel was recently published (Kilic et al., 2010). The camel had clinical signs of severe keratoconjunctivitis that resolved after surgical resection of the mass.

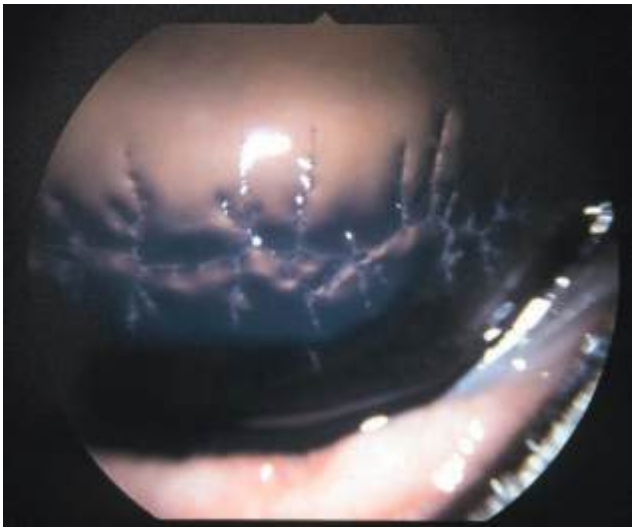


Figure 32.11 A superficial "dendritic" ulcer in a llama cornea. It resembles a herpesvirus ulcer in a cat, but the etiologies of these ulcers have never been demonstrated. (Courtesy of Michael Blair, Diplomate ACVO, Richmond, VA, USA.)

Treatment

Aggressive, prompt treatment of corneal ulcers, lacerations, and abscesses in camelids is important for a successful outcome. Numerous opportunistic bacterial pathogens such as *Pseudomonas* spp. grow in the conjunctival sacs of normal camelids, and therefore topical broad-spectrum ophthalmic antibiotics should be used in all cases in which the corneal epithelium has been compromised (Gionfriddo, 1994). If an infection is present, then aerobic and anaerobic bacterial culture and sensitivity testing should be performed (J. Gionfriddo, unpublished data, 2009). Topical antibiotics and antifungal drugs that can be used in horses can be used in camelids. Ofloxacin appears to be a good antibiotic choice for treatment of infected ulcers in camelids (J. Gionfriddo, unpublished data, 2009). Topical silver sulfadazine and miconazole have been successfully used to treat mycotic keratitis in camelids (J. Gionfriddo, unpublished data, 2011).

The optimal treatment of corneal lacerations, perforations, and ulcers depends on the initial depth of the lesion, the desires of the owner, the duration of the problem, and whether or not the lesion is infected. Greater than half-depth lacerations, which have little to no corneal tissue missing, may be sutured directly with small-gauge (7-0 to 8-0), absorbable suture material. Deep ulcers and ulcers with perforations may be successfully repaired using a conjunctival pedicle graft or corneal conjunctival transposition. An adult alpaca in the Zoo-Aquarium in Madrid with a corneal perforation and a secondary prolapsed iris received repair with a pedicle graft harvested from the bulbar conjunctiva (Rodriguez-Alvaro et al., 2005). After amputation of the protruding iris, the graft was sutured to the cornea with 6-0 Vicryl® (Ethicon, Somerville, NJ, USA) in a simple interrupted pattern. Rotation of the globe was minimized by

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paralyzing the animal with atracurium, and the anterior chamber was maintained with viscoelastic material (Rodriguez-Alvaro et al., 2005). This procedure allowed the eye to stay visual, as all that remained long term was a corneal scar and dyscoria.

Debridement of spontaneous chronic corneal epithelial defects may be done with a cotton-tipped applicator and grid keratotomy or a diamond burr. Grid keratotomy was reported to treat an "indolent ulcer" in a 13-year-old llama (Jones et al., 2007). The ulcer had been present for 12 days and was unresponsive to medical therapy. After debridement and a grid keratotomy using a 64 Beaver blade, the cornea healed slowly and was fluorescein-negative at 38 days post debridement. Diamond burr removal of the loose epithelium and "polishing" of the basement membrane have been described in dogs (Garcia da Silva et al., 2011; Sila et al., 2009) and has been successfully used to promote rapid healing in camelids (E. Garcia da Silva, unpublished data, 2010).

Anterior Segment

Anatomy

The iris of the camelid is similar to that of the cow except for the more pronounced "pupillary ruff" in camelids, which is a modification of the *corpora nigra* (*granula iridica*; see Fig. 32.5). This structure is an unusual and interesting adaptation to life in areas of excessive UV radiation. It is present on the dorsal and ventral papillary margins, but is more prominent dorsally as it acts to shade the pupil. Anatomically, the pupillary ruff is a modified portion of the posterior pigment epithelium of the iris, which is very large, protrudes into the pupil, and is folded vertically.

The iris pigmentation is usually moderate to dark brown, but not uniform in color. There are generally various shades of brown scattered through an individual iris, and heterochromia irides is common in color-dilute camelids. Clear blue or gray irides are also normal in camelids having low amounts of pigment. As in many other species (e.g., cats), coat and iris color may be associated with hearing loss. A study examined the correlation between deafness and iris pigmentation in llamas and alpacas (Gauly et al., 2005). None of the animals that had pigment in their coats or irides was hearing impaired, while 7 out of 10 of the pure white animals were bilaterally deaf, 1 was unilaterally deaf, and 2 had normal hearing ability. Blue-eyed animals having pigment in their coats, all-white animals with iris pigmentation, and one animal having one iris pigmented and one nonpigmented had normal auditory function. This study, along with numerous anecdotal observations, clearly suggests that there is a strong association between iridal hypopigmentation and congenital deafness in llamas and alpacas (Gauly et al., 2005). The blue-eyed white (BEW) phenotype inheritance pattern has not been proven, but a strong association between the BEW phenotypes and two microsatellite alleles at KIT-related markers has recently been demonstrated (Jackling et al., 2014). It has long been rumored among breeders that blue-eyed llamas are blind, but there is no evidence to support this.

The ciliary body of the camelid is anatomically very similar to that of other species. It is usually heavily pigmented even in color-dilute animals.

Normal aqueous humor composition in both llamas and alpacas is similar to that of other species (Aubin et al., 2001). Chemical analysis including measurements of ions, pH, and osmolality of aqueous humor has been reported (Table 32.1). With the exception of potassium concentrations, values for aqueous humor composition did not differ significantly between llamas and alpacas. Potassium concentrations were significantly higher in llamas. The reason for this is unknown.

Diseases

Many diseases affect both the anterior and posterior uvea, leading to panuveitis. Those that affect mainly the anterior uvea are discussed below, while those that affect both are discussed under "Posterior Segment."

Congenital

PPMs have been reported as congenital, and possibly hereditary, ocular defects in crias. A high incidence of PPMs was reported in 40 llamas that were examined (Webb et al., 2006). In all of the affected animals, the PPMs were iris to iris and did not cause any visual deficits. Heterochromia iridis and iris coloboma have been reported in closely related alpacas (Knickelbein et al., 2018; Fig. 32.12, Fig. 32.13, and Fig. 32.14).

Table 32.1 Chemical analysis of aqueous humor.

Camelid	Sodium (mEq/L)	Potassium (mEq/L)	Magnesium (mg/dL)	Chloride (mEq/L)	Bicarbonate (mEq/L)	Phosphorus (mg/dL)	Glucose (mg/dL)	Total Protein (mg/dL)	Osmolality (mOsm)
Llama	154.7 ± 2.1	5.3 ± 0.4	1.8 ± 0.1	130.0 ± 1.6	19.2 ± 1.5	2.7 ± 0.3	80.3 ± 3.9	29.0 ± 8.6	305.8 ± 11.8
Alpaca	152.7 ± 2.1	4.6 ± 0.4	1.7 ± 0.1	127.0 ± 3.3	20.2 ± 2.3	2.5 ± 0.4	80.8 ± 7.3	31.5 ± 10.1	306.2 ± 4.9

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Figure 32.12 Congenital ocular defects such as this iris coloboma (thought to be two colobomas abutting) are sometimes seen in camelids such as this alpaca. In most cases the etiologies are unknown, but in this case a hereditary origin is likely (see Fig. 32.14). (Reproduced with permission from Knickelbein, K.E., Maggs, D.J., Reilly, C.M., et al. (2018) Multiple ocular developmental defects in four closely related alpacas. *Veterinary Ophthalmology*, **21**(5), 544–551.)

Acquired

Anterior uveitis is a common sequela of traumatic ocular injury and systemic disease in camelids. Clinical signs of anterior uveitis can range from mild blepharospasm and epiphora to severe pain signs, episcleral injection, synechiae, and corneal edema (Fig. 32.15). Gelatt et al. (1995) found that several alpacas examined in South America had evidence of previous uveitis. This consisted of cataracts and anterior and posterior synechiae (Gelatt et al., 1995). In the 1997 VMDB study, 18% of the llamas with eye disease had active anterior uveitis (Gionfriddo et al., 1997).

Infectious diseases causing anterior uveitis include bacterial septicemia in neonates and crias with juvenile llama immunodeficiency syndrome, equine herpesvirus type 1 (EHV-1); (Paulsen et al., 1989; Rebhun et al., 1988), and toxoplasmosis, among others (Gionfriddo et al., 1997). Uveitis may also be secondary to deep corneal ulcers and cataracts (lens-induced uveitis; R. Dubielzig, unpublished data, 2009). Many of these problems cause both anterior and posterior uveitis (panuveitis).

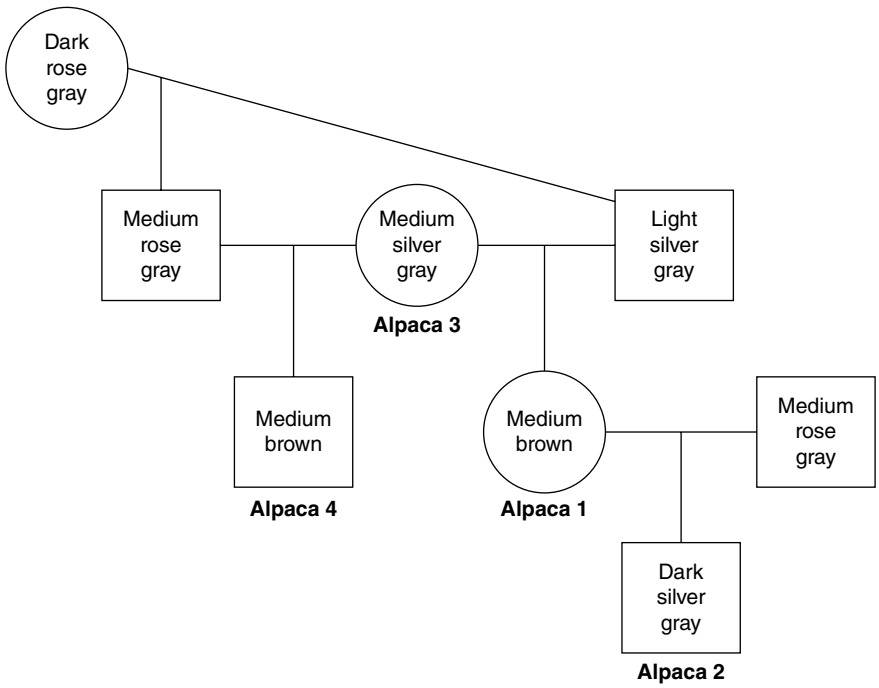


Figure 32.13 Pedigree showing the relationships among the four alpacas studied by Knickelbein et al. Circles represent females and squares represent males. Alpaca 1 is the affected subject of the case report that had hypoplasia of the retinal pigment epithelium (RPE) and suspected optic nerve hypoplasia. Alpaca 2 is her affected 2-year-old son (iris colobomas in both eyes and choroidal dysplasia/hypoplasia in the right eye). Alpaca 3 is the mother of Alpaca 1. She was affected with heterochromia iridis, cataracts and a subalbinotic fundus. Alpaca 4 was the 2-year-old half-brother of Alpaca 1 that had an RPE and choroidal coloboma in the left eye. (Adapted with permission from Knickelbein, K.E., Maggs, D.J., Reilly, C.M., et al. (2018) Multiple ocular developmental defects in four closely related alpacas. *Veterinary Ophthalmology*, **21**(5), 544–551.)

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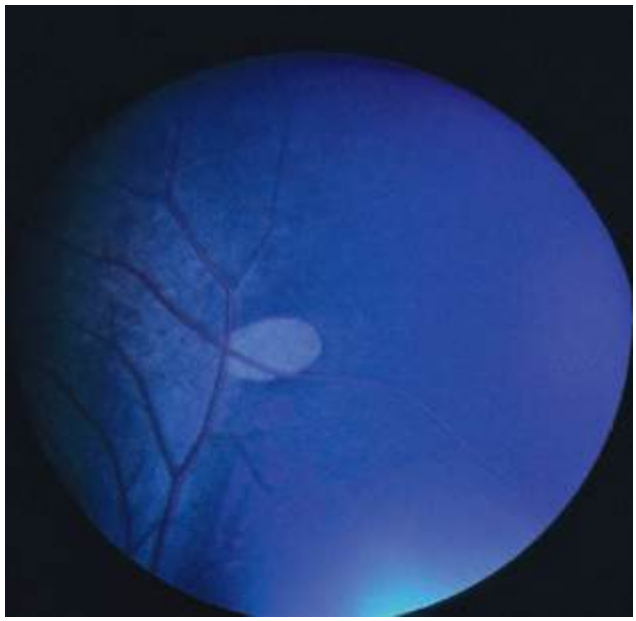


Figure 32.14 Funduscopic photograph of the right eye of an approximately 2-year-old alpaca studied by Knickelbein et al. The dense choroidal and retinal pigment epithelial (RPE) pigmentation obscures the choroidal blood vessels. A well-demarcated, nonraised region of low melanin density was present in the peripheral temporal fundus. This was thought to be an RPE coloboma. (Reproduced with permission from Knickelbein, K.E., Maggs, D.J., Reilly, C.M., et al. (2018) Multiple ocular developmental defects in four closely related alpacas. *Veterinary Ophthalmology*, **21**(5), 544–551.)

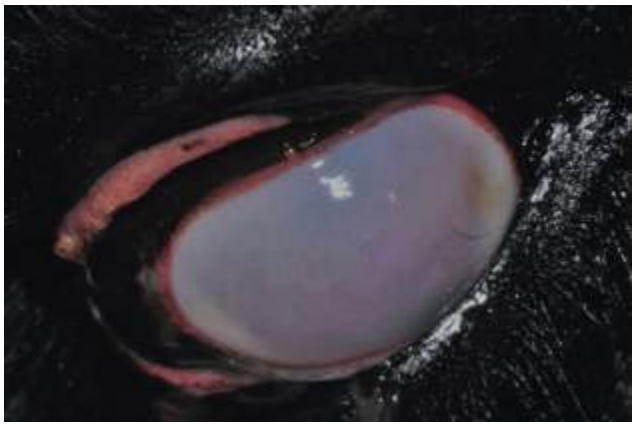


Figure 32.15 Anterior uveitis in an alpaca. There is hypopyon (the white, curving line in the ventral anterior chamber) and severe corneal edema. Camelids seem to develop corneal edema readily when the corneal endothelium is disturbed. This animal also had glaucoma secondary to the uveitis, which further compromised the corneal endothelium.

Posterior Segment

Anatomy

The appearance of the camelid fundus is highly variable among individuals and often between eyes of the same individual. This variability is attributable to the amount of pigment in the choroid, which in turn depends on the coat color of the animal. When observed ophthalmoscopically, it may appear dark brown, red-brown, or nonpigmented. A single fundus can contain streaks of dark pigment in some areas while other areas are nonpigmented. The prominent choroidal vessels provide a red coloration of the fundus that is seen in many camelids (Fig. 32.16 and Fig. 32.17). The colors of the iris and fundus are directly related to the coat and skin color of the individual (Webb & Cullen, 2010). Hypopigmented animals with light coat colors generally have various combinations of gray, blue, and brown irides and reduced pigmentation of the fundus. Those with dark coat colors generally have brown irides and pigmented fundi (Webb & Cullen, 2010).

The retinal vasculature and optic disc of the camelid are similar to those of the bovine. A prominent holangiotic vascular pattern is easily visible, and there are often anastomoses on the surface of the optic disc (Fig. 32.18 and Fig. 32.19). Three to five pairs of prominent retinal vessels emerge from the optic disc periphery; one pair of vessels emerges dorsally and extends peripherally, with the artery and vein spiraling around each other. Two pairs of vessels leave the optic disc horizontally and are usually accompanied by myelin, which extends several disc diameters peripherally into the fundus. A large Bergmeister's papilla (hyaloid remnant) may protrude from the disc into the vitreous (see Fig. 32.3).

Disease

Diseases of the posterior segment are relatively common in camelids. Congenital abnormalities, inflammatory diseases, parasitic diseases, toxic retinopathy, and retinal and optic nerve degenerations have been noted. In the VMDB study, 12 of 65 animals were reported to have posterior segment problems. These were either confined to a single structure such as the retina, choroid, or optic nerve or, more often, involved multiple structures and even the entire globe (Gionfriddo et al., 1997).

Congenital

Congenital defects of the posterior segment have been observed antemortem in camelid crias; most reported defects have been identified from histopathologic evaluation of eyes postmortem (R. Dubielzig, unpublished data, 2017; Gelatt et al., 1995; Gionfriddo et al., 1997; Schuh et al., 1991). In the COPLOW database, there were histopathologic reports of the eyes of 8 camelid crias under 8 weeks of age that had multiple ocular defects. Six of these eyes had peripapillary colobomas, which suggested that the ocular fetal fissures

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Figure 32.16 An immature cataract of unknown etiology in a middle-aged llama. Due to the site of the cataract (cortical) within the lens and its stage of maturity, it is likely to progress. The streak on the central cornea is mucus.

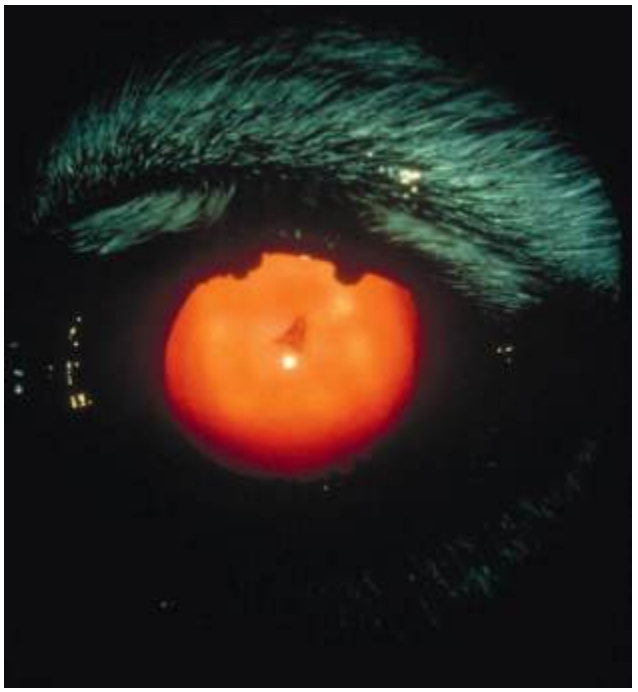


Figure 32.17 An immature, posterior polar cataract in a young alpaca. This cataract is unlikely to progress.

failed to close. Of eight eyes, two were microphthalmic; one of these also had a lens rupture, and the other had a coloboma and retinal dysplasia. Other congenital posterior segment findings in cria eyes included a retinal detachment in an eye that also had vitreous fibrosis and ossification, optic nerve hypoplasia, tunica vasculosa lentis, and suspected retinal aplasia (R. Dubielzig, unpublished data, 2017). Hostnik et al. (2011) described a 5-day-old alpaca cria with multiple neurologic abnormalities. Following euthanasia, the brain

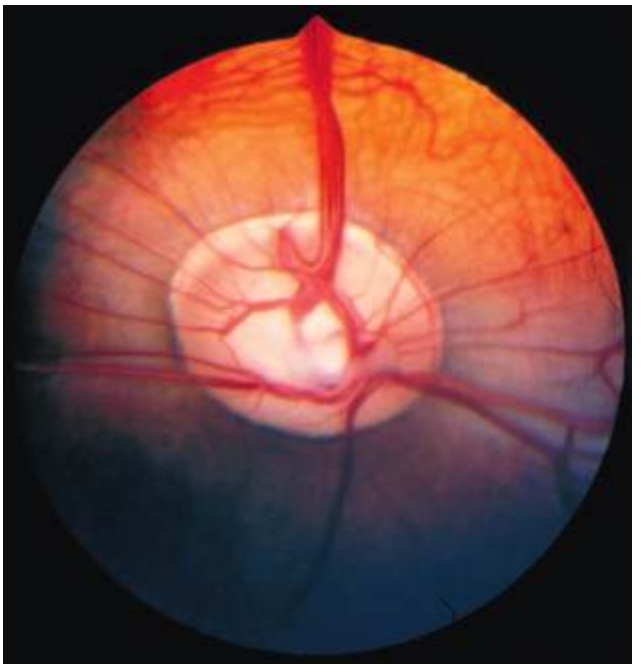


Figure 32.18 Funduscopic photograph of a normal camelid eye. The fundus is holangiotic, having large vessels that often stand out from the surface. The dorsal veins sometimes wind around each other. The optic nerve is large, often oval, and the retinal vessels course over the top of it. Pigment in the fundus can be heavy, light, or absent, or combinations of these.

and eyes were examined on necropsy. The brain lacked olfactory bulbs and tracts, and there were "smaller than normal" optic tracts. The eyes had bilaterally detached, dysplastic retinas and persistent hyperplastic primary vitreous (Hostnik et al., unpublished data, 2011).

Only a few congenital posterior segment defects have been reported in living animals. Schuh et al. (1991) described an adult llama with a large coloboma near the optic disk in one eye. In the 1997 VMDB study, congenital optic nerve disease was reported in two llamas: one had optic nerve hypoplasia and the other had a coloboma (Gionfriddo et al., 1997). These reports, along with anecdotal reports of finding colobomas in allegedly normal adult camelids, suggest that they may be relatively common defects, but go undiagnosed due to an absence of obvious visual defects. Although there are no studies documenting the heritability of colobomas in camelids, they are hereditary in some breeds of cattle (Lavach, 1990) and dogs (Roberts, 1960). Knickelbein et al. (2018) described a group of four closely related alpacas, each with ocular defects (see Fig. 32.13 and Fig. 32.15). All had different sizes and types of colobomas in one or both eyes. Other defects included choroidal dysplasia/hypoplasia, subalbinotic fundi, and cataracts. Although it could not be proven, the authors hypothesized that these defects were likely hereditary. A pedigree showing the filial relationships among the four alpacas is shown in Fig. 32.14.

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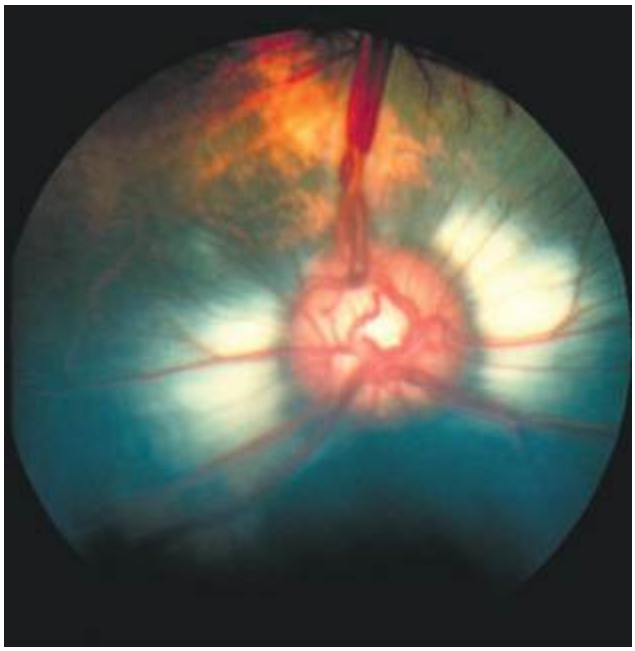


Figure 32.19 Funduscopic photograph of a normal camelid eye showing large amounts of myelin radiating from the optic disc onto the nerves. Many camelids have some myelin around the optic disc, but this is a more extreme example. There is thought to be no clinical significance to this phenomenon.

Acquired

Causes of acquired uveitis include systemic infections, ocular parasites, and toxicities. Several systemic infectious diseases have been reported to cause posterior segment inflammatory disease in camelids; the most notorious is EHV-1, which is discussed later. Other infectious diseases reported to cause posterior uveitis in llamas include aspergillosis, toxoplasmosis, and septicemia (Adams & Garry, 1992; Pickett et al., 1985; D. Tinsley, unpublished data, 2011).

In a 1992 report describing six camelid crias (five llamas and one alpaca) with Gram-negative septicemias attributed to perinatal factors and poor transfer of maternal antibodies, only two crias survived (Adams & Garry, 1992). After initiation of treatments for the infections, one cria developed secondary, bilateral retinal detachments and chorioretinitis. Other clinical signs of septicemia included obtunded mentation, convulsions, diarrhea, and respiratory distress.

Aspergillosis was implicated as a cause of neurologic disease and chorioretinitis in a wild-caught, zoo-housed alpaca (Pickett et al., 1985). During postmortem examination, *Aspergillus* was identified in the lung and eye. The fungus was thought to have spread hematogenously from the lungs to the eye (Pickett et al., 1985).

The most well-known viral cause of both anterior and posterior uveitis, as well as neurologic disease, in camelids is EHV-1 (Rebhun et al., 1988). Camelids acquire EHV-1 by contact with members of the family Equidae, such as horses and zebras. It was first described in 1988 in a mixed herd of camelids of which many members became blind after close contact with infected zebras. The neurologic signs that developed included head tilt, nystagmus, and paralysis. Signs of panuveitis developed in two alpacas, as evidenced by hypopyon, iritis, vitritis, retinitis, and optic neuritis. All attempted treatments failed to restore vision to any animal. Rising serum antibody titers to EHV-1, along with the histologic finding of eosinophilic inclusions in the brain, and isolation of the virus from tissues of affected animals confirmed this virus as the cause (Rebhun et al., 1988).

A similar outbreak occurred in a herd of llamas in Illinois in 1989 (D. Friedman, unpublished data, 1989). Of these llamas, 28 were exposed to zebras with rhinitis; 10–17 days after exposure, most of the llamas developed blindness, deafness, head tilt, and circling. Ophthalmic examination showed severe anterior uveitis and chorioretinitis. EHV-1 was confirmed as the cause of this outbreak based on serology and histopathologic evidence (D. Friedman, unpublished data, 1989).

To further document EHV-1 as a severe neurologic pathogen, House et al. (1991) experimentally infected three llamas with EHV-1. Two of the three developed clinical signs that were similar to those that were naturally infected. These consisted of blindness, staggering, head tremors, and obtunded mentation. Histopathologic evaluation of the brain and optic nerve revealed severe neuronal changes; however, isolation of EHV-1 was successful in only one (the most clinically ill) of the three animals. This suggested that it may be difficult to isolate the virus from infected animals.

A case report described a llama that had severe clinical ocular and cerebral signs that consisted of chorioretinitis, optic neuritis, and encephalitis (Paulsen et al., 1989). Serologic tests failed to implicate EHV-1, and no intranuclear inclusion bodies were seen on histopathologic evaluation of any tissues. The similarity of the clinical signs of this animal to those of the alpacas described by Rebhun et al. (1988) suggests that it may have been a case of chronic EHV-1 in which the virus was not identified. To the author's knowledge, no outbreaks of this disease have been reported in camelids since the 1990s. The reason for this is unknown, but could possibly be that there is greater awareness of the disease and therefore better separation of mixed herds or quarantine of sick equids.

Toxoplasmosis, a known cause of chorioretinitis in dogs and cats, may also cause chorioretinitis and blindness in camelids (L. Johnson, unpublished data, 1993; D. Tinsley, unpublished data, 2011). During an investigation of causes of late-term abortions in llamas, a serologic survey showed an extremely high antibody titer for *Toxoplasma gondii* in a blind llama that did not abort (L. Johnson, unpublished data, 1993). The llama had lesions consistent with chronic panophthalmitis. Tinsley described a 15-year-old llama with signs of bilateral chorioretinitis secondary to suspected toxoplasmosis. Vitreous humor was collected from one eye at hospital admission and 1 month later. Vitreous convalescent

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Toxoplasma antibody titers showed a marked rise, although serum antibody titers were negative. These results suggested that an ocular *T. gondii* infection may have caused the posterior uveitis (D. Tinsley, unpublished data, 2011).

Harrison et al. (2006) reported on a possible enrofloxacin-induced toxic retinopathy in a male guanaco in a zoo. The animal underwent surgery to repair an abdominal laceration and had been treated with penicillin G procaine, benzathine, and enrofloxacin (2.4 mg/kg intramuscularly every 24 h for 10 days) postoperatively. Later, trimethoprim-sulfadiazine was added. At 26 days after surgery, the guanaco was blind, with optic nerve pallor on fundoscopic examination. Histopathologic examination of the eyes following euthanasia revealed diffuse retinal outer-layer atrophy, which was more pronounced in the central retina. The brain had scattered areas of neuronal necrosis, microgliosis, and cerebral edema. The authors surmised that this was a case of enrofloxacin toxicity because of its similarity to the toxicity found in cats; however, this could not be confirmed (Harrison et al., 2006).

A case of *ophthalmomyiasis interna* has been described in a 12-year-old female llama that had an acute onset of recumbency and blindness (Dunkel et al., 2011). Upon ophthalmoscopic examination, a 2 cm long mobile helminth larva was observed in the posterior vitreous near the retina of the right eye. Despite antihelminthic and anti-inflammatory therapy, the neurologic condition worsened and the llama was euthanized. No progression in ocular clinical signs was seen during therapy. Necropsy results were unremarkable aside from the central nervous system and right eye. In the vitreous of the right eye, there was a live 2.5 cm parasite. Based on the necropsy results, parasitic migration into the eye was most likely through the spinal cord, along the brainstem, through the optic nerve, and into the eye. A diagnosis of ocular nematodiasis by the nematode *Parelaphastrongylus tenuis* was made. The blindness in this case was thought to be due to the central nervous system pathology caused by the parasite rather than by ocular invasion (Dunkel et al., 2011).

To the author's knowledge, no hereditary atrophic retinal diseases like progressive retinal atrophy have been reported in camelid species. In adult camelid eyes in the COPLOW database, retinal atrophy was reported in one 10-year-old alpaca whose eye had been enucleated due to chronic glaucoma. Retinal detachments were reported in two glaucomatous eyes in older llamas (R. Dubielzig, unpublished data, 2009).

A case of bilateral optic nerve degeneration has been reported in a 2-year-old guanaco (Czasch et al., 2001). The animal presented with dilated pupils and sudden blindness. Histopathology demonstrated optic nerve degeneration of unknown cause. No RGC loss or degeneration was noted. Both toxin and trauma were considered as potential primary causes.

Treatment

In not all cases of uveitis can a cause be identified. A case of idiopathic uveitis in a 9-year-old female llama was published in 2001. The llama had a "several-month" history of red eye followed by the development of photophobia and ocular discharge just prior to presentation (Grahn & Cullen, 2001). Ophthalmic examination showed bilateral focal corneal degeneration, multiple areas of anterior and posterior synechiae (with iris bombé in the right eye), and aqueous and vitreous flare. Basic blood work values were within the reference ranges, and further diagnostics were declined by the owner. A diagnosis of bilateral idiopathic uveitis was made and intense anti-inflammatory therapy was instituted, which consisted of frequent topical applications of atropine, flurbiprofen, and prednisolone acetate, and oral flunixin meglumine (1 mg/kg every 24 h for 7 days). The llama was rechecked at 4 days and again at 1 month, and by the 1-month recheck the right eye had lost vision and had developed glaucoma. A poor prognosis for vision was given due to the glaucoma (Grahn & Cullen, 2001).

Camelids with uveitis that is not attributable to an obvious cause should be examined carefully for signs of systemic disease. A thorough history and physical and ophthalmic examinations should be performed. Routine blood work is indicated in these cases, as well as serology that is appropriate for the geographic area and physical examination findings. Titers should be performed for infectious diseases including toxoplasmosis, leptospirosis, brucellosis, and systemic fungal infections including blastomycosis, coccidioidomycosis, and aspergillosis (rare; Pickett et al., 1985). Even though, to our knowledge, several of these diseases have not specifically been demonstrated to cause uveitis in camelids, the fact that they have been shown to do so in other species is reason enough to look for them in camelids with uveitis.

If a cause for the uveitis is found, then specific directed therapy should be instituted along with anti-inflammatory therapy. If not, the animal should be given intensive anti-inflammatory therapy and monitored carefully for the development of other signs of local or systemic disease. This generally includes topical nonsteroidal anti-inflammatory (NSAIDs) or topical steroidal medications. Topical atropine is also indicated to prevent synechiae and alleviate pain. Systemic NSAIDs may also be instituted and are relatively safe in camelids. Intravenous, intramuscular, or subcutaneous flunixin meglumine can be administered at a dose of 1 mg/kg once daily or 5 mg/kg of oral etogesic can be given once daily. Systemic steroids should be avoided in pregnant camelids as they can lead to abortions (Bruce Graham, unpublished data, 2004) and hepatic lipidosis.

Lens

Anatomy

The lens of the camelid is large and spherical in shape (Johnson, 1901). Its structure and function are very similar to those of cattle, sheep, and goats.

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Disease

As in other mammalian species, cataracts are the most common abnormalities of the camelid lens. Cataracts have been reported in survey studies of apparently normal camelids as well as in individual case reports. They were seen in 10% of the animals in the 1997 VMDB study (Gionfriddo et al., 1997). In a South American herd of 29 alpacas, Gelatt et al. (1995) found one behaviorally visual animal with nuclear cataracts. In a survey of camelids in Canada, Webb and Cullen (2010) found incipient anterior cortical cataracts in two llamas and three alpacas, incipient posterior cortical cataracts in five llamas and one alpaca, as well as immature posterior capsular and cortical cataracts in three llamas.

Mature, hypermature, and immature cataracts, as well as both congenital and acquired opacities, have been reported (Barrie et al., 1978; Donaldson et al., 1992; Gelatt et al., 1995; Gionfriddo, unpublished data; Gionfriddo & Blair, 2002; Gionfriddo & Friedman, 1993; Gionfriddo et al., 1997; Ingram & Sigler, 1993; Middleton et al., 2005; Powell et al., 2002; see Fig. 32.16 and Fig. 32.17). The significance of small, immature cataracts in camelids is unknown. Some have been thought to progress to maturity, while others have not. It also has not been determined whether or not they are genetically transmitted. Many of these immature cataracts are located at the posterior "Y" sutures of the lens, similar to the inherited, but usually nonprogressive, cataracts in Golden Retrievers (Barrie et al., 1978; Fowler, 1989; Gelatt, 1972; Ingram & Sigler, 1993).

Congenital cataracts can be solitary findings or may be found in conjunction with other ocular abnormalities (Gionfriddo & Blair, 2002; Knickelbein et al., 2018). In a case report documenting cataract surgery in a 9-month-old female llama, a persistent hyperplastic primary vitreous, persistent tunica vasculosa lentis, and persistent hyaloid artery (filled with blood) were present in the right eye and were thought to be the cause of the cataracts (Gionfriddo & Blair, 2002). These abnormalities, however, were not discovered until the lens was being removed. Thus, color Doppler ultrasound was performed prior to surgery in the contralateral eye on which a patent hyaloid artery and tunica vasculosa lentis could be seen. Surgery including an anterior vitrectomy with vessel cautery was performed and vision was restored in both eyes (Gionfriddo & Blair, 2002). Because of the possibility of retrolental abnormalities in camelids with cataracts, ocular ultrasonography is recommended prior to cataract surgery in these species (Gionfriddo, 2002).

While type 1 diabetes mellitus occurs in camelids, the incidence of diabetic cataracts is not known. In a 2005 case report of a diabetic alpaca, the authors reported that the animal had bilateral opacities that covered over 50% of the posterior lens capsule (Middleton et al., 2005). It is unknown if these were secondary to the systemic disease, but their appearance was dissimilar to diabetic cataracts in dogs that develop rapidly and progress to maturity (Middleton et al., 2005).

Surgical removal of cataracts in camelids has proven successful in restoring vision (Donaldson et al., 1992; Gionfriddo & Blair, 2002; Powell et al., 2002). With recent developments and improvements in the procedure (Gionfriddo & Blair, 2002; Powell et al., 2002), the severe postoperative complications reported by Ingram and Sigler (1993) can be avoided. In that case report of cataract surgery in a llama, manual lens extraction was followed by severe corneal edema, ulcerative keratitis, and, eventually, phthisis bulbi (Ingram & Sigler, 1993).

The changes that have radically improved the success rate of lens removal surgery include use of phacoemulsification technique during which endothelial-sparing methods are employed. Irrigation with balanced salt solution (BSS)-plus (a BSS containing glutathione) rather than normal saline, intensive application of pre- and postoperative anti-inflammatory drugs, and the use of copious amounts of viscoelastic during surgery all aid in protecting the corneal endothelium. A recent report documents the first published use of cis-attracurium as a neuromuscular blocker to assist in the removal of bilateral cataracts in a 6-month-old alpaca undergoing general anesthesia (Alexandru et al., 2016). The total dose of cis-atracurium needed to maintain sufficient paralysis for surgery was 14 μg/kg/min. Atracurium and rocuronium have also been used for neuromuscular blockade in camelids (Donaldson et al., 1992; Yamaoka & Auckburally, 2015). To the authors knowledge, intraocular lens placement has not been attempted in camelids.

Senile cataracts were reported in a 14-year-old llama (Powell et al., 2002). The cataracts were not associated with any other ocular defects. Surgery was done with routine phacoemulsification, as described by Gionfriddo and Blair (2002). Although the surgery was uncomplicated, the llama developed severely elevated IOPs postoperatively, with protrusion of the vitreous face into the anterior chamber nearly touching the cornea. At a second surgery, the posterior capsule was surgically perforated, and the IOPs returned to normal. This suggested that the elevated IOPs were due to blockage of the pupil and drainage angle by the vitreous, which had imbibed fluid and moved anteriorly (aqueous misdirection; Powell et al., 2002).

Luxated lenses, traumatic lens ruptures, and lens colobomas are rare. A lens coloboma was seen in the temporal quadrant of the left lens of a female guanaco. This abnormality was observed in conjunction with nuclear and perinuclear cataracts and corneal edema, and a hereditary cause was suspected for the defects (Barrie et al., 1978). In an eye of a 1-day-old cria that was recorded in the COPLOW database, a lens rupture was noted. Other abnormalities, such as microphthalmia and an "ocular coloboma," may occur together (R. Dubielzig, unpublished data, 2018). Lens ruptures can also occur secondarily to severe ocular trauma.

Glaucoma

Glaucoma is uncommon in llamas and alpacas, and there are no known cases of primary, potentially inherited, glaucoma in

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these species. Therefore, glaucoma is considered to be either congenital or, more commonly, secondary to intraocular inflammation. A few reports of congenitally abnormal drainage angles appear in the literature. Barrie et al. (1978) used gonioscopy to examine the drainage angle of a guanaco with corneal edema. They found that the animal had "closed" drainage angles due to goniodysgenesis; however, it had normal IOPs (Barrie et al., 1978). A 6-month-old female llama was diagnosed with congenital glaucoma (Cullen & Grahn, 1997). Since birth, the owners noticed that she had prominent eyes, epiphora, and corneal cloudiness, but was not blind. Ocular examination showed numerous anomalies including PPMs, corneal edema and striae, buphthalmos, and vitreous prolapse. Histopathologic examination of the globes after euthanasia revealed iris hypoplasia and poorly developed iridocorneal angles. Since the dam and sire had been bred several times prior to the birth of this cria and had produced only normal animals, the etiology was thought to be a congenital anomaly rather than a hereditary condition (Cullen & Grahn, 1997).

In the VMDB study in 1997, only two llamas were reported to have glaucoma, but no cause was proposed (Gionfriddo et al., 1997). Three cases of secondary glaucoma were described in the COPLOW database: one had a lens rupture, one was due to suppurative endophthalmitis, and one was "due to unknown inflammation" (R. Dubielzig, unpublished data, 2018). Despite these case reports, the incidence of goniodysgenesis and subsequent glaucoma in camelids is apparently low. Routine tonometry and gonioscopy on diseased and healthy eyes, however, may reveal a higher incidence of glaucoma or goniodysgenesis than has been previously reported.

Amaurosis

Visual deficits of unknown origin have been reported. At the Colorado State University Veterinary Teaching Hospital, 11 blind neonatal crias with apparently normal fundi were seen over a 20-year period (G. Severin, personal communication, 1993). Vision gradually returned to all crias; however, no cause was found. Congenital nystagmus and amblyopia have also been diagnosed in crias. There are also anecdotal reports of blindness with no apparent ocular defects or diseases in adult llamas (L. Johnson, personal communication, 1999). These cases may be an undiagnosed optic nerve or brain disorder.

An electroretinogram (ERG) may be performed in blind camelids to distinguish between a retinal disorder and an optic nerve or cerebral cortical lesion. The ERG amplitude of a normal camelid is much higher than that of most normal dogs and cats (J. Gionfriddo, unpublished data, 2011). A recent study of ERGs in alpacas used a portable, handheld ERG system (Handheld MultiSpecies Electroretinograph®, Oculoscience, Kansas City, MO, USA) to document the magnitude of the ERG responses of 12 normal animals. The active corneal electrode used was a DTL microfiber electrode, and single white flashes of light intensities of 10, 3000, and 10,000 mcd.s/m^2 were administered. The mean amplitudes and elicit times of the a- and b-waves were recorded at each time period. At both 3000 and 10,000 mcd.s/m^2 intensities, the alpacas had very high mean a-wave amplitudes (162 and 200 μv) and b-wave amplitudes (441 and 446 μv; Reinstein et al., 2011). Visual evoked potentials can also be generated in camelids to test the visual pathways and explore the cause of the blindness (Reinstein et al., 2011).

Ocular Neoplasia

Ocular and periocular neoplasia appear to be more common in domestic camelids than previously thought. In the VMDB study published in 1997, only two cases of neoplasia, an intraocular medulloepithelioma and an unspecified corneal tumor, were reported in llamas (Gionfriddo et al., 1997). At least five case reports of intraocular tumors in llamas and alpacas have appeared in the literature (Fugaro et al 2005; Hamor et al., 1999; Hendrix et al., 2000; Hill & Hughes 2009; Schoeniger et al., 2000).

Three of these were primitive embryonic tumors derived from the inner layer of the optic cup (two from the ciliary body and one from the retina) prior to differentiation and were considered to be congenital tumors. One of these was described as a malignant, intraocular, teratoid medulloepithelioma containing tissues not usually found in the eye in one eye of a 1-year-old llama (Hendrix et al., 2000). Presenting signs in this patient included anterior uveitis, corneal cloudiness, blindness, and retinal detachment. Because these findings were suggestive of infectious uveitis, blood work and serology for *Toxoplasma*, *Blastomyces*, and *Histoplasma* were performed. The *Toxoplasma* IgM titer was positive, so the llama was placed on sulfadimethoxine. When the symptoms worsened, the eye was removed and the tumor was diagnosed upon histopathologic examination of the globe (Hendrix et al., 2000). Histologic evidence of teratoid medulloepithelioma consisted of multilayers of poorly differentiated neuroepithelial cells, among which were islands of hyaline cartilage, some of it mineralized.

In 2000, a case of a malignant nonteratoid medulloepithelioma was published (Schoeniger et al., 2000). This patient was a 6-year-old female llama who had epiphora, buphthalmos, and a visible intraocular mass. The eye was removed, but a mass appeared in the orbit 1 month later. While radiation therapy initially reduced the size of the mass, it returned along with lymphadenopathy and masses in the mandible. Euthanasia was performed, and metastatic disease was seen in the orbit, mandible, mandibular lymph nodes, lungs, liver, and mesenteric and sublumbar lymph nodes. Histopathologic evaluation of all of the masses was similar with a diagnosis of primary intraocular medulloepithelioma with systemic metastases (Schoeniger et al., 2000).

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A retinoblastoma, another type of primitive intraocular neoplasia, was found in the enucleated left eye of a pregnant, 6-year-old llama that had clinical signs of chronic epiphora, buphthalmos, and vision loss that failed to respond to therapy. Histopathologic results and results of immunohistochemical analysis showed that the tumor was a retinoblastoma (Fugaro et al., 2005). In humans, retinoblastomas occur in children, are often hereditary (Ellias et al., 2001), and malignant. No metastases were reported in this llama, and she was still alive 4 years after the eye was removed (Fugaro et al., 2005).

Three cases of intraocular melanomas in alpacas have been reported. One case was a 2-year-old alpaca with an intraocular melanoma that had been presented for a corneal opacity (Hamor et al., 1999). The opacity was corneal edema secondary to two large pigmented iridal masses in contact with the corneal endothelium. Histopathologic examination showed that these masses originated from a single melanoma. A 10-year-old pregnant female alpaca presented to a veterinary clinic in New Zealand for evaluation of a "discolored" and enlarged right eye. The enucleated globe was very firm, and histopathologic examination revealed a soft tissue mass surrounding a 25 × 6 mm piece of bone. Immunohistochemistry confirmed that the mass was a melanoma. The tumor cells were thought to have induced metaplastic neoplasia in the surrounding tissue (Hill & Hughes, 2009). Another alpaca was examined by LaCroix (unpublished data, 2018) several years ago and was tentatively diagnosed as having an intraocular mass in the left eye. The eye was removed. Unfortunately, the referring veterinarian neglected to send in the eye for histopathology and a year later the tumor returned and filled the orbit (Fig. 32.20). Histopathology showed that the mass in the orbit was a malignant melanoma. In addition, a mass that was removed from the skin of the same animal proved to be a fibrosarcoma. This is the first report to the authors' knowledge that documents the presence of two malignant tumors in the same camelid. This case exemplifies the importance of submitting all tissues taken by surgical means for histopathology as soon as possible! While the tumor reported here might have returned regardless, knowing its type could have led to the use of adjunctive therapy and possibly saved the animal from pain and distress.



Figure 32.20 Regrowth of an intraorbital tumor that was excised but not treated with additional adjunctive modalities.

Conclusions

Information regarding the South American camelid eye continues to be generated and published. Anecdotal reports are useful, but recent publications of llama and alpaca diseases, surveys, case reports, and studies are even more informative. Excitingly, studies of the genetics of potentially heritable eye diseases are ongoing, and with this knowledge we may be soon able to advise owners and breeders on the inheritance of conditions such as congenital nasolacrimal anomalies, cataracts, and colobomas.

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Laboratory Animal Ophthalmology

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As trained experts in comparative ophthalmology, veterinary ophthalmologists are often called upon by biomedical and pharmaceutical research professionals to provide their knowledge and expertise regarding the eyes and visual systems of laboratory animals. There are many reasons why these collaborations may be sought and numerous settings in which they may take place, from academic laboratories to vivaria in the private sector. Today, perhaps the most common partnerships between vision research professionals and veterinary ophthalmologists involve the need for expertise in the conduct of ophthalmic examinations and interpretation of examination findings from laboratory animals used in ocular toxicology and preclinical drug development and safety evaluation studies.

Ocular drug and device development is a rapidly growing area of the pharmaceutical industry. Even over the past 10–15 years, the repertoire of drug classes and therapeutic approaches to treating human eye disease has expanded remarkably, seeking to overcome historically frustrating barriers to drug efficacy. For example, the development of novel anti-vascular endothelial growth factor (VEGF) biopharmaceuticals, like ranibizumab and aflibercept, has revolutionized the treatment of age-related macular degeneration (AMD), a common cause of human blindness (Eandi et al., 2016; Villegas et al., 2017). Furthermore, approval of these drugs has somewhat changed the landscape of physician-based retinal practice, with intravitreal (IVT) injections now being performed exponentially more frequently than before (Campbell et al., 2010). Following these clinical paradigm changes is intensive investigation of other novel drug classes and routes of administration, including suprachoroidal and subretinal injections, intraocular sustained-delivery implants/devices, and subretinal gene and cell therapy platforms (Christoforidis et al., 2012; Jacobson et al., 2015; Kumaran et al., 2018; Ochakovski et al., 2017; Short, 2008).

Supporting these advances is an extraordinarily large body of preclinical research in animal models, frequently involving the expertise and input of veterinary ophthalmologists. The role of the veterinary ophthalmologist may vary, ranging from expert consultation in study planning, to direct involvement in the execution of examinations and microsurgical procedures, and interpretation of ophthalmic images. Ultimately, the engagement of a veterinary ophthalmologist in the planning and execution of preclinical studies helps to ensure that (1) study procedures will be sound and appropriate for the laboratory animal model chosen; (2) ocular examination findings and results of other clinical endpoints will be acquired appropriately; (3) the integrity of the results will help ensure the safety of the public; and (4) the welfare of all involved animals is guaranteed.

As stewards for animal health, consulting veterinary ophthalmologists bear an implicit responsibility to ensure that laboratory animal use in any preclinical study is appropriate and humane. In 1959, Russell and Burch coined the "3 Rs" of laboratory animal welfare: *replacement*, when possible, of *in vivo* methods with *in vitro* or *in silico* alternatives; *refinement* of the *in vivo* methods and procedures currently practiced; and *reduction* in the number of animals used in research (Russell & Burch, 1959). Veterinary ophthalmologists are positioned to help ensure the fulfillment of the 3 Rs by using their expertise and experience to refine and improve the meaningfulness of study endpoints, to recall previously published data and avoid inadvertent repetition of a prior study, and to help develop *in vitro* alternatives to complement or even replace use of some animal models.

The cornerstones of any veterinary ophthalmologist's involvement as a consultant in laboratory animal ophthalmology include a fundamental knowledge of the spectrum of ocular anatomic and physiologic features in common laboratory species and strains, and a firm understanding of what is clinically *normal* for each species. In ocular toxicology and drug safety studies, for example, it is essential for the examiner to be able to accurately differentiate an incidental background finding on ophthalmic examination from a lesion (s) attributable to the microsurgical procedure or

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ocular drug/device being investigated. The veterinary ophthalmologist should also be familiar with features of the most common systems used to grade or score ocular examination findings and how they should be applied. Furthermore, he or she should understand the considerations necessary when performing ancillary ophthalmic diagnostics in laboratory species, and have some familiarity with the advanced ocular imaging modalities commonly used in preclinical studies.

This chapter provides the reader with an introduction to the fundamentals of clinical ophthalmology in laboratory animals. The species discussed include the mouse, rat, guinea pig, rabbit, miniature pig (minipig), and nonhuman primate (NHP). Particular emphasis is placed upon ocular examination, specifically the normal ocular anatomic and physiologic features of these species, as well as the background lesions and spontaneous ocular diseases commonly observed in each. These attributes are discussed in the context of the unique challenges associated with ocular examination and scoring of ocular findings in laboratory animals. Normative biometric and clinical values are presented, as well as brief discussions of advanced ophthalmic imaging, and common animal models of ocular disease. While species like the dog and cat may be subjects of some laboratory studies or act as animal models for certain diseases, the reader is referred to other chapters in this book for detailed descriptions of their respective ocular anatomy, physiology, and spontaneous diseases. Likewise, detailed discussions of therapeutic interventions for spontaneous ocular diseases in those laboratory species with increasing popularity as pets (e.g., rodents, rabbits, minipigs), will be discussed in other chapters.

Considerations for Ophthalmic Examinations in Laboratory Species

Ocular examination in laboratory species presents a number of unique challenges to the examiner. The foremost of these challenges is gaining familiarization with what is normal for a given species. Among laboratory species and even between different strains, a diverse spectrum of anatomic, physiologic, and pathologic features is observed (Fig. 33.1 and Fig. 33.2), and is discussed at length in this chapter. While this knowledge is important for any examination during the course of a study, it is particularly essential for the prestudy examination. The prestudy examination is performed prior to study initiation to identify any findings

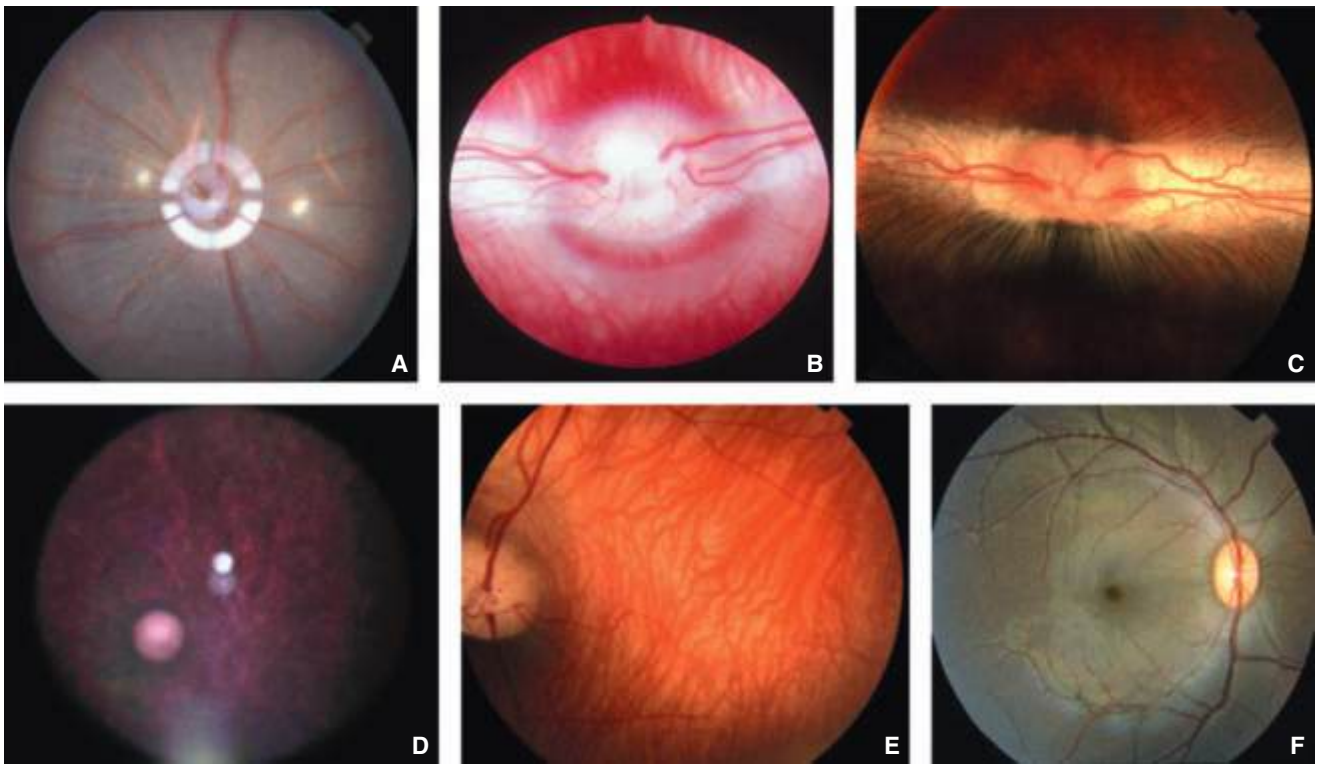


Figure 33.1 Normal fundus features from a pigmented mouse (**A**), albino rabbit (**B**), pigmented rabbit (**C**), guinea pig (**D**), Göttingen miniature pig (**E**), and cynomolgus macaque (**F**). Note the range of vascular patterns (holangiotic in the mouse, pig, and macaque; merangiotic in the rabbit; anangiotic in the guinea pig), differences in optic disk morphology, and absence of tapetum lucidum. Also note the presence and appearance of the normal macula and fovea in the macaque. (Courtesy of the UC Davis Veterinary Ophthalmology Service and Ellison Bentley, DVM, DACVO, University of Wisconsin–Madison.

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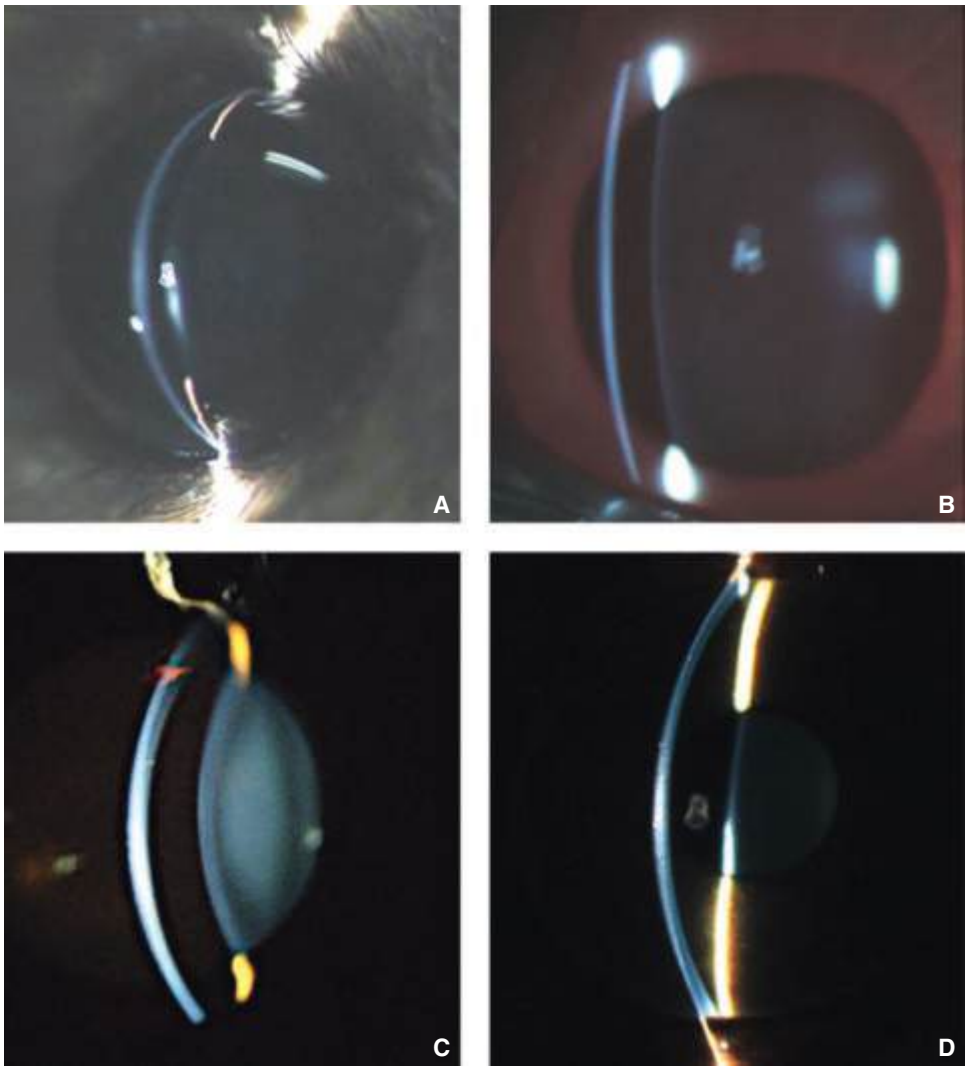


Figure 33.2 Representative slit-lamp photographs of the anterior segments of a normal pigmented mouse (**A**), albino rabbit (**B**), dog (**C**), and cynomolgus macaque (**D**). (Reproduced with permissions from Eaton, J.S., Miller, P.E., Bentley, E., et al. (2017) Slit lamp-based ocular scoring systems in toxicology and drug development: A literature survey. *Journal of Ocular Pharmacology and Therapeutics*, **33**, 707–717.)

eliminating an animal's candidacy for inclusion. Findings warranting exclusion typically include corneal and/or lens opacities that preclude intraocular examination, or that may *progress* to preclude examination during the course of a study (Wilkie, 2014). Other findings necessitating exclusion include active keratitis or corneal ulceration, uveitis, or intraocular hemorrhage (e.g., from a persistent hyaloid remnant). The prestudy examination also permits identification and documentation of any incidental or "background" lesions so that they may be (1) definitively distinguished from any procedure- or drug-related findings that follow once the study begins, and (2) monitored for changes throughout study progression.

For laboratory animals, the "minimum database" for an ophthalmic examination is no different than for other species and includes evaluation of the pupillary light reflex (PLR); pharmacologic mydriasis; slit-lamp biomicroscopic examination of the anterior segment and anterior vitreous; and dilated examination of the vitreous and fundus via ophthalmoscopy (indirect and/or direct). PLR evaluation is straightforward in most laboratory species, indicated to assess the briskness and symmetry of the afferent and efferent components. Of the species discussed in this chapter, all have ovoid/round pupils and varying degrees of neural decussation at the optic chiasm, enabling a consensual (indirect) PLR. Under natural conditions, laboratory species' pupils should respond relatively briskly to bright light. However, it is important to remember that prey species like the mouse, rat, and rabbit may exhibit slow PLRs due to sympathetic overdrive experienced during handling. This is particularly prominent in animals that are not sufficiently acclimated to a laboratory or vivarium or its personnel.

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In all mammalian laboratory species, pupil dilation is essential for thorough examination of the lens and posterior segment and is easily achieved with topical short-acting antimuscarinics like 0.5%–1.0% tropicamide. While not always necessary, some references advocate use of topical phenylephrine in combination with agents like tropicamide, particularly in pigmented rodents (Kern, 1997; Williams, 2012). Across the species discussed in this chapter, 10–15 minutes is the minimum amount of time required to sufficiently dilate the pupils following instillation, with pigmented strains and species requiring more time than albinos (Wilkie, 2014). Ocular pigmentation will also influence the duration of dilation. Adequate dilation may only last for 1 hour in albino strains, but may persist for up to 3–5 hours in pigmented animals (Wilkie, 2014). These metrics are of particular importance in general toxicity studies investigating systemically administered drugs. These studies often include large numbers of animals (typically hundreds of mice or rats), requiring dilation to be performed at intervals during the examination period to ensure that all animals maintain sufficient mydriasis.

Slit-lamp biomicroscopy is essential for examining the anterior segment and anterior vitreous of laboratory species. While table-mounted instruments may offer examiners a wider range of illumination settings and other functionalities, handheld slit lamps are most commonly used in larger laboratories and vivaria. Portable handheld units like the Kowa SL-15® and SL-17® (Kowa, Tokyo, Japan), Keeler Classic® (Keeler, Malvern, PA, USA), Reichert PSL® (Ametek, Berwyn, PA, USA), Haag-Streit BA 904® (Haag-Streit, Koeniz, Switzerland), and Zeiss HSO-10® (Carl Zeiss Meditec, Oberkochen, Germany) provide more versatility, enabling examination of large numbers of laboratory animals of all sizes. In some settings, particularly those in which smaller numbers of animals are routinely anesthetized for examinations, table-mounted slit lamps may be used.

Assessment of the posterior segment in laboratory species is also a requisite part of the complete ophthalmic examination, most commonly carried out with indirect ophthalmoscopy using an ophthalmoscopic headset and condensing lenses. When combined with pupil dilation, this technique enables examination of the entire fundus and enhances efficiency when examining large numbers of animals. In laboratory species, the range of globe and pupil sizes requires examiners to use condensing lenses of different dioptric strengths. Lenses like the 14 D, 20 D, Volk 2.2 PanRetinal, and the specialized Volk 5.5 D Macula Plus® (Volk Optical, Mentor, OH, USA) are often used for NHPs; the 28 D for rabbits, minipigs, dogs, and cats; and the 40 D and 60 D for rats and mice, respectively (Eaton et al., 2017b). Examiners must also be mindful of the inverse relationship between a species' globe dimensions and the lateral and axial magnification of the ocular fundus when viewed ophthalmoscopically (Murphy & Rowland, 1987). Rodents' small globes, bearing short optical focal distances, produce considerable magnification. In rodents, for example, this phenomenon makes the normal retinal vasculature appear to "float." If the examiner is unfamiliar with this artifact, it could be falsely interpreted as a retinal detachment. From a comparative perspective, a fundus lesion with identical dimensions in a pig and mouse may carry greater clinical significance in the pig, since the higher inherent magnification in the rodent eye artifactually renders a lesion larger than its true size.

In any preclinical study, it is essential that an examiner use a standard semi-quantitative scoring (grading) system to document the severity of lesions or abnormalities observed on biomicroscopy and ophthalmoscopy. Use of a scoring system permits an examiner to (1) more finitely and objectively characterize lesions or adverse effects (e.g., ocular inflammation); (2) ascribe clinical significance to lesions or clinical observations and determine whether intervention is required to ensure animal welfare; and (3) longitudinally monitor those lesions or adverse effects for progression or improvement. Furthermore, use of scoring systems in preclinical drug development provides objective semi-quantitative measurements that may be useful in determining potential risks to human patients.

Scoring systems like those published and validated by Hackett–McDonald and McDonald–Shadduck (Hackett & McDonald, 1996; McDonald & Shadduck, 1977), or modifications thereof, have long been used in ocular toxicology and drug development programs for scoring of biomicroscopic findings involving the anterior segment (Munger, 2002). When using these two systems, however, the examiner should be mindful that they were originally described for scoring of examination findings in New Zealand white (NZW) rabbits, whose ocular morphology and ocular reactivity (Bito, 1984) differ from other strains and laboratory species. This can complicate the applicability of a number of their scoring criteria to those other strains and species.

The Standardization of Uveitis Nomenclature (SUN) system was developed to standardize assessment of naturally occurring uveitis in human patients. As the systems of Hackett–McDonald and McDonald–Shadduck lack scoring criteria for anterior chamber (AC) cells, the SUN criteria are often used in preclinical studies involving animals (Eaton et al., 2017a; Jabs et al., 2005; Munger & Collins, 2013; Wilkie, 2014). There are, however, considerable anatomic differences between the anterior chambers of humans and laboratory animals (see Fig. 33.2 and Fig. 33.3) that may complicate use of the SUN system in species other than the human. A recent mathematic analysis demonstrated the influence of anatomy on semi-quantitative scoring by geometrically modeling the anterior chambers of different species and comparing AC cell counts yielded using the SUN system in each (Thomasy et al., 2016). The analysis demonstrated that use of SUN in pigs, dogs, and cats underestimated human values by 12%, 29%, and 33%,

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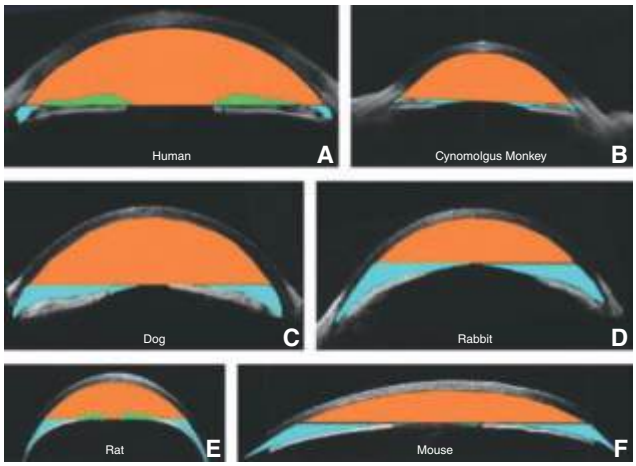


Figure 33.3 Central cross-sectional optical coherence tomography images from a normal adult human (**A**), cynomolgus macaque (**B**), dog (**C**), rabbit (**D**), rat (**E**), and mouse (**F**). Geometric attributes defining anterior chamber (AC) volume differ between species depending on features such as corneal curvature, anterior lens curvature, and iris volume. In all species, AC volume is largely defined by AC depth and corneal curvature (represented in orange). Anterior lens curvature additionally contributes to differences in AC volume (represented in blue). Iris volume (represented in green) also contributes, but may be more dynamic depending on status of pupil dilation. (Reproduced with permissions from Thomasy, S.M., Eaton, J.S., Timberlake, M.J., et al. (2016) Species differences in the geometry of the anterior segment differentially affect anterior chamber cell scoring systems in laboratory animals. *Journal of Ocular Pharmacology and Therapeutics*, **32**, 28–37.)

respectively; and overestimated counts in rats and mice by 442% and 772%, respectively.

Despite the limitations associated with these systems, they do provide semi-quantitative scoring criteria that are familiar to investigators in vision science and toxicology, which is of value when communicating or comparing scoring results between studies or programs. However, when these systems were developed, the majority of ocular therapeutics being investigated were administered topically. Therefore, certain elements of their scoring schemes are more difficult to apply to the intraocular routes of ocular drug administration widely studied today. Recently, a group of veterinary ophthalmologists heavily engaged in preclinical toxicology and drug development studies described the Semiquantitative Preclinical Ocular Toxicology Scoring (SPOTS) system, which addresses the limitations of the aforementioned systems by (1) providing standard slit-lamp settings for handheld instruments; (2) expanding their criteria to facilitate scoring of small and large pigmented and albino strains and species; and (3) modifying the criteria to befit the therapeutic approaches utilized in modern drug development (Eaton et al., 2017b).

Performing ocular examination in laboratory animals requires awareness of several important practical

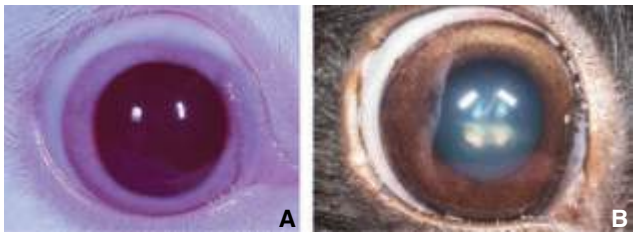


Figure 33.4 Anterior segment features of albino (**A**) and pigmented (**B**) rabbits. A corticonuclear cataract is also present in the lens of the pigmented rabbit in (**B**). (Courtesy of Ocular Services On Demand (OSOD) and the UC Davis Veterinary Ophthalmology Service.)

considerations. In mice and rats, for example, it is noteworthy that the retinal and choroidal vasculature in an otherwise normal rat or mouse fundus can be easily blanched with heavy manual restraint, falsely mimicking retinal degeneration or a retinal anomalous finding. Therefore, an examiner should request that an animal handler adjust their restraint in any animal exhibiting retinal or choroidal vascular attenuation. Both albino and pigmented rabbits are very commonly used in toxicologic studies, but differences between pigmented and albino strains can considerably influence examination and scoring. In the pigmented rabbit, for example, melanin distributed around the limbus can preclude complete evaluation of the predominantly perilimbal conjunctival vasculature; and iris pigmentation can mask lower degrees of iridal vascular hyperemia and congestion, complicating the diagnosis and scoring of iritis (Fig. 33.4). In the minipig with its thicker eyelids and periocular cutaneous tissue, gaining sufficient exposure to perform an examination can be a challenge, particularly if the animal is not sedated. NHPs are nearly always examined sedated or anesthetized to facilitate safe examination. A prominent brow ridge and conjunctival pigmentation in many macaques can complicate evaluation for conjunctival hyperemia. Furthermore, the examiner must be very familiar with the normal appearance of the macula and fovea in this species, as well as the reflective "sheen" normally produced by its inner limiting membrane (Fig. 33.5), which can be mistaken for perivascular sheathing or other pathology if the examiner is not conversant with its appearance (Fig. 33.6).

General Features of the Eyes of Laboratory Species

The following sections will provide a review of the relevant functional morphology and spontaneous lesions and diseases of the eyes of rodents (mice and rats), guinea pigs, rabbits, minipigs, and NHPs. For detailed information regarding comparative ocular anatomic dimensions and volumes, the reader is referred to the data in Table 33.1.

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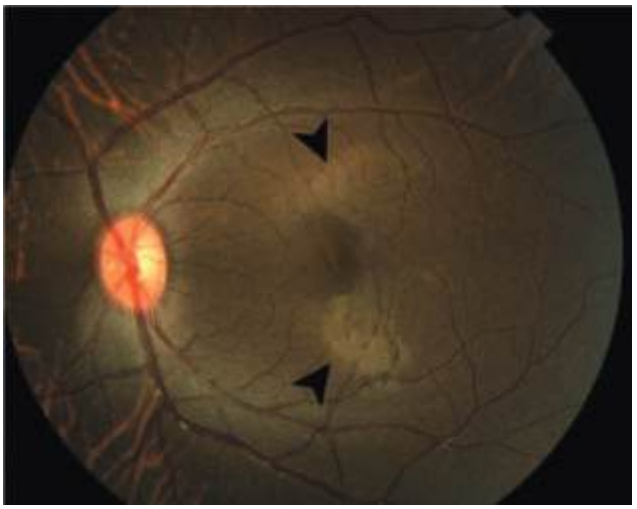


Figure 33.5 A perivascular "sheen" is observed adjacent to the macula and fovea (arrowheads) due to reflected light from the retinal inner limiting membrane in a cynomolgus macaque. (Courtesy of Paul Miller, DVM, DACVO, University of Wisconsin–Madison.)

Mouse and Rat

The mouse and rat are commonly used as animal models of ocular disease and as subjects in toxicologic studies. Compared to other laboratory species, rodents are cost-effective, relatively easy to handle without anesthesia, require comparatively less space and resources for housing, and can be transgenically modified. Before an ocular drug or device is considered for use in human clinical trials, the Food and Drug Administration (FDA) currently requires preclinical studies to be conducted in at least two nonhuman species, one of which is often a rodent (Mirowski & Van Horn, 2005). Furthermore, they are a preferred species for general toxicity studies that require large numbers of animals to screen for ocular adverse effects associated with systemically administered drugs. In preclinical ocular studies, the most commonly used mouse strains include inbred pigmented strains like the C57BL/6J and DBA1/J, and albino strains like the inbred BALB/c and outbred ICR (CD-1). Commonly used rat strains include the pigmented Long-Evans and Brown Norway, and albino strains like the Sprague-Dawley, Wistar, and Fischer 344 (F344).

Functional Morphology

The visual systems of the rat and mouse are fundamentally similar to one another, but differ in many ways from those of other laboratory species and humans. In mice, lateral placement of the globes yields only a small, approximately 40° area of binocular overlap (Drager, 1978; Heesy, 2004; Scholl et al., 2013). Similarly, binocular overlap in the rat has been reported to fall in the range of 40–60° (Heesy, 2004; Montero, 1973). Some investigators have reported a slight difference in binocular field between pigmented and albino rat strains, attributed to a slight difference in eye position (Lund et al., 1974). As crepuscular species, mice and rats possess vision of relatively low acuity (0.5 and 0.94 cycles per degree [cpd], respectively) and slow temporal processing, but high sensitivity (Wang et al., 2011). This is largely due to their rod-dominated retinas, which represent 95%–98% and 98% of all photoreceptors in the mouse and rat, respectively (Smith et al., 2001; Wang et al., 2011). The small percentage of cones in mouse and rat retinas absorb light in the blue-ultraviolet (359 nm) and mid-green (510 nm) spectra (Jacobs et al., 2001; Szél et al., 1992). It is noteworthy that albino mice and rats have approximately 30% fewer photoreceptors than pigmented animals (Ilia & Jeffery, 2000) which likely contributes to the generally lower visual acuity reported in those strains (Prusky et al., 2000).

A noteworthy variation in the mouse is the differential distribution of shorter-wavelength blue cones and longer-wavelength green cones in the retina. It has been shown that cones with blue spectral sensitivity (S-cones) are higher in density in the ventral retina, thus referred to by some as the "S-field" (Szél et al., 1992). Some have proposed that this cone-dense region in the ventral retina of prey species like mice enables them to more readily identify a predator against the blue background of the sky (Gouras & Ekesten, 2004; Szél et al., 1994). However, others have suggested that the primary advantage is not color differentiation, but instead involves enhancement of contrast (Baden et al., 2013).

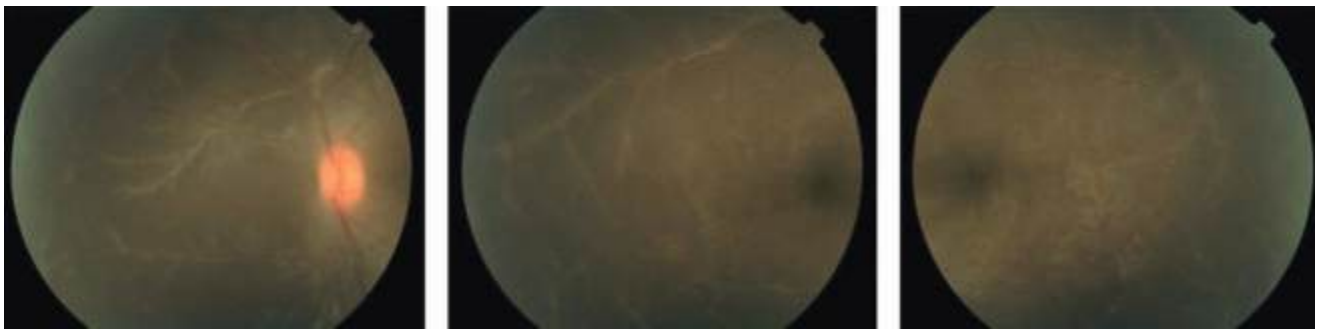


Figure 33.6 Retinal perivascular sheathing in a cynomolgus macaque. (Courtesy of Paul Miller, DVM, DACVO, University of Wisconsin–Madison.)

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Table 33.1 Published values for biometric ocular dimensions and chamber volumes in the adult mouse, rat, guinea pig, rabbit, pig, cynomolgus macaque, and rhesus macaque. *Note*: Included values were taken from *in vivo* studies or schematic investigations, where available.

		Axial Globe Length (mm)	Anterior Chamber Depth (mm)	Axial Lens Diameter (mm)	Vitreous Chamber Depth (mm)	Central Corneal Thickness (mm)	Anterior Chamber Volume (ml)	Lens Volume (ml)	Vitreous Chamber Volume (VCV)	Reference
Mouse		3.4	0.45	2.15		0.095				Puk et al. (2006)
		3.289	0.385	2.037	0.854					Tkatchenko et al. (2010)
		3.256	0.416	1.917	0.583					Chou et al. (2011)
	C57BL/6	3.262								Park et al. (2012)
						0.0908				Zhou et al. (2008a)
						0.117				Zhou et al. (2008b)
						0.113				Wang et al. (2010)
						0.103				Hanlon et al. (2011)
		3.302	0.278	2.004	0.609					Barathi et al. (2008)
	BALB/c					0.106				Schulz et al. (2003)
						0.12				Reichard et al. (2010)
		3.16	0.56	1.73						Brown et al. (2005)
	CD1						0.0072			Zhang et al. (2002)
								0.0057*		Brown et al. (2005)
	Unspecified strain								0.02	Short (2008)
Rat	*Brown Norway*	6.91	1.03	4.57	1.32					Lozano & Twa (2013)
		5.6		3.3	1.5		0.0136			Guggenheim et al. (2004)
	Wistar					0.17				Reichard et al. (2010)
						0.15908				Schulz et al. (2003)
	Sprague-Dawley								0.0565	Berkowitz et al. (1998)
								0.043*	0.0524	Sha & Kwong (2006)
Guinea pig		9.01	0.84	4.33	3.26					Rajaei et al. (2016)
						0.23				Cafaro et al. (2009)
									0.15	Dong et al. (2011)

(Continued)

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Table 33.1 (Continued)

		Axial Globe Length (mm)	Anterior Chamber Depth (mm)	Axial Lens Diameter (mm)	Vitreous Chamber Depth (mm)	Central Corneal Thickness (mm)	Anterior Chamber Volume (ml)	Lens Volume (ml)	Vitreous Chamber Volume (VCV)	Reference
Rabbit		17.1			7.1					Toni et al. (2010)
		15.12								Bozkir et al. (1997)
		18.28		6.28	9.26	0.5				Adel (2011)
	Albino		2.08			0.388				Yüksel et al. (2015)
				7.26				0.585		Langner et al. (2010)
						0.354				Reichard et al. (2010)
						0.391				Riau et al. (2012)
							0.25			Freddo et al. (1990)
							0.15			Yablonski et al. (1987)
						0.385				Wang & Wu (2013)
	Pigmented					0.39				Wang et al. (2014)
									1.2	Gao et al. (2006)
Pig*		24.9					0.3			McMenamin et al. (1991)
		23.9	2.7	7.4		0.8776				Sanchez et al. (2011)
		21.64	2.47			0.98				Bartholomew et al. (1997)
			2.13			0.96				Asejczyk-Widlicka et al. (2008)
					10.49					Coile & O'Keefe (1988)
						0.666				Faber et al. (2008)
								0.5191		Langner et al. (2010)
									2.29	Shafiee et al. (2008)
Cynomolgus macaque		18								Quigley et al. (1991)
		17.16	2.79	3.18	11.25		0.085		1.9	Kaufman et al. (1981)
			3.35			0.55				Lapuerta & Schein (1995)
							0.0998			Toris et al. (2005)
								0.125		Nishi et al. (2014)
Rhesus macaque		18.95								Bradley et al. (1999)
			3.4							Denlinger et al. (1980)
		17.14	3.06	3.59	10.48					Qiao-Grider et al. (2010)
							0.134			Pederson et al. (1978)
							0.106			Johnson et al. (1977)
								0.1359		Borja et al. (2010)

* Except for the value from Faber et al. (2008), all values were from *ex vivo* studies of enucleated globes.

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In terms of the refractive state in rodents, some investigations have suggested that their eyes (and possibly eyes of other small species) may be naturally hyperopic (Murphy & Howland, 1987; Schaeffel et al., 2004). Clinically, this is supported by the need for an examiner to use a +8 to +9 dioptric lens to clearly view the rat retina in a normal eye when performing direct ophthalmoscopy (Murphy & Howland, 1987). In performing any refractive assessment, however, it is important to remember that the retinal reflex in any species is generated at its inner limiting membrane; and while the axial globe length of species' eyes will vary, retinal thickness is relatively constant among species. Thus, the apparent hyperopia observed ophthalmoscopically may actually be an artifact of the biometric and optical properties of very small eyes (Murphy & Howland, 1987).

Mice and rats have a relatively shallow orbit that largely lacks bony structures dorsally (Hwang et al., 2012; Smith et al., 2001). Soft tissue structures therefore contribute considerably to the tissues that surround and support the globe in both species. These structures, however, differ from other larger species, bearing important clinical implications. In both species, three orbital glands, the intraorbital, extraorbital, and Harderian, contribute to normal lacrimal secretions. Secretions from the extraorbital gland are carried toward the ocular surface via a duct that joins that of the intraorbital gland, delivering the secretions of both to the conjunctival fornix and ocular surface in the lateral region of the upper or lower eyelid (Beaumont, 2002; Lorber, 1993). The comparatively large harderian gland is irregular in shape and occupies a large portion of the posterior and medial orbit, lying in close proximity to the base of the third eyelid where its duct empties into the conjunctival fornix (Djeridane, 1996; Payne, 1994; Seely, 1987). Harderian gland secretions are high in lipid content, believed to play an important role in corneal and ocular surface health (Sbarbati et al., 2002). The gland also produces porphyrin pigments and melatonin, and putatively plays a role in rodent sexual behavior through the production of pheromones (Beaumont, 2002; Djeridane, 1994; Payne et al., 1979). It is the production and presence of photodynamic porphyrins in the gland that are also believed to render it susceptible to photic toxicity, characterized by swelling, inflammation, and even necrosis after prolonged exposure to high-intensity light (Johnson et al., 1979; Kurisu et al., 1996).

Both species possess large orbital venous structures. In the rat, the orbital venous plexus is formed by numerous anastomoses between the external dorsal and ventral ophthalmic veins (Timm, 1979). The analogous structure in the mouse, the orbital venous sinus, receives venous blood from the globe via the episcleral, anterior and posterior ciliary, central retinal, and vortex veins, as well as from the soft tissues of the orbit (Smith et al., 2001). Compared to the venous plexus of the rat, the mouse's venous sinus is larger relative to total orbital volume (Smith et al., 2001). Historically, these venous structures have been used as sites for routine venous blood collection, easily accessed via the species' relatively open orbit, and carrying a reportedly low complication rate of 1%–2% (Parasuraman et al., 2010). However, these complication rates are proven to be significantly impacted by technician experience (Van Herck et al., 1998), and studies have reported that complication rates are likely higher, as painful and potentially blinding adverse effects such as corneal ulceration, penetrating ocular injury, intraocular hemorrhage, retinal detachment, optic nerve damage, and harderian gland necrosis may not be recognized by lab personnel (Diehl et al., 2001; McGee & Maronpot, 1979). Furthermore, there is evidence that animals undergoing orbital bleeding have comparatively higher circulating stress hormone levels and more pronounced behavioral indicators of stress (reduced activity/locomotion, reduced grooming, slower recovery) in comparison to animals undergoing other techniques (Fitzner Toft et al., 2006; Harikrishnan et al., 2018; Van Herck et al., 2000, 2001). Despite the fact that this technique is used less frequently than in previous decades, these data support a clear need for thorough ocular assessment of animals in any study where orbital blood collection is performed.

A unique anatomic feature of the mouse and rat eye is a nearly spherical lens, occupying the majority of the intraocular volume. The lens's profile and curvatures create narrow anterior and vitreous chambers in comparison to other laboratory species (Fig. 33.7). The slender dimensions of these chambers present challenges in vision research and drug development, particularly for intraocular dosing and procedures like aqueo- and vitreocentesis, where the risk of inadvertent lens contact is higher than in other species. The ciliary musculature is also described as either remarkably underdeveloped in mice and rats or even histologically absent in some studies, indicating that accommodation contributes less to their visual capability than in other larger species (McMenamin & Al-Shakarchi, 1989; Rodriguez-Ramos Fernandez & Dubielzig, 2013). Also differing from other larger species, some of the major ciliary processes in mice and rats are anterior in distribution, originating from the peripheral posterior iris (Smith et al., 2001). Moreover, the ciliary body lacks a distinct pars plana, resulting in an abrupt anatomic transition between the retina and the ciliary processes (Smith et al., 2001).

Despite the morphologic features that differentiate the mouse and rat from larger laboratory species, the aqueous outflow pathway in both bears important similarities to that of the NHP and human. The trabecular meshwork (TM) is comparatively similar in structure to that of NHPs and humans; and both mice and rats possess a true Schlemm's canal, the primary aqueous-collecting channel characteristic of NHPs and humans but lacking in most other laboratory species (van der Merwe & Kidson, 2014). Due to these morphologic and functional similarities, mice and rats are often used as animal models of glaucoma in investigational studies (Johnson & Tomarey, 2010).

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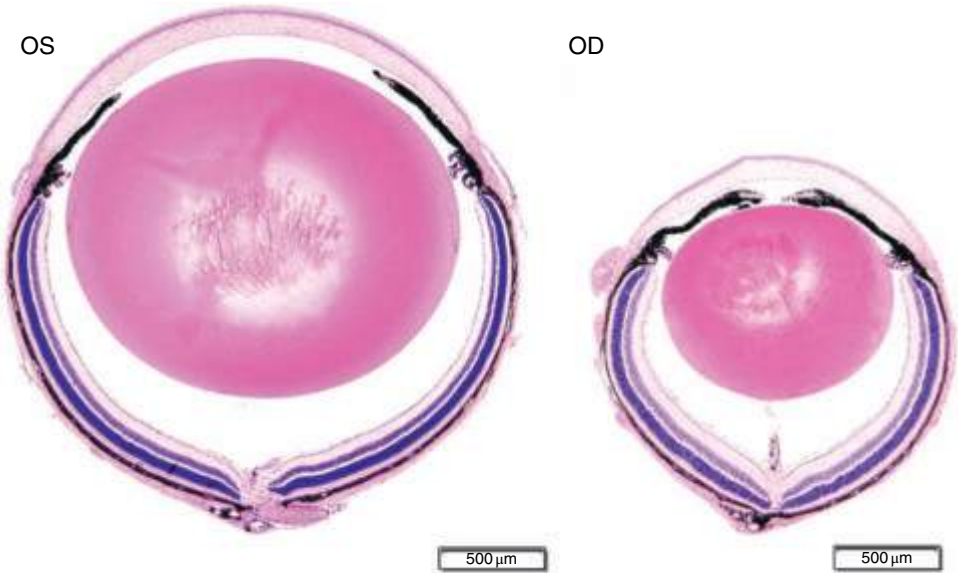


Figure 33.7 Microphthalmia and persistent hyaloid artery in the right eye (OD) of a mouse. The normal left eye (OS) is provided for comparison. Note the anterior–posterior diameter of the normal mouse lens and correspondingly narrow anterior and vitreous chambers. (Courtesy of Leandro Teixeira, DVM, DACVP, COPLOW, University of Wisconsin–Madison.)

Mice and rats lack a tapetum lucidum. Both species have holangiotic retinas, with retinal venules and arterioles (typically 5–6 of each) oriented in a spoke-like pattern, radiating from a small, nonmyelinated optic disk (Kern, 1997; McLenachan et al., 2015). Central retinal thickness is approximately 189–230 µm for mice and 200 µm for rats (Buttery et al., 1991; Ferguson et al., 2013; Mohan et al., 2012; Zhou et al., 2008). However, mice do not possess a visual streak, area centralis, or analogous structure (Smith et al., 2001). The same has been reported historically for rats based upon regional retinal thickness or using methods such as retinal ganglion cell (RGC) count (Buttery et al., 1991; Danias et al., 2002). However, more recent immunohistochemical investigation has demonstrated a dense distribution of RGCs in the dorsal retina, strongly suggestive of a structure at least analogous to a visual streak (Salinas-Navarro et al., 2009).

In both mice and rat, axons of the RGCs form the optic nerve and, before exiting the globe, traverse a lamina cribrosa, similar in structure to that of NHPs and humans (Morrison et al., 1995). Additionally, the mouse optic nerve bears some features that resemble those of NHPs and humans, such as a central retinal artery that branches to form the retinal arterioles (Smith et al., 2001). These features further underscore the relevance and possible translatability of rodent models of the glaucomas to those of the human condition (John et al., 1998).

Spontaneous Lesions and Diseases

In mice and rats, spontaneous ocular lesions may be observed with considerable frequency, particularly in certain strains. Even though most of these lesions are incidental, some can impede examination of the eye and significantly complicate identification and interpretation of findings in toxicologic and drug safety studies. Therefore, the examining veterinarian must be familiar with their clinical appearances in order to appropriately interpret their significance in a toxicologic study and, if necessary, exclude them.

Congenital/Developmental Anomalies

Microphthalmos and anophthalmos have been reported in both mice and rats. Though microphthalmos is rare in most strains, the inbred pigmented C57BL/6J mouse carries a higher relative risk, with a reported incidence of up to 12% (Smith et al., 1994). Furthermore, one study has reported that microphthalmos affects female mice 6.2 times more often than males and, interestingly, affects the right eye 5.8 times more often than the left (Tyan, 1992), though the reason for both predispositions is unclear. Microphthalmos has also been reported to predominantly affect female Fischer 344 rats (Lee, 1989). Breeding studies in the rat provide evidence for an autosomal recessive inheritance pattern with variable expressivity (Kinney et al., 1982; Rao & Seserikan, 1992). However, microphthalmos has also been experimentally induced by exposure to certain toxins (Cook et al., 1987; Szabo, 1989) and has also been reported in association with environmental and nutritional factors such as hypoxia, breeding practices, irradiation, toxins, maternal hyperthermia, maternal hypo- or hypervitaminosis A, and niacin or zinc deficiency (Chamberlain & Nelson, 1963; Dickman et al., 1997; Germain et al., 1985; Hurley et al., 1971; Padmanabhan et al., 1981; Pierro & Spiggle, 1969; Shirai, 1978; Strömland et al., 1991; Tyan, 1992).

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Clinically, microphthalmos presents as an abnormally small globe (see Fig. 33.7), unilaterally or bilaterally, often with concurrent anomalies such as engorged or tortuous episcleral and/or iridal vessels, microcornea, corneal opacities, anterior segment dysgenesis, cataract and/or microphakia, retinal dysplasia and detachment, and colobomas (both anterior and/or posterior; Cook, 1991; Williams, 2012). The associated palpebral fissure will be proportionally reduced in size (Cook, 1991). In affected eyes, the small size of the globe may predispose to chronic conjunctivitis and ocular discharge, which may be exacerbated by poor tear production and lack of a functional nasolacrimal system (Cook, 1991; Smith et al., 1994; Sundberg et al., 1991). As with other species, true microphthalmos must be differentiated from acquired phthisis bulbi.

The pathogenesis of microphthalmos in rodents may result from multiple embryologic deficiencies such as insufficiency of the hyaloid artery (Browman & Ramsey, 1943); deficient interaction and induction between the lens vesicle and surface ectoderm (Cook & Sulik, 1986); abnormal lens differentiation (Kobayashi & Otani, 1981); or incomplete closure of the optic fissure associated with colobomatous lesions (Robinson et al., 1993). Colobomatous microphthalmos has been reported in Sprague-Dawley rats with retinal degeneration, as well as other ocular defects such as retinal dysplasia, optic nerve hypoplasia and/or aplasia, and medullation of the retinal nerve fiber layer (Wyse & Hollenberg, 1977).

Anophthalmos occurs with less frequency and is nearly impossible to diagnose without histologically confirming lack of any distinguishable ocular structures (Shibuya et al., 2000). Further complicating diagnosis, spontaneous resorption of a microphthalmic remnant may occur in some affected animals, mimicking the anophthalmia phenotype (Kinney et al., 1982). There are reports of anophthalmia in certain rat strains including a mutant CFY strain and an F344-derived strain (Rao & Sesikeran, 1992; Shibuya et al., 2000); the latter was associated with lack of detectable ocular structures and histologic evidence of sphenoid bone dysplasia and optic canal stenosis, despite the presence of grossly normal harderian and lacrimal glands.

Congenital anomalies of the optic nerve have also been described in mice and rats, but may be difficult to identify ophthalmoscopically unless associated with other ocular abnormalities. Furthermore, most reports cannot identify a definitive pathogenesis. One report described unilateral or bilateral optic nerve dysplasia in male and female Sprague-Dawley rats, characterized by truncated and malformed intracranial and intraorbital optic nerve tissue, but no concurrent ocular anomalies (Shibuya et al., 1998). While a pathogenesis could not be confirmed, the features strongly suggested a relationship to insufficient meningeal blood supply to the developing optic nerve. Complete optic nerve aplasia has been reported in tandem with retinal dysplasia and hypoplasia in both F344 and Wistar rats (Shibuya et al., 1992, 1989). In both reports, however, the optic canal and foramen were structurally normal, and the globes were normal in size, arguing against stenosis or embryologic mesodermal failure. Idiopathic degenerative atrophy of the optic nerve has also been reported in young Wistar and F344 rats (Lee et al., 1990; Shibuya et al., 1993).

Spontaneous colobomas of the anterior uvea have been reported in rats, sometimes observed in association with other intraocular colobomas (e.g., optic disk) and/or microphthalmos (Taradach et al., 1984). Corectopia involving the ventral iris, suggestive of a typical coloboma, has also been described in young mice (Rubin & Daly, 1982). Iridal colobomas must be differentiated from a posterior synechia, since the two lesions bear a similar appearance, and the clinical significance of each may differ in the context of a toxicologic study. Optic disk colobomas have been reported with low incidence in rats (Hubert et al., 1994; Matsui & Kuno, 1987; Taradach et al., 1981). In one study, electron microscopy demonstrated concurrent vascular malformations associated with serous retinal and retinal pigment epithelial (RPE) detachment (Ninomiya et al., 2005), but a definitive pathogenesis has not been determined. Ophthalmoscopic diagnosis of optic disk colobomas in mice and rats may be complicated by the disk's normally small and cupped appearance and lack of myelin.

Conjunctivitis

Conjunctivitis may be observed in mice or rats. In both species, clinical signs are generally nonspecific, including serous to mucoid/mucopurulent ocular discharge, conjunctival hyperemia, chemosis, blepharospasm, and chromodacryorrhea. In laboratory rodents, primary conjunctivitis is most commonly of infectious etiology. Numerous bacterial organisms have been implicated in naturally occurring conjunctivitis in mice and rats, including *Mycoplasma* spp., *Pseudomonas aeruginosa*, *Salmonella* spp., *Pasteurella* spp., *Streptobacillus moniliformis*, *Staphylococcus aureus*, and *Corynebacterium kutscheri* (Beaumont, 2002; Glastonbury et al., 1996; Hill, 1974; Kern, 1997; Needham & Cooper, 1975; Roberts & Gregory, 1980). Viral agents have also been implicated, including lymphocytic choriomeningitis virus (LCV), ectromelia virus (the causative agent of mousepox, which primarily causes dermatologic disease), and Sendai virus (Beaumont, 2002). Regardless of whether the primary conjunctivitis is viral or bacterial, clinical disease is particularly common and typically more severe in younger mice and rats (Williams, 2007).

Despite the prevalence of primary infectious causes, conjunctivitis may also be secondary in mice and rats. Prior to pursuing a diagnosis of primary infectious conjunctivitis, any potentially causative nutrition- or husbandry-associated factors should be identified. Though carrying minimal risk in animals receiving a commercial diet, noninfectious

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keratoconjunctivitis has been reported in association with nutritional deficiency of vitamin A (Kern, 1997). Husbandry-related risk factors such as local irritation from coarse bedding, insufficient ventilation, or ventilation that disperses fine bedding particulates can also cause conjunctivitis and can even predispose to secondary conjunctival infection (Griffin et al., 1995; Young & Hill, 1974). Conjunctivitis in either species may also be secondary to adjacent inflammatory or infectious disease involving the respiratory tract. A complete ophthalmic examination should always be performed to rule out predisposing conditions or other concurrent ocular disease (e.g., corneal ulceration, uveitis).

Chromodacryorrhea

Chromodacryorrhea is a unique finding in mice and rats that develop due to excess secretion of harderian gland porphyrins onto the ocular surface. Clinically, this is characterized by red to red-orange discoloration and staining around the eye or eyes (Sakai, 1981; Williams, 2012). The porphyrin pigments are also autofluorescent, which can be used to differentiate chromodacryorrhea from hemorrhage (Seely, 1987). Porphyrin pigment can also be observed on the feet of affected animals as a result of grooming behavior. Chromodacryorrhea most commonly develops in association with primary ocular diseases such as sialodacryoadenitis virus (SDAV) or ocular mycoplasmosis, but can also be observed in association with general nutritional deficiency or environmental stressors such as transport and rehousing (Djeridane, 1994; Williams, 2002). Other causes include dental disease associated with insufficient husbandry practices leading to secondary nasolacrimal duct obstruction (Kern, 1997; Wagner & Farrar, 1987). Since excessive parasympathetic stimulation of the harderian gland is one the physiologic factors associated with chromodacryorrhea, systemic administration of a parasympatholytic agent like atropine has been shown to mitigate clinical severity in an experimental model (Harkness & Ridgway, 1980).

Corneal Opacities

Corneal opacities in rodents may be categorized as traumatic, iatrogenic, toxic, infectious, or heritable (e.g., corneal dystrophy). Since most mice and rats are group housed, corneal opacities/scars related to trauma are common, and may present with or without concurrent uveitis and/or intraocular findings (e.g., hyphema, fibrin, dyscoria, synechia; Taradach et al., 1981). Studies have also demonstrated associations between anesthesia and corneal opacification in both species. In one study, nonreversible corneal opacities were observed in adult rats following even brief periods of general anesthesia (< 25 minutes) induced by injectable anesthetics, particularly ketamine and xylazine (Turner & Albassam, 2005). In some animals, opacities were observed within 18 hours of the anesthetic event. The contributory role of the anesthetic, particularly xylazine, was supported by the fact that lesion severity was comparatively reduced in animals receiving yohimbine reversal following anesthesia. Additionally, this study demonstrated strain-related predisposition, with higher incidence in Wistar, Long-Evans, and F344 rats in comparison to Sprague-Dawley and Lewis rats. A subsequent study described a similar association between ketamine–xylazine anesthesia and subepithelial calcific band keratopathy in mice (Koehn et al., 2015). The pathogenesis of these corneal opacities in either species is not well understood, but hypotheses implicate corneal temperature fluctuations during anesthesia, as well as constriction of iridal and ciliary vessels, resulting in local hypoxia of the anterior segment.

Other causes for keratitis and corneal opacity in mice and rats include frequent administration of topical agents like proparacaine or tropicamide that contain preservatives such as benzalkonium chloride (Lin et al., 2011). Multifocal corneal opacities yielding a stippled, "orange-peel" appearance have been described in association with keratoconjunctivitis secondary to SDAV in rats (Taradach et al., 1981). While rare, lesions such as epithelial inclusion cysts, dermoids, and ocular surface neoplasia have also been reported in rats (Williams, 2002). Corneal opacification with keratitis (ulcerative or nonulcerative) may also be associated with exposure in either species, caused by space-occupying orbital disease, buphthalmos, and even routine blood sampling from the orbital venous sinus.

Corneal Dystrophy

Corneal dystrophy (CD) is a common, bilateral, opacifying disease in mice and rats with a putatively heritable cause and no association with underlying systemic disease. Given the often high incidence of corneal dystrophic lesions in some rodent strains, particularly rats, they may risk confounding both examination and interpretation of ophthalmic findings in preclinical toxicology and drug safety studies (Gillet et al., 1995). Therefore, the examiner must be aware of their respective appearances.

In general, CD is more common in rats than in mice (Wegener & Jochims, 1994). In rats, the incidence of CD is variable, depending primarily on the age, sex, and strain of the animal. Incidence in both mice and rats increases with age (Taradach et al., 1984). CD typically presents as fine or punctate, granular, translucent-to-opaque white corneal opacities in the anterior subepithelial corneal stroma, often observed in the nasal and/or axial cornea (Wilkie, 2014; see Fig. 33.8). However, lesion appearance and distribution, and incidence, will vary in different strains.

In the Sprague-Dawley rat, CD is more common in males, particularly in young animals, with an incidence of between 20% and 50% (Wilkie, 2014). In this strain, most CD lesions are mild, with a characteristic subepithelial granular or

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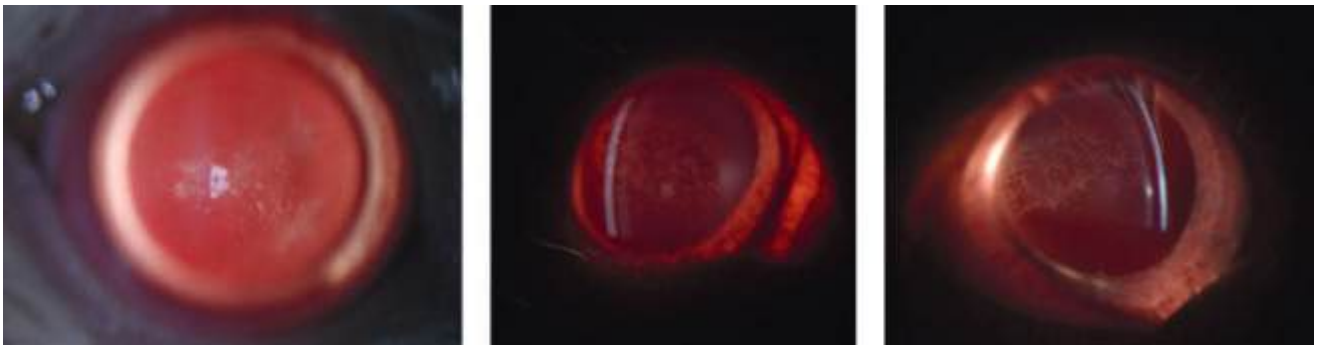


Figure 33.8 Corneal dystrophy in Sprague-Dawley rats. (Courtesy of Paul Miller, DVM, DACVO, University of Wisconsin–Madison; and Hugh Wabers, BS, Ocular Services On Demand (OSOD).)

crystalline appearance corresponding to extracellular calcium and/or phosphorus, typically in the central cornea (Wilkie, 2014). In the Wistar rat, CD has been reported to affect > 65% of animals (Eiben, 2001; Hashimoto et al., 2013; Wilkie, 2014; Wojcinski et al., 1999), characterized by larger, often linear, and more opaque lesions than in the Sprague-Dawley. Histologically, CD opacities in the Wistar are localized to the epithelial basement membrane. It is also noteworthy that CD lesions in both the Sprague-Dawley and Wistar rats may span the entire thickness of the epithelial basement membrane and involve the basal corneal epithelial cells (Bellhorn et al., 1988).

In the F344 rat, CD is remarkably common, with some references indicating an incidence of up to 100% (Wilkie, 2014), observed even in animals as young as 10 weeks of age (Bruner et al., 1992). Prior reports citing lower incidence in this strain may not have involved examinations with slit-lamp biomicroscopy, and therefore decreased sensitivity for lesion identification. In comparison to CD lesions in the Sprague-Dawley, those in the F344 are larger and more numerous, typically distributed linearly across the axial cornea. Furthermore, these lesions tend to increase in severity as an animal ages; and while they are not commonly associated with clinical inflammation or discomfort early in life, secondary keratitis (ulcerative and nonulcerative) will often develop in older animals (Losco & Troup, 1988). Histologically, lesions in the F344 rat are associated with a thickened epithelial basement membrane with or without overlying epithelial changes (e.g., epithelial blebs, loss, or erosion/ulceration). Interestingly, evaluation of other organ systems in affected rats has also shown basement membrane disease in other organs, such as the renal tubules and gastric basement membranes (Bruner et al., 1992).

The difference in incidence in CD between different rat strains supports its putative primary heritable cause. However, there are environmental and husbandry-related factors that can influence the appearance and presentation of these lesions (Williams, 2007). In particular, iatrogenic factors such as general anesthesia and orbital bleeding can worsen the appearance of CD lesions (Fabian et al., 1967; Wilkie, 2014). Other factors that can worsen CD lesions in rats include excessive ventilation (with subsequent ocular surface desiccation) and poor bedding care, leading to ocular irritation secondary to locally high ammonia concentrations (Van Winkle & Balk, 1986).

CD in mice has a similar appearance to the condition in rats, typically presenting as ovoid and/or polygonal opacifying lesions in the central/paracentral anterior corneal stroma, with increasing incidence in older animals (Taradach et al., 1984). As with rats, the cause is largely believed to be heritable predisposition. However, one report cited a suspected association between CD-like corneal lesions and hypercalcemia (Hoffman et al., 1983). Subepithelial corneal mineralization has also been described in severe combined immunodeficiency (SCID) mice, in tandem with cardiac mineralization (Meador et al., 1992).

Sialodacryoadenitis Virus

SDAV is a coronavirus that naturally infects the orbital, lacrimal, and salivary glands of the rat, and can also cause upper respiratory tract disease (Hanna et al., 1984). Though clinical infection is of low mortality and typically self-limiting, it is associated with high morbidity and clinical disease that can persist for up to 4 weeks. The infection is highly contagious and is spread via direct contact between animals, aerosolization, or via fomites (e.g., bedding; Innes & Stanton, 1961).

Disease associated with SDAV is only rarely observed in its acute form, and is more commonly recognized in a milder subacute or chronic stage, or not recognized at all (Bhatt & Jacoby, 1985; Eisenbrandt et al., 1982). It is this unrecognized subclinical "carrier" state that risks inadvertent introduction of infected animals into otherwise pathogen-free colonies. Therefore, new rats are best introduced to a colony only after screening and observation and/or serologic testing (Gannon & Carthew, 1980). The total reported serologic positivity for SDAV is 0.29% (Gannon & Carthew, 1980; Pritchett-Corning et al., 2009).

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In affected rats, ocular disease often precedes involvement of the salivary glands. Acute ocular disease is characterized by conjunctivitis or keratoconjunctivitis, often associated with periorbital swelling and exophthalmos, and chromodacryorrhea resulting from swelling and inflammation of the harderian and lacrimal glands (Percy et al., 1989). Other clinical manifestations may include blepharospasm, photophobia, and self-trauma, which may exacerbate the other features of the disease (Carthew & Slinger, 1981; Innes & Stanton, 1961; Lai et al., 1976; Williams, 2002). Though uncommon, intraocular disease including uveitis, cataract, glaucoma, and retinal degeneration has been reported in severe cases (Kern, 1989). Infections that are more subacute or chronic/enzootic may not present any of the above features, and instead be characterized by persistent keratoconjunctivitis putatively associated with quantitative and/or qualitative tear deficiency (Weisbroth & Peress, 1977).

In laboratory rat strains, SDAV is the most common naturally occurring cause of space-occupying orbital disease and exophthalmos. It is noteworthy, however, that similar clinical signs may be observed due to retrobulbar abscess, most commonly associated with dental disease. Furthermore, harderian gland inflammation and swelling as a consequence of orbital venous blood collection may also produce exophthalmos and similar signs (McGee & Maronpot, 1979). If SDAV-associated orbital disease is suspected in a laboratory animal, culling from the colony is indicated and histopathology with coronaviral polymerase chain reaction (PCR) and/or serology recommended to confirm the diagnosis (Homberger et al., 1991). Histologically, SDAV-associated disease is characterized by acute or chronic harderian and lacrimal adenitis (e.g., interstitial edema and neutrophilic infiltration, gland necrosis, and eventual gland fibrosis), as well as squamous metaplasia of the lacrimal duct epithelium (Doi et al., 1980; Jacoby et al., 1975), features that aid differentiation from other sources of disease affecting the orbital glands.

While any rat can be infected with SDAV, exogenous or environmental factors may influence susceptibility, nature and severity of clinical signs, and course of disease. For example, rehousing of animals and/or poor husbandry practices are reported to predispose some animals to acute infection and protracted periods of shedding (Williams, 2002). Furthermore, strain has been reported to influence the clinical severity and manifestation of disease (Bhatt & Jacoby, 1985; Carthew & Slinger, 1981; Percy et al., 1984). The immune status of infected animals may also influence the severity and course of disease. While immunosuppressed or immune-compromised rats may develop disease with comparatively longer duration and shed SDAV more persistently, their clinical signs are considerably less severe, suggesting that the effects of both acute and chronic infection may be largely immunopathologic (Hanna et al., 1984).

To date, there are no reports that definitively link SDAV to ocular or respiratory disease in mice. Infectious dacryoadenitis has only been reported in mice in association with the bacteria *Pasteruella pneumotropica* (Kern, 1997).

Anterior Uvea

Lesions of the anterior uvea are less common in rodents. Persistent pupillary membranes (PPMs) have been described in both species (Beaumont, 2002; Saari, 1975; Taradach et al., 1984; Young et al., 1974), and may rarely be associated with glaucoma or hyphema (Saari, 1975; Young et al., 1974). Incidence is variable, with one study reporting a 1% incidence of PPMs in Sprague-Dawley rats and another describing unilateral or bilateral PPMs in 50% (15/30) of a colony of Wistar rats (Chacaltana et al., 2017; Heywood, 1973). As the latter study was conducted in rats from a closed colony, the high incidence of PPMs is strongly suggestive of a heritable etiology.

Uveitis is clinically described but uncommon in mice and rats (Taradach et al., 1984). Clinical signs are similar to those of other species including blepharospasm and/or photophobia, miosis, aqueous flare and cells, hyphema, and hypopyon. In accordance with other species, uveitis in the rodent can result from an endogenous systemic inflammatory or infectious disease, as well as external trauma. A challenge in rodents, however, is the clinical differentiation of hyphema associated with uveitis from noninflammatory hemorrhage associated with vascular leakage from persistent hyaloid vasculature or patent remnants of the tunica vasculosa lentis (see "Vitreous"). Synechiae are also common sequelae to active or chronic uveitis, and must be clinically distinguished from iridal colobomas (Taradach et al., 1984).

Glaucoma

Naturally occurring glaucomas have been reported in mice and rats. Clinical descriptions of sporadic primary congenital glaucoma have been reported in F344 and Wistar rats (Heywood, 1975; Shibuya et al., 2001). Heritable glaucoma has also been reported in a subset of Royal College of Surgeons (RCS) rats, affecting both males and females (Naskar & Thanos, 2006; Thanos & Naskar, 2004). In affected animals, intraocular pressure (IOP) gradually increases during the first 12–18 months of life, with clinical signs of progressive unilateral or bilateral buphthalmos and optic disk cupping, with eventual RGC loss. Another report in a rat described a form of primary glaucoma attributed to obstruction of the iridocorneal angle by PPMs and peripheral anterior synechiae (Young et al., 1974). The DBA/2J mouse, a strain commonly used in vision science, is predisposed to spontaneous hypertensive glaucoma that develops secondary to pigment dispersion, and therefore may be a model for pigmentary glaucoma in humans (McKinnon et al., 2009).

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Clinically, signs of glaucoma in rodents may be difficult to recognize as signs like episcleral congestion, corneal edema, mydriasis, or behavioral changes indicating vision deficits may not be as prominent as in other species. In the laboratory setting, buphthalmos is often the first sign observed, frequently developing with little delay in the face of elevated IOP due to the rodent's comparatively thin sclera.

Cataract

Among laboratory species, the mouse is one of the most commonly used models for human inherited cataract, with early- and late-onset cataracts described in association with numerous mutations, representing varying modes of genetic inheritance (Graw, 1999; Tripathi et al., 1991; Wolf et al., 2005; Zhang et al., 2017; Zigler, 1990). The slightly larger eye of the rat is also a viable animal model for cataract development, particularly for age-related cataractogenesis given the rat's comparatively longer lifespan (Balazs et al., 1970; Taradach et al., 1984). Even in nonpredisposed rodent strains like those commonly used in toxicology and drug development, spontaneous lens opacities are frequently observed as background findings. Therefore, an understanding of the causes, features, and clinical appearances of spontaneous cataracts in rodents is a critical aspect of ocular assessment in preclinical drug safety studies, as naturally occurring opacities must be differentiated from those induced by the test articles or material platforms being studied.

Large studies in pigmented and albino laboratory mice have reported lens opacities in 10%–13% of young animals, both males and females (Hubert et al., 1999; Taradach et al., 1984). Incidence generally increases with age, with one study reporting a 20% incidence in 18-month-old mice, and another citing histologic evidence of cataract in approximately 40% in 25–30-month-old mice (Taradach et al., 1984; Tucker & Baker, 1967). Opacities are typically very small, precluding them from being observed grossly (without biomicroscopy), and may be uni- or bilateral. Spontaneous opacities most commonly involve the anterior cortex, anterior suture lines, and/or subcapsular region and variably involve the anterior capsule. Nuclear opacities, typically bilateral and presumably congenital, are also reported. Posterior opacities are less common and, when present, are commonly associated with persistent hyaloid remnants in the axial anterior vitreous in younger mice (Hubert et al., 1999). In older animals, cortical/equatorial vacuoles and mature cataracts may also be sporadically observed (Tucker & Baker, 1967). Cataracts in mice may also be observed in association with other ocular anomalies such as microphthalmia and anterior segment dysgenesis, or secondary to uveitis (Kern, 1997).

Spontaneous cataracts are also observed in rats, often as presumed congenital lesions, or in association with advancing age (Balazs & Rubin, 1971; Durand et al., 2001; Hartman, 1968; Tripathi et al., 1991). Some spontaneous lens opacities in rats have characteristic clinical appearances such as the arcuate lens opacities of the Sherman rat and anterior cortical striations observed in the Sprague-Dawley (Balazs & Rubin, 1971; Balazs et al., 1970; Heywood, 1973). Incidence of lens opacities commonly increases with age, with one study reporting an 11% incidence of spontaneous cataract in rats over 24 months of age (Taradach et al., 1984). Other spontaneous age-related opacities have been reported in the Sprague-Dawley strain, including anterior suture vacuoles, refractile opacities, nuclear cataracts, and, though uncommon, spontaneous complete cataracts (Balazs et al., 1970; Heywood, 1973; Hubert et al., 1994; Taradach et al., 1981, 1984). An identifiable zone of optical discontinuity between the lens cortex and the nucleus has also been described in older Sprague-Dawley rats and may be analogous to nuclear sclerosis (Taradach et al., 1984).

Spontaneous cataracts in rats may be observed in association with other ocular conditions. As observed in the mouse, opacities involving the posterior capsule and/or cortex in rats are commonly associated with hyaloid remnants (Taradach et al., 1981). In the RCS rat, cataracts commonly develop in association with heritable retinal degeneration (Al-Ghoul & Kuszak, 1999; Zigler & Hess, 1985). Spontaneous nuclear cataracts have been reported in young, spontaneously hypertensive Sprague-Dawley rats (Koch et al., 1977). In the Wistar-derived Alderley Park rat, an unusual bilateral equatorial cataract has been described, affecting 4% of males and 14% of females by 2 years of age. Interestingly, similar opacities were not observed in gonadectomized male or female rats of the same strain; the authors therefore proposed a possible role of higher circulating estrogen levels in the pathogenesis of these opacities (Lazenby et al., 1993). A wealth of experimental evidence in humans and animal models, however, conversely suggests a protective role of estrogens in age-related cataractogenesis (Zetterberg & Celojevic, 2015). The reason for this discrepancy is not understood, but in the context of general toxicology investigations in rodents, the possible influence of estrogen should be kept in mind when performing and interpreting examinations in animals treated with drugs that can alter sex hormone status.

Iatrogenic transient lens opacities in rodents have been described in association with prolonged eyelid separation while under anesthesia, putatively a result of changes in the osmotic environment and/or temperature in the AC (Kern, 1989). Xylazine has also been implicated as an agent carrying the potential to induce reversible cataracts, even at published doses, in both mice and rats (Calderone et al., 1986). Cataracts are also observed in rats fed diets containing high levels of galactose (Kador et al., 2007; Lim et al., 2017).

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Vitreous

Persistence of the hyaloid vasculature is a common spontaneous finding in both mice and rats, typically visible on examination as a white filamentous structure spanning the axial vitreous. This finding is most common among weanling rodents, often regressing as animals age until it is negligible or no longer visible shortly after sexual maturity (Kern, 1989; Taradach et al., 1984; Wilkie, 2014). The incidence of this finding in Sprague-Dawley rats can be as high as 50%–60% at 6 weeks of age (Poulsom & Marshall, 1985; Taradach et al., 1984). A persistent hyaloid remnant may be partial and isolated to only the axial vitreous and/or optic disk (Fig. 33.9), or it can be complete with attachment to the axial posterior lens capsule. In some reports, this anomaly has been reported in association with apparent papilledema (Parr, 1976; Taradach et al., 1984). In most cases, a patent hyaloid remnant is benign, with no structural or functional consequence for the eye. When patent, however, it can be associated with vitreous hemorrhage (Taradach et al., 1984).

Persistent hyaloid remnants are presumed to be heritable, though a mode of inheritance has not been clearly demonstrated. One study reported some degree of persistent hyaloid vasculature in almost one-third of BALB/c mice examined ophthalmoscopically (Park et al., 2006). Another study reported remnants in approximately 15% of adult mice up to 25 weeks of age using posterior segment angiography. Furthermore, this study also identified anastomoses between the remnants and the retinal vasculature in some animals (McLenachan et al., 2015). Ultimately, these findings underscore the likelihood that many of these remnants may go unnoticed on routine ophthalmoscopic examination.

Retina

The retinal arterioles and venules of the mouse and rat follow a very straight course, branching minimally as they travel from the optic disk to the peripheral fundus. This can facilitate identification of vascular anomalies such as preretinal loops, which have been reported in up to 12% of Sprague-Dawley rats (Hubert et al., 1994; Matsui & Kuno, 1987). Other vascular lesions include spontaneous saccular aneurysms of the retinal vessels, observed sporadically in older mice and rats (Bellhorn, 1973; Heywood, 1973).

As described in other species, transient peripheral retinal folds have been observed in the young mouse, presumptively caused by discrepancy in relative growth rate between the neuroretina and the other ocular tunics (Hubert et al., 1999). Nontransitional retinal folds consistent with retinal dysplasia have been described and histologically characterized in adult rats from several strains, including the Sprague-Dawley, RCS, Long-Evans, and Wistar-derived WAG rats (Kuno et al., 1991; Lai & Rana, 1985; Poulsom & Hayes, 1988). The histologic classifications of these lesions, described in one report as "A-form" and "T-form," may actually represent a spectrum of disease rather than two distinct lesion categories (Lai & Rana, 1985). A-form lesions are characterized by minor infolding of the retina, with focal photoreceptor (PR) detachment from the underlying RPE (Fig. 33.10). The more severe T-form is associated with an expanded "fungiform" space within the retinal fold, as well as shortening of the PR inner and outer segments and distortion of the PR disk membranes (Lai & Rana, 1985). There also appear to be strain-related differences in the characteristics of these lesions. In the Sprague-Dawley, for example, folds are more common peripherally and increase in number with age. Conversely, these folds typically localize to the posterior retinal zone and decrease in number with advancing age in WAG rats. Another report described retinal folds in the Sheffield-Wistar rat that bear some histologic features resembling the A-form lesions just described. In this strain, however, which is also predisposed to cataract and microphthalmos, lesion severity differed. Milder lesions involved only the inner layers and a small detachment of the retina, as well as rosettes, phagocytic cells, and lipid debris. More

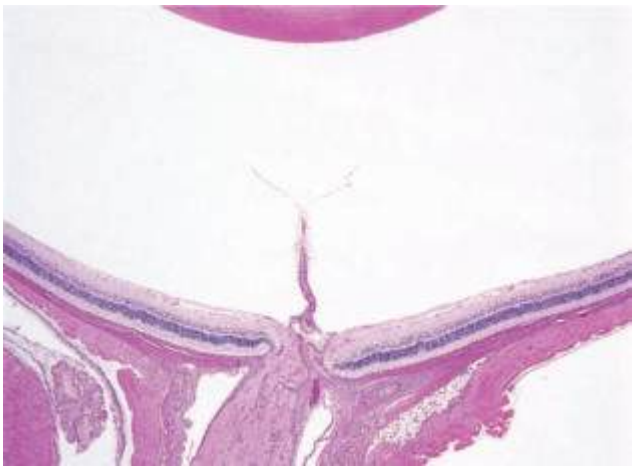


Figure 33.9 Persistent hyaloid artery in a rat. (Courtesy of Leandro Teixeira, DVM, DACVP, COPLOW, University of Wisconsin–Madison.)

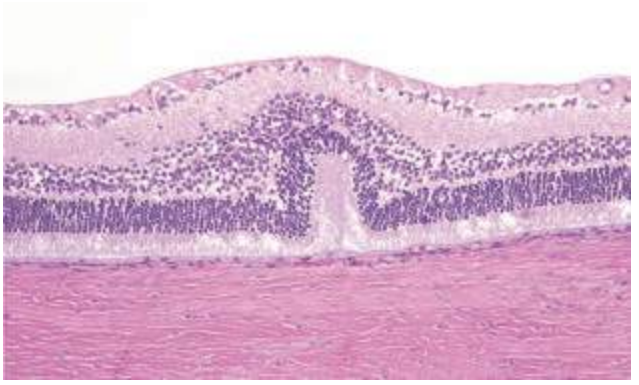


Figure 33.10 Focal retinal fold in a rat. (Courtesy of Leandro Teixeira, DVM, DACVP, COPLOW, University of Wisconsin–Madison.)

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severe lesions involved all retinal layers and were associated with subretinal hemorrhage and outer segment debris, with similar debris on the adjacent vitreal surface (Poulsom & Hayes, 1988). The functional significance of these lesions is unknown, and while most investigators propose a heritable etiology, some have suggested that they may represent reattachment of a previously detached retina (Heywood, 1976).

Linear retinopathy is a spontaneous degenerative retinal abnormality unique to the rat. Described in the Sprague-Dawley and other albino strains like the Wistar, lesions are typically observed unilaterally and are often described as single or multiple, well-demarcated pale linear "streaks" of the ocular fundus. Lesions are commonly observed in young animals and increase in incidence from 0.3% in weanlings to approximately 3% in animals 14 weeks old (Hubert et al., 1994; Roman et al., 2016). Histologically, these pale streaks correlate with areas of retinal thinning, primarily loss of the retinal outer layers, as well as localized lack of underlying choroidal vasculature (Schafer & Render, 2012). Some references refer to this condition as retinochoroidal degeneration/atrophy or label it retinal dystrophy. The heritability, pathogenesis, and clinical significance of linear retinopathy, however, are not known.

Retinal degeneration is well characterized in mice and rats, categorized as hereditary, senile (age related), phototoxic, or postinflammatory. In the mouse, there are numerous forms of hereditary retinal degeneration (Chang et al., 2002). Perhaps the most well-characterized form, and the one that commonly serves as a phenotypic model for human retinitis pigmentosa, is the form associated with the *rd* mutation, also known as *rd1* or *Pde6brd1* (Keeler, 1970). The *rd* mutation is associated with reduced activity of the beta subunit of cGMP-phosphodiesterase (PDE) within rod PRs, leading to toxic accumulation of cGMP. Retinal degeneration associated with the *rd* mutation is early onset and bears an autosomal recessive pattern of heritability. Due to its progressive nature, affected animals are often functionally blind at a young age, and bear funduscopic abnormalities such as generalized retinal pallor, retinal vascular attenuation, and pigmentary changes in pigmented strains (Hawes et al., 1999; Taradach et al., 1984). Since the characterization of the *rd* mutation, numerous related mutations have been discovered, each varying in the mechanism, onset, and progression of the retinal degeneration it causes (Chang et al., 2002). Mutations may result in early-onset "fast" forms of retinal degeneration or "slower" mutations resulting in disease with later onset and more gradual progression.

In the rat, perhaps the best-characterized model of hereditary retinal degeneration is the autosomal recessive form in the RCS strain. This form of retinal degeneration results from a deficiency in the RPE's ability to routinely phagocytose rod outer segments after they are shed from PRs. This form is early onset, beginning within the first few weeks of life. Furthermore, it is commonly associated with progressive lens opacities as well as progressive atrophy of the ciliary pars plicata (Bourne et al., 1938; Yamaguchi et al., 1991; Zigler & Hess, 1985). Ophthalmoscopically, features of RCS retinal degeneration include generalized fundus pallor and progressive retinal vascular attenuation (Taradach et al., 1984). The clinical course and severity of this form of retinal degeneration can be exacerbated by environmental and husbandry-related factors such as excessive light exposure (LaVail & Battelle, 1975). Furthermore, studies have suggested that, like some forms of retinal degeneration in other species, immunopathology may play a considerable role in both the initiation and the progression of disease in affected animals (Chant & Meyers-Elliott, 1982).

Senile or age-related retinal degeneration putatively exists in mice and rats. One study has described a focal to diffuse outer retinal degeneration disease in approximately 4% of adult Sprague-Dawley rats, with a higher prevalence in females (Schardein et al., 1975). A similar form has been reported to affect as many as 10% of older Wistar rats (Lin & Essner, 1988; Tucker, 1997). A slowly progressive outer retinal degeneration has also been described in the F344 rat (DiLoreto et al., 1994a, 1995; Lai et al., 1978). Subtle retinal changes are observed in young F344 rats, with progression occurring slowly throughout the animal's lifespan. Additionally, males and females exhibit different courses of disease, with the male developing a more rapid peripheral degeneration after 12 months of age, and females demonstrating a more progressive degeneration after 18 months of age. Age-related cystoid degeneration has also been observed in some rats, with a prevalence for males (DiLoreto et al., 1994a).

Any veterinary practitioner working with laboratory mice and rats must be aware of the possibility of light-induced phototoxic effects on the retina, as these can not only pose a welfare concern in the laboratory setting, but can also complicate interpretation in toxicologic studies. Furthermore, the prominence of phototoxic retinopathy in some strains has complicated the determination of the true background incidence of senile retinal degeneration in rodent populations. Phototoxic retinopathy was originally described in pigmented and albino rats exposed to 24 hours of continuous fluorescent lighting, and has subsequently been described in both mice and rats (Noell et al., 1966; Fig. 33.11). Phototoxic retinopathy is principally mediated by activation of rhodopsin, which can induce degeneration via two mechanisms. The first occurs after brief exposure (< 48 hours) to high-intensity light, and the second occurs after long-term exposure to low-intensity but continuous illumination (Penn et al., 1985). The former leads to damage to the PRs and RPE, resulting in damage and subsequent apoptosis, whereas the latter only induces degenerative changes to the PRs (Malik et al., 1986). Electroretinographic changes may be observed as early as one day following prolonged light exposure, whereas ophthalmoscopic findings such as retinal vessel

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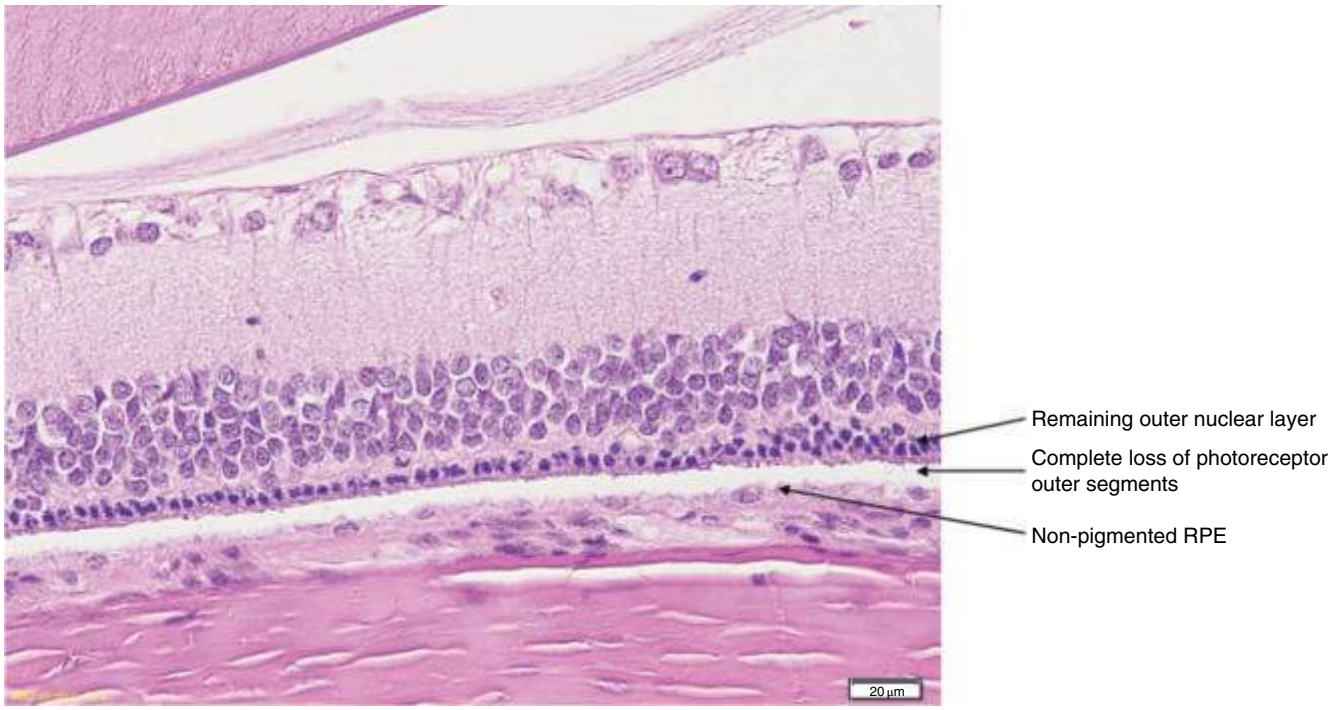


Figure 33.11 Retinal degeneration secondary to excessive light exposure in a rat. Note the considerable loss of outer retinal structures, including the photoreceptors and outer nuclear layer. (Courtesy of Leandro Teixeira, DVM, DACVP, COPLOW, University of Wisconsin–Madison.)

attenuation and fundus pallor will be delayed, typically observed 7 days following exposure. Even under what would be considered standard vivarium lighting conditions, over 10% of 2-year-old rats have been shown to have retinal lesions consistent with phototoxicity (Williams, 2002).

The mechanistic link between rhodopsin activation and eventual apoptosis, however, is not well understood. Some theories propose an association with production of a toxic agent from vitamin A or another toxic metabolic byproduct, while others propose the generation of damaging oxidative reactions at the level of the retina and RPE (Gordon et al., 2002; Organisciak & Vaughan, 2010). Determining a straightforward pathogenesis for phototoxic retinopathy, however, is further complicated by a number of environmental and animal-related factors that can affect its onset and progression. It is generally accepted that the intensity, duration, and quality of the light exposure will influence the subsequent damage to the retina. The age of the animal, however, also plays an important role, with younger rats (<1 month of age) being less predisposed to the toxicity than adults (Joly et al., 2006; Malik et al., 1986). A higher body temperature at the time of excessive light exposure is also shown to exacerbate the toxic effects on an individual animal (Organisciak et al., 1995). Furthermore, there may be a protective effect of ovariectomy in female rats (O'Steen, 1980), though other studies have shown a general tendency toward a higher incidence in females (De Vera Mudry et al., 2013). Strain also may influence susceptibility to phototoxic retinopathy, with one study demonstrating relative resistance in the F344 and Wistar compared to the Lewis rats (Borges et al., 1990). A greater degree of ocular pigmentation has also been shown to be protective (Rapp & Williams, 1980; Rapp et al., 1990).

Certain husbandry-related practices can be applied in the vivarium to minimize phototoxic effects on the retinas of rodents. In general, light levels approximating 325 lux at approximately 1 m above the floor surface in the center of an animal housing room are considered standard and below the threshold for inducing phototoxicity. However, this degree of illumination may still approach levels that are too high for long-term studies in albino animals (Bellhorn et al., 1980; De Vera Mudry et al., 2013). It is also noteworthy that light flux within animal housing rooms can vary, and an animal's relative position to light fixtures will influence their exposure, as will the cage material (i.e., plastic vs. metal, clear vs. opaque). Animals housed in clear plastic cages on the top row of a bank of cages will be at higher risk, but daily rotation of animal cages will mitigate the influence of cage position, and providing areas for animal shelter/retreat within housing cages will also serve to decrease light exposure (Kern, 1997). In general, cyclic room illumination (i.e., 12 hours on, 12 hours off) is also recommended, provided that light intensity is acceptable.

Postinflammatory retinal degeneration is putatively described in rats affected by SDAV-related ocular and periocular disease. However, the characteristic multifocal retinal

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lesions are often incidental findings and detectable changes in visual behavior are very rare (Kern, 1997). Multifocal chorioretinal atrophy has also been described in Sprague-Dawley rats, characterized by polygonal-to-rectangular, demarcated lesions, histologically correlated with outer retinal and RPE degeneration, also affecting the underlying choroidal vasculature (Tanaka et al., 1993). While the exact pathogenesis of these lesions is not known, they were invariably preceded clinically by multifocal petechial retinal hemorrhage, suggesting an underlying inflammatory etiology. Chorioretinal scars representing focal retinal atrophy can be observed in some rodents, even at an early age. Iatrogenic degenerative lesions of the retina have also been observed in association with orbital bleeding (Van Herck et al., 1992; Wilkie, 2014).

In mice, the most common infectious cause of retinal degeneration is LCV. Mice are the natural carrier for this potentially zoonotic arenavirus, shedding the organism in saliva, urine, and/or feces (Mims, 1966). LCM virus can also be transmitted between animals horizontally via aerosolization and direct contact, or vertically from dam to offspring. Despite many mice being carriers for LCM virus in the wild mouse population, ocular lesions are not commonly seen (Monjan et al., 1972). In a study in which newborn rats were inoculated with the virus, however, a primarily immunopathologic retinitis occurred (Monjan et al., 1972). In another study investigating the chronic consequences of experimental infection in rats, a progressive effacement of the neuroretinal tissue developed (del Cerro et al., 1982). It is proposed that acute infection and necrotizing retinitis in rats leads to liberation of previously sequestered retinal autoantigens, inciting an ongoing autoimmune attack that perpetuates damage to the retina (del Cerro et al., 1982).

Spontaneous Ocular Neoplasia

While rare, spontaneous neoplasms involving the globe and periocular/orbital structures have been reported in both mice and rats. Compared to other strains, the F344 rat appears to carry greater susceptibility. Amelanotic melanomas of the eyelids and intraocular and orbital malignant Schwannomas have been reported in the F344 (Yoshitomi & Boorman, 1991, 1993). Leiomyoma of the iris and intraocular Schwannomas of the iris, ciliary body, and choroid have also been reported in Sprague-Dawley rats (Chandra & Frith, 1993; Owen & Duprat, 1987). Intraocular melanomas of the ciliary body and iris have been reported in the F344, Sprague-Dawley, Long-Evans, and Wistar rats (Magnusson et al., 1978; Manning et al., 2004).

Primary orbital tumors have been reported in mice and rats. In both species, spontaneous neoplasms involving the harderian gland have been reported, affecting approximately 18% of mice older than 18 months in one study (Holland & Fry, 1982). Orbital fibrous histiocytomas have been reported in Sprague-Dawley rats (Greaves & Faccini, 1981) and optic nerve meningiomas have been described in F344 rats, reportedly possessing considerably more aggressive biologic behavior than the human counterpart (Yoshitomi et al., 1991). Other primary orbital tumors reported have included various adenocarcinomas, carcinomas, and sarcomas (Rothwell & Everitt, 1986). It is noteworthy that conjunctival hyperemia and/or swelling may be the only detectable clinical sign of an orbital neoplasm in a mouse or rat.

Guinea Pig

While the guinea pig is not a commonly employed species in toxicologic or drug safety evaluations, it still plays a role in vision science. In particular, it has been an important model in studies investigating the pathogenesis and inheritance of cataracts, retinal physiology, neonatal ocular development, ocular complications of systemic disorders, and refractive error.

While numerous guinea pig breeds are kept as pets, the most common breed used in research and vision science is the Dunkin-Hartley, an outbred albino breed. However, outbred British and American short-haired breeds are also used in laboratory investigations (Jiang et al., 2009).

Functional Morphology

Like those of other rodents, the guinea pig retina is rod dominant (Jacobs & Deegan, 1994). The presence of cones in the guinea pig retina has historically been debated. However, more recently publications have confirmed the presence of cones, and categorized the guinea pig as a dichromat, with short- and middle-wavelength sensitive photopigments with peak sensitivities of 429 and 529 nm, respectively (Jacobs & Deegan, 1994; Lei, 2003). Electrophysiologic investigations have also demonstrated ERG patterns similar to those of humans and NHPs, suggesting that this species may be a reasonable substitute for the NHP in studies of retinal electrophysiology, particularly for the photopic ERG (Lei, 2003; Racine et al., 2004, 2005). Based on histologic photoreceptor density, visual acuity in the guinea pig has been designated as 2.7 cpd, but this value does not take into consideration refractive state (Buttery et al., 1991). Numerous investigations have demonstrated that spontaneous refractive error is relatively common among guinea pigs, ranging from high myopia to hypermetropia, and even anisometropia (Jiang et al., 2009; Wang et al., 2007). Albinism may also play a role in the development of refractive error, as one study showed that albino guinea pigs were prone to high myopia, compared to pigmented animals who were mildly hypermetropic (Wang et al., 2007).

Relative to its cranial dimensions, the guinea pig possesses a large, open orbit that is open caudoventrally (Cox et al., 2012; Hargaden & Singer, 2012). In comparison to smaller rodents whose orbits are roughly ovoid in shape, the guinea pig orbit assumes a more spherical conformation

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(Jekl et al., 2015). The frontal and lacrimal bones comprise the bony limits of the orbit rostrally and dorsomedially, with soft tissue structures largely defining the inferior and lateral limits (Cooper & Schiller, 1975). As in rodents, the globes are situated laterally in the skull, yielding an approximately 325–340° visual field, but only a small 20–63° region of binocular overlap (Zhou et al., 2011).

Like mice and rats, the guinea pig possesses intra- and extraorbital lacrimal glands, as well as a prominent harderian gland (Cooper & Schiller, 1975; Kittel, 1962). A recent anatomic investigation further characterized the primary lacrimal gland of the guinea pig, describing a roughly triangular "infraorbital" gland located ventrally and laterally, attached to the outer aspect of the zygomatic bone, spanned by the orbital ligament (Gasser et al., 2011). In this same investigation, an extraorbital gland could not be identified (Gasser et al., 2011). The presence of a large zygomatic salivary gland has also been reported in guinea pigs, occupying a large portion of the caudal and superior orbit (Gelatt et al., 2012). The noteworthy absence of this gland, however, was also reported in the aforementioned anatomic investigation, suggesting that previous descriptions of a zygomatic gland may have actually represented a portion of the large harderian gland (Gasser et al., 2011).

The harderian gland is lobulated and roughly round in shape, in apposition with the posterior globe, and surrounds the optic nerve and extraocular muscles (Hittmair et al., 2014). Its solitary excretory duct courses rostrally to empty onto the ocular surface adjacent to the third eyelid, which is rudimentary in the guinea pig (Hittmair et al., 2014; Sakai, 1981). Like in mice and rats, harderian secretions in guinea pigs are high in lipid content; however, the guinea pig harderian gland does not produce porphyrins (Elgayar et al., 2015; Seyama et al., 1984).

In addition to the orbital lacrimal glands, the presence of two subconjunctival sebaceous glands has been described (Walde & Nell, 2008). These two glands are found laterally within the subconjunctival tissue of the upper and lower eyelids. The secretions of these glands are primarily lipid, and are therefore believed to contribute to the lipid layer of the tear film (Gasser et al., 2011).

The guinea pig cornea is large, occupying approximately 85%–90% of the interpalpebral fissure, with a mean central thickness of 227.85 µm (Cafaro et al., 2009). Furthermore, corneal thickness is not significantly different between the central and more peripheral corneal regions (Cafaro et al., 2009). In comparison to larger mammals, the guinea pig possesses lower overall corneal sensitivity, in one study measuring 7.75 g/mm^2 (Wieser et al., 2013). The guinea pig is also one of few nonhuman species with a distinguishable Bowman's layer in the anterior corneal stroma, subtending the epithelial basement membrane (Cafaro et al., 2009).

The dynamics of the tear film and ocular surface in the guinea pig appear to differ considerably from other mammals and from humans. The low blink rate in guinea pigs (2–5 blinks/20 minutes) suggests the presence of an inherently very stable tear film (Gasser et al., 2011; Trost et al., 2007). This could be at least partially attributed to the lipid-rich secretions of the harderian gland as well as those of the paired subconjunctival sebaceous glands (Gasser et al., 2011). In other species like the rabbit, enhancement of tear stability has also been attributed to comparative differences in tear and corneal mucins (Leonard et al., 2016). While the guinea pig lacrimal gland has been suggested to be an accessory source of mucin production, conjunctival goblet cell densities in guinea pigs are demonstrably lower than in dogs and horses, species that do not historically possess enhanced tear stability and low blink rate (Gasser et al., 2011). Very few studies have quantitatively evaluated tear film stability in the guinea pig, but a published tear film breakup time (TBUT) value of 4.98 seconds seems to contradict the notion of an exceptionally stable tear film in this species (Cafaro et al., 2009).

Other than studies reporting tonometric methods and normative IOP values in guinea pigs (see Table 33.2), little information has been published regarding aqueous humor dynamics in the guinea pig. However, it is noteworthy that, like mice and rats, the guinea pig appears to possess a true Schlemm's canal, which may support its applicability as a model for human aqueous humor dynamics and glaucoma (Rodriguez-Ramos Fernandez & Dubielzig, 2013).

Like mice and rats, guinea pigs are atapetal. Unlike smaller rodents, however, the guinea pig fundus is clinically anangiotic, as it lacks a grossly identifiable retinal vasculature. Histologically, blood vessels are present within the guinea pig optic disk; therefore, there is controversy as to whether this species is anangiotic or paurangiotic like equids (Rodriguez-Ramos Fernandez & Dubielzig, 2013). The guinea pig also possesses a well-organized collagenous lamina cribrosa, better resembling that of the human than the noncollagenous laminae of smaller rodents like the mouse and rat (Johansson, 1987; Ostrin & Wildsoet, 2016).

Spontaneous Lesions and Diseases

In the largest published clinical survey on guinea pigs, ophthalmic examinations revealed at least one ocular abnormality or lesion in 45% of the animals examined (Williams & Sullivan, 2010). Another large survey identified ocular lesions in only approximately 12%–16% of animals, though the authors indicated that subclinical findings such as lens opacities were not as thoroughly documented (Minarikova et al., 2015).

Congenital/Developmental Anomalies

While congenital lesions are not commonly observed in guinea pigs, microphthalmos and anophthalmos have been reported (Fariss & Botz, 1975; Komich, 1971; Williams & Sullivan, 2010). Of 1000 guinea pigs in one study, microphthalmos and anophthalmos were observed in a total of

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Table 33.2 Published values for ocular ancillary diagnostic tests in the adult mouse, rat, guinea pig, rabbit, pig, cynomolgus macaque, and rhesus macaque.

	IOP – applanation (mmHg)	IOP – rebound (mmHg)	STT I (mm/min)	PRTT (mm/15 s)	TBUT (s)	Reference
Mouse	12.36*					Reitsamer et al. (2004)
	13.7					Cohan & Bohr (2001a)
	15.3‡					Grozdanic et al. (2003a)
		8.1–15.4†				Saeki et al. (2008)
		9.8*				Danias et al. (2003)
		7.6**				Danias et al. (2003)
		13.3–16.4				Wang et al. (2005)
		11.7–13.2				Johnson et al. (2008)
		11.4**				Millar et al. (2011)
			2.8–3.3 mm/**2 min**			Hoffman et al. (1984)
				2.98 mm/**1 min**		Dursun et al. (2002)
					2.5–3.0	Kojima et al. (2014)
Rat	15.5					Cohan & Bohr (2001b)
	17.3†					Mermoud et al. (1994)
		18.4				Wang et al. (2005)
		9.6–13.9**				Kontiola et al. (2001)
			8.8†∫			Batista et al. (2012)
Guinea pig		17.3–22.7				Ostrin & Wildsoet (2016)
	18.27		3	21.26		Coster et al. (2008)
	16.5					Williams & Sullivan (2010)
	10.93	13.2				Cairó et al. (2018)
	16.34	6.19				Ansari-Mood et al. (2016)
		10.3				Di et al. (2017)
		6.81		14.33		Rajaei et al. (2016)
			0.36–0.6	16		Trost et al. (2007)
					4.98	Cafaro et al. (2009)
Rabbit	15.44	9.51				Pereira et al. (2011)
	17.5–18.1					Sarchahi & Bozorgi (2012)
		18.37–19.69				Zhang et al. (2014)
			5.3			Abrams et al. (1996)
			4.85	20.88		Gürkan & Hayat (2005)
			7.58			Whittaker & Williams (2015)
			8			Zhu et al. (2003)
			20.57 mm/**3 min**			Burgalassi et al. (1999)
					1788	Wei et al. (2013)
					50	Toshida et al. (2007)
Pig	15.2†					Ruiz-Ederra et al. (2005)
	26.8					Rosolen et al. (2003)
	22.43					Galdos et al. (2012)
		15.8∞	11.17∞			Jangamreddy et al. (2018)

(Continued)

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Table 33.2 (Continued)

	IOP – applanation (mmHg)	IOP – rebound (mmHg)	STT I (mm/min)	PRTT (mm/15 s)	TBUT (s)	Reference
Cynomolgus macaque	19.2					Hahnenberger (1980)
	8.36*					Kaufman & Davis (1980)
Rhesus macaque	14.3*					Toris et al. (2005)
	15.8*					Dawson et al. (1998)
		17.95*				Yu et al. (2009)
			15.1*			Jaax et al. (1984)

* Anesthetized with ketamine.
** Anesthetized with ketamine, acepromazine, and xylazine.
† Anesthetized with ketamine and xylazine.
‡ Anesthetized with inhalant anesthesia.
§ Anesthetized with intravenous propofol.
∫ Modified Schirmer tear strip.
∞ Mean of control values (n not specified).
IOP, intraocular pressure.
PRTT, phenol red thread test.
STT, Schirmer tear test.
TBUT, tear breakup time.

18 eyes, with roan × roan cross Abyssinian guinea pigs overrepresented compared to other breeds (Williams & Sullivan, 2010). True anophthalmos has also been reported in other previous investigations. While primary entropion is not commonly reported in guinea pigs, it may develop as a secondary consequence of a congenitally small globe (Williams & Sullivan, 2010).

There are numerous reports in the literature of ocular surface dermoids in guinea pigs, primarily affecting the cornea, conjunctiva, and corneoconjunctival junction (Alessandarini, 1907; Brunschwig, 1928; Chan, 1932; Gupta, 1972; Otto et al., 1991; Wappler et al., 2002). Many of the published reports do not specify a breed, and breed predisposition has not been reported. Given the sporadic nature of this anomaly in the species, a hereditary mechanism has not been determined.

Retrobulbar Disease

Space-occupying orbital disease or exophthalmos has been reported in guinea pigs in association with dental disease and/or retrobulbar abscess (Minarikova et al., 2015). Primary retrobulbar neoplasia has not been described in guinea pigs, but bilateral exophthalmos has been reported in association with ocular infiltration due to disseminated lymphoma (Steinberg, 2000). Bilateral exophthalmos has also been reported in association with hyperadrenocorticism, though the pathogenesis was not investigated (Zeugswetter et al., 2007).

Eyelids and Conjunctiva

Eyelid abnormalities are sporadically reported in guinea pigs. Blepharitis may be a manifestation of primary dermatophytosis, but may also develop secondary to the extension of generalized dermatologic disease or conjunctivitis (Shomer et al., 2015). A spontaneous liposarcoma has also been reported in the eyelid of a guinea pig (Quinton et al., 2013).

Conjunctivitis is a common ophthalmic diagnosis in guinea pigs, observed in 3.4% of eyes in a survey of 1000 animals (Williams & Sullivan, 2010). As for the cornea (see below), trauma and/or presence of conjunctival foreign bodies are commonly proposed etiologies for conjunctivitis, particularly proliferative conjunctivitis (Williams & Sullivan, 2010). Infectious conjunctivitis is also reported in guinea pigs, most commonly in young animals. *Chlamydia caviae* is one of the most commonly implicated bacterial organisms, resulting in a conjunctivitis that is typically self-limiting within 3–4 weeks (Belij-Rammerstorfer et al., 2016; Hawkins & Bishop, 2012; Lutz-Wohlgroth et al., 2006). Diagnosis is facilitated by the identification of inclusions on conjunctival cytology or by conjunctival PCR, but false negatives and false positives may be encountered with each, respectively (Hawkins & Bishop, 2012). Other causative bacterial organisms include *Pasteurella multocida* (Shomer et al., 2015), *Listeria monocytogenes* (Williams & Sullivan, 2010), *Bordetella bronchiseptica*, *Streptococcus* spp. (Kern, 1997), and both *Salmonella* and *Shigella* spp. (Hawkins & Bishop, 2012; Voĭno-Iasenetskiĭ et al., 1977). Conjunctivitis has also been reported in association with nutritional deficiencies such as hypovitaminosis C and vitamin E/selenium deficiency (Barthold et al., 2016; Hawkins & Bishop, 2012).

Conjunctival masses are common in guinea pigs. Smooth, benign conjunctival protrusions, known by guinea pig breeders and enthusiasts as "fatty eye," were observed in 1.9% of eyes in the aforementioned survey of 1000 animals (Williams

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& Sullivan, 2010). These masses are composed of lipids, and may be associated with diet and increased body condition (Gelatt et al., 2012). Prolapse of lacrimal tissue is the putative cause of "flesh eye" or "pea eye," a lesion observed in 0.4% of eyes surveyed (Kern, 1997; Williams & Sullivan, 2010). The exact pathophysiologic basis for these clinically similar conditions, however, has not been determined. While less common, conjunctival neoplasms such as lymphosarcoma have been reported in guinea pigs (Hawkins & Bishop, 2012).

Cornea

In a large survey of 1000 animals, findings attributed to ocular trauma were observed in 25 eyes (1.25%), largely manifesting as corneal lesions (e.g., scars, edema, ulcerations; Williams & Sullivan, 2010). In another investigation of 20 male and female guinea pigs (pigmented and nonpigmented American and Dunkin-Hartleys), fluorescein staining confirmed the presence of punctate and linear superficial corneal erosions in both eyes of all animals examined, despite the absence of clinical discomfort or overt corneal opacification on examination (Cafaro et al., 2009). The authors of both of these studies propose that the relatively high incidence of corneal lesions in guinea pigs is likely due to environmental trauma, particularly contact with hay or straw bedding. Other proposed factors include the low blink frequency and comparatively lower corneal sensitivity previously demonstrated in the species. Also common to both studies was the lack of report of corneal vascularization accompanying the corneal erosions in any animals. This conflicts with a prior report citing the clinical and histologic observation of superficial stromal perilimbal blood vessels in eyes of both newborn and adult female Dunkin-Hartley guinea pigs (Dwyer et al., 1983). These authors proposed that these vessels were a normal feature of the guinea pig cornea; however, this has not been corroborated by any subsequent studies, including histologic investigations (Cafaro et al., 2009).

Keratitis has also been reported in association with low STT values and suspected aqueous tear deficiency in guinea pigs (Williams, 2012). However, a thorough characterization of the condition, its underlying etiology, and standard for treatment have not yet been determined. It is noteworthy that, unlike dogs, a reduction in tear production following systemic administration of trimethoprim sulfa is not observed in guinea pigs (Asadi et al., 2016).

Corneal lipidosis has been described in guinea pigs and may be observed in association with conjunctival lipid deposits. Such lesions may also represent a bilateral condition with a similar, axial-to-paraxial distribution and a clinical appearance similar to stromal lipid dystrophies reported in dogs (Williams & Sullivan, 2010). An etiology or definitive pattern of inheritance, however, has not been determined.

Heterotopic Bone Formation (Osseous Metaplasia)

Formation of bone in the ocular soft tissues is a unique but relatively common and well-characterized finding in guinea pigs, particularly in older animals (Brooks et al., 1990; Cullen et al., 2000; Donnelly et al., 2002; Griffith et al., 1988; Minarikova et al., 2015; Schäffer & Pfleghaar, 1995; Williams & Sullivan, 2010). The most commonly affected structure within the eye is the ciliary body, but other anterior segment structures (e.g., iris base, iridocorneal angle, and/or peripheral cornea) as well as extraocular sites have also been reported (Brooks et al., 1990; Donnelly et al., 2002; Griffith et al., 1988). Lesions are clinically visible when they extend anteriorly, commonly appearing as well-demarcated white lesions originating at the limbus, and extending into the adjacent cornea (Fig. 33.12). Lesions involving only the

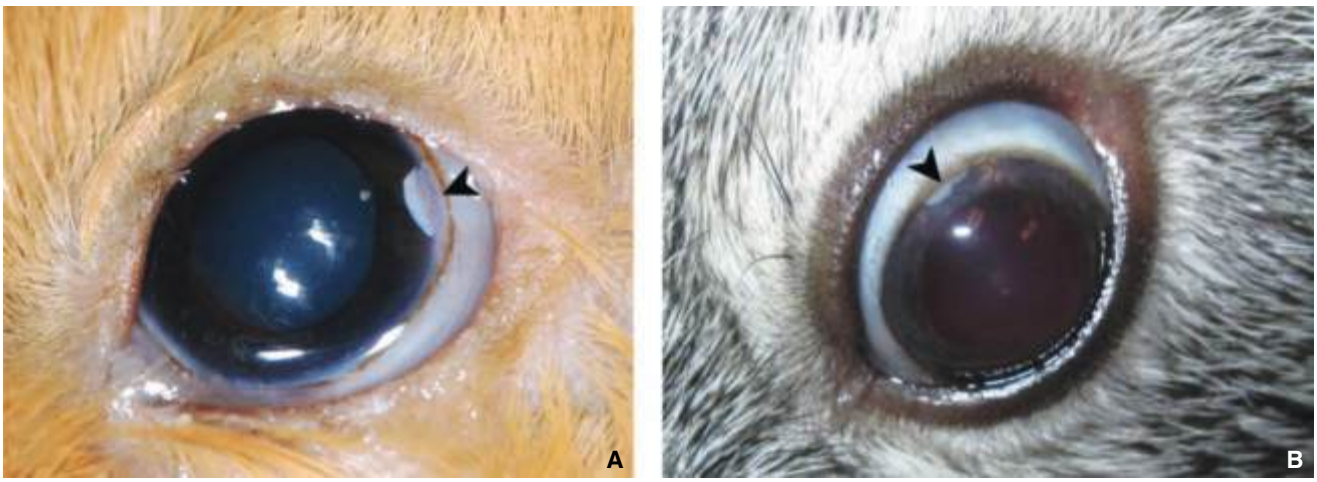


Figure 33.12 Focal osseous metaplasia (arrowheads) of the anterior segment in guinea pigs. (Courtesy of Ellison Bentley, DVM, DACVO (**A**); and the UC Davis Veterinary Ophthalmology Service (**B**).)

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ciliary body or iridocorneal angle will not be visible clinically, and may not produce any clinical signs. One report identified an association between osseous metaplasia of the iridocorneal angle and secondary glaucoma on postmortem examination (Schäffer & Pfleghaar, 1995).

Histologically, lesions are characterized by osseous transformation of affected tissue and, when affecting the ciliary body, may focally replace the ciliary stroma and extend anteriorly into the anterior segment. When extending into the posterior cornea, bony lesions focally replace Descemet's membrane and are often fused to lesions from adjacent structures such as the anterior iris and iridocorneal angle (Griffith et al., 1988). Osseous foci may also be vascularized by the adjacent iris and cornea and contain hematopoietically active marrow (Cullen et al., 2000). Cataracts have been reported in eyes with osseous metaplasia, but a direct relationship between the two lesions has not been proven (Griffith et al., 1988).

A definitive pathogenesis for osseous metaplasia has not been determined. Heterotopic bony lesions form in normal eyes, in the absence of antecedent ocular disease, and have not been linked to a hereditary cause. It is believed that the mineral composition of some commercial guinea pig diets may be a risk factor (Cullen et al., 2000; Griffith et al., 1988). One theory implicates the relatively high concentration of vitamin C in the ciliary body, which putatively acts as an antioxidant when secreted into the aqueous humor (Garland, 1991). Since vitamin C is also an essential cofactor in bone remodeling and osteoblast activation (Xiao et al., 1997), it has been proposed that high local concentrations put the ciliary body and adjacent ocular tissues at risk for bone deposition (Williams, 2012). Vitamin C is commonly supplemented in the diet of guinea pigs since they cannot produce it endogenously (Hawkins & Bishop, 2012), and levels in the aqueous humor and lens can be easily modulated by modifying dietary intake of ascorbic acid (Mody et al., 2008). There is not, however, evidence to directly associate excessive supplementation with development of ocular lesions. Another report has demonstrated osseous metaplasia of the eye and multiple organ systems in association with chronic renal disease and metabolic disturbance in 3 guinea pigs (Griffith et al., 1988); however, only 1 of 3 guinea pigs in that report had systemic hypercalcemia.

Cataract

In the aforementioned survey of 1000 guinea pigs, cataract was the most commonly observed spontaneous ocular lesion on ophthalmic examination, identified in 16.9% of eyes (Williams & Sullivan, 2010). The vast majority were observed in older animals, often presenting as an incipient or immature lens opacity (2.2% and 4.9% of eyes, respectively). Congenital cataracts were observed in 3.7% of eyes. Congenital cataracts have also been described in the 13/N strain, associated with a mutation that yields a deficiency of lens zeta crystallines in affected homozygotes (Bettelheim et al., 1997; Goenka & Rao, 2000; Stone & Amsbaugh, 1984). Diabetic cataracts, some reaching maturity, have also been reported in guinea pigs (Lang et al., 1977; Shomer et al., 2015). Naturally occurring diabetic cataracts have also been described in diabetic guinea pigs in association with l-tryptophan-deficient diets (Reid & Von Sallmann, 1960). The survey of 1000 animals also identified nuclear sclerosis or nuclear rings in 20.5% and 8.0% of eyes, respectively.

Rabbit

The rabbit is one of the most widely used laboratory species in ocular drug development and toxicology studies, including pharmacokinetic studies, proof-of-concept investigations, and safety assessments for topical and intraocular drugs and devices. Rabbits are also very commonly used in contact lens and IOL implantation studies. The popularity of the species is largely attributable to the ease of handling in comparison to others, the ability to examine animals unanesthetized, and some noteworthy similarities to the human eye in terms of ocular anatomic dimensions and volumes. The anatomy and physiology of the rabbit eye, however, bear some very important differences from those of humans and other laboratory species. If not taken into consideration when planning or interpreting the results of a study, these differences may considerably confound data and impact translatability. The veterinary ophthalmologist or laboratory animal veterinarian must be aware of these differences in order to confirm that the rabbit is indeed a suitable model for a given study and to enable accurate interpretation of acquired study data (Werner et al., 2006).

In ocular toxicology and drug development, the albino NZW and the slightly smaller pigmented Dutch belted (DB) rabbits are the most commonly utilized strains. Other less commonly used strains include the pigmented New Zealand Red and Japanese Harlequin. The popularity of the NZW in vision science and ocular toxicology is chiefly due its historical sensitivity when evaluating the ocular tolerability and toxicity of topical medications (Munger, 2002). However, the noteworthy influence of ocular pigmentation on intraocular pharmacokinetics and drug bioavailability, as well as the FDA requirement for evaluation of a drug or device in at least one pigmented species, has expanded the use of the DB and other pigmented strains (Katz & Berger, 1979; Mirowski & Van Horn, 2005; Salminen et al., 1984; Urtti et al., 1984).

Functional Morphology

As a prey species, many features of the rabbit's ocular system are inherently adapted for efficient scanning of their environment. The rabbit retina is dichromatic and rod-dominant (~95% of rods), well suited to scanning dim-lit

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and dark environments (Davis, 1929). The rabbit also possesses a horizontally oriented visual streak, just inferior to the optic disk (Juliusson et al., 1994). Based on the high percentage of cones and ganglion cells in this area, the visual streak is putatively the rabbit's region of highest visual acuity. Interestingly, however, the rabbit visual streak is composed primarily of cones with green spectral sensitivity, with a secondary, crescent-shaped, cone-dense region at the far inferior periphery comprising exclusively blue cones (Juliusson et al., 1994). As proposed by some to explain the functional significance of the "S-field" in the ventral retina of the mouse (see previous discussion in "Mouse and Rat"), this variation may enable rabbits to more effectively scan the sky for predators, with the cone complement of its visual streak better adapted to surveying the grasses and foliage at eye level (Juliusson et al., 1994; Temple, 2011). Determination of visual acuity for the rabbit has proven difficult due to these anatomic and physiologic features, as well as reported variability in acuity between individual animals ranging from 0.3 to 2.7 cpd (Vaney, 1980; Van Hof, 1967; Williams, 2012).

Also characteristic of herbivorous prey species, rabbits' orbits are placed laterally, situated approximately 85° to the transverse plane of the head (Davis, 1929). The resulting position of the globes results in a small field of binocular overlap, not exceeding 30° horizontally (Hughes, 1971). However, this conformation affords the rabbit wide monocular visual fields and the ability to see nearly 360 horizontal degrees of its environment, theoretically leaving only small blind spots immediately beneath and behind the head (Hughes, 1971; Osofsky et al., 2007). It has also been suggested that, depending on head and globe position and other factors like body condition, some rabbits may be able to effectively eliminate the blind spot behind their heads (Williams, 2012).

Orbit

The rabbit has an open orbit with an anatomic conformation and orientation that result in a very prominent globe whose superior aspect is largely unprotected by bone (Davis, 1929). While this likely enhances the animal's visual field, it also leaves the eye at higher risk for trauma. This ocular susceptibility can be used to explain the evolutionary and protective advantage of the characteristically robust and often fibrinous intraocular inflammatory response in the rabbit (Bito, 1984).

The rabbit's four orbital glands include the lacrimal, harderian (deep gland of the third eyelid), infraorbital, and nictitating membrane gland (superficial gland of the third eyelid; Davis, 1929). When compared to those of other species, the rabbit lacrimal gland is large, with distinct upper and lower portions whose separate ducts empty onto the conjunctiva laterally, adjacent to the superior and inferior lids, respectively. Smaller secondary lobes have also been described, with or without small ducts emptying onto the conjunctiva separately (Davis, 1929). In comparison to mice and rats, the rabbit lacrimal gland possesses features with greater histologic resemblance to the human lacrimal gland, including distinctly ovoid-to-round acinar lumina and a loose stroma. Furthermore, similar immunoregulatory functions in the rabbit and human lacrimal glands have been proposed (Schechter et al., 2010).

While the secretions of the rabbit lacrimal gland are presumed to be largely serous, more recent investigations have demonstrated histologic evidence supporting a role in the production of tear mucins as well (Ding et al., 2011). The infraorbital gland is smaller, and adjacent to the lower portion of the lacrimal gland, though its exact function is unknown. The superficial gland of the third eyelid is situated on the bulbar surface of the third eyelid, in association with the base of its cartilaginous backbone. The harderian gland is also large, lying in direct contact with the posterior globe, and occupies a large portion of the medial and ventral orbit (Björkman et al., 1960; Sakai, 1981). It is also intimately associated with and surrounded by the orbital venous sinus (see below). The rabbit harderian gland has upper and lower lobes. The gland's primary function is to produce lipids, contributing its secretions to the lipid layer of the precorneal tear film via ducts that empty onto the ocular surface adjacent to the third eyelid (Ham et al., 2006; Seyama et al., 1992).

The rabbit has a large orbital vascular sinus in the ventronasal orbit, providing venous drainage for the orbital soft tissues. The orbital venous sinus is intimately associated with other structures, including the extraocular muscles and harderian gland (Davis, 1929). Surgical trauma to the sinus during enucleation or surgical manipulations of the third eyelid and/or harderian glands risk hemorrhage, which can be life-threatening. Therefore, careful soft tissue dissection (blunt dissection when possible) must be observed during enucleation or exenteration.

Nasolacrimal System

The nasolacrimal system of rabbits bears unique anatomic features that differentiate it from those of other laboratory species and the human. The proximal opening to the rabbit nasolacrimal duct (NLD) consists of a single punctum, located in the bulbar conjunctiva of the medial lower eyelid, approximately 3–4 mm from the margin (Davis, 1929). From the single lacrimal punctum, the proximal aspect of the system comprises a short and relatively narrow canaliculus and lacrimal sac, thereafter forming the NLD and coursing into the maxilla via a foramen in the lacrimal bone. At the entry into this foramen, the duct abruptly narrows. Within its bony encasement in the maxilla, the duct travels in proximity to the molar roots. Further distally, the narrow duct's

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course abruptly changes, shifting medially and dorsally to circumduct the base of the maxillary incisor. At this location, another sudden narrowing of the duct occurs. Thereafter, the duct courses medial to the root of the incisor, before reaching its distal ostium to empty into the nasal cavity at the ventral and medial aspect of the alar fold (Burling et al., 1991; Kern, 1997; Marini et al., 1996). In combination with noteworthy ductal epithelial undulations and the small size of the distal ostium, as well as the relatively high incidence of tooth root disease in rabbits, these features make this species uniquely predisposed to obstructive disease of the NLD and dacryocystitis (Florin et al., 2009). Furthermore, these attributes make the rabbit a suboptimal animal model for the human nasolacrimal system (Florin et al., 2009; Frame & Burkat, 2009).

Cornea and Ocular Surface

The rabbit is one of the most commonly employed species in comparative studies of the ocular surface, and also in safety and efficacy evaluation of topical ophthalmic drugs. There are, however, important anatomic and physiologic features of the rabbit's ocular surface that must be considered when assessing the cornea and conjunctiva, and in interpreting findings from preclinical investigations. Firstly, the rabbit has a remarkably long blink interval, averaging 10–12 blinks/hour according to one study (Peiffer et al., 1994). Comparatively, the human blinks 1000 times per hour, on average (Maurice, 1995). This physiologic parameter is considerably different from other species and the human, but is often not taken into account in topical drug efficacy studies. Despite similar tear volumes and tear flow rates between rabbits and humans, factors like low blink rate as well as a higher corneal epithelial permeability rate for some drugs in rabbits may lead to results that falsely overestimate drug penetration in pharmacokinetic studies (Maurice, 1995).

Compared to other larger laboratory species like the dog and NHP, the rabbit has a large cornea, occupying approximately 30% of the globe's surface area (Andrew, 2002). The rabbit cornea is also comparatively thin, typically measuring approximately 0.4 mm centrally in adult animals (T. Chan et al., 1983). The rabbit sclera varies in thickness, ranging from 0.18 mm at the posterior pole, to 0.25 mm near the equator, to 0.5 mm adjacent to the limbus (Davis, 1929). Recent investigation has also highlighted interspecies differences in corneal mucin expression, demonstrating a difference in expression profiles between humans, NHPs, dogs, and rabbits (Leonard et al., 2016). While human, NHP, and canine corneal epithelial cells (CEC) tend to express only one membrane-bound mucin (MUC16), rabbit CECs express three (MUC1, MUC4, and MUC16) at relatively equal levels. Given the roles of both secretory and membrane-bound mucins in stabilization of the tear film, this difference may at least partially explain the need for such a low blink rate in rabbits. Furthermore, the tear lipid layer is thicker in rabbits compared to dogs and humans, which may explain the apparent resistance of the rabbit tear film to evaporation, and the species' longer TBUT, measured in one study to be as long as nearly 30 minutes (Holly & Lemp, 1977; Korb et al., 1994, 1998; Wei et al., 2013).

The rabbit corneal endothelium has been shown to carry greater regenerative capacity than in other species. While most other species' endothelial cells respond to injury by nonmitotic mechanisms like cellular enlargement and migration, those of the rabbit undergo replication in response to wounding (Van Horn et al., 1977). It is noteworthy, though, that this regenerative capacity is not as robust in older rabbits (at least 50% slower in rate of cellular division), with a greater incidence of endothelial polymegathism (variation in individual endothelial cell area) by 9–12 months of age (Doughty, 1994; Staatz & Van Horn, 1980).

Anterior Segment and Aqueous Outflow

The rabbit pupil bears a slightly ovoid shape vertically. The rabbit ciliary body lacks a robust ciliary musculature, but does bear prominent ciliary processes (both major and minor), as well as anteriorly situated iridal processes originating from the posterior iris (Morrison et al., 1987a). These two groups of processes are supplied by a dual system of arterioles, a feature also observed in NHPs but not in other domestic or laboratory species (Morrison et al., 1987a, 1987b).

Rabbits are commonly used as models for the human glaucomas (Bouhenni et al., 2012). While the general physiologic mechanisms of aqueous outflow are similar between humans, NHPs, and rabbits, there are some important morphologic differences. Unlike NHPs, rabbits have a distinct trabecular endothelial layer, continuous with the corneal endothelium, which may play a role in aqueous outflow resistance and may also influence the response of the rabbit eye to certain topical anti-hypertensive drugs (Bergmanson, 1985). Furthermore, the rabbit lacks a true Schlemm's canal, instead possessing an intrascleral venous plexus (also referred to as an angular aqueous plexus; Newell, 1965; Nishida et al., 2005; Ruskell, 1961; Tripathi, 1971).

Lens

The rabbit lens is relatively similar in morphology and dimensions to those of other species (see Table 33.1). Perhaps the most noteworthy feature that differentiates the rabbit lens is its capacity for cortical regeneration, as demonstrated by series of investigations in NZW rabbits. These studies demonstrated that, following lens extraction using phacoemulsification, lens epithelial cells underwent differentiation and migration along the intact lens capsule, with histologic evidence of elongation and early lens fiber differentiation as early as 6–7 days postoperatively (Gwon et al., 1990).

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Clinically, gross evidence of lens regrowth can be observed even at 2–3 weeks postoperatively, and complete filling of the capsular bag with regenerated lens material may be observed at 3 months (Gwon et al., 1993). These studies also confirmed that the rate of lens regrowth is accelerated in younger rabbits (Gwon et al., 1992).

Posterior Segment and Retina

The rabbit fundus is atapetal and, in albino species, lacks melanin in the retinal pigmented epithelium, permitting the examiner to view the underlying choroidal vasculature ophthalmoscopically. The rabbit's retinal vasculature is classified as merangiotic, characterized by relatively linear retinal arterioles and venules that extend medially and laterally from the optic disk in tandem with myelinated nerve fibers (medullary rays; De Schaepdrijver et al., 1989). Within these regions, larger blood vessels tend to lie vitread or within the nerve fiber layer (Davis, 1929). Away from the medullary rays, however, the retina is avascular. The majority of the rabbit retina measures approximately 120 μm in thickness, decreasing to 90 μm peripherally at the ora serrata. It increases to approximately 160 μm in the area of the visual streak inferior to the optic disk, and is remarkably thinner (< 40 μm) beneath the myelinated medullary rays and retinal vessels (Davis, 1929).

The optic nerve head and medullary rays are situated in the dorsal aspect of the fundus, with the medial and lateral medullary rays largely obscuring the view of the medial and lateral disk margin. The optic nerve head is horizontally ovoid and deeply cupped, at least partially due to the fact that the rabbit lacks a true lamina cribrosa, instead replaced by a loosely organized fibrous membrane formed from the pia mater of the nerve and the choroid (Davis, 1929). The normal physiologic appearance of the rabbit optic nerve head can complicate clinical detection of pathologic optic disk cupping associated with glaucoma (see below).

Spontaneous Lesions and Diseases

Naturally occurring ocular disease is relatively uncommon in laboratory rabbits. In a very large study of purpose-bred laboratory rabbits (males and females, albino and pigmented strains), 9.6% of animals (6.3% of eyes) had spontaneous lesions on ophthalmic examination (Holve et al., 2011). Another large study of almost 600 NZW rabbits (male and female) reported an identical overall incidence of spontaneous abnormal ocular findings (9.6%; Jeong et al., 2005).

Congenital/Developmental Anomalies

Congenital abnormalities of the globe such as microphthalmos or anophthalmos are uncommon in rabbits. A case of colobomatous microphthalmos has been described in a NZW rabbit, suspected to be associated with vitamin E deficiency (Nielsen & Carlton, 1995).

Blepharitis

In one survey, blepharitis, typically unilateral, was the most common spontaneous background finding in a large population of NZW rabbits (Jeong et al., 2005). The finding affected both male and female animals, but a cause was not identified in that study. In general, most blepharitis in laboratory rabbits, particularly those that are group housed, is presumed to be traumatic in etiology. It is noteworthy that, in that survey, affected rabbits originated predominantly from two facilities. Therefore, husbandry-related practices and/or facility-related factors may have contributed. Bacterial blepharitis has been described in association with *Treponema cuniculi*, a spirochete bacterium that can be vertically transmitted from dam to offspring (Kern, 1997). Rabbit poxvirus can also cause blepharitis, primarily due to local extension of cutaneous disease (Kern, 1997).

Conjunctivitis

Like blepharitis, conjunctivitis is uncommon in purpose-bred rabbits. In the laboratory setting, it is important to remember that conjunctivitis, particularly unilateral conjunctivitis, is a common manifestation of underlying dental disease due to the anatomic proximity between the tooth roots and the ventral orbit. Furthermore, factors such as trauma, underlying conformational disease (e.g., entropion), and poor husbandry practices (e.g., dusty, loose, or unclean bedding) can contribute to conjunctivitis in some animals (Buckley & Lowman, 1979; Kern, 1997). When possible, these factors should be ruled out prior to pursuing diagnostic investigation for primary infectious conjunctivitis.

While rare, infectious conjunctivitis can be observed in laboratory rabbits and, if unrecognized and untreated, can represent a potentially serious management concern for a vivarium. The most commonly reported infectious cause of conjunctivitis in rabbits is *Pasteurella multocida*, but other bacterial organisms such as *Staphylococcus aureus*, *Chlamydia* spp., and *Pseudomonas* spp. have also been implicated (Kern, 1997; Snyder et al., 1976). Viral conjunctivitis/keratoconjunctivitis caused by the rabbit myxoma virus and rabbit fibroma virus is also described, but the natural hosts are typically domestic or wild animals. Rabbit fibroma virus (family *Poxviridae*, genus *Leporipoxvirus*) can be transmitted between animals via direct contact and can cause a rapidly progressive and clinically dramatic keratoconjunctivitis, typically in tandem with cutaneous disease (Joiner et al., 1971; Keller et al., 2007). Rabbit myxoma virus, transmitted by arthropod vectors like the flea or mosquito, can cause conjunctivitis/blepharoconjunctivitis, often accompanied by severe periorbital edema, with progressive disease carrying a high mortality rate in infected rabbits (Kern, 1997; Patton & Holmes, 1977).

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Adnexa

Corneal dermoids are uncommon but have been reported in rabbits, including a clinical description in an NZW (Styer et al., 2005; Wagner et al., 2000). Trichiasis secondary to entropion has been reported in a number of strains, including the NZW, but is uncommon (Fox et al., 1979; Yanoff, 1983). Distichiasis has also been reported in rabbits (Kern, 1997). While these conditions are not commonly observed in purpose-bred rabbits, an examination should be performed in any rabbit with chronic keratitis/keratoconjunctivitis to rule out these conformational conditions.

Dacryocystitis

Due to the anatomic features of the rabbit nasolacrimal system (see above), the rabbit is particularly predisposed to obstructive duct disease and/or duct inflammation (dacryocystitis), whether the animal resides in the laboratory setting or is kept as a pet. Numerous species of Gram-negative and Gram-positive bacteria can be cultured from the normal rabbit NLD, including *Pasteurella* spp., *Neisseria* spp., *Moraxella* spp., *Bordetella* spp., *Enterobacter cloacae*, and *Pseudomonas aeruginosa* (Florin et al., 2009; Kern, 1997; Petersen Jones & Carrington, 1988; Williams, 2007). According to one study comparing rabbits with clinical signs of NLD disease and those without, there was no significant difference in incidence of positive culture for any microbial species between the two groups (Quinton et al., 2014). It is also important to remember that nasolacrimal disease can develop secondary to tooth root disease and/or chronic rhinitis due to the proximity of the NLD to these other structures (Kern, 1997; Petersen Jones & Carrington, 1988). In one study, an underlying cause could not be found in approximately one-third of cases of dacryocystitis (Florin et al., 2009).

Pseudopterygium

This unique condition, also referred to as precorneal membranous occlusion or conjunctival centripetalization, is a benign, idiopathic condition in rabbits. Dwarf rabbits are overrepresented, and although this condition is not commonly observed in laboratory strains, it has been described in a purpose-bred albino rabbit (Katsuta et al., 2008). Pseudopterygium involves progressive and centripetal formation of bilaterally symmetric (or near symmetric), circumferential conjunctival growth over the corneal surface. The conjunctival growth is not adherent to the underlying cornea and is not associated with conjunctivitis or preexisting structural conjunctival abnormalities (Allgoewer et al., 2008; Dupont et al., 1995; Katsuta et al., 2008). Pseudopterygium is not responsive to medical therapy or simple surgical resection, but surgical techniques to transect and reposition the overgrowth into the conjunctival fornix have met with improved success (Allgoewer et al., 2008).

Corneal Opacities and Keratitis (Ulcerative and Nonulcerative)

Corneal opacities are commonly observed in laboratory rabbits. In a large survey of over 1000 rabbits, spontaneous lesions most commonly affected the cornea in comparison to other structures (Holve et al., 2011). While not as common as in mice and rats, an anterior CD is observed with relative frequency in the DB rabbit, bearing some morphologic similarities to corneal dystrophies of humans (Moore et al., 1987). In rabbits, dystrophic lesions are not associated with underlying systemic disease, are noninflammatory, and are typically located in the central/paracentral cornea. Lesions may be focal or multifocal, epithelial or subepithelial, and are typically linear or curvilinear in shape. Lesion density may vary from fine and granular to dense, opaque, and plaque-like. Lesions are typically bilateral, but their sizes and appearances may be asymmetric. Histologically, dense plaque-like lesions are characterized by thickening and irregularity of the epithelial basement membrane (BM), and may also be accompanied by collagen abnormalities in the adjacent anterior corneal stroma. Basal epithelial cells may be nonadherent to the underlying BM, and overlying epithelium is often thinned and disorganized.

A strain-specific corneal epithelial dystrophy has been described in NZW rabbits, characterized by raised, white corneal opacification(s) primarily in the perilimbal region, with secondary lesions extending toward the corneal axis in a circumferential distribution (Port & Dodd, 1983). The principal histologic feature corresponding to these lesions is epithelial irregularity (thickening and/or thinning). Another spontaneous, nonprogressive pattern of noninflammatory corneal opacification described in NZW rabbits is characterized by well-circumscribed, focal or multifocal opacities deep within the central and/or peripheral corneal stroma (Durand-Cavagna et al., 1998). On light microscopy, these lesions are associated with aggregations of displaced (ectopic) corneal endothelial cells, immediately anterior to Descemet's membrane. A heritable cause is suspected, but the pattern of inheritance is unknown.

Corneal lipidosis in rabbits is a nondystrophic opacification, typically associated with a high-fat/cholesterol diet (e.g., fish-meal or all-milk diets), or due to susceptibility in strains like the Watanabe rabbit that are predisposed to familial hyperlipidemia (Andrew, 2002). Clinical appearance is variable, with some lesions appearing faint and translucent, and others more opaque and even slightly raised (Andrew, 2002; Gwin & Gelatt, 1977). Some corneal lesions may be associated with secondary vascularization. Histologically, lesions are typically localized to the epithelium and epithelial BM, and may also be present in the anterior corneal stroma. Lesions are associated with amorphous lipid debris and necrosis as well as cellular infiltrates comprising predominantly macrophages and lymphocytes (Garibaldi & Goad, 1988; Sebesteny et al., 1985). Lesions associated with diet may also be observed in other ocular

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tissues like the nictitating membrane, sclera, and uvea (Andrew, 2002).

Traumatic corneal scars, with or without vascularization, are commonly observed in rabbits. In one large survey, scars were significantly more common in males, supporting the likely role of inter-animal aggression in their incidence (Holve et al., 2011). Other causes of keratitis (ulcerative or nonulcerative) in rabbits include trauma secondary to bedding; conformational trichiasis caused by conditions such as distichiasis and entropion; and corneal exposure related to exophthalmos or facial nerve paralysis/paresis with impaired blink. Superficial nonulcerative keratitis localized to the ventral and nasal cornea has also been reported in association with dacryocystitis (Petersen Jones & Carrington, 1988). As with other species, progression to deep stromal ulceration can be observed in association with septic keratitis (particularly associated with *Pseudomonas aeruginosa*; (Andrew, 2002). Sequestered corneal stromal abscesses have also been described in rabbits, and may theoretically be caused by bacterial or fungal organisms (Bourguet et al., 2016).

Anterior Uvea

Spontaneous lesions involving the anterior uvea are not common in laboratory rabbits, but PPMs, incidental synechiae, or anterior uveitis were observed in a small percentage of NZW rabbits examined in one study (Fig. 33.13; Jeong et al., 2005). A cause for synechiae and uveitis in the two affected rabbits was not cited. Given the unilateral presentation for both diagnoses, blunt trauma should be considered. However, the two findings may also be a manifestation of endogenous infection with *Pasteurella* spp. or *Staphylococcal* spp. (Kern, 1997; Williams, 2007), or with the protozoan *Encephalitozoon cuniculi*, which carries a primary tropism for the lens (Felchle & Sigler, 2002; Wolfer et al., 1993).



Figure 33.13 Anterior uveitis in a New Zealand white rabbit. Note the iridal vascular congestion, anterior chamber fibrin, and ventral posterior synechia. (Courtesy of Paul Miller, DVM, DACVO, University of Wisconsin–Madison.)

Intraocular neoplasms are rarely reported in rabbits, but a recent case series described the clinical and histologic features of spontaneous iridociliary tumors in rabbits (one of which was albino; Swisher et al., 2018). Follow-up was limited in two of the four rabbits in this study, but no clinical evidence of metastasis had been reported for the others. Based on the preliminary data provided by these four cases, these tumors may be associated with a low risk for metastasis and a good prognosis. It is important, however, that they be differentiated from melanoma or a metastatic neoplasm, as these may carry a poorer prognosis due to more biologically aggressive behavior.

Glaucoma

Heritable glaucoma associated with the *bu* gene is well characterized in the NZW rabbit (Edward & Bouhenni, 2011; Hanna et al., 1962; Tesluk et al., 1982). The inheritance pattern is putatively autosomal recessive with incomplete penetrance (Edward & Bouhenni, 2011). It is noteworthy that this form of glaucoma is also reported in pigmented rabbits, and a genetic study has confirmed that the *bu* gene is found on the same locus in both albino and pigmented animals (Bunt-Milam et al., 1987). It is also noteworthy that the *bu* gene is semi-lethal, and heterozygotic animals may therefore give birth to unthrifty or unusually small litters (Williams, 2007).

Young rabbits homozygous for the gene (*bu*/*bu*) develop a slowly progressive increase in IOP. In affected eyes, IOP typically exceeds 25 mmHg by 3–6 months of age, and in some animals as early as 1 month of age. This form of glaucoma can present unilaterally or bilaterally. Clinical signs are often limited to observation of buphthalmos and corneal edema. Exposure secondary to buphthalmos may also result in keratitis and/or corneal ulceration (Andrew, 2002). In chronic cases, eventual atrophy of the ciliary body may result in normalization of IOP, though most affected eyes remain buphthalmic (Harkness & Wagner, 1995). Manifestations of pain and/or vision impairment are uncommon, likely due to the disease's characteristically gradual progression and behavioral characteristics of the species.

The underlying cause for the IOP elevation is a decrease in aqueous outflow facility associated with goniodysgenesis involving the pectinate ligament fibers as well as TM dysplasia (Williams, 2007). Morphologic investigation has shown that intertrabecular openings are smaller in affected eyes, particularly in those spaces adjacent to the aqueous plexus (Knepper et al., 1997). Furthermore, replacement of trabecular tissue with a thick extracellular matrix has been demonstrated in affected eyes (Ueno et al., 1999), as well as exaggerated thickening of intraocular BMs such as the anterior lens capsule and Descemet's membrane (Edward & Bouhenni, 2011). Proteomic analysis of aqueous humor from affected eyes has demonstrated significant decreases in proteins like histidine-rich glycoprotein and alpha-2-HS-glycoprotein (fetuin A) in comparison to normal controls

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(Edward & Bouhenni, 2011). These proteins have known effects on the extracellular matrix and may therefore be related to the aforementioned structural and ultrastructural alterations in eyes with this form of glaucoma.

It is also noteworthy that *bu*/*bu* rabbits with chronic elevation of IOP did not demonstrate significant impairment or loss of axonal transport in optic nerve fibers in one study (Bunt-Milam et al., 1987). This observation has been attributed to the lack of a true lamina cribrosa in the rabbit, which may represent a protective mechanism.

While heritable glaucoma is the most studied and characterized form in the rabbit, other forms such as secondary glaucoma resulting from uveitis, or elicitable glaucoma associated with drugs like corticosteroids, have also been reported in rabbits (François et al., 1984).

Cataract

Incidental cataracts, typically punctate to incipient cortical and/or nuclear lens opacities, are occasionally observed in laboratory rabbits (Kern, 1997; see Fig. 33.4B). The results of one large survey demonstrated a 3.6% overall incidence of cataract in pigmented and albino rabbits (Holve et al., 2011). In another study, the incidence of cataract in NZW rabbits was 1.9%, most commonly diagnosed in younger animals (2–4 months; Jeong et al., 2005). In another large survey of NZW and New Zealand Red × NZW F1 crosses (a pigmented strain), spontaneous cataracts were also similarly observed in younger animals, but with higher overall incidence (5.1%; Munger et al., 2002). This same study demonstrated a higher incidence in NZW rabbits in comparison to the F1 crosses (5.7% and 1.1%, respectively). It is noteworthy that, in one of the studies cited above, the animal supplier was a statistically significant factor influencing the incidence of lens lesions in female rabbits (Holve et al., 2011). Other references have cited more frequent observation of cataract in rabbits, with incidence of up to 17% (Williams, 2012). Supplier, geographic location, technique(s) used for examination, and experience of the examiner may represent sources of variation to explain these differences.

Retina

In comparison to other species, spontaneous disease of the retina and posterior segment is rare in laboratory rabbits. In one large survey, the only spontaneous finding involving the posterior segment was choroidal hypoplasia, a typically bilateral lesion, affecting 1.2% of examined animals (Jeong et al., 2005). Since 6 of 7 animals with this finding were from one supplier, a heritable etiology associated with population inbreeding was proposed. Retinal degeneration resembling human retinitis pigmentosa has been described in a small population of pigmented rabbits, characterized by progressive loss of central retinal pigmentation and photopic and/or scotopic ERG deficits that correlated with lesion severity. Clinical lesions in that study correlated histologically with loss of photoreceptor outer segments (Reichenbach & Baar, 1985).

Orbital Disease

Prolapse of both glands of the nictitating membrane have been reported in the rabbit. As observed in dogs with "cherry eye," prolapse of the membrane's superficial gland presents as a smooth, ovoid-to-round mass at the medial canthus. The underlying cause for prolapse is not well understood, but as for dogs, the gland can be successfully surgically repositioned using the Morgan pocket technique (Williams, 2012). Unlike the dog, however, the rabbit has a larger deep NM gland (the harderian gland), which can also prolapse and is distinguishable from the superficial gland not only by its size, but also by its bilobed conformation (Janssens et al., 1999). Orbital gland prolapse may also be observed in association with space-occupying orbital disease and exophthalmos (Fig. 33.14).

As observed in other species, space-occupying orbital disease in rabbits presents with exophthalmos and is commonly caused by inflammation and/or infection. Infectious disease affecting the orbit most typically originates from adjacent cranial structures such as the tooth roots or nasal passages and paranasal sinuses, though hematogenous spread of infection to the orbital tissues has been suggested (Fig. 33.15; Ward, 2006; Williams, 2012). Orbital neoplasia is rare, but lymphoma involving the harderian gland has been reported (Volopich et al., 2005). A parasitic orbital cyst associated with *Taenia serialis* (canine tapeworm) has been described in a rabbit, an intermediate host for that parasite (O'Reilly et al., 2002).

Exophthalmos may also be observed in rabbits with cranial thoracic and/or mediastinal neoplasms, such as thymoma or lymphoma (Kostolich & Panciera, 1992; Künzel



Figure 33.14 Retrobulbar mass effect with third eyelid gland prolapse in a pigmented rabbit. (Courtesy of UC Davis Veterinary Ophthalmology Service.)

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Figure 33.15 Postmortem section demonstrating a retrobulbar abscess (arrowhead) in a pigmented rabbit. (Courtesy of Leandro Teixeira, DVM, DACVP, COPLOW, University of Wisconsin–Madison.)

et al., 2012; Vernau et al., 1995; Wagner et al., 2005). These masses can partially occlude venous circulation returning from the head and neck, leading to hydrostatic engorgement of the rabbit's large orbital venous sinus and forward displacement of the globe. Depending on the size and distribution of the mass, the resulting exophthalmos may be unilateral or bilateral (with or without symmetry). In some affected animals, exophthalmos may be elicited upon neck ventroflexion, or may be prominent in association with sympathetic overdrive/anxiety (Wagner et al., 2005; Williams, 2012).

Miniature Pig

The miniature pig (minipig) is increasingly being used as an animal model in vision science and toxicologic investigations. This is partially attributable to anatomic and biometric similarities between features of the porcine eye and the human eye, including a similar complement of photoreceptors, retinal vessels with similar caliber and distribution, and an area centralis that is considered by some to be an excellent analogue of the human macula (De Schaepdrijver et al., 1992; Svendsen, 2006). This increase in popularity is also attributable to increasing restrictions on the use of NHPs in biomedical research, particularly in the European Union (Prescott, 2010; Svendsen, 2006).

Minipigs are approximately 25% of the size of a regular domestic pig, and several breeds have been cited in scientific investigations (Gutierrez et al., 2015). The Göttingen and Yucatan are the most commonly cited breeds in ocular investigations. Others that may be cited include the Hanford, Sinclair, Ossabaw Island hog, Vietnamese potbellied pig, and the Chinese bama minipig (Liu et al., 2008). It is also noteworthy that unlike the Yucatan and other minipig breeds, the Göttingen is often bred as a pathogen-free strain (Smith & Swindle, 2006). Therefore, Göttingens should be handled prior to other breeds when conducting examinations and/or procedures involving multiple breeds in one day.

Functional Morphology

The domestic pig's eyes are relatively laterally positioned, yielding a total visual field of approximately 260–275° and a binocular field of 30–50° (Middleton, 2010). There is a paucity of data in the published literature regarding visual acuity in pigs, particularly for the minipig. The available literature largely concludes that, while pigs and minipigs have the capacity to discriminate color and pattern, their visual acuity is likely less than that of humans (Moustgaard et al., 2004; Tanaka et al., 1998). Evidence indicates that the domestic pig is a dichromat, but with a comparatively higher ratio of cones to rods than smaller laboratory species, with cones representing approximately 7% of all photoreceptors (Neitz & Jacobs, 1989). Superior to the optic disk and extending nasally and medially is a well-developed, cone-dense area centralis (Chandler et al., 1999; Loget & Saint-Macary, 2000). Unlike the human macula and fovea, however, the porcine area centralis is not completely avascular (De Schaepdrijver et al., 1992; Simoens et al., 1992).

Domestic and miniature pigs both have deep open orbits, with globes that are relatively deep set, particularly in the Yucatan (Loget & Saint-Macary, 2000; Štembírek et al., 2012). The pig has a harderian gland located within the ventromedial orbit, posterior to the globe (Klećkowska-Nawrot & Dzięgiel, 2008; Munkeby et al., 2006). An orbital venous sinus has also been identified in the porcine orbit and, as for the rodent, was formerly used as a site for venous blood collection (Muirhead, 1981).

Combined with their deeply set globes, thick palpebrae with large and coarse cilia, and periorbital fat pads, achieving exposure for biomicroscopic and ophthalmoscopic examination can be a challenge in pigs, particularly in unanesthetized animals. The pig also has an NM supported by an anchor-shaped cartilage, and an associated superficial gland at its base (Klećkowska-Nawrot & Dzięgiel, 2007; Sanchez et al., 2011; Schlegel et al., 2001). In Yucatan minipigs, the medial caruncle and leading edge of the NM are commonly pigmented. The sclera in Yucatan and Göttingen minipig will appear grayish or slightly brown in color, respectively; and the iris may also vary in color, typically appearing brown-blue or blue in the Göttingen (Fig. 33.16) and brown in the Yucatan (Loget & Saint-Macary, 2000). It is noteworthy that domestic and miniature pigs have only a single nasolacrimal punctum, found just internal to the eyelid margin on the medial aspect of the superior eyelid (Vézina, 2012).

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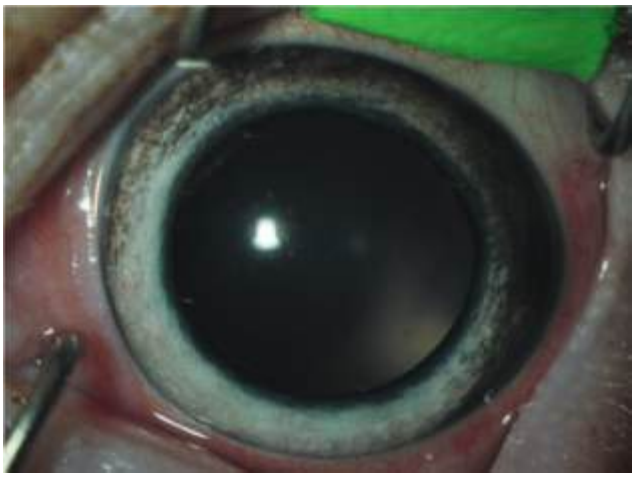


Figure 33.16 Normal heterochromia iridis in a miniature pig. (Courtesy of Ocular Services On Demand (OSOD).)

In one study involving clinical ophthalmic examination in adult animals, the authors subjectively described the PLRs in both adult Yucatans and Göttingens as slower and with a smaller amplitude than in other laboratory species (Loget & Saint-Macary, 2000). On slit-lamp examination in the same study, the profiles of the minipig lens and its anterior and posterior curvatures were similar to those of the dog and NHP (Loget & Saint-Macary, 2000). The aqueous outflow system of the domestic pig bears many morphologic similarities to other mammalian species like the dog and rabbit; however, a detailed anatomic investigation has also confirmed the presence of corneoscleral TM bearing greater resemblance to that of NHPs and humans (McMenamin & Steptoe, 1991).

The pig retina is holangiotic with no tapetum lucidum (Loget & Saint-Macary, 2000; Vézina, 2012). The retinal arterioles originate from four principal bundles at the medial and lateral aspects of the ovoid optic disk, dichotomously branching toward the periphery (Loget & Saint-Macary, 2000). The miniature pig also has a large retinal border venule that is particularly prominent ventrotemporally (Simoens et al., 1992). While the arrangement of the intraretinal capillary system and other features of retinal vascular anatomy in pigs resemble those of humans, it is noteworthy that the major vessels of the porcine retina tend to lie more vitread in the nerve fiber layer in comparison to the human retina (Bloodworth et al., 1965; Simoens et al., 1992). On ophthalmoscopic examination, the fundus of the Göttingen and Yucatan is commonly tigroid in appearance due to the relative lack of pigmentation of the RPE and exposure of the underlying choroid. This is particularly common in the Göttingen, which may be naturally blue-eyed or have heterochromia iridis (Loget & Saint-Macary, 2000; Sanchez et al., 2011).

Spontaneous Lesions and Diseases

While minipigs bred for laboratory studies are often clinically normal on ophthalmic examination (Wilkie, 2014), spontaneous lesions and naturally occurring diseases may be observed in a number of the breeds used in vision science and toxicology. Therefore, the examiner should have familiarity with their characteristics and significance in the context of scientific and drug safety studies. Note that the majority of clinically significant infectious diseases of the domestic pig eye, particularly systemic diseases with ocular manifestations, are rarely observed in purpose-bred laboratory species of minipig, and will therefore be discussed in greater detail in other chapters.

Congenital/Developmental Anomalies

Microphthalmos (and less commonly anophthalmos) with or without retinal dysplasia and other ocular anomalies has been described in young piglets in association with maternal hypovitaminosis A (Goodwin & Jennings, 1958; Huston et al., 1978; Palludan, 1976; Watt & Barlow, 1956). Microphthalmos may also be related to heritable causes in certain domestic breeds, but this has not yet been reported in the minipig (Middleton, 2010). While rare, polycoria and suspected anterior uveal colobomas have been described in pigs, and colobomatous lesions involving the optic disk and choroid have been described specifically in minipigs (Rubin, 1974; Saint-Macary & Berthoux, 1994).

Adnexa and Anterior Segment

Entropion is commonly diagnosed in minipig breeds such as the Vietnamese pot-bellied pig, related to robust subcutaneous periocular and forehead fat. In some cases, the conformational entropion may be severe enough to impair vision. While this condition is not common in other minipig breeds, it has been reported in the Göttingen (Helke et al., 2016). Primary conjunctivitis is uncommon in purpose-bred minipigs, but a transient, self-limiting blepharoconjunctivitis has been described in young (6–8-week-old) Göttingens, though the cause was unknown (Loget & Saint-Macary, 2000). Possible infectious causes of primary blepharitis and/or conjunctivitis in domestic pigs may be associated with *Chlamydia suis*, *Chlamydia pecorum*, *Chlamydia abortus*, *Escherichia coli*, *Mycoplasma* spp., *Klebsiella* spp., *Pasteurella* spp., and African swine fever virus (Longbottom, 2004; Middleton, 2010; Rogers et al., 1991, 1993; Vestre, 1984).

A clinical syndrome of cutaneous malignant melanomas and associated uveitis has been reported in up to 54% of miniature Sinclair pigs at birth, affecting up to 85% of animals by 1 year of age. The associated tumors may affect the eyelids and periocular skin, may be associated with localized cutaneous depigmentation, and spontaneously regress. Uveitis develops in affected animals due to a predominantly monocytic immunopathologic destruction of intraocular melanocytes (Feeney-Burns et al., 1988).

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Incidental lesions involving the anterior uvea have also been reported in domestic and miniature pigs. PPMs are relatively commonly observed in both Yucatan and Göttingen minipigs. The cause is not completely understood, but a genetic predisposition has been proposed (Loget & Saint-Macary, 2000). In one study, PPMs were observed in 66.1% of Yucatan minipigs (between 7 and 12 months of age), with incidence decreasing with increasing age (Saint-Macary & Berthoux, 1994). In another study, PPMs were observed in 33.3% and 13.0% of juvenile and adult Göttingens, respectively (Loget & Saint-Macary, 2000). PPMs may involve the anterior lens capsule, but do not appear to adversely impact vision behaviorally (Loget & Saint-Macary, 2000).

Spontaneous lens opacities have been described in both Yucatan and Göttingen minipigs. One study in Yucatans described punctate posterior cortical lens opacities in 14.3%–20.5% of 7–12-month-old animals (Loget & Saint-Macary, 2000; Saint-Macary & Berthoux, 1994). Similar posterior cortical opacities have been observed in both juvenile and adult Göttingens, affecting 19.4% and 11.7%, respectively (Loget & Saint-Macary, 2000). The incidence of cortical lens opacities in either breed, however, does not appear to correlate with increasing age (Loget & Saint-Macary, 2000). Other opacities involving the nucleus and posterior capsule have been described in both breeds (Loget, 1995; Loget & Saint-Macary, 2000). Posterior capsular opacities are often observed in association with hyaloid remnants (see below), but are also occasionally observed in the absence of any other structural lesions (Saint-Macary & Berthoux, 1994; Taradach et al., 1984).

Posterior Segment

Incidental abnormalities involving the vitreous are common in minipigs. In one study, hyaloid remnants were observed in 82.1% of Yucatans, in some persisting through 33 months of age and over (Saint-Macary & Berthoux, 1994). In Göttingens, hyaloid remnants were observed in 83.3% and 70.4% of juveniles and adults, respectively (Loget & Saint-Macary, 2000). Hyaloid remnants may vary in clinical appearance, forming either a linear structure spanning the vitreous from the optic disk to the posterior lens capsule, or as a fragment of the original structure, observed free-floating or in close association with the posterior lens capsule.

One study has also described small refringent vitreous opacities ("refringent points") on biomicroscopic examination of the anterior vitreous of 7.1% of adult Yucatans, and 5.6% and 4.9% of juvenile and adult Göttingens, respectively (Loget & Saint-Macary, 2000).The origin and significance of these findings are unknown, but they do not appear to correlate with other biomicroscopic findings or have any detectable impact on vision.

Lesions involving the optic disk are uncommon in minipigs. Bilateral optic nerve hypoplasia has been described in purpose-bred piglets, and has been clinically coupled to efferent PLR deficits, though a definitive etiology has not been reported (Rubin, 1974).

Nonhuman Primate

In many respects, the NHP eye represents the "ideal" animal model for the human eye in vision science and ocular toxicology, as the two species share numerous ocular anatomic and physiologic similarities. Conducting ophthalmic research in NHPs, however, also carries safety concerns and zoonotic infectious disease risks that require husbandry staff, handlers, and examiners to be experienced in the necessary health and safety practices and precautions. Furthermore, ethical and welfare concerns regarding the use of NHPs in research and drug development have resulted in the implementation of certain laws and provisions, particularly in the European Union, placing restrictions on NHP use in biomedical research (Chapman et al., 2015).

The NHP remains a widely used species in ocular drug and device development in North America, believed by many to be the most translatable model for evaluating the efficacy, safety, and tolerability of ocular drugs and devices. Therefore, the veterinary ophthalmologist or qualified examiner must be familiar with the commonly used species and the relevant features of the primate eye in order to ensure their welfare in such studies, and to ensure that study results are interpreted accurately and appropriately. The most commonly used NHP species in preclinical eye research are Old World NHPs (parvorder Catarrhini) such as the cynomolgus macaque ("crab-eating macaque"; *Macaca fascicularis*) and the rhesus macaque (*Macaca mulatta*). Others used less commonly include the African green monkey (*Chlorocebus sabaeus*) and the common marmoset (*Callithrix jacchus*), a New World monkey (parvorder Platyrrhini).

Functional Morphology

In many ways, the visual system of the NHP is similar to that of humans. In most NHP species the globes are oriented frontally, yielding a higher degree of binocular overlap than in other laboratory species (Abee et al., 2012; Heesy, 2004). One reference confirmed a binocular overlap of 140° in the rhesus macaque, identical to that of the human (Ross, 2000). In prosimian NHPs (Strepsirrhini and tarsiers; e.g., lemurs and lorises), the orientation of the globes is slightly more lateral. Reported visual acuity in rhesus and cynomolgus macaques ranges between 46 and 53.6 cycles per degree (Kirk & Kay, 2004). Also like humans, Old World monkeys are trichromatic, with one study demonstrating a relative uniformity of color vision and spectral sensitivity across all catarrhines (Jacobs, 1986). While New World primates and some prosimians bear the genetic capacity for trichromacy, only females express the trichromat phenotype. This polymorphic pattern of expression is a result of the X-linked nature of medium- to long-wavelength opsin, meaning that

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only females with two different alleles for these opsins will be trichromats; and that all males of these species are dichromats (Jacobs, 2007; Mollon et al., 1984; Valenta et al., 2018; Veilleux & Bolnick, 2009).

Like the human, the orbits of NHPs have a frontal orientation, allowing the convergence that enables enhanced binocular vision in most species (Hwang et al., 2012). In contrast to other laboratory species, the orbit is closed laterally by a postorbital bar; and in anthropoids and tarsiers, a postorbital septum separates the orbit from the temporal fossa (Heesy et al., 2007). Among Old and New World monkeys and prosimians, however, there are considerable variations in orbital size and scale, influenced by a number of evolutionary and ecologically divergent factors including activity pattern (e.g., diurnal vs. nocturnal) and body size (Heesy, 2004; Kay & Kirk, 2000; Kirk, 2004, 2006). Unlike smaller mammals, primates lack a retractor bulbi (RB) muscle. However, it has been suggested that an accessory lateral rectus muscle, observed in the cynomolgus macaque, may represent a vestigial structural analogous to the RB (Gonnering et al., 1984; Spencer & Porter, 1981). It is noteworthy that, unlike other mammalian species whose orbits and ocular structures are largely supplied by the internal maxillary artery, a branch of the external carotid artery, the NHP orbit and globe receive the majority of their vascular supply from the internal ophthalmic artery, a branch of the internal carotid artery (Prince et al., 1960).

Likewise, there are variations among NHP species with respect to lacrimal anatomy. Old World monkeys like the macaques possess similar anatomy to humans, with a primary orbital lacrimal gland located in the superotemporal aspect of the orbit (Ankel-Simons, 2010). However, one morphologic report has described lacrimal tissue within the orbital fissure in the cynomolgus (Gonnering et al., 1984). In the tufted capuchin (*Cebus apella*), the primary lacrimal gland comprises intraorbital and extraorbital portions, an anatomic feature more characteristic of rodents (Neto et al., 1992). The presence of an extraorbital lacrimal gland has also been reported in the marmoset, another New World monkey (Katsuta et al., 2000). Like humans, the NHP does not usually possess an NM or associated glands.

Many anatomic features of the Old World NHP cornea mimic those of humans, including the presence of a Bowman's membrane in the anterior stroma (Merindano et al., 2003). Despite general similarities in morphology, though, it is noteworthy that central corneal thickness and diameter are comparatively smaller in macaques, particularly the cynomolgus (Lapuerta & Schein, 1995; Zurawski et al., 1989). This difference could have an impact on the pharmacokinetics of topically applied drugs when compared to humans (Miller, 2013). Furthermore, corneal diameter in primates tends to vary according to activity, with nocturnal species generally possessing larger corneas, believed to contribute to enhanced visual sensitivity in low-light conditions (Kirk, 2004). Attributes of lens anatomy are also relatively similar between humans and macaques, though axial diameter is smaller in both rhesus and cynomolgus (Borja et al., 2010; Lapuerta & Schein, 1995; Qiao-Grider et al., 2010). In nocturnal New World species with larger corneas, the lens is typically wider in diameter with a more spherical profile (larger axial diameter), and the posterior nodal point is displaced posteriorly toward the retina, believed to produce a larger image across more ganglion cell fields (Kirk, 2004).

Aqueous humor dynamics have been extensively studied in macaques, and these species tend to respond to topical glaucoma medications in a predictable manner that mimics the human response (Miller, 2013). Macaques possess other anterior segment structures that resemble those of humans, such as a well-developed ciliary musculature, corneoscleral and uveal TM, and Schlemm's canal (Lütjen-Drecoll, 1999).

Like most other laboratory species, the fundus of most Old World NHPs is atapetal and the retina is holangiotic. However, the NHP is the only laboratory species whose retina possesses a true macula and cone-dense fovea, analogous to the same structures providing high visual acuity in the human (Abee et al., 2012; Finlay et al., 2008). This is of particular importance in the assessment of ocular drug and device safety, as toxicity or adverse effects involving these structures carry a higher translational significance and risk in human patients. The New World owl monkey (*Aotus* spp.) has a more rod-dominant retina and lacks a macula (Abee et al., 2012). Strepsirrhine species (e.g., lemurs and lorises) do possess tapeta, but lack a true macula or fovea (Fleagle, 2013). NHPs also have a well-defined lamina cribrosa (Lockwood et al., 2015) and a central retinal artery (Wilkie, 2014).

Spontaneous Lesions and Diseases

According to one report, naturally occurring ocular disease only represented 0.8% of all clinical cases over a 4-year period at a large primate research center (Ribka & Dubielzig, 2008). In a large study involving *noncaptive* rhesus macaques in India, traumatic injuries to the eye were very common, showing correlation between proximity to urban areas and a likely relationship with inter-animal aggression over food and/or territory (Kumar et al., 2015). While the same environmental and social factors in noncaptive animals are not necessarily reproduced in the laboratory setting, nearly one-third of ocular abnormalities in the aforementioned primate center study were secondary to trauma or wounding (Ribka & Dubielzig, 2008). The increasingly popular practice of social housing in laboratory NHPs (often referred to as "European housing") may also increase the incidence of ocular or periocular trauma in the vivarium. However, agency report does indicate that these risks in inherently social species like macaques do not necessarily outweigh the welfare benefits of group housing (Reinhardt et al., 1995).

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Adnexal and Ocular Surface Disease

Blepharitis and conjunctivitis are reported with relative frequency in NHPs. In one survey conducted in a large primate research facility, blepharitis and conjunctivitis accounted for 29% and 21% of observed ophthalmic abnormalities, respectively (Ribka & Dubielzig, 2008). Primary infectious blepharitis, however, is not commonly cited and is more likely to be observed secondary to extension of primary infectious conjunctivitis (see below) or due to trauma. The examiner must also be aware of iatrogenic causes of eyelid inflammation and/or swelling in NHPs. As with humans and other species, administration of morphine or morphine derivatives may cause intense periocular and facial pruritus after intravenous administration or even following epidural injection (Horne, 2001). Examiners must also remember that routine subdermal tuberculosis (TB) testing is commonly performed adjacent to the superior eyelid in NHPs (Johnson-Delaney, 1994).

Primary infectious conjunctivitis may be observed in captive NHPs. Viral infection with herpesvirus simiae B, an endemic alpha herpesvirus of macaques, may cause mild conjunctivitis (Weigler, 1992). While routine screening and breeding practices have decreased the incidence of this virus in purpose-bred macaques, examiners and handlers must still be acutely aware of possible manifestations, since zoonotic transmission of this virus to humans via aerosolization, mucous membrane exposure, or wound exposure can risk causing a fatal encephalitis (Benson et al., 1989). Conversely, herpesvirus simplex type I, a common and typically benign cause of mucosal lesions in humans, can produce conjunctivitis in NHPs and can even progress to cause fatal disease in some animals, particularly New World monkeys (Mätz-Rensing et al., 2003). While less common, other viruses reported to cause conjunctivitis NHPs include the measles virus (rubeola) and simian adenovirus (SV15 and SV17; Kumar et al., 2015; Landon & Bennett, 1969; Lowenstine & Osborn, 2012; Tyrrell et al., 1960).

The normal bacteriologic flora of the ocular surface have been investigated in the capuchin monkey, confirming growth of only Gram-positive bacteria such as *Streptococcus* spp., *Micrococcus* spp., and *Corynebacterium* spp. (Montiani-Ferreira et al., 2008). As with other species, however, these organisms carry the potential to be pathogenic in the face of immunosuppression and/or ulceration of the corneal surface. Recurrent conjunctivitis of suspected bacterial etiology was treated in one study with local deep subconjunctival/periorbital injection of gentamicin (Gografe et al., 2015). Noninfectious causes of conjunctivitis may include allergy, incidental contact with irritants, or conjunctival foreign bodies (Williams, 1999).

Corneal disease is occasionally observed in captive NHPs. In one large survey of captive macaques, corneal ulcerations were diagnosed in 2.9% of animals with ocular lesions (Ribka & Dubielzig, 2008). In a smaller survey, corneal abrasions with or without conjunctivitis were the most common lesions observed in rhesus macaques (Schmidt, 1971). In the aforementioned study of noncaptive macaques in India, corneal opacities of presumed traumatic origin were very common, and similar opacities in purpose-bred macaques are also likely to be traumatic (Kumar et al., 2015).

Anterior Segment Disease

Glaucoma is uncommon in purpose-bred NHPs. However, a potential naturally occurring primary glaucoma was described in a now well-characterized colony of adult rhesus macaques from Cayo Santiago, an island off the coast of Puerto Rico (Dawson et al., 1993, 1998). Many affected animals in this frequently studied colony had possible primary open-angle glaucoma (POAG), but there were also animals with "normotensive" eyes. The investigation was eventually discontinued as the model (elevated IOP and optic nerve degeneration) could not be validated in multiple generations.

Secondary glaucoma is uncommonly reported in NHPs but, as in other species and in humans, antecedent inflammatory intraocular disease may predispose any animal to impaired aqueous outflow. Endogenous uveitis is uncommon in purpose-bred macaques, but zoonotic transmission of *Mycobacterium tuberculosis* from handlers or other vivarium employees to captive NHPs may occur (Flynn et al., 2015; West et al., 1981).

Cataracts are commonly reported in macaques and other laboratory NHP species. Fortunately, the majority of lens opacities historically described in young animals are incidental and carry no detectable significance when it comes to functional vision in affected animals (Sasaki et al., 2011). As observed in humans, however, the incidence of cataracts increases with age in NHPs, and they especially affect those over 20 years of age. Descriptions of opacities in older rhesus macaques have ranged from progressive involvement of the anterior and/or posterior cortex and spicular opacities to more mature opacities with water clefts and even mild brunescence (Kaufman & Bito, 1982). Heritable cataracts have also been reported in African green monkeys (Suzuki et al., 1988). Predominantly bilateral subcapsular (anterior and posterior) cataracts have also been described in gray mouse lemurs, affecting 21% and 48% in two colonies, respectively (Beltran et al., 2007). The cause of the cataracts in those colonies, however, was undetermined.

Successful surgical removal of cataracts has been reported in various species of NHP (Clouser, 2010; de Faber et al., 2004; Leiva et al., 2012; Montiani-Ferreira et al., 2010; Warwick et al., 2017; Whitley et al., 1980), and is generally associated with good postoperative outcomes. This is particularly noteworthy as, compared to other species, quality of life in NHPs is largely dependent on the maintenance of normal social interactions, which can be negatively impacted by vision impairment. Compared to cataract surgeries in companion animals and equids, however, surgical

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approaches in NHPs must often be made laterally due to the prominent supraorbital crest of many species. Furthermore, NHPs have much shallower anterior chambers and lenses with shorter anterior-posterior widths in comparison to other animal species, and a particularly thin lens capsule. As observed in human patients, postoperative uveitis tends to be relatively mild in NHPs, requiring a more abbreviated course of anti-inflammatory medications (Leiva et al., 2012).

Posterior Segment Disease

Lesions involving the posterior segment are more common than those of the anterior segment in NHPs. In one study of over 2000 wild-caught cynomolgus macaques, nearly 8% of the animals had some sort of ophthalmic lesion, the majority of which were observed in the posterior segment (Kuhlman et al., 1992). While most macaques that are used in preclinical and toxicologic studies are purpose bred instead of wild caught, some lesions such as incidental chorioretinal scars may still be observed. Other lesions described in the posterior segment of NHPs include lipemia retinalis in cynomolgus monkeys (Suzuki et al., 1989), and choroidal and optic nerve colobomas (Suzuki, 1986; Williams, 1999). Central retinal arterial occlusion, a common and vision-threatening condition in human patients, has also been described in a primate (Williams, 1999). Peripheral cystoid retinal degeneration and pars plana cysts may be observed in older animals (El-Mofty et al., 1980).

In both rhesus and cynomolgus macaques, there is a considerable spectrum of normal variation with respect to fundus pigmentation. In one study examining rhesus macaques (including some from Cayo Santiago), animals with a lighter coat ("golden" rhesus) commonly exhibited nasal hypopigmentation of the fundus, with or without temporal hypopigmentation, resulting in visualization of the underlying choroidal vasculature (Dawson et al., 2004). Macular pigmentation, however, was maintained in these animals. While veterinary ophthalmologists engaged in preclinical studies are not likely to examine NHPs of this coat color variation, there is still a spectrum of fundus pigment variation in the more typical brown-tan rhesus and cynomolgus macaques that may bear some resemblance to those described in golden rhesus. It is particularly important that such variations be identified on prestudy examination to ensure that they are not mistaken for an adverse effect of a drug or device in safety evaluations.

In rhesus and cynomolgus macaques, a spontaneous form of AMD analogous to human early to intermediate dry AMD has been described and investigated (Bellhorn et al., 1981; Dawson et al., 1989a, 1989b; El-Mofty et al., 1980; Francis et al., 2008; Hope et al., 1992; Neuringer et al., 2010; Nicolas et al., 1996; Suzuki et al., 2003; Umeda et al., 2005a, 2005b). In both species, the lesions are characterized by pigmentary changes within the macular region, consistent with accumulation of subretinal or RPE drusen. Despite the general similarity in the clinical appearance of AMD lesions in both species, there are important features that distinguish the disease in cynomolgus and rhesus. In cynomolgus monkeys, lesions are earlier in onset, observed in animals as young as 2 years of age, progressing thereafter.

Histologically, lesions comprise lipofuscin within the RPE. Investigation has proven that the inheritance pattern for these lesions in cynomolgus macaques is autosomal dominant. In contrast, lesions in rhesus macaques are observed later in life (typically after 9 years of age), comprising drusen within Bruch's membrane and under/within the RPE. Furthermore, the inheritance pattern in rhesus macaques has not been definitively identified. Investigation has been carried out in the Cayo Santiago rhesus colony, where this form of AMD has been identified in a large number of aged animals. The predominance of AMD within certain lines has facilitated identification of key contributing gene polymorphisms such as the *ARMS2* gene and the *HTRA1* promoter region. These findings at least partially support a shared genetic basis for this complex disease between humans and affected macaques (Francis et al., 2008). It is noteworthy that, despite the apparent resemblance between lesions in macaques and humans with dry AMD, very few animals experience disease progression to lesions that resemble the human wet form of AMD, characterized by proliferative choroidal neovascularization.

In the rhesus macaque, an idiopathic form of bilateral optic nerve atrophy (BOA) has been reported. The primary clinical feature is pallor of the temporal optic disk, a lesion that is invariably bilateral in affected animals and bears similar degrees of severity bilaterally (Fortune et al., 2005). This condition is not associated with detectable visual deficits, instead being recognized as an incidental finding on ophthalmoscopic examination. Histologically, the finding is correlated with degeneration of ganglion cell axons and gliosis. Lesions are invariably restricted to the temporal and anterior aspect of the optic nerve, though an overall reduction in the nerve's cross-sectional area has also been documented. Within the retina, there is corresponding thinning of the temporal retinal nerve fiber layer (RNFL) as well as loss of macular ganglion cells. Functionally, full-field flash ERG is normal, but pattern electroretinogram (PERG) demonstrates reduced function of the RGCs and optic nerve. Further investigation has shown that blood flow and normal vascular autoregulatory functions in affected retinas are reduced in *all* retinal regions, not just the temporal region, despite its comparatively greater loss of RNFL thickness (Piper et al., 2013). No underlying systemic disease has been associated with this condition, nor has a heritable etiology or inheritance pattern been confirmed. From a clinical perspective, BOA poses a considerable challenge to examiners since the lesions, even those corresponding to moderate histologic severity, are subtle and may go unrecognized.

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Normative Ancillary Diagnostic Values in Laboratory Species

Values for ancillary clinical endpoints such as tonometry, STT, and TBUT have been published for most of the species discussed in this chapter (see Table 33.2). When choosing optimal equipment or methodology or when considering which animal model is most appropriate for a given study, there are important factors that must be kept in mind for both the acquisition and interpretation of diagnostic values.

Tonometry

Measurement of IOP is an essential endpoint in many ocular toxicology and drug/device development studies. Low IOP (hypotony), for example, is commonly observed with uveitis, whether resulting from the procedure required to deliver a drug or device or the drug/device itself. Abnormally high IOP is an important finding in any study evaluating drug toxicity, as it potentially represents a clinically significant adverse effect. Furthermore, accurate measurement of IOP is essential in studies using animal models to specifically evaluate the efficacy of drugs indicated for the treatment of glaucoma in human patients.

Manometry is the gold standard for direct measurement of IOP in any species, but this technique is invasive and requires anesthesia, making it impractical in toxicologic studies. Instead, less invasive IOP measurement is performed using commercial handheld tonometers that indirectly determine IOP using algorithms based on principles of corneal applanation (flattening of an area of the cornea) or corneal rebound (the acceleration/deceleration properties of an incident object projected onto the corneal surface). Some commonly used commercial applanation tonometers such as the Tono-Pen® (Reichert Technologies, Ametek, Berwyn, PA, USA) have been redesigned with a smaller probe tip, optimized and calibrated for animals, and marketed for veterinary use (e.g., the Tono-Pen Vet®). Likewise, a laboratory version of the TonoVet® rebound tonometer (Icare, Vantaa, Finland), the TonoLab®, has been optimized for use in mice and rats. When using the TonoVet instrument in larger laboratory species like the rabbit, minipig, and NHP, the calibration should be set to the "d" (dog) setting; however, it is noteworthy that this setting is still not perfectly suited to accurate IOP measurement in any of these species (Elsmo et al., 2011; Miller, 2013).

In a veterinary study involving dogs, IOP measurements collected using handheld applanation and rebound tonometers yielded a precise, linear relationship to manometric IOP, but both underestimated true IOP (Görig et al., 2006). Similar results have been demonstrated in laboratory species (Acosta et al., 2007; Cohan & Bohr, 2001b; Lewin & Miller, 2017). Differences in comparison to manometry can be attributed to numerous factors, including corneal anatomic variables like central thickness and curvature, which will vary among different laboratory species (Liu & Roberts, 2005; Park et al., 2011). Other sources of tonometer error in laboratory species may include (but are not limited to) sedation or anesthesia (Dogan et al., 2016; Holve et al., 2013), pharmacologic dilation (Taylor et al., 2007), excessive or improper restraint (Broadwater et al., 2008; Klein et al., 2011), use of topical anesthetics (Sarchahi & Bozorgi, 2012), tonometrist technique and experience (Miller, 2013), and, in particular, poor animal acclimation to IOP measurement (Dinslage et al., 1998; McLaren et al., 1996). Furthermore, in laboratory studies involving animal models of ocular surface disease or toxicology studies involving topically applied drugs, variables such as ocular surface drying, corneal surface irregularities, or changes in tear film viscosity may introduce additional error into measurements obtained using handheld tonometers (Liu & Roberts, 2005).

In any study including tonometry as an endpoint, personnel involved with animal handling, collection of IOP data, and interpretation of tonometric results should be aware of these sources of variability. With respect to study planning, efforts to control for these variables should be practiced. Acclimation to the designated personnel and tonometry procedures should be carried out prior to study initiation. Furthermore, the same type of tonometer and, when possible, the same instrument should be used for IOP measurements throughout study duration. Since diurnal fluctuations in IOP have been documented for all of the species commonly used in toxicology and drug development studies (see species-specific sections below), measurements should be collected at the same time of day during the course of a study. Normative mean values reported for IOP in different species are presented in Table 33.2.

Rodents

In addition to use in toxicology studies, mice and rats are commonly used as animal models for glaucoma (Johnson & Tomarey, 2010). Both species are naturally crepuscular (active at twilight), with diurnal fluctuation in IOP characterized by higher IOP under dark conditions and lower IOP during light conditions in animals on a 12 h/12 h dark/light cycle (Aihara et al., 2003; Moore et al., 1996). Some studies have demonstrated loss of circadian IOP fluctuations in rodents housed under nondiurnal light cycles (e.g., continuous dim light). The magnitude of this effect, however, is debated, as other studies have demonstrated only a dampening of these normal diurnal fluctuations (Lozano et al., 2015).

Tonometric measurements have been made in mice and rats using a range of applanation and rebound tonometers. Using the Tono-Pen XL, one study in mice reported a high degree of reproducibility and accuracy in comparison to manometry (Reitsamer et al., 2004). Others have supported

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the utility and reproducibility of the Tono-Pen in mice, particularly if the latex cover is not used, and the equipment is frequently cleaned with alcohol between readings (Pang et al., 2005). Conversely, other investigators have demonstrated poor reproducibility using the Tono-Pen (Dalke et al., 2005; Pease et al., 2006; Saeki et al., 2008). Much of the criticism of the Tono-Pen (and Tono-Pen XL) in mice stems from the size of the instrument's 3.2 mm footplate (which surrounds its 1.0 mm transducer tip), in comparison to the diameter of the typical laboratory mouse cornea at approximately 2.6 mm (Henriksson et al., 2009). The Goldmann applanation tonometer has also been modified for use in awake mice, with studies reporting acceptable reproducibility, though it has been shown to underestimate manometric IOP and, in one study, to overestimate IOP at levels > 20 mmHg (Cohan & Bohr, 2001a, 2001b). Therefore, much investigation has shifted to the use of rebound instruments like the TonoLab in rodents due to the instrument's considerably smaller probe size.

Studies have shown that measurements taken using a rebound tonometer specifically calibrated for laboratory species (TonoLab) are superior to those via an applanation tonometer for predicting manometric values in mice and rats (Kim et al., 2007; Pease et al., 2006; Saeki et al., 2008; Wang et al., 2005). In mice, measurements taken using the TonoLab were also shown to be reproducible and accurate and able to detect small changes in IOP in conscious mice, underscoring that this instrument may be sensitive for identifying changes that could be missed in sedated or anesthetized animals (Johnson et al., 2008). Furthermore, investigators have endorsed the rebound tonometer's ease of use, lack of need for topical anesthesia and chemical restraint, and reduced stress on the animals (Millar & Pang, 2015).

Guinea Pigs

Studies investigating aqueous humor dynamics and IOP measurement in the guinea pig are less commonly published than in other rodents. This may be, in part, due to the apparently nebulous and arrhythmic sleep–wake cycles observed in this species (Tobler et al., 1993). One study demonstrated a diurnal fluctuation that mimics that of mice and rats, with lower IOPs measured during the light phase and higher IOPs during the dark phase (Ansari-Mood et al., 2016). Conversely, another study demonstrated a peak IOP during the early morning, followed by a predictable decrease throughout the course of the day thereafter (Ostrin & Wildsoet, 2016). Both studies utilized rebound tonometry to obtain IOP measurements. Another study using both the TonoVet and the Tono-Pen Vet demonstrated that IOPs in younger animals tend to be lower than those in older animals (Cairó et al., 2018). One study cited the use of different calibration settings in the TonoVet as a possible source of variability between studies for measurements obtained using rebound tonometry (Cairó et al., 2018). To this author's knowledge, the optimal calibration setting for use in the guinea pig has not been determined, nor have the suitability and accuracy of the TonoLab been studied in larger rodents like the guinea pig.

IOP measurements have been reported in guinea pigs using both applanation and rebound tonometers, with most studies reporting values obtained in awake animals (Ansari-Mood et al., 2016; Cairó et al., 2018; Coster et al., 2008; Di et al., 2017; Ostrin & Wildsoet, 2016; Rajaei et al., 2016). Among these investigations, there was wide variability in reported values regardless of the type of tonometer used. In general, studies that utilized applanation tonometry (Tono-Pen Vet; Ansari-Mood et al., 2016; Cairó et al., 2018; Coster et al., 2008) reported mean IOPs that tended to be higher (range 10.93–18.28 mmHg) than in studies that utilized rebound tonometry (range 6.19–20.0 mmHg; Ansari-Mood et al., 2016; Cairó et al., 2018; Di et al., 2017; Ostrin & Wildsoet, 2016; Rajaei et al., 2016).

Rabbit

Rabbits are one of the most commonly utilized species for safety evaluation of topical and intraocular drugs and devices, and are also commonly used as models for experimental glaucoma (Bouhenni et al., 2012). Most studies in rabbits have described a diurnal variation in IOP characterized by increased IOP during darkness, and decreased IOP during times of light (Percicot et al., 1996; Pereira et al., 2011; Rowland et al., 1981; Wang et al., 2013; Zhao et al., 2010). Furthermore, one study demonstrated that the rabbit's circadian rhythm could be completely eliminated under continuous light conditions (Rowland et al., 1981).

Given the rabbit's popularity as a species in toxicology and drug development, numerous studies have been published reporting the use of applanation and rebound tonometry in rabbits. In many studies, applanation tonometry using the Tono-Pen or Tono-Pen XL has been associated with generally acceptable reproducibility (Abrams et al., 1996; Lim et al., 2005; Ma et al., 2016; Mermoud et al., 1995). However, one study reported considerable variability in measurements taken using the Tono-Pen XL (Acosta et al., 2007), underscoring the difficulties that may be encountered when using an instrument designed for human patients in a nonhuman species. Common to all studies using applanation tonometers in rabbits was underestimation of manometric IOP, with two studies reporting acceptable accuracy only at levels under 30 mmHg (Abrams et al., 1996; Acosta et al., 2007). In comparison to applanation tonometers, rebound tonometers like the TonoVet have demonstrated less variability, improved reproducibility, and generally good correlation with manometric values (Ma et al., 2016; Pereira et al., 2011; Zhang et al., 2014). In some studies, however, the TonoVet still showed a tendency to underestimate IOP values in comparison to manometry (Ma et al., 2016; Zhang et al., 2014).

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Minipig

The minipig is increasingly used in toxicology and drug development, as well as in novel models of experimental glaucoma (Galdos et al., 2012; Ruiz-Ederra et al., 2005; Vecino et al., 2007). Recently, both applanation and rebound tonometers have been evaluated against manometry in enucleated pig eyes (Lewin & Miller, 2017; Löbler et al., 2011). One study found that rebound tonometry using the TonoVet provided a more accurate approximation of IOP than applanation tonometry, with slight underestimation of IOP at low pressures and slight overestimation at high pressures (Lewin & Miller, 2017). The other study utilized a rebound tonometer calibrated for human eyes, which demonstrated a tendency to underestimate true IOP in pigs (Löbler et al., 2011). It is noteworthy that these two studies differ from others conducted in laboratory species as they were performed *ex vivo* with enucleated globes, and this should be taken into consideration when interpreting their results. However, the conformational features of the minipig eye (e.g., deep-set globes, thick eyelids), often oily or waxy tear film, and challenges associated with restraint in this species could also result in considerable variability in measurements if conducted *in vivo* (Miller, 2013).

Nonhuman Primate

NHPs, specifically rhesus and cynomolgus macaques, are commonly used in drug safety evaluations, and also as models for induced experimental glaucoma (Burgoyne, 2015). A colony of rhesus macaques with potential naturally occurring POAG on an island offshore from Puerto Rico (Cayo Santiago) has also been intensively studied, but its usefulness was not able to be validated. In a study utilizing clinically normal monkeys from two Cayo Santiago breeding colonies, young animals demonstrated a gradual decrease in IOP between the morning and early afternoon, whereas older animals exhibited very little fluctuation (Bito et al., 1979). In another study from this colony comparing IOP fluctuations between normal macaques and those with hypertensive or normotensive glaucoma, those with hypertensive glaucoma exhibited greater daily variation in IOP and, as well as a significant tendency toward higher IOP during the course of the day, the findings mirrored those in humans with POAG (Komáromy et al., 1998).

Applanation tonometry has been used frequently for measurement of IOP in macaques, and does not appear to be significantly altered by ketamine sedation, which is commonly used to facilitate examination and other clinical procedures (Bito et al., 1979; Dawson et al., 1993; Kaufman & Davis, 1980; Millar & Pang, 2015). Evaluation of applanation tonometry in comparison to manometry in cynomolgus macaques demonstrated good repeatability, but a general underestimation of true IOP at levels above 5 mmHg (Peterson et al., 1996). A small study evaluating rebound tonometry using the TonoVet in rhesus macaques demonstrated excellent correlation between tonometer readings and manometric IOP (Yu et al., 2009). However, another study evaluating the TonoVet and Tono-Pen against manometry in a set of normal rhesus macaques identified considerable variability using both instruments, both within individual animals and also between different animals (McAllister et al., 2018). Given the aforementioned fluctuations that are commonly observed in eyes of NHPs with laser-induced experimental glaucoma, these data would support animal-specific calibration of tonometers. Such a practice, however, may not be practical in all laboratory settings or in drug safety and efficacy studies.

Tear Testing

All veterinary ophthalmologists are familiar with quantitative tear testing, particularly in canine ophthalmology. This is largely due to the prevalence of naturally occurring keratoconjunctivitis sicca (KCS) in the species and the standard diagnostic tools used to identify and monitor disease, namely STT and TBUT. Quantitative tear testing has also been reported in laboratory species and may be indicated in investigative or preclinical studies, particularly those involving animal models for ocular surface disease and dry eye disease (DED). However, due to the anatomic and physiologic diversity of these species and the paucity of naturally occurring KCS in species other than the dog, systematic approaches and/or standardization and validation of these tests are less robust. Furthermore, the effects of age, gender, and time of day must be considered, as these have been shown to influence aqueous tear production in other species (Giannetto et al., 2009; Hartley et al., 2006; Webber et al., 1987). Among others, these factors are likely what has also complicated identification of "ideal" animal models of human dry eye. Regardless, objective values for the STT and TBUT as well as the phenol red thread test (PRTT) have been reported in all laboratory species (see Table 33.2). The veterinary ophthalmologist should be aware of the approaches and species-specific considerations that guide tear testing in these species.

Rodents

Rodents, particularly mice, are among the most commonly used species in animal models for dry eye and human Sjögren's syndrome (SS). However, the size of the globe in these species complicates objective tear testing using methods like the STT. Commercial STT strips are too large for placement in the conjunctival fornices of rodents. Some studies have reported modifications to the standard tear strip to facilitate use in the smaller rodent eye, as well as an increase in testing time (e.g., 2 minutes instead of 1 minute; Batista et al., 2012; Fujihara et al., 2001; Hoffman et al., 1984). Instead, tests like the cotton thread test and PRTT have been used, but test times vary between studies, and

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mean values reported in the literature are associated with wide ranges, indicating a need for more rigorous standardization and validation (Dursun et al., 2002; Verhagen et al., 1995). In a more recent study, absorbent endodontic paper points were used to measure aqueous tear production in a range of small species, including mice and rats (Lange et al., 2014). Similar to the procedure for other tear tests, this approach involves insertion of the paper point into the inferior conjunctival fornix and measurement of paper wetting after 1 minute. The results indicated that this test was safe and relatively easy to perform in conscious animals, though additional studies to determine reference ranges and validation are needed. Values for TBUT have also been reported in rodents, typically cited in drug efficacy investigations using dry eye models (Ikeda et al., 2018; Kojima et al., 2014, 2018).

Guinea Pig

The guinea pig is less commonly used than other species in ocular surface investigations, but given the popularity of the species as household pet, normative data has been described in several published studies. Normative STT values have been reported for the guinea pig using commercially prepared paper strips, and were well tolerated according to the results of one study (Trost et al., 2007). It is noteworthy, however, that in that study aqueous tear production was low enough that it frequently did not even reach the standard notch in the tear strip, requiring direct measurement of a very small amount of paper wetting. Furthermore, STT in the guinea pig appears to be subject to wide variation, as another study reported a mean value at least 5× greater than that of the aforementioned study (Coster et al., 2008). Likewise, values for the PRTT have also been reported in guinea pigs, though with variable results (Coster et al., 2008; Rajaei et al., 2016; Trost et al., 2007). Normative TBUT values are not as commonly reported, but one study demonstrated an unexpectedly low mean value among male and female animals (Cafaro et al., 2009). The authors commented on the surprising nature of this result given the low blink rate of this species and presumed stability of the tear film (see previous discussion under "General Features of the Eyes of Laboratory Species").

Rabbit

Like rodents, the rabbit is commonly used as an animal model for various forms of experimental DED. Furthermore, spontaneous ocular surface disease is not uncommon in rabbits in the laboratory setting (Holve et al., 2011). Therefore, there is a relatively large body of literature focused on objective tear film measurements in rabbits. Normative values for the Schirmer tear test are commonly reported in rabbits, but, as observed with other species, results are associated with considerable variability (Abrams et al., 1990; Burgalassi et al., 1999; Gürkan & Hayat, 2005; Whittaker & Williams, 2015; Zhu et al., 2003). Furthermore, the test has not been standardized for the species, with some investigations utilizing a longer test time than the 1 minute used in most others (Burgalassi et al., 1999). Values for TBUT are also reported for the rabbit. Similar to the guinea pig, the rabbit has a low blink rate in comparison to other species (Korb et al., 1998) and values for TBUT in normal animals reflect the stability of the rabbit tear film (Toshida et al., 2007; Wei et al., 2013). One of these studies reports a remarkably long normative TBUT of nearly 30 minutes (Wei et al., 2013). While this value might seem exceptionally unlikely, comparative study of corneal epithelial mucins, which play a critical role in tear film stability, has demonstrated a constitutively wider range of mucin expression in the rabbit cornea (Leonard et al., 2016).

Minipig and Nonhuman Primate

Whether due to its infrequent role as a model for DED or in ocular surface investigations or difficulties associated with handling and husbandry, there is a paucity of normative data for quantitative tear tests in the minipig. Likewise, normative values are infrequently cited for tear tests in the species of NHP commonly used in preclinical and toxicologic investigations. However, STT has been studied in the rhesus macaque, with one investigation demonstrating a wide degree of variability (mean of 15.1 mm/min; range 6–26 mm/min; Jaax et al., 1984). Furthermore, this study showed that neither ketamine sedation nor gender appeared to influence STT values. A similar mean STT value has been reported for the capuchin monkey (*Cebus apella*), which, while not commonly used as an animal model in preclinical investigations, has been used in comparative studies of peripheral and central visual pathways (Montiani-Ferreira et al., 2008).

Advanced Ophthalmic Imaging in Preclinical Studies

Accompanying the expanding range of therapeutic approaches to ocular disease is a rapidly growing list of diagnostic endpoints used to enable detailed clinical assessment of the eye. The most noteworthy field of innovation has been advanced ophthalmic imaging, with technologies such as confocal microscopy and optical coherence tomography (OCT) providing real-time images that approach the resolution of histology. In clinical trials for ophthalmic drugs, these endpoints are commonly used to monitor the progress of enrolled patients, enhancing the information with which to evaluate their response to therapy. Furthermore, the images provided using these techniques offer new opportunities to identify and characterize biomarkers and indicators of adverse events associated with investigational drugs and devices.

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From a regulatory standpoint, the biomarkers that have been discovered using advanced imaging techniques have been identified by the FDA as critical factors for improvement of the overall drug development process (Nork et al., 2012b). Therefore, preclinical ophthalmic drug and device studies have largely mirrored the use of these endpoints in toxicology and safety studies using laboratory animal models. The information provided by these techniques complements and improves the value of the findings reported on ophthalmic examinations, from other more traditional imaging endpoints such as fluorescein angiography (FA), and from functional testing such as ERG. Most importantly, they provide the means for acquiring nonconsumptive data from preclinical studies, reducing the necessary number of animals required. From the standpoint of a drug company, the better information provided by ophthalmic imaging guides more informed decision making early in the process of drug development. What follows is a brief summary of the ophthalmic imaging endpoints used most commonly in preclinical drug development studies today.

Since most of the commercially available instrumentation for advanced imaging is designed and marketed for human patients, modifications are often necessary for use in laboratory species. This may require removal of chin rests designed for human positioning, use of modified techniques or settings of illumination (particularly in tapetal or subalbinotic animals), and, above all else, experienced technical staff with excellent restraint skills. It is also noteworthy that the vast majority of advanced imaging procedures require validated protocols for sedation or even general anesthesia in some instances to facilitate positioning and minimize the likelihood of motion artifacts. Once anesthetized, species with NMs (third eyelids) may develop some degree of membrane protrusion, which can complicate acquisition of images.

Ophthalmic Imaging

Fundus Imaging

In preclinical studies, high-resolution fundus imaging is a fundamental technique that should ideally be incorporated into any study investigating disease and/or treatment of the posterior segment. Fundus imaging, particularly color fundus imaging, provides valuable documentation of the fundus appearance at prestudy and at points thereafter. Fundus imaging is most commonly facilitated by mydriasis, though use of nonmydriatic fundus cameras that do not require pharmacologic dilation has been reported in some laboratory species (Di et al., 2014; Lu et al., 2014). It is noteworthy that the working distances for many commercially available fundus imaging systems may not be capable of delivering incident light through the tiny pupil of a mouse or rat. Therefore, photographic equipment may need to be modified or other methodologies used to capture high-quality fundus images in rodents (Butler & Sullivan, 2015; DiLoreto et al., 1994b; Paques et al., 2007). Alternatively, instruments like the Micron® Series (Phoenix Research Labs, Pleasanton, CA, USA) are designed specifically for use in small laboratory species.

While this endpoint should not be considered a replacement for the ophthalmic examination in preclinical studies, fundus cameras provide images that carry higher resolution than that provided by indirect ophthalmoscopy. Therefore, these images do have the ability to detect subtle lesions that might be occasionally missed by an examiner or permit characterization of a lesions(s) in greater detail. Furthermore, fundus images provide a point of comparison for other imaging endpoints performed during the course of a study, and can also be used to facilitate histologic sectioning.

Fundus Angiography

Fundus angiography has been performed for decades in vision science and preclinical studies, and is most commonly used to evaluate the vascular systems of the posterior segment. Angiography utilizes intravenous (IV) fluorescent dyes to evaluate the integrity of ophthalmic vessels and identify sites of breakdown of the blood–retinal barriers that may be compromised in the face of inflammation (Fig. 33.17). FA utilizing IV fluorescein sodium is most commonly used to evaluate the retinal vasculature. Indocyanine green angiography uses indocyanine green dye, which emits light of longer wavelength than fluorescein, permitting capture of fluorescent signal behind the RPE and evaluation of the choroidal vasculature. Furthermore, FA can be modified to permit evaluation of the anterior segment vasculature (Alario et al., 2013a, 2013b; Pirie & Alario, 2014).

In vision science, FA is essential for the establishment of certain animal models of human disease (Alnawaiseh et al., 2016; Li et al., 2016). In animal models of choroidal neovascularization (CNV), the hallmark pathologic process in human patients with wet-form AMD, FA is used to confirm the growth of leaky, immature vessels into the subretinal space and retina (Grossniklaus et al., 2010). In preclinical safety studies, FA is commonly used in studies investigating drugs or devices administered via intravitreal (IVT), suprachoroidal, or subretinal routes (Einmahl et al., 2002; Krzystolik et al., 2002; Qiu et al., 2006). As with fundus imaging, it can also provide useful information for correlation of findings on ophthalmic examination and other imaging modalities like fundus imaging and OCT.

Very recently, OCT angiography (OCTA) has been reported in studies involving animal models. OCTA does not require injection of fluorescent dyes to visualize vascular structures and lesions. Furthermore, this modality can create three-dimensional reconstructions of retinal blood vessels, and can also quantify blood flow within certain vessels,

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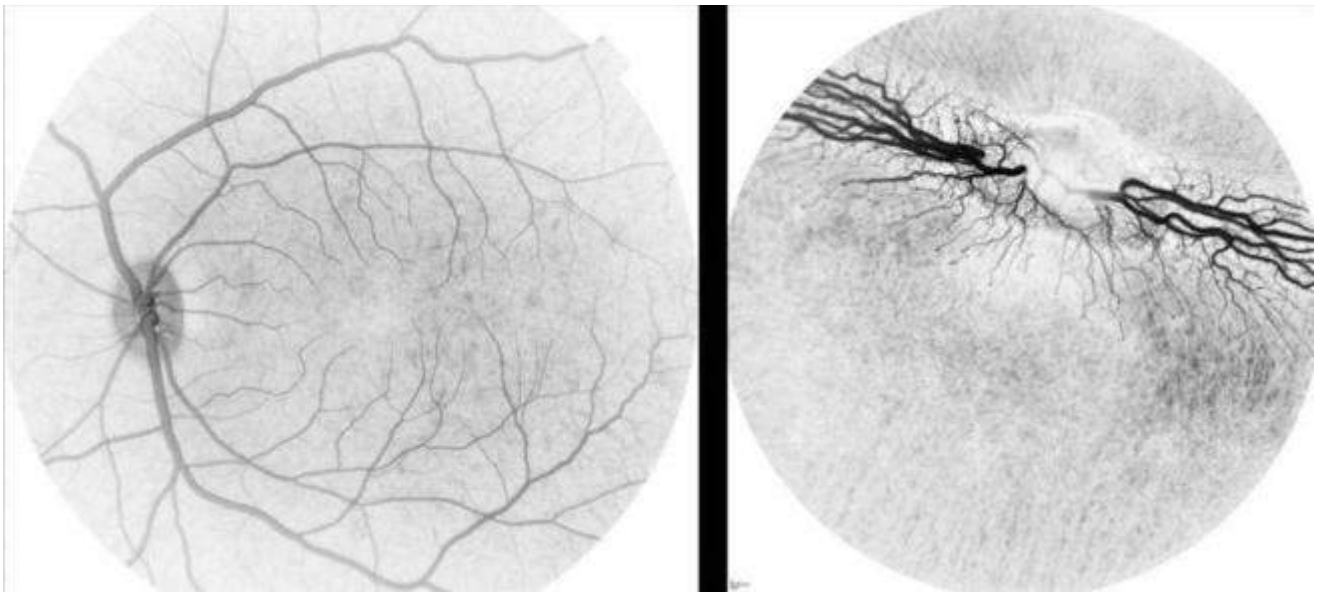


Figure 33.17 Normal late-phase fluorescein angiograms from a cynomolgus macaque (**A**) and a pigmented rabbit (**B**). (Courtesy of Ocular Services On Demand (OSOD).)

depending on the orientation of the image (Matsunaga et al., 2014). Despite the early promise of this modality in the investigation of ocular disease and in drug development, its use in preclinical ophthalmology is still in its infancy, and its utility as a therapeutic monitoring tool is not yet well established (Sadda, 2017). Furthermore, an interpreter must be experienced with OCTA images, as they are prone to artifacts during acquisition as well as processing.

Optical Coherence Tomography

OCT is an imaging modality that has largely changed the clinical paradigms for the diagnosis and monitoring of retinal diseases in human patients. Additionally, it has greatly influenced the standard methodologies used in the preclinical and clinical evaluation of ophthalmic drugs and devices. OCT is now widely used in human clinical evaluations to monitor patients with retinal diseases like AMD and diabetic retinopathy (DR), among others (Adhi & Duker, 2013). Furthermore, retinal OCT images can be segmented to distinguish the different layers of the retina, a technique that can be a robust tool for monitoring the structural consequences of glaucoma within the retina and optic nerve (Huang et al., 2013). OCT is also a valuable tool in the evaluation of the anterior segment, providing high-resolution cross-sectional images of the cornea and iridocorneal angle (Ramos et al., 2009).

Likewise, the advantages provided to human patients are also useful in veterinary ophthalmology and in preclinical studies involving animals (Fig. 33.18). There are now numerous reports in the veterinary literature describing the use of OCT to evaluate a range of animal species (Famose, 2014; Gekeler et al., 2007; McLellan & Rasmussen, 2012; Pinto & Gilger, 2014; Strom et al., 2013). In vision science, OCT has enabled highly detailed characterizations of animal models of human ocular disease and is a valuable endpoint in preclinical studies of drug efficacy and safety (Nork et al., 2011, 2012a; Qiu et al., 2006; Strouthidis et al., 2011). Depending on the species being imaged, however, there are important considerations influencing the successful use of OCT in preclinical studies. Other than the anesthetic considerations that must be observed in mice and rats (see previous discussion under "Mouse and Rat"), OCT units must be modified via use of a condensing lens or a commercially available attachment to accommodate the small rodent eye, particularly that of the

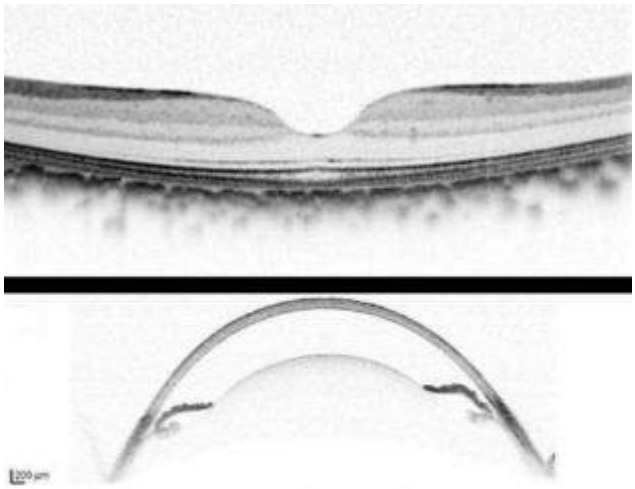


Figure 33.18 Optical coherence tomography images of the normal retina of a cynomolgus macaque (**A**) and the normal anterior segment of a rat (**B**). (Courtesy of Ocular Services On Demand (OSOD).)

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mouse (McLellan & Rasmussen, 2012). Rabbits are large enough not to require instrument modifications, but the dorsal location of the optic nerve and medullary rays can complicate positioning for image acquisition. Minipigs also present positioning challenges due to their size and generally limited neck mobility (McLellan & Rasmussen, 2012). Lack of melanin in albino rodents and rabbit strains also creates challenges, largely since the altered reflectivity from albino retinas may complicate differentiation of layers on OCT images, particularly the outer retinal layers and choriocapillaris (Berger et al., 2014).

Specular Microscopy

Specular microscopy is a technique that has been used in humans and animals for decades to allow qualitative and quantitative assessment of the corneal endothelial cells *in vivo*. In animals, previous studies have used specular microscopy to obtain normative data regarding corneal endothelial cell counts and morphology, and to monitor changes associated with aging (Franzen et al., 2010; Gwin et al., 1982; Morita, 1995). Use in animal models of glaucoma and ocular inflammatory disease has also been described (Ollivier et al., 2003; Zheng et al., 2000). Given the poor regenerative capacity of corneal endothelial cells in most species, identification of toxicity is a critical component of preclinical assessment of ocular drugs, particularly those administered topically or intracamerally (IC; Somps et al., 2009). Today, both contact specular microscopy and newer noncontact instruments are commercially available and both have been used in animal studies. It is noteworthy, however, that agreement between contact and noncontact instruments is considerably poor and therefore the same type of instrument (and preferably the same model) should be used during the course of a study (Szalai et al., 2011).

Corneal Confocal Microscopy

Unlike specular microscopy, which only evaluates the corneal endothelium, corneal confocal microscopy enables *in vivo* acquisition of images of all corneal layers with resolution at the cellular level (Nork et al., 2012b). In addition to being applicable in the investigation of animal models of structural and infectious corneal disease (Avunduk et al., 2003; Twa & Giese, 2011), confocal microscopy facilitates evaluation of corneal drug toxicity even to the level of a single population of cells (Baghdasaryan et al., 2019; Hsiao et al., 2018; Kovoor et al., 2004). Furthermore, it presents an excellent example of technology's impact on the practice of Russell and Burch's 3 Rs, as confocal microscopy enables toxicology investigators to nonconsumptively study corneal effects for much longer periods of time than was previously possible. It is noteworthy, however, that specular microscopy is still widely considered a superior modality for quantitative evaluation of the corneal endothelium, principally because it samples a larger total number of cells than confocal microscopy (Nork et al., 2012b).

Animal Models in Research and Preclinical Drug Development

The use of animal models in toxicology and drug development has contributed not only to the safety and evaluation of drugs and devices, but also to the understanding of ocular diseases in both animals and human patients. However, no animal model is ideal or perfectly replicates any condition or disease in the human. Therefore, those engaged in vision science or toxicologic studies must be knowledgeable regarding their respective limitations and be able to advise study teams and investigators in the appropriate and meaningful implementation of an animal model.

In general, pharmacokinetic and tolerability and/or safety studies use normal (unaltered, disease-free) animals, and the majority of this chapter introduces the reader to the normal ocular anatomic and physiologic features of the species commonly used. This information is essential in the understanding and interpretation of the results of such studies. However, in studies seeking proof of concept for a drug or device, or those with more specific purposes such as the investigation of disease pathogenesis or characterization of biomarkers, disease-specific models are used and are discussed in this section.

Animal models of ocular disease can be divided into those that occur naturally (spontaneous disease) or those that are induced, whether experimentally (i.e., surgically) or via transgenic modification. In general, spontaneous models are considered to more accurately mimic human disease, but the necessary time and resources to establish colonies of affected animals are often not practical for all laboratory environments. Therefore, induced models are more typically used in toxicology and drug development. The most common models that veterinary ophthalmologists will encounter are those used to investigate retinal disease (predominantly AMD and DR), glaucoma, and DED. A summary of some of these models is presented in Table 33.3.

Animal Models of Retinal Disease

Given the worldwide prevalence of AMD and DR, the body of preclinical and clinical investigation of the underlying mechanisms and treatment of these acquired retinal diseases is large and rapidly growing. In AMD research, the majority of toxicologic and drug development studies have targeted the later stage of the disease spectrum, "wet" AMD, characterized by CNV as well as subretinal hemorrhage, edema, and neovascular membrane formation. This research has resulted in several FDA-approved therapies for wet AMD, such as the intravitreal biologic agents ranibizumab and aflibercept (CATT Research Group, 2011). These agents act by inhibiting VEGF, a key component in the pathogenesis of wet AMD.

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Table 33.3 Features of animal models commonly used in ocular toxicology and ocular drug and device development.

	Mechanism	Characteristics of Disease	Primary Limitation(s)	Reference(s)
Mouse				
Dry Eye Disease				
MRL/lpr mouse	Lymphoproliferative model of SS and systemic lupus erythematosus with spontaneous T-cell infiltration of lacrimal and salivary glands	Ocular surface disease onset ~1 month of age, most predominantly in female animals. Serologic biomarkers of SS also observed	Clinical signs of DED may not be detectable	Toda et al. (1999)
NOD mouse DED	Spontaneous development of lacrimal lymphocytic infiltrates (also of the pancreas, salivary glands, and thyroid). Model of human SS	Lacrimal adenitis leads to decreased tear secretion	Clinical signs are subtle or absent. Disease preferentially affects males, which differs from the human condition. Concurrent systemic disease may complicate study design	Takahashi et al. (1997)
Id3-deficient mouse	Id3 is a protein that indirectly suppresses lymphocyte differentiation and activity. Deficiency is believed to result in lymphocytic inflammatory disease	Lacrimal insufficiency and serologic characteristics of SS. Not associated with systemic disease like other models of SS	Mechanism of disease not completely characterized, which complicates interpretation of some study results	Li et al. (2004)
Glaucoma				
Microbead injection	Injection of microbeads to obstruct the ICA and reduce aqueous outflow	Increase in IOP (~5–10 mmHg) for approximately 3 weeks following injection. *Also performed in rats, in which effect may last for up to 2 weeks, but may be extended to up to 8 weeks with two injections*	Relatively short efficacy compared to other methods. May not be a predictive model for drugs that increase aqueous outflow. Strain and age may result in variable response	Sappington et al. (2010)
Translimbal laser photocoagulation	Circumferential laser scarification of the iridocorneal angle impairing aqueous outflow and increasing IOP. Modifications may include paracentesis to flatten the AC and/or pretreatment with ICG to enhance laser effects. Also results in optic nerve degeneration	IOP elevation for at least 30 days with loss of RGC and reduced inner retinal function. Effects are lengthened to at least 4 months, with chamber flattening at the time of treatment. *Also performed in rats, in which IOP increases to ~40–50 mmHg, slowly decreasing thereafter over 3–4 weeks*	Albino strains require higher laser energy, which may have collateral effects. May also result in corneal decompensation due to damage to limbal stem cells	Feng et al. (2013); Grozdanic et al. (2003b); Levkovitch-Verbin et al. (2002)
Episcleral vessel cauterization	Increased IOP due to cauterization of episcleral vessels and decreased aqueous outflow facility	Studies indicate that cauterization of 2 or 3 vessels is recommended for IOP between 20 and 30 mmHg (1 vessel is ineffective and more than 3 may be too severe). Typically increases IOP for 2–4 weeks. *Also performed in rats, in which IOP increases by 5–25 mmHg for 1–5 weeks*	Retinal vessel congestion may develop secondary to the procedure. Degree of IOP may be variable. Duration of IOP increase is lesser than with other models and may also be variable	Garcia-Valenzuela et al. (1995)

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Rat				
Retinal Disease				
STZ-induced diabetic retinopathy	Intraperitoneal STZ injection ablates pancreatic beta cells, inducing Type I diabetes 3 days after injection, eventually leading to secondary ocular effects	Retinal lesions include neural changes (loss of RGCs), followed by vascular changes including vascular leakage and blood–retinal barrier breakdown	Vascular lesions typically follow neural retinal changes and may be variable, differing between animals. Onset of disease is remarkably strain dependent	Anderson et al. (1995)
Laser induction of CNV	Laser-induced rupture of Bruch's membrane leads to proliferation of choroidal vasculature through the defect into the subretinal space and retina	Neovascular membranes typically form within 1–2 weeks of treatment. *Also performed in mice, with similar onset of structural changes*	Variability in incidence of successful induction of fluorescein leakage. Mimics an acute model, which is not necessarily reflective of the features of chronic disease characteristic of human patients	Dobi et al. (1989); Frank et al. (1989)
Rabbit				
Dry Eye Disease				
Adoptive transfer model for lacrimal adenitis	Injection of lymphocytes that have been co-cultured with autologous lacrimal acinar cells into the contralateral eye leads to *bilateral* lacrimal adenitis	Results in reduced tear production, abnormal corneal surface staining, and altered tear film stability within 2 weeks of injection	Requires technical cell culture expertise. Invariably results in bilateral disease, so no control eye available in treated animals	Guo et al. (2000); Mircheff et al. (2016)
Surgical induction of DED	Cauterization of primary lacrimal gland duct with removal of Harderian and third eyelid glands leads to tear deficiency	Changes in tear osmolality occur, but no significant change in STT or clinical signs of DED	Does not necessarily result in clinical signs of ocular surface disease or STT change and, therefore, may not be an ideal model for testing drug efficacy	Gilbard et al. (1987)
Glaucoma				
Spontaneous glaucoma	Spontaneously increased IOP resulting from goniodysgenesis and trabecular meshwork dysplasia	Increased IOP by 3–6 months, gradually leading to buphthalmos and optic nerve/retinal degeneration	Colony establishment and maintenance not practical for most drug development studies	Hanna et al. (1962); Tesluk et al. (1982)
IVT hypertonic saline	IVT injection of hypertonic saline leads to altered osmotic flow and vitreous overhydration and increased IOP	Short-lived (4–6-hour) acute IOP increase	Short/acute duration of IOP increase limits the applicability for evaluation of efficacy for most drugs. Most applicable for evaluating a drug's ability to *prevent* IOP increase rather than reduce it from baseline	Krauss et al. (2011)
Orogastric water loading	Orogastric administration of warm water leads to vitreous overhydration and increased IOP	Increase of IOP to 20–30 mmHg for ~2–3 hours after administration, with peak effects at ~20–30 minutes	Short/acute duration of IOP increase limits the applicability for evaluation of efficacy for most drugs. Most applicable for evaluating a drug's ability to *prevent* IOP increase rather than reduce it from baseline	Gual et al. (1989)

(Continued)

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Table 33.3 (Continued)

	Mechanism	Characteristics of Disease	Primary Limitation(s)	Reference(s)
IV glucose infusion	IV administration of 5% glucose reduced blood osmolality and osmotic flow into the eye, leading to IOP elevation	IOP increase may increase to up to 2× baseline for ~1–2 hours after administration, with slightly better predictability than the water loading model	Short/acute duration of IOP increase limits the applicability for evaluation of efficacy for most drugs. Most applicable for evaluating a drug's ability to *prevent* IOP increase rather than reduce it from baseline	Shah et al. (2000)
Corticosteroid-induced ocular hypertension	Administration of a corticosteroid alters biochemical characteristics of the trabecular meshwork, leading to resistance to aqueous outflow. Corticosteroid administration can be IVT, subconjunctival, or topical	Onset and degree of IOP increase may depend on the route chosen	Variability is high between animals, likely highly dependent upon some rabbits' genetic predisposition to being steroid "responders"	François et al. (1984); Melena et al. (1998); Song et al. (2011)
Retinal Disease				
Surgical induction of CNV	Subretinal injection of FGF-containing microspheres to induce CNV	CNV develops by 2–6 weeks following injection. Persistence of CNV lesions for up to 3 years in some animals	Procedure requires specialized equipment and skills. The degree of inflammation induced by the procedure exceeds that typically observed in human patients	Kimura et al. (1995); Ni et al. (2005)
Dog				
Dry Eye Disease				
Surgical induction of DED	Removal of the third eyelid and/or lacrimal gland leads to aqueous tear deficiency	Depending on the gland(s) removed, onset of KCS may be within 2 days or up to 4 months	Variable time and degree of onset of disease in different animals. Severity and characteristics are not an ideal model for human DED	Helper et al. (1974); Kern et al. (1988); Moore et al. (2001); Saito et al. (2001)
Nonhuman Primate				
Glaucoma				
Laser-induced experimental glaucoma	Scarification of the trabecular meshwork reduces aqueous outflow and increases IOP	Establishment of IOP increase requires weeks to months, depending on the number of treatments needed	Procedure requires specialized equipment and personnel and typically demands several treatments. There are often dramatic fluctuations in IOP in individual animals, even from day to day	Gaasterland & Kupfer (1974)
Microbead injection	Injection of microbeads (15 μm diameter) to obstruct the ICA, reduce aqueous outflow, and induce retinal/optic nerve degeneration	May require up to 8–12 injections until response is consistent. Increase in IOP may be maintained from 4–40 weeks	Establishment of increased IOP is labor intensive. May still observe large IOP fluctuations, as with the laser-induced model	Weber & Zelenak (2001)
Retinal Disease				
Laser-induced CNV	Laser-induced rupture of Bruch's membrane leads to proliferation of choroidal vasculature through the defect into the subretinal space and retina	Lesions typically develop within 2–4 weeks of treatment, but spontaneously involute within 2 months to 1 year	Not all animals respond by developing CNV. The features of CNV in young animal eyes differ from humans. This model also represents an acute wounding model, which differs from human patients	Ryan (1979)

AC, anterior chamber; CNV, choroidal neovascularization; DED, dry eye disease; FGF, fibroblast growth factor; ICA, iridocorneal angle; ICG, indocyanine green; IOP, intraocular pressure; IV, intravenous; IVT, intravitreal; KCS, keratoconjunctivitis sicca; NOD, nonobese diabetic; RGC, retinal ganglion cell; SS, Sjögren's syndrome; STZ, streptozotocin.

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While naturally occurring AMD has been described in NHPs, disease rarely progresses beyond the early to intermediate forms of disease ("dry" AMD). Transgenic rodent models are available, but largely comprise disease caused by single mutations involving genes not associated with human AMD (Pennesi et al., 2012; Zeiss, 2010). Therefore, most studies of wet AMD in animal models are induced, by either laser or surgery. Laser induction of CNV has been described in numerous laboratory species, but the NHP model is perhaps the best characterized in toxicology and drug development studies, largely due to the present of a true macula and other similarities between human and NHP eyes. A diode laser is used to induce multifocal rupture of Bruch's membrane in the macular region, with subsequent CNV expected within 1 week, typically reaching maximal severity by 2–4 weeks after treatment (Ryan, 1979). Within 2 months to 1 year, neovascularization spontaneously recedes in most animals (Zeiss, 2010).

Despite the popularity of this model in drug development studies, it is associated with noteworthy limitations. Firstly, like many models, it is created in young animals with otherwise normal retinas, which does not accurately replicate the disease states present in most aged patients with AMD. Furthermore, successful induction of CNV lesions is variable and histologic studies have demonstrated a discrepancy between lesion appearance and leakage on FA and histologic evidence of CNV (Fig. 33.19; Grossniklaus et al., 2010; Wang et al., 2015). In addition, the model is costly and ethical considerations in any studies utilizing NHPs require consideration. Laser-induced rabbit CNV models are generally limited by the merangiotic vascular pattern and lack of a macula. Pigs also lack a true macula, but as laser-induced models in this species are refined, they may be more commonly applied. Surgically induced models created via subretinal or suprachoroidal injections of various compounds may be alternatives to laser-induced models (Fig. 33.20; Cui et al., 2000; Lassota et al., 2007; Ni et al., 2005; Schmack et al., 2009; Shen et al., 2006), but may be limited by the local inflammation they induce, which is in excess of that typically observed in patients with AMD.

Spontaneous and induced models of DR are available in several species. However, the late proliferative form of DR, which is of particular interest in drug development, does not typically develop in spontaneous animal models, largely due to their limited lifespans in comparison to humans. Furthermore, spontaneous diabetes in species with comparatively longer lifespans like the dog is often associated with cataract formation, which precludes subsequent evaluation of the retina. Induced rodent models may be produced via streptozotocin-assisted pancreatic beta cell ablation, but development of retinal vascular lesions is variable (Chen & Stitt, 2016; Robinson et al., 2012). Ultimately, the development and management of most DR models require extensive time and resources and, to date, none adequately replicates features of proliferative DR. Therefore, nondiabetic VEGF models like those described above for AMD are often used to simulate proliferative DR in toxicology and drug development, despite the differing pathophysiologies between the two diseases.

Glaucoma

Like AMD, glaucoma is a human disease with worldwide implications for human blindness. Spontaneous glaucoma is also well characterized in a number of animal species, including the NZW rabbit, dog, cat, and NHPs. However, the

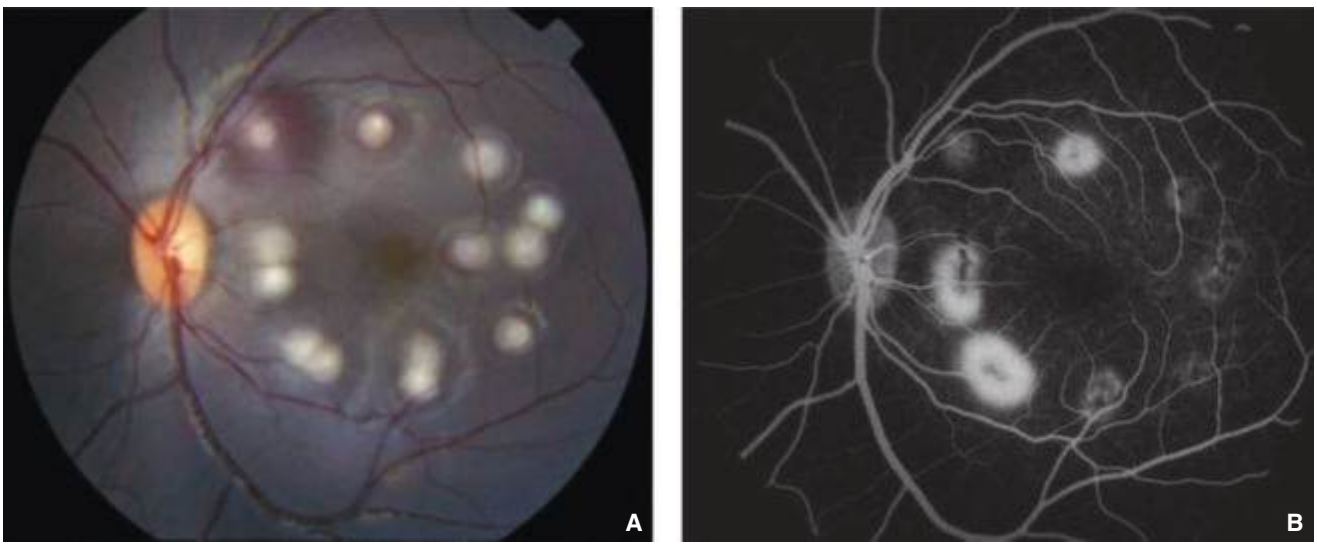


Figure 33.19 Laser-induced choroidal neovascularization in a nonhuman primate. **A**. Fundus photograph demonstrates clinical appearance of laser lesions around the macula. **B**. Corresponding fluorescein angiogram demonstrates variable fluorescein leakage associated with the laser lesions. (Courtesy of Ocular Services On Demand (OSOD).)

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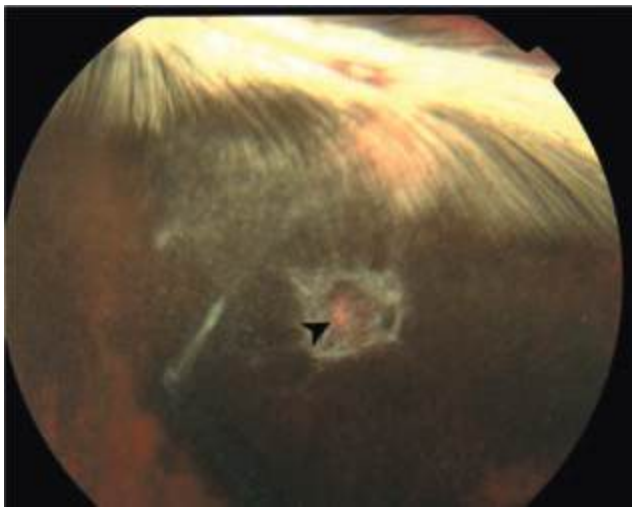


Figure 33.20 Fundus photograph of choroidal neovascularization (arrowhead) induced by subretinal injection of a biomaterial containing fibroblast growth factor. (Courtesy of Michael Neider and Ocular Services On Demand (OSOD).)



Figure 33.21 Optic disk cupping in a cynomolgus macaque with experimental glaucoma. (Courtesy of Leandro Teixeira, DVM, DACVP, COPLOW, University of Wisconsin–Madison.)

complexities and ambiguities of glaucoma pathophysiology and differences between species complicate identification of an ideal model. Furthermore, it is critical in glaucoma drug development that an animal model possess the appropriate complement of receptors and comparable aqueous humor dynamics to allow meaningful evaluation of drug response (Miller, 2013). In addition to these concerns, the resources necessary to establish and maintain a colony of animals with spontaneous glaucoma is often prohibitive in drug development. Therefore, induced models are commonly used.

Rodent models of glaucoma can be induced using a number of approaches, including cauterization or ablative injection of the episcleral veins or TM (Levkovitch-Verbin et al., 2002; Morrison et al., 1997). However, these techniques may only produce IOP elevation with variable success and often require multiple treatments (Johnson & Tomarev, 2016). Steroid-induced ocular hypertension can be produced with topical application of dexamethasone, but the increase is typically low in magnitude and only transient (Zode et al., 2014). Outflow obstruction has been achieved using intracameral injection of synthetic microbeads in both rodents and NHPs, but strain- and species-related variability must be considered (Cone et al., 2010; Sappington et al., 2010; Weber & Zelenak, 2001).

The laser-induced model of experimental glaucoma in NHPs is commonly used in the development of glaucoma drugs. This model involves laser scarification of the TM, leading to sustained IOP elevation and eventual RGC and optic nerve degeneration (Fig. 33.21; Gaasterland & Kupfer, 1974). Despite the success of this model in comparison to others, there are noteworthy limitations that must be considered. The resulting degree of IOP elevation can be variable and, in many animals, dramatic daily IOP fluctuations must be expected (Ollivier et al., 2004). Therefore, evaluation of a drug intended to reduce IOP with this model should only rely on measurements taken in the hours following a single administration of a drug (or 1–2 days at the maximum). Furthermore, it is noteworthy that laser treatment can result in blood–aqueous barrier (BAB) compromise and influence pharmacokinetics or intraocular and systemic drug distribution (Miller, 2013).

Investigations have identified other pertinent factors when interpreting the results of studies evaluating the efficacy of glaucoma drugs using this model. Firstly, there is still no industry consensus on the clinical staging of glaucoma in NHPs with experimental glaucoma, which complicates comparison between different studies. Furthermore, animal age may be a source of variability, as study has shown that older animals may respond differently than younger ones (Burgoyne, 2015). Today, many of the newer drugs being investigated and brought to market in some countries (e.g., the rho kinase inhibitors) act by targeting and altering the TM to enhance aqueous outflow. A recent biomechanical investigation of the nonlasered trabecular tissue in eyes with experimental glaucoma demonstrated invariable softening of this tissue to a maximal degree (Raghunathan et al., 2017). This indicates that these areas are likely undergoing a mechanocompensatory change to accommodate an increased aqueous outflow burden. Of greater importance in drug development is the possibility that maximal softening of functional outflow tissue in eyes with experimental glaucoma will effectively truncate any detectable response to hypotensive drugs that act by targeting and altering the TM. The undesirable result could be the removal of potentially effective and beneficial drug candidates from development.

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Dry Eye Disease

Human evaporative and nonevaporative DED is commonly diagnosed and current therapeutic approaches are supported by a growing body of literature into its pathophysiology. Currently, the most successful marketed drugs are topical agents that reduce lacrimal inflammation and enhance the abundance and quality of natural tears (Rodríguez-Pomar et al., 2017). Despite the successful preclinical and clinical development of such drugs, there is still no ideal animal model for DED, at least partially due to considerable species-related differences in lacrimal anatomy, tear film dynamics, and endocrine factors (Schechter et al., 2010). Rodent models like the MRL and MRL/lpr mouse and nonobese diabetic (NOD) mouse develop spontaneous forms of T-cell-dominant lacrimal adenitis that mimic human DED and SS in many respects; however, clinical signs of DED in affected animals are very difficult to detect (Humphreys-Beher et al., 1994; van Blokland & Versnel, 2002). Therefore, these models are generally poor candidates for use in studies investigating the clinical efficacy of DED therapeutics and are better suited to investigations of pathogenesis. Canine KCS is a spontaneous form of DED bearing many similarities to human disease, though clinical manifestations in dogs tend to reach greater overall severity. Establishment and maintenance of a canine KCS colony, however, is not necessarily practical in drug development. Surgical models involving lacrimal gland removal have been described in both small and large laboratory species, but inconsistently yield clinical signs of disease and bear only variable resemblance to human DED (Li et al., 2013; Maitchouk et al., 2000; Qin et al., 2014; Schrader et al., 2008).

Immunopathologic models of DED in rabbits are showing some promise for use in toxicology and dry eye drug development. An autoimmune lacrimal adenitis can be induced by an adoptive transfer method wherein activated lymphocytes that have been co-cultured with lacrimal acinar cells from one lacrimal gland are injected directly into the contralateral gland (Guo et al., 2000). Within 2 weeks, this results in a bilateral reduction in tear secretion and ocular surface disease. Furthermore, more recent refinements of this model have been able to produce DED at differing severities, more closely mimicking the spectrum of disease in human patients (Mircheff et al., 2016).

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34

Small Mammal Ophthalmology

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In this chapter the ophthalmic conditions of the rabbit, guinea pig, chinchilla, ferret and to a lesser extent degu, sugar glider and hedgehog are considered. Readers seeking information on rodent species such as rat and mouse are directed to the Laboratory Animal Ophthalmology chapter and those aiming for information on what we might call more exotic species such as squirrels, marsupials, and primates should consult the Exotic Animal Ophthalmology chapter.

Rabbits

Ocular disease in rabbits has a significant impact on the welfare of these animals kept as pets and several diseases, from dacryocystitis to corneal ulceration, cataract, and uveitis are chronic and can be difficult to manage. In many ways the rabbit eye is analogous to that of the cat or dog, but in others it has several differences, not only anatomical and physiological, but also concerning the response to infectious agents causing pathology. These variations from the ocular conditions one might encounter in the dog or cat should be taken into account when treating diseases of the eye and adnexa in rabbits. We have just completed a study of ocular abnormalities in 1,000 otherwise normal rabbits, a sister project to our guinea pig study (Williams & Sullivan, 2010), and although the paper is yet to be published, the results will be used here to give some indication of the relative prevalence of conditions in the rabbit population.

Rabbit Ocular Anatomy and Physiology

The eye of each species is adapted to the ecological niche occupied by that specific animal (Hughes, 1972). The rabbit, as a prey animal, has laterally placed prominent eyes with a large ocular surface relative to the size of the animal, giving a wide field of vision but also potentially an exposed ocular surface prone to traumatic damage or evaporative tear loss. Perhaps because of this the species has a number of orbital glands producing different components of the tear film. The rabbit lens is near spherical to focus light beams from the wide cornea to the retina, with a focal distance of only 8 mm (de Graauw & van Hof, 1978). To compensate for the resulting spherical aberration, the lens has concentric layers of different refractive index, which can make it appear that nuclear sclerosis is occurring even in young rabbits. The retina is perhaps the area of the eye most different from that of the dog or cat. Whereas those species have holangiotic retinas with blood vessels coursing across the fundus, the rabbit has a merangiotic fundus with a horizontal band of blood vessels and myelinated nerve fibres but otherwise no retinal blood vessels (Fig. 34.1). The rabbit has a band of retina containing a high density of photoreceptors ventral to this vascularized strip, allowing it to see at a higher resolution along the horizon, something highly valuable for a prey species. The visual acuity of rabbits is not high – reports give a range between 1.5 and 3 cycles per degree, a Snellen visual acuity of between 6/120 and 6/60 vision, 10 to 20 time worse than human vision (Vaney, 1980). Their responses to moving stimuli are much increased compared with their acuity for static objects. Consistent with rabbits being predominantly nocturnal and crepuscular animals, the retina is mostly a rod-based visual system. Interestingly, the cone photoreceptors in the ventral retina (i.e., looking dorsally) are maximally responsive to blue light whereas those in the dorsal fundus, looking ventrally, are maximally responsive to green light (Juliusson et al., 1994). Thus, it appears that the lagomorph retina is attuned to detect predators moving either along the ground or through the air, as might be expected with the natural predators of rabbits being predominantly raptors and ground-based carnivores such as foxes. The question then remains, can a blind rabbit be content in captivity with shelter and food provided? It is of course impossible to know the mind of a prey species such as the rabbit, where stress is rarely overtly shown. But rabbits that are blind from bilateral cataract or longstanding glaucoma

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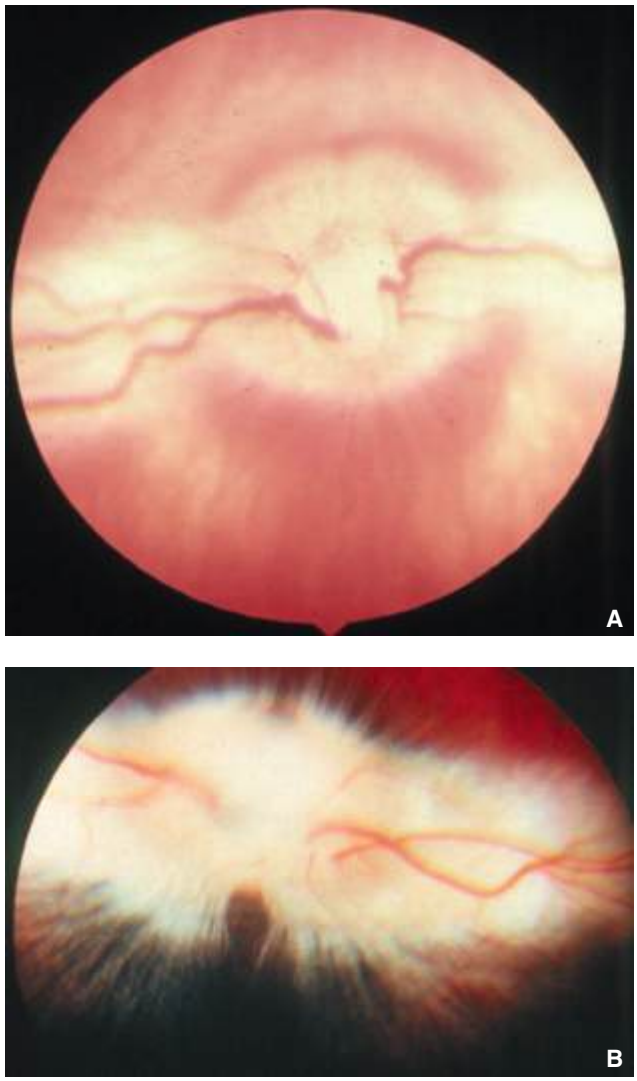


Figure 34.1 The merangiotic fundus of the albino rabbit (**A**), and pigmented rabbit (**B**) with a horizontal band of myelinated nerve fibers and blood vessels.

appear to live in captivity behaving in a very similar manner to sighted animals. Even so, our aim must surely be to minimize ocular pain and blindness in these animals. There are several conditions which are difficult to manage.

Dacryocystitis and Epiphora

Perhaps the most common and one of the most frustrating ocular conditions in the rabbit is dacryocystitis (Fig. 34.2). Our recent study showed nasolacrimal disease in 3.5% of the pet population we examined (Innes & Williams, 2018). Obstruction of the duct without inflammation or infection leads to epiphora, found to some degree in 1.3% of the rabbits we examined, whereas overt dacryocystitis was found in 1.2%. Although this figure is higher than in a laboratory population (Jeong et al., 2005) and lower than



Figure 34.2 Dacryocystitis in a rabbit with purulent discharge around the eyelid margin.

in a referral pet population (Florin et al., 2009), it probably reasonably accurately represents the prevalence of the disease in rabbits seen in veterinary practice: one in every 30 normal pet rabbits is a substantial proportion. This considerable problem relates in many ways to the number of animals with dental problems, these related to dietary calcium deficiency (Harcourt-Brown, 2009a,b). The nasolacrimal duct in this species begins with a single punctum in the ventral eyelid and thence courses across the roots of both molar and incisor teeth (Fig. 34.3A) (Burling et al., 1991). Thus, a maxillofacial bone abnormality, molar tooth root abscess, or overgrown incisor teeth may well lead to nasolacrimal duct pathology resulting in dacryocystitis or epiphora. Diagnosis is readily achieved by physical examination, but dacryocystorhinography can be valuable in defining the degree of nasolacrimal duct dilation or rupture (Fig. 34.3B).

The dilatation and blockage of the duct as it passes over overgrown tooth roots can lead to copious white discharge leaving the nasolacrimal punctum often causing matting around the eye (Fig. 34.2) or, if it solidifies and hardens, results in corneal abrasion (Fig. 34.4). Alternatively, blockage without infection can lead to epiphora, initially a less severe condition but which can give severe facial dermatitis (Fig. 34.5). Bacteria isolated from such discharge range from the Gram-negative bacillus *Pasteurella multocida* to the Gram-positive *Staphylococcus*, so a broad-spectrum antibiotic with activity against both Gram-positive and -negative organisms is to be recommended. Both *Pasteurella* and *Staphylococcus* can be commensal organisms in the rabbit nasal mucosa (El Tayeb et al., 2004; McCartney & Olitsky, 1923). It is only when nasolacrimal duct pathology supervenes that they take on a pathogenic role. As noted above this is predominantly associated with dental disease and thus assessment and treatment of the animal's teeth and their problems must be concurrent with management of the ocular condition.

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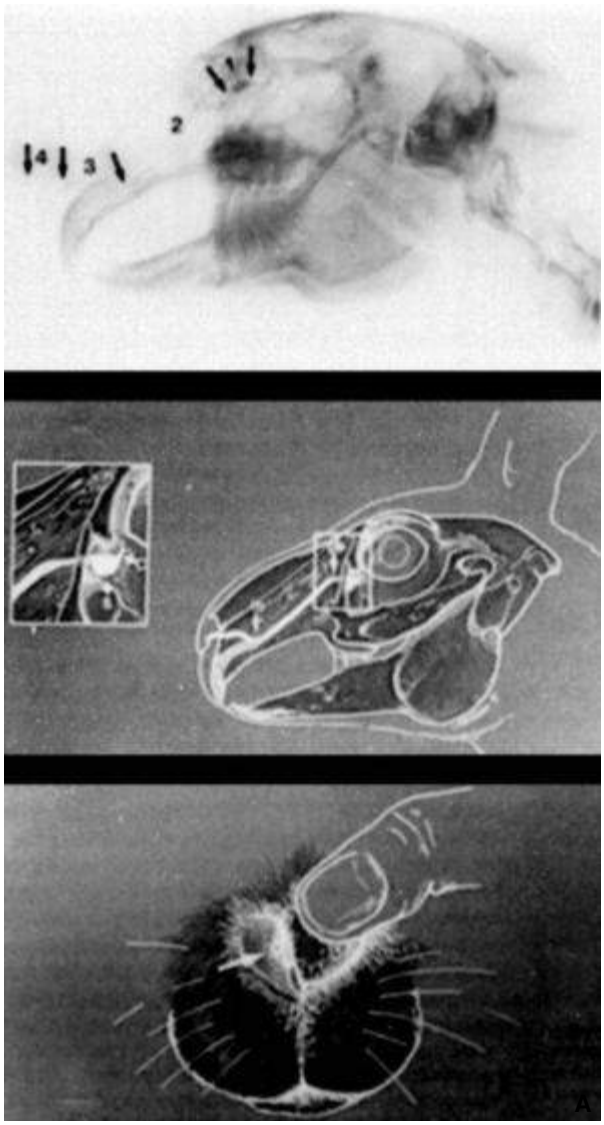




Figure 34.3 **A.** The anatomy of the normal nasolacrimal duct in the rabbit. (*Source*: With kind permission from Burling, K., Murphy, C.J., Curiel, J.S., et al. (1991) Anatomy of the rabbit nasolacrimal duct and its clinical implications. *Progress in Veterinary and Comparative Ophthalmology*, **1**, 33–40.) **B.** Dacryocystorhinogram showing dilation of nasolacrimal duct through blockage.



Figure 34.4 Severe dermatitis in a rabbit with epiphora from a blocked nasolacrimal duct.



Figure 34.5 Concreted plug of nasolacrimal discharge with associated corneal abrasion in a rabbit with dacryocystitis.

The key feature of successful treatment and the key problem with an unsuccessful treatment are that a merely topical agent is unlikely to treat the infection deep in the nasolacrimal duct. The copious discharge needs to be flushed out, and this done regularly until the condition resolves. Cannulation of the single ventral nasolacrimal punctum is best achieved with pressure exerted on the lower lid at the medial canthus which causes the punctum to 'pout' allowing entry of a narrow (23 gauge) nasolacrimal cannula. This can be difficult especially in cases where severe conjunctivitis is also present (Fig. 34.6A). Entering the duct from the nasal aspect is possible (Fig. 34.6B) but generally more difficult than from the eye. Flushing of the duct can be undertaken with sterile water or saline or with injectable enrofloxacin solution, although the pH of this is said by some to be irritant to the duct epithelium.

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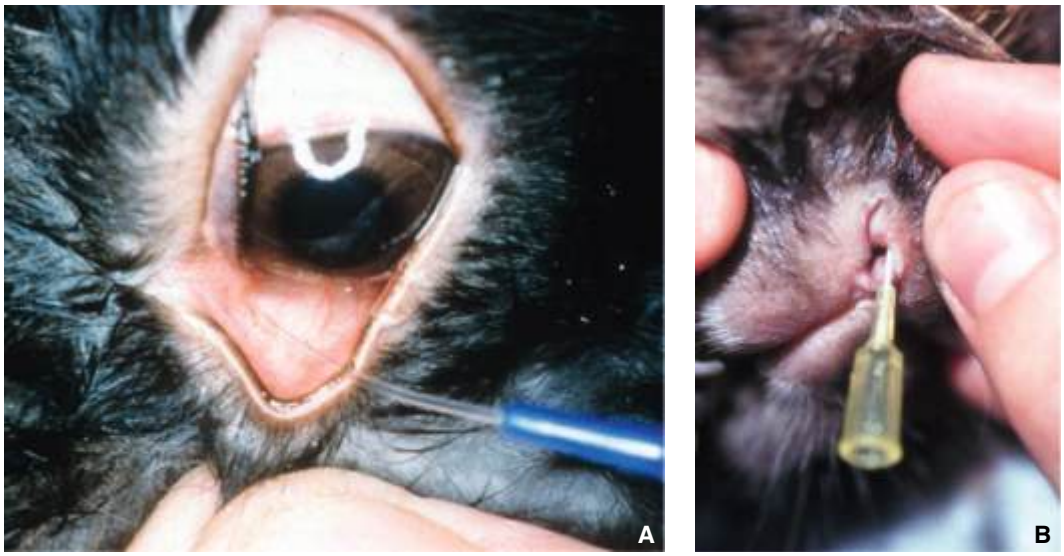


Figure 34.6 **A.** Cannulation of the single ventral nasolacrimal punctum. **B.** Cannulation of the nasolacrimal duct retrograde up the nostril is possible but difficult.

Another therapeutic regime involves systemic medication either of enrofloxacin or azithromycin per os. Both have been found useful when persistent flushing has been unsuccessful, but such antibiosis does not cure the problem, merely controls it, and after a period of remission it may recur, requiring further antibiotic treatment. Such parenteral therapy can have concerning side effects – some antibiotics delivered per os can have lethal effects on gut flora but it appears that enrofloxacin in the oral formulation, azithromycin when given as a pediatric elixir, or potentiated sulfonamides again as a pediatric elixir, can be safe and effective.

Conjunctivitis and Blepharitis

As noted previously, many rabbits with ocular discharge have dacryocystitis not merely conjunctivitis. But rabbits can present with inflamed conjunctiva (Fig. 34.7), possibly from dusty hay or even a hay awn acting as a foreign body. Infectious agents may cause the condition, from *Pasteurella* or other Gram-negative organisms, to the myxomatosis virus, although this latter agent usually causes a fulminant blepharitis with copious white discharge (Fig. 34.8A, B). The virus has this effect through profound effects on the immune system (Spiesschaert et al., 2011). As a DNA pox virus with a large genome, it hijacks genes from the host and mutates them to reduce vital immune functions such as antigen presentation and cytokine production by T cells. This allows a wide range of normal commensals to become pathogenic. The importance of regular vaccination cannot be overstated. Even vaccinated individuals can be affected, developing the benign myxomatous tumor growths that give the virus its name (Fig. 34.8C).

Another cause of lid swelling can be a presumed allergic reaction against staphylococci (Fig. 34.9A). Such lid swelling can cause entropion, otherwise quite a rare condition in this species. Management is difficult but hot water compresses can give a useful resolution of lid swelling. Ulcerative blepharitis occurs because of infection with *Treponema cuniculi*, rabbit syphilis (Fig. 34.9B). Diagnosis can be confirmed using a wet preparation of a skin scrape sample viewed microscopically against dark field illumination or by histopathological examination of a biopsy specimen. Treatment with 50,000 IU/kg of depot penicillin by subcutaneous injection once weekly for 3–4 weeks is the key to resolving such lesions



Figure 34.7 Conjunctivitis can make nasolacrimal intubation difficult.

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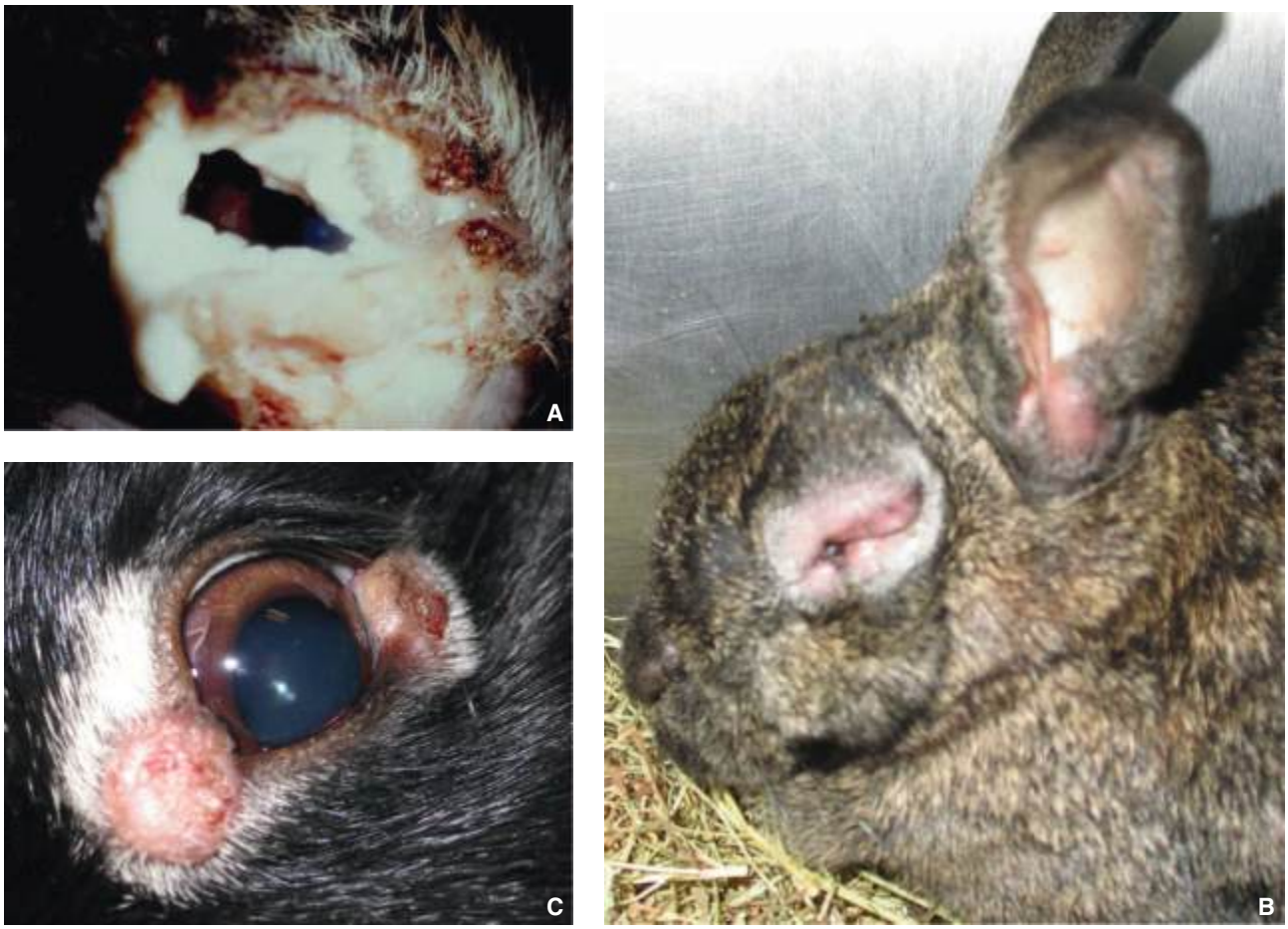


Figure 34.8 **A.** Myxomatosis in a wild rabbit with copious white discharge from secondary bacterial infection. **B.** Eyelid swelling in a pet unvaccinated rabbit with myxomatosis. **C.** Eyelid myxomas in a vaccinated rabbit with myxomatosis.



Figure 34.9 **A.** Nonulcerative blepharitis with *Staphylococcus* infection. **B.** Ulcerative blepharitis and conjunctivitis with *Treponema cuniculi* infection.

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Conjunctival Overgrowth

Whereas conjunctivitis is a condition seen across the companion animal species we deal with, conjunctival overgrowth, otherwise termed conjunctival centripetalization, epicorneal membrane or pseudopterygium, is a condition seen only in the rabbit (Allgoewer et al., 2008). It is not common, with only one case in our survey of a 1,000 animals, but has a classic appearance of an annulus of conjunctiva growing over the cornea from the limbus. This may be a narrow band of tissue (Fig. 34.10A) or a sizeable ring with only a small aperture centrally (Fig. 34.10B). The term pseudopterygium is less than helpful, because pterygium is a lesion within the cornea, not a band of conjunctiva overlying it as in this conjunctival overgrowth. Resection of this tissue merely leads to its regrowth but an operation to suture the band of tissue back onto the sclera is a successful procedure preventing excessive growth occluding vision (Kim et al., 2013).

Orbital Disease and Exophthalmos

An important difference between the rabbit eye and that of the cat or dog is the fact that the rabbit orbit contains a large orbital venous sinus, relevant to potential hemorrhage during enucleations and also to an unusual form of exophthalmos discussed later. Most cases of exophthalmos, however, are caused by retrobulbar abscesses, usually originating from the tooth root (Fig. 34.11). These can be very difficult to manage, as can any rabbit abscess, but some groups have reported success with endoscopic curettage after dental extraction (Martínez-Jiménez et al., 2007). In many cases, in this author's experience, the compromise to the animal's welfare, even if long-term treatment is successful, means that often this condition calls for the euthanasia of the rabbit.

Other retrobulbar space-occupying lesions which can cause exophthalmos can be neoplasms or parasitic cysts (O'Reilly et al., 2002), although both of these are much less common than a retrobulbar abscess. Another condition causing intermittent exophthalmos, most often occurring when the animal is handled, is the situation when a mass, usually a thymoma, wraps itself around the jugular veins, preventing adequate venous return from the head region (Künzel et al., 2012). This engorges the orbital venous sinus in the retrobulbar space and causes apparently painless exophthalmos while the blood pressure is raised (Fig. 34.12). The cervical mass preventing venous return is very difficult to remove surgically in most cases.

The rabbit has several orbital glands which may prolapse to give a condition analogous to 'cherry eye' or prolapse of the nictitans gland in the dog (Fig. 34.13A) (Janssens et al., 1999). Treatment of this should be to replace the gland using the Morgan pocket technique where an incision is made on either side of the gland, after which it is replaced before suturing the two sides of the 'pocket' (Fig. 34.13B) rather than to excise the gland, both because it makes an important contribution to tear production but also to avoid trauma to the orbital venous sinus.

Corneal Ulceration

As noted previously, rabbits have particularly protuberant eyes with a large exposed ocular surface relative to their body mass. This means that ocular surface trauma is common, but as with any species, the continual cycle of corneal epithelial cell migration from the limbus at the periphery to the central cornea where those cells desquamate and are lost into the tear

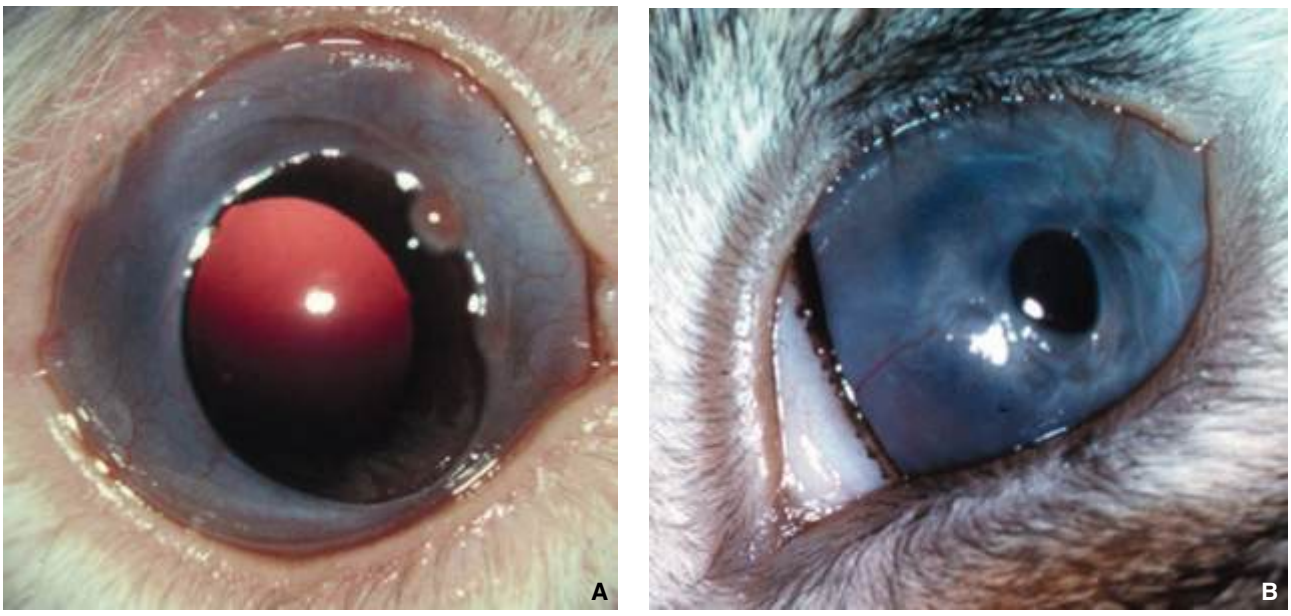


Figure 34.10 **A.** Narrow band of conjunctival overgrowth with visual axis remaining clear. **B.** Wide band of conjunctival overgrowth occluding vision.

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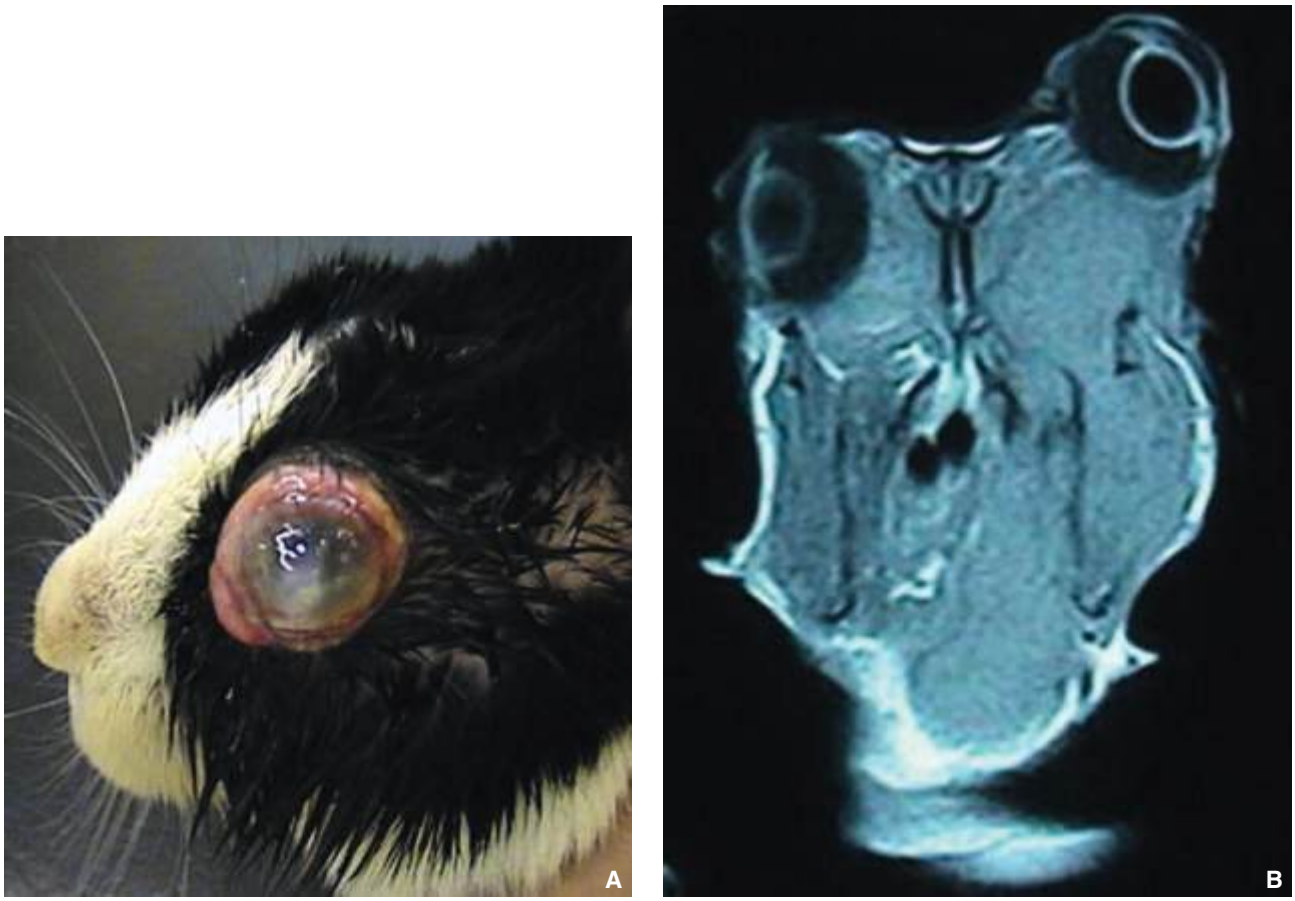


Figure 34.11 **A.** Severe exophthalmos in a dwarf rabbit. **B.** Magnetic resonance imaging of the skull of rabbit pictured in **(A)**.

film is a critical determinant (Andrew, 2002). Every posttraumatic corneal ulcer, such as this linear erosion (Fig. 34.14), should thus heal in under one week. What is needed in such a situation is protection for the healing ulcer with a tear replacement gel such as a carbomer-based product or cross-linked hyaluronic acid polymer and an antibiotic to prevent infection on the compromised surface of a corneal ulcer. One problem here is that every topical antibiotic medication contains stabilizers and preservatives such as benzalkonium chloride. This tertiary ammonium compound inhibits cell migration and may actually cause apoptosis, programmed cell death, in migrating cells. This is clearly not what is needed in a healing corneal ulcer, and as such many human ophthalmologists only use preservative free antibiotic drops. This conundrum of on the one hand needing an antibiotic to prevent infection yet on the other not wanting to inhibit healing, seems impossible to solve. An ulcer which has had a topical antibiotic for several days might be considered to be sterile, as long as the antibiotic is active against ocular surface pathogens. If it is not healing, then holding back on the antibiotic may be just the thing that is needed to promote ulcer healing, as long as regular examination is undertaken to ensure that supervening infection is not occurring.

It may be, however, that the adhesion between those epithelial cells and the basement membrane is not adequate. In such cases, as occur in indolent corneal ulcers in some dog breeds, the edge of the ulcer appears as a ring of devitalized nonadherent epithelium. This devitalized epithelium prevents healthy cells migrating and adhering onto the ulcer bed. These dystrophic ulcers do occur in rabbits (Fig. 34.15) and the treatment is similar to that in affected dogs. After topical anesthetic administration, a sterile cotton bud or bacteriology swab is used to debride the nonadherent epithelium at the edge of the ulcer. A sterile needle (23 or 25 gauge) is used to breach the abnormal basement membrane either as focal punctures or a grid across the ulcer (Fig. 34.16) or diamond burr debridement. This has to be done with considerable caution in the rabbit because the cornea is substantially thinner than in the dog. Protection for the healing ulcer is also important and although a frequent carbomer-based tear replacement may be sufficient others have recently used collagen shields or contact lenses (Eshar et al., 2011). Nictitating membrane flaps can be difficult to maintain in the rabbit as the third eyelid cannot readily be extended greater than halfway across the cornea, and is retracted by a powerful muscular extension of the levator

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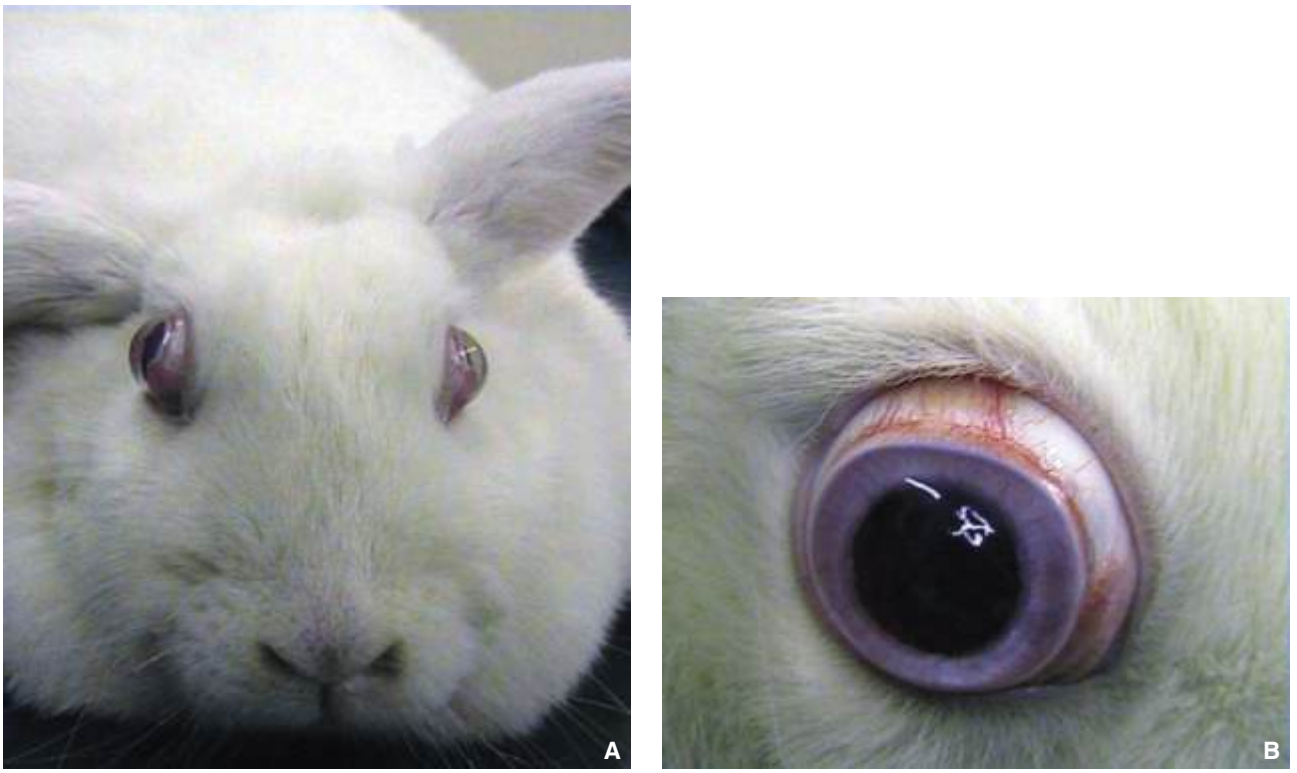


Figure 34.12 **A.** and **B.** Exophthalmos caused by obstructed venous return through a thymoma occluding the jugular veins.



Figure 34.13 **A.** Prolapsed orbital gland. **B.** Replacement of prolapsed gland with the Morgan pocket technique.

palpebrarum superioris muscle, rendering sutures placed to protract the lid across the eyelid liable to pulling through the nictitating membrane.

Cataract

Our study of 1,000 guinea pigs showed that a large number had some degree of lens opacification. Our evaluation of 1,000 rabbits, however, showed a much lower proportion of animals with cataract with only 45 animals from that 1,000 having lens changes (Fig. 34.17A) (Innes & Williams et al., 2018). Many of these were congenital opacities both in the nucleus or the posterior capsule of the lens, with an average age of rabbits with these lens changes being 2.7 and 3.6 years, respectively, whereas nuclear sclerosis, the aging change in which the continually growing cortex compresses the lens nucleus, was found in rabbits with an average age of 6.0 years. Many of these cataracts are small opacities with little effect on vision, whereas some may be much more rapidly maturing and hence blinding (Fig. 34.17B, C).

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Figure 34.14 Linear corneal epithelial erosion from trauma with hay awn.

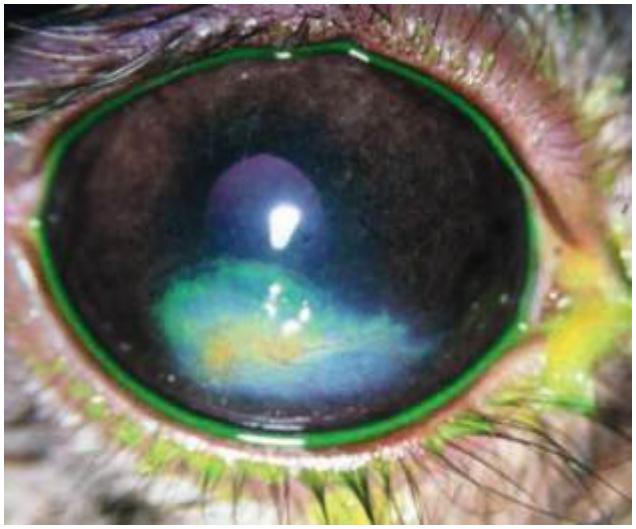


Figure 34.15 Recurrent recidivistic epithelial erosion in a rabbit with basement membrane dystrophy-like lesion, and devitalized rim of nonadherent epithelium.

These cataracts, usually seen in older rabbits, mirror the age-related cataract seen in other species. Yet one form of cataract unique to the rabbit is that caused by *Encephalitozoon cuniculi* (Fig. 34.18). This remarkable obligate intracellular microsporidian generally infects rabbits through ingestion of contaminated urine and may cause renal or neurological symptoms (Künzel et al., 2008). Yet the involvement of the organism in cataract occurs because many parasites are transmitted transplacentally and enter the rabbit while still *in utero*. If the organism migrates to the developing lens, it may lie dormant for many months, before moving through the lens, causing cataract and then erupting through the anterior lens capsule to liberate lens material into the anterior chamber (Giardano et al., 2005). This elicits lens-induced uveitis, which, although it may cause the cardinal signs of intraocular inflammation, namely miosis, iridal redness and swelling, and hypopyon, is much more likely to result in a white or pink mass protruding into the anterior chamber of the eye (Fig. 34.18B).

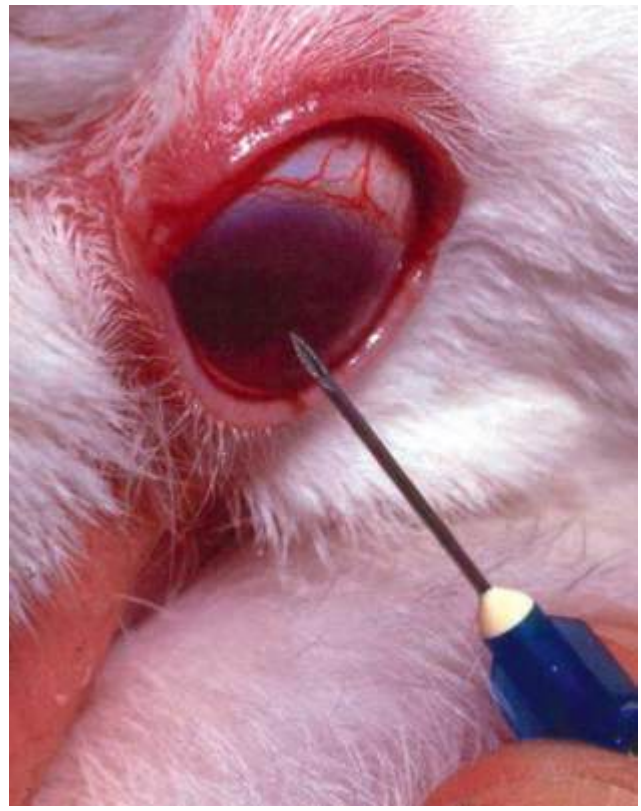


Figure 34.16 Grid keratotomy cautiously applied to the type of nonhealing ulcer illustrated in Fig. 34.15.

While any such appearance is usually held to be characteristic of *E. cuniculi* lens-induced uveitis, it can be confused with uveitis associated with *Staphylococcus* or *Pasteurella*. Thus obtaining an *E. cuniculi* titer is always helpful in rabbits presenting with these abnormalities. Any uveitis should be treated with topical anti-inflammatory medication – steroid drops such as prednisolone acetate (Pred Forte, Allergan, Irvine, CA, USA) or dexamethasone alcohol (Maxidex, Alcon, Ft. Worth, TX, USA) or a topical nonsteroidal such as ketorolac (Acular, Allergan, Ft. Worth, TX, USA) but uveitis caused by *E. cuniculi* should also be treated with oral fenbendazole to kill the parasites causing the cataract.

Another method that has been reported in such cases is phacoemulsification removal of the lens and its associated parasites (Felchle & Sigler, 2002). Pre-emptive treatment with topical steroids will reduce the intraocular inflammation which would otherwise be detrimental to the success of cataract removal.

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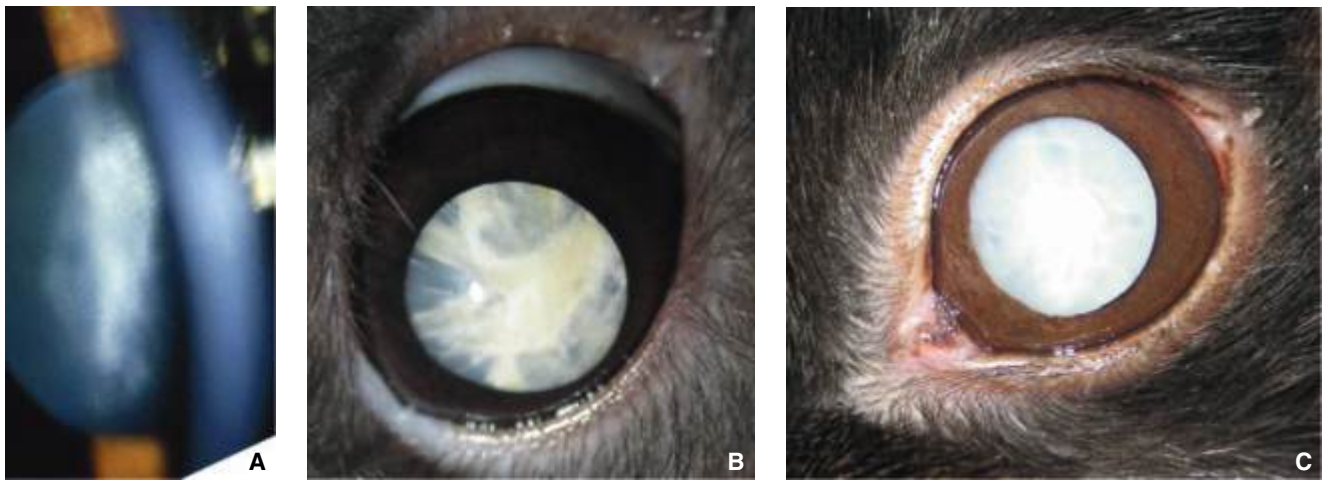


Figure 34.17 Different types of cataracts in rabbits. **A.** Anterior capsular cataract in a 3-year-old rabbit. **B.** Suddenly acquired severe potentially posttraumatic cataract in a 12-year-old rabbit. **C.** Mature cataract in 7-year-old diabetic rabbit.

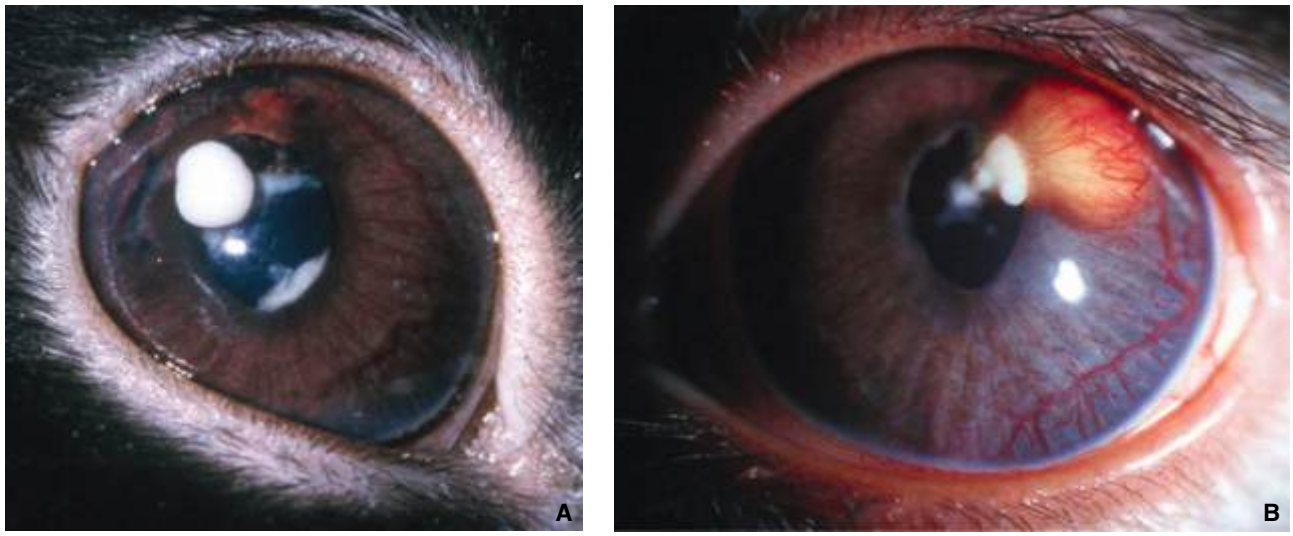


Figure 34.18 **A.** *Encephalitozoon cuniculi*-related phacoclastic uveitis with characteristic white focal lesion and cataract. **B.** Hyperemic phacoclastic uveitis lesion.

As in other species, phacoemulsification is used to remove the lens without undue postoperative complications (Sanchez et al., 2018), but the rabbit as a species has an unusual propensity to reform lens fibers after removal surgically (Gwon, 2006; Stewart & Espinasse, 1959). When intraocular lens implants have been used, these have sometimes been forced out of the lens capsule by the regrowth of lens tissue. Careful removal of all lens fibers from the lens capsule reduces this risk.

Uveitis

As noted previously, *E. cuniculi* lens-induced uveitis is relatively common in rabbits (Wolfer et al., 1993) although in our study only five rabbits showed signs of the disease out of 1,000. Other causes of uveitis include inflammation induced by *Pasteurella* and staphylococcal infection. The latter usually appears as a yellow–cream abscess filling a large proportion of the eye (Fig. 34.19) and the former gives signs more usually seen in uveitis of mild hypopyon and miosis (Fig. 34.20), whereas the *E. cuniculi* lesion, as noted previously is generally a whiter color (Fig. 34.18A), unless neovascularization also occurs in which case it can be pink/red (Fig. 34.18B). Aqueous paracentesis with a 25 gauge needle entering the eye obliquely can provide bacteriological and cytological samples for definitive diagnosis, although does have the disadvantage of eliciting an inflammatory reaction itself and so is not to be advised in many cases (Unger et al., 1975). Where this diagnostic step is not possible, treatment with oral fenbendazole, topical antibiotics, atropine, and corticosteroid covers all eventualities, although, as noted

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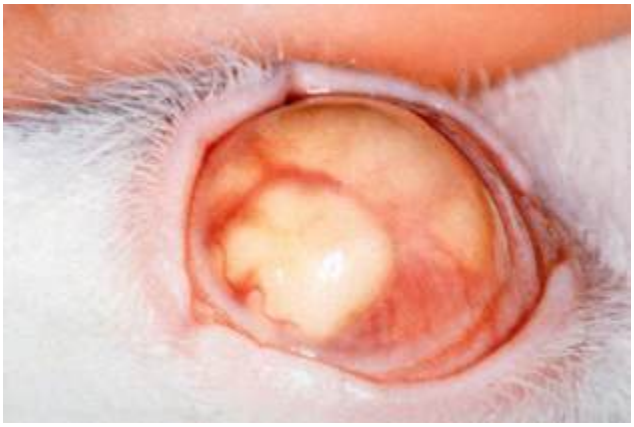


Figure 34.19 Staphylococcal panophthalmitis.

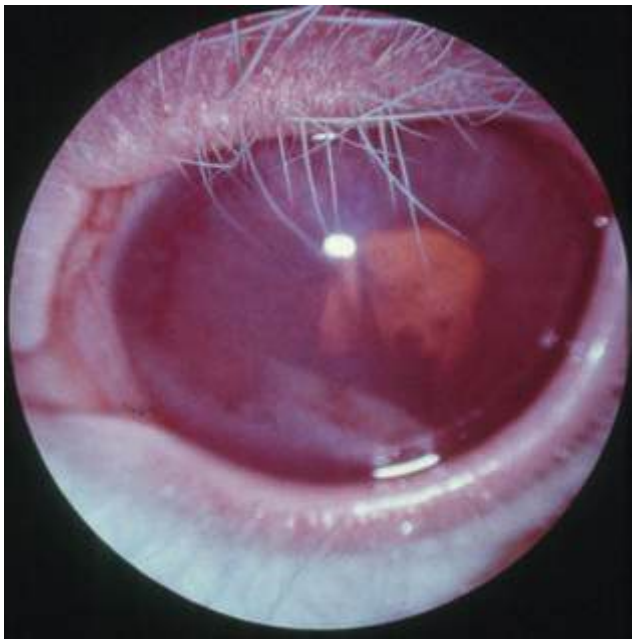


Figure 34.20 *Pasteurella multocida* uveitis with hypopyon and synechiae.

above, generally the appearance of the eye gives a good differentiation between *E. cuniculi* and *Staphylococcus*- or *Pasteurella*-induced uveitis.

Glaucoma

Increased intraocular pressure (IOP) might be regarded as relatively uncommon in the rabbit with only three cases seen in the 1,000 normal rabbits we surveyed. Yet this is a significant number compared with the prevalence in other companion animals. One reason for this may be that the New Zealand White, as a laboratory strain, is affected by a genetic trait of buphthalmos, where increased IOP early in the animal's life results in an increase in globe size, or buphthalmos



Figure 34.21 Glaucoma in the New Zealand White rabbit.

(Fig. 34.21). The *bu* gene also causes prenatal mortality. Even though this is a recessive gene, it would appear that it can affect New Zealand White crosses and giant breeds. Purulent material in the anterior chamber in cases of uveitis can also lead to secondary glaucoma.

The normal IOP in the rabbit measured with a TonoPen applanation tonometer (Fig. 34.22), or a TonoPen XL (Reichert, Inc., Depew, NY, USA) or a TonoVet rebound tonometer (Reichert, Inc., Depew, NY, USA) (Fig. 34.23) is generally considered to be between 15 and 20 mmHg although a recent study found the TonoVet to give significantly lower values (mean value 9.5 ± 2.6 mmHg) compared with the TonoPen (mean value 15.4 ± 2.1 mmHg) (Pereira et al., 2011). Glaucomatous rabbits can show IOP values up to 50 mmHg but without apparent pain, which one would expect to be seen in other species with this severe a glaucoma. Here we see a key problem in assessing pain in a prey species such as the rabbit. Are these animals in severe pain but just not showing it, so as not to be an obvious prey item? Treatment with topical carbonic anhydrase inhibitors such as dorzolamide (Trusopt, Allergan) three times daily reduces the IOP but appears to make no difference to behaviour of the affected animal.

Enucleation

The orbital sinus or retrobulbar plexus has been discussed previously with regard to stress-related transient exophthalmos but this vascular structure is most important to be aware of when performing an enucleation. A transpalpebral approach runs the risk of entering this sinus with the potentially severe side effect of blood loss. The transconjunctival technique, generally preferred in all species by most ophthalmologists yet little used by many general veterinary surgeons, enables one to remove only the globe and not exenterate the orbit and its contents, including the orbital sinus. The conjunctiva is first incised for the entire perimeter of the cornea, and then the extraocular muscles, very easy to

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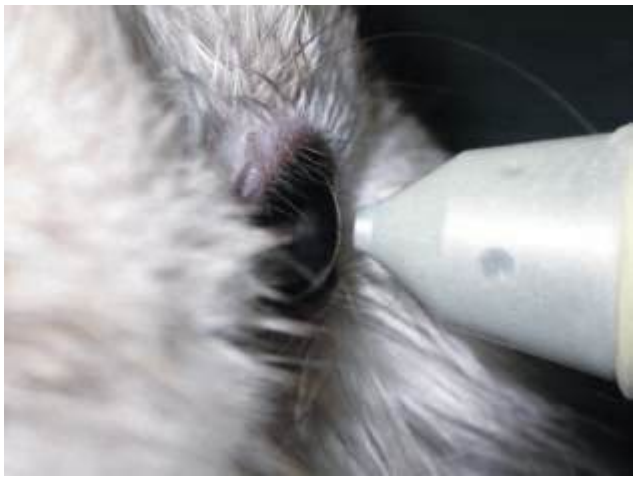


Figure 34.22 TonoPen applanation tonometer used in a rabbit.

identify in the rabbit, are transected at their insertion on to the globe. As the muscles are relieved from their attachment to the globe, the eyeball can be raised gently from the orbit and the optic nerve transected. The nerve does not need to be ligated. That is only the case in primates where the central retinal artery courses up the middle of the optic nerve, but in subprimate mammals the retinal blood supply occurs predominantly through the ciliary arteries, flow from which can readily be stopped by firm pressure with a sterile gauze swab placed in the orbit while the eyelids are removed. In the rabbit, the central retinal artery only enters the optic nerve 2 mm from its entry to the globe, so incising the nerve further from the eye than this avoids the artery altogether. Some surgeons choose to remove the third eyelid, but the risk of perforating the orbital sinus means that the third eyelid is perhaps better retained, incorporated into the closure of orbital fascia prior to skin closure.



Figure 34.23 TonoVet rebound tonometer used in a rabbit.

Guinea Pigs

There is very little work published on ocular disease in this species, even though it is a commonly kept animal in laboratories and as a pet, and has a high prevalence of ocular disease. In our survey of ocular disease in 1,000 apparently normal guinea pigs, we found 45% to have some ocular disorder, ranging from cataracts to heterotopic bone formation (Williams & Sullivan, 2010).

A number of these conditions will render the animal blind, yet with little apparent deterioration in their behavior. This is somewhat perplexing, because guinea pigs, unlike the rat and mouse, are highly visual animals, using their sight from the moment they are born fully furred and alert. Their visual acuity has been assessed as 2.7 cycles per degree, an equivalent of a Snellen acuity of 6/70, although this estimate was made by counting retinal ganglion cells and not by behavioral visual evaluation (Buttery et al., 1991). Most guinea pigs appear to be somewhat hypermetropic on refraction (Jiang et al., 2009); one report shows albino animals to be spontaneously myopic to varying degrees (Wang et al., 2007).

Congenital defects ranging from those as severe as clinical anophthalmos (Fig. 34.24) to posterior polar subcapsular cataracts (Fig. 34.25) are seen in a significant proportion of guinea pigs, particularly those of roan × roan matings. Congenital cataracts have been reported in a litter of guinea pigs also affected with urogenital abnormalities after treatment of pregnant sows with the antibiotic, tylosin. This oculourinogenital association is interesting given the human conditions Alport's and Potter's syndrome (Swan & Patel, 2005). For laboratory animal veterinarians, it shows how important it is to be aware



Figure 34.24 Anophthalmos in a guinea pig.

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Figure 34.25 Posterior polar subcapsular cataract in a guinea pig.



Figure 34.26 Trichiasis and ocular surface ulceration in a Texel guinea pig.

of potential teratogenic consequences from medicating gestating females (Wilson et al., 1978).

Ocular surface defects in young animals may be caused by trichiasis in Texel animals where the coat is composed of short bristly hairs which can easily abrade the eye in the first few days of life in these precocious young. Breeders use Vaseline to encourage periocular hairs to be directed away from the ocular surface but corneal ulceration and edema can still occur (Fig. 34.26). Dermoids have been reported several times in guinea pigs, both haired (Gupta, 1972) and hairless (Otto et al., 1991) (Fig. 34.27).

Conjunctivitis among guinea pigs has been regularly associated with chlamydial organisms since first reports in the early 1960s (Murray, 1964). Some animals have only slight reddening of the eyelid margins, whereas others have thick, purulent exudate. Infection in young animals is characterized by inclusion bodies in conjunctival epithelial cells with leukocytic infiltrates, but in many cases, it resolves spontaneously in 1 month. The disease is now recognized to be associated with *Chlamydia psittaci*. Guinea pigs also develop a particularly severe keratoconjunctivitis when infected with *Listeria monocytogenes*, which is an organism producing only mild disease in other rodents, rabbits, and nonhuman primates. This is of interest from the perspective of the guinea pig as a useful model for the disease, but it is also important to remember when confronted with a guinea pig having severe conjunctivitis (Stams, 1967). Other infectious causes of conjunctivitis in guinea pigs include salmonellosis (Voĭno-Iasenetskiĭ et al., 1997). Infectious agents are also not the only cause of conjunctival lesions in this species. For example, because they are incapable of forming their own



Figure 34.27 Dermoid in a guinea pig.

vitamin C, guinea pigs are at considerable risk of scurvy, one of the early signs of which is conjunctival disease. Individual cases of entropion in guinea pigs have been reported as well, as have posttraumatic lid defects. It is important in cases with proliferative conjunctivitis to assess for an irritative focus, be that dusty hay or a focal foreign body, as in this case where a hay awn can be recognized protruding from the upper conjunctiva (Fig. 34.28).

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Figure 34.28 Proliferative conjunctivitis resulting from a hay awn in a guinea pig.



Figure 34.29 Keratoconjunctivitis in a guinea pig.

Guinea pigs may be presented with ocular irritation secondary to keratoconjunctivitis sicca (Fig. 34.29). The average Schirmer tear test (STT) wetting in one minute has been reported as 3 mm with a range from 0 to 12 mm/min in one study (Coster et al., 2008), whereas another, specifically addressing tear production in Duncan Hartley cavies, reported the average STT value to be 0.4 mm/min (Trost et al., 2007). This profound difference shows the importance of taking a set of normal readings from cage mates of the same breed, age and gender.

So-called 'fatty eye' involves excess lipid deposition in the inferior conjunctiva and is particularly seen in animals being fed to put on weight prior to showing (Fig. 34.30). Note that this latter animal also has diabetes with an associated cataract. 'Flesh eye' on the other hand involves a smaller pink-colored mass in the medial canthus (Fig. 34.31) and is probably analogous to prolapsed nictitating membrane in the dog or rabbit although histopathological confirmation of this has yet to be reported. Neither of these two conditions show a high prevalence in our study of a 1,000 animals, but 'fatty eye' is particularly seen in somewhat obese animals being prepared for guinea pig shows.



Figure 34.30 'Fatty eye' in a guinea pig.



Figure 34.31 'Flesh eye' in a guinea pig, presumed nictitans gland prolapse.

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Bony spicules surrounded by a fibrous envelope have been reported in the ciliary body of guinea pigs (Fig. 34.32). Some investigators have likened these lesions to osseous choristomas in the choroid of humans (Griffith et al., 1988), but others have more cautiously termed them heterotopic bone formations (Brooks et al., 1990). Whereas calcification of diseased tissue is termed dystrophic calcification, heterotopic bony metaplasia and calcification occurs in healthy tissue and is regularly seen among guinea pigs in various non-ocular sites. In one recent report, a link was suggested between secondary glaucoma with buphthalmos and heterotopic bone formation (Schäffer & Pfleghaar, 1995). It is difficult to be sure that a causal relationship was occurring given the prevalence of this heterotopic bone formation in the normal guinea pig eye, but with the proximity of the abnormality to the iridocorneal angle, it is easy to envisage a pathogenetic link between the two conditions. In our study (Williams & Sullivan, 2010), animals with this condition did not have a raised IOP, but animals in which the entire circumference of the iridocorneal angle, or indeed the entire globe is filled with calcium, might be expected to have an increased IOP (Fig. 34.32). Regarding the cause of this bone formation, the role of the guinea pig ciliary body in concentrating plasma ascorbic acid into the aqueous humor may be important. Ascorbic acid is known to promote bone formation in the presence of a rich blood supply, such as occurs in the ciliary body.

As noted previously, cataracts are commonly seen in guinea pigs – 18% of outbred animals in our study were affected whereas inherited cataracts have been reported in the N13 strain of guinea pigs (Bettelheim et al., 1997). Lens opacities in these animals are caused by a single splice-site mutation in the zeta-crystallin gene. Quite apart from these rare inherited cataracts, the frequent occurrence of lens opacities in outbred guinea pigs in our study differs markedly from the case in the rabbit wherein a comparative study of 1,000 outbred rabbits, as yet unpublished in the peer reviewed literature, the prevalence of lens opacities is significantly lower (Innes & Williams, 2018). The reason for the difference in two species otherwise similar in habits and diet is unclear. It may well be associated with the inability of the guinea pig to synthesize ascorbic acid; lenticular ascorbate is essential in the guinea pig and rabbit as a lenticular ultraviolet filter and antioxidant, so reduced levels in poorly supplemented cavies may be a causative factor in cataractogenesis (Matsukura et al., 2001). It is known that high levels of dietary ascorbate protect guinea pig lenses from ultraviolet irradiation damage, but whether this is relevant to normal dietary intake and daylight-associated damage is unclear (Blondin et al., 1986). Nuclear sclerosis as an early lens change prior to overt opacification can be found in the guinea pig as in other species (Fig. 34.33). Diabetic animals are often noted to have mature cataracts (Fig. 34.34) but whether these occur in the majority of diabetic animals is as yet unclear.

The guinea pig has an anangiotic retina (Fig. 34.35) but no reports of fundus abnormalities have been reported in the literature, although a recent report documents a spontaneous disorder of rod function as determined by electroretinography in a group of animals as a result of consanguineous mating (Racine et al., 2003).

Chinchillas

The scientific literature yields little regarding diseases of the chinchilla eye and nothing on their visual capabilities or refraction. They are nocturnal and crepuscular animals with a vertical pupil that can close to a narrow slit, protecting their scotopically adjusted retina from bright light, which

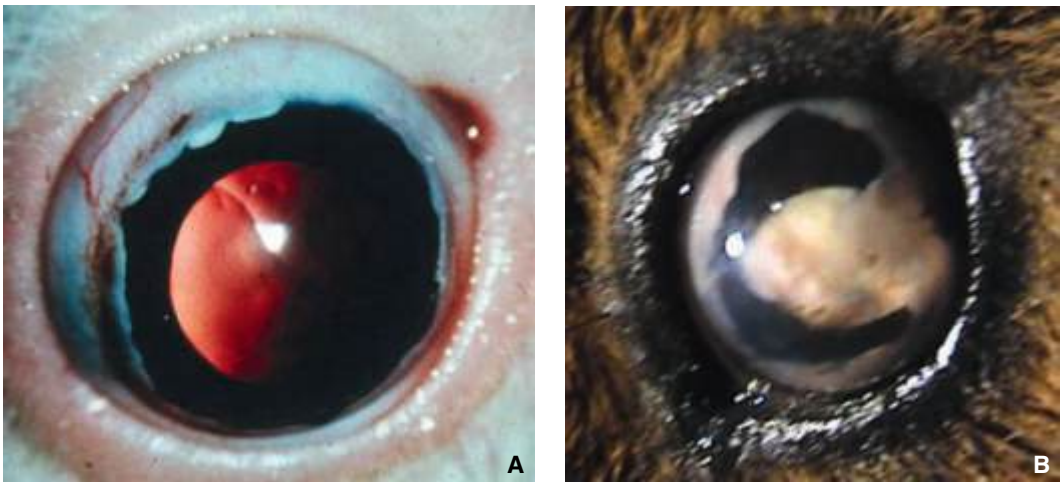


Figure 34.32 **A.** Focal areas of heterotopic bone formation in a guinea pig. **B.** Entire globe filled with bone in extreme heterotopic bone formation in a guinea pig.

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Figure 34.33 Nuclear sclerosis in a 5-year-old guinea pig.



Figure 34.34 Mature cataract in a diabetic guinea pig.

can render fundoscopy somewhat difficult without mydriasis. Examination of 14 aged chinchillas revealed a shallow orbit, a rudimentary nictitating membrane, a large cornea, a densely pigmented iris in pigmented individuals with a vertical slit pupil, and an anangiotic fundus with variable vascularization of the optic disc (Peiffer & Johnson, 1980). Pupil constriction and dilation is less complete in light and dark conditions in lightly pigmented individuals than in those with a darkly pigmented iris. Mean IOP was 18.5 ± 5.8 mmHg. Bilateral posterior cortical cataracts and asteroid hyalosis

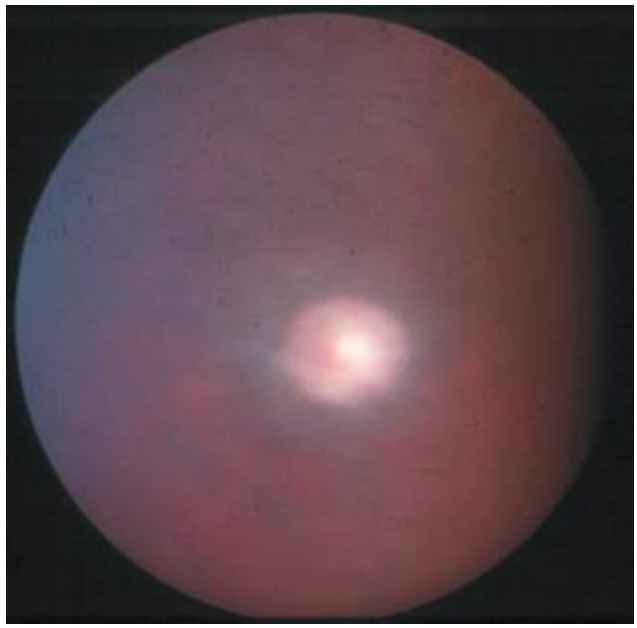


Figure 34.35 Anangiotic retina in a guinea pig.

were observed in two animals. Reference values for diagnostic tests in 61 healthy normal chinchillas have been reported (Müller et al., 2010). STTs were low and inconsistent, whereas phenol red thread test values averaged wetting length of 14 mm in 15 seconds. Average IOP as measured with a TonoVet rebound tonometer was 2.9 ± 1.8 mmHg. In another report, STT readings of 0.1 ± 0.5 mm/min and IOP, again measured with the TonoVet, of 17.7 ± 4.2 mmHg (Lima et al., 2010). The tonometric differences between these two reports are difficult to explain. A more recent paper showed IOP measured with the TonoVet rebound tonometer on setting 'd' in chinchillas to be 9.7 ± 2.5 mmHg, and the 95% reference interval was 4.7–14.7 mmHg (Snyder et al., 2018).

A significant problem in this species when kept in captivity is dental disease (Crossley, 2001). Like the rabbit, the chinchilla has hypsodont dentition, with continually growing teeth. Without adequate wear from a rough coarse dietary intake, the molar teeth lengthen (Crossley & Miguélez, 2001) with resulting root extension into the orbit and subsequent epiphora. The use of imaging techniques such as computerized tomography to detect such changes at a subclinical level has been shown to be valuable (Crossley et al., 1998).

Ferrets

Ocular disease in pet ferrets has been well reviewed and readers are directed to Good (2002) for detailed coverage of the subject and the ferret chapter in Williams (2012). The ferret eye is, as for many species in this chapter, optimized for dim light conditions, with predatory activities occurring

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between dawn and dusk on even in daytime within the scotopic conditions of rabbit warrens and prairie dog burrows. Thus the ferret retina is predominantly rod-based, although, as with the cat, there is a cone-rich strip, the area centralis, allowing a higher acuity to be achieved. The ferret's visual resolution reaches photopic and scotopic Snellen acuity of 20/170 and 20–350, respectively. Thus the ferret's vision is markedly inferior to that of the cat (around 20/100), but its visual sensitivity, the lower limit of light needed for vision, appears much better. The threshold of light needed for vision in the ferret is estimated to be five to seven times lower than in man. Ferrets seem particularly attuned to moving objects.

Reference values for IOP (14.5 ± 3.2 mmHg) and STT (5.3 ± 1.3 mm/min) have been reported (Montiani-Ferreira et al., 2006). Ocular biometry confirmed globe size as 7.0 ± 0.2 mm and lens thickness as 3.4 mm (Hernández-Guerra et al., 2007).

Congenital ocular disease in this species is relatively rare, although persistent hyaloid artery, tunica vasculosa lentis, and hyperplastic primary vitreous have been reported (Lipsitz et al., 2001). The young ferret (kit) does not open its lids until about 20 days, and perhaps it is this late opening that accounts for the relative prevalence of ophthalmia neonatorum in this species. Careful manual eyelid margin separation should be followed by topical and systemic broad-spectrum antibiotics. Note carefully whether nursing mothers have mastitis because this can lead to conjunctivitis or more severe adnexal infection (Miller, et al., 1993). Ferrets are affected by conjunctivitis associated with human influenza, canine distemper, together with systemic mycobacteriosis and salmonellosis. Canine distemper in this species may cause serous oculonasal discharge, which becomes mucopurulent, with associated chemosis and corneal ulceration. Brown crusts form around the mouth and eyes, often causing ankyloblepharon. Animals may appear to be photophobic. The diagnostic signs are a skin rash, occurring days later, and hyperkeratosis of the foot pads (Besch-Williford, 1987). Death is almost inevitable in this condition, but with influenza, the almost identical early signs often resolve. Conjunctival scrapings may be useful in arriving at a diagnosis: intracytoplasmic eosinophilic inclusions often containing refractile particles may be detected at routine cytology in distemper, or indirect immunofluorescence may be used to arrive at a definitive diagnosis (Fox et al., 1988). Viral isolation from blood and serologic evaluation is diagnostic in the case of influenza. Salmonellosis is characterized by hemorrhagic diarrhea and fever in addition to conjunctivitis. Conjunctivitis may be a constant sign in systemic mycoplasmosis (Dubielzig & Miller, 1995).

The ferret has a large retrobulbar venous sinus that has been suggested as a site for blood collection (Fox et al., 1984). Given the ease of blood collection from the ventral tail vein or jugular in this species, however, orbital blood collection cannot be recommended. The importance of recognizing the venous sinus in ferrets comes during enucleation, in which hemorrhage from this plexus should be controlled by direct pressure, packing with gelatin sponge, or applying bovine thrombin at a concentration of 1000 IU/mL (Miller, 1997).

The depth of the orbit in a ferret renders detection of an orbital space-occupying lesion difficult until it has reached a considerable size (He & Kiliaridis, 2004; Poddar & Jacob, 1997). A large, poorly encapsulated zygomatic salivary gland is located posteroinferior in the orbit in the ferret, and head trauma may result in a salivary mucocele with associated exophthalmos (Miller & Pickett, 1989).

Microphthalmos has been reported in ferrets in one anecdotal report (Morton & Morton, 1985) and a second focusing on cataract formation in these animals (Miller & Dubielzig, 1995). This latter report documented the autosomal dominant inheritance of microphthalmos with cataract and retinal dysplasia in a colony.

Cataracts have been reported several times in ferrets (Fig. 34.36). In one paper, two groups were documented in one ferret colony (Miller et al., 1993). One group manifested a continuum of lens changes, from fine, multifocal punctate lens opacities through cortical change to complete, mature cataracts. The second group showed cataracts associated with microphthalmos and, in some cases, unusual PAS-positive material in the lens capsule. Lens luxations have been reported in ferrets as primary lens dislocations and as secondary to chronic cataract. Removal is taxing because of the small size of the globe but because glaucoma can supervene it is considered necessary. The small size of the globe also renders phacoemulsification for cataract difficult, but irrigation-aspiration techniques can be used with a smaller diameter handpiece. Uveitis and glaucoma are both seen after trauma and can be treated as for the conditions in any mammal species (Fig. 34.37).

Ferrets have a holangiotic retina with a reflective tapetum in pigmented animals but also unusually a tapetum in albino individuals (Wen et al., 1985). Retinal degeneration is believed to be common in the ferret with inherited atrophy

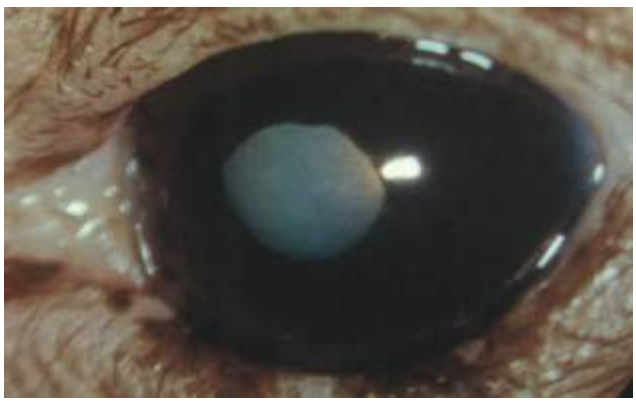


Figure 34.36 Cataract in a 6-year-old ferret.

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Figure 34.37 Posttraumatic uveitis in a ferret.



Figure 34.38 Apparently proptotic globes in a normal hedgehog.

and degeneration associated with taurine deficiency in this obligate carnivore noted in review but not reported in the primary literature.

Sugar Gliders

There is little information on ocular disease in these predominantly nocturnal marsupials which are increasingly kept as pets, particularly in the United States. We have to date no reports in the veterinary ophthalmic literature on eye diseases in sugar gliders. The size of the globe and exposed corneal surface render the animals prone to ocular surface injury; the animals can be aggressive towards each other during mating or when new adults are introduced into a group, and so ocular trauma is not uncommonly seen. Facial abscesses are also seen, sometimes with proptosis and



Figure 34.39 Cataract in a diabetic degu.

facial swelling. Cataracts have been reported in general articles on sugar glider medicine although we have no ophthalmic details on these ocular defects. Some exotic specialists consider that the white lesions in the eyes of these animals indicate an excess of lipid in the diet, although from the accounts in the literature it is difficult to know whether these are corneal lesions or lens opacities. Clearly more work needs to be undertaken on ocular abnormalities in this species. The retina of these animals is avascular.

Hedgehogs

The ophthalmic literature regarding pet hedgehogs is sparse. One study on IOP and tear production in clinically normal long-eared hedgehogs (*Hemiechinus auritus*) give a mean ± standard deviation of STT values for 28 eyes as being 1.7 ± 1.2 mm/min with a range of 0–4 mm/min (Ghaffari et al., 2012). The mean IOP value measured with the TonoPetVet was 20.1 ± 4 mmHg. Other papers involve individual cases of orbital tumors with exophthalmos (Fukuzawa et al., 2004; Kuonen et al., 2002) or animals with orbital cellulitis and proptosis (Wheler et al., 2001). Williams and colleagues have described ocular abnormalities in 300 wild European hedgehogs (*Erinaceus europaeus*) in rehabilitation centers but caution should be exercised when making extrapolations to animals of species such as the African pigmy hedgehog (*Atelerix albiventris)* kept as pets (Williams et al., 2017). Given that all hedgehogs of whatever species have shallow orbits, these animals are naturally somewhat exophthalmic and ocular surface pathology is commonly seen (Fig. 34.38). Nuclear cataract in a number of small poorly growing wild hedgehogs was seen, but it is difficult to know what relevance

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this might have to the pet population. The wild rescued population had a mean IOP of 12.6 ± 1.8 mmHg whereas those with intraocular inflammatory disease showed hypotony with a mean IOP of 6.25 ± 1.7 mmHg. STTs gave values of less than 1 mm/min in normal eyes and thus were not considered particularly valuable.

Degu

The degu (*Octodon degus*) is an Andean hystricomorph rodent native to northern and central Chile. They are herbivorous, generally, with a diet of bulbs, tubers, twigs and bark, which probably explains their propensity to developing diabetes when fed in captivity on a diet much richer than they are used to in the wild. Their primary ophthalmic complaint, at least as far as the literature is concerned, is diabetic cataract. This is particularly well described not only because of the number of diabetic degus in captivity but also because the lens has a high level of aldose reductase, the enzyme system which metabolizes sugar to the sugar alcohol sorbitol, which has the osmotic effect of drawing water into the lens resulting in mature cataract (Fig. 34.39) (Brown & Donnelly, 2001). The aldose reductase inhibitor sorbinil has been used in laboratory studies to prevent diabetic cataract in this species (Datiles & Fukui, 1989). Other cataracts with differing aetiology have also been reported, including congenital lens opacities (Worgul & Rothstein, 1975). A relatively recent review of disease in 300 degus brought to an Austrian veterinary clinic noted that 16% had ocular disease including uveitis (2 cases), corneal erosions (6 cases), and keratoconjunctivitis (4 cases) but cataracts were noted in 40 cases, some unilateral but most bilateral (Jekl et al., 2011).

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Exotic Animal Ophthalmology

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As public interest in natural history, conservation, and ecology has peaked, demand for competent diagnosis and treatment of the medical disorders of captive nondomestic animals has been thrust upon the veterinary profession. Its response has been timely and comprehensive. Once primarily preventative medicine, nondomestic animal medicine has evolved to incorporate the increasingly sophisticated treatment of individual animals commonly available for conventional pet and companion animal species as well as species targeted for conservation. This trend has fired keen interest in the improvement in the diagnosis, characterization, research, and management of the ocular disorders of these once "alien" patients.

The challenges that fish, amphibians, reptiles, birds, and wild mammals present for diagnosis and treatment are potentially daunting. Despite the availability of sophisticated instrumentation and technology to both ophthalmic specialists and non-ophthalmologists, the anatomy, physiology, and biology of many creatures seem often to defy their practical use. Nonetheless, in the diagnosis and management of ocular disorders of these special species, the clinician is wisely advised to: (1) learn and regularly review the ocular anatomy, physiology, and visual ecology of the species of current interest; (2) employ the same quality of complete ocular examination, albeit modified accordingly, performed on conventional species; and (3) articulate the limitations inherent in the examination techniques and ophthalmic diagnostic testing, in order to assess, accurately and realistically, ocular signs and to formulate specific, directed diagnostic and treatment plans.

Ophthalmic Examination

Despite the aforementioned caveats, a surprisingly complete ocular examination may be performed on many species, especially those with reasonably large eye size. External and anterior segment examination may be facilitated by magnification provided by a slit-lamp biomicroscope, head loupe, or indirect condensing lens, used with bright illumination in the (at least momentarily) immobilized patient. Posterior segment examination is possible in many species with direct or indirect ophthalmoscopy, or both, even without mydriasis, which is often difficult or impossible to achieve in some species. Indirect condensing lenses in the 28–60 D range facilitate panoramic fundus examination in small eyes and through small pupils. Applanation tonometry is possible in most eyes large enough to accommodate the tonometer's tip (TonoPen XL, Reichert, Buffalo, NY USA; Tonopen Avia, Reichert). Rebound tonometry (TonoVet, TonoVet Plus, and Tonolab, Icare, Vantaa, Finland) utilizes an even smaller tip and may be used on small eyes and does not require topical anesthesia. Normative values have been published for an expanding cohort of species (see Chapter 10, Part 1). Even though they may not be well documented in many species of interest, measurements from normal fellow eyes and eyes of other normal individuals of the same species provide good reference values. Similarly, normative values for Schirmer tear tests (STTs) and phenol red thread tests have been reported for many species and like tonometry values can be extrapolated for species for which they are not published. Fluorescein dye examinations of cornea and nasolacrimal systems, conjunctival culture collection, and exfoliative cytology may be performed in most species, modified as dictated by eye size and external anatomical features. Of late the literature contains detailed anatomical and physiological data and descriptions for many more species than it did a decade ago.

Among exotic species, broad variations exist in all parameters of vision: color perception, ultraviolet (UV) wavelength detection, acuity, accommodative ability, motion detection, and stereopsis. Assessment of vision-directed behavior in exotic species presents several challenges. Often, animals are examined outside of their familiar habitats under stressful restraint, precluding observation of the animal's visual

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orientation to its environment. Owners and even experienced animal owners, handlers, curators, and keepers may be unaware of the normal visual ecology of their charges and thus may not provide dependable observations of behavioral changes. Conversely, their observations and insight may prove more accurate than those of the attending clinicians. The most accurate and reliable assessment of vision-directed behavior in many species is made by observation of them unstressed in familiar and appropriate habitats. Inappropriate husbandry practices may be the ultimate source of ocular complaints.

The important categories of ocular disorders of nondomestic species resemble those of domestic species: congenital anomalies, infections, inflammations, degenerations, neoplasia, and traumatic injuries. The relative importance of each category varies with animal class and species. In some classes of animals (e.g., reptiles and amphibians), infectious causes of ocular disorders predominate. In others (e.g., some endangered mammal species in captive breeding programs), genetic congenital and developmental disorders are frequent. However, responsible clinicians should assess ocular complaints in exotic species comprehensively without bias, considering all categories. Remember: you may be examining the index case of a previously unknown ophthalmic disease in a novel species!

Fish

Ophthalmic Anatomy

Most modern fish belong to the class of teleosts (bony fishes); the others are elasmobranchs (cartilaginous fishes). Most fish lack eyelids (except elasmobranchs). The presence of a membrane covering the cornea or folds of tissue around the eyes is common. In teleosts, the orbit is bony and enclosed; some species have a tenacular ligament that anchors the globe to the orbit. Elasmobranchs possess an optic pedicle, a cartilaginous process connecting the cranium to the posterior pole of the globe. Extraocular muscles are present and variably developed, allowing independent ocular movement, although targeting is usually effected by positioning of the body. A binocular field of vision exists for many species. The typical globe shape is a flattened ellipse with a short anteroposterior axis because of corneal flattening, but some deep-sea-dwelling teleosts have tubular-shaped globes and a few cave-dwelling or bottom-dwelling species have vestigial blind eyes. Extraocular muscles are variable in number and development and ocular motility is present but variable among species. Having the same refractive index as water, the cornea serves no refractive function in water. Corneal anatomy in most fish follows the mammalian pattern, except that it is relatively thicker and the epithelium is the layer primarily responsible for maintaining corneal hydration (Fig. 35.1). Some fish have a double-layered cornea (a primary cornea and secondary spectacle) with a potential space in between, where pigment granules responsible for corneal iridescence lie. In some species these granules are migratory within small channels as light conditions vary (Schwab, 2012). Corneal thickness is generally greater in freshwater than in marine fish. Central corneal thickness of Koi increases with increasing age, body length, and corneal diameter; mean intraocular pressure (IOP) by rebound tonometry was 4.9 mmHg (Lynch et al., 2007). Corneal iridescence and pigmentation in some species appear to function to shade the globe and reduce glare. At its periphery, the corneal endothelium thickens to form the annular ligament, which fills the iridocorneal angle as it reflects onto the anterior peripheral iris. Anteriorly, the sclera contains a circumferential ring of cartilage, variably supplemented by scleral ossicles. Many teleosts have a lipid or guanine tapetum lucidum in the retinal pigment epithelium and many larval forms (but fewer adult fish) possess an outer choroidal argentea consisting of guanine-containing cells in the choroid that continues over the anterior iris, contributing with the iris pigments to the color and iridescence of the iris. Most teleosts have an occlusible tapetum. Occlusion occurs most commonly by light-induced vitread migration of melanin within the retinal pigment epithelium. Less commonly, retinomotor movement effects occlusion. Elasmobranchs have one or more layers of guanine crystals in the choroid; this tapetum may be occlusible by movement of the pigment epithelial processes themselves over the photoreceptors (Ollivier et al., 2004). The choroidal gland is a well-developed vascular plexus present within the choroid of many species at the posterior pole, where it wraps around the optic nerve and communicates with an accessory gill (pseudobranch). Its functions presumably include nutrition and local temperature regulation. Indirect ophthalmoscopy has been used to document the fundus morphology of several fish species (Grover & Zigman, 1984; McLaughlin et al., 1996). Adult elasmobranchs possess an entirely avascular retina; it depends completely on the choriocapillaris for its nutrition and there is no accessory vascular organ (choroid gland). The choriocapillaris is supplied by one major artery and is drained by a dorsal and ventral vein (Bellhorn, 1997). Teleosts possess either a falciform process or a membrane, the tunica vasculosa retinae. The falciform process is an infolding of choroid through the fetal fissure into the vitreous (Fig. 35.2). The tunica vasculosa retinae is derived from a branch of the internal ophthalmic artery that enters the eye near the optic disc; it lies in the vitreous in front of the retina (Bellhorn, 1997).

The ciliary body is rudimentary, when present. Ciliary processes are absent. Complete separation of aqueous and vitreous is not present and the mechanisms of aqueous production and loss are poorly understood. The pupil is generally round or pear shaped; the iris is thin and, with few exceptions, immobile. The sphincter and dilator muscles are rudimentary or absent except in elasmobranchs. The very large spherical lens supported by the zonule and a dorsal suspensory ligament is the important refractive structure in the eye.

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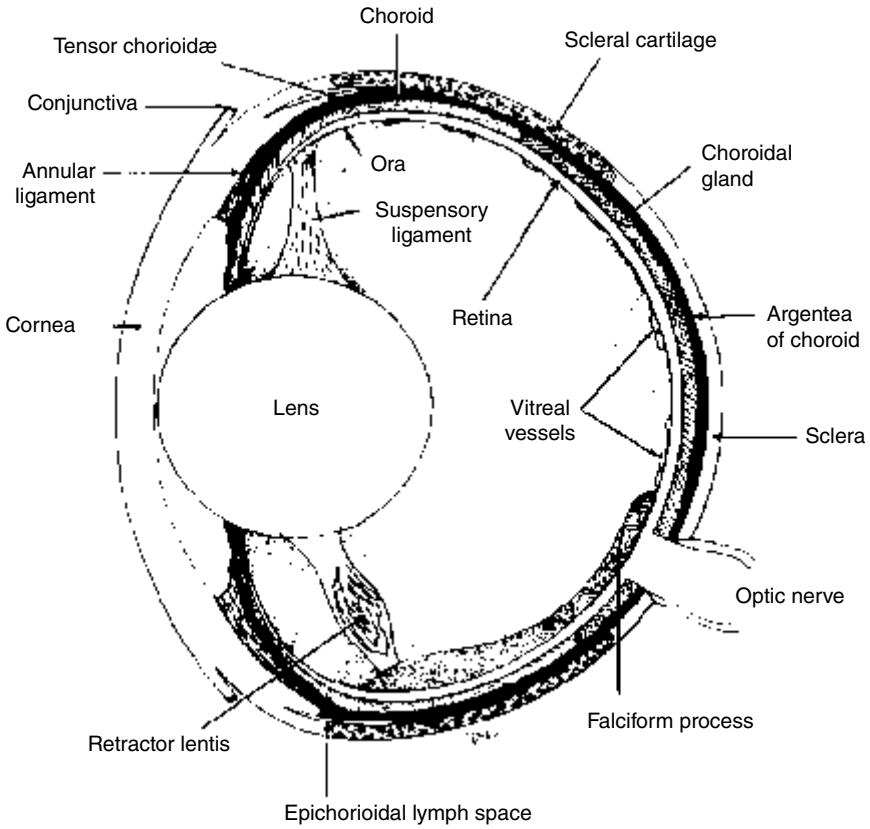


Figure 35.1 The teleost eye. (*Source*: Adapted from Duke-Elder, S. (1958) *System of Ophthalmology*, Vol 1, *The Eye in Evolution*. London: Kimpton.)

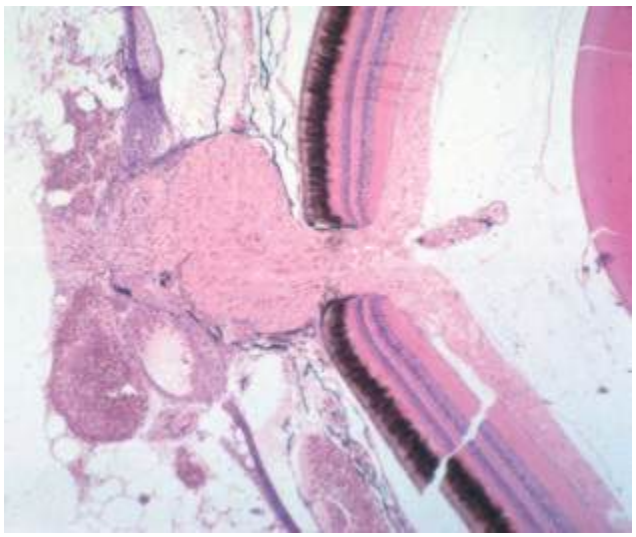


Figure 35.2 Rainbow trout. Falciform process overlying the optic nerve. (Hematoxylin & eosin. Original magnification. ×40.)

It consists of a hyaline lens capsule surrounding the lens epithelium, cortex, and nucleus. The anterior surface nearly touches the corneal endothelium, forming a very narrow anterior chamber. The fish lens has the highest refractive index of all vertebrates (~1.69), and the refractive index gradients within it essentially eliminate chromatic and spherical aberration in the image presented to the retina. A posterior muscle, the retractor lentis, is present in teleosts; it arises ventrally from the falciform process of the retina and inserts anterior to the lens equator on the ventral lens capsule. The suspensory ligament/retractor mechanism allows changing the lens position within the pupil as well as alteration of the lens–retina distance. There is a medial aphakic crescent in the pupil, which aligns with a far temporal fovea; this facilitates binocular vision when the fish targets objects in front of it by tilting the eyes forward, allowing light to obliquely pass through the lens and stimulate the fovea (Schwab, 2012). Predatory fish in general have well-developed accommodation, whereas bottom feeders have little or no accommodative range. An anterior muscle, the protractor lentis, is present in some elasmobranchs.

The ocular anatomy of the black pacu (*Colossoma macropomum*) has been recently investigated and described in detail (Gustavsen et al., 2018). Utilizing gross and histologic examinations complemented by CT and MRI the authors confirmed that the pacu's ocular anatomy is typical of teleost eye with an additional variation that is very uncommon in fish. The choroid occupied one-third of the

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anteroposterior length of the globe, its bulk composed of adipose tissue. The choroidal rete (incorrectly labeled the choroidal gland) was imbedded within the adipose tissue. The presence of a retinal pigment epithelial tapetum was suggested by the presence of a golden fundus reflection but was not substantiated histologically (Gustavsen et al., 2018).

Anatomic variation in retinal structure and photoreceptor type and morphology exists (Ali, 1976; Nicol, 1989; Schwab, 2012). Both rods and cones are typically present: diurnal species have cone-dominated retinas, deep-sea and nocturnal species have rod-dominated retinas, with gradations dictated by species' visual ecology. Twin and double cones and oil droplets may be present. A fovea is present. The optic nerve enters the eye via one or more optic discs near the posterior border of the falciform process, where present. Described above, two protective mechanisms have evolved to shield photoreceptors from excessive light promoted by the immobile pupil and lack of eyelids (retinomotor responses). Photoreceptors may contract or elongate between pigmented processes of pigment epithelial cells or alternatively pigment may migrate along the apical processes of pigment epithelium.

Schwab has exhaustively summarized and illustrated the evolutionary path of the piscine eye and described many of the unusual anatomical and physiological adaptations of modern-day fish (Schwab, 2012).

Ophthalmic Examination

Ocular examination of fish in water is of necessity limited to gross observation. Close examination is facilitated by aerial examination, often under anesthesia. Buffered tricaine methane sulfonate (Tricaine-S-SMS-222, Syndel USA, Ferndale, WA, USA) delivered at 50–200 mg/L depending on species in tank water is usually satisfactory (McLaughlin et al., 1996; Williams & Whitaker, 1997). Gross examination of the external eye and anterior segment may be performed with a focal light source and magnification or by slit-lamp biomicroscopy. Sample collection for culture and cytology of the cornea and lid folds may be done as for other vertebrates, as can fluorescein staining to show corneal ulceration. Applanation tonometry may be performed only in species with large eyes (TonoPen). Mean IOP by rebound tonometry in growing Koi was 4.9 mmHg (TonoVet) (Lynch et al., 2007). Fundus examination may be possible by aerial examination using indirect ophthalmoscopy and a 60 D condensing lens. Central corneal thickness was 0.202 mm in channel catfish in which IOPs were not recordable with a TonoPen; fundus evaluation was performed by indirect ophthalmoscopy (McLaughlin et al., 1996).

Ophthalmic Diseases

The ocular disorders of fish result from infectious diseases, nutritional deficiencies, trauma, metabolic disorders, degenerations, neoplasia, and teratogenic and spontaneous malformations (Dukes, 1975; Stoskopf et al., 1985; Van Duijn, 1973; Wilcock & Dukes, 1989; Williams & Whitaker, 1997).

Infectious agents include parasites, bacteria, fungi, and viruses. Parasites include: ciliated protozoans (*Ichthyophthirius*, *Cryptocaryon*, *Tetrahymena*); myxosporidians (the proliferative kidney disease agent (*Tetracapsuloides bryosalmone*); *Myxosoma heterospora*; *Henneguya*; *Myxobilatus*; *Sphaerospora*; *Myxobilus*); trematodes (*Diplostomum* spp. and related genera); crustaceans (copepods, *Lernaea* spp., *Argulus* spp.); cestodes (*Gilquinia squali*), and microsporidia (*Glugea*). *Ichthyophthirius multifilis*, a highly pathogenic ciliated protozoan, afflicts farm-raised food and ornamental fish and infects the skin and gill epithelium as an immature theront, where it matures into a trophozoite, which detaches. Death results from respiratory and excretory exchange problems (Klesius & Rogers, 1995; Pesut & Goldschmidt, 1983). The corneal epithelium or stroma are commonly involved; however, relatively little corneal edema and fibroplasia develop (Dukes & Lawler, 1975; Wilcock & Dukes, 1989). Exophthalmos is a feature of proliferative kidney disease of salmonids (Klesius & Rogers, 1995). *Henneguya lagodon* was identified as the cause of periocular cutaneous cysts in pinfish, *Lagodon rhomboids* (Hall & Iversen, 1967). *Dermocystidium gasterostei* was identified in the cornea and skin of sticklebacks (Elkan, 1962). *Myxobilatus* and *Sphaerophora* have been identified in the choroidal rete of fish with exophthalmos and hyphema (Williams & Whitaker, 1997). *Myxobolus couseii* was associated with iris cyst formations. Metacercariae of *Diplostomum* spp., a digenetic trematode whose definitive hosts are aquatic birds, infect the eyes of a wide variety of fish, with specific predilection to infect the lens, causing cataract. Several species, at least, of *Diplostomum* and related genera have been identified in different fish species: *Diplostomum scheuringi* (brown trout, yellow perch), *Ornithodiplostomum ptychocheilus* (brassy minnow, creek chub), *Neascus* spp. (creek chub, brassy and fathead minnows) (Hendrickson, 1978), *D. gasterostei* (sticklebacks) (Williams, 1956), and *Diplostomum spathaceum*, from which the classic lenticular lesions were originally described (Ashton et al., 1969; Bylund & Sumari, 1981; Dwyer & Smith, 1989; Karvonen et al., 2004; Palmieri et al., 1976; Shariff et al., 1980; Sweeting, 1974). Successful removal of cataracts caused by a *Diplostomum* species by phacoemulsification and aspiration from 20 Gulf sturgeons (*Acipenser oxyrinchus*) has been reported (Bakal et al., 2005). Digenean metacercariae of an unidentified species were found in the corneas and iridocorneal angles of oyster toadfish (*Opsanus tau*), in which corneal edema and vascularization were prominent features of encystations (Riis et al., 1981). A broad range of ocular lesions may develop in marine and freshwater fish associated with copepod infestation. Some are relatively harmless surface inhabitants of the corneoscleral recess (Wilcock & Dukes, 1989). Some species

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penetrate only the corneal epithelium, causing only local epithelial and fibrous tissue hyperplasia. A few perforate the eye and embed their mouthparts into the choroid; the Pacific arrowtooth flounder is infected by *Phrixocephalus cincinnatus* in this manner, causing extensive intraocular damage (Wilcock & Dukes, 1989). Attachment and perforation of the eye with subsequent keratitis, lens rupture, and endophthalmitis were observed associated with attachment of adult anchorworms (*Lernaea piscinae*) in farm-raised bighead carp (*Aristichthys nobilis*) in Malaysia (Shariff, 1981). *Gilquina squali* has been associated with hemorrhagic uveitis, cataract, lens rupture, retinal detachment, and globe rupture (Williams & Whitaker, 1997). *Glugea* may infect the cornea.

A broad spectrum of pathogenic bacteria infects both marine and freshwater fish. Bacterial septicemia commonly results in intraocular involvement. Infections with *Staphylococcus aureus* (Shah & Tyagi, 1986), group B streptococci (Rasheed et al., 1985), *Aeromonas*, *Pseudomonas*, and *Vibrio* (Dukes, 1975; Wilcock & Dukes, 1989) have been documented. Granulomatous uveitis in Atlantic salmon has been reported after intraperitoneal vaccination with a commercial product containing mineral oil adjuvant and antigens of *Aeromonas*, *Moritella*, *Vibrio*, and infectious pancreatic necrosis virus (Koppang et al., 2004). Mycobacterial infections and infection with *Nocardia* and *Flavobacterium* cause granulomatous endophthalmitis (Backman et al., 1990; Pesut & Goldschmidt, 1983; Wilcock & Dukes, 1989). Ocular mycobacteriosis was caused by *M. chelonae* in a piranha (Evely et al., 2011). *Pseudomonas koreensis* caused epidemic panophthalmitis in farmed Indian golden mahseer (Shahi & Mallik, 2014).

Viral infections with endothelial tropism (e.g., rhabdoviruses) may cause uveitis (Wilcock & Dukes, 1989). At least three epizootic salmonid virus diseases (infectious pancreatic necrosis, infectious hematopoietic necrosis, and viral hemorrhagic septicemia) have exophthalmos as a characteristic sign (Yasutake, 1970). Lymphocystis, caused by a DNA virus, causes primarily verrucose skin lesions of marine and freshwater fish associated with marked hypertrophy of connective tissue cells (Roberts, 1989; Russell, 1974). Ocular lesions have been reported, including orbital involvement causing exophthalmos, uveal, and corneal invasion (Dukes & Lawler, 1975). Other viruses with reported ocular involvement include a salmonid retrovirus, a salmonid hepatic herpesvirus, a nodavirus, and a picornavirus (Williams & Whitaker, 1997).

Mycotic ocular disorders of fish include corneal infections, orbital cellulitis, and endophthalmitis. Corneal infection with *Saprolegnia* usually accompanies multifocal integumentary mycosis of marine and freshwater fish (Pesut & Goldschmidt, 1983). Experimental infection of tilapia by feeding *Aspergillus flavus*-contaminated food caused periocular, orbital, and intraocular infection associated with generalized infection (Olufemi & Roberts, 1986). *Sarcinomyces crustaceus* caused unilateral exophthalmos, gas accumulation, and corneal and lens opacification in black seabream (*Spondyliosoma cantharus*) (Williams & Whitaker, 1997).

Nutritional ocular disorders have been extensively described in salmonids and recently in red drum and channel catfish. Deficiencies of riboflavin (Hughes, 1985; Hughes et al., 1981; Poston et al., 1977), thiamine (Hughes, 1985), vitamin A (Hughes, 1985), methionine and cystine (Poston et al., 1977), tryptophan (Poston & Rumsey, 1983), and zinc (Ketola, 1978) produce cataract (Fig. 35.3). In riboflavin-deficient fish, corneal thickening with edema was noted (Hughes et al., 1981). Excess calcium and phosphorus fed to juvenile Chinook salmon produced cataract (Richardson et al., 1986). Thioacetamide fed to rainbow trout produced blinding cataract characterized by massive proliferation of lens epithelium (Von Sallman et al., 1966). Multiple ocular lesions were induced by ascorbic acid deficiency in juvenile red drum (*Sciaenops ocellatus*), including reduced globe size, lack of globe rigidity, vascular congestion, intraocular hemorrhage, lenticular lesions (posterior cortex disorganization and vacuolation, posterior migration of lens epithelium), and severe central retinal degeneration. The retinopathy was suspected to be phototoxic injury enhanced by the deficiency. The causes of the cataract were unclear but were ascribed potentially to direct nutritional effect or indirect result of retinal degeneration (Collins et al., 1993). Niacin-deficient channel catfish developed exophthalmos (Andrews & Murai, 1978). Corneal edema, cataract, ocular perforation, and phthisis were suspected to be of unspecified nutritional

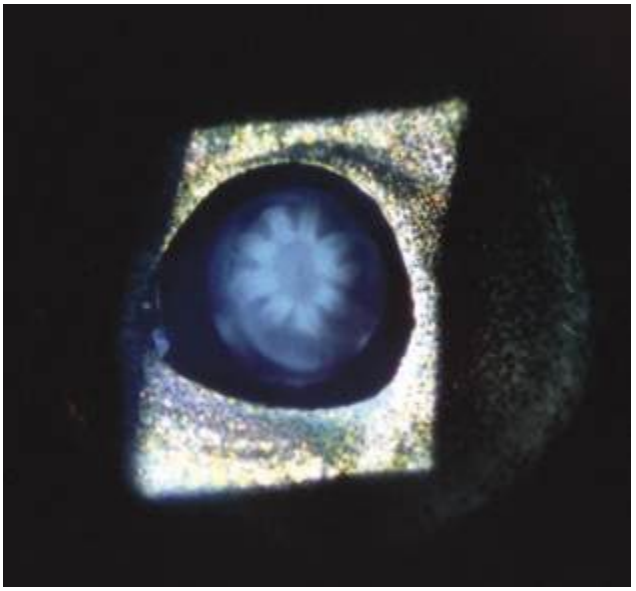


Figure 35.3 Rainbow trout. Nutritional deficiency cataract involving nucleus and perinuclear and anterior subcapsular cortex.

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origin in farmed rainbow trout in Malawi (Lee et al., 1976). In farmed Atlantic salmon, high dietary levels of vitamin C and astaxanthin reduced the frequency of spontaneous cataract, whereas high dietary lipid level, iron, and manganese were associated with increased cataract frequency (Waagbo et al., 2003).

Traumatic injury was postulated to occur in Atlantic stingrays (*Dasyatis sabina*) associated with the turbidity from heavy silting of inshore waters (Nicol, 1981). Corneal ulceration, remodeling, and scarring were noted in histologic specimens. Corneal epithelial erosion was associated with overcrowding during transport in largemouth bass (Brandt & Jones, 1986; Ubels & Edelhauser, 1987). Experimental removal of corneal epithelium from rainbow trout, alewife, and sculpin resulted in transient corneal edema and cataract (Ubels & Edelhauser, 1987). Corneal ulceration caused by transport, aggression, and handling is common (Williams & Whitaker, 1997). Corneal infection by the parasitic copepod *Ommotokoita elongata* in Greenland sharks (*Somniosus microcephalus)* has been recorded (Borucinska et al., 1998). Corneal lipid deposition was described in individual captive moray eels of three species associated with hyperlipidemia (Clode et al., 2012).

Metabolic disturbances in fish may cause exophthalmos, a common sign in certain infections as well. Gas bubble disease of marine and freshwater fish is a noninfectious, physically induced process caused by uncompensated hyperbaric pressure of total dissolved gases (Bouck, 1980; Dehadrai, 1966; Speare, 1990; Humborstad et al., 2017). When pressure compensation is inadequate, the dissolved gases may form emboli and tissue emphysema. When gas bubbles develop behind the globe, exophthalmos – frequently dramatic and occasionally resulting in total proptosis with loss of the eye – results. Intraocular gas bubble accumulation causes a variety of pathologic changes, including panophthalmitis, synechia formation, and cataract (Speare, 1990). Experimental administration of androgens produced exophthalmos in young fish of two species of teleosts; the cause of the exophthalmos was not determined (Matty et al., 1958).

Ocular neoplasia has been rarely reported in fish. Retinoblastoma was described in a spring cave fish (*Chologaster agassizi*) (Fournie & Overstreet, 1985), a porkfish (*Anisotremus virginicus*) (Reimschuessel et al., 1989), and a brown bullhead (*Ictalurus nebulosus*) (Reimschuessel et al., 1989). Of 11 neuronal embryonal tumors of captive marine and freshwater teleost fish reported in one series, eight were ocular; of those, seven were retinoblastoma and one was a teratoid medulloepithelioma (Kagan et al., 2010). Intraocular lymphosarcoma was reported in an Atlantic cod (*Gad morhua*); a complete necropsy was not performed (Wolke & Wyand, 1969). A medulloepithelioma of the ciliary body was identified in a goldfish (*Carassius auratus*) (Lahav & Albert, 1978). Bilateral ocular neuroectodermal tumors with central nervous system invasion were diagnosed in a telescope goldfish (Bartlett et al., 2010). Adenocarcinoma of the retinal pigment epithelium was reported in a guppy (Fournie et al., 1992). An iridociliary melanoma causing lens luxation was reported in a long-horned cowfish (*Lactoria cornuta*) (da Silva et al., 2010). Unilateral acquired ventral strabismus was reported in an adult aquarium-raised silver arowana (*Osteoglossum bicirrhosum*) associated with development of a non-neoplastic dorsal subconjunctival cyst (Chow et al., 2016).

Degenerations of the lens and retina in fish occur for some of the same reasons as in mammals and are associated with a few unusual circumstances. Possibly inherited cataract was reported in aquarium-raised tilapia (Noga et al., 1981). Partially reversible cold cataract has been described *in vitro* in fish; its relationship to spontaneous cataract development *in vivo* has not been clearly shown (Loewenstein & Bettelheim, 1979). Excessive exposure to sunlight was postulated to cause cataract in hatchery-reared lake trout (Steucke et al., 1968). Retinal degeneration suspected to be phototoxic in origin was reported in wild-caught Atlantic menhaden (*Brevoortia tyrannus*) after 4 weeks of captivity in an indoor open culture system (Nasisse et al., 1989). Hyphema, iris hemorrhage, and incipient cataract were variably present. Electroretinograms were totally extinguished in all affected fish. Histologically, the most extensive retinal lesions occurred in the central retina. Cataract with lens rupture was noted in wolffish (Bjerkas et al., 1998). Cataracts have been noted commonly in both wild and farmed Atlantic salmon (Bjerkas et al., 1996, 200l, 2003; Ersdal, 2001; Ferguson et al., 2004; Wall, 1998; Wall & Richards, 1992). Successful unilateral extracapsular cataract removal was performed on a dollar sunfish (*Lepomis marginatus*) (Adamovicz et al., 2015). Intraocular oxygen tensions were investigated in normal and diseased eyes of farmed halibut (Williams & Brancker, 2004; Williams et al., 1995). Experimental retinal phototoxicity has been documented in several fish species (Penn, 1985; Raymond et al., 1988). Hereditary retinal degeneration was reported in celestial goldfish, a breed with exophthalmos and abnormal globe position and in which the iris plane is horizontal (Matsumura et al., 1981). The retina develops fully and normally until 105 days posthatching, when the globes begin to protrude laterally (Sakaue et al., 1987, 1988). Idiopathic cystic degeneration of the choroid causing apparent exophthalmos was noted in five species of captive rockfish (*Sebastes* spp.) (Engelman et al., 1984). The cysts were filled with fluid, not gas, and associated with minimal inflammation and variable retinal degeneration. Corneal degeneration characterized by corneal thinning, ulceration, and variable rate of perforation were reported in aged captive lake trout (Hoffert & Fromm, 1965). Inherited retinal degeneration occurs in mutant zebrafish (*Danio rerio*) with cranial malformations, in which the retina begins to develop normally, then undergoes degeneration within 2 days of fertilization *in vivo* (Daly & Sandell, 2000).

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Teratogenic influences of pesticides, heavy metals, fungicides, and polychlorinated biphenyls on developing eyes of embryos of Atlantic silversides (*Menidia menidia*) have been reported (Hughes, 1985). Spontaneous tyrosinase positive oculocutaneous albinism has been studied in the goldfish (Abramowitz et al., 1977). Exophthalmos caused by thyroid tissue in the choroid was reported in a *Coris gaimard* (Schubert, 1969). Orbital exenteration with prosthesis placement has been performed in fish (Nadelstein et al., 1997).

Amphibians

Ophthalmic Anatomy

The anatomy of amphibian eyes varies with order (anuran vs. urodele) and stage of development (larval vs. adult). The eyes of larval amphibians resemble teleost fishes. Those of urodeles (tailed amphibians) are poorly developed compared with anurans. The eyes of larval anurans (frogs and toads) have poorly developed eyelids; in adults, the upper lid is immobile and, associated with the lower lid, a false nictitating membrane is formed by an elastic translucent fold of conjunctiva in the lower fornix. When the globe is retracted, it passively covers the eye; this retraction facilitates swallowing because the globe depresses the thin membrane separating the orbit and pharynx, forcing food down the throat. There is no orbital septum separating the two orbits. Eyelid glands are present in some salamanders and a harderian gland is present in most frogs. The puncta and nasolacrimal duct are present. The retractor bulbi is the most important extraocular muscle, which retracts the globe and aids in swallowing. The globe is spherical with hyaline cartilage in the inner sclera from the posterior pole as far as the equator (Fig. 35.4). Other anurans lack cartilage or have a ring of bones within the sclera. Urodeles lack scleral cartilage. The adult cornea has the mammalian pattern, but larval anurans have a duplex cornea with a dermal portion separated from the sclera. A triangular ciliary body is present with hypertrophied folds dorsally and ventrally that extend to the pupillary border to form pupillary nodules. Two protractor lentis muscles arise from the peripheral cornea to insert on the ciliary folds; contraction causes zonular tension, which moves the lens forward to effect accommodation. The lens in tadpoles is spherical and near the cornea; in adult frogs it is somewhat flattened and positioned more posteriorly, leaving a visible anterior chamber. The urodele lens is large and the anterior chamber is shallow. Urodeles lack ciliary folds and the dorsal protractor lentis muscle. The aqueous is drained through an iridocorneal angle into dorsal and ventral ciliary sinuses. The iris is thin and often highly colored by various stromal pigments; a metallic sheen is associated with the presence of guanine crystals (Fig. 35.5). Myoepithelial sphincter and dilator muscles are present. Iridal arteries have an irregular pattern and communicate with deeper veins. Pupillary excursions are present but limited. Resting pupil size and shape are

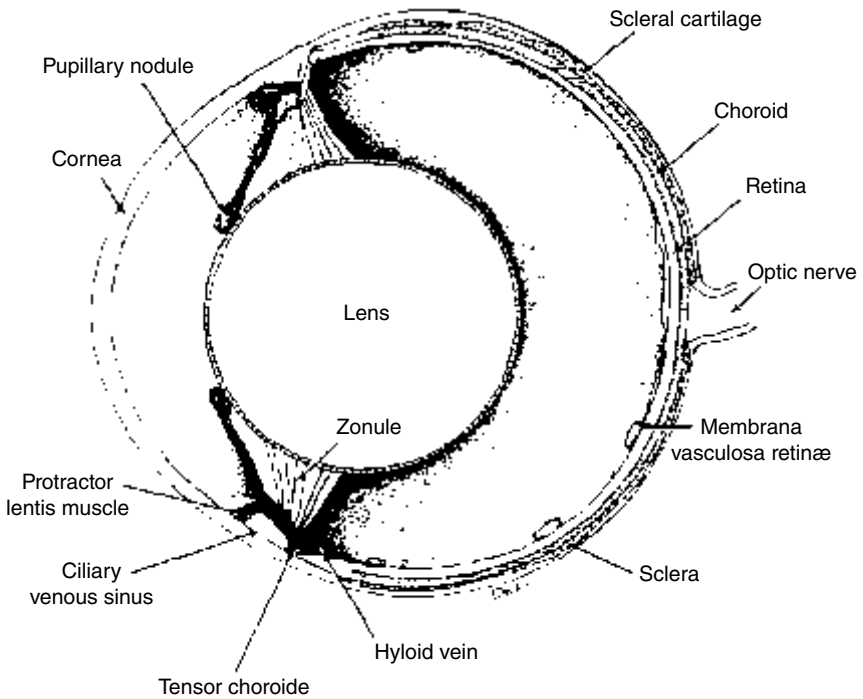


Figure 35.4 The amphibian eye. (*Source*: Adapted from Duke-Elder, S. (1958) *System of Ophthalmology*, Vol 1, *The Eye in Evolution*. London: Kimpton.)

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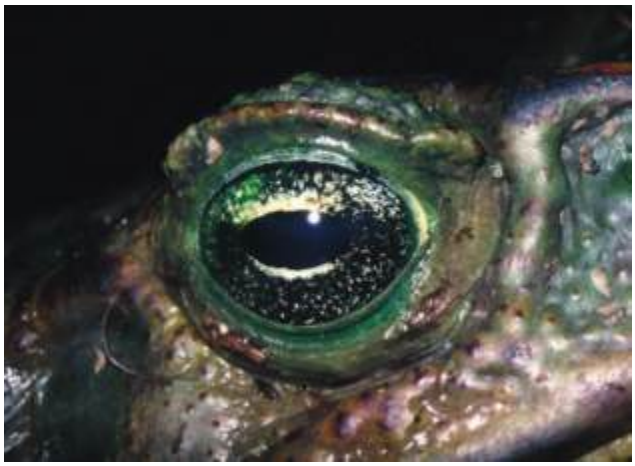


Figure 35.5 Normal American bullfrog eye.

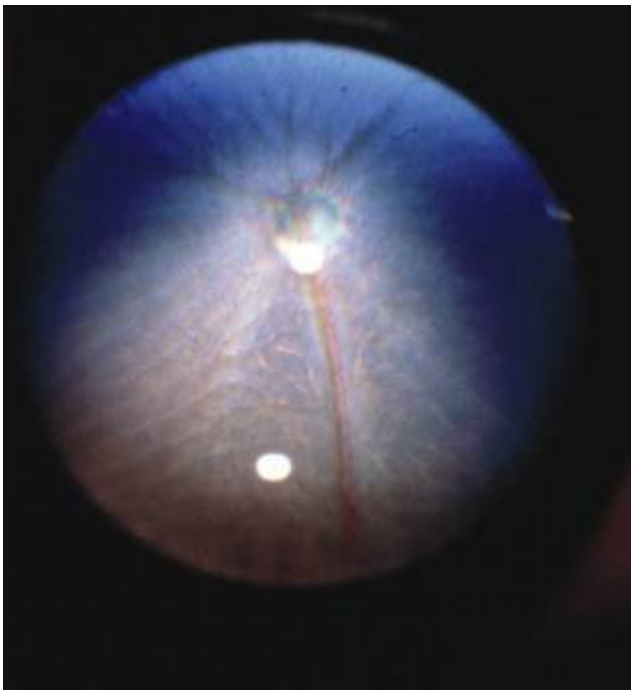


Figure 35.6 Membrana vasculosa retinae. American bullfrog.

remarkably variable, but it is spherical when dilated. The avascular retina derives its blood supply from the vascular choroid alone in urodeles and from both the choroid and a membrana vasculosa retinae in the vitreous on the retinal surface in anurans (Bellhorn, 1997) (Fig. 35.6). The choroid contains a choriocapillaris but no tapetum, but cells may contain guanine crystals or carotenoid pigments. The optic disc is circular or elongated. The retina contains at least four types of photoreceptors types based on visual pigments in the rods and cones. Oil droplets are present at the distal end of the ellipsoid of some cones. Anuran photoreceptors have been the subject of extensive research involving photochemistry, renewal, and electrophysiology.

Normative Values

Few normative values have been reported for amphibians. Median rebound tonometry values for American bullfrogs and six frog species in Oklahoma were 4 mmHg (Cannizzo et al., 2017) and 5.1 ± 1.4 mmHg (Hahn et al., 2014), respectively. Median applanation tonometer values in the same bullfrogs were 16 mm Hg. The authors preferred rebound tonometry for its ease of use and no need for topical anesthesia. IOPs were reported for three species of Central and South American tree frogs by applanation/rebound tonometry to be 9.1 ± 1.2 and 10.8 ± 1.4 mmHg; 14.8 ± 1.5 and 18.8 ± 3.1 mmHg; and 15.1 ± 2.5 and 15.6 ± 4.1 mmHg, respectively (Lewin et al., 2017).

Ophthalmic Diseases

Considerable research interest has been directed toward amphibian retinal and central visual pathway physiology (Kagan et al., 1973), retinal injury (Kagan et al., 1973; Lolley et al., 1977; Reyer, 1977), and lens injury and repair (Rafferty & Goossens, 1977; Worgul et al., 1982). However, reports of spontaneous ocular diseases of amphibians are scarce. The ophthalmic disorders of amphibians have been reviewed previously (Millichamp, 1991; Williams & Whitaker, 1994). Mycobacterial panophthalmitis was reported in a South American bullfrog (*Leptodactylus* spp.) (Rowlatt & Roe, 1966). Corneal edema and panophthalmitis have been noted in both natural and experimental infections of leopard frogs (*Rana pipiens*) with *Flavobacterium indologenes* (Olsen et al., 1992).

Severe panophthalmitis and otitis interna were reported in a large group of recently imported fire-bellied toads (*Bombina orientalis*) (Brooks et al., 1983). Corneal stromal infiltrates, scleritis, hyphema, hypopyon, iridocyclitis, cataract, and chorioretinitis were prominent. Opisthotonus, circling, head tilt, and loss of righting reflexes were associated with otitis interna. Several bacteria were cultured from affected eyes and normal viscera, including *Aeromonas hydrophila*, *Citrobacter freundii*, *Providencia alcalifaciens*, *Klebsiella oxytoca*, and an unidentified oxidase-positive, Gram-negative bacillus, resistant to tetracycline. Treatment of affected fire-bellied toads with oxytetracycline (26 mg/L of water) was not effective but may have prevented infection in normal toads (Fig. 35.7).

Periocular blood-filled blisters were reported in bullfrogs (*Rana catesbiana*) with classic red-leg septicemia caused by *A. hydrophila* and *C. freundii* (Glorioso et al., 1974). Conjunctivitis, dacryocystitis, and uveitis have been associated in individual frogs with unspecified systemic infections (Williams & Whitaker, 1994).

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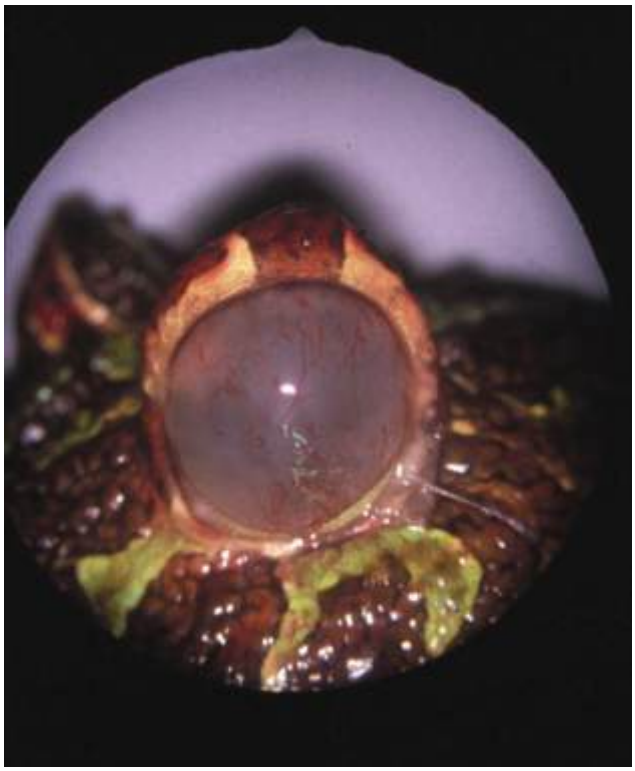


Figure 35.7 Panophthalmitis in an Argentine frog.

Topical treatment of presumptive or proven bacterial ocular infections in amphibians must be undertaken with recognition of the potential for systemic toxicity. Gentamicin diluted to 2 mg/mL has been recommended (Williams & Whitaker, 1994). Parenteral antibiotic or corticosteroid administration may be preferable because an exact dosage may be delivered.

With ulcerative keratitis, the false third eyelid may be sutured to the upper lid for protection (Williams & Whitaker, 1994). Butylcyanoacrylate tissue adhesive has been used to stabilize deep corneal ulcers (Williams & Whitaker, 1994).

Corneal opacities in amphibians have several potential causes. The most extensively reported and investigated disorder is lipid keratopathy (Fig. 35.8). Originally discovered in Cuban tree frogs (*Osteopilus septentrionalis*) (Carpenter et al., 1986; Russell et al., 1990), it has since been identified in species of captive hylid, leptodactylid, and ranid frogs either as a corneal and hepatic lesion or as part of a generalized xanthomatosis affecting brain, some viscera, peripheral nerves, periarticular soft tissues, and digital pads (Millichamp et al., 1990). Hypercholesterolemia has been noted in animals with disseminated xanthomatosis (Russell et al., 1990). Clinically, dense white stromal opacities are seen, often raised with corneal thickening and surface epithelial irregularity. Stromal neovascularization and superficial pigmentation may be present (Millichamp et al., 1990). In advanced cases, the densest opacities are in the central cornea.



Figure 35.8 Lipid keratopathy in a tree frog. (*Source*: Courtesy of Dr. Nicholas Millichamp.)

Histologically, empty cholesterol clefts within keratocytes and between corneal collagen lamellae are present with occasional foamy macrophages in the stroma and between epithelial cells. Corneal endothelium vacuolation was present in severely affected frogs. Biochemical analysis of affected corneas and livers showed elevated levels of cholesterol esters. Affected frogs have all been females, many with massive egg development, suggesting that excessive lipid mobilization associated with oogenesis may play a role. Dietary fat has been suggested as a factor, but affected animals have been fed several different diets. In an experimental study of Cuban tree frogs fed normal or high-cholesterol diets, corneal lipidosis was more prevalent in but not confined to frogs on the high-cholesterol diet; affected frogs of both sexes had elevated serum total cholesterol and low-density lipoproteins compared with unaffected frogs. Increased serum cholesterol was not associated with vitellogenesis in female frogs in this study (Shilton et al., 2001).

Buphthalmos with glaucoma was found in a captive toad (*Bufo bufo*) (Williams & Whitaker, 1994). Globe enlargement prevented complete globe retraction into the orbit, which interfered with swallowing. Because of concerns about swallowing difficulties after enucleation, globe protection was achieved alternatively by suturing the false nictitating membrane across the cornea.

Cataracts have been noted regularly by some observers (Williams & Whitaker, 1994), occurring both in conjunction with other ocular disorders of the anterior segment and alone. Phacoemulsification was successfully performed on a loggerhead sea turtle (*Caretta caretta*) (Kelly et al., 2005). Dendrobatid frogs receiving 5% dextrose supportive therapy rapidly developed reversible cataract (Williams & Whitaker, 1994).

Reports of neoplasia in amphibians are rare but include an ophthalmic adenocarcinoma in an African clawed frog

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(*Xenopus laevis*) (Williams & Whitaker, 1994) and a corneal and retrobulbar epithelioma in a grass frog (*Rana temporaria*) (Reichenbach-Klinke & Elkan, 1965).

Reptiles

Ophthalmic Anatomy

Four of the five orders within the class Reptilia have anatomically similar eyes: lizards, chelonians, crocodilians, and the tuatara. The fifth order, snakes, lost the prototype reptilian anatomical pattern during a fossorial period in their evolution, only to re-evolve eyes with certain differences from other reptiles. Features of the external eye and adnexa have great clinical significance. In most reptiles, except snakes and certain ablepharine skinks and geckoes, the upper and lower eyelids are well developed, the lower being the more mobile, and a nictitans is present (not in chameleons). Crocodilians possess a bony tarsus in the upper lid and lizards with mobile eyelids have a cartilaginous tarsus in the lower eyelids. The eyelids of chameleons are constricted around the cornea and move with the very mobile globe. In some lizards of the families Lacertidae, Scincidae, and Teidae, the lower lid is variably transparent, allowing useful vision in harsh environments when the eyelids remain closed. Snakes and ablepharine geckoes and skinks possess a spectacle covering the cornea, developed from fused eyelids and separated from the cornea by an epithelial-lined subspectacular space. This tertiary spectacle contains an extensive vascular network, optically transparent but demonstrable by microsilicone injection (Mead, 1976) and fluorescein angiography (Bellhorn et al., 2018). The anterior layers of the spectacle are shed during normal ecdysis with the rest of the skin (Maderson, 1965). Prior to ecdysis, the spectacle becomes cloudy and thicker caused by separation of the superficial cuticular layer from the stromal layer. Spectacular ecdysis has been investigated in the royal python (*Python regius*) by spectral domain optical coherence tomography (SD-OCT) (Tusler et al., 2015) in the corn snake (*Pantherophis guttatus*), in the California king snake (*Lampropeltis getulus*) by SD-OCT and scanning laser ophthalmoscopy (Cazalot et al., 2015**)**, in the ball (royal) python by OCT, scanning laser ophthalmoscopy, light (LM) and transmission electron microscopy (TEM) (Da Silva et al., 2014; Da Silva et al., 2015a), and in 14 species (boids, colubrids, and pythons) by LM and TEM (Da Silva et al., 2016). The spectacle is transparent immediately before its surface is shed. During the period the spectacle is cloudy, the animal is blind; many species become more irritable and aggressive during this period. The spectacle is impervious to topically applied medications; thus, topical ocular therapy is ineffective. The biometry of the eyes and spectacles of four species of snakes has been described using high frequency ultrasound imaging (Hollingsworth et al., 2007) and in three python and two boid species (Lauridsen et al., 2014). The ocular surface in reptiles is bathed by fluids secreted by lacrimal (except snakes) and harderian glands. Harderian glands usually are present in the ventral or ventromedial orbit and the lacrimal glands lie in the superior orbit. Harderian glands are large in chelonians, especially in marine species; the lacrimal gland functions as an extrarenal site of salt excretion (Dunson, 1976). The nasolacrimal duct, absent in chelonians, drains from the medial canthus to the roof of the mouth to emerge at the base of or behind the vomeronasal organ. The detailed anatomy of the head of boa constrictors has been described using conventional radiography, computed tomography, and dissection (Banzato et al., 2011). The gross, histologic and microcomputed tomographic anatomy of the lacrimal system of 10 snake species have been reported (Souza et al., 2015). After fluorescein, barium, and latex injections into the subspectacular spaces the variable courses of the tortuous nasolacrimal ducts were followed to their openings near the vomeronasal organ in the oral cavity. A single large retrobulbar gland was noted as well as a single punctum in the ventronasal subspectacular space. The ocular morphology of the leatherback sea turtle (Brudenall et al., 2008) and Kemp's Ridley sea turtle (Rival et al. 2015; Gornik et al., 2016), and various lizards, snakes, and chelonians have been profiled by SD-OCT.

Anatomic features of the globe that distinguish reptiles include poorly developed rectus muscles (except in lizards), well-developed retractor bulbi muscle (except in snakes), and limited rotational movements (except in chameleons) (Fig. 35.9). Hyaline cartilage is present in the sclera of lizards and chelonians from the equator to the posterior pole, with scleral ossicles extending to the limbus anteriorly from the equator. These form a sclerocorneal sulcus, giving shape to the anterior segment and apposing the ciliary body to the lens equator, which provides leverage for action of the ciliary muscle. Snakes lack both scleral ossicles and cartilage and crocodilians lack scleral ossicles. Morphometric analysis of the corneal endothelium of caiman (*Caiman yacare*) using scanning electron microscopy showed primarily hexagonal cells, with a cell density similar to crocodiles but higher than that of one gecko species (Pigatto et al., 2004). The soft pliable lens of crocodilians and lizards has an equatorial pad which is absent in snakes and poorly developed in chelonians. Accommodation in most reptiles (except snakes) occurs by pressure exerted by the ciliary body, mediated by the ciliary muscle, against the lens equator to increase anteroposterior diameter of the lens. Ciliary processes are fused to the lens equator. The lenses of chameleons (*Chamaeleo dilepis*) have a negative refractive power, unlike other vertebrate eyes, and are capable of very rapid accommodation (up to 60 D per second) and very broad accommodative range (up to 45 D) (Ott & Schaeffel, 1995). Accommodation in snakes appears to occur by forward movement of the lens accomplished

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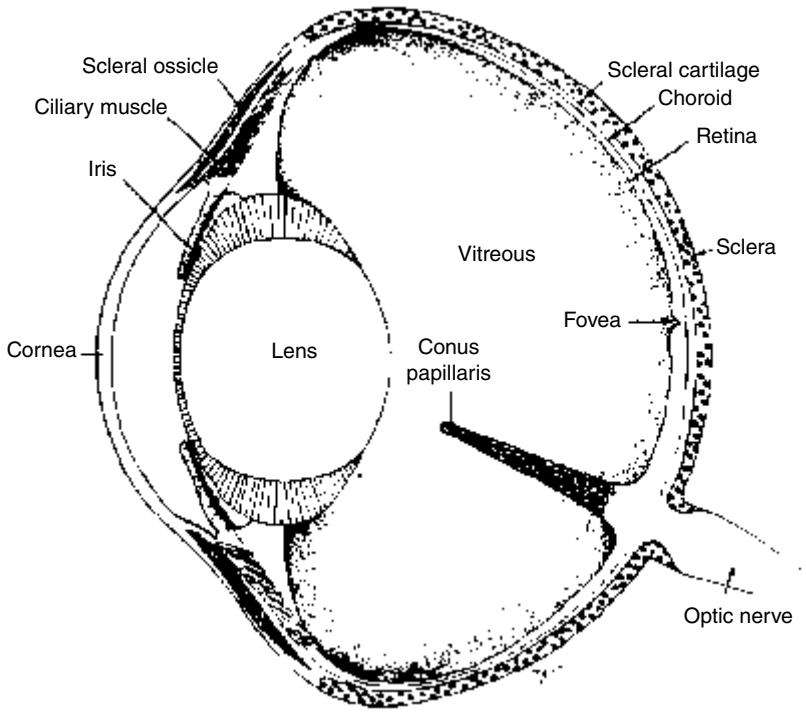


Figure 35.9 The lacertilian eye. (*Source*: Adapted from Duke-Elder, S. (1958) *System of Ophthalmology*, Vol 1, *The Eye in Evolution*. London: Kimpton.)

indirectly by increased pressure on the vitreous which suggests that they focus images well in air but are severely defocused underwater, where other sensory systems must be operative for prey location (Fleischman et al., 1988) (Fig. 35.10).

The iridocorneal angle resembles the mammalian pattern but is not as well developed. In young growing American alligators (*Alligator mississippiensis*), mean IOP measured by applanation tonometry (TonoPen II, Oculab, Glendale, CA, USA) was approximately 16 mmHg (range 5–35 mmHg) and was inversely correlated to body length and presumably age. Gender differences were not identified (Whittaker et al., 1995). In juvenile Yacare caiman, IOP by applanation was 10 ± 3 mmHg (Ruiz et al., 2015). Normal IOP values have been reported for: yellow-footed tortoises (*Geochelone denticulata*), approximately 14 mmHg (Selmi et al., 2003); red-footed tortoises (*Geochelone carbonaria*), values similar to yellow-footed tortoises (Selmi et al., 2002); juvenile loggerhead turtles (*Caretta caretta*), values 4–23 mmHg, varying with head position (Chittick & Harms, 2001); juvenile Kemp's Ridley sea turtles (*Lepidochelys kempii*), 4–7 mmHg by rebound tonometry (Gornik et al., 2016); and European pond turtles (*Ems orbicularis*), 3–9 mmHg, mean 5, by rebound tonometry (Rajaei et al., 2015). In inland bearded dragons (*Pogona vitticeps*) IOP was 6 mmHg by rebound tonomentry (Schuster et al., 2015). Normative values for IOP and some other ophthalmic tests have been reported for red-eared slider turtles (*Trachemys scripta elegans*) (Somma et al., 2015), captive red-footed tortoises (*Chelonoidis carbonaria*) (Oriá et al., 2015c), North American box turtles (Gomes et al., 2016), and broad-snouted caiman (*Caiman larirostris*) (Oriá et al., 2015b).

Iris color, pupil shape, and uveal vascular pattern in reptiles are variable. In general, diurnal lizards have round pupils and nocturnal lizards and crocodiles have vertically elliptical pupils. Ciliary processes are present in all reptiles except lizards. The general pattern of iris vascularity is two arteries entering the iris stroma temporally and inferiorly, running circumferentially, then forming a capillary plexus around the iris sphincter. A radial plexus of superficial iris veins is visible. Both ciliary and iris sphincter muscles are striated; thus, mydriasis is not achieved by parasympatholytic drugs. Mydriasis can be achieved by general anesthesia or by intracameral injection of curariform drugs. In red-eared slider turtles (*Trachemys scripta elegans*), topical application of 0.4% vecuronium bromide four times at 15-minute intervals increased pupil size by 28%, whereas atropine had no effect (Dearworth et al., 2007). A parallel trial in the same species documented that topical 2.5% phenylephrine administered every 15 minutes for four doses dilated the turtles' pupils and that a combination of 2.5% phenylephrine with 0.4% vecuronium bromide dilated pupils more rapidly but to the same degree as phenylephrine alone. These findings suggest the potential presence of a smooth dilator pupillae muscle in turtles that has not been confirmed anatomically (Dearworth & Cooper, 2008).

The avascular retina is supplied by the choroid in all reptiles. All have a choriocapillaris and, during ocular

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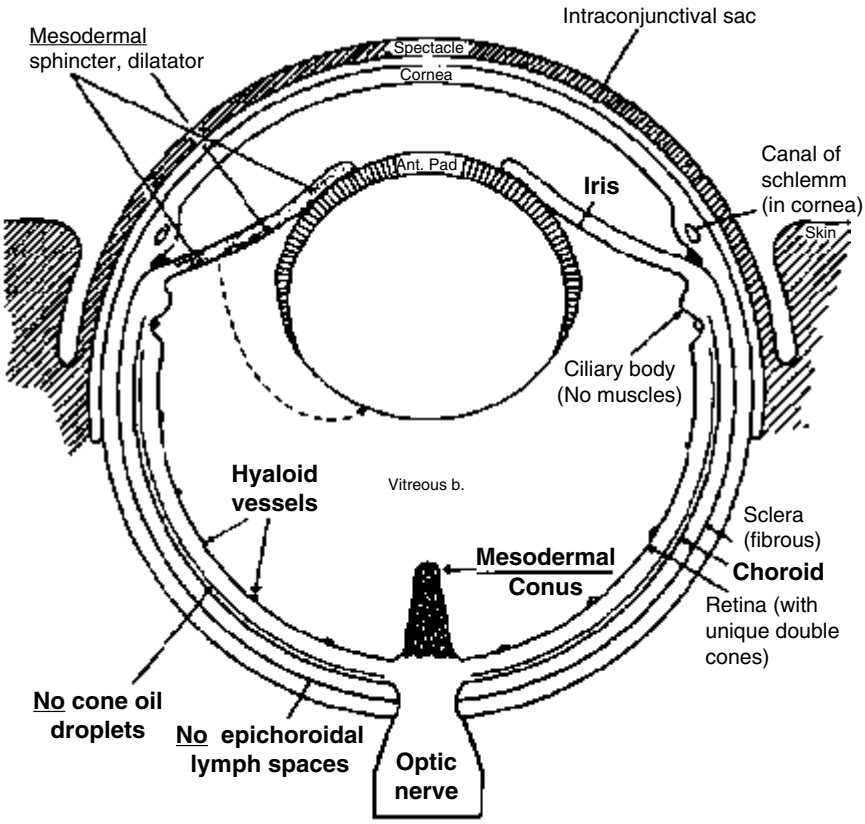


Figure 35.10 Snake eye. (*Source*: Adapted from Duke-Elder, S. (1958) *System of Ophthalmology*, Vol 1, *The Eye in Evolution*. London: Kimpton.)

development, a transient intravitreal hyaloid vascular system (Bellhorn, 1997). In lizards, this is complemented by a vascular conus papillaris derived from the hyaloid vasculature; it projects from the optic nerve head into the vitreous, in some species as far as the posterior pole of the lens and is presumed to have a nutritive function. In alligators, turtles, and tortoises, the retina is totally dependent on the choriocapillaris after the hyaloid system regresses; the alligator does have a conus that regresses. Snakes possess a conus during ocular development, but it regresses in most. In a few (e.g., vipers), the conus persists. In all snakes, a permanent preretinal vascular meshwork develops from the embryological hyaloid. In one colubrid (*Tarbophis*), this meshwork subsequently becomes an intraretinal vascular system known only in eels and few mammals (Bellhorn, 1997). In crocodilians, guanine crystals and calcium salts of guanine in the retinal pigment epithelium form a semicircular superior retinal tapetum (Ollivier et al., 2004). The relative proportion of rod and cone photoreceptors varies among reptiles, probably correlated with their relative diurnality and nocturnality. A single fovea is present in lizards, the tuatara, and only a few snakes. The distal end of the ellipsoid of lizards, but not snakes, contains oil droplets. Chelonians have predominantly cones; crocodilians have predominantly rods, as well as a few cones without oil droplets (Fig. 35.11). Some snakes have a primarily or purely cone retina. Retinal response to dark and light adaptation by cone contraction and pigment epithelial migration is minimal in reptiles. A single parietal eye located on the dorsum of the head is present in the tuatara and some lizards. These generally resemble lateral/frontal eyes histologically but not in all details. They are part of the epithalamus, which includes the pineal gland. They detect light differently than the retinas of conventional eyes and probably play a role in circadian rhythms.

Ophthalmic Diseases

The important ocular disorders of reptiles have been reviewed (Frye, 1981, 1991; Millichamp et al., 1983; Williams, 1996). The reported ocular disorders of reptiles include malformations, infections, nutritional disorders, degenerations, neoplasia, and trauma.

Ocular Malformations

Malformations include anophthalmos, microphthalmos, coloboma, cystic globe, cyclopia/synophthalmia, multiple ocular anomalies, exophthalmos, and corneal and pupillary defects (Sabater & Perez, 2013). Anophthalmos and corneal and pupillary defects were clinically identified in a wild population of gharial (*Gavialis gangeticus*), an Indian crocodilian

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Figure 35.11 American alligator fundus.

(Singh & Bustard, 1982a, 1982b). Microphthalmos occurs unilaterally and bilaterally alone or with other cranial malformations, including cleft jaw and palate, maxillary hypoplasia, and vertebral abnormalities (Bellairs, 1981; Ensley et al., 1978; Millichamp et al., 1983). Solitary microphthalmos has been seen in a Nile crocodile (*Crocodilus niloticus*), an Indian gharial, a Burmese python, and a boa constrictor (Millichamp et al., 1983), and in clutches of red-headed ratsnakes (*Elaphe moellendorfi*) (Ensley et al., 1978). In lacertid lizards (*Lacerta* spp.) and anacondas, microphthalmos was associated with other craniofacial anomalies (Bellairs, 1981). The clinical anophthalmos occasionally described in crocodilians, chelonians, and snakes may represent extreme nanophthalmos insofar as it is an exceedingly rare phenomenon in humans and other animals; unfortunately, histologic confirmation has not accompanied these reports (Frye, 1981; Millichamp, 1991; Singh & Bustard, 1982a). Cyclopia has been reported in pythons and turtles, often associated with microcephaly or other severe somatic abnormalities (Millichamp, 1991; Millichamp et al., 1983). Congenital exophthalmos was reported in a rhinoceros viper (Cooper, 1975) and alligators (Millichamp, 1991). In the viper, the blind affected eye was proptosed by a retrobulbar cyst derived from conjunctiva. Unilateral microphthalmia or anophthalmia associated with ipsilateral orbital malformation was reported in eight pythons and characterized by MRI and histopathology (Da Silva et al., 2015b). Genetic,



Figure 35.12 Boid with facial malformation and nonophthalmos. (*Source*: Courtesy of Dr. Nicholas Millichamp.)

nutritional, teratogenic, and environmental factors, at least, may be involved in the genesis of these malformations. In reptiles, abnormal temperatures maintained during gestation or incubation of eggs is known to influence the incidence of congenital anomalies (Ensley et al., 1978; Millichamp, 1991; Singh & Bustard, 1982a) (Fig. 35.12).

Infections

Viral, bacterial, fungal, and parasitic infections have been reported as causes of ocular disease in reptiles. Herpesvirus infection in mariculture-raised green sea turtles (*Chelonia mydas*) between 56 days and 12 months of age caused extensive proliferative ulcerative skin lesions frequently involving the eyelids (gray patch disease and fibropapillomatosis). Intranuclear inclusions were noted histologically (Fig. 35.13). Secondary bacterial infections needed antibacterial therapy (Jacobson et al., 1986; Rebell et al., 1975). Herpesvirus infections have been associated with an ocular respiratory syndrome in several tortoise species and in green sea turtles (Coberly et al., 2001; Curry et al., 2000).

Captive spectacled caiman (*Caiman crocodilus*) infected by poxvirus developed raised skin papules initially confined to the eyelids (Fig. 35.14). Eosinophilic intracytoplasmic inclusions were present histologically. Spontaneous regression occurred (Jacobson et al., 1979). Infection by a herpes-like virus of Argentine and red-footed tortoises (*G. chilensis* and *G. carbonaria*, respectively) caused necrotizing stomatitis, ocular discharge (presumably from conjunctivitis), weight loss, and death (Jacobson et al., 1985).

Bacterial Infections

Bacterial infections have been associated with several ocular disorders. Bacterial blepharitis with abscess formation occurs commonly (Fig. 35.15). Abscesses are usually focal and contain inspissated pus. Both Gram-negative (*Escherichia coli*, *Pseudomonas*) and acid-fast organisms

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Figure 35.13 Sea turtle with generalized cutaneous herpes infection. (*Source*: Courtesy of Dr. Nicholas Millichamp.)

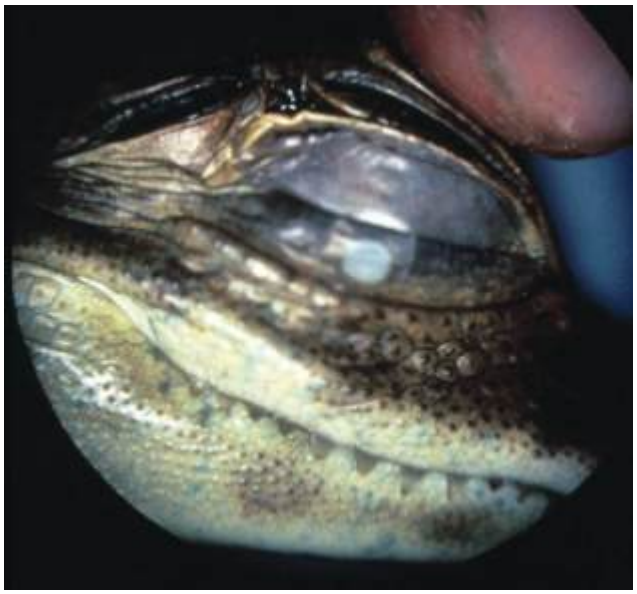


Figure 35.14 Caiman with poxvirus lesion on inferior eyelid. (*Source*: Courtesy of Dr. Nicholas Millichamp.)

have been incriminated (Leonard & Shields, 1970; Millichamp, 1991; Millichamp et al., 1983). Surgical excision or draining and curettage are indicated. Abscesses that dissect through periocular tissues may cause exophthalmos, blepharedema, panophthalmitis, exposure keratitis, ocular perforation, or septicemia. Bacterial conjunctivitis, although rarely documented in the literature, is probably common. *Aeromonas liquefaciens* was identified as the cause of blepharoconjunctivitis in a laboratory colony of lacertid lizards (Cooper et al., 1980). *Pseudomonas* was incriminated as the cause of blepharoconjunctivitis in a colony of anoles (*Anolis caroliniensis*). Conjunctivitis in desert tortoises (*Gopherus* sp.) with respiratory disease was ascribed to *Pasteurella* infection (Snipes, 1984). *Pseudomonas* was cultured from a retrobulbar abscess in a Jackson's chameleon (*Chamaeleo jacksoni*) (Millichamp et al., 1983). Attempted surgical drainage was unsuccessful. A periocular abscess resulting from *Pseudomonas* infection in another Jackson's chameleon was successfully treated by excision and antibiotic therapy (Schumacher et al., 1996). Periocular swelling in chameleons has several causes, including infections, contact irritants, hypovitaminosis A, foreign bodies, metabolic bone disease, and decreased ventilation and humidity (Coke & Couillard, 2002). Uveitis with hypopyon associated with bacteremia/septicemia can be found occasionally in reptiles. Hypopyon in four Tokay geckos (*Gekko gekko*) was secondary to *Klebsiella pneumoniae* infection (Bonney et al., 1978). *Aeromonas* was associated with hypopyon in an alligator (Millichamp et al., 1983) and *Pseudomonas* was the cause of uveitis in an Indonesian blue-tongue skink (*Tiliqua gigas*) (Millichamp et al., 1983). Hypopyon in a red-footed tortoise with pneumonia was ascribed to hematogenous spread of the respiratory infection (Tomson et al., 1976).



Figure 35.15 Iguana with periorbital cellulitis.

Subspectacular abscesses develop unilaterally or bilaterally secondary to ascending infection from the oral cavity through the nasolacrimal duct or from penetrating injuries to the spectacle or from systemic infections. Chronic stomatitis may be a predisposing factor in the former. Clinical signs include distension of the spectacle to cause apparent buphthalmos or exophthalmos and cloudiness. White or yellow exudate is often visible below the spectacle. Therapy is directed at establishing drainage by careful excision of a 30° wedge of inferior spectacle, culture and cytology of the expressed exudate for antibiotic sensitivity testing, and flushing of the space with antibiotic solutions (Miller, 1986; Millichamp, 1991; Millichamp et al., 1983). Bacterial isolates have included *Pseudomonas* and *Proteus* spp., and *Providencia rettgeri* (Millichamp et al., 1983). Hemoprotozoa

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are sometimes identified in the material; their presence is considered incidental, probably facilitated by inflammation of the blood vessels of the spectacle (Millichamp, 1991). Complete physical examination is warranted to identify oral abnormalities and systemic infections. Some cases resolve spontaneously without treatment, whereas others progress to corneal perforation and panophthalmitis despite appropriate treatment.

Blockage of the nasolacrimal duct occurs in snakes associated with congenital malformation, inflammation associated with necrotic stomatitis and subspectacular infections, and pressure from nearby tumors and granulomas (Millichamp, 1991) (Fig. 35.16). Sometimes termed pseudobuphthalmos (Boniuk & Lauquette, 1963), congenital and some acquired cases may resolve without treatment (Bellairs, 1981; Cooper, 1981) (Fig. 35.17). Discrimination from subspectacular abscess is potentially difficult on inspection, except that simple obstruction causes spectacle distention at first with clear or slightly turbid fluid. Abscess formation may follow simple obstruction. If spontaneous resolution does not occur in a reasonable period, drainage by partial excision of the spectacle to establish drainage is indicated as for subspectacular abscess. Recurrence is possible. Spectacle wound healing in the royal python (*Python regius*) has been recently studied experimentally. After 25% of each spectacle was surgically removed, regeneration of a normal spectacle in the defect occurred by 3 months postoperatively. The healing process was documented by serial clinical examinations paired with histopathology (Maas et al., 2010). A blood python was treated by repeated surgical conjunctivoralostomy with some success (Millichamp et al., 1986). A dacryocystitis syndrome reported in tortoises with foamy ocular discharge appears to be of questionable validity in view of the reported absence of a nasolacrimal duct in tortoises (Frye, 1981; Millichamp et al., 1983; Williams, 1996).



Figure 35.16 Rhinoceros viper with nasolacrimal duct obstruction and secondary distension of the spectacle and subspectacular space.



Figure 35.17 Hog-nose snake. Nasolacrimal duct obstruction resulting in pseudobuphthalmos with secondary axial spectacle injury.

Panophthalmitis, generalized inflammation of the eye usually associated with infection, develops in reptiles secondary to perforating injuries and infections of the ocular surface and by hematogenous distribution with bacteremia/septicemia. Hypopyon may be extensive and periocular swelling may be dramatic (Fig. 35.18). Any bacteria may be responsible; among others, *Staphylococcus* has been isolated from a tortoise (Holt et al., 1979). Enucleation may be the most expedient and humane treatment for reptiles without systemic infections. Performed similarly to the procedure in mammals, reptile enucleations may present the challenge of adequate closure of skin over the orbital defect (Zwart et al., 1973). Sliding skin grafts may be necessary (Frye, 1981).

Fungal Infections

Fungal infections may cause superficial or deep ocular disease. Fungal infections of the skin may extend onto the



Figure 35.18 Mangrove snake with panophthalmitis. Note chemosis. (*Source*: Courtesy of Dr. Nicholas Millichamp.)

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spectacle in snakes or the eyelids in chelonians (Millichamp, 1991; Millichamp et al., 1983). Traumas to green sea turtles and damp environments in captive snakes have been identified as predisposing factors. Cultures from skin may not yield growth; skin biopsy may be necessary to identify the nature of the infection. Correction of environmental deficiencies may be adequate treatment; snakes may then shed infected skin with the next ecdysis. Snakes can be soaked in dilute chlorhexidine (0.26 mL/L of water) for 1–2 hours daily. Pacific Island boas in a zoologic collection with spectacle involvement by mycotic dermatitis died with fungal pneumonia (Millichamp, 1991). Ketoconazole was used unsuccessfully to treat severe fungal dermatitis in king snakes (Millichamp, 1991). Bilateral fungal endophthalmitis caused by *Fusarium oxysporum* was reported in a rainbow boa (*Epicrates cenchria maurus*) (Zwart et al., 1973). Mycotic keratitis progressed to endophthalmitis in a reticulated python (*Python reticulatus*) (Collette & Curry, 1978). Both snakes were managed by enucleation. An outbreak of fungal dermatitis, stomatitis, and ophthalmitis was reported in a wild population of Florida pygmy rattlesnakes (*Sistrurus miliarius barbouri*) (Cheatwood et al., 2003). Fungi of the genera *Sporothrix*, *Pestalotia*, *Geotrichum*, and *Paecilomyces* were isolated. Affected snakes had enlargement and distortion of the spectacle. Keratomycosis in a wild gopher tortoise (*Gopherus polyphemus*) caused by *Curvularia* and *Aspergillus* species was successfully treated with a compounded topical 1% miconazole solution (Myers et al., 2009).

Parasitic Infections

Parasites occasionally cause ocular disease. Leeches (*Ozobranchus* spp.) have been noted on the conjunctiva of green sea turtles in mariculture (Millichamp et al., 1983). Local removal followed by topical antibiotic therapy resolves the condition. Oxyspirura and filarid nematodes have been found and manually removed from the conjunctival sacs of lizards and turtles (Millichamp et al., 1983). In captive snakes, mites are commonly found (*Ophionyssu*s spp. and others) attached to the scales at the margin of the spectacle. Mites can be treated using a 1-inch (2.5 cm) dichlorvos strip suspended in a perforated container in the cage for 2–3 days followed by cage disinfection and repeat treatment 14 days later (Millichamp, 1991). Alternatively, covering the animal with a thin film of olive oil (to asphyxiate the mites) or spraying with a pyrethroid (*not* pyrethrin) mite spray have been recommended as safer than organophosphate treatment (Mader, 1996). Ticks occasionally are found in this location in newly imported snakes; manual removal is necessary with local treatment as needed. Unidentified nematode larvae were found densely packed in the choroid of a red-eared slider (*Pseudemys scripta elegans*) on histologic section (Millichamp et al., 1983). Swollen eyelids associated with infestation with *Foleyella*, a filarial nematode, were managed in a wild-caught Oustalet's chameleon (*Chamaeleo oustaleti*) by incision and removal on two occasions 4 months apart. At each surgery, five adult worms of both sexes were removed. The chameleon had received thiabendazole as a parasiticide after importation (Thomas et al., 1996). *Neopolystoma elizabethae* was recovered from the conjunctival sac of Western painted turtles (*Chrysemys picta belli*) in Michigan (Platt, 2000).

Neoplasia

Fibromas, fibropapillomas, and fibrosarcomas develop on the integument of green sea turtles as part of a proliferative connective tissue response to the eggs of the trematode *Laraedius laraedii*, which lodge in small vessels of the skin and conjunctiva after hematogenous release from the parasite. Tumors may involve eyelids and conjunctiva (Brooks et al., 1994; Millichamp et al., 1983). A keratoacanthoma involving the entire spectacle associated with multiple retained spectacles was reported in a royal boa (*Constrictor constrictor*) (Hardon et al., 2007). A lacrimal cystadenoma was surgically removed from a Chinese box turtle (*Cuora flavomarginatus*) (Kottwitz et al., 2008). A periorbital squamous cell carcinoma in a veiled chameleon (*Chameleo calyptratus*) was treated surgically with good results (Abou-Madi & Kern, 2002).

Degenerations

Lenticular degeneration with opacification, cataract, occurs sporadically in reptiles, especially snakes and tortoises, probably for most of the same reasons mammals are afflicted. Cataract in very aged captive specimens has been noted (Fig. 35.19). Successful bilateral phacoemulsification has been performed in a 10-year-old Texas rat snake (*Elaphe obsolete lindheimeri*) (Ledbetter, 2017). Secondary cataract caused by uveitis or perforating injuries is common. Posthibernation blindness caused by cataract development, vitreal opacification, and central nervous system deficits in European tortoises has been reported (Millichamp, 1991). Phacoemulsification was performed on an adult savannah



Figure 35.19 Twenty-year-old indigo snake with dense cataract.

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monitor lizard (*Varanus exanthematicus*) (Colitz et al., 2003). Iris cysts were incidental findings at necropsy in a Western fence lizard (Frye, 1991). Dacryops in an aged red-eared slider turtle (*Chrysemys scripta elegans*) was successfully managed by surgical excision (Allgoewer et al., 2002).

Retinal degenerations have rarely been identified or reported, certainly explained by the difficulty of examination. Focal altered fundus pigmentation and presumed multifocal retinopathy has been observed or suspected by a few clinicians (Frye, 1981; Millichamp, 1991). Retinal degeneration was documented histologically in a reticulated python that died of cerebrovascular thrombosis (Millichamp et al., 1983).

Retained Spectacles and Other Spectacle Abnormalities

Retained spectacles in snakes present a challenge to manage. In a large case series of snakes with ophthalmic abnormalities presented to a veterinary teaching hospital, 61% of the snakes had retained spectacles (Hausmann et al., 2013). Their causes include generalized integumentary disease, dry environment, local injury to the spectacle, mite or tick infestation, and systemic illness. Over several ecdysis cycles, a thick layer of old spectacles accumulates. Spectacle opacification may render the snake blind in one or both eyes and unable or unwilling to feed. Conservative management is often effective and is safest, consisting of increasing humidity in the environment by misting or soaking the snake and lubrication with ophthalmic petrolatum ointment promoting natural shedding during the next cycle (Fig. 35.20 and Fig. 35.21). Manual spectacle removal may be carefully attempted. If unsuccessful or if the spectacle has been previously damaged and is unlikely to be shed, application of acetylcysteine (Mucomyst, Shirley, NY, USA) to the spectacle may loosen it enough to allow atraumatic removal with forceps. Extreme care must be taken to avoid corneal injury. In the aforementioned teaching hospital series, conservative treatment or manual removal resolved the problem in 70% of the affected snakes that had follow-up.



Figure 35.20 Normal ecdysis of spectacle.

Bilateral spectacle opacification in king snakes (*Lampropeltis* spp.) was suspected to be associated with exposure to organophosphate insecticide (Frye & Gillespie, 1984).

Necropsy findings in 60 snakes with pathologic changes in the spectacle submitted to a private diagnostic pathology service showed spectacle inflammation and/or dysecdysis (Da Silva et al., 2015a). Fifty-two had inflammatory changes in one or more layers of the spectacle associated with mites (2), fungi (8), or bacteria (30) either alone or in combination. Special stains identified three times more Gram-positive cocci than Gram-positive or Gram-negative rods; only one had Gram-negative cocci and none showed acid-fast bacteria. Cultures were not performed.

Other Ophthalmic Disorders

Opacification and degeneration of the third eyelid in aged American alligators associated with calcium or other deposition has been reported (Millichamp et al., 1983). An idiopathic acquired orbital varix was treated by exenteration in a green iguana (Whittaker et al., 1997). Except for the trematode-induced cutaneous fibromas seen in green sea turtles, spontaneous neoplasia seems very uncommon in reptiles.

Traumatic injury no doubt accounts for a substantial proportion of ocular conditions in reptiles, whether as the only cause or as the inciting reason for infection or inflammation. Ocular lesions in farmed American alligators were ascribed to trauma from handling and overcrowding (Millichamp et al., 1983) (Fig. 35.22). Unilateral phthisis and corneal and anterior segment scarring of presumptive traumatic origin was reported in a small cohort of American crocodiles (*Crocodylus acutus*) in Costa Rica (Rainwater et al., 2011).

Photodermatitis and photokeratoconjunctivitis were reported in a collection of snakes and skinks associated with excessive exposure to artificial UV light (Gardiner et al., 2009).



Figure 35.21 Snake (*Cribo* species) with multiple retained spectacles. (*Source*: Courtesy of Dr. Nicholas Millichamp.)

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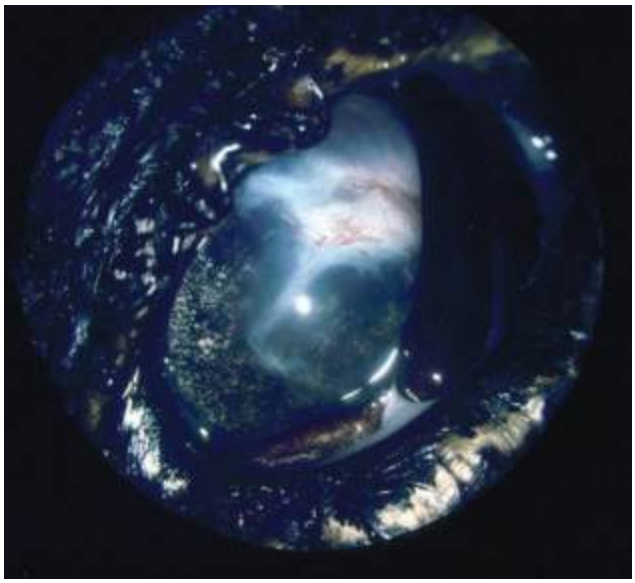


Figure 35.22 American alligator. Healed traumatic corneal perforation.



Figure 35.23 Young red-eared slider with periorbital swelling associated with hypovitaminosis A. (*Source*: Courtesy of Dr. Nicholas Millichamp.)

Vitamin A Deficiency

Hypovitaminosis A is commonly recognized in chelonians. Most frequent in aquatic species, especially rapidly growing young turtles fed diets of meat and insects, the deficiency causes squamous metaplasia of the orbital glands and their ducts (Elkan & Zwart, 1967). The glands increase in size as desquamated cells block their ducts. The eyelids become edematous and blepharoconjunctivitis ensues. The palpebral fissure becomes closed, and secondary bacterial conjunctivitis and keratitis are common (Fig. 35.23). Concomitantly, squamous metaplasia of renal, pancreatic, gastrointestinal, and respiratory epithelia progress to fatal consequence. In the early stages of the disease while animals are still eating, a change of diet to commercial trout pellets supplemented with cod liver oil initially can reverse the problem. Later, parenteral vitamin A (5,000–10,000 IU) (Aquasol-A-USV Pharmaceutical, New York, NY, USA) is recommended weekly until resolution (Millichamp, 1991; Williams, 1996). Topical antibiotic ointment is recommended to control bacterial infection (Millichamp, 1991).

In a survey of spontaneous ocular disease in captive leopard geckos, 46% of 112 geckos examined showed some ocular abnormality, most commonly corneal or conjunctival disease (Wiggans et al., 2018**)**. Animals receiving supplemental vitamin A were less likely to have ophthalmic abnormalities, which may suggest a role of hypovitaminosis A in development of ocular disease in this species.

Mammals

The class Mammalia is comprised of three subclasses: placental mammals (the largest), monotremes, and marsupials. Among the 15 orders of placental mammals, considerable diversity exists in normal anatomy, but in general the eye conforms to the prototypical pattern described in Chapter 2. The other two subclasses show features of evolution from a reptilian to a placental mammal ocular morphology (Walls, 1942). The texts of Walls and Duke-Elder may be consulted for detailed anatomic information about the eyes of particular species (Duke-Elder, 1976; Walls, 1942). The anatomy and ocular disorders of laboratory rodents, lagomorphs, and laboratory primates are discussed in Chapter 33. Ocular disorders of nonlaboratory primates are discussed in this chapter (Chapter 35). Camelid ocular anatomy and disorders are detailed in Chapter 32. Disorders of ferrets, hedgehogs, and chinchillas are discussed in Chapter 34. Ocular disorders of pinnipeds and cetaceans were extensively covered in Chapter 33 in the fifth edition of this text (Kern & Colitz, 2013). Readers are referred to this source for detailed information about species in these orders.

Ocular examination in exotic mammals often requires manual restraint or chemical immobilization. Many if not most ocular disorders that afflict domestic carnivores and herbivores at least occasionally involve exotic species. In addition, husbandry and management practices play a direct role in the development of ocular disease in some species (e.g., marine mammals). Delivery of effective therapy is often difficult and inconsistent, requiring inventive compromises (Millichamp, 1997).

Comparative Anatomy, Biometry, Physiology, and Normative Diagnostic Test Values

The ocular biology and visual ecology of some exotic mammals has recently received attention. Detailed topographic

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mapping of the retina of the African elephant identified a horizontal visual streak inferior to the optic disc and additional ganglion cell concentrations in the upper temporal retina, the latter possibly functioning to monitor movements of the trunk (Stone & Halasz, 1989). More recently, these findings were confirmed as well as the presence of a tapetum (Pettigrew et al., 2010). Retinoscopic and keratoscopic measurements in Asian elephants (*Elephas maximus*) documented a net spherical refraction of +0.23 D with 5 D or greater astigmatism. The mean corneal power by photokeratometry was 21.3 D. Accommodative range was 3 D. Refraction was not affected by cycloplegia, and a thin, meridionally oriented smooth ciliary muscle was observed histologically (Murphy et al., 1992). The biometry of the Asian elephant was investigated by transpalpebral ultrasonography in 53 subjects and reported in detail (Bapodra et al., 2010). Dissection of the anterior adnexal structures of five adult Asian elephants identified no lacrimal or tarsal glands or lacrimal drainage apparatus (puncta, lacrimal sacs or ducts) (Wong et al., 2012). However, mixed-secretion accessory glands were identified in the third eyelid and the eyelid stroma posterior to the tarsus. Prominent sebaceous glands were present at the bases of the hairs near the eyelid margins.

Baseline assessment of ophthalmic parameters in the greater one-horned rhinoceros (*Rhinoceros unicornis*) documented STT values (18.2+/-3.5 ± mm/minute), IOP by applanation (31.2 ± 6.62 mmHg), conjunctival microflora (multiple bacteria and fungus species, *Staphylococcus* the most common), and ultrasonographic biometry parameters (axial length, corneal thickness, anterior and posterior segment depths, and lens thickness measurements) (Bapodra & Wolfe, 2014). Refraction studies in the white rhinoceros (*Ceratotherium simum*) showed moderately poor optical quality of the eye based upon lack of crispness of retinoscopic reflexes; moderately hyperopic at rest (+1–1.5 D), rhinos were able to accommodate through a range of 3–4 D (Howland et al., 1993). In a study of retinal ganglion cell topography and spatial resolving power, the white rhinoceros showed a well-developed central visual streak with highest ganglion cell density at its nasal and temporal periphery (Coimbra & Manger, 2017). The spatial resolving power was calculated to be 4.4 cycles/degree in the visual streak and 7 and 6.6 cycles/degree in the temporal and nasal peripheries. A similar study performed in a black rhinoceros (*Diceros bicornis*) showed a similar ganglion cell distribution to that of the white rhinoceros and a calculated spatial resolution of 6 cycles/degree, one-tenth that of humans (60 cycles/degree), less than the cat (9 cycles/degree), comparable to the rabbit (6 cycles/degree), but greater than many other mammals (seals, dolphins, microbats, rats) (Pettigrew & Manger, 2008). A study of the ontogeny of refractive state of Thomson's gazelles (*Eudorcas thomsoni*) documented that early hyperopia resolved to emmetropia by day 50 (Ofri et al., 2004). The anatomy and physiological optics of the eyes of several cetaceans and pinnipeds have been carefully investigated and described (Cartee et al., 1995; Dawson 1980; Landau & Dawson, 1970; Sivak et al., 1989). Anatomic features of the cetacean globe (Miller et al., 2013a) and the California sea lion (*Zalophus californianus*) (Miller et al., 2010) have been detailed more recently.

A study using Schiotz tonometry in anesthetized lions showed significantly higher IOP in males than in females (24.9 ± 2.0 mmHg in males; 20.9 ± 2.4 mmHg in females) (Ofri et al., 1998a). In a different study, elevated serum progesterone during the luteal phase of estrus in lionesses was associated with higher IOP than in nonluteal phase lionesses (27.07 ± 2.15 mmHg vs. 21.61 ± 2.70 mmHg) (Ofri et al., 1999b). IOP was significantly associated with increasing age and globe size in lions, with IOP in lions older than 1 year nearly twice that of those younger than 1 year of age (Ofri et al., 2008). In a survey of normal beavers, the typical eye had an anangiotic retina IOP of 18 mmHg, and the normal conjunctival microflora consisted predominantly of Gram-positive organisms (Cullen, 2003). The light microscopic features of the iridocorneal angles and their putative function have been investigated in the West Indian manatee, short-finned pilot whale, hippopotamus, and African elephant (Hatfield et al., 2003).

Normal IOPs and STT values were reported in eight captive wild herbivore species in Israel, and tear production was reported in an additional three herbivore species (Ofri et al., 1998b, 1999a, 2001, 2002). A study of the iridocorneal angle of the water buffalo included scanning electron microscopy (Kassab et al., 2001). A survey of ocular examinations and conjunctival bacterial flora in North American bison reported similarities to cattle (Davidson et al., 1999). The distribution of lactoferrin and the lack of lysozyme in the lacrimal and other tear glands were also similar in cattle and bison (Pinard et al., 2003a, 2003b). In dromedary camels (*Camelus dromedarius*), IOPs measured by applanation tonometry were 27–31 mmHg (Marzok & El-khodery, 2015). Reference values for selected ophthalmic tests have been established for Barbary sheep (aoudad) (Fornazari et al., 2016), Sambar deer (*Rusa unicolor)* (Oriá et al., 2015a), and four other wild ruminants: fallow deer (*Dama dama)*, mouflon (*Ovis aries*), alpine ibexes (*Capra ibex)*, and alpine chamois (*Rupicapra rupicapra)* **(**Kvapil et al., 2017).

The comparative ocular anatomy of the western lowland gorilla (*Gorilla gorilla gorilla*) has been recently reported (Knapp et al., 2007). The gross and microscopic findings closely resembled that of the mountain gorilla (*Gorilla gorilla beringei*) (Rohen, 1962) and another gorilla, species not identified (Heine, 1906). Ophthalmic examinations of six captive gorillas aged 12–48 years yielded the following results: mean spherical equivalent refraction +1.20 ± 0.59 D; mean IOP 12.0 ± 4.3 mmHg Schiotz; mean cup : disc ratio 0.42 ± 0.11; mean axial length by A-scan 22.75 ± 0.71 mm;

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and mean keratometry reading of 44.38 ± 1.64 D (Liang et al., 2005). Video dynamic photorefraction confirmed that sea otters are emmetropic in both air and under water (Murphy et al., 1990). Reference values for selected ophthalmic tests of the Capuchin monkey (*Cebus apella*) were also recently reported (Montiani-Ferreira et al., 2008b). STT values were 14.9 ± 5.1/minute; IOP was 18.4 ± 3.8 mmHg by applanation; and central corneal thickness was 0.46 ± 0.03 mm by ultrasonic pachymetry. The normal fundus pigment distribution in Rhesus monkeys has been described (Dawson et al., 2004). Tear production measurements were reported using Schirmer I, phenol red thread test, endodontic absorbent paper points (size 30) in black-tufted marmosets (*Callithrix penicillata*) (Lange et al., 2012). Values obtained were 0.46 ± 3.41 mm/minute; 13.27 ± 5.41 mm/15 seconds; and 9.32 ± 3.09 mm/minute, respectively. Blink frequency was 9.32 ± 5.9 times/minute and palpebral fissure length was 7.83 ± 0.72 mm. Ophthalmic parameters were reported for captive adult lowland pacas (*Cuniculus paca*) (da Silveira et al., 2018). STTs, tonometry, and conjunctival flora description have been reported for the red kangaroo (*Macropus rufus*) (Takle et al., 2010); the capybara (*Hydrochaeris hydrochaeris*) (Montiani-Ferreira et al., 2008a), and the brown brocket deer (*Mazama gouazoubira*) (Martins et al., 2007). STT and IOP values were determined for conscious captive and anesthetized wild koalas (*Phascolarctos cinereus*) (Grundon et al., 2011). The ocular parameters of 30 fruit bats of three species (*Pteropus vampyrus*, *Pteropus pumilis*, and *Pteropus hypomelanus*) were determined, including phenol red thread test and tonometric values while hanging upside down, palpebral fissure length, vertical and horizontal corneal diameters, and anterior segment and lens findings from ocular examination (Blackwood et al., 2010). Normal conjunctival flora was described for the North American raccoon (*Didelphis virginiana*) and raccoon (*Procyon lotor*) (Pinard et al., 2002)

Electroretinographic parameters have been reported for western gray kangaroos (*Macropus fuliginosis*) (Labelle et al., 2010), koala (*Phascolarctos cinereus*) (Liddle, 2015), and fishing cat (*Prionailurus viverrinas*) and leopard cat (*Prionailurus bengalensis*) (Sussadee et al., 2017).

Morphology of the optic nerve head of the Eastern gray squirrel (*Sciurus carolinensis*) (Kuester et al., 2004), an unusual intraorbital osseous structure in the large fruit-eating bat (*Artibeus lituratus*) (Machado et al., 2006), and the papillated choroid and retina of another fruit bat (*Nyctimene robinsoni*) (Schwab & Pettigrew, 2005) have been detailed.

Population Surveys of Ocular Disorders

Health assessment of 81 Asian elephants under human care in India documented ocular lesions in 8.5% of them, consisting of cataracts and corneal opacities (Ramanathan & Mallapur, 2008). Ocular adnexal and anterior segment examination of both eyes was performed as part of an annual health check in 1478 Asian elephants under human care in Thailand (Kraiwong et al., 2016). Eighteen percent of the elephants had unilateral or bilateral lesions. The most common lesions were frothy ocular discharge, corneal edema, and conjunctivitis (all three approximately 5% incidence), with phthisis bulbi, lens abnormalities, keratitis, and uveitis less prevalent.

In a survey of free-ranging Rhesus macaques (*Macaca mulatta*) in northern India, the incidence of traumatic injuries, corneal opacity, and cataract were statistically significantly higher in macaques from urban compared with peri-urban areas (Kumar et al., 2015).

Anterior segment lesions in 18 wild and captive dolphins of five species were characterized (Colitz et al., 2016). The most common lesions were unilateral or bilateral keratopathy, followed by unilateral or bilateral cataract and traumatic corneal and eyelid injuries. A virologic survey utilizing polymerase chain reactions of ocular tissues of California sea lions, northern elephant seals (*Mirounga angustirostris*), and Pacific harbor seals (*Phoca vitulina richardii*) in rehabilitation discovered adenoviruses and herpesviruses in all three species but found no association with ocular disease (Wright et al., 2015).

Malformations, infections, inflammatory disorders, nutritional disorders, neoplasia, and trauma are all important etiologic factors in ocular disorders of mammals, of variable importance in different orders and species.

Ophthalmic Malformations

Cyclopia and limb deformity of unknown cause have been reported in a collared peccary (Hellgren et al., 1984). Anophthalmos and microphthalmos were associated with nasomaxillary and central nervous system abnormalities in two unrelated raccoons (Render et al., 1983). Unilateral congenital obstruction of the nasolacrimal duct of a young lowland gorilla was successfully treated by temporary stenting with vinyl tubing (Nagashima et al., 1974). Eyelid agenesis was surgically corrected in a Geoffroy's cat (Millichamp, 1991) and a cougar (Cutler, 2002). A conjunctival dermoid in a captive African lion cub was successfully treated by excision (Robinson & Benirschke, 1981). The brain of a white tiger with strabismus showed abnormal lamination of the lateral geniculate nucleus similar to abnormalities noted in other animals with reduced pigmentation (Guillery & Kaas, 1973). Mink affected with Chediak–Higashi syndrome have pale irides, photophobia, and hypopigment atapetal fundi. An autosomal recessive disorder, it is manifest in several mammalian species as partial oculocutaneous albinism (Collier et al., 1979; Prieur & Collier, 1978). Heterochromia iridis was described in a wild koala (Kempster et al., 1996a).

Multiple ocular colobomas (eyelid, optic nerve) and retinal dysplasia of probable genetic origin have been reported

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in captive snow leopards on two continents (Barnett & Lewis, 2002; Phillips, 1981; Schaffer et al., 1988; Wahlberg & Tarkkanen, 1980; Wahlberg et al., 1982). Bilateral multiple ocular anomalies including corneal dermoid and cataract were reported in a dromedary camel (Moore et al., 1999). Unilateral anterior segment dysgenesis similar to Peters anomaly was diagnosed in a young red kangaroo (*Macropus rufus*) (Suedmeyer, 2014).

Congenital cataract afflicted a large proportion of Malayan mouse deer in a European zoo; no familial pattern was detected and vitamin E deficiency was suspected (van der Hage et al., 1989). Microphthalmia and cataract were found in white-tailed deer fawns (Howard et al., 1976). Retinal dysplasia has been reported in wild otters (*Lutra lutra*) (Williams et al., 2004). Multiple ocular anomalies were described in an infant Rhesus macaque (Ribka & Dubielzig, 2008).

Ophthalmic Inflammations and Infections

Most reported ocular inflammatory disorders have been infectious. A few were not. Ocular nodular fasciitis in an Asiatic black bear was treated by keratectomy and subconjunctival corticosteroid administration (Mainka & Christmas, 1987). Bilateral chronic superficial keratitis in a Mexican wolf resembling pannus was treated with beta-irradiation and subconjunctival corticosteroids (Harwell et al., 1985). Nonseptic uveitis associated with mast cell infiltration was the cause of glaucoma in a lion cub treated by evisceration with silicone prosthesis implantation (Gerding et al., 1987). Idiopathic follicular conjunctivitis was found in 42% of African elephants shot at a national park (McCullagh & Gresham, 1969). A corneal stromal abscess in an aged Asian elephant was medically managed to resolution with topical antibiotic and antifungal treatment (Wiedner et al., 2006). California sea lions with corneal ulcers in rehabilitation were treated successfully with a subconjunctiva antimicrobial gel containing 2% enrofloxacin without additional topical therapy (Simeone et al., 2017).

Panophthalmitis was a manifestation of *Trypanosoma cruzi* and *Bacillus piliformis* infection in a lesser panda (Bonney & Schmidt, 1975). Conjunctivitis in jungle cat kittens was ascribed to streptococcal and staphylococcal infection (Gray, 1972).

Keratoconjunctivitis resulting from *Chlamydia psittaci* has been reported in both wild and captive koalas in Australia (Canfield et al., 1991a; Cockram & Jackson, 1974, 1981; Hirst et al., 1992a, 1992b; Kempster et al., 1996b; Weigler et al., 1988). Experimental and naturally occurring infections follow a similar course (Kempster et al., 1996b). Acute unilateral or bilateral infection may affect up to 30% of wild populations, most commonly in the summer months. Serous ocular discharge, conjunctival injection, and blepharospasm are followed by chemosis with eyelid eversion. By 3 weeks after infection, corneal neovascularization is evident and may progress to vision impairment. Diagnosis is effected by culture of the organism or positive specific immunofluorescence of epithelial cells collected by conjunctival or urogenital swab (Canfield et al., 1991b). Two distinct forms of *Chlamydia* have been identified (Girjes et al., 1988, 1993). The outcomes following diagnosis and treatment of 88 koalas with this infection has been summarized (Griffith & Higgins, 2012).

Infectious keratoconjunctivitis of wild ungulates has many of the same causes as in domestic cattle, sheep, and goats. Conjunctival habronemiasis was diagnosed on biopsy and successfully treated in a white rhinoceros (Horowitz et al., 2016). An epizootic of chlamydial keratoconjunctivitis that affected 60% of bighorn sheep in Yellowstone National Park resulted in significant mortality (Meagher et al., 1992). Keratoconjunctivitis in wild mule deer was associated with infection with *Chlamydia*, *Moraxella* spp., and *Thelazia californiensis* (Taylor et al., 1996). *Myobacterium bovis* was isolated from a common waterbuck (Fletcher, 1979) with corneal ulceration and conjunctivitis. Keratitis in red deer responsive to subconjunctival penicillin/streptomycin was suspected to be caused by *Moraxella* spp. (Wilson et al., 1981). *Mycoplasma ovis* was isolated from moose and mule deer with severe keratoconjunctivitis in Wyoming (Dubay et al., 2000a). Keratitis in reindeer in Scandinavia has been extensively investigated (Winqvist & Rehbinder, 1973; Rehbinder 1997). The clinical signs appear identical to infectious bovine keratoconjunctivitis in North America. Summer epizootics occur in forest herds. Microbiologic evaluation has documented the presence of *Neisseria ovis*, *Colesiota*-like organisms, and other bacteria, but the definitive causative agent has not been conclusively determined (Kummeneje, 1976; Rehbinder, 1977; Rehbinder & Glatthard, 1977). Corneal injury from first instar larvae of *Cephenomyia trompe*, the nostril fly, in the conjunctival sac may act as a predisposing factor. Lesions predominate in calves in which central corneal ulceration may progress to perforation. Minor superficial ulceration and conjunctivitis are frequent. Ultrastructural examination of infected corneas failed to show an agent (Winqvist & Rehbinder, 1973).

Necrotizing panophthalmitis and bilateral blindness in a black-tailed deer resulted from plague (*Yersinia pestis*), proven by culture (Jessup et al., 1989). Conjunctivitis of unknown cause was described in a Grant's gazelle and a nyala in a zoologic collection (Rehbinder, 1977).

An Indian buffalo developed ulcerative keratomycosis caused by *Aspergillus fumigatus*, perhaps associated with topical antibiotic–corticosteroid treatment; results of therapy were not reported (Pal, 1983).

Keratomalacia associated with yeast and staphylococcal infection was successfully treated both medically and surgically with a conjunctival graft in a greater one-horned rhinoceros (Gandolf et al., 2000) and in another of the same species by tarsoconjunctival graft (Esson et al., 2006). In a

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survey of corneal ulcers in domesticated Asian elephants in Sri Lanka, two-thirds yielded positive bacterial cultures, and more than half of these were concurrently infected with fungi (Kodikara et al., 1999). Exotic felids are susceptible to infection with feline herpesvirus and calicivirus. As in domestic cats, these respiratory pathogens also cause conjunctivitis; ulcerative keratitis may be caused by the rhinotracheitis virus (Fowler, 1986). Facial and eyelid cutaneous ulcers were proven by culture and histopathology to be caused by feline herpesvirus-1 infection in a cheetah cub with a history of conjunctivitis and corneal ulceration (Junge et al., 1991). Proliferative vernal-like conjunctivitis was reported in a western lowland gorilla that was unsuccessfully treated with appropriate topical medication but responded to systemic immunosuppressive therapy (Hopper et al., 2018).

Uveitis and corneal edema developed in a young maned wolf (*Chrysocyon brachyurus*) vaccinated 14 days previously with a combination vaccine containing canine hepatitis virus (Thomas-Baker, 1985). Intraocular granulomas associated with disseminated tuberculosis were identified in a Rhesus monkey (Kessler & Brown, 1979). Disseminated cryptococcosis with ocular involvement was found in a guenon (*Cercopithecus ascanius*) (Helke et al., 2006).

Ocular encephalitozoonosis occurred in blue fox pups farmed in Norway (Arnesen & Nordstoga, 1977). Foxes naturally infected with *Encephalitozoon cuniculi* had mainly encephalitis, with uveitis and cataracts. Vascular lesions in the eyes resembled polyarteritis nodosa; the posterior ciliary arteries and small vessels of the retina and uvea were involved. The retinas were detached and necrotic and many organisms were found in the cataractous lenses. Bilateral lenticular *Encephalitozoon cuniculi* strain III (dog) infection associated with cataract development and chronic uveitis was reported in a young snow leopard (*Panthera uncia*) (Scurrell et al., 2015). Lens capsule rupture, cataract and intralenticular organisms were positively identified by polymerase chain reaction. The leopard was seropositive and infection was suspected to be by vertical transmission from its dam.

Malignant catarrhal fever (MCF) was fatal to Indian gaur in which it caused pyogranulomatous scleritis and keratitis but not uveitis or retinitis (Zimmer et al., 1981). Nonsuppurative uveitis, scleritis, and keratitis characterized fatal MCF infection in farmed Rusa deer (Denholm & Westbury, 1982; Sanford & Little, 1977). Farmed deer in New Zealand are susceptible to MCF with ocular manifestations (Fletcher, 1982). An outbreak of blepharoconjunctivitis and uveitis and oral ulceration was ascribed to infection with a virus indistinguishable from bovine herpesvirus-1 in the United Kingdom (Inglis et al., 1983).

Poxviral keratoconjunctivitis and dermatitis were reported in free-ranging mule deer in Wyoming (Williams et al., 1985). Contagious ecthyma in Alaskan musk oxen and Dall sheep caused raised crusted lesions of the eyelids, nostrils, and lips (Dieterich et al., 1981). Diagnosis was confirmed by immunofluorescence and transmission studies to domestic sheep. In the Dall sheep, affected corneas opacified and perforation occurred in one animal.

Bilateral nonsuppurative panuveitis, retinitis, and optic neuritis caused epizootic blindness in eastern and western gray kangaroos and red kangaroos in Australia (Durham et al., 1996). A viral etiology was suspected. Subsequently, orbiviruses of the Warrego and Wallal serogroups caused epidemic blindness typified by chorioretinitis and encephalitis in Australian kangaroos (Durham et al., 1996; Hooper, 1999; Hooper et al., 1999; Raddacliff et al., 1999). Mink develop chronic nongranulomatous iridocyclitis as a manifestation of Aleutian disease, an immune complex-mediated glomerulonephritis induced by a parvovirus infection (Hadlow, 1982). Lesions in the posterior segment are less common, primarily a mild choroiditis causing retinal detachment. Cataracts associated with anterior uveitis were described in wild mink, probably associated with Aleutian disease (Helgebostad et al., 1979).

Disseminated blastomycosis has been reported in a rhesus monkey (Wilkinson et al., 1999).

Wallabies appear to be very susceptible to toxoplasmosis. Uveitis has been noted in captive wallabies, associated with cataract, mild retinitis, and focal outer retinal degeneration (Ashton, 1979). A wallaby succumbed to generalized toxoplasmosis after successful cataract surgery performed by the author, probably secondary to related stress.

Nematodes infect the conjunctival sacs of deer. *Thelazia californiensis* was recovered from one-third of black-tailed deer in Oregon, with increased prevalence in females and older animals (Beitel et al., 1974), and from California mule deer with conjunctivitis (Oberhansley, 1940). *Thelazia skrjabini*, an eyeworm of cattle, was recovered from a white-tailed deer in Alberta (Kennedy et al., 1993). *Thelazia californiensis* were found in 8–15% of hunter-harvested mule deer and 40–66% of live deer in Utah (Dubay et al., 2000b). The trematode *Oculotrema hippopotami* was found in the conjunctival sac of hippos without clinical signs (Thurston & Laws, 1965).

The filarid *Elaeophora schneideri* may cause unilateral or bilateral chorioretinitis in elk. A vascular parasite, the nematode infects and occludes the large arteries of the head and neck, resulting in ischemic necrosis of the brain, eyes, and other tissues of the head. Calves and yearlings are most commonly affected. Blindness occurs with or without neurologic deficits and may be secondary to ocular or central nervous system lesions or both. Retinal and optic nerve atrophy may be visible ophthalmoscopically through tonically dilated pupils. Retinal edema and necrosis, optic neuritis, and optic atrophy are present histologically. Microfilariae may be seen in ocular blood vessels (Adcock & Hibler, 1969). In sheep with elaeophorosis, iridocyclitis has also been noted in addition to the typical lesions in elk (Abdelbaki & Davis, 1972).

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Intraocular nematodiasis caused by *Parelaphostrongylus tenuis* resulted in enucleation in an eland antelope in Ohio (Gandolf et al., 2003). In Texas, fire ant bites frequently cause blepharitis and ulcerative keratitis in white-tailed deer fawns. Corneal lesions vary in severity, from pinpoint erosions or subepithelial opacities to melting corneal ulceration and perforation. Topical antibiotic therapy is effective; conjunctival flap placement has been necessary on occasion.

Corneal Degenerations and Keratopathies

A presumptive corneal endothelial degeneration or dystrophy was described in aged (6–11 years) ranch mink, primarily of the royal pastel coat color. Fifty-three percent of mink were affected, bilaterally in two-thirds. Progressive corneal edema and keratoglobus was not associated with neovascularization or melanosis. Histologically, the endothelium was attenuated or absent, with guttata of a thickened Descemet's membrane (Hadlow, 1987).

Focal to multifocal keratopathy is a common finding in pinnipeds and cetaceans under human care (Colitz et al., 2010a, 2010b; Colitz et al., 2016). Inappropriate water quality and excessive illumination in captive environments are believed to be risk factors for its development. In a retrospective survey of ocular histopathology of pinnipeds corneal disease was the most common abnormality, followed by cataract (Miller et al., 2013b).

Cataract Formation

The causes of cataract include congenital defects, advanced age, trauma, nutritional deficiencies and imbalances, inherited defects of the lens, metabolic disorders, and environmental effects (Fig. 35.24). In a breeding colony of vervet monkeys (*Chlorocebus aethiops*) more than one-quarter of 55 offspring produced over a 6-year period were diagnosed with cataract; a genetic basis was suspected. Elimination of monkeys related to ones with cataract from the breeding pool resulted in elimination of cataract from the next generation (de Villiers et al., 2001). A high incidence of cataracts was observed in two colonies of gray mouse lemurs (*Microcebus murinus*)—48% and 21% (Beltran et al., 2007). Bilateral cataract with unilateral ocular perforation was diagnosed in a wild coyote (Pence & Meinzer, 1977). In Sweden, dense cataracts have been observed in wild moose (Kronevi et al., 1977).

Cataracts of suspected nutritional origin in timber wolf pups were ascribed to deficiency or imbalance of arginine (Vainisi et al., 1981). Posterior subcapsular sutural opacification developed first in pups fed a commercial milk replacement diet from 9 to 10 days of age. Anterior cortical cataract followed. By 2.5 weeks on the diet, generalized cataract had developed. When the milk replacement was discontinued in favor of commercial dog food, the lens opacities partially regressed, leaving perinuclear opacities. Arginine deficiency was suspected after dietary experiments with succeeding litters of wolves. An age susceptibility to cataractogenesis was shown; pups receiving the deficient diet from 5 days of age were more severely affected than those receiving it after 12 days of age. In addition, pups fed lactose in addition to the milk supplement did not develop cataracts, suggesting that lactose may influence arginine absorption or metabolism. Partial bilateral cataract resorption was observed in an 8-month-old timber wolf (Williams et al., 1977).

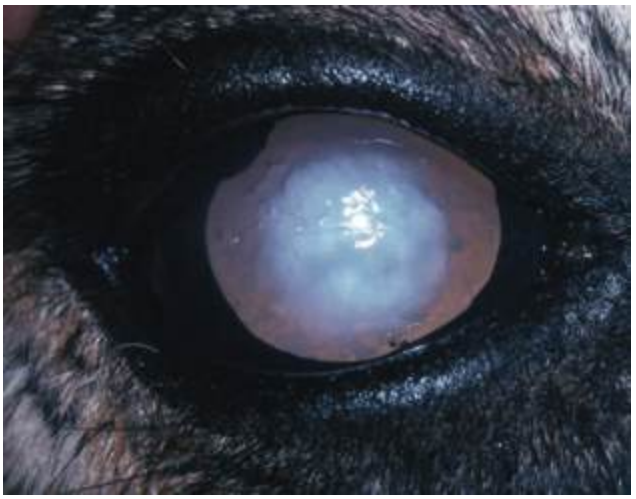


Figure 35.24 Congenital nuclear cataract in a roan antelope calf.

Cataracts are common in pinnipeds under human care. Factors increasing the risk of lens luxation and cataract formation include age greater than 15 years, insufficient access to shade, history of fighting or of other ocular disease (Colitz et al., 2010c). Successful cataract surgery has been performed in pinnipeds (Barnes & Smith, 2004; Esson et al., 2015; Kern & Colitz, 2013).

Bilateral extracapsular cataract extraction was performed with good results on an eland with senile cataracts and a young Siberian tiger with cataracts of suspected genetic origin (Austin & Porter, 1975; Magrane & VanDeGrift, 1975). Bilateral phacoemulsification without intraocular lens implantation has been performed by the author on two clouded leopard cubs (*Neofelis nebulosa*) and a roan antelope calf (*Hippotragus equinus*). Phacoemulsification was successfully performed without intraocular lens implantation in a mature spider monkey (*Ateles geoffroyi*), a 3-month-old clouded leopard cub, and adult orangutans (*Pongo pygmaeus*) (Cooley, 2001; Montiani-Ferreira et al., 2010; Whitley et al., 1980) and with foldable intraocular lens implantation in two young lowland gorillas (de Faber et al., 2004) and in a gorilla, chacma baboon chimpanzee, and orangutan (Leiva et al., 2012). Intracapsular lensectomy for lens luxation was performed without intraocular lens implantation was performed on an adult Matschie's tree kangaroo (*Dendrolagus matschiei*) (McLean & Zimmerman, 2015).

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Galactosemic cataracts have been reported to occur in kangaroos, wallabies, wombats, Australian possums, and cuscus (Slatter et al., 1980; Stephens et al., 1974). Affected animals had been orphaned or hand-reared for other reasons and had received cow's milk. These neonatal marsupials progress through a monogastric phase of gastrointestinal development to a polygastric (ruminant) form of adult digestive system. Prior to maturity, they may be variably deficient in either galactokinase or galactose-1-phosphate uridyl transferase, which limits conversion of galactose in cow's milk to lactose. Dulcitol accumulation in the lens causes an osmotic cataract. These nutritional cataracts may be prevented by feeding proprietary milk substitutes designed for human infants with inherited galactosemia that lack galactose and lactose. Surgical lensectomy has been generally unsuccessful because most affected animals have vitreous opacified by an unidentified material.

Cataracts were found in 16 of 300 African elephants culled from Tsavo National Park, Kenya (McCullagh & Gresham, 1969); only two were bilateral. Lens luxation and hypermaturity and active and inactive uveitis were noted in some elephants. Cataracts have been recognized in captive elephants as well (Schmidt, 1986).

Cataracts of presumed traumatic origin were noted in Turkish dancing bears from a circus, associated with corneal scarring and phthisis in some animals (F.C. Stades, personal communication).

Diseases of the Ocular Fundus

Central retinal degeneration typical of taurine deficiency in the domestic cat was reported in a white Bengal tiger in the United States and in three unrelated cheetahs in Israel (Beehler et al., 1984; Ofri et al., 1996). Serum taurine level was lower in the white tiger compared with other orange tigers, but not low enough compared with domestic cats with central retinal degeneration to account for the tiger's retinopathy (Pickett et al., 1990). Levels were not reported for the cheetahs prior to initiation of dietary supplementation (Ofri et al., 1996). Retinal degeneration of uncertain cause has been noted in culled wild African elephants with cataracts (McCullagh & Gresham, 1969) and in captive Asian elephants. The unrelated Asian elephants showed behavioral signs of reduced vision and ophthalmoscopically reduced fundus vascularity; the normal paurangiotic fundus is difficult at best to assess. Retinal degeneration of unknown cause occurred in aged ranch mink (Hadlow, 1984). Presumptive hypertensive retinopathy and uveal vasculopathy were reported in a 40-year-old captive hippopotamus with a pheochromocytoma (Duncan et al., 1994). Histologic lesions included retinal detachment, retinal pigment epithelial degeneration, degeneration of small blood vessels of the uvea with hemorrhage, and hypertrophied tunic media and edematous tunica adventitia of the larger uveal blood vessels. Idiopathic bilateral optic atrophy has been described in Rhesus macaques (Fortune et al., 2005). Clinical diagnosis of hypertensive encephalopathy and retinopathy were confirmed at necropsy in a western lowland gorilla (*Gorilla gorilla gorilla*) (Niemuth et al., 2014). Presumptive age-related macular degeneration was diagnosed clinically in a mature captive western lowland gorilla (Steinmetz et al., 2012).

Neoplasia

Neoplasia in exotic species seems relatively uncommonly reported in the literature. No doubt diagnostic pathology laboratories harbor extensive collections of neoplasms from these species that are not reflected in veterinary publications. An extensive corneal squamous cell carcinoma in a 5-year-old cheetah was managed by exenteration; the animal was free of local recurrence and radiographic evidence of thoracic metastasis 1 year later (Caligiuri et al., 1988). Intestinal and unilateral ocular lymphosarcoma was reported in a captive adult striped hyena (Porter et al., 1987). The optic nerve, uvea, retina, and vitreous were infiltrated by neoplastic lymphocytes. Bulbar conjunctival ganglioneuromas were diagnosed in two adult Indian water buffalo; clinical signs and outcome were not reported (Gupta & Singh, 1978). An African green monkey (*Cercopithecus* [*Chlorocebus*] *pygerythrus*) developed extensive bilateral periocular and eyelid squamous cell carcinoma after a long-term carcinogenicity trial (Fincham et al., 1982). A harderian gland adenocarcinoma caused exophthalmos in a Beechey ground squirrel (*Spermophilus beecheyi*) (Morrow & Day-Lollini, 1990). Bilateral corneal papilloma in a Malayan tapir resolved with repeated subconjunctival injections of 25 mg fluorouracil (Karpinski & Miller, 2002). A transitional cell carcinoma of ovarian origin was metastatic to the eye of a collared peccary (McCowan et al., 2002). Focal limbal corneoconjunctival intraepithelial neoplasia in an Asian elephant was excised, treated with cryotherapy and was apparently cured (Fraunfelder et al., 2006). Recurrent eyelid sebaceous carcinoma in an Amur tiger (*Panthera tigris altaica*) was successfully treated by excision and intralesional bevacizumab (Edelmann et al., 2013). Surgical excision of a conjunctival squamous cell carcinoma was curative for a reindeer (*Rangifer tarandus tarandus*) (Gonzalez-Alonso-Alegre et al., 2013).

Nutritional Disorders

Nutritional disorders have been relatively rarely implicated in ocular disorders of exotic species. Bilateral ocular lipidosis occurred in a 2-year-old cottontail rabbit fed an all-milk diet for 20 months (Gwin & Gelatt, 1977). Histologically, lipid deposits were most extensive in the anterior corneal stroma and posterior iridal epithelium. Focal lipid

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depositions were detected in the sclera and choroid. Complete necropsy was not performed. The rabbit is highly susceptible to systemic manifestations of high dietary cholesterol (Gwin & Gelatt, 1977). Ocular lipidosis and aortic atherosclerosis are readily induced by dietary manipulation. In this rabbit, absence of dietary fiber may have enhanced systemic lipidosis (Gwin & Gelatt, 1977).

Nutritional cataracts in wolf pups were investigated and characterized (see previous discussion).

Central retinal degeneration indistinguishable from the taurine deficiency-induced lesion in domestic cats has been reported in cheetahs and a white tiger (Beehler et al., 1984; Ofri et al., 1996) (see previous discussion).

Trauma

Traumatic injury is no doubt a frequent cause of ocular disease in nondomestic animals (Fig. 35.25). Extensive epithelial downgrowth was described in the buphthalmic eye of a harbor seal that was postulated to be secondary to a perforating injury (Glover et al., 1995). In addition to extensive anterior synechiae, a layer of stratified squamous epithelium covered the posterior surface of the iris, ciliary body, and retina. Glaucoma of unknown etiology was treated by evisceration and intrascleral silicone prosthesis in a slow loris (*Nycticebus coucang*) (Kim et al., 2016).



Figure 35.25 Wild Indian leopard cub with traumatic corneal ulcer.

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36

Neuro-Ophthalmology

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The nervous system is sometimes a daunting system to consider conceptually in a clinical setting. The reasons for this are numerous. The nervous system is divided into central, peripheral, and autonomic components and these components are, with the exception of the head of the optic nerve and the retina, not readily available for external visual inspection. Instead, however, we rely upon examining the behavior of the animal to various stimuli to interpret indirectly normal from abnormal function of particular pathways within the nervous system. Therefore, a solid foundation in the understanding of basic neuroanatomy is important. If the neuroanatomical basis for particular reflexes and responses to various stimuli is understood, where a lesion lies within the nervous system can be deduced and a neuroanatomic diagnosis can be formulated. Upon reaching a neuroanatomic diagnosis, and while simultaneously taking into consideration the patient's signalment and clinical history (anamnesis), an appropriate differential diagnostic list can be created, thus steering an appropriate diagnostic plan.

Neuro-ophthalmology is focused with respect to the anatomical portions of the nervous system being evaluated. Of equal importance is the distant examination of every patient. In some instances, especially where systemic disease is suspected, it is essential to complete full physical and neurological examinations.

Finally, and often ignored in textbooks, it is important to consider the biolifestyle–social history of the patient with respect to its owner when formulating diagnostic and treatment plans. Careful consideration of how the patient "fits-in" with the owner's life, and understanding the expectations and limitations of the owner, will help to determine appropriate diagnostic and treatment plans. For example, recognizing that the patient is a herd animal and is primarily being raised for food may alter diagnostic planning and may warrant a herd examination and postmortem examination of one or more affected individuals in a herd, whereas patients who are primarily pets, or considered members of the family, may warrant an exhaustive diagnostic plan aimed at treating the individual. Further, an owner's ability to comply with multiple daily life-long treatments may not be appropriate and, instead, other options may require investigation (e.g., enucleation, euthanasia).

Although many excellent textbook chapters and review papers have been written about veterinary neuro-ophthalmology, it is difficult to provide essential information that does not oversimplify such a complex and important subject. However, much of the knowledge on neuroscience of the ophthalmic system, especially vision, is beyond the scope of this chapter. Rather than describe the neuro-ophthalmology of every species of animal, this chapter provides salient information about neuro-ophthalmology in the clinical setting, focusing on mammalian species.

Gross Topographical Neuroanatomy

Prior to discussing the neuro-ophthalmic examination, and the corresponding neuro-anatomic pathways, an understanding of gross topographical neuroanatomy is important. An understanding of the general regions and names of sections of the brain and spinal cord helps provide a frame of reference as to the location of the neuronal nuclei, axonal pathways, etc.

General Organization of the Nervous System

The nervous system is divided into the central and peripheral nervous systems (Behan, 2004). Generally speaking, the central nervous system (CNS) comprises any structure covered by meninges, whereas the peripheral nervous system is not covered by meninges. Accepting this, the CNS is made up of the brain, spinal cord, and optic nerves. Groups of neuronal cell bodies serving a similar function and that are located within the CNS are referred to as nuclei, whereas groups of cell bodies, serving a similar function, in the peripheral nervous system, are known as ganglia.

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The nervous system can also conceptually be divided functionally into the somatic and autonomic nervous systems (Behan, 2004). The somatic portion of the nervous system is concerned with the voluntary control of muscles whereas the autonomic portion is concerned with involuntary or visceral functions (e.g., control of cardiac muscle, glands, etc.).

With respect to the autonomic nervous system, this system is further subdivided into the parasympathetic, sympathetic, and enteric nervous systems. However, it should be recognized that some classify the enteric nervous system as a separate entity, given that it can function independent of CNS input (Goyal & Hirano, 1996). Given the topic of this chapter, the enteric nervous system will not be discussed further. Instead, it is important, clinically, to recognize that the parasympathetic and sympathetic nervous systems have a very specific arrangement with regard to the location of their preganglionic neuronal cell bodies. Specifically, preganglionic neuronal cell bodies for the parasympathetic nervous system have a so-called cranio (cranial nerves [CN] III, VII, IX, X)–sacral distribution, whereas the preganglionic neuronal cell bodies for sympathetic neurons have a thoracolumbar distribution (Deuchars & Lall, 2015; Horn, 2018). That is, all sympathetic preganglionic neurons (SPNs) are located within the spinal cord. Preganglionic neuronal cell bodies of the parasympathetic and sympathetic nervous systems extend their axons peripherally to their respective ganglia where they make cholinergic synapses, whereas postganglionic neurons make either cholinergic or noradrenergic synapses for parasympathetic and sympathetic systems, respectively (Fig. 36.1). Importantly, however, this long-held belief of the organization of the parasympathetic and sympathetic outflow from the CNS has been recently challenged (Espinosa-Medina et al., 2016, 2018).

The Brain

During development, the CNS is essentially tubular and derived from a tube of neuroectoderm known as the neural tube (Noden & de Lahunta, 1985). The neural tube is the product of fusion of folds of neuroectoderm. The fusion does not occur randomly, however. Instead, the neural folds fuse rostrally and caudally from a region that will ultimately become a region of the brain known as the rhombencephalon (hindbrain) (Noden & de Lahunta, 1985). The caudal portion of the neural tube ultimately becomes the spinal cord, whereas the rostral portion of the neural tube becomes the brain. One can simplistically think of the neural tube zipping up like a zip-lock bag beginning in the center of the zipper,

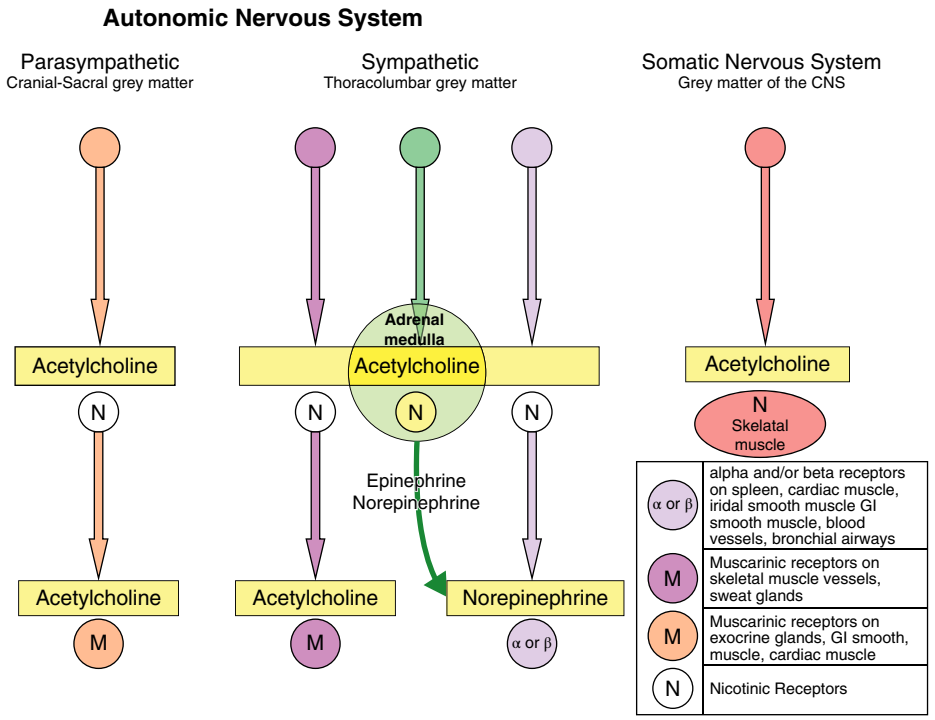


Figure 36.1 Some differences between the efferent components of the parasympathetic, sympathetic, and somatic nervous systems. Preganglionic cell bodies for the parasympathetic nervous system are distributed in a craniosacral distribution, whereas the sympathetic nervous system has a thoracolumbar distribution. Efferent neurons for the somatic nervous system are distributed throughout the central nervous system and make connections directly with the effector organ. Sympathetic and parasympathetic nervous systems have postganglionic neurons that make contact with the effector organ, or in the case of the adrenal medulla, neurotransmitters are dispersed via the bloodstream. GI, gastrointestinal.

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recognizing, of course, that it is not quite this simple. Failure of closure of the neural tube results, clinically, in what are termed neural-tube defects (for review see Copp & Greene, 2010). Examples of neural-tube defects involving the rostral and caudal portions of the neural tube, respectively, include anencephaly and spina bifida (Copp & Greene, 2010).

As neurodevelopment proceeds, the more rostral portion of the neural tube develops into three vesicles, namely, the prosencephalon, the mesencephalon, and the rhombencephalon (Fig. 36.2). The prosencephalon gives rise to the optic vesicles, laterally, which ultimately develop into the adult eyes (see Chapter 1) (Noden & de Lahunta, 1985). Two additional vesicles form rostrolaterally, giving rise to the telencephalon, ultimately becoming the cerebral hemispheres (Fig. 36.2). The remaining rostral prosencephalon gives rise to the diencephalon, a structure in the adult containing many nuclei of the thalamus, metathalamus, epithalamus, hypothalamus, and subthalamus (Noden & de Lahunta, 1985). Additionally, the diencephalon also contains the tracts of the optic nerve having originated from the axons extending from the retinal ganglion cells in the retina (Noden & de Lahunta, 1985).

Caudal to the developing diencephalon are the mesencephalon and rhombencephalon (Fig. 36.2). The mesencephalon is known as the midbrain in the adult, whereas the rhombencephalon further divides into two vesicles known rostrally as the metencephalon and caudally as the myelencephalon (Noden & de Lahunta, 1985). The metencephalon ultimately develops dorsally into the cerebellum, whereas the ventral metencephalon develops into the pons (Fig. 36.2) (Noden & de Lahunta, 1985). The myelencephalon is known commonly in the adult as the medulla oblongata. The midbrain, the pons, and the medulla oblongata are collectively known as the "brainstem" in the adult (Fig. 36.2).

Remembering that the CNS is an essentially tubular structure, the space within the different regions of the brain becomes the ventricular system (Fig. 36.3) (Noden & de Lahunta, 1985). Specifically, the spaces within the region of the cerebral hemispheres are known as the lateral ventricles; the relatively smaller canal within the diencephalon is known as the third ventricle and is connected to the lateral ventricles by way of the interventricular foramina (de Lahunta et al., 2015b). An even smaller space within the mesencephalon, known as the mesencephalic aqueduct, joins the third ventricle with the fourth ventricle that is located within the rhombencephalon (de Lahunta et al, 2015b). The cerebrospinal fluid (CSF), produced by the choroid plexus of the lateral, third, and fourth ventricles (Gomez & Potts, 1981), fills the ventricular system and exits the brain via bilateral lateral openings in the fourth ventricle (lateral apertures) which allow drainage of CSF into the subarachnoid space thereby bathing the entire CNS (Fig. 36.3) (de Lahunta et al., 2015b). Additionally, CSF flows from the ventricular system caudally in the central canal of the spinal cord. CSF normally is absorbed via structures known as arachnoid villi within the venous sinuses, although alternate pathways (e.g., via cribriform plate) exist (Leeds et al., 1989; Mann et al., 1978). The arachnoid villi act as one-way valves to the flow of CSF.



Figure 36.2 The brain and spinal cord each start as a relatively straight neural tube. The cranial portion of the neural tube is dramatically modified by unequal growth and the appearance of flexures. This results in the formation of three enlargements: the forebrain, midbrain, and hindbrain. The shape and size of the neural tube vary greatly, reflecting the regional modification of the neural tube during the development. (*Source*: Reproduced with permission from Uemura, E.E. (2015) *Fundamentals of Canine Neuroanatomy and Neurophysiology*. Oxford: Wiley-Blackwell.)

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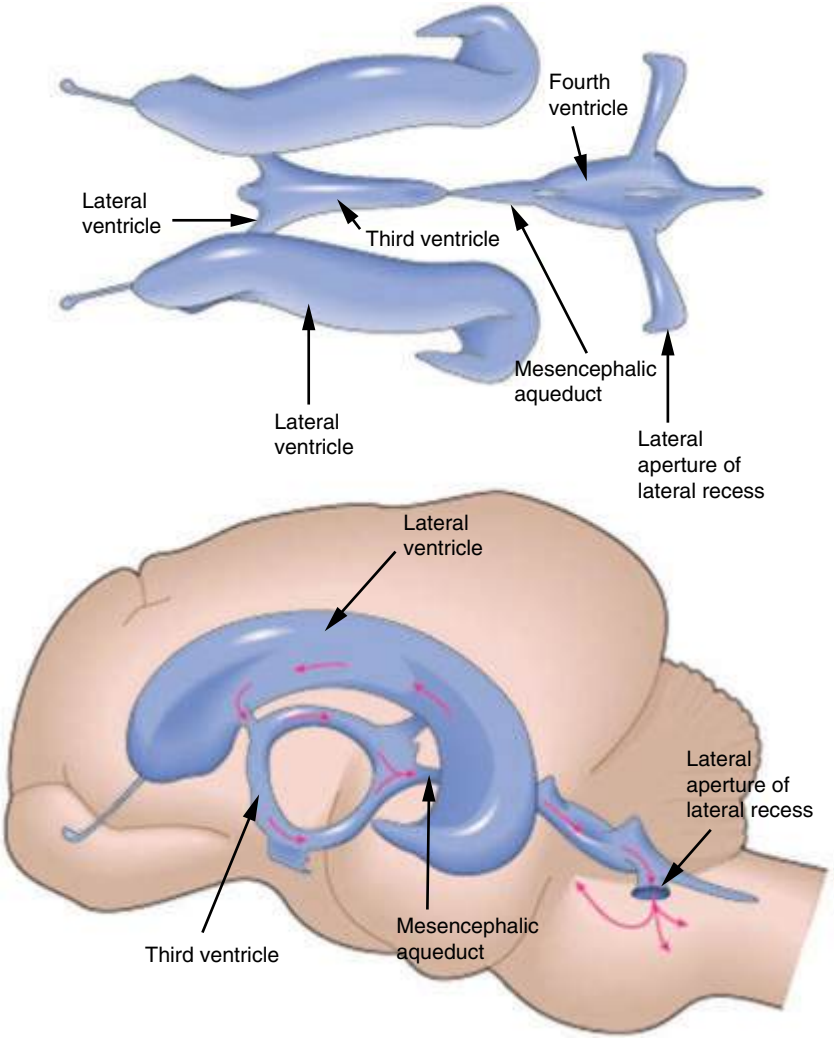


Figure 36.3 The brain ventricular system. Cerebrospinal fluid (CSF) is produced within the lateral, third, and fourth ventricles. Fluid moves through the ventricular system beginning in the lateral ventricles, then through the third ventricle to the fourth ventricle. CSF exits the ventricular system via the lateral apertures to bath the brain and spinal cord. (*Source*: Revised from De Lahunta et al., 2009.)

CSF can act as a sink for CNS waste products that cannot cross the blood–brain barrier. CSF can flow into the interstitial space of the brain parenchyma via the periarterial space and associated endothelial astrocytic endfeet aquaporin-4 channels (Bower & Hogan, 2018; Louveau et al., 2017). CNS interstitial fluid and solutes can then flow back in the subarachnoid space via perivenous spaces and then out of the brain via the arachnoid villi (Bower & Hogan, 2018; Louveau et al., 2017). This movement of CSF to interstitial fluid and back to the CSF is known as the glymphatic system. CSF and macromolecules can also leave the CNS through meningeal lymphatics (Louveau et al., 2015), an important finding with regard to understanding CNS immunobiology.

As may be apparent after considering where CSF is produced, and also the flow of CSF from the ventricular system, stenosis or obstruction of connecting portions of the ventricular system, or impairment of CSF absorption, can result in an increased volume of CSF – hydrocephalus (de Lahunta et al., 2015b). As will be discussed later, hydrocephalus can result in vestibular, cerebellar, or thalamocortical impairment and thus manifest ophthalmologically.

Important neuroanatomic structures that are viewed clinically with magnetic resonance imaging (MRI) are outlined in Figure 36.4, Figure 36.5, Figure 36.6, Figure 36.7, and Figure 36.8 (Leigh et al., 2008). The reader is referred to several excellent manuscripts identifying the clinical neuroanatomy of dogs, cats, horses, and ruminants (Arencibia et al., 2001; Arencibia et al., 2005; Couturier et al., 2005; Leigh et al., 2008; Gomes et al., 2009; Schmidt et al., 2012). Table 36.1 provides a list of important cranial nerve ganglia and nuclei considered in clinical veterinary neuro-ophthalmology, including their origin and termination, entry to or from the CNS, and their general function.

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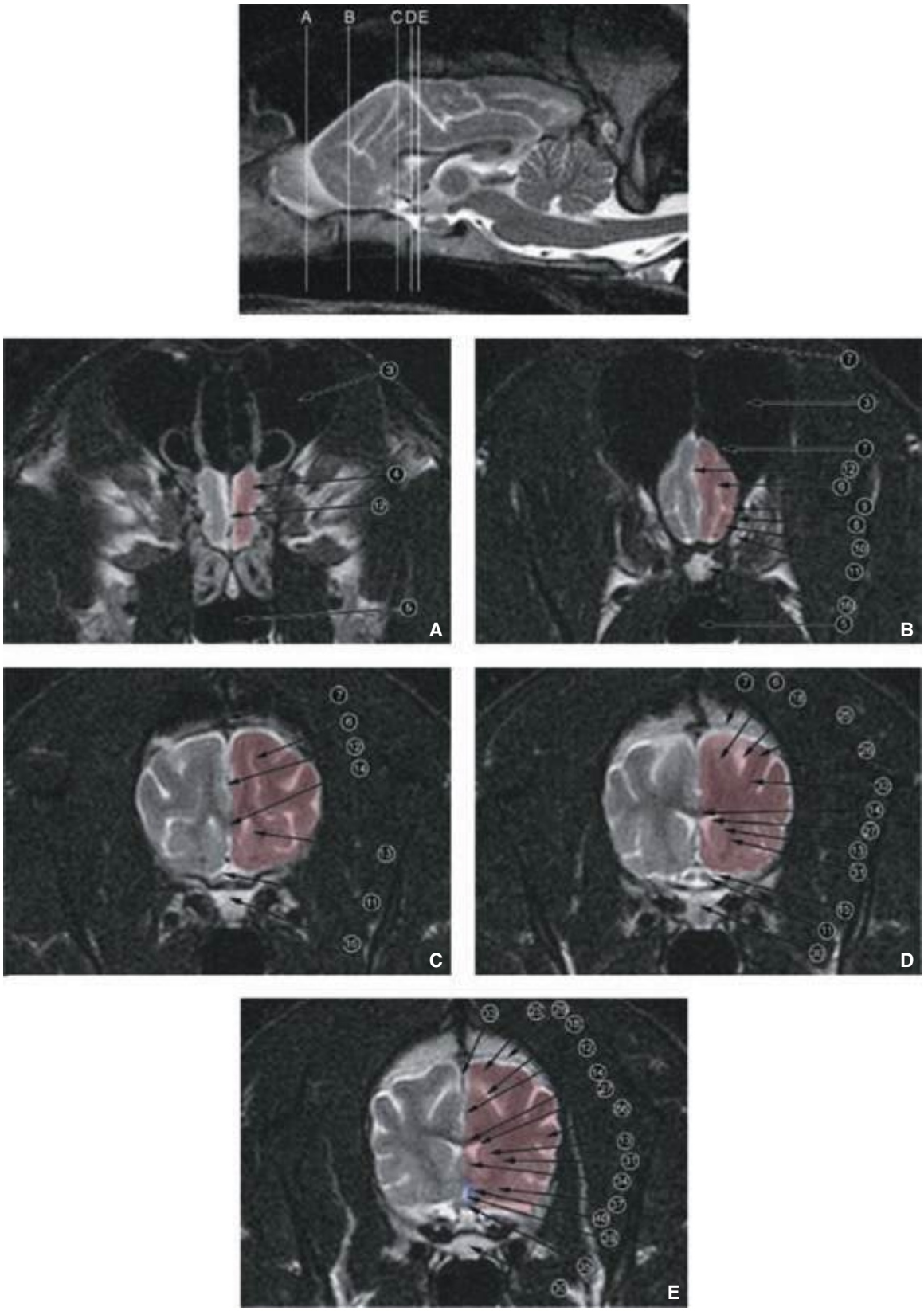


Figure 36.4 **A–E.** 3. frontal sinus, 4. olfactory bulb, 5. nasopharynx, 6. frontal lobe, 7. frontal bone, 8. palatine bone, 9. lateral rhinal sulcus, 10. olfactory peduncle, 11. optic nerve, 12. longitudinal cerebral fissure, 13. caudate nucleus, 14. corpus callosum, 15. rostral cerebral artery, 16. presphenoid bone, 18. cruciate sulcus, 25. parietal lobe, 26. parietal bone, 27. lateral ventricle, 30. basisphenoid bone, 31. internal capsule, 32. corona radiata, 33. falx cerebri, 34. septal nuclei, 35. optic chiasm, 37. lentiform nucleus, 39. third ventricle, 40. hypothalamus, 56. temporal lobe. , telencephalon; , diencephalon. (*Source*: Reproduced with permission from Leigh et al., 2008.)

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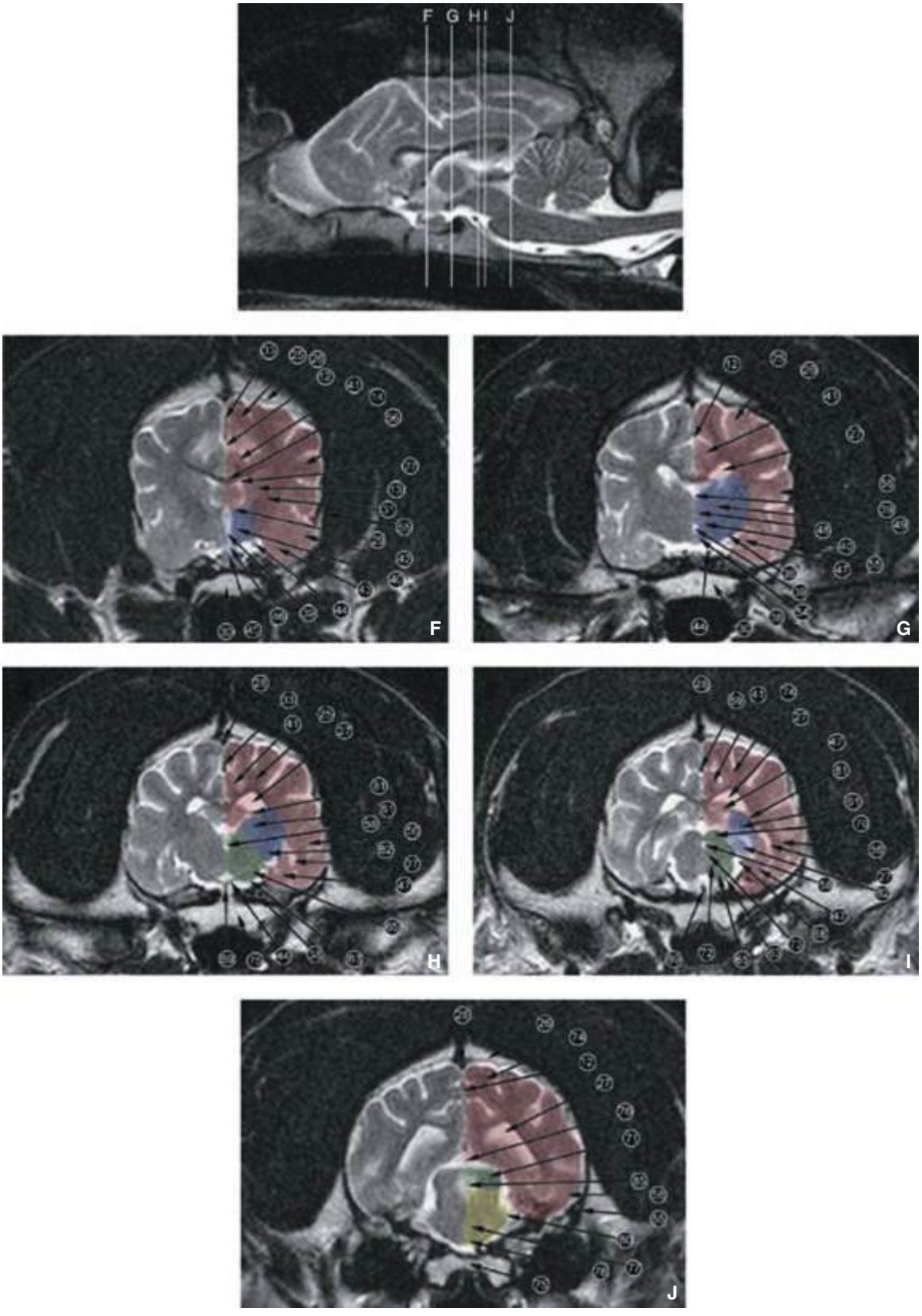


Figure 36.5 **F–J.** 12. longitudinal cerebral fissure, 13. caudate nucleus, 14. corpus callosum, 25. parietal lobe, 26. parietal bone, 27. lateral ventricle, 28. dorsal sagittal sinus, 29. columns of the fornix, 30. basisphenoid bone, 31. internal capsule, 33. falx cerebri, 36. optic tract, 38. cavernous sinus, 39. third ventricle, 40. hypothalamus, 41. cingulate gyrus, 42. piriform lobe, 43. amygdala, 44. communicating branch of the arterial circle, 45. hypophysis (pituitary gland), 46. pituitary recess/infundibulum, 47. hippocampus, 48. interthalamic adhesion, 49. thalamus, 54. mamillary body, 55. temporal bone, 56. temporal lobe, 58. mesencephalic aqueduct, 59. ventral sagittal sinus, 61. lateral geniculate body, 62. medial geniculate body, 63. crus cerebri, 65. substantia nigra, 68. caudal cerebral artery, 69. basilar artery, 70. rostral colliculus, 71. caudal colliculus, 72. red nucleus, 73. oculomotor nucleus, 74. occipital lobe, 75. basioccipital bone, 76. quadrigeminal cistern, 77. pons, 78. pons- transverse fibers, 80. CN V, 81. crus of the fornix, 85. rostral vermis (at mesencephalic aqueduct). , telencephalon; , diencephalon; , mesencephalon; , ventral metencephalon (pons) and myelencephalon. (*Source*: Reproduced with permission from Leigh et al., 2008.)

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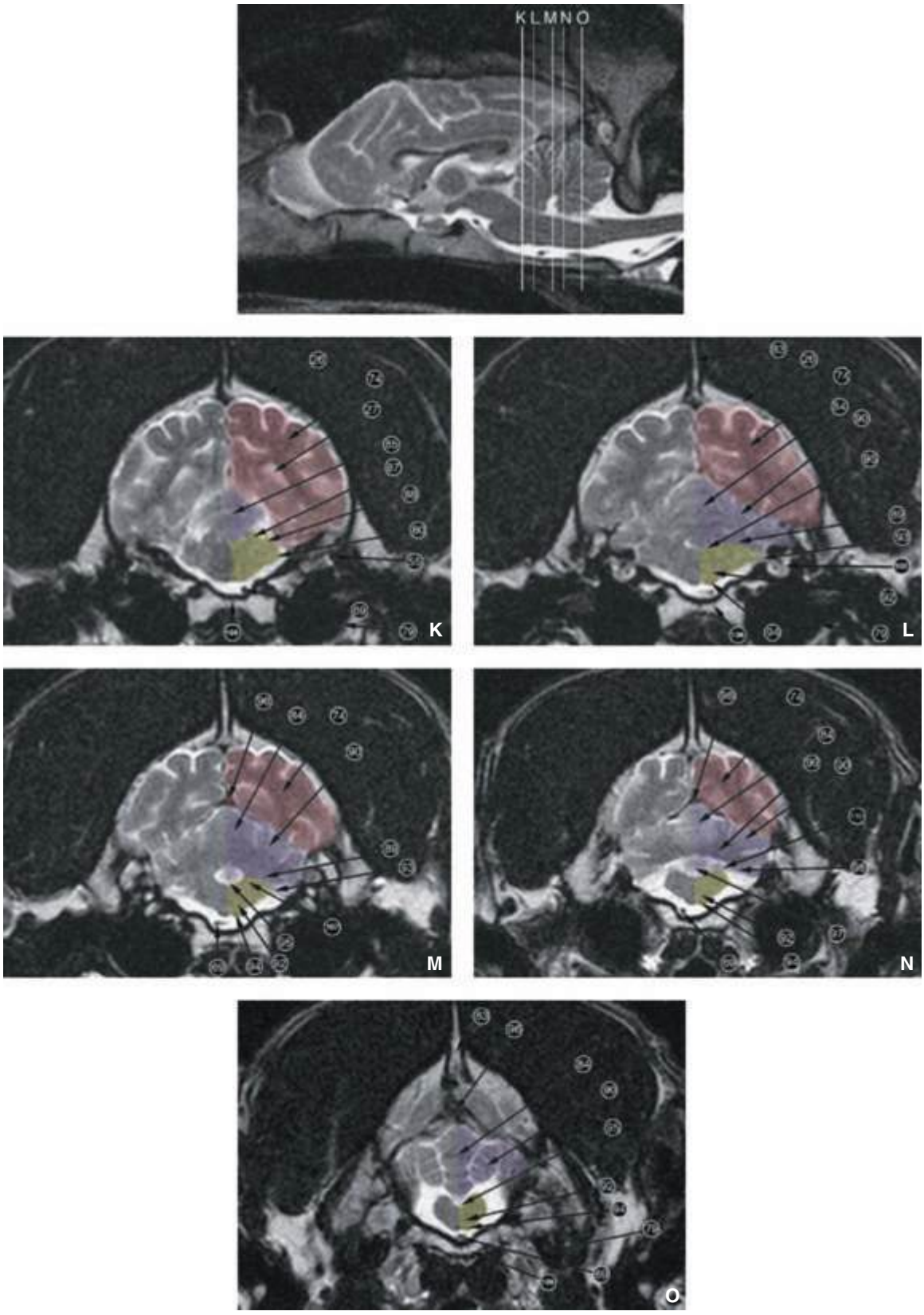


Figure 36.6 **K–O.** 26. parietal bone, 27. lateral ventricle, 55. temporal bone, 69. basilar artery, 74. occipital lobe, 79. tympanic bulla, 80. CN V, 83. sagittal ridge, 84. vermis, 85. rostral vermis, 87. rostral cerebellar peduncle, 88. middle cerebellar peduncle, 89. confluence of cerebellar peduncles, 90. cerebellar hemisphere, 92. reticular formation, 93. CN VIII, 94. pyramid, 95. fourth ventricle, 96. osseous tentorium cerebelli, 97. nodulus, 98. flocculus, 99. cerebellar medulla, 100. membranous labyrinth, 106. occipital bone, 107. vestibular nuclei, 110. choroid plexus in the lateral aperture of the fourth ventricle. , telencephalon; , dorsal metencephalon (cerebellum); , ventral metencephalon (pons) and myelencephalon. (*Source*: Reproduced with permission from Leigh et al., 2008.)

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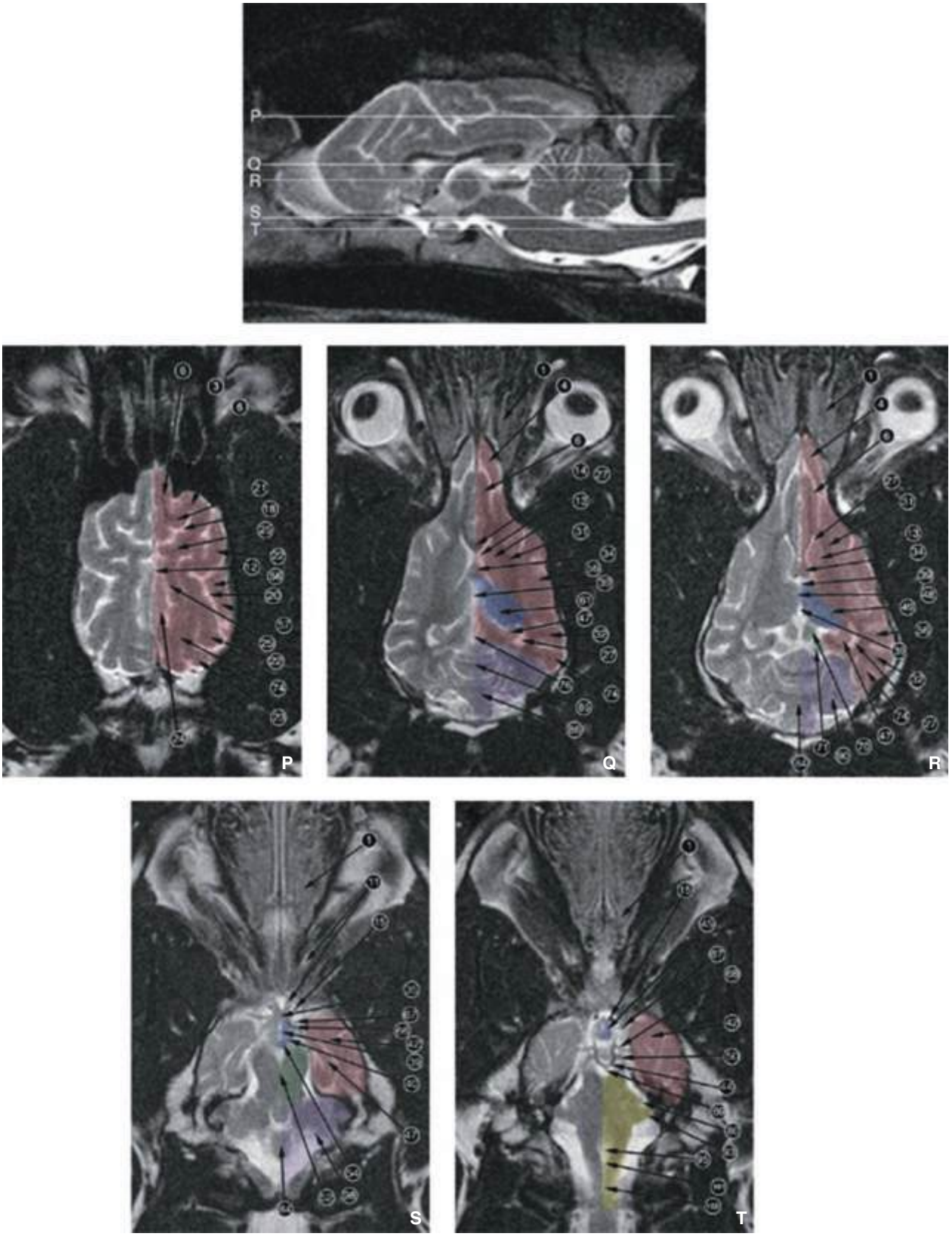


Figure 36.7 **P–T.** 1. ethmoturbinates, 3. frontal sinus, 4. olfactory bulb, 6. frontal lobe, 11. optic nerve, 12. longitudinal cerebral fissure, 13. caudate nucleus, 14. corpus callosum, 15. rostral cerebral artery, 18. cruciate sulcus, 20. suprasylvian sulcus, 21. precruciate gyrus, 22. suprasylvian gyrus, 23. ectomarginal gyrus, 24. marginal gyrus, 25. parietal lobe, 27. lateral ventricle, 31. internal capsule, 32. corona radiata, 34. septal nuclei, 35. optic chiasm, 39. third ventricle, 40. hypothalamus, 42. piriform lobe, 44. communicating branch of the arterial circle, 45. hypophysis (pituitary gland), 47. hippocampus, 48. interthalamic adhesion, 49. thalamus, 50. rostral cerebellar artery, 52. tegmentum, 54. mamillary body, 56. temporal lobe, 57. ectomarginal gyrus, 61. lateral geniculate body, 66. internal carotid artery, 67. middle cerebral artery, 68. caudal cerebral artery, 69. basilar artery, 70. rostral colliculus, 71. caudal colliculus, 74. occipital lobe, 76. quadrigeminal cistern, 80. CN V, 84. vermis, 85. rostral vermis, 86. caudal vermis, 90. cerebellar hemisphere, 93. CN VIII, 95. fourth ventricle, 98. flocculus, 101.obex, 102. central canal. , telencephalon; , diencephalon; , mesencephalon; , dorsal metencephalon (cerebellum); , ventral metencephalon (pons) and myelencephalon. (*Source*: Reproduced with permission from Leigh et al., 2008.)

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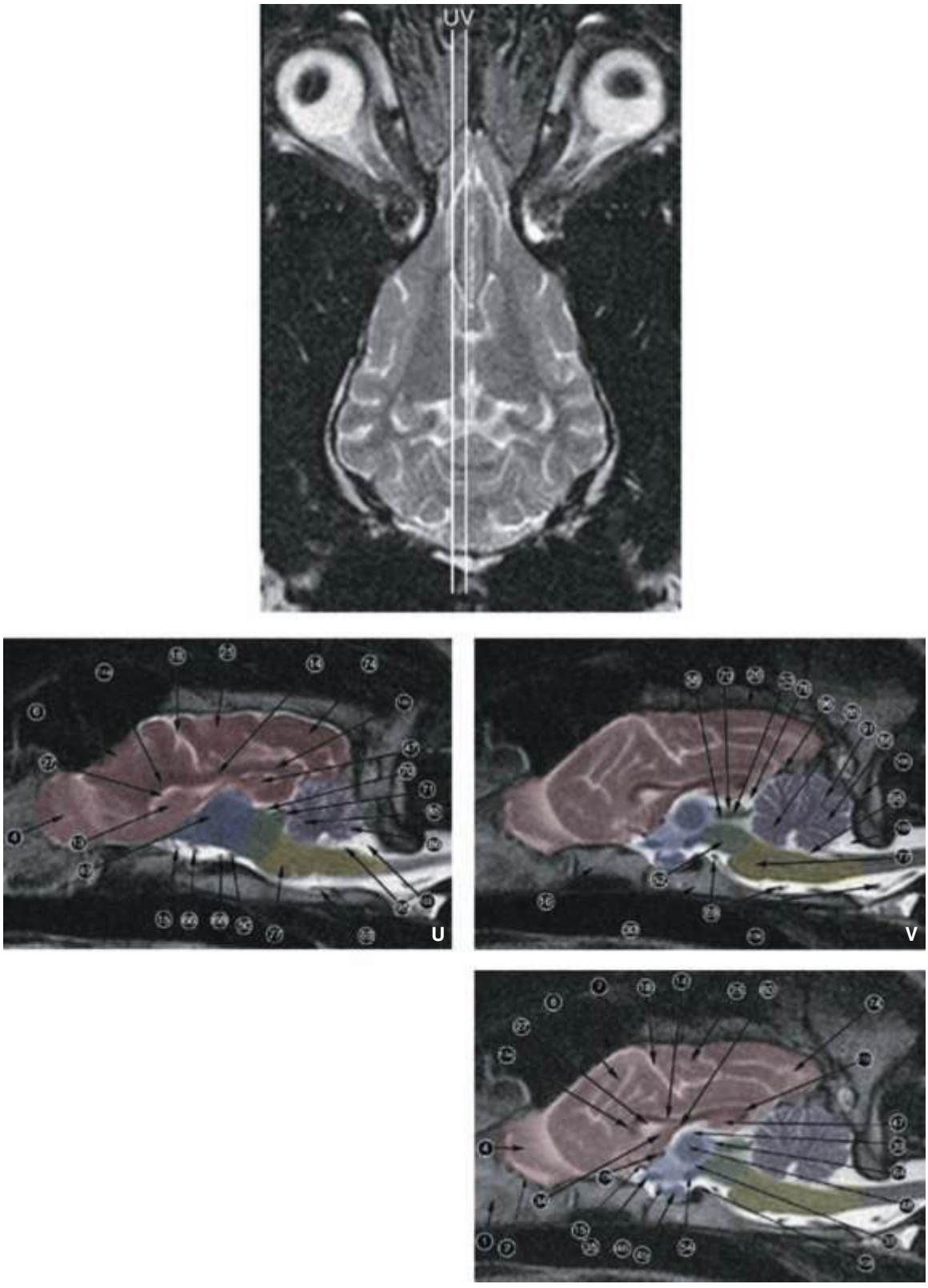


Figure 36.8 **U–V.** 1. ethmoturbinates, 2. cribriform plate, 4. olfactory bulb, 5. nasopharynx, 6. frontal lobe, 7. frontal bone, 13. caudate nucleus, 14. corpus callosum, 14a. genu of corpus callosum, 14b. splenium of corpus callosum, 15. rostral cerebral artery, 16. presphenoid bone, 18. cruciate sulcus, 25. parietal lobe, 26. parietal bone, 27. lateral ventricle, 30. basisphenoid bone, 34. septal nuclei, 35. optic chiasm, 39. third ventricle, 45. hypophysis (pituitary gland), 46. pituitary recess/infundibulum, 47. hippocampus, 48. interthalamic adhesion, 49. thalamus, 50. rostral cerebellar artery, 52. tegmentum, 53. tectum, 54. mamillary body, 58. mesencephalic aqueduct, 60. body of the fornix, 64. pineal body, 66. internal carotid artery, 68. caudal cerebral artery, 69. basilar artery, 70. rostral colliculus, 71. caudal colliculus, 74. occipital lobe, 76. quadrigeminal cistern, 77. pons, 85. rostral vermis, 86. caudal vermis, 91. arbor vitae, 95. fourth ventricle, 96. osseous tentorium cerebelli, 103. cerebellomedullary cistern, 106. occipital bone, 108. dorsum sellae, 109. rostral commissure. , telencephalon; , diencephalon; , mesencephalon; , dorsal metencephalon (cerebellum); , ventral metencephalon (pons) and myelencephalon. (*Source*: Reproduced with permission from Leigh et al., 2008.)

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Table 36.1 Neuroanatomic location of various nuclei and ganglia important in neuro-ophthalmology.

Cranial nerve or brain nuclei	Origination	Entry/exit to/from the cranial vault	Termination	Function
Cranial nerve II (optic nerve)	Retinal ganglion cells in retina	Optic canal	Lateral geniculate nucleus Rostral colliculi Thalamic nuclei Note: variable decussation at the optic chiasm (species dependent)	Vision Afferent arm of pupillary light reflex Afferent arm of menace response Afferent arm of dazzle reflex
Motor nucleus of cranial nerve III (oculomotor nucleus)	Tegmentum (floor) of the midbrain Caudal to pretectal nucleus Rostral to trochlear nucleus	Orbital fissure	Medial, dorsal, ventral recti muscles Ventral oblique muscle Levator palpebrae superioris muscle All ipsilateral to the nucleus	Ocular movements (see Table 36.2)
Parasympathetic nucleus of cranial nerve III (Edinger–Westphal nucleus)	Tegmentum (floor) of the midbrain Caudal to pretectal nucleus Rostral to trochlear nucleus	Orbital fissure	Ciliary ganglion	Efferent arm of pupillary light reflex – pupillary constriction via constriction of ciliary muscle of iris (sphincter pupillae muscle)
Motor nucleus of cranial nerve IV (trochlear nerve)	Caudal mesencephalon at level of caudal colliculi Caudal to oculomotor nuclei	Orbital fissure	Dorsal oblique muscle on side opposite the location of the nucleus	Ocular movement (see Table 36.2)
Motor nucleus of cranial nerve VI (abducens nerve)	Rostral medulla oblongata	Orbital fissure	Lateral rectus and retractor bulbi muscles ipsilateral to the nucleus	Ocular movement and retraction (see Table 36.2)
Motor nucleus of cranial nerve V (trigeminal nerve)	Pons at level of middle and rostral cerebellar peduncles	Canal for the trigeminal nerve in petrous temporal bone and then exits with the *mandibular branch* of the nerve via the oval foramen	Masseter, temporal, pterygoid, rostral digastricus and mylohyoideus muscles	Motor to muscles of mastication
Sensory ganglion of cranial nerve V (trigeminal nerve)	Neuron cell bodies of the mandibular, ophthalmic, and maxillary branches are located in trigeminal ganglion located in the canal for the trigeminal nerve in the petrous temporal bone Receiving sensory information from the head	Canal for the trigeminal nerve in the petrous temporal bone	Various somatic efferent nuclei within the brainstem Spinal tract of the trigeminal nerve	Mandibular branch – sensory to cheek, mandibular teeth, tongue Ophthalmic branch – sensory to orbit, medial part of upper eyelid, dorsum of the rostral nose Maxillary branch – sensory to most of face, cheek, lateral aspect of nose, lateral aspect of eyelids

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Table 36.1 (Continued)

Cranial nerve or brain nuclei	Origination	Entry/exit to/from the cranial vault	Termination	Function
Motor nucleus of cranial nerve VII (facial nerve)	Rostral medulla oblongata	Stylomastoid foramen via the facial canal in the petrous temporal bone	Muscles of facial expression Caudal portion of the digastricus muscle	Motor to muscles innervated
Parasympathetic nucleus of cranial nerve VII	Rostral medulla oblongata	Preganglionic traverse in the facial canal and exit with the maxillary and mandibular branches of the trigeminal nerve	Preganglionic: synapse in pterygopalatine ganglion Postganglionic: innervate lacrimal, palatine, and nasal glands	Lacrimation Nasal wetting
Cranial nerve VIII (vestibular portion)	Pons and medulla oblongata	Internal acoustic meatus	Rostral, medial, lateral, and caudal vestibular nuclei Minority to fastigial nucleus and flocculonodular lobe of the cerebellum	Coordinate eye, neck, trunk, and limb position with position and movements of the head Maintain balance
Lateral geniculate nucleus	Diencephalon	Not applicable	Visual cortex (lateral, caudal, and medial aspects of the occipital lobe)	Project visual information from optic tracts to visual cortex
Pretectal nucleus	Mesencephalon	Not applicable	Bilateral projections to parasympathetic nuclei of cranial nerve III (Edinger– Westphal nuclei)	Maintenance of the pupillary light reflex

The Neuro-Ophthalmic Examination

The Distant Examination

Though often overlooked in written descriptions of the neuro-ophthalmic examination, the distant examination provides essential and important information about the neuro-ophthalmic system. Using careful observation of the patient from a distance permits one to not lose sight of the forest for the trees. Information collected during the distant examination should include species and size of the patient, its coat color or coat color pattern, an assessment of the animal's mental acuity, body condition, gait, head and body posture, ability to navigate, presence of tremor, signs of impaired ocular function (e.g., nystagmus, pupil size at rest in various lighting conditions, strabismus, etc.). All this information will ultimately be used in conjunction with proximal neuro-ophthalmologic findings to arrive at a neuroanatomic diagnosis. For the purposes of this chapter, however, discussion of the distant examination will be limited to distant clinical examination findings relating to only the eye. The reader is encouraged to consider referring to a textbook relating to veterinary neurology (de Lahunta et al., 2015g; Dewey & da Costa, 2015; Platt & Olby, 2013; Vite, 2010) when considering other clinical neurological signs, although we have provided a list of clinical neurological syndromes (later in the chapter) that are useful in arriving at a neuroanatomic diagnosis. Alternatively, partnering or working with someone with expertise in veterinary neurology can often be invaluable in arriving at a neuroanatomic diagnosis.

Nystagmus

Upon first examining a patient from a distance, it may be clearly evident that the patient exhibits nystagmus, strabismus, or inappropriate pupil size(s). Nystagmus can be described as a rhythmic and involuntary movement of the eyes. Nystagmus may be pendular (spontaneous ocular movements without predilection for a fast or slow movement in any particular direction) and may represent abnormalities of the visual pathway, as can be found sometimes in Siamese, and other pointed-coat colored cats (Kaas, 2005; Webb & Cullen, 2010). Nystagmus may also be in a particular direction and is described as being in the direction of the fast-phase of the ocular movement. For example, a left nystagmus is one in which the fast phase of the ocular movement is to the left.

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Spontaneous, pathologic nystagmus represents dysfunction of the vestibular system (for review see Pike, 1923; discussed in detail with vestibulo-ocular reflex testing), and is a result of asymmetric input to the motor nuclei of the cranial nerve nuclei responsible for extraocular muscle control (i.e., CN nuclei III, IV, VI). Vestibular dysfunction can be described as being either central or peripheral in origin. The central vestibular system is that portion of the nervous system located within the CNS and includes the vestibular nuclei and the vestibulocerebellum (i.e., flocculonodular lobe and the fastigial nuclei of the cerebellum) (de Lahunta et al., 2015f). The peripheral vestibular system neuroanatomically includes the bilaterally located vestibular apparatus (i.e., the utricle, saccule, three semicircular canals within the petrous temporal bone) and the vestibular portion of the vestibulocochlear nerve (de Lahunta et al., 2015f). Normally, there is tonic input from the peripheral vestibular apparati onto the vestibular nuclei which in turn exerts control over the nuclei of CN III, IV, and VI. This tonic and equal input results in stationary ocular position when the patient's head, neck, and body are stationary. If, however, there is asymmetric input onto these CN nuclei, the contralateral side is tonically stimulated more often than the side ipsilateral to the disease process and nystagmus results (see oculocephalic reflex later for more detail about the neuroanatomical basis of spontaneous vestibular nystagmus).

Strabismus

With respect to abnormalities of eye position that can be determined during a distant examination, these can be the result of vestibular disease or a disease process involving the extraocular muscles or the cranial nerves innervating the extraocular muscles (CN III, IV, VI) (Fig. 36.9). With respect to vestibular strabismus, this is most often evident when the patient's head is held in extension (de Lahunta et al., 2015f). Normally, the eyes remain in a central position, although animals with vestibular disease may have a strabismus characterized by ventral strabismus ipsilateral to the side of the lesion. It is important to recognize that, in clinically normal horses and ruminants, these animals will not keep their eyes central when holding their head in extension and instead, vestibular strabismus is evident without extending these animals' heads (Fig. 36.10) (de Lahunta et al., 2015f; Mayhew, 2008).

Before discussing strabismus resulting from diseases affecting the extraocular muscles, directly (e.g., extraocular myositis) or indirectly (e.g., orbital disease), or the cranial nerves controlling these extraocular muscles, it is important to consider the anatomy and function of the extraocular muscles (see Chapter 2 for more discussion) and the innervation of these muscles (Table 36.1 and Table 36.2). It should be noted that all extraocular muscles are present in common domestic species of animals (Prince, 1960).

After considering the function of the various extraocular muscles and their innervations, the direction of the

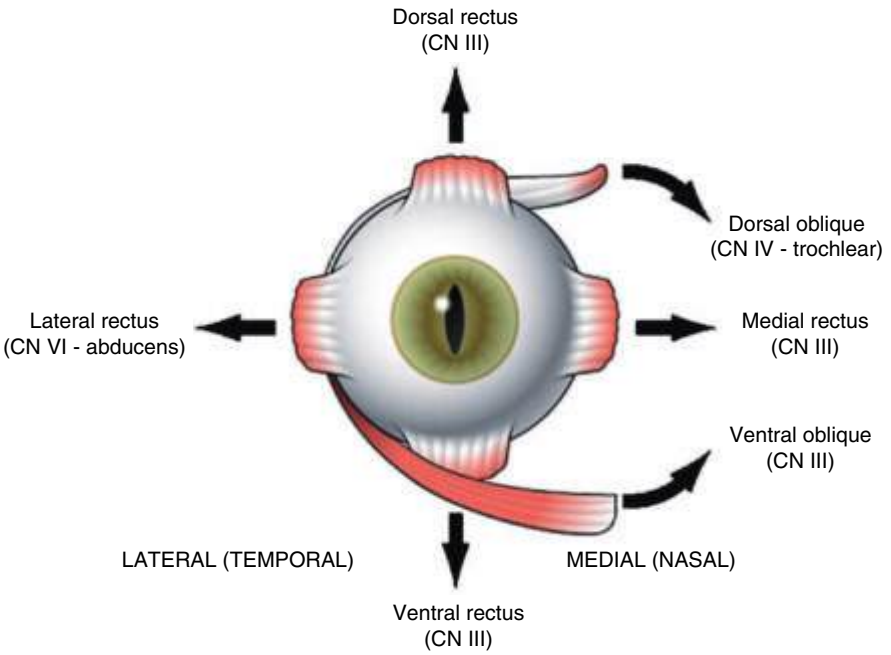


Figure 36.9 The insertions of the various extraocular muscles on the globe of the eye, and the innervation of the various muscles. Arrows indicate the direction of movement of the eye with contraction of the respective muscle.

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Figure 36.10 Infection with *Listeria monocytogenes* caused ventral strabismus in this sheep. Positional ventral strabismus is normal in ruminants when the head is elevated. In this sheep, the strabismus was evident when the head was in a normal position. (*Source*: Reproduced with permission from Shamir & Ofri, *Veterinary Ophthalmology*, 4th edition, 2007.)

strabismus after primary disease to the muscle(s) or denervation of a muscle(s) is somewhat predictable (see Table 36.3). Worth considering, in arriving at a neuroanatomic diagnosis, are the origins of CN III, IV, and VI nuclei and their course to their point of insertion. Conveniently, the motor nuclei of these cranial nerves are located in chronological order along a rostral to caudal path within the brainstem.

All of the cranial nerve nuclei are paired bilaterally, although we will discuss their location and course taken from an individual nucleus perspective (for anatomic location, see Fig. 36.11, Fig. 36.12, Fig. 36.13, Fig. 36.14, Fig. 36.15, Fig. 36.16, and Fig. 36.17) (Parry & Volk, 2011). The nucleus of CN III (oculomotor nerve) is located most rostrally. The nucleus of CN III is found within the tegmentum of the midbrain within the ventral part of the periaqueductal gray, that is, a gray matter region that surrounds the mesencephalic aqueduct (de Lahunta et al., 2015d). The axons of this nucleus pass ventrally through the reticular formation of the tegmentum, medial to the red nucleus, substantia nigra, and crus cerebri. These axons exit the brainstem as part of the third cranial nerve, at the ventral aspect of the midbrain. Axons exit predominantly on the ipsilateral side in common mammalian species, although one should be cognizant that phylogenetic differences exist (for review see Buttner-Ennever, 2006; Evinger, 1988). CN III then courses rostrally, lateral to the hypophysis, and enters the orbit through the orbital fissure. After entering the orbit, it sends branches to the ventral oblique and to the dorsal, medial, and ventral rectus muscles, but it also innervates the superior levator palpebral muscle and provides parasympathetic innervation to the iris and ciliary body (thus controlling pupillary constriction and lens accommodation, respectively) (de Lahunta et al., 2015d).

The motor nucleus of the CN IV (trochlear nerve) is located just caudal to the nucleus for CN III yet still within the midbrain. CN IV is the only cranial nerve in which most of the axons cross over to innervate the contralateral

Table 36.2 Innervation and function of the extrinsic muscles of the eye.

Muscle	Innervation	Function
Dorsal rectus	Cranial nerve III (oculomotor nerve)	Rotate globe dorsally
Ventral rectus	Cranial nerve III (oculomotor nerve)	Rotate globe ventrally
Medial rectus	Cranial nerve III (oculomotor nerve)	Rotate globe medially
Ventral oblique	Cranial nerve III (oculomotor nerve)	Extorsion
Lateral rectus	Cranial nerve VI (abducent nerve)	Rotate globe laterally
Retractor bulbi (absent in primates)	Cranial nerve VI (abducent nerve)	Retract globe
Dorsal oblique	Cranial nerve IV (trochlear nerve)	Intorsion

Table 36.3 Direction of strabismus due to unilateral denervation of extraocular muscles.

Nerve or nucleus affected	Direction of strabismus
Cranial nerve III, nucleus of cranial nerve III	Ipsilateral, ventrolateral + ptosis
Cranial nerve IV	Ipsilateral, extorsion
Unilateral nucleus of cranial nerve IV	Contralateral, extorsion
Cranial nerve VI, nucleus of cranial nerve VI	Ipsilateral, medial

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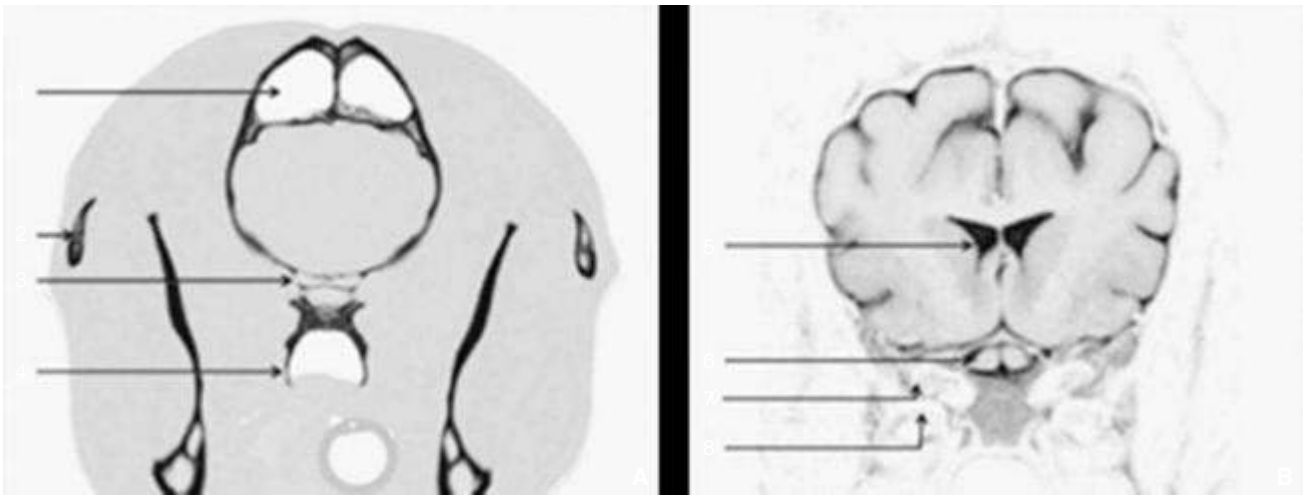


Figure 36.11 Transverse computed tomography (**A**) and T2-weighted magnetic resonance (**B**) images at the level of the most caudal aspect of the optic nerves, just rostral to the optic chiasm. 1, frontal sinus; 2, zygomatic arch; 3, optic canal; 4, hamulus of the pterygoid; 5, lateral ventricle; 6, CN II; 7, CN III, IV, VI and ophthalmic branch of CN V in orbital fissure; 8, maxillary branch of CN V rostral to the rostral alar foramen. (*Source*: Reproduced with permission from Parry & Volk, 2011.)

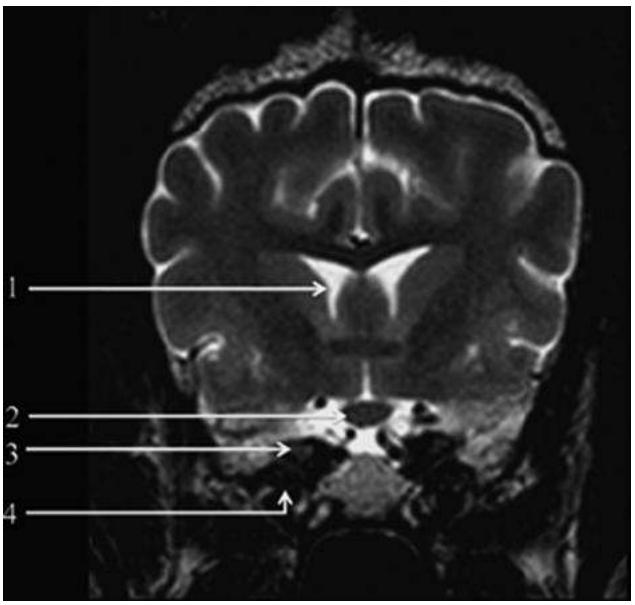


Figure 36.12 Transverse T2-weighted magnetic resonance image at the level of the optic chiasm. 1, lateral ventricle; 2, optic chiasm; 3, CN III, IV, VI and ophthalmic branch of CN V in orbital fissure; 4, maxillary branch of CN V rostral to the rostral alar foramen. (*Source*: Reproduced with permission from Parry & Volk, 2011.)

extraocular muscle. In all mammals studied thus far, only a very small percentage (2%–4%) of the motor neurons of CN IV send projections to the ipsilateral dorsal oblique muscle (Buttner-Ennever, 2006). CN IV exits the brain from the dorsal surface of the brainstem just caudal to the caudal colliculus and on the contralateral side from the nucleus the axons arose. After exiting the midbrain, CN IV passes rostroventrally over the side of the midbrain to reach the floor of the cranial vault. Eventually, CN IV exits the cranial vault via the orbital fissure to innervate the dorsal oblique muscle (Buttner-Ennever, 2006; de Lahunta et al., 2015d).

The final of the three extraocular motor nuclei, the nuclei of CN VI (abducent nerve), is located just ventral to the floor of the fourth ventricle in the rostral part of the medulla oblongata (de Lahunta et al., 2015d). The axons leaving these nuclei course ventrally through the reticular formation (a complex network of neurons believed to be important for arousal [Brown et al., 2012], modulation of pain [Martins & Tavares, 2017], and cardiovascular control [Ghali, 2017]), medially to the nucleus of the trapezoid body, and emerge through the trapezoid body (a portion of the hearing pathway), lateral to the pyramid on both sides of the medulla, as CN VI. CN VI exits the cranial vault via the orbital fissure with CN III and CN IV, to then innervate the lateral rectus and the retractor bulbi muscles (Evinger, 1988; de Lahunta et al., 2015d).

Anisocoria and Pupil Size

Anisocoria, or unequally sized pupils, is a useful finding during the distant examination. The presence of anisocoria, however, should be evaluated in conjunction with history, pupillary light reflex (PLR), and vision testing.

During the distant examination, anisocoria should be observed in normal ambient light (photopic) and in dim light (scotopic) conditions. In so doing, it will become evident which eye is abnormal. For example, anisocoria may be characterized by the right pupil being more mydriatic compared with the left in photopic conditions, although, if the anisocoria resolves in scotopic conditions this implies that there is a disease process involving the constrictor ability of the right pupil.

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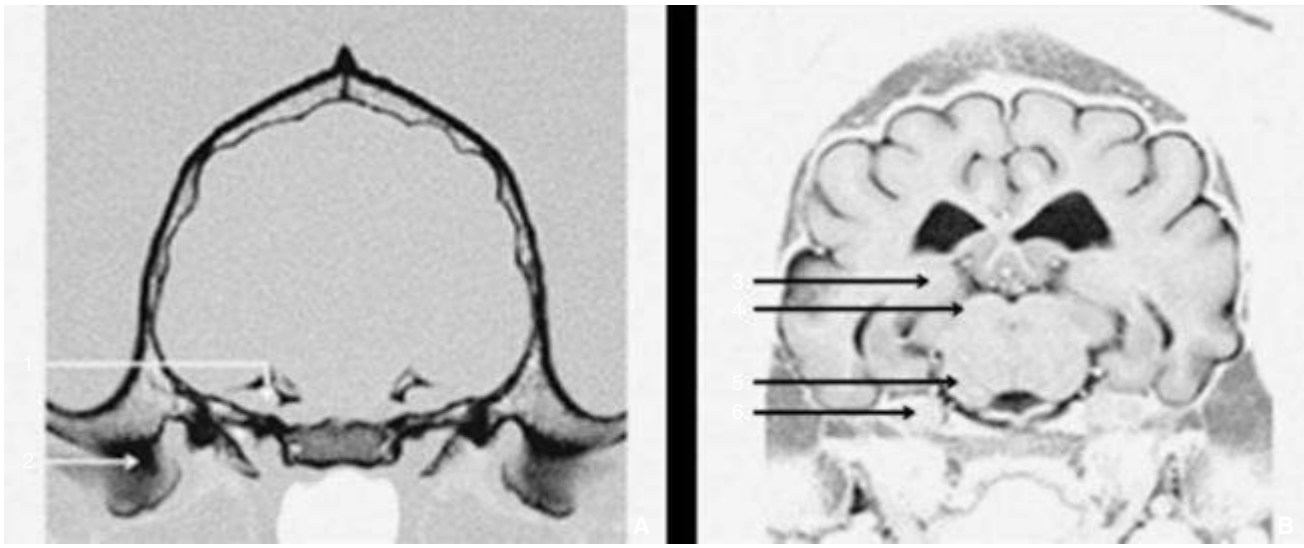


Figure 36.13 Transverse computed tomography (**A**) and T2-weighted magnetic resonance (**B**) images at the level of the rostral end of the trigeminal canal. 1, canal for CN V; 2, retroarticular process of the temporal bone; 3, lateral geniculate nucleus; 4, rostral colliculus; 5, crus cerebri; 6, CN V within canal. (*Source*: Reproduced with permission from Parry & Volk, 2011.)

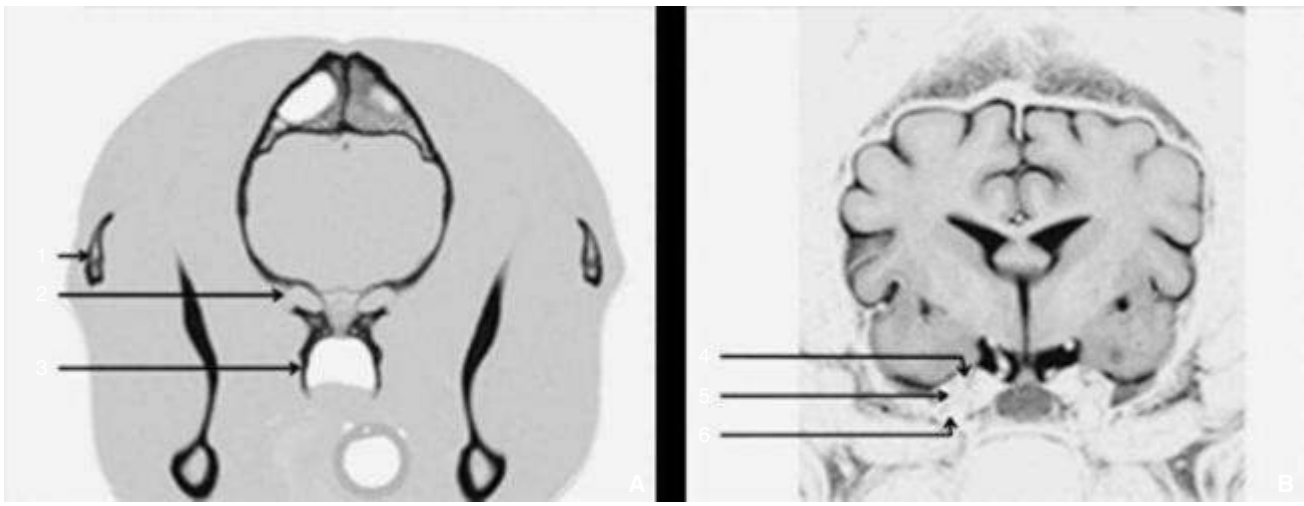


Figure 36.14 Transverse computed tomography (**A**) and T2-weighted magnetic resonance (**B**) images at the level of the orbital fissure. 1, zygomatic arch; 2, orbital fissure; 3, hamulus of the pterygoid; 4, CN III, IV, VI; 5, ophthalmic branch of CN V in orbital fissure; 6, maxillary branch of CN V just rostral to the rostral alar foramen. (*Source*: Reproduced with permission from Parry & Volk, 2011.)

In patients without anisocoria, it is important to observe pupil size carefully under photopic and scotopic conditions. As with anisocoria, however, this observation should be noted and only interpreted in conjunction with results of patient history, PLR, and vision testing. For example, the observation of bilaterally symmetric mydriasis under photopic conditions and with history and behavior consistent with not being blind may be misleading if the patient was recently pharmacologically dilated prior to examination. To gain an appreciation why it is important to not consider anisocoria and pupil size in isolation of history, PLR, and vision testing, it is important to discuss the neurologic control of pupil function.

In our common domesticated mammalian species, two groups of antagonistic muscles within the iris control pupil size, shape, and reaction to light. The dilator muscle consists of smooth muscle fibers distributed radially throughout the iris. The smooth iris sphincter muscle forms a ring around the pupillary margin. It has been shown that the iris sphincter and dilator muscles receive double reciprocal innervation by both the sympathetic and the parasympathetic systems (Fig. 36.18) (Yoshitomi & Ito, 1986). This is important

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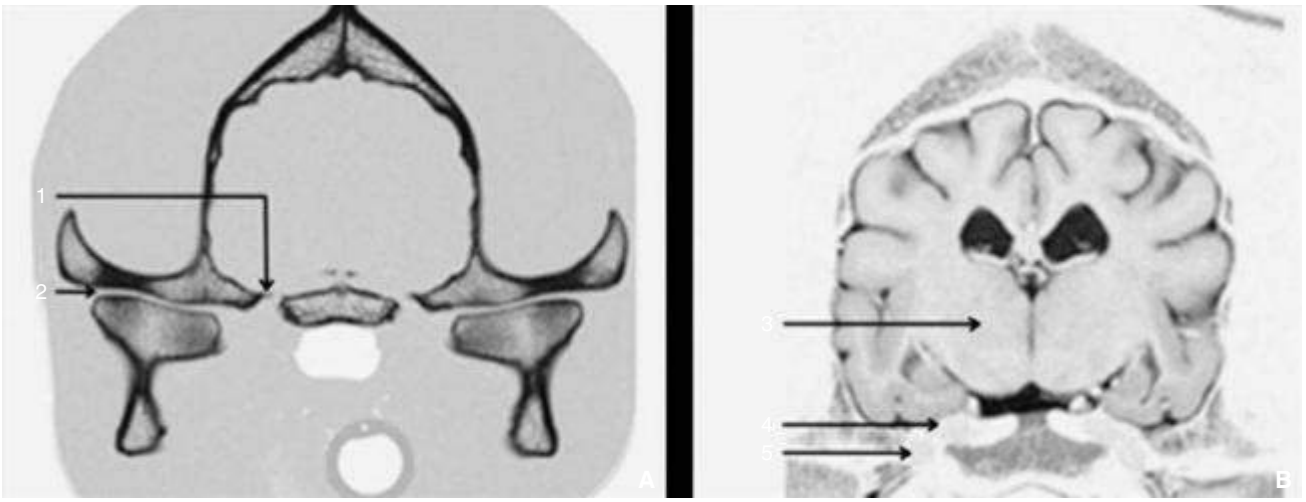


Figure 36.15 Transverse computed tomography (**A**) and T2-weighted magnetic resonance (**B**) images at the level of the oval foramen. Note the mandibular branch of the trigeminal (V) nerve within the foramen. 1, oval foramen; 2, temporomandibular joint; 3, thalamus; 4, ophthalmic and maxillary branches of CN V; 5, mandibular branch of CN V descending through the oval foramen. (*Source*: Reproduced with permission from Parry & Volk, 2011.)

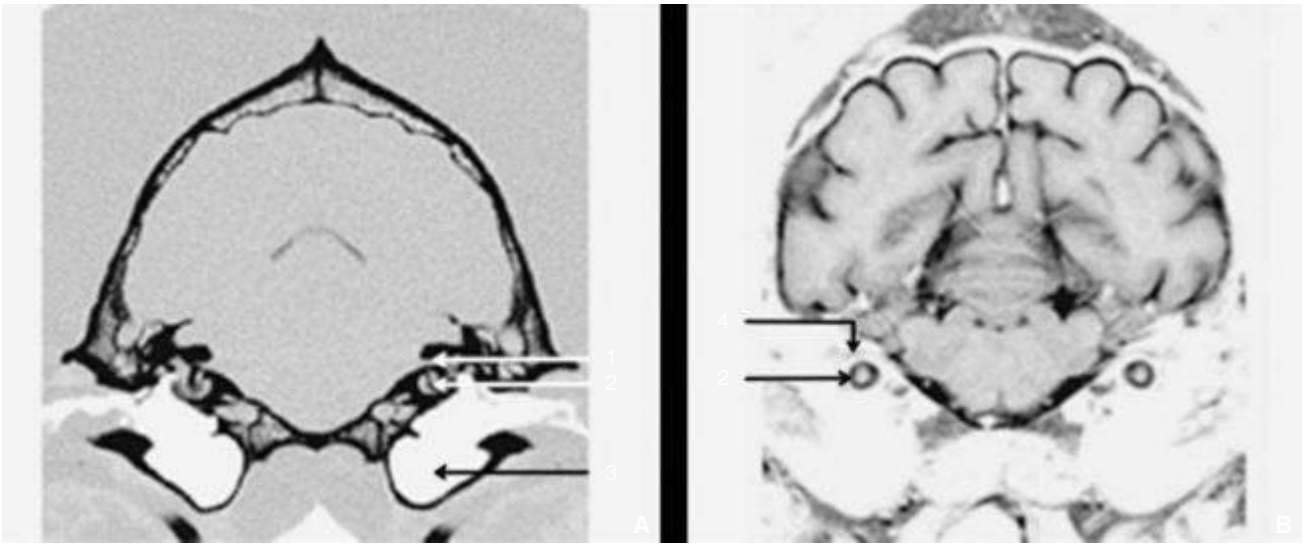


Figure 36.16 Transverse computed tomography (**A**) and T2-weighted magnetic resonance (**B**) images at the level of the facial canal. 1, facial canal; 2, cochlea; 3, tympanic cavity; 4, CN VII. (*Source*: Reproduced with permission from Parry & Volk, 2011.)

biologically because it ensures that an accurate and appropriate amount of pupillary dilation or constriction can occur rapidly depending on the environmental circumstance (e.g., changing light conditions, need to escape from predators, etc.). Specifically, it has been shown that cholinergic (parasympathetic) excitatory nerves causing contraction of the iridal sphincter work together with cholinergic inhibitory nerves to cause relaxation of the counteracting dilator muscle (Narita & Watanabe, 1981; Yoshitomi & Ito, 1986). These reciprocal parasympathetic actions result in pupillary constriction. Mydriasis is caused by direct adrenergic (sympathetic) excitatory input to the iris dilator muscle, causing it to contract. At the same time, an adrenergic inhibitory input further relaxes the iris sphincter muscle. The cholinergic (parasympathetic) inhibitory effect on the dilator muscle has been shown in a variety of species including dogs, cats, rats, cattle, and humans (Ehinger et al., 1968; Narita & Watanabe, 1981; Schaeppi & Koella, 1964; Yoshitomi & Ito, 1986). Adrenergic (sympathetic) inhibition of the sphincter muscle has been shown in the canine and bovine iris (Tachado et al., 1989; Yoshitomi & Ito, 1986), although further research is required to decipher the exact role of the

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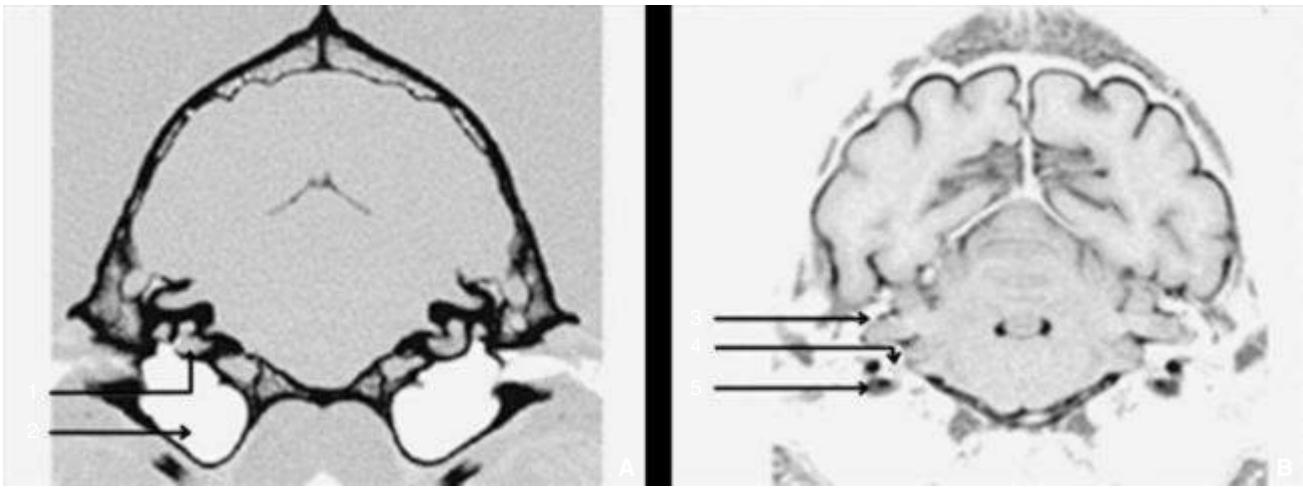


Figure 36.17 Transverse computed tomography (**A**) and T2-weighted magnetic resonance (**B**) images at the level of the internal acoustic meatus. Note the T2-weighted hyperintense perilymph within the inner ear. 1, vestibular component of the inner ear; 2, tympanic cavity; 3, cerebellar parafloccul us; 4, CN VIII; 5, endolymph and perilymph in the vestibular part of the inner ear. (*Source*: Reproduced with permission from Parry & Volk, 2011.)

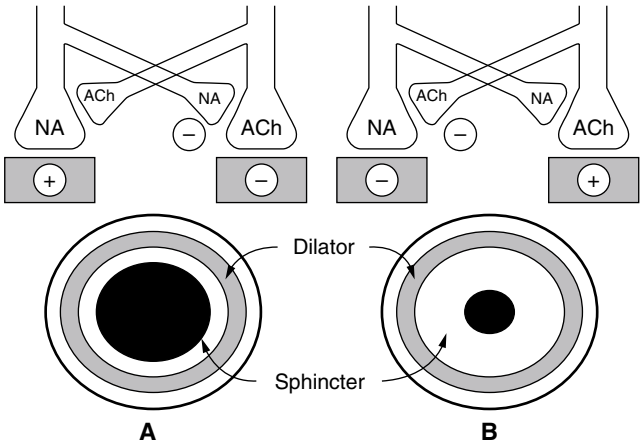


Figure 36.18 Double reciprocal innervation of the intraocular muscles. The iris sphincter and dilator muscles receive functional, double reciprocal innervation by both cholinergic and adrenergic systems. Stimulation of one of the iris muscles is accompanied by a reciprocal inhibition in its antagonist. **A.** Mydriasis consists of direct adrenergic excitatory input to the iris dilator muscle, causing it to contract. At the same time, the cholinergic output to the sphincter is inhibited. **B.** Cholinergic excitation to the sphincter causes it to contract, but at the same time, cholinergic inhibition nerves to the dilator cause it to relax, enhancing miosis. (*Source*: From Scagliotti, Veterinary Ophthalmology 3rd edition, 1999.)

various adrenergic receptor subtypes in this response. For a comprehensive comparative description of the autonomic control of the eye see McDougal & Gamlin (2015) and Neuhuber & Schrodl (2011).

With respect to sympathetic innervation of the iris muscle, the reader is reminded of the thoracolumbar distribution of the SPNs. As such, SPNs, important in pupillary constriction, are located in the intermediolateral gray matter of the upper thoracic spinal cord segments (up to approximately the third thoracic spinal cord segment) (de Lahunta et al., 2015e; Neuhuber & Schrodl, 2011; Strack & Loewy, 1990). Sympathetic preganglionic neurons exit the spinal canal with the ventral spinal nerve roots. Prior to the spinal nerve branching, the SPNs join with the thoracic sympathetic trunk (de Lahunta et al., 2015e). The sympathetic trunk ascends through the thorax adjacent to the vertebral bodies and courses cranially to the cranial cervical ganglion as a component of the vagosympathetic trunk (located within the carotid sheath). The cranial cervical ganglion is located ventromedial to the tympanic bulla (de Lahunta et al., 2015e). The postganglionic sympathetic fibers arising from the cranial cervical ganglion cross the middle ear cavity, enter the cavernous sinus, and eventually join the internal carotid artery or the ophthalmic branch of the trigeminal nerve as they enter the orbit (de Lahunta et al., 2015e). Together with fibers of the ophthalmic nerve (branch of the CN V [trigeminal nerve]), they course rostrally in the periorbita as the nasociliary nerve and enter the globe via the long ciliary nerve (Christensen, 1936). Therefore, the long ciliary nerve provides both sympathetic efferent fibers and somatosensory afferent fibers (Christensen, 1936). The pupillary sympathetic fibers run in the suprachoroidal space to the ciliary body, iris dilator muscle, and iris sphincter muscle (keep in mind reciprocal iris innervation). Sympathetic fibers also innervate the smooth muscles of the periorbita, Müller's muscles of the upper and lower eyelids, and the dilator muscle of the iris, and provide inhibitory input to the antagonistic sphincter. Normal sympathetic tone in these

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smooth muscles keeps the globe slightly protruded, the palpebral fissure opened, the nictitating membrane retracted, and the pupil partially dilated. Increased sympathetic tone is caused by emotional responses such as fear, excitement, anger, and pain and these emotions are regulated by the hypothalamus. Given this, and recognizing the importance of the hypothalamus in the "fight or flight" response and that neurons located in a region of the hypothalamus, known as the paraventricular nucleus, make contact with SPNs in the thoracolumbar spinal cord (Ranson et al., 1998), damage to this pathway can ultimately affect sympathetic output and may manifest as first-order Horner's syndrome (see Horner's syndrome).

Having just considered the sympathetic innervation of the eye, the following discussion pertains to the parasympathetic innervation of the iris. Autonomic preganglionic nerve fibers for controlling pupillary constriction originate in the parasympathetic nucleus of CN III (oculomotor nerve). This nucleus is also known as the Edinger–Westphal nucleus (see Table 36.1). The parasympathetic nucleus of CN III is located at the most rostral part of the rostral colliculus of the tectum within the central gray substance, next to the midline. Axons from this nucleus course ventrally with the somatic efferent axons of CN III and leave the midbrain medial to the crus cerebri. The crus cerebri is a large ventrally visible band of fibers at the level of the midbrain. The preganglionic parasympathetic efferent fibers are located superficially on the medial side of the oculomotor nerve (Christensen, 1936), where they are susceptible to injuries caused by compression of the nerve from midbrain swelling or displacement. These parasympathetic fibers enter the orbit as part of CN III (oculomotor nerve) and synapse in the ciliary ganglion (de Lahunta et al., 2015e). The ciliary ganglion is a collection of postganglionic parasympathetic neuronal cell bodies located lateral to the optic nerve. Axons originating from neurons in the ciliary ganglion form the short ciliary nerve (de Lahunta et al., 2015e). The parasympathetic component of the short ciliary nerve innervates the iridal sphincter muscle (Butler & Hodos, 2005) and, because of the presence of dual reciprocal innervation, the iris dilator muscle. As the short ciliary nerve enters the globe, it receives somatosensory contributions from the first division of the nasociliary nerve (a branch of the ophthalmic portion of the trigeminal nerve) (Dakrory, 2011).

Interestingly, there exists many differences among various species of animals with regard to the ciliary ganglion and the ciliary nerves arising from it (for review see Dakrory, 2011). Specifically, two short ciliary nerves arise from the ciliary ganglion in the cat (Christensen, 1936; Dakrory, 2011). The lateral one is called the malar nerve; the medial one is called the nasal nerve. The malar nerve innervates the lateral half of the iridal sphincter muscle, and the nasal nerve innervates the medial half of the sphincter. Meanwhile, the dog has five to eight short ciliary nerves (as cited by Scagliotti, 1999). Therefore, parasympathetic denervation in the dog will cause pupillary dilation, whereas in the cat, lesions to either the nasal or the malar short ciliary nerves will result in sphincter hemiplegia and a D-shaped or reversed-D-shaped pupil, respectively.

The sensory innervation of the iris is particularly dense. A fine plexus courses along the blood vessels and among the muscle fibers. This plexus is made up of the sensory fibers of the long ciliary nerve (a branch of the ophthalmic nerve, i.e., CN V) (Neuhuber & Schrodl, 2011). Additional unmyelinated filaments occur throughout the stroma, from which branches arise to supply the anterior epithelial layer. No fibers have been traced in the posterior pigmented epithelium (Neuhuber & Schrodl, 2011).

Reflex and Response Testing

Prior to our discussion of reflex and response testing in neuro-ophthalmology, it is likely important to provide a definition of reflex and how this differs from other stimulus-responses. A reflex is an almost instantaneous, transient, predictable, and unconscious reaction to a given stimulus. A reflex follows a typical reflex arc characterized by some sensory receptors, an afferent neuron, one or more interneurons, and an efferent neuron. Reflexes, unlike responses, are not learned and do not require input from "higher centers" in the brain.

Pupillary Light Reflex

The PLR is a reflex where after the retina is stimulated by light a resultant constriction of the pupil ipsilateral (direct PLR) and contralateral (indirect/consensual PLR) to the stimulus results. With regard to the clinical annotation used to describing the consensual PLR, there appears to be a lack of consensus amongst veterinary ophthalmologists (Stonex et al., 2018). This has resulted in a call for consistent annotation when describing the consensual PLR. It has been suggested that the following annotation be adopted for reporting the direct and indirect PLRs (Stonex et al., 2018):

Right: Direct -/Consensual (Indirect) + (L → R)
Left: Direct +/Consensual (Indirect) - (R → L)

Nevertheless, the PLR is present as early as when the eyes are open after birth (10–16 days postnatally in puppies, 5–14 days postnatally in kittens), albeit PLRs may be initially sluggish and may not react similarly to the adult until maturation of the retina is complete (28 days postnatally in the puppy) (Lavely, 2006). The PLR is present immediately after birth in foals (Adams & Mayhew, 1984).

The afferent pathway of the PLR runs through the CN II (optic nerve) to the optic chiasm to synapse bilaterally on neurons located in the pretectal nuclei (PTN) (Hultborn

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et al., 1978). These nuclei are located in the transition zone between the diencephalon and the midbrain. Axons from each PTN relay to both the left and the right parasympathetic nuclei of CN III (oculomotor nerve), although the majority of axons cross over and synapse in the contralateral parasympathetic nucleus (Kozicz et al., 2011). The parasympathetic nucleus of CN III is located in the tegmentum of the midbrain (Fig. 36.19). Because neurons in each PTN send projections to the parasympathetic nuclei bilaterally, both the right and the left pupils will constrict in response to light stimulation of either eye (Fig. 36.19). Since the afferent PLR pathway contains two levels of fiber crossings, first at the optic chiasm and later after exiting the PTN, in most species the direct PLR is stronger than the indirect one. More precisely, the direct PLR is stronger in those species that have more than 50% decussation at the optic chiasm because it is assumed that the same percentage of fibers that cross over at the optic chiasm cross again between the PTN and the parasympathetic nucleus at the tegmentum (Lowenstein et al., 1953). Following this reasoning, in humans, where the decussation rate is 50%, the direct and consensual PLRs are of equal amplitude. In species such as pigeons, in which all the optic nerve fibers cross over, there has been thought that there is no consensual PLR (Gamlin et al., 1984). However,

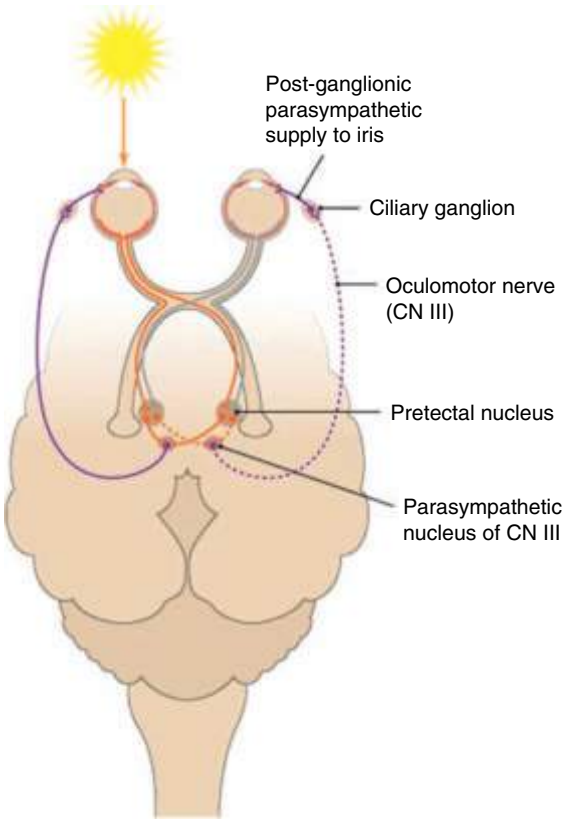


Figure 36.19 The neuroanatomic pathway for the pupillary light reflex. (*Source*: Modified from Platt & Olby, BSAVA Manual of Canine and Feline Neurology, 2013, Wiley.)

in some avian species, a thin interorbital septum separating the two eyes may allow light shone into one eye to pass through and stimulate the contralateral retina, resulting in a pseudoindirect PLR (Levine, 1955). Importantly, however, a true consensual PLR has been shown to exist in White Leghorn chicks (Li & Howland, 1999). In this study, chicks underwent unilateral complete optic nerve transection followed by examination of the direct and consensual PLRs for each eye. It was shown that chicks had a negative direct PLR and positive consensual PLR in the eye having had the transection thereby indicating that, in the chick, the consensual PLR truly exists.

Swinging Flashlight Test

The swinging flashlight test is performed by moving a focal light source from the tested eye to the opposite eye to check the direct and indirect light reflexes. In a clinically normal animal, the pupil that is not directly stimulated will partially constrict (caused by the consensual reflex) and will then constrict further when it is directly stimulated by the swinging flashlight. If the pupil dilates during direct light stimulation instead of performing the expected constriction, the swinging flashlight test is said to be positive for the eye with the dilating pupil. A positive swinging flashlight test is strongly suggestive for unilateral retinal disease or unilateral prechiasmal optic nerve disease (or both) (Levatin, 1959). Such a lesion does not prevent the constriction resulting from the indirect PLR when the unaffected eye is stimulated. However, when the flashlight is swung to the affected eye, the loss of the indirect stimulation (combined with lack of direct stimulation) causes mydriasis. Therefore, this test is used to differentiate lesions at these locations from other neurological causes of anisocoria. A positive swinging flashlight test is indicative of what is termed a relative afferent pupillary defect in human medicine. Importantly, however, and although rare, postchiasmal lesions in humans can result in a positive swinging flashlight test in the eye contralateral to the lesion (Chen et al., 2004; Kawasaki et al., 2010). This finding has been explained by the unequal decussation of axons at the optic chiasm that has been observed in humans (i.e., 53% crossed, 47% uncrossed fibers) (Chen et al., 2004; Kawasaki et al., 2010). In species of animals dealt with in veterinary medicine, decussation of fibers is much greater than that of humans; one would expect to see positive swinging flashlight tests in patients with contralateral postchiasmal lesions, as has been described in humans.

The swinging flashlight test is also considered to be positive if, as the light shifts from the normal to the abnormal eye, the direct stimulus is no longer sufficient to maintain the previously evoked degree of pupillary constriction; therefore, both pupils dilate while maintaining the relative anisocoria usually present in domestic animals with optic nerve disease (Scagliotti, 1999). There are two more important tests of pupillary reaction to light.

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A positive swinging flashlight test should be followed by a cover–uncover test performed in normal room light where the alternation of light stimulus is done by using the examiner's hand to cover and uncover the examined eye. This test is performed to eliminate the influence of scatter illumination.

Dazzle Reflex (Photic Blink Reflex)

Another reflex used to evaluate the integrity of a portion of the visual pathway is the dazzle reflex. This reflex is characterized by bilateral, partial eyelid blink in response to a very bright light shone into each eye separately (Burke & Hackley, 1997; Marquis, 1936; Plainis et al., 2006). Closure of the eye contralateral to the eye being stimulated is less obvious, and possibly absent, when compared with the ipsilateral eye (Sherman et al., 1981). Importantly, animals having facial nerve paresis or paralysis may have a reduced or absent dazzle reflex on the ipsilateral side to the facial nerve lesion. The dazzle reflex is present as early as 1–2 days postnatally in puppies and kittens (Lavely, 2006).

Although the anatomical path of the dazzle reflex has not been elucidated in animals, evidence from the human literature suggests that it is present when the optic nerve is intact to the level of the midbrain, and particularly to reflex centers in the rostral colliculi and/or the supraoptic nuclei of the hypothalamus. The reflex also requires association fibers between these nuclei to the facial nuclei in the medulla, as well as intact facial nerves. Results of studies in animals have consistently shown that decerebrate animals blink in response to a bright light (Marquis, 1936; Schaltenbrand, 1931). Other studies, conducted in monkeys, after total ablation of the striate cortex, have shown that the dazzle reflex is absent when an ordinary flashlight is used as a stimulus, but an intense light can cause a brisk and highly reliable reflex (Klover, 1942). Likewise in cats, the reflex is maintained after striate cortex ablation (Schaltenbrand, 1931). A reflex pathway, based upon known neuroanatomical connections within the brainstem, has been proposed (Fig. 36.20).

The dazzle reflex is particularly useful when the pupils cannot be observed to evaluate the PLR (e.g., in cases of severe corneal edema or hyphema) or in patients with cataracts where the retina cannot be visualized directly. However, because the exact anatomical pathway of this reflex has not been described, this test should not be used as the only tool for localizing subcortical lesions in the visual pathway.

Menace Response

The menace response is performed by making a threatening movement toward the eye being evaluated, remembering to not touch the patient or cause stimulation of the cornea or eyelashes. An appropriate response is characterized by the patient blinking, retracting their globe, and/or turning their head away from the menacing stimulus. As opposed to a simple reflex, the menace response is learned, as is suggested

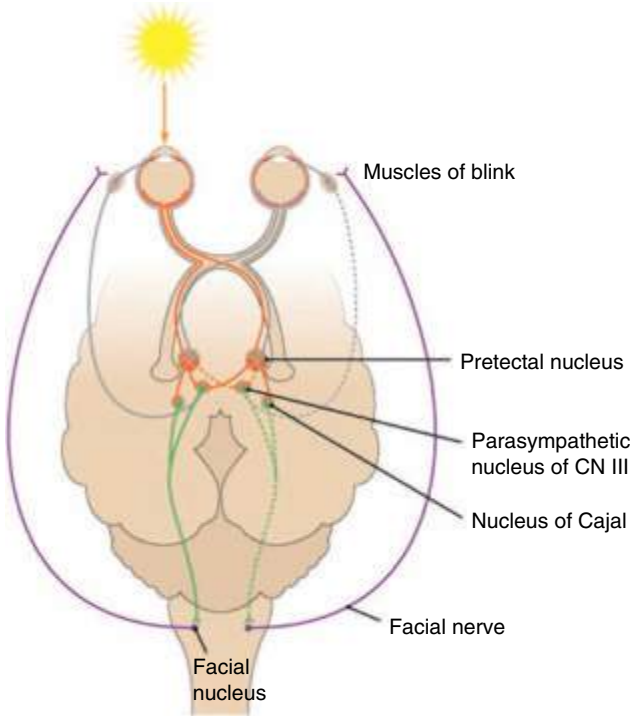


Figure 36.20 The postulated pathway of the dazzle reflex – a subcortical reflex blink associated with a bright light stimulus. (*Source*: Modified from Platt & Olby, BSAVA Manual of Canine and Feline Neurology, 2013, Wiley.)

by a recent study demonstrating that calves reared in isolation for prolonged periods of time take longer to develop a menace response compared with those that were raised in a group setting earlier postnatally (Raoofi et al., 2009). Additionally, this response takes longer to develop compared with a simple reflex like the PLR and may not be present for up to 4 weeks postnatally in puppies and kittens (Lavely, 2006), or 8 and 14 days postnatally in lambs and goat kids (Raoofi et al., 2011), respectively. The menace response is not complete until 2–3 weeks postnatally (Adams & Mayhew, 1984; Enzerink, 1998). In contrast, the PLR is present in precocial species such as foals, calves, lambs, and goat kids within the first 24 hours after birth (Adams & Mayhew, 1984; Enzerink, 1998; Raoofi et al., 2011), and is present upon eye opening in puppies and kittens (Lavely, 2006).

Prior to discussing the hypothesized neuroanatomic pathway of the menace response it is important to review briefly the central visual pathway. The afferent component of the central visual pathway consists of optic nerve axons projecting to the lateral geniculate nucleus (LGN) as the optic tract, after having decussated varying amounts (species dependent) at the optic chiasm. After having projected to neurons within the LGN, optic tract axons synapse on neurons within the LGN. In turn, LGN neurons project as the optic radiation to the visual cortex in the occipital lobe where an image is perceived. A more detailed description

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of this pathway is found in Chapter 4. From the visual cortex, the visual information is transmitted through communication fibers to different regions of the cortex and finally to the primary motor cortex, which initiates the efferent component of the menace response. As suggested earlier, the menace response involves cerebral cortical integration and interpretation and therefore is not a reflex. Rather, it is a cortical response that requires the entire peripheral and central visual pathways, as well as the visual cortex and the facial nucleus of CN VII, to be intact for the response to occur (Scagliotti, 1999).

In addition to the neuroanatomic structures required to elicit a positive menace response, the menace response requires functional integrity of additional neuroanatomical structures. In all domestic species, it has been observed that diffuse cerebellar cortical degenerative lesions cause bilateral absence of the menace response without any associated visual deficits or facial nerve dysfunction (de Lahunta et al., 2015h). Varying degrees of this deficit have been observed in horses, cattle, pigs, dogs, and cats with cerebellar cortical lesions (de Lahunta et al., 2015a). This implies that the pathway between the visual cortex and the facial nucleus must pass through the cerebellum.

Interestingly, there is a well-studied conditioned eyeblink response phenomenon that is used to study the role of various neuroanatomic structures in eyeblinking and also is used as a model of learning and memory in the neurosciences (Freeman & Steinmetz, 2011). Recently, with use of trans-synaptic tracing, using green fluorescent protein (GFP)-expressing pseudorabies virus injected into the mouse orbicularis oculi muscle, resulted in labeling of the ipsilateral facial nucleus, bilateral labeling of the red nuclei (with a contralateral predominance) in the midbrain, the interposed nucleus of the cerebellum and Purkinje cells within the cerebellar cortex (Sun & Clark, 2012). Given this, it is possible that the menace response uses the following pathway:

> Visual input via the central visual pathway to the contralateral visual cortex ➔ Projection fibers rostrally from the visual cortex to the motor cortex contralateral to the eye stimulated ➔ Projections from the motor cortex to the pontine nucleus with projections (mossy fibers) from the pontine nucleus projected to the cerebellar nuclei and the granule cell neurons within the cerebellar cortex ipsilateral to the side of visual stimulation (the cerebropontocerebellar pathway) ➔ Projections from the Purkinje neurons to the interposed nucleus of the cerebellum ➔ Projections from the interposed nucleus to the red nucleus contralateral to the source of visual stimulation ➔ Projections from the red nucleus contralateral to the source of visual stimulus to the facial nucleus on the side ipsilateral to the side of visual stimulation

Although this is only a postulated pathway, it may be that the menace response represents the conditioned eye blink response that is studied experimentally (Freeman & Steinmetz, 2011). The pathway proposed above may account for why unilateral cerebellar lesions cause a deficit of the menace response on the same side as the lesion in otherwise visual patients.

Palpebral Reflex

The palpebral reflex is elicited by touching the skin of the lateral and medial canthi of the eye, separately, and observing an appropriate response after each touch. An expected and appropriate response is a blink of the eyelids after a single touch. The afferent portion of this reflex is via the ophthalmic and maxillary branches of CN V (trigeminal nerve) for medial and lateral canthus stimulation, respectively. The efferent component of the reflex is via CN VII (facial nerve). The palpebral reflex is reportedly present as early as 2–4 days postnatally in the puppy, and 1–3 days postnatally in the kitten (Lavely, 2006). Palpebral reflexes are present immediately after birth in foals (Adams & Mayhew, 1984). In order to fully understand the afferent and efferent components of the palpebral reflex, and in order ultimately to be better able to neuroanatomically localize where a disease process is occurring, it is worth considering the neuroanatomy of the afferent and efferent components of this reflex.

CN V (trigeminal nerve) is the main sensory nerve of the face. Its ophthalmic and maxillary divisions are those that provide sensory innervation to the eye and its accessory organs. The ophthalmic nerve (i.e., the ophthalmic branch of the trigeminal nerve) divides into three branches: the frontal, lacrimal, and nasociliary nerves (de Lahunta et al., 2015c). The lacrimal nerve innervates the lateral part of the orbit and gives branches to the lacrimal gland, to the upper eyelid, and to the skin in the lateral canthus region of the eye (König & Liebich, 2007). The frontal nerve innervates the upper eyelid, the forehead, and the mucosa of the frontal sinus (König & Liebich, 2007). The nasociliary branch gives rise to a sensory root, which passes through the ciliary ganglion to contribute to the short ciliary nerves (König & Liebich, 2007). The nasociliary nerve, located at the medial side of the optic nerve, gives rise to two to three branches that comprise the long ciliary nerves. The latter penetrate the posterior aspect of the eye to innervate the cornea and iris and also contain somatosensory innervation to the ciliary body, trabecular meshwork, and sclera (König & Liebich, 2007). Another division of the nasociliary nerve is the infratrochlear nerve, which provides sensory innervation to the skin and conjunctiva in the medial canthal region (as well as parts of the frontal sinus mucosa) (König & Liebich, 2007). In ruminants, the infratrochlear nerve is also the main nerve to supply the horn (Madekurozwa et al., 2000).

The largest branch of the trigeminal nerve is the maxillary nerve (König & Liebich, 2007). The maxillary nerve

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innervates the upper buccal cavity and nasopharynx (König & Liebich, 2007). The first branch of the maxillary nerve is the zygomatic nerve. The zygomatic nerve provides the afferent limb of the palpebral reflex resulting from stimulation of the skin at the lateral canthus of the eye (König & Liebich, 2007). Specifically, the zygomatic nerve is divided into the zygomaticofacial branch that innervates the skin and conjunctiva of the upper eyelid, and the zygomaticotemporal nerve branch that innervates the skin and the conjunctiva of the lower eyelid (Esteves, 2009).

The maxillary and ophthalmic branches of the trigeminal nerve have their cell bodies located within the trigeminal ganglion (König & Liebich, 2007). The trigeminal ganglion is situated in the canal of the trigeminal nerve within the petrous temporal bone (Table 36.1) (de Lahunta et al., 2015c). Axons from cells of the trigeminal ganglion enter the brainstem as the trigeminal nerve at the caudolateral aspect of the pons, just rostral to the origin of the facial and vestibulocochlear nerves (de Lahunta et al., 2015c). Synaptic connections are then made with various motor nuclei and the large sensory nucleus of the trigeminal nerve (de Lahunta et al., 2015c).

The sensory nucleus of the trigeminal nerve extends rostrally from the upper cervical part of the spinal cord, through the medulla, pons, and midbrain (de Lahunta et al., 2015c). The sensory trigeminal nucleus is subdivided into three continuous sensory nuclei: the mesencephalic nucleus of the trigeminal nerve, the nucleus of the spinal tract of the trigeminal nerve, and the principal (pontine) sensory nucleus of the trigeminal nerve (Cody et al., 1972; de Lahunta et al., 2015c). Axons of the neuronal cell bodies in the principle sensory nucleus project to other cranial nerve nuclei (including nuclei of CNs III, IV, VI, and VII) in order to complete reflex arcs needed for protection of the eye. Therefore, afferent impulse from the maxillary or ophthalmic branches of the trigeminal nerve enter the spinal tract of the trigeminal nerve and subsequently synapse on neurons of the principle sensory nucleus of the trigeminal nerve. The second order neuron within the principle sensory nucleus connects to neurons within the motor nucleus of CN VII that, in turn, sends efferent projections to the orbicularis oculi to cause a blink. Additionally, in the case of the corneal reflex (see later) and reflex tearing (see Schirmer tear testing), neurons in the trigeminal nucleus receive sensory stimulation from the cornea through cells in the trigeminal ganglion and produce a reflex response by stimulating cells in the facial nerve nucleus as is done for the palpebral reflex, but also, sensory stimulation of the cornea leads to an increase in tear production through activation of neurons within the parasympathetic nucleus of CN VII (parasympathetic facial nucleus).

The neuronal cells bodies for the somatic efferent component of the palpebral reflex are located within the motor nucleus of CN VII (facial nucleus) (de Lahunta et al., 2015d). The CN VII nucleus is located within the medulla oblongata (de Lahunta et al., 2015d). These fibers innervate the muscles of facial expression, including those responsible for eyelid closure. The facial nerve exits the brainstem together with CN VIII (vestibulocochlear nerve) at the lateral extremity of the trapezoid body (an important pathway involved in hearing, located at the level of the rostral medulla oblongata), and the two nerves run within a common meningeal sheath to the internal acoustic meatus of the petrous temporal bone (de Lahunta et al., 2015d). Here CN VII and VIII separate and the CN VII enters the facial canal within the temporal bone and exits through the stylomastoid foramen (de Lahunta et al., 2015d). The main trunk turns around the mandible and branches into the dorsal and ventral buccal branches, and continues as the auriculopalpebral nerve (König & Liebich, 2007). The auriculopalpebral nerve crosses the zygomatic arch, heading for the space between the upper eyelid and the ear. There, the auriculopalpebral nerve divides into two branches: the rostral auricular and zygomatic branches. The zygomatic branch ultimately innervates the orbicularis oculi, retractor anguli oculi lateralis, and retractor anguli oculi medialis muscles, which are responsible for the blinking response (de Lahunta et al., 2015d; König & Liebich, 2007).

Corneal Reflex

The corneal reflex is elicited by touching the surface of the cornea with a relatively noninjurious object (e.g., cotton-tipped applicator or fiber from a Cochet–Bonnet aesthesiometer) and then observing an expected and appropriate eyelid blink. As with the palpebral reflex, the afferent arm of this reflex is mediated via CN V (trigeminal), whereas the efferent arm is mediated by the CN VII (facial). The cornea is highly sensitive to touch and painful stimuli. Branches of the long ciliary nerves enter the corneal stroma in a radial manner from the sclera, episclera, and conjunctiva. Once within the stroma, all myelinated fibers lose their myelin sheaths and form an unmyelinated sensory nerve plexus. This plexus provides the cornea with the densest three-dimensional network of sensory nerves in the body. In fact, it has been estimated that the nerve density in the cornea is three to four times higher than that of the finger pad (Rozsa & Beuerman, 1982).

Although not routinely evaluated in clinical practice, corneal touch threshold (CTT) is measured by determining the minimum amount of force required to stimulate a consistent corneal blink reflex. Humans have the highest number of corneal stromal nerve terminals and therefore possess the greatest corneal sensitivity and lowest CTT. They are followed, in order of decreasing sensitivity, by the cat, rabbit, and dog (Barrett, 1991; Blocker & van der Woerdt, 2001; Millodot & Larson, 1969; Millodot et al., 1978). In the dog, it has been shown that the central cornea is the most sensitive region, followed by the nasal and temporal cornea (Barrett,

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1991). This pattern also exists in humans (Millodot, et al. 1978). Those regions of the cornea that are less exposed to potential injury (i.e., the dorsal and ventral corneal regions near the lid margins) are the least sensitive. In diseases such as diabetes mellitus, it has been shown that CTT is greater in diabetic compared with non-diabetic patients (Cullen et al., 2005; Good et al., 2003). This implies that diabetes mellitus likely induces a diabetic neuropathy involving the long ciliary nerve of the cornea and these patients may be more prone to corneal injury.

Vestibulo-Ocular Reflex and Physiologic Nystagmus

The vestibulo-ocular reflex is a reflex that permits stabilization of an image on the retina during movement of the head. Without an appropriate vestibulo-ocular reflex, images would appear blurred. For example, attempt to read this sentence while turning your head. Now, compare your ability to read this sentence, instead, by moving the book and keeping your head stationary. It becomes readily apparent that one is able to read this sentence when the head moves and the book remains stationary. This is because of the vestibulo-ocular reflex. The vestibulo-ocular reflex is present for rotational or translational movement of the head and assists in stabilizing images on the retina (as exemplified in the example). This reflex results in a rapidly adjusting movement of the eyes in a direction opposite that of the direction of the head movement. For example, for the vestibulo-ocular reflex, if one moves their head in the counterclockwise direction, the person's eyes move at an appropriate speed in the clockwise direction, that is, until the physical limitations of the eye movement have been met and a compensatory, relatively fast, "resetting" of the eye position occurs (Curthoys, 2002). If this resetting of the eye position does not occur, the eyes would be driven to an extreme position in the orbit; also, ocular movement is physically limited by the extraocular muscles themselves (Curthoys, 2002). It is this alternation between slow and fast phases that comprises the normal physiologic nystagmus that is evaluated clinically in veterinary medicine. Like the example mentioned above, the vestibulo-ocular reflex is evaluated by inducing a physiologic nystagmus by rotating the patient's head in a clockwise and counterclockwise direction. The expected and normal response is that the patient will slowly move its eyes, relative to the orbit, in a position opposite that of the head being turned. A fast, compensatory, movement of the eyes will occur toward the direction of the head rotation. Similar eye movements occur when the patient's head is rotated dorsally or ventrally, with the fast phase of eye movements being in the direction of head movement. Importantly, it should be noted that the vestibulo-ocular reflex occurs independent of a patient having vision, although visual experience appears necessary for the development of a vestibulo-ocular reflex (Sherman & Keller, 1986). In fact, the vestibulo-ocular reflex is purely driven by the vestibular system. This is evidenced by patients having bilateral disease processes affecting their vestibular system. These patients will lack a vestibulo-ocular reflex, and consequently, a nystagmus cannot be induced (e.g., Webb, et al., 2019; Wilkes & Palmer, 1992). It is worth briefly discussing the basic neuroanatomical pathway of the vestibulo-ocular reflex. In so doing, it will hopefully become more apparent as to why spontaneous nystagmus results in patients with unilateral disease processes affecting their vestibular system.

The vestibular system is that portion of the nervous system involved in relaying information about the linear and angular acceleration of the head (Goldberg et al., 2013). The vestibular system is found within the peripheral and central nervous systems (de Lahunta et al., 2015f; Goldberg et al., 2013). It is because of this that we refer, clinically, to diseases of the vestibular system as being either peripheral or central in nature.

The peripheral vestibular system is made up of the vestibular labyrinth of the inner ear, the corresponding vestibular ganglion, and the vestibular portion of CN VIII (vestibulocochlear nerve) (de Lahunta et al., 2015f). The central components of the vestibular system are made up of the vestibular nuclei that are located within the medulla oblongata, and the flocculonodular lobe of the cerebellum (i.e., vestibulocerebellum) (de Lahunta et al., 2015f). Information traveling to and from the vestibulocerebellum does so via the caudal cerebellar peduncle (de Lahunta et al., 2015f).

As with all reflexes, there has to be a stimulus that is initially transduced into electrical impulses that can be relayed throughout the reflex pathway. Sensory transduction occurs within the peripheral vestibular system, namely the vestibular membranous labyrinth, which is located within the petrous temporal bone in close association with the hearing apparatus (i.e., the cochlea) (Goldberg et al., 2013). The membranous labyrinth is epithelial lined. Fluid within the membranous labyrinth is known as endolymph (Goldberg et al., 2013). Endolymph is high in potassium and low in sodium and calcium, and it is the inward movement of potassium that is responsible for depolarization of hair cells found within the vestibular labyrinth, similar to that seen in the cochlear hair cells (Goldberg et al., 2013; Hibino & Kurachi, 2006). The bony component that forms adjacent to the membranous labyrinth is known as the bony labyrinth. Between the membranous and bony labyrinths, there is fluid known as perilymph. Perilymph is similar in its composition to CSF and, as such, it does not intermix with endolymph (Hibino & Kurachi, 2006). The vestibular labyrinth and cochlea are found bilaterally (i.e., right and left sides). The vestibular labyrinth is made up of the utricle, saccule, and three semicircular canals that are orthogonal to each other (de Lahunta et al., 2015f; Goldberg et al., 2013). The utricle and saccule are located within a bony region called the vestibule. The semicircular canals are found within the respectively named bony semicircular canals (de Lahunta et al., 2015f; Goldberg et al., 2013).

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Semicircular canals are known as the anterior vertical, posterior vertical, and horizontal canals (Goldberg et al., 2013). Located at the end of each semicircular canal is a dilatation known as the ampulla (Goldberg et al., 2013). Fluid cannot freely move throughout the entirety of a particular semicircular canal, however. Instead, each semicircular canal is bounded by a gelatinous structure known as the cupula (Goldberg et al., 2013). The cupula spans the diameter of the ampulla. A thickened epithelial region within the ampulla, known as the ampullary cristae, contains hair cells that extend into the cupula. The hair cells are oriented in a similar fashion within the cupula. Rotation of the head causes a mechanical opening or closing of ion channels as stereocilia move toward or away from a single kinocilium on the hair cell. This opening or closing is caused by shearing forces generated because of the inertia of the endolymph as the head accelerates or decelerates rotationally (Goldberg et al., 2013). Depolarization results in synaptic vesicle release and subsequent stimulation of the bipolar neurons of the vestibular ganglion (i.e., Scarpa's ganglion) (Goldberg et al., 2013). It is the axonal processes of these bipolar neurons that make up the vestibular portion of CN VIII (vestibulocochlear nerve). The vestibular ganglion is located within the petrous temporal bone of the skull (de Lahunta et al., 2015f).

As for detections in linear acceleration or deceleration, these are determined by the utricle and saccule (Goldberg et al., 2013). The macula is a region found within each of the utricles and saccules that contains a high abundance of hair cells. The hair bundle for each hair cell is embedded, apically, within a gelatinous mass known as the otolithic membrane. Within and on the surface of the otolithic membrane are calcium carbonate containing particles known as otoconia (Goldberg et al., 2013). It is the inertia of the otolithic membrane that causes subsequent movement of stereocilia toward or away from the kinocilium on the hair cell, thus resulting in mechanical opening or closing of the ion channels, respectively (Goldberg et al., 2013). Like the situation for the hair cells of the ampulla, opening of the ion channels results in an influx of potassium within the hair cell with subsequent depolarization of the cell membrane. Given the orientation of the maculae within the utricle and saccule, the saccule relays information pertaining to primarily vertical acceleration, whereas the utricle relays information predominantly concerned with horizontal acceleration (Goldberg et al., 2013). Like the situation described previously for the hair cells conveying information about rotational acceleration, the hair cells within the maculae make synaptic contact with primary afferent fibers of vestibular ganglion neurons (Goldberg et al., 2013).

Primary afferent neurons of the vestibular ganglion enter the cranial vault via the internal acoustic meatus (de Lahunta et al., 2015f). CN VIII (vestibulocochlear nerve) then travels along the lateral aspect of the rostral medulla oblongata at the cerebellomedullary angle. The cerebellomedullary angle is that region between the trapezoid body and the attachment of the caudal cerebellar peduncle (de Lahunta et al., 2015f). The vestibular axons enter the medulla oblongata of the brainstem at approximately the level of the caudal cerebellar peduncle. These primary afferent fibers synapse within the vestibular nuclei or within the cerebellum on neurons located within the fastigial nucleus or those located within the cortex of the flocculonodular lobe (de Lahunta et al., 2015f). Axons from vestibular nuclei make connections with the cerebellar fastigial nucleus and within the cortex of the flocculonodular lobe (de Lahunta et al., 2015f). Additionally, axons from the vestibular nuclei make excitatory or inhibitory connections with neurons located within the motor nuclei for CNs III, IV, and VI, among other neurons within the brainstem and spinal cord (de Lahunta et al., 2015f). It is these connections that are responsible for the vestibulo-ocular reflex (Fig. 36.21) (Straka & Dieringer, 2004). Please note that axons from neurons within the vestibular nuclei travel rostrally or caudally within a fiber tract known as the medial longitudinal fasciculus. Please also note that the presence of a vestibulo-ocular reflex and physiologic nystagmus require intact peripheral or central vestibular components, the medial longitudinal fasciculus, and the motor nuclei of CN III, IV, or VI.

The fast phase of physiologic nystagmus occurs at a time point when excitatory and inhibitory burst neurons located just rostral to the abducent nucleus (nucleus of CN VI) are activated. The fast phase movement is ended by bursting of "pause neurons" that are located just rostral and along the midline relative to the abducens nucleus – this ultimately inhibits firing of excitatory and inhibitory burst neurons (for detailed review see Curthoys, 2002).

Of further clinical importance is the pathophysiologic rationale for the direction of the nystagmus seen in pathologic conditions of the peripheral and central portions of the vestibular system. It should be apparent that at rest, and in the absence of head movement, the eyes remain stationary. This is because normally, there is tonic excitatory input onto the vestibular nuclei and as such, there is equal input onto motor neurons within CNs III, IV, and VI. In the instance of unilateral peripheral vestibular disease, it becomes apparent (after examining Fig. 36.21) that the fast phase of the nystagmus will be toward the side opposite that of the affected side. It is important to recognize that pathologic nystagmus may not be present in patients with subacute or chronic unilateral vestibular disease. This is because of the plasticity of the vestibular system to injury (for review see Dutia, 2010). In instances of vestibular compensation, however, a pathologic nystagmus can sometimes be elicited by placing the patient on their back or in some other position to cause "decompensation" of their vestibular system. We also mention that patients exhibiting bilateral vestibular disease will lack both a normal physiologic nystagmus and a pathologic nystagmus (Webb et al, 2019). Given the pathophysiologic mechanisms

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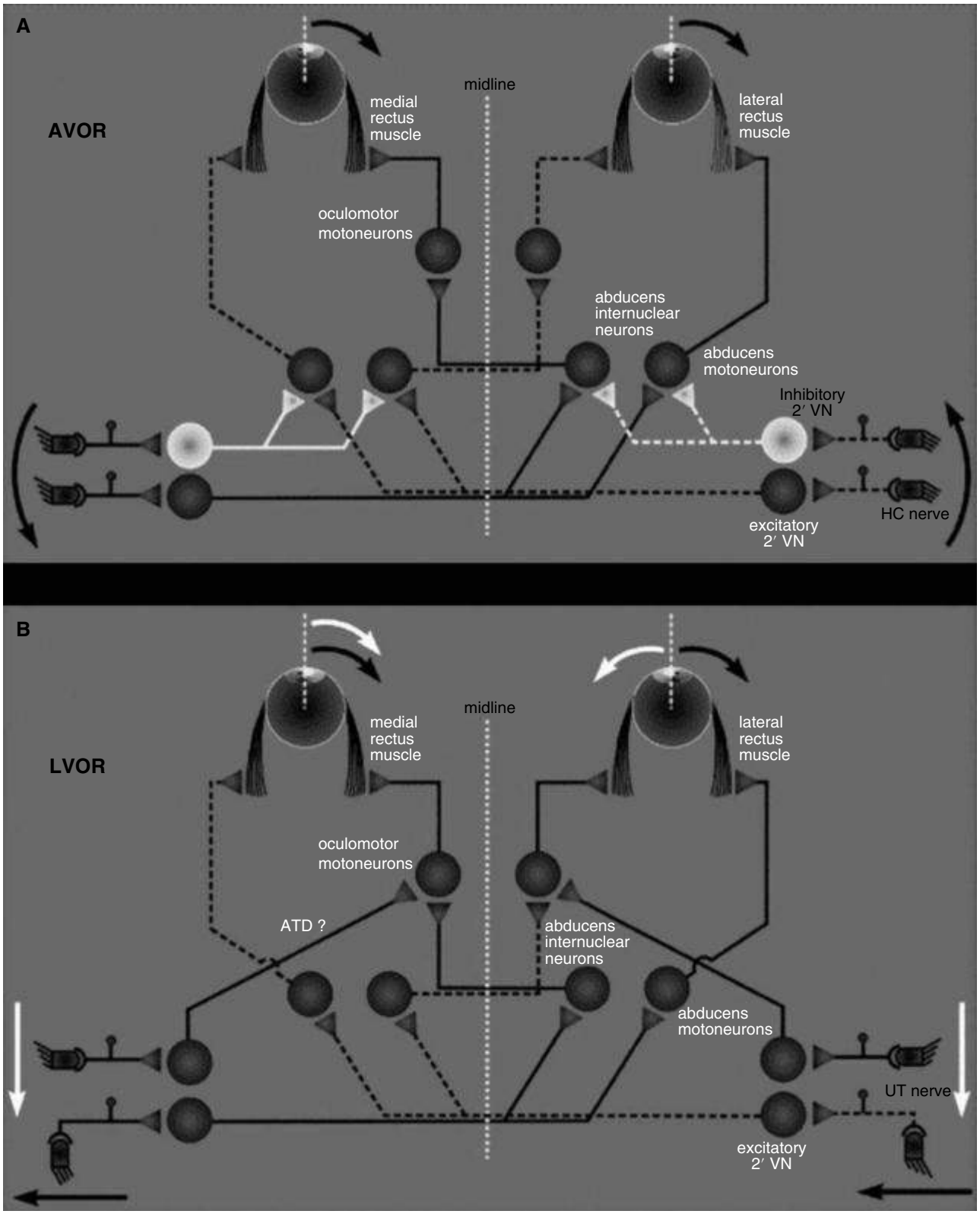


Figure 36.21 Comparison between the neural organizations of the horizontal angular and the horizontal linear vestibulo-ocular reflex. **A.** Counterclockwise head rotation increases the discharge rate in horizontal canal afferent and in second-order vestibular neurons on the left side, whereas the resting rates decrease in these neurons on the right side. Excitatory second-order vestibular neurons (2°VN) project across the midline of the brainstem and converge monosynaptically with uncrossed axons from inhibitory 2°VN upon abducens motoneurons and internuclear neurons. The latter contact monosynaptically medial rectus motoneurons in the contralateral oculomotor nucleus, whereas the former innervate the lateral rectus muscle. **B.** A push–pull organization as for the angular vestibulo-ocular reflex (AVOR) is not present in the linear vestibulo-ocular reflex (LVOR), because inhibitory 2°VN are not activated during linear oscillation. Transverse oscillation activates contralateral abducens motoneurons and internuclear neurons, whereas longitudinal oscillation is assumed to activate ipsilateral medial rectus motoneurons in the oculomotor nucleus directly via fibers in the ascending tract of Deiters (ATD). (*Source*: Reprinted with permission from Straka & Dieringer, 2004.)

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accounting for the absence of nystagmus in these patients, however, a pathologic nystagmus cannot be elicited by a change in these animals' posture.

Vision Testing

Prior to discussing clinical tests used for evaluating vision, we provide a brief discussion about anatomy and physiology of the visual pathway. For a more detailed discussion please see Chapters 2 and 4 (for comparative review of retinal ganglion cells, optic nerve, and optic chiasm see Brooks et al., 1999). See Figure 36.22 for the basic visual pathway.

As with any sensory modality, the ability to sense something is dependent firstly upon stimulating a receptor. In the case of vision, photons of light pass through the cornea, ocular humors, and lens, and finally activate an exquisite cascade of molecular events within the photoreceptors of the retina, ultimately resulting in conversion of transduction of light to electrical activity that can be transmitted to the brain. Once photoreceptor stimulation has occurred, retinal ganglion cells of the retina are stimulated and action potentials are carried by way of the retinal ganglion axons (CN II, optic nerve) to the LGN. The optic nerve is a tract of the CNS and originates in the embryonic optic vesicle and is surrounded by meninges, including a subarachnoid space. Remember that anything covered by meninges is considered a part of the CNS. In addition, the optic nerve contains neuroglial cells similar to those of the brain, and oligodendrocytes form the myelin for the axons of the optic nerve. However, there is marked species difference regarding the starting point of the myelin sheath, and this is observed ophthalmoscopically. In birds and some mammals, such as the rabbit, the axons are myelinated in the retina, forming visible medullary rays (Won et al., 2000). Meanwhile, myelination begins at the level of the optic disc in some species, such as the dog, but more caudally in other species, such as the cat, accounting for the difference in color and shape of the optic disc between these species.

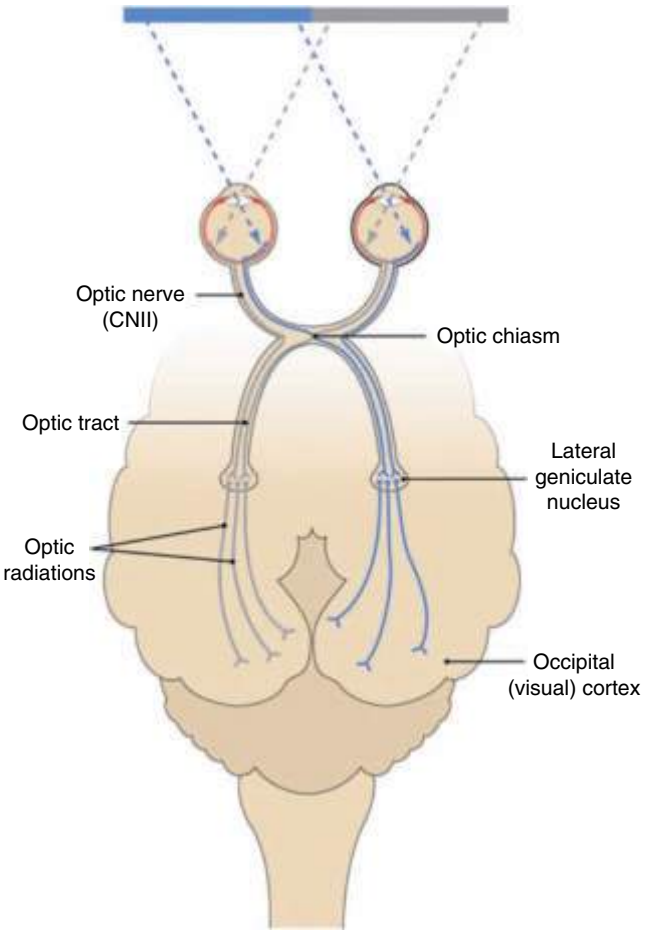


Figure 36.22 The visual pathways, demonstrating how each side of the visual field is represented within the opposite occipital (visual) cortex. As the degree of binocular vision in different species decreases, so a greater proportion of optic nerve fibers decussate at the optic chiasm. (*Source*: Modified from Platt & Olby, BSAVA Manual of Canine and Feline Neurology, 2013, Wiley.)

The arrangement of the ganglion cell axons within the optic nerve is not random. Instead, the fibers are arranged in a retinotopic manner, meaning that the precise spatial arrangement of the retina is maintained within the nerve (Brooks et al., 1999). Fibers from the superior/dorsal retina form the superior/dorsal half of the optic disc, and fibers from the inferior/ventral retina form the inferior/ventral half. Fibers from the central retina are in the center of the nerve, whereas those from the peripheral retina form the nerve periphery. This precise arrangement is a condition for the subsequent accurate projection of the visual field in both the LGN and the visual cortex.

The optic nerve exits the orbit through the optic foramen/canal of the presphenoid bone and runs beneath the rostroventral aspect of the brainstem cranial to the optic chiasm (de Lahunta et al., 2015h). Axons within the mammalian nerve are grouped into bundles, or fascicles, which are separated from each other by collagen fibers. These fascicles help maintain the structural integrity of the optic nerve during eye movement, allowing the bundles to undulate together as the eye (and nerve) move into extreme positions.

The optic chiasm, at the base of the hypothalamus, is the location where the two optic nerves meet, and in some cases interdigitate. In many species, there is significant reorganization of the axons at the chiasm before the fibers separate again to form the optic tracts. However, this reorganization, or decussation, varies between species (Herron et al., 1978; Jeffery & Erskine, 2005; Myers, 1901). Broadly speaking, in most fish, amphibian, reptilian, and avian species, all of the fibers cross over to the contralateral side. However, it is important to note there are many exceptions to this generalization, with uncrossing fibers found in avian, amphibian (e.g., the frog), and fish species (e.g., the jawless fish) (Grant et al., 2003; Ward et al., 1995).

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In mammalian species, with the evolution of binocular vision, some of the fibers do not cross over. The fibers remaining on the ipsilateral side are invariably those originating in the temporal retina. The proportion of the uncrossed (temporal) fibers increases in species with more frontal eyes and with larger binocular fields. However, in all mammals, the proportion of crossing fibers is larger than that of the uncrossing fibers, with the exception of humans, where half the fibers remain on the ipsilateral side. In the horse and other farm animals, 10%–20% of the fibers remain on the ipsilateral side, as do 25% in the dog and 33% in the cat. Because the topography of decussating fibers is characterized by spatial precision, lesions in different areas of the chiasm (or the optic nerve) will cause specific visual deficits.

The bundles exiting the chiasm are called the optic tracts (de Lahunta et al., 2015h). As a result of the decussation in the chiasm (in those species in which it occurs), each tract contains fibers from the opposite visual fields of both eyes. For example, the right tract carries information from the two left visual fields. A lesion in the optic tract, therefore, will cause a homonymous hemianopia, or a bilateral opposite visual field deficit. However, the size of these fields varies. In humans, the tract carries fibers from the temporal hemifield of the ipsilateral retina and the nasal hemifield of the contralateral retina. In the cat, it carries one-third of the fibers from the temporal retina and two-thirds of the fibers from the nasal, contralateral retina.

The optic tract courses caudodorsolaterally over the side of the diencephalon to reach the level of the LGN of the thalamus (de Lahunta et al., 2015h). At this point, the optic tract diverges into two basic paths: 20% of the fibers project to different brainstem nuclei to enable reflexes connected to visual stimuli; the remaining fibers (80% in the cat) are those that synapse in the LGN (de Lahunta et al., 2015h). The fibers that synapse in the LGN (located in the thalamus) project to the visual area of the cortex as the caudal part of the internal capsule in a band called the optic radiation (de Lahunta et al., 2015h). These axons terminate in the cerebral visual cortex on the lateral, caudal, and medial aspects of the occipital lobe. The functional, retinotopic anatomy and organization of the LGN and visual cortex are discussed in detail in Chapter 4. This pathway from the optic tract to the LGN of the thalamus to the internal capsule and the visual cortex must be intact for normal perception of vision to occur.

Obstacle Course (Maze) Testing

For obstacle course testing, the patient is placed in an unfamiliar environment and allowed to move freely. Within the environment, there are randomly placed objects that the patient must navigate through during their exploratory behavior. Obstacle course testing is performed in well lit (photopic) and dimly lit (scotopic) conditions. In instances when the patient is believed to have hemianopia, having the patient navigate the obstacle course with each eye separately blindfolded can be valuable. For canine patients who are seemingly nervous, it is often valuable to have the owner present and calling the patient's name on the side of the room opposite that of the patient. The examiner watches for and notes any evidence of the patient bumping into or stumbling over objects, or signs of them being apprehensive while navigating. If such behaviors happen consistently, this leads the examiner to believe there is a problem with the patient's vision.

Visual Placing

In patients that are small enough, the animal is held up, supporting its sternum and abdomen, and is brought toward the edge of a flat hard surface. Importantly, the flat surface should be able to be seen by the animal. A normal response is for the animal to attempt to place its limbs on the top of the flat surface. If an animal fails to attempt to place its limb on the surface, this implies that the surface was not seen. One must keep in mind that the animal should be alert and strong enough to attempt to place its limb, however. It is important to recognize that the patient's limb should not touch the edge of the flat surface. Animals that are blind, without any evidence of other neurologic disease, will attempt to step-up when their limb makes contact with the edge of the hard surface. When this happens, one is evaluating tactile placing and not visual placing.

Schirmer Tear Testing

Although not traditionally considered a part of the neuro-ophthalmic examination, quantitative testing of tear production provides relevant information concerning the function of the parasympathetic nervous system. Specifically, measurement of tear production can be done by way of the Schirmer tear test type I (see Chapter 10, Part 1). The test involves placing a standardized piece of filter paper in the ventrolateral conjunctival fornix for 1 minute and then measuring the length of wetting along the strip of paper. Though diseases other than those involving the parasympathetic nervous system can affect tear production, this test compliments findings where parasympathetic dysfunction is suspected (e.g., patients with diseases affecting the facial nerve or distal trigeminal nerve). To illustrate the utility of Schirmer tear testing in arriving at a neuroanatomic diagnosis, it is important to consider the anatomy of the parasympathetic innervations of the lacrimal gland.

The preganglionic parasympathetic neurons responsible for lacrimal secretion originate from the parasympathetic nucleus of the facial nerve (i.e., the rostral salivatory nucleus) located within the rostral portion of the medulla oblongata (Arenson & Wilson, 1970, 1971; Neuhuber & Schrodl, 2011). The lacrimal gland's preganglionic parasympathetic fibers run as part of the facial nerve through the facial canal of the

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petrous temporal bone (König & Liebich, 2007). Within the facial canal, some of these preganglionic fibers branch off as the major (greater) petrosal nerve. The major (greater) petrosal nerve exits the temporal bone and synapses on neurons (postganglionic neurons) within the pterygopalatine ganglion (König & Liebich, 2007). With respect to lacrimal gland innervations, postganglionic parasympathetic axons join with branches of the trigeminal nerve – the zygomatic nerve (a branch of the maxillary nerve), and the lacrimal nerve (a branch of the ophthalmic nerve). Both zygomatic and lacrimal nerves innervate the lacrimal gland and hence are important in tear production. As is hopefully apparent, some instances of diseases affecting the trigeminal nerve (e.g., trigeminal neuritis) may result in reduced tear production.

Another branch of the facial nerve (branched while still within the facial canal), the chorda tympani, runs through the middle ear and also carries preganglionic parasympathetic fibers and these fibers join the mandibular branch of the trigeminal nerve to ultimately synapse in the submandibular and sublingual ganglia which, in turn, send postganglionic fibers to their respective salivary glands (König & Liebich, 2007). Given that preganglionic parasympathetic fibers run through the middle ear, it is possible for preganglionic fibers to become affected during diseases like otitis media, thus resulting in neurogenic keratoconjunctivitis sicca.

Sensory innervation to the lacrimal gland is provided by the lacrimal nerve, the first branch of the ophthalmic nerve after it enters the orbit through the orbital fissure (König & Liebich, 2007). The nerve runs to the lateral part of the orbit and gives branches to the lacrimal gland, to other deeper structures, and then to the skin of the lateral canthus of the eye (König & Liebich, 2007).

Given that the Schirmer tear test I involves quantitatively measuring reflex production of tears, it is important to remember the afferent arm of this measurement involves the trigeminal nerve whereas the efferent component involves the parasympathetic output onto the lacrimal gland. As such, conditions causing loss of sensation from the cornea and conjunctiva (e.g., diabetes mellitus) can also result in reduced Schirmer tear test values (Cullen et al., 2005).

Pharmacologic Testing

In some instances, arriving at a neuroanatomic diagnosis, that is, identifying where along the neuroanatomic pathway a lesion is located, one must provocatively test the nervous system pharmacologically. Herein we describe the pharmacologic approach to differentiating between pre- and postganglionic lesions of the parasympathetic and sympathetic nervous systems, respectively. The basis for pharmacologic testing, whether parasympathetic or sympathetic, relies upon (1) the ability of neurotransmitter to be released from the postganglionic neuron, or (2) the phenomenon of denervation hypersensitivity (Ramsay, 1986).

Parasympathetic Lesions

In order to differentiate between pre- and postganglionic parasympathetic lesions the following series of tests can be attempted. The drugs used include:

- *Indirect parasympathomimetic drugs such as physostigmine (anticholinesterase)*. This class of drug requires an intact postganglionic neuron to induce miosis. The drug acts to extend the action of endogenous acetylcholine being released at the neuromuscular junction by the postganglionic parasympathetic neuron.
- *Direct-acting parasympathomimetic drugs, such as pilocarpine*. These drugs act on the iris sphincter itself by binding to the acetylcholine receptor. These drugs will cause miosis in both pre- and postganglionic lesions. If the lesion is postganglionic, however, denervation hypersensitivity can be observed (Ramsay, 1986). Therefore, application of a direct-acting drug in such a patient will cause a more complete and longer constriction than in a patient with a preganglionic neuron lesion.

A drop of 0.5% physostigmine causes rapid pupillary constriction in cases of a preganglionic neuron lesion. A normal eye will constrict more slowly, 40–60 minutes after application of the drug. If no constriction is observed after applying physostigmine, two drops of 2% pilocarpine are administered. Rapid and complete constriction of the pupil will indicate a postganglionic neuron lesion. The direct-acting drugs should only be administered 24 hours after testing the indirect-acting drugs. It has recently been shown that dilute solutions of pilocarpine (0.05%) administered topically can also show supersensitivity (Ramsay, 1986).

If in both pharmacological tests the normal pupil constricts but the dilated one does not, then the mydriasis could only be caused by pretreatment with parasympatholytic agents (e.g., atropine) or by an iridal disease. For example, iris degeneration and/or atrophy will cause ipsilateral mydriasis with variable degrees of response to light. This condition is more common in older dogs and in extreme cases may result in complete absence of pupillary constriction. Likewise, glaucoma and annular posterior synechia may cause an ipsilateral mydriasis that is unresponsive both to light and to miotic agents.

Sympathetic Lesions (Bistner et al., 1970)

In order to differentiate between pre- and postganglionic sympathetic lesions, the following series of tests can be attempted. The drugs used include:

- *Indirect-acting sympathomimetic drugs, such as 1% hydroxyamphetamine*. These drugs will induce release of norepinephrine from vesicles in the postganglionic neurons. After application of one to two drops of 1% hydroxyamphetamine, if the lesion is in the central component (i.e., hypothalamospinal pathway) of the sympathetic pathway or along the preganglionic neuron, the pupil will

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dilate immediately and fully. If a lesion involves the postganglionic neuron, norepinephrine cannot or will be minimally released, and therefore treatment will cause minimal or no dilatation of the pupil.

- *Direct-acting sympathomimetic drugs, such as 0.001% epinephrine*. Such a test is based on the fact that a lesion involving the postganglionic neuron causes denervation hypersensitivity of the smooth dilator muscle of the iris. The sensitized muscle will respond to low concentrations of a direct-acting sympathomimetic drug that would be ineffective under normal conditions. For example, 0.001% epinephrine (0.1 mL) will cause mydriasis within 20 minutes after topical administration to a denervated pupil. The same response will take about 40 minutes to occur if the lesion is in the central part of the sympathetic pathway (i.e., hypothalamospinal pathway) or if the lesion involves the preganglionic neuron. Similarly, instillation of 10% phenylephrine will cause mydriasis of a normal eye, or an eye having first-order Horner's syndrome, in approximately 60–90 minutes. Meanwhile, animals with second-order Horner's syndrome will have pupillary mydriasis at between 20 and 60 minutes, and animals with postganglionic (third-order Horner's syndrome) lesions will respond within 20 minutes (Bistner et al., 1970). The direct-acting drugs should only be administered 24 hours after testing with indirect-acting drugs. Topical testing with adrenergic agents is less conclusive in most cases (Kern et al., 1989).

Interestingly, a dilute solution of phenylephrine can be used (i.e., 1% phenylephrine) with similar results to using 10% phenylephrine (Ramsay, 1986). The authors commonly use this dilute concentration method.

Neuroanatomic Lesion Localization

Localization of the lesion is, as previously stated, one of the most important steps in reaching a diagnosis. Without an accurate neuroanatomic diagnosis, one will be unable to formulate an appropriate differential diagnostic list or diagnostic plan. The following section aims at not reiterating the neuroanatomy of the various components of the neuro-ophthalmic examination in prose; rather, we have provided a variety of tables and schemata to aid in reaching a neuroanatomic diagnosis. The use of such tables and schemata is intended to aid you, the reader, through deductive reasoning, recognizing the outcome of disease processes involving the neuro-ophthalmic system.

Additionally, we have also provided a list and description of Braund's neurologic syndromes that may involve abnormalities of the eye and its adnexa (Braund, 1994; Braund, 1999; Vite, 2010). Understanding such syndromes is helpful when presented with a patient having a constellation of clinical neurologic signs in addition to those detected after completing the neuro-ophthalmic examination. The exact neuroanatomic substrates and pathophysiologic reasoning for the extra-neuro-ophthalmic clinical signs are beyond the scope of this chapter, however, although the reader is directed to an appropriate veterinary neurology textbook for more in-depth discussion (e.g., de Lahunta et al., 2015g).

Braund's Syndromes

Behavior can be defined as the motor and autonomic manifestation of physiological processes; various components of the nervous system are responsible for various behaviors, However, it is important to recognize that the nervous system is very "plastic" and not "hard-wired." Given the plasticity of the nervous system, abnormal behaviors may initially manifest and be compensated (e.g., nystagmus) or may not manifest until the lesion affecting the nervous system is of sufficient magnitude such that the nervous system cannot compensate for any lost function.

Though first published and revised many years ago, clinical syndromes observed in veterinary neurology are very useful in arriving at a neuroanatomic diagnosis (Braund, 1994, 1999; Vite, 2010). Although one may consider such syndromes a simplified approach to arriving at a neuroanatomic diagnosis (i.e., relying heavily on pattern recognition), it is well known that disease processes affecting the central and peripheral nervous systems manifest with a group of characteristic clinical signs (i.e., syndrome). As mentioned previously, arriving at a neuroanatomic diagnosis is key prior to formulating a list of differential diagnoses. Of paramount importance to arriving at a list of differential diagnoses is consideration for the historical severity of the clinical signs (Fig. 36.23).

Although details of the neuroanatomic rationale accounting for clinical syndromes in veterinary neurology are beyond the scope of this chapter (for discussion see de Lahunta et al., 2015g), we provide a list of Braund's clinical syndromes that may include neuro-ophthalmic clinical

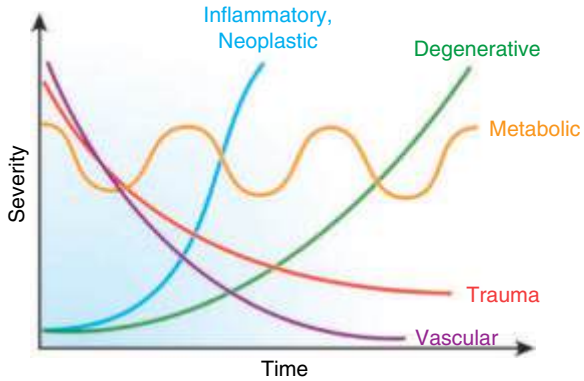


Figure 36.23 Onset and progression of neurological diseases of differing causes. (*Source*: Modified from Platt & Olby, BSAVA Manual of Canine and Feline Neurology, 2013, Wiley.)

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Table 36.4 Cerebral syndrome (Braund, 2003).

Normal gait
Altered mentation (e.g., apathy, somnolence, depression, disorientation, lethargy, coma)
Change in behavior (e.g., loss of trained behaviors, forgetfulness [e.g., not recognizing owner/surroundings], aggression, hyperexcitability)
Abnormal movements/postures (e.g., pacing, wandering, circling, head pressing, pleurothotonus)
Postural reactions deficits in contralateral limbs
Alterations in vision (e.g., failed obstacle course, menace deficit contralateral to lesion with normal pupillary light reflexes)
Seizures
±Papilledema

signs. In addition, we also provide a description of other syndromes important in neuro-ophthalmology. In performing neuro-ophthalmic assessment, it is important to consider clinical signs other than those attained from the neuro-ophthalmic examination itself.

Cerebral Syndrome (Table 36.4) (Vite, 2010)

The cerebral syndrome is a group of clinical signs that may be observed in disease processes involving the cerebral cortex. Of course, however, it should be recognized that the cerebral cortex is organized in such a way that it serves sensory, motor, and cognitive functions. For example, the frontal lobe is concerned with executive functions (i.e., integration of sensorimotor behavior for judgement, planning, etc.) and motor control, the temporal lobe with hearing, memory, and emotion, and the parietal lobe with somatosensation. Also important to recognize, the sensorimotor function of one particular hemisphere of the cerebral cortex is concerned with the contralateral region of the body. This is because of the decussation of fibers running to and from the cerebral cortex from various structures in the body.

Table 36.4 provides a list of clinical signs that comprise the cerebral syndrome. It is important to recognize that a veterinary patient may have only some or all of the clinical signs. Again, the presence or absence of particular clinical signs varies depending upon the location of the cerebral cortex that is involved and the ability of the cerebral cortex to "compensate" for a particular disease process. It is of paramount importance to recognize that some of the clinical signs of this syndrome may not be evident in a patient in the hospital setting, although when the patient is in a comfortable "home" setting the behaviors manifest. As such, it is important to carefully glean these atypical behaviors through the clinical history with appropriate use of open- and closed-ended questioning techniques and request, if possible, that video recordings of the animal's behavior be brought into the appointment for evaluation.

Diencephalic Syndrome (Table 36.5) (Vite, 2010)

The diencephalic syndrome is a group of clinical signs that may be observed in disease processes involving the diencephalon. The diencephalon is that region of the brain that is home to various structures responsible for autonomic functions such as thermoregulation, state of arousal, sexual activity, sleep–wake cycles, cardiovascular function, emotion, and endocrine functions. As such, disease processes involving this region of the brain can cause abnormal mentation, visual impairment at the level of the optic chiasm (as the diencephalon is where the optic chiasm is located), inability to thermoregulate, and evidence of endocrine disease. Table 36.5 lists clinical signs that can be observed in patients with a disease process involving the diencephalon.

Table 36.5 Diencephalic syndrome (Braund, 2003).

Gait is normal (hypothalamic disease) or may appear ataxic (with thalamic disease)
Altered mentation (e.g., depressed, lethargic, disoriented, coma)
Change in behavior (e.g., more aggressive or hyperexcitable)
Abnormal movements/postures
• e.g., pacing, wandering, hiding, head pressing, trembling
Bilateral deficits of cranial nerve II (optic nerve) – localized at the level of the optic chiasm
• Visual field deficits
• Mydriasis
• Altered/depressed pupillary light reflexes
Altered thermoregulatory ability
Altered appetite (i.e., increased or decreased)
Concurrent endocrine disease
• Hyperadrenocorticism
• Diabetes mellitus
• Acromegaly
• Diabetes insipidus
• ±Seizures

Midbrain Syndrome (Table 36.6) (Vite, 2010)

The midbrain syndrome is a group of clinical signs that may be observed in disease processes involving the midbrain. The midbrain is home to CN III (oculomotor nerve), parasympathetic nucleus of CN III, and the lateral geniculate nuclei. As such, ocular signs seen in this syndrome may include

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Table 36.6 Midbrain syndrome (Braund, 2003).

Spastic paresis/paralysis observed to involve one of the following: • All four limbs • Limbs contralateral to the lesion
Increased spinal reflex response and muscle tone in all limbs or limbs contralateral to the lesion
Postural reaction deficits in all limbs or limbs contralateral to the lesion
Altered mentation (e.g., depressed, stuporous, coma)
Ipsilateral deficits of cranial nerve III (oculomotor nerve) • Ventrolateral strabismus • Mydriasis at rest with internal ophthalmoparesis/paralysis • Ptosis
Hyperventilation
±Head pressing (i.e., obstinate progression)
±Bilateral miosis (i.e., after severe cranial trauma; animals will become midriatic afterward)

unilateral or bilateral ventrolateral strabismus, internal ophthalmoparesis from involvement of the parasympathetic nucleus of CN III (i.e., dilated pupil), ptosis of the upper eyelid, and menace deficit may be observed contralateral to the lesion if extension of the lesion involves the lateral geniculate nuclei (in the diencephalon). Other clinical signs of this syndrome are related to the motor (i.e., decerebrate rigidity, obstinate progression –walking until coming into contact with object and then head pressing against object) or respiratory (i.e., rapid regular breathing pattern) systems.

Vestibular Syndrome (Vite, 2010)

The vestibular syndrome is a group of clinical signs that may be observed in disease processes involving the vestibular system (central or peripheral). This is a common clinical syndrome. As discussed previously, the central components of the vestibular system are located within the medulla oblongata and the vestibulocerebellum whereas the peripheral vestibular system involves CN VIII (vestibulocochlear nerve) and the membranous labyrinth of the vestibular component of the inner ear. See Table 36.7 for clinical signs that are present and help to differentiate central from peripheral vestibular disorders (Webb et al., 2009a). Of course, nystagmus, ventrolateral strabismus, and impaired vestibulo-ocular reflexes (e.g., bilateral vestibular disease) are the principle ocular signs of vestibular disease. Other signs of vestibular disease may include: absent menace response ipsilateral to the lesion in the case of unilateral cerebellar disease, facial paresis/paralysis in cases of peripheral (e.g., otitis media/interna) or central vestibular disease (i.e., involvement of the nucleus of CN VII), or Horner's syndrome (peripheral vestibular disease only, e.g., otitis media/interna).

Cerebellar Syndrome (Table 36.8) (Vite, 2010)

The cerebellar syndrome is a group of clinical signs that may be observed in disease processes involving the cerebellum. It is important to recall that the cerebellum is involved in the fine-tuning of coordinated motor movements. As such, disease processes involving the cerebellum often manifest as over- and undershooting of the body during intentional movement of a body part (e.g., truncal sway, intention tremor of the head/neck). In addition, given the importance of the cerebellum in the menace response pathway (without visual field loss) and in the vestibular system, animals with cerebellar disease may lack a menace response ipsilateral to the lesion, and may have nystagmus, respectively. Opsoclonus has also been observed with cerebellar disease (Ives et al., 2018). Also sometimes seen in cerebellar disease is anisocoria with the dilated pupil being present contralateral to the lesion. Finally, in instances of severe and acute cerebellar

Table 36.7 Clinical signs associated with unilateral vestibular disease (Webb et al., 2009b).

Vestibular syndrome	Mentation	Ataxia	Head tilt and/or body rolling	Spontaneous systagmus	Proprioceptive deficits	Involvement of other cranial nerves	Horner's syndrome	Cerebellar signs
Peripheral	Appropriate for a clinically normal animal (consider history, age, breed, species)	+	+, toward the side of lesion	+, horizontal or rotary and fast phase away from side of lesion – acute stage	–	±, same side as the lesion, cranial nerve VIII	±	–
Central (nonparadoxical)	Usually inappropriate (e.g., lethargic, somnolent)	+	+, toward the side of lesion	+, horizontal, rotary, or vertical, fast phase away from lesion	±, ipsilateral to the lesion	±, same side as the lesion, cranial nerve V, VI, VII	–	–
Central (paradoxical)	Usually inappropriate (e.g., lethargic, somnolent)	+	+, away from the lesion	±, horizontal, rotary, or vertical, fast phase away from lesion	±, ipsilateral to the lesion	±, same side as the lesion, cranial nerve V, VI, VII	–	±

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Table 36.8 Cerebellar syndrome (Braund, 2003).

Hypermetric, spastic, jerking stepping of limbs with normal strength
Truncal ataxia with broad-based stance
Postural reactions possibly delayed with exaggerated responses in all four limbs or of limbs ipsilateral to the lesion
Intention tremors that resolve at rest • Head – e.g., over and undershooting of head/neck movements • Eyes – fine pendular or oscillatory eye movements
Absent menace response (ipsilateral to side of lesion)
Normal mentation
±Decerebellate rigidity (opisthotonus with extended forelimbs and hind limbs flexed)
±Mydriasis of eye contralateral to lesion
±Vestibular signs

disease, patients may present with a characteristic decerebellate posture (i.e., opisthotonus with hind limbs tucked up under the abdomen). Importantly, however, patients with cerebellar disease alone have normal mentation.

Pontomedullary Syndrome (Table 36.9) (Vite, 2010)

The pontomedullary syndrome is a group of clinical signs that may be observed in disease processes involving the pons and medulla oblongata. Given the location of various cranial nerve nuclei along the pons and medulla oblongata (CN V [trigeminal] to CN XII [hypoglossal]), a variety of clinical signs referable to injury to these cranial nerve nuclei can be observed (see Table 36.1, Table 36.2, and Table 36.3). Upper motor neuron signs (i.e., increased muscle tone, hyperreflexia, etc.) can be observed in the limbs of patients with pontomedullary syndrome. Given the location of various pattern generators of the respiratory system, various changes in ventilatory patterns can be observed in patients with severe pontomedullary lesions. In addition, alteration in arousal is expected given the involvement of the ascending reticular activating system.

Cervical Syndrome (Table 36.10) (Vite, 2010)

The cervical syndrome is a group of clinical signs that may be observed in disease processes involving the cervical spinal cord (spinal cord segments C1–C5). Clinical signs result from damage to tracts within the white matter that carry sensory and motor information to and from the brain. With respect to ocular signs, injury to presympathetic spinal pathways may result in Horner's syndrome ipsilateral to the lesion (i.e., first-order Horner's syndrome). The remainder of the clinical signs that may be seen in patients with cervical syndrome are the result of preventing sensory information (e.g., proprioceptive and somatosensory information) and motor commands to lower motor neurons (e.g., interruption of the rubrospinal, vestibulospinal, and reticulospinal pathways). See Table 36.10 for clinical signs referable to patients presenting with cervical syndrome.

Table 36.9 Pontomedullary syndrome (Braund, 2003).

Weakness/paralysis observed to involve one of the following: • All four limbs • Limbs on the same side of body as lesion
Normal or increased reflexes and muscle tone in all limbs in all limbs
Postural reaction deficits (e.g., impaired knuckling, hopping) in all four limbs or of limbs ipsilateral to the lesion
Possible multiple cranial nerve deficits (cranial berves V–XII)
Altered ventilatory pattern
Dull mentation (i.e., involvement of the ascending reticular activating system [ARAS])
Partial Horner's syndrome

Cervicothoracic Syndrome (Table 36.11) (Vite, 2010)

The cervicothoracic syndrome is a group of clinical signs that may be observed in disease processes involving the cervical spinal cord (spinal cord segments C6–T2) (i.e., the cervical intumescence that is home to alpha-motorneurons (lower motor neurons) to the forelimbs). In addition, this region of the spinal cord is home to SPNs responsible for sympathetic innervation of the eye. As such, animals with a disease process involving the cervicothoracic region of the spinal cord may have lower motor neuron signs (i.e., hypo- to areflexia of the forelimb(s), flaccid paresis/paralysis of the forelimb musculature, varying degrees of neurogenic atrophy of forelimb musculature), upper motor neuron signs to the ipsilateral hind limb with reduction or absence of proprioceptive abilities in the ipsilateral hind limb. In addition, the cutaneous trunci may be absent ipsilateral to the lesion. Finally, ophthalmic signs include partial or complete Horner's syndrome ipsilateral to the lesion (see Horner's syndrome below).

Horner's Syndrome (Table 36.12)

The sympathetic innervation of the eye has already been discussed previously in this chapter (see Fig. 36.24 for simplified pathway) (for reviews and case series see Firth, 1978; Green et al., 1992a; Kern et al., 1989; Morgan & Zanotti, 1989; Simoens et al., 1990; Simpson et al., 2015; Smith & Mayhew, 1977; Van den Broek, 1988). Horner's syndrome is that cluster of clinical signs referable to the loss of ocular sympathetic innervation. Remember that the sympathetic nervous pathway to the eye essentially involves presympathetic neurons from the brain to the SPNs located in the intermediolateral gray matter of spinal cord segments T1–3, and finally postganglionic sympathetic neurons located in the cranial cervical ganglion. Postganglionic sympathetic

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Table 36.10 Cervical syndrome (Braund, 2003).

Weakness/paralysis observed to involve one of the following: • All four limbs • Limbs on the same side of body as lesion • Only one thoracic limb
Normal or increased reflexes and muscle tone in all limbs ± extensor rigidity in limbs ipsilateral to the lesion or in all limbs
Postural reaction deficits (e.g., impaired knuckling, hopping) in all four limbs or of limbs ipsilateral to the lesion
Neck muscle spasms, signs suggestive of pain (e.g., vocalization, impaired voluntary motion of neck, stiff/rigid and low carriage of neck)
Root signature (i.e., thoracic limb held in partial flexion during standing or sitting, seemingly adjusting affected limb to "get comfortable")
±Ventilatory difficulty
±Horner's syndrome (partial or complete)

Table 36.11 Cervicothoracic syndrome (Braund, 2003).

Weakness/paralysis observed to involve one of the following: • All four limbs • Limbs on the same side of body as lesion • Only one thoracic limb
Depressed reflexes and flaccid muscle tone of the forelimb(s) + segmental neurogenic muscle atrophy of the forelimb(s)
Normal to increased responses of spinal reflexes and muscle tone of hind limb(s)
At-level hyperesthesia
Below-level hypoesthesia
Depressed or absent cutaneous trunci reflex (unilaterally or bilaterally)
Horner's syndrome (partial or complete)

fibers innervate the ciliary body, iris dilator, and iris sphincter muscles (keep in mind reciprocal iris innervations), the smooth muscles of the periorbita, and Müller's muscles of the upper and lower eyelids. Normal sympathetic tone in these smooth muscles keeps the globe slightly protruded, the palpebral fissure opened, the third eyelid retracted, and the pupil partially dilated. When there is a disease process affecting the sympathetic innervation, however, the following signs are found with variable expression:

- miosis (Fig. 36.25)
- ptosis
- enophthalmos
- protruded third eyelid (Fig. 36.25)
- facial sweating (only in horses) (may see neck sweating if preganglionic lesion involved) (Fig. 36.26)
- hyperthermia of the facial area
- anhydrosis of the planum nasolabiale in cattle (Fig. 36.27)
- hyperthermia of the ear (ruminants).

Please see Table 36.12 for clinical signs that are seen in Horner's syndrome depending upon the region of the nervous system affected. To further substantiate the neuroanatomic diagnosis, provocative pharmacologic testing can be used to differentiate first- (presympathetic), second- (preganglionic), and third-order (postganglionic) Horner's syndrome (see previously).

Cavernous Sinus Syndrome (Table 36.13) (Theisen et al., 1996; Rossmeisl et al., 2005)

Cavernous sinus syndrome is that group of clinical signs that refers to disease processes involving the cavernous sinus. The cavernous sinus is a venous sinus located bilaterally on the floor of the middle cranial vault and extending from the orbital fissure to the petro-occipital canal. Each cavernous sinus is connected rostrally and caudally by rostral and caudal intercavernous sinuses, respectively. Neuro-ophthalmically important structures that are in close proximity to the cavernous sinus include CNs III, IV, VI and the ophthalmic and maxillary branches of CN V. In addition, postganglionic sympathetic axons are also found near the cavernous sinus. It is from this close association with the cavernous sinus, and the constellation of clinical signs that are referable to these nerves' dysfunction, that this syndrome gets its name. Importantly, however, it should be recognized that disease processes involving the orbit and orbital fissure (i.e., where these cranial nerves exit or have exited) may result in cavernous sinus syndrome. It should be recognized also that cavernous sinus syndrome can be either unilateral or bilateral, although bilateral cavernous sinus syndrome is rarer. The clinical signs found in cavernous sinus syndrome typically include:

- external and internal ophthalmoparesis
- ptosis
- mydriasis
- reduced corneal sensation
- reduced periorbital and nasofacial sensation
- ± Horner's syndrome.

Hemifacial Spasm (Hemifacial Tetany) (Motta & de Lahunta, 2015; Parker et al., 1973; Roberts & Vainisi, 1967; Van Meervenne et al., 2008)

The clinical sign of hemifacial spasm is where the facial muscles on one side are in a constant state of contraction. As such, the term hemifacial spasm is more aptly termed hemifacial tetany. Hemifacial tetany may manifest as primarily blepharospasm, ipsilateral deviation of the nasal planum, ipsilateral narrowing of the palpebral fissure, and ipsilateral elevated or caudal displacement of the ear. Other clinical

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Table 36.12 Neuroanatomic localization of Horner's syndrome.

Neuroanatomic location	First-, second-, or third-order disease	Possible concurrent clinical signs	Potential causes
Brainstem	First	Altered level of consciousness	Neoplasia
		Abnormalities in thermoregulation, eating, drinking, breathing pattern, endocrine function	Inflammatory (primary or secondary)
			Vascular
			Trauma
		Cranial nerve abnormalities	
Cervical spinal cord	First	Ipsilateral hemiparesis/paralysis	Neoplasia
		Tetraparesis/quadriplegia	Trauma
		Upper motor neuron signs to all four limbs	Ischemic myelopathy (e.g., fibrocartilagenous embolism)
		±Signs of neck pain	
			Intervertebral disk disease
T1–T3 spinal cord	Second	Lower motor neuron signs to the forelimb(s)	Neoplasia
		Upper motor neuron signs to the hind limbs	Trauma
		Upper motor neuron bladder Upper thoracic back pain	Ischemic myelopathy (e.g., fibrocartilagenous embolism)
		Ipsilateral or bilateral loss of cutaneous trunci reflex	Intervertebral disk disease
T1–T3 ventral nerve roots	Second	Lower motor neuron signs to ipsilateral limb	Trauma to brachial plexus
		Ipsilateral forelimb lameness	Nerve sheath tumor
		Ipsilateral loss of cutaneous trunci reflex	
Sympathetic trunk	Second	Dysphagia	Mediastinal mass
		Cough	Trauma (e.g., IV injection and carotid ligation for surgery in horses)
		Lethargy	
		Regurgitation	
		Cough	
		Reduced compressibility of thorax	
Middle ear	Third	Ipsilateral signs of peripheral vestibular disease	Otitis media
			Middle ear mass
		Ipsilateral facial nerve paralysis	Guttaral pouch disease
		Ipsilateral keratoconjunctivitis sicca	Trauma
Cavernous sinus	Third	Internal, external, or complete ophthalmoplegia	Neoplasia
			Inflammatory disease (primary or secondary)
			Vascular disease (e.g., aneurysm)
Retrobulbar	Third	Signs of orbital disease (e.g., exophthalmos and pain upon opening mouth)	Neoplasia
			Abscess
		Involvement of one or more of cranial nerves II, III, IV, V, VI	Trauma

neurologic signs may occur concurrently, especially if there is brainstem involvement. The clinical sign of hemifacial tetany is seen rarely in dogs. However, when noticed, it is important to recognize this clinical sign as it is a symptom of a disease process of the facial nerve or the nucleus of CN VII. Disease processes having been reported in dogs with hemifacial spasm include degenerative or neoplastic brainstem disease and otitis media-interna. The clinical signs of hemifacial tetany should not be confused with chronic facial nerve paralysis with neurogenic atrophy and fibrosis of the facial

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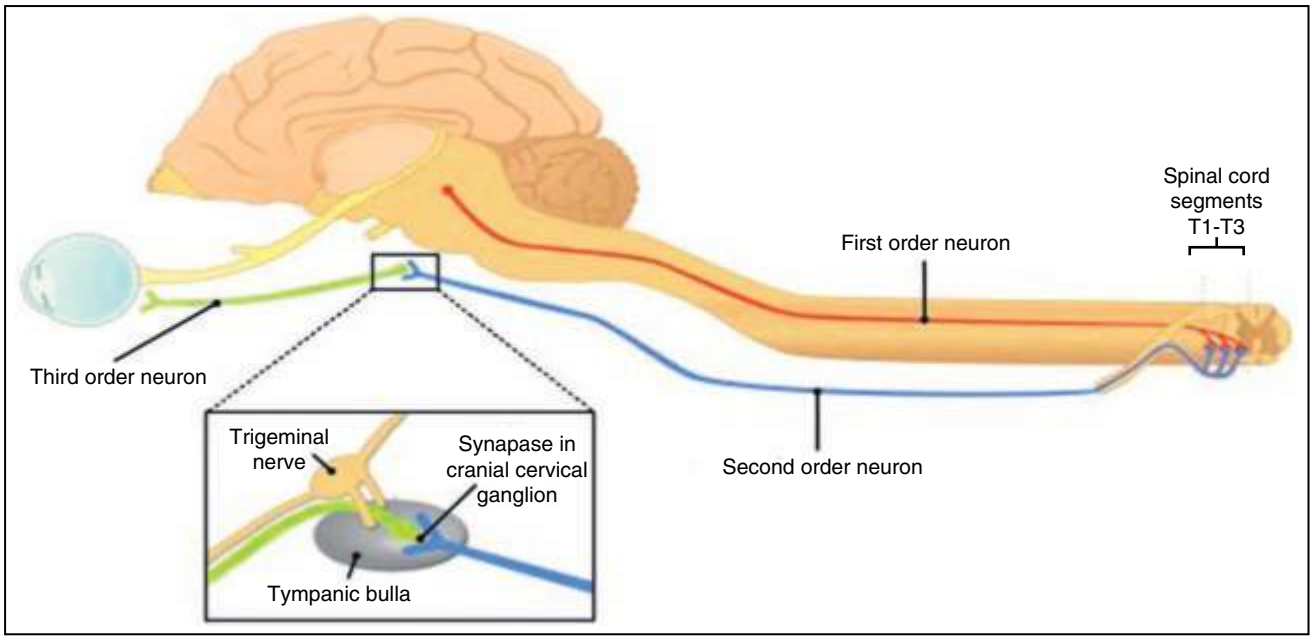


Figure 36.24 The "three-order" neuron pathway for sympathetic control of the eye. Note that the first order neuron is located within the hypothalamus and makes connections with the sympathetic preganglionic neurons (SPN) (second order neurons) located in the intermediolateral gray matter of the upper thoracic spinal cord. SPNs send projections to third order neurons located within the cranial cervical ganglion (located adjacent to the tympanic bulla). Neurons within the cranial sympathetic ganglion send postganglionic fibres to the effector organs in the eye and face. Axons of third order neurons enter the cranial vault and pass near the cavernous sinus prior to exiting the cranial vault via the orbital fissure.



Figure 36.25 Shetland Sheepdog having sustained right-sided brachial plexus injury 2 days prior to photograph. Note the partial Horner's syndrome of the right eye (i.e., miosis and slight protrusion of the right nictitating membrane).

muscles. In cases of chronic facial nerve paralysis, these patients will have a diminished or absent palpebral reflex.

Pourfour du Petit Syndrome (Boydell, 2000)

Pourfoud du Petit syndrome is described in humans as consisting of mydriasis, widened palpebral fissure, exophthalmos, and cool periocular skin with increased sweating. A similar condition has been described in cats having undergone flushing of the middle ear during diagnostic work-up of middle ear disease. In these cats, anisocoria was noted with the affected pupil being mydriatic with a brisk but incomplete direct PLR, ipsilateral exophthalmia, and an enlarged palpebral fissure without evidence of third eyelid protrusion. Menace response and palpebral reflexes were normal. Mydriasis resolves within 1 week. Although not known for certain, it is speculated that these clinical signs occur because of a transient irritative (neuritis) lesion to postganglionic sympathetic fibers. In some instances, patients may go on to develop ipsilateral Horner's syndrome.

Static Anisocoria (Spastic Pupil Syndrome) and Hemidilated Pupil (Nell & Suchy, 1998)

Static anisocoria describes a clinical sign seen in cats where miosis, or less commonly mydriasis, of the affected pupil occurs. In cats with miotic static anisocoria, the miosis does not respond to dark adaptation.

Hemidilated pupil can be found in cats and is characterized by a D-shaped or reverse D-shaped pupil. The proposed pathophysiology of hemidilated pupil is explained by a

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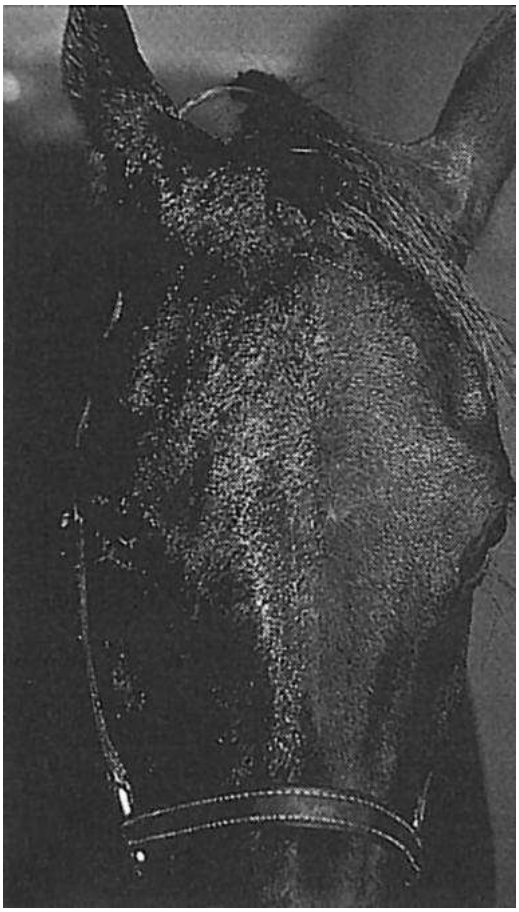


Figure 36.26 Horner's syndrome in a horse is characterized by profuse ipsilateral facial sweating. (*Source*: Reproduced with permission from Shamir & Ofri, Veterinary Ophthalmology 4th edition, 2007.)

lesion involving the malar (lateral) or nasal (medial) short ciliary nerves. Pharmacologic testing with pilocarpine supports this notion. It has been shown, however, that postmortem persistence of this dyscoria could likely be explained by iridal infiltration with lymphosarcoma (Fig. 36.28).



Figure 36.27 Horner's syndrome in a cow is characterized by ipsilateral absence of sweating (anhydrosis) of the planum nasolabiale. (*Source*: Reproduced with permission from Shamir & Ofri, Veterinary Ophthalmology 4th edition, 2007.)

Static anisocoria in the cat can be seen as a result of feline leukemia virus, lymphosarcoma, and feline dysautonomia.

Schemata for Neuroanatomically Localizing Blindness and Anisocoria (Fig. 36.29, Fig. 36.30, Fig. 36.31, and Fig. 36.32)

We have provided a variety of schemata that can be used to help in arriving at a neuroanatomic diagnosis for patients presenting for visual impairment and/or anisocoria. The intent of these schemata is to provide the reader with varying views in how one might arrive at a neuroanatomic diagnosis for patients presenting with these clinical signs. It is not the intent to provide a "recipe" for lesion localization. There is no substitute for understanding basic neuroanatomy and applied clinical neuroscience when arriving at a neuroanatomic diagnosis for patients who may not "fit" within a particular schema.

Table 36.13 Cavernous sinus syndrome.

Cranial nerve	Clinical signs
III (oculomotor) including parasympathetic fibers of cranial nerve III	Mydriasis
	Paralysis or paresis of levator palpebrae, dorsal rectus, medial rectus, ventral rectus, and retractor bulbi muscles
IV (trochlear)	Paralysis or paresis of the dorsal oblique
VI (abducens)	Paralysis or paresis of the lateral rectus and retractor bulbi muscles
V (ophthalmic branch)	Corneal anesthesia
	Periorbital and medial canthal anesthesia
V (maxillary branch)	Periorbital and facial anesthesia
Postganglionic sympathetic	Horner's syndrome – ptosis, enophthalmos, miosis, protruding third eyelid

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Figure 36.28 Right eye of a 7-year-old cat: D-shaped pupil in miosis, fibrinous exudate in the nasal inferior part of the anterior chamber, and moderate rubeosis iridis resulting from anterior uveitis. (*Source*: Reproduced with permission from Nell & Suchy, 1998.)

Formulating an Appropriate Differential Diagnosis List

Rather than listing every possible disease process that can result in neuro-ophthalmic signs, we discuss the rationale behind arriving at an appropriate differential diagnostic list. Although pattern recognition is a valid approach to arriving at a differential diagnosis, it is important, especially for those patients that do not "fit" a typical pattern, to return to the basics of formulating a list of appropriate differential diagnoses. The first step in formulating a differential diagnostic list is to neuroanatomically localize the problem. In combination with the neuroanatomic diagnosis, it is of utmost importance to consider the signalment and clinical history of the patient. To illustrate, one would not include enrofloxacin toxicity as a differential diagnosis for a dog presenting with a slowly progressive onset of visual disturbance and subacute history of altered mentation.

One must also consider the broad etiologic/pathophysiologic categories of clinical disease:

- vascular
- infectious
- traumatic/toxic
- anomalous
- metabolic
- inflammatory
- neoplastic/nutritional
- degenerative.

In so doing, one can begin to consider some disease processes more likely than others, especially if a clinical sign : time graph is considered (see Fig. 36.23). Although this rudimentary approach is commonly taught early in our careers, it serves a significant function by assisting in the creation of an appropriate differential diagnosis list and also an appropriate diagnostic plan.

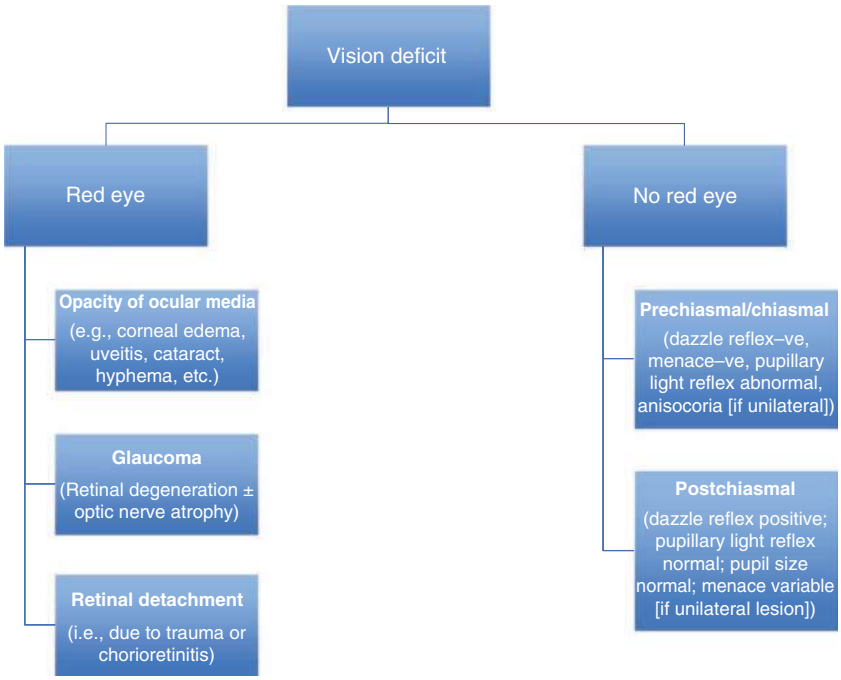


Figure 36.29 An approach to reach a neuroanatomic diagnosis in animals with red eye and vision loss.

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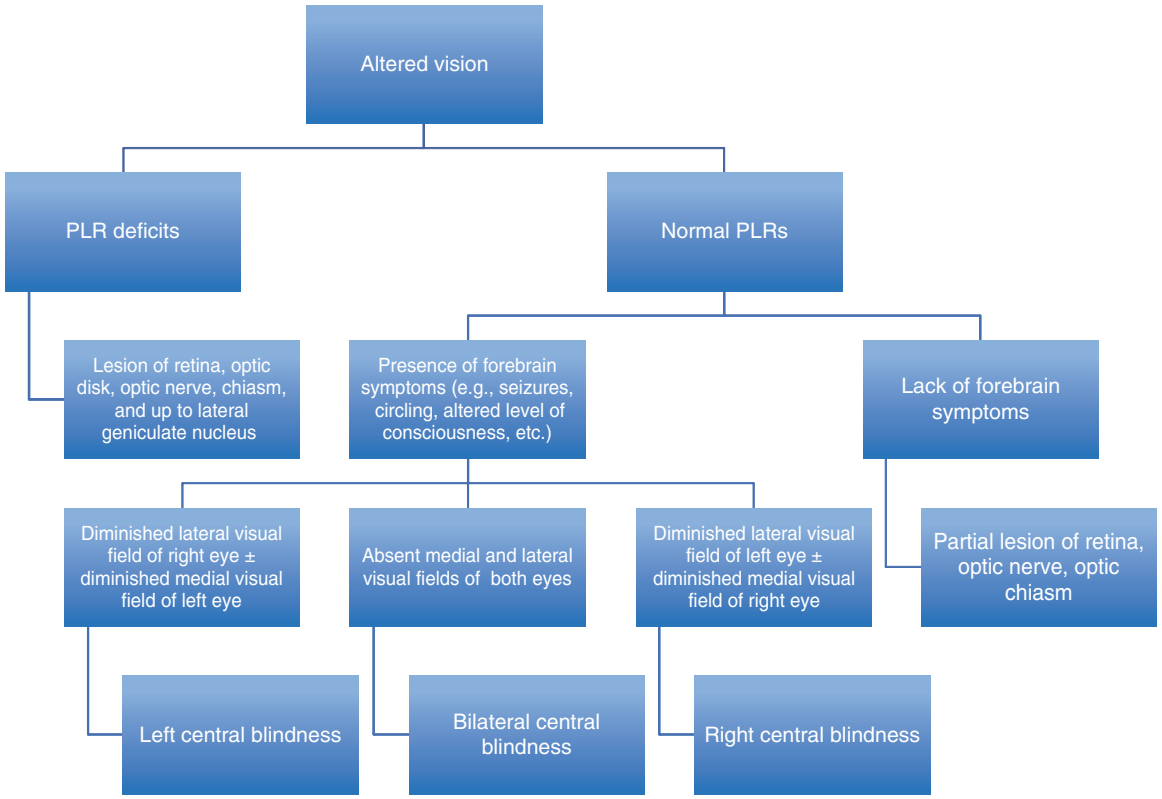


Figure 36.30 An approach to reach a neuroanatomic diagnosis in animals with vision loss with or without pupillary light reflex abnormalities. PLR, pupillary light reflex.

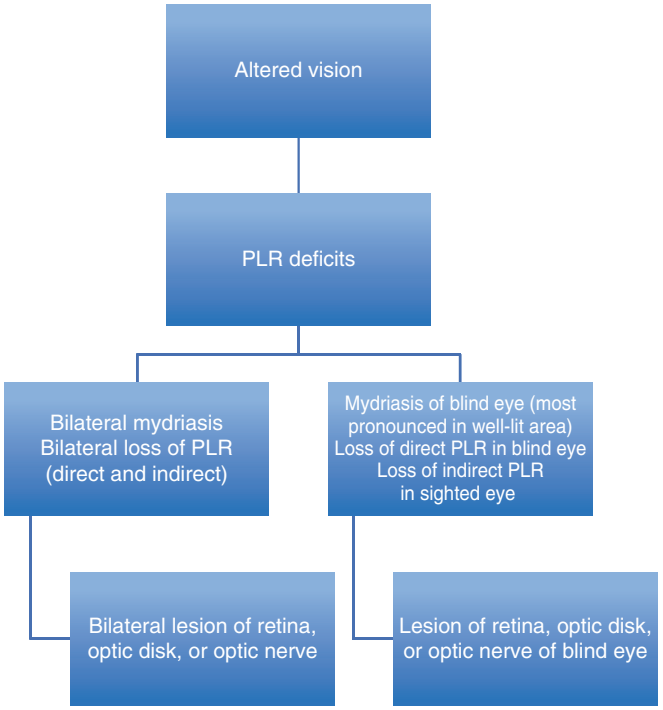


Figure 36.31 An approach to reach a neuroanatomic diagnosis in animals with vision loss and having pupillary light reflex abnormalities. PLR, pupillary light reflex.

Neuro-Ophthalmic Diseases

Thus far, we have discussed the neuro-ophthalmic examination, pertinent neuroanatomy, a variety of neurologic syndromes where neuro-ophthalmic symptoms may be present, and an approach for formulating a list of differential diagnoses. In this section, we provide a discussion of various, and important or newly advanced, diseases in which neuro-ophthalmic findings may be found. For diseases of a systemic nature that may manifest neuro-ophthalmically, please refer to Chapter 37. It should be noted, for the purposes of brevity, inborn errors of metabolism, the various inherited retinal degenerative diseases, and other causes of preretinal blindness are discussed elsewhere in this textbook. This section is divided into Canine, Feline, and Equine. Within each of these categories, we have further subdivided diseases into congenital, developmental, or acquired. The various diseases discussed under each of these headings have been alphabetized, and these include diseases for common domesticated species.

Canine: Congenital

Achiasmatic Sheepdog

An autosomal recessive defect resulting in lack of decussation of the optic nerve (achiasmatic) has been described in

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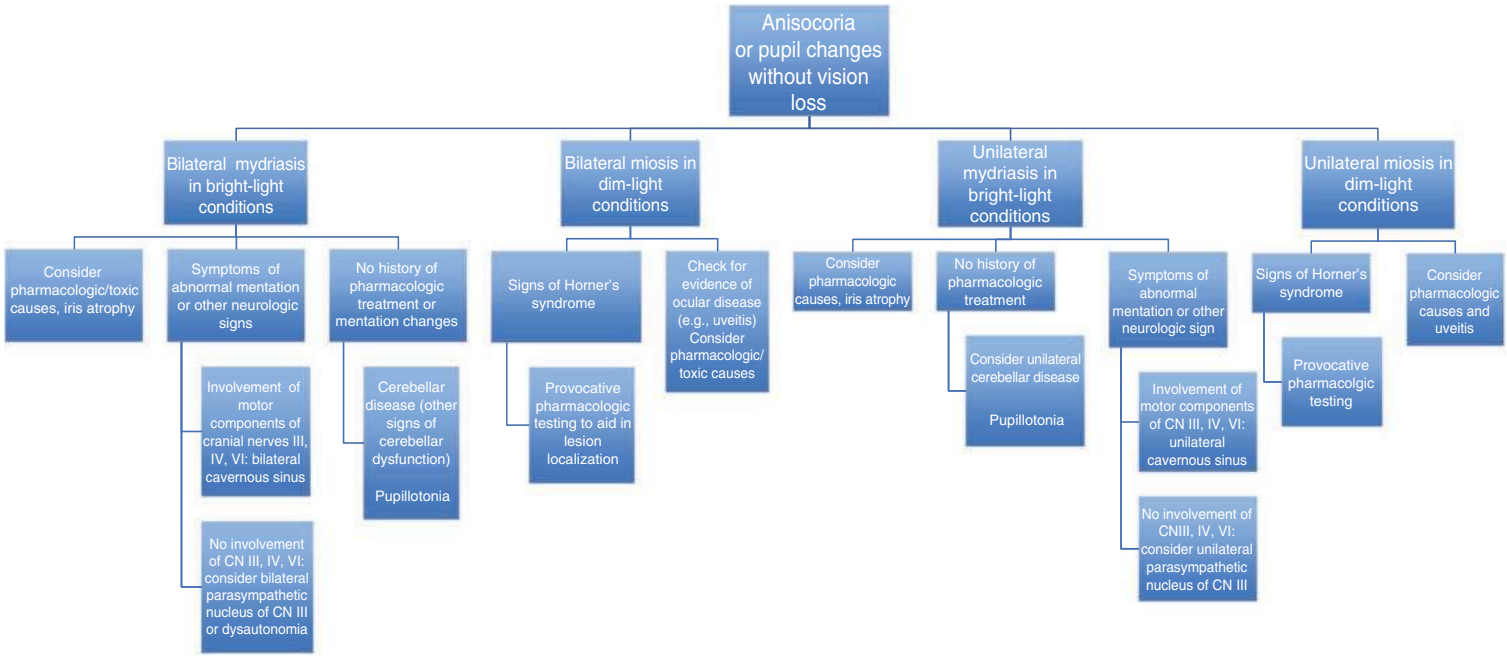


Figure 36.32 An approach to reach a neuroanatomic diagnosis in animals with anisocoria.

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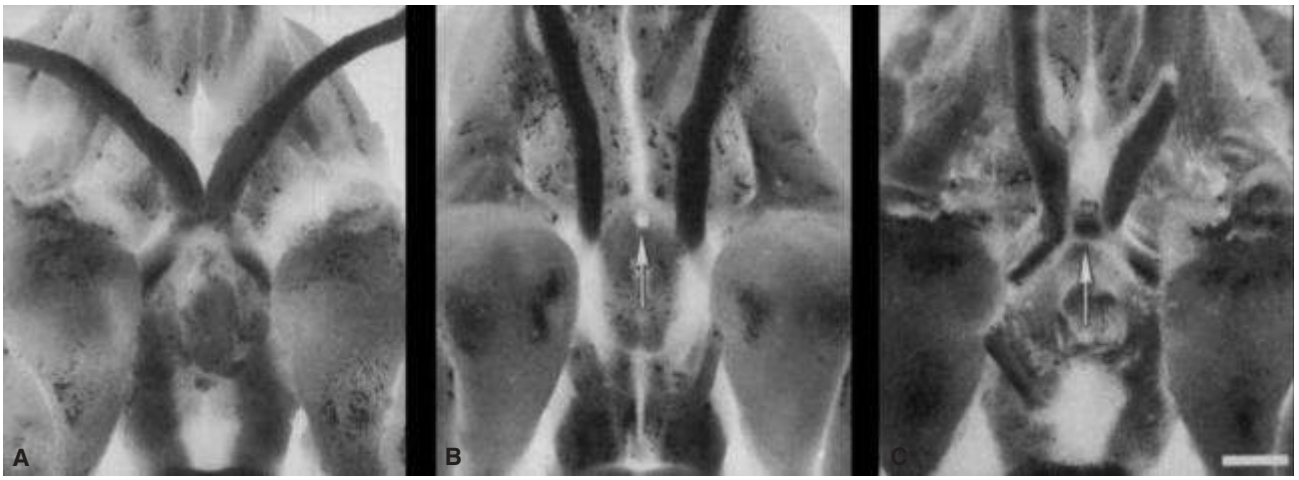


Figure 36.33 Ventral views of the brains of dogs showing chiasm area. **A.** Normal sheepdog. **B.** Mutant sheepdog with no chiasm. Arrow indicates the lamina terminalis, which is usually covered by the chiasm. **C.** Sheepdog with a partial chiasm. (*Source*: Reproduced with permission from Hogan & Williams, 1995.)

Belgian sheepdogs (Dell'Osso & Williams, 1995; Dell'Osso et al., 1998; Hogan & Williams, 1995; Hogan et al., 1999; Williams et al., 1994). In these dogs, all optic nerve axons from one eye project directly into the ipsilateral optic tract (Fig. 36.33). Nasal optic nerve axons (i.e., those that should have decussated) make synaptic contact in the LGN as although they had crossed at the chiasm. This results in non-congruent, mirror-image maps of visual space in adjacent layers of the LGN. Affected animals have pronounced horizontal pendular nystagmus (Dell'Osso et al., 1998).

Congenital Deafness and Vestibular Disease

Bilateral congenital deafness and vestibular disease has been described in the Doberman Pinscher (Chrisman, 1980; Wilkes & Palmer, 1992; Webb et al., 2019). The condition is present at birth, is bilateral, and affected puppies have varying degrees of neurologic impairment. Affected puppies will tend to fall over and roll, may have a head tilt, have a "bobble-head" appearance, have wide-head excursions, have evidence of vestibular ataxia, lack vestibulo-ocular reflex, lack postrotational nystagmus, and have significant bilateral sensorineural hearing loss ranging from profound elevations in hearing threshold bilaterally to being bilaterally deaf. Cochlear histopathology shows complete degeneration of the organ of Corti. Histopathology of the vestibular labyrinth reveals an absence or abnormality of the otoconia, although no degeneration of vestibular hair cells has been detected. As with any static vestibular disease process, affected animals have variable resolution of clinical signs, although the lack of vestibulo-ocular reflex and hearing loss are persistent. We have recently described this condition to be inherited in an autosomal recessive fashion with a mutation in the *MYO7A* gene (Webb et al., 2019). As opposed to human Usher syndrome resulting from *MYO7A* mutations where children develop retinitis pigmentosa, this canine condition has not been associated with visual disturbances (Wilkes & Palmer, 1992; Webb et al, 2019). A temporal study evaluating affected dogs for signs of retinal dysfunction needs to be completed.

Aside from the condition occurring in Doberman Pinschers with bilateral vestibular dysfunction and deafness, there has been one Doberman puppy affected with unilateral vestibular dysfunction and deafness resulting from mutation in the protein tyrosine phosphatase, receptor type Q (*PTPQR*) gene (Guevar et al., 2018).

Cranial Dysinnervation Disorders

The term congenital cranial dysinnervation disorder (CCDD), developed in 2002, describes a group of disorders characterized by being congenital, nonprogressive, sporadic or familial, and causing abnormal eye, eyelid, or facial movements (Gutowski & Chilton, 2015). Originally, these disorders were thought to result from extraocular muscle maldevelopment and subsequent extraocular muscle fibrosis (Fels, 2017). In human medicine, many of the CCDD are inherited in an autosomal recessive fashion (Fels, 2017). The main types of CCDD described in humans include: Duane's retraction syndrome; congenital fibrosis of the extraocular muscles Types 1, 2, and 3; Möbius syndrome; horizontal-gaze palsy with progressive scoliosis; congenital facial palsy; and congenital ptosis (Fels, 2017). Of these, an extraocular muscle dysinnervation syndrome similar to Duane's retraction syndrome has been described in a French Bulldog puppy (Mari et al., 2017). In this puppy, mild ptosis of the left upper eyelid, mild lateral strabismus, and external ophthalmoparesis of the left eye were noted (Mari et al., 2017). Retraction and ventral deviation of the left eye globe with protrusion of the third eyelid and elevation of the upper

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eyelid were elicited on attempted voluntary adduction of the left eye (Mari et al., 2017) (Fig. 36.34). A presumed diagnosis of a CCDD was made based upon history, clinical signs, and excluding other causes of this puppy's clinical signs (Mari et al., 2017).

Other subcategories of CDDs include the synkinesis disorders (Bursztyn & Makar, 2014). Synkinesis refers to when there is an involuntary movement of one part of the body when an intentional movement is made by another (Eminaga et al., 2015). Cranial nerve synkineses may be either congenital (Bursztyn & Makar, 2014; Pearce et al., 2017) or acquired via inadvertent exogenous (McGovern et al., 1986; Nelson & Kline, 1990) or iatrogenic trauma after orbital surgery (Park & Oh, 2013). Until now, only a single case of synkinesis, involving the eye, has been described in the dog (Eminaga et al., 2015). In this single reported case, the patient was a 10-year-old neutered-male Rhodesian Ridgeback-cross with trigemino-abducens synkinesis of unknown etiology (Eminaga et al., 2015). This patient exhibited nonprogressive bilateral protrusion of the nictitating membranes when chewing. Clinical and diagnostic examinations were unremarkable except for an elevated CSF protein concentration in spite of a normal nucleated cell count and absence of evidence for infectious disease (Eminaga et al., 2015).

Hydrocephalus

Hydrocephalus refers to the active enlargement of the brain ventricular system. However, ventriculomegaly (enlargement of the brain ventricles) is not necessarily synonymous with hydrocephalus (Estey, 2016; Thomas, 2010). The most



Figure 36.34 Serial still images of the left eye of a French Bulldog puppy, on attempted right (medial) gaze. Note the absent or reduced adduction, the retraction and down-shoot of the globe with protrusion of the third eyelid, and the upper eyelid elevation.

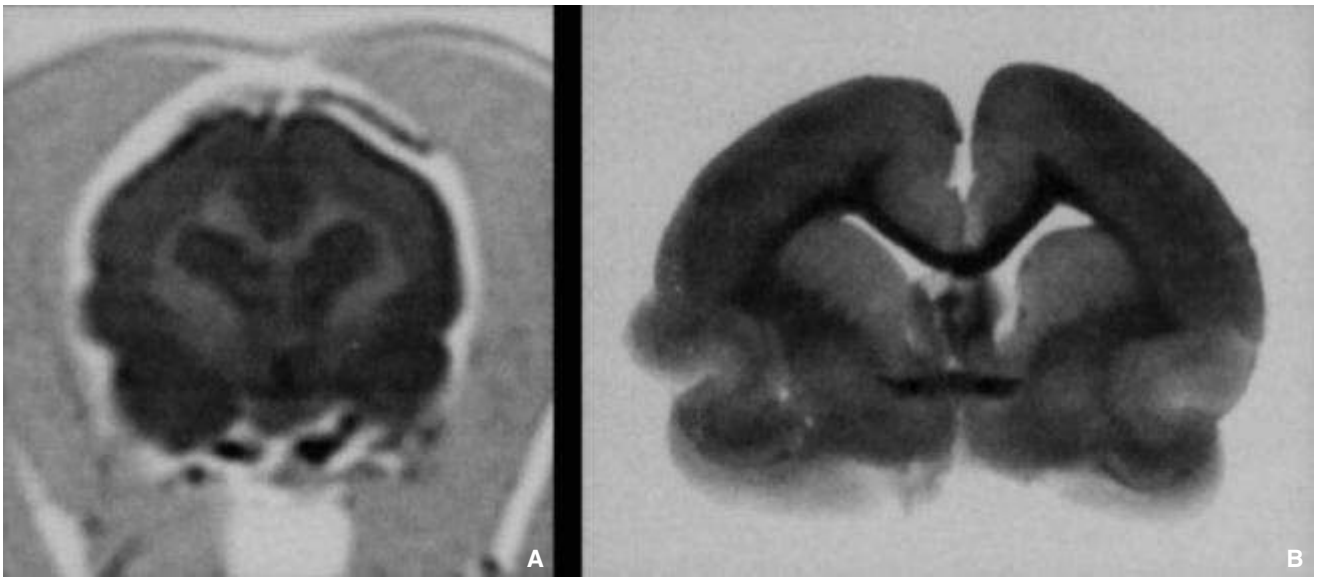


Figure 36.35 Magnetic resonance images of a 3-year-old Lhasa Apso dog. Transverse proton density magnetic resonance image (**A**) and transverse section of gross specimen (**B**) at the site corresponding to (**A**). The surface of the cerebrum is smooth with only a few gyral formations. The thick cortical gray matter and absence of the corona radiata are visible. (*Source*: Saito et al., 2002.)

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common cause of congenital hydrocephalus is a primary congenital stenosis or aplasia of the mesencephalic aqueduct associated with fused rostral colliculi (Thomas, 2010). Congenital hydrocephalus is common in some breeds of dogs, with toy and brachycephalic breeds at highest risk for the disease, thereby suggesting a hereditary basis in many of these dogs (Selby, 1979). Hydrocephalus resulting from impediment of CSF outflow from the ventricular system is referred to as obstructive or noncommunicating hydrocephalus. In cases where there is no associated malformation in the mesencephalic aqueduct, the cause of congenital hydrocephalus remains unknown. Congenital hydrocephalus may produce enlargement of the calvarium and failure of closure of the suture lines of the skull. Consequently, affected puppies may have a persistently open fontanelle. Clinical signs of hydrocephalus include behavioral changes, ataxia, and seizures. Ventrolateral strabismus is a common ocular manifestation of congenital hydrocephalus due, in part, to enlargement of the calvarium with subsequent impingement on the orbits from the dorsolateral aspects. This consequently pushes the eyes in a ventrolateral direction and produces a "sunset" appearance to the corneas. Congenital hydrocephalus may also cause cranial nerve compromise and subsequent ventrolateral strabismus. On relatively rare occasions, hydrocephalus may produce papilledema.

Lissencephaly

Lissencephaly is a condition characterized by a lack of gyri and sulci over the cerebral cortex (i.e., a smooth cortex) (Fig. 36.35). Affected individuals also have abnormalities in cerebrocortical neuronal organization. The condition is presumed inherited in Lhasa Apso dogs (Greene et al., 1976; Saito et al., 2002) but is observed in other breeds (Fraser et al., 2016; Lee et al., 2011; MacKillop, 2011; Shimbo et al., 2017). Affected puppies have abnormal behavior, may be difficult to train, may have evidence of altered postural reactions and may lack, or have reduced, menace responses. All of these clinical signs are attributed to abnormalities of the cerebral cortex.

Quadriplegia and Amblyopia

A syndrome of decreased vision with nystagmus, ataxia, and tremors has been described in the Irish Setter. This syndrome is thought to be inherited as a postnatally lethal, autosomal recessive trait (Palmer et al., 1973; Sakai et al., 1994). Most animals are unable to stand at birth, although walking movements are made that propel them in a "seal-like" manner when prone. Vision is difficult to evaluate in a very young animal, but those affected lack fixation responses as well as menace responses and dazzle reflexes. The PLRs are normal. The ocular fundus is normal on fundic examination as well. Electroretinographic findings have not been reported. CNS lesions include degeneration and necrosis of the cerebellar cortex, with severe loss of Purkinje cells. Histopathologic findings do not correlate well with clinical neurologic or ocular findings.

Canine: Developmental

Fibrosing Esotropia

Fibrosing esotropia is a progressive esotropia that can be found in juvenile large or giant breed dogs affected by extraocular muscle myositis (Allgoewer et al., 2000). The disease is of unknown origin; it causes fibrosis of the medial rectus, ventral rectus, and ventral oblique muscles (Allgoewer et al., 2000). The condition can be unilateral but generally is bilateral, and there does not seem to be a sex predilection (Allgoewer et al., 2000). Affected animals may have impaired vision caused by the severity of the esotropia.

Forced duction testing (i.e., passive or active manipulation to cause the globe to move in a particular direction) is generally indicative of the problem. Passive forced duction tests are indicative of mechanical restriction, because the globe cannot be forced into the direction of gaze limitation, thereby indicating muscle entrapment or fibrosis of the muscle. Active forced duction tests reveal a lateral rectus capable of pulling the globe caudally but not capable of rotating it laterally. No active contraction can be felt on the medial side of the globe, indicating either entrapment or degeneration of the muscle. Surgical correction may restore eye position and vision in some patients (Allgoewer et al., 2000).

Lafora Disease (Myoclonic Epilepsy)

Lafora disease is an adult onset condition characterized by progressive development of episodic myoclonus of the head, neck, and whole body. The condition has been described in a variety of breeds of dogs, although an expanded repeat mutation in the *NHLRC1* (*EPM2B*) genes have been described in Miniature Wire-Haired Dachshunds, Bassett Hounds, and Beagles (Hajek et al., 2016; Lohi et al., 2005). Patients may present with a complaint of a visual disturbance causing these attacks. Periodic episodes of myoclonus can be triggered by auditory and/or visual stimulation (e.g., stroboscopic light – the flicker from a television or alternating patterns of light and dark as one drives by a row of trees) (Lohi et al., 2005; Webb et al., 2009a). Clinical signs develop in affected animals between 3.5 and 12 years of age (Swain et al., 2017). Over one-third of dogs with Lafora disease have complaints of poor vision or blindness (Swain et al., 2017). Dogs are typically euthanized when clinical signs become so frequent as to deleteriously affect their quality of life (Swain et al., 2017). In children, however, signs develop typically in their teens and children typically die within 10 years from the onset of clinical signs. Diagnosis is made based upon signalment, clinical signs, and histopathologic identification of intracellular periodic acid Schiff-staining inclusions (Lafora bodies) (i.e., poorly branched glycogen-like polysaccharides

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[polyglucosan] intracellular inclusions) within a variety of tissues including liver, muscle, spleen, skin, and retina. Alternatively, a genetic test is available (Ahonen et al., 2018). Genetic testing has resulted in a significant decline in the prevalence of the mutation in Miniature Wire-Haired Dachshunds (Ahonen et al., 2018).

Canine: Acquired

Canine Distemper

Canine distemper virus (CDV) is caused by an enveloped, single-stranded RNA Morbillivirus in the Paramyxoviridae family (for review see Deem et al., 2000). CDV infects a wide variety of families of animals including Canidae (e.g., dogs), Procyonidae (e.g., raccoons), Ursidae (e.g., bears), Mustelidae (e.g., ferrets, skunks), and Hyaenidae (e.g., hyaena). The virus is spread mainly by inhalation of viral particles in aerosolized respiratory or other infected secretions such as urine. Widespread vaccination of dogs has markedly decreased the incidence of typical disease, and partial immunity may produce disease syndromes characterized more by neurologic signs than catarrhal signs of pneumonia and gastroenteritis. Clinical signs of CDV will vary with the strain of virus, immunity, and age of the host.

Acute ocular signs of CDV are usually associated with a bilateral conjunctivitis with serous ocular discharge that progresses to mucopurulent in nature. The palpebral conjunctiva is primarily involved but the cause of this conjunctivitis may be difficult to diagnose if respiratory and gastrointestinal signs are either minimal or subclinical. The cornea has not been described as being a target for the virus unless a lacrimal adenitis or dehydration has resulted in a marked reduction in tear production (i.e., keratoconjunctivitis sicca [KCS]). The CDV may produce an inflammatory reaction in the lacrimal gland characterized by mononuclear and neutrophilic inflammatory infiltration as well as by marked degenerative changes in the glandular tissue (Martin & Kaswan, 1985). Corneal ulceration is often profound with the development of multiple descemetoceles with or without corneal perforations in one or both eyes. KCS usually resolves in 4–8 weeks if the animal recovers from the systemic infection. Another mechanism for corneal involvement is distemper encephalitis producing a fifth cranial nerve palsy (i.e., neurotrophic keratitis).

CDV often produces a multifocal, nongranulomatous chorioretinitis, which is usually an incidental finding. The incidence of chorioretinitis is unknown but probably varies, as do those of the neurologic signs, with the strain of virus and the immunocompetency of the host. In one study, dogs with neurologic forms of CDV had a 41% overall prevalence of chorioretinal lesions; in contrast, 83% of dogs with chronic leukoencephalopathy syndromes had chorioretinal lesions (Thomas et al., 1993). These lesions are typically multifocal, and they are reportedly more frequent in the peripheral to midperipheral non-tapetal fundus (Fischer, 1971). Acute lesions must be differentiated from scars, because the latter will not correlate well with acute systemic signs. Active lesions in the non-tapetal region are white, somewhat fluffy, and have mildly indistinct borders. Acute lesions progress to scars that are white, flat, and have sharply demarcated borders. In the tapetal region, the acute lesions are subtle, with loss of tapetal detail, and they may have a mild, overlying haziness. With time, these develop into hyperreflective lesions with sharp borders and varying degrees of pigment clumping. Lesions in both the tapetal and non-tapetal areas are typically circular to oval in shape and often become confluent with adjacent lesions, thus producing a scalloped pattern. Occasionally, chorioretinal lesions are diffuse, blinding, and may mimic the genetic syndrome of progressive retinal atrophy, with diffuse tapetal hyperreflectivity, optic nerve atrophy, and non-tapetal pigment dispersion.

Histopathologic retinal changes are characterized by retinal degeneration with, in some instances, perivascular cuffing. Lesions may be focal or diffuse, characterized by loss of ganglion cells, proliferation and clumping of the retinal pigment epithelium, focal or diffuse atrophy of photoreceptors, disorganization of retinal layers, focal gliosis, choroidal atrophy, and CDV inclusion bodies in glial cells. Acute cases may have retinal edema, vascular congestion, and perivascular cuffing (Jubb et al., 1957). The variations in reported ocular lesions may result from the stage of examination, immunocompetence of the animal, and the multiple mechanisms by which the lesions are produced. In the CNS, lesions of acute infections in young or immunocompromised patients are characterized by neuronal necrosis, with a minimal inflammatory reaction. With immunocompetent hosts or chronicity, the CNS lesions are characterized by mononuclear inflammation and secondary demyelinization (Thomas et al., 1993).

The most dramatic clinical ocular problem associated with CDV is optic neuritis (Fig. 36.36), which is characterized by an acute onset of bilateral blindness and mydriasis. If inflammation extends rostrally to the optic disc/papilla, ophthalmoscopic signs of peripapillary hemorrhages and edema, retinal vascular congestion, and elevation of the papilla are observed. If the optic neuritis remains retrobulbar, however, the diagnosis is made on the basis of exclusion (i.e., blind eyes with dilated pupils and normal retinal function as tested by electroretinogram [ERG]). The optic neuritis syndrome may be isolated, prodromal, or concurrent with other neurologic signs of CDV. Distemper-associated blindness also may occur with inflammation of the optic tracts, LGN, optic radiation, or occipital cortex.

Ocular signs are suggestive of, but not definitive for, CDV. Acute lesions of chorioretinitis usually correlate well with concurrent systemic disease, but chorioretinal scars may not. CDV inclusions may be identified in infected monocytes, lymphocytes, neutrophils, or red blood cells during evaluation of a stained peripheral blood smear. Alternatively,

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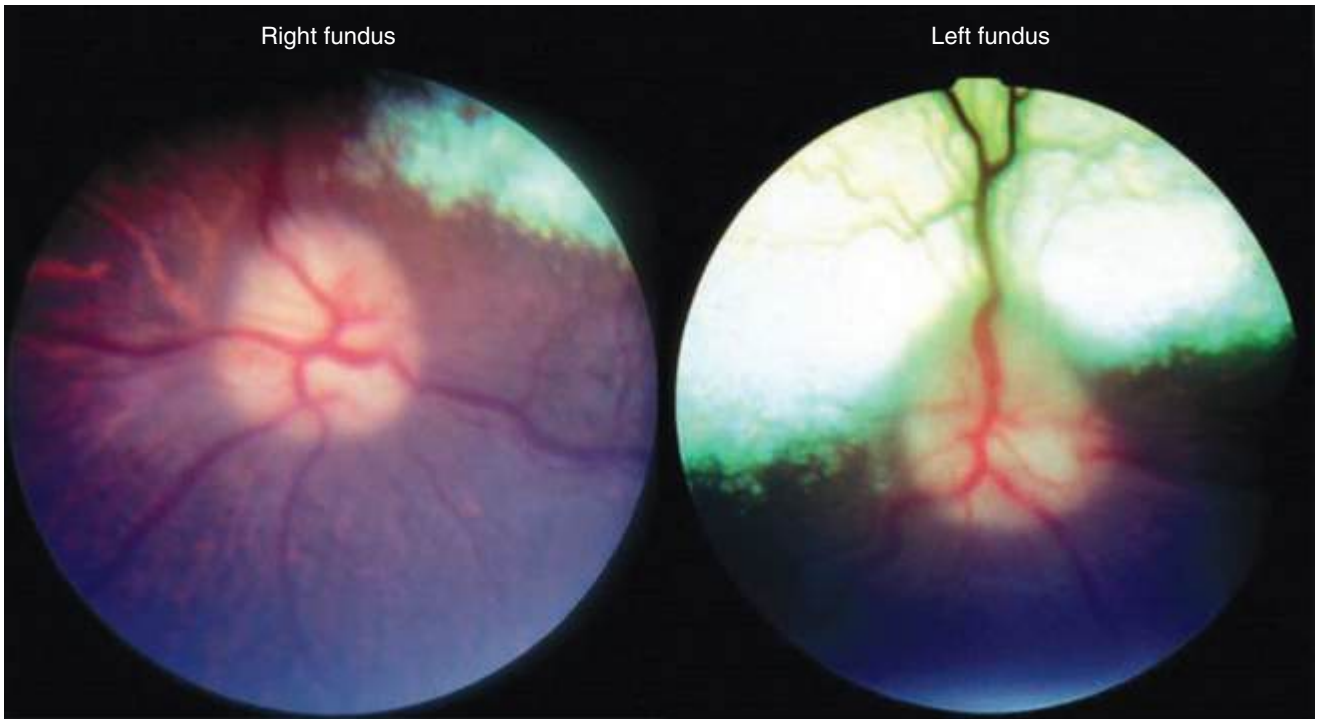


Figure 36.36 Right and left fundus photographs for a Jack Russell Terrier. Notice the indistinct margins of the optic nerve, the peripapillary edema, and the swollen optic nerve heads. (*Source*: Richards et al., Can Vet J, 2011.)

positive immunofluorescence by detection of viral antigen from conjunctival swabs/scrapings or blood smears, using methods such as fluorescent antibody testing may be helpful in diagnosing CDV early in the course of systemic disease (5–21 days postinoculation), but negative findings are inconclusive (Fairchild et al., 1967). This should not inhibit the examiner from performing immunofluorescent antibody testing, however, because one report on encephalomyelitis found an overall positive rate of 54% (and one as high as 75%) despite the mean duration of neurologic signs being 20 days (Fischer, 1971). Further, CDV has immunohistochemically been identified and diagnosed in skin and footpads from infected dogs (Haines et al., 1999). RT-PCR assays have been shown to be both sensitive and specific for detection of experimentally induced CDV (Frisk et al., 1999). Because no specific antiviral therapy against CDV is available, treatment is mainly symptomatic. Conjunctivitis and decreased tear production are treated with topical antibiotics and lubricants. Acute optic neuritis is treated with systemic anti-inflammatory dosages of glucocorticoids if other signs of CDV are absent. Vaccination is the key to preventing CDV. The prognosis for dogs with neurologic disease is considered guarded to poor.

Cerebrovascular Accidents

Cerebrovascular disease causing neurologic dysfunction is not uncommon in dogs (Boudreau, 2018). Cerebrovascular accidents can either manifest as strokes or transient ischemic attacks (TIAs). Strokes are defined as rapidly occurring focal or generalized cerebral dysfunction lasting longer than 24 hours, or resulting in death, and occur because of vascular disease (Boudreau, 2018). TIAs, however, are characterized by rapid onset focal cerebral dysfunction occurring when no other cause for the clinical signs is found. The character of the dysfunction, during a TIA, implicates a region of the brain served by one vascular supply (Boudreau, 2018).

Cerebrovascular accidents can be the result of cerebral hemorrhage (hemorrhagic stroke) from diseases such as systemic hypertension (primary or secondary), vascular malformations, intracranial neoplasia, coagulopathies, or trauma. Cerebrovascular accidents can also arise from blockage of blood flow to the brain (ischemic stroke) resulting from thrombosis, embolic events, atherosclerosis, vasculitis, or neoplasia. Regardless of the cause of the cerebrovascular accident, ocular manifestations of impaired brain function may manifest and will vary according to the neuroanatomic location of the cerebrovascular accident. Because cerebrovascular accidents are acute, clinical signs are acute. Ophthalmic manifestations of cerebrovascular disease may occur at the time of the cerebrovascular accident or develop shortly thereafter. In addition, considering that cerebrovascular accidents typically affect relatively large areas of the brain, abnormal neuro-ophthalmic findings have not been reported as the sole manifestation of cerebrovascular accidents in dogs. For reviews on cerebrovascular accidents in dogs see Garosi (2010) and Boudreau (2018).

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Dysautonomia

Canine dysautonomia is an idiopathic disease resulting from a generalized loss of autonomic function. Dogs affected are typically young adults of medium to large physical stature that typically live in rural areas. It is important to note, however, that animals ranging in age from 5 weeks to 15 years of age and of a variety of breeds can be affected (Berghaus et al., 2002; Harkin et al., 2002a). Canine dysautonomia has been reported in Europe (Rochlitz & Bennett, 1983; Presthus & Bjerkas, 1987) and the United States (Berghaus et al., 2001; Harkin et al., 2002a; Longshore et al., 1996). The disease is prevalent in dogs living in the midwestern United States, specifically, Kansas and Missouri. Affected dogs present with an acute (days) or subacute (2 to 3 weeks) history of clinical signs referable to loss of autonomic (sympathetic and parasympathetic) function (Berghaus et al., 2001; Harkin et al., 2002a). Common nonocular clinical signs include regurgitation, vomiting, diarrhea, anorexia, weight loss, dry mucous membranes, and purulent nasal discharge (Longshore et al., 1996; Harkin et al., 2002a). Dogs may present with limited clinical signs that progress to involve more signs of autonomic failure during the course of the disease. Ocular signs include ocular discharge, protruding third eyelid, mydriasis, and a reduction in Schirmer tear test values (Harkin et al., 2002a,b; Longshore et al., 1996). Ocular pharmacologic testing with topical 0.05% pilocarpine in dogs with mydriatic pupils, and signalment, history, and clinical signs consistent with dysautonomia provides useful information supporting a diagnosis of dysautonomia. In affected dogs, instillation of 0.05% pilocarpine will cause rapid (<45 minutes) miosis compared with unaffected animals (O'Brien & Johnson, 2002). Severe neuronal degeneration has been reported in a variety of autonomic ganglia including the cranial cervical and ciliary ganglia (Harkin et al., 2002a). In addition, neuronal degeneration of various brainstem nuclei, including the facial, oculomotor, and motor nucleus of the trigeminal nerve, has also been reported (Harkin et al., 2002a). At least 85% of dogs affected with dysautonomia succumb to the disease and are euthanized (Harkin et al., 2002a).

Idiopathic Oculomotor Neuropathy

Oculomotor neuropathy of undetermined etiology has been described in 14 dogs (Tetas Pont et al., 2017). Affected dogs were between 3 and 10 years of age and without sex predilection. Average duration of clinical signs prior to presentation was 73 ± 195 days (mean ± SD). Eleven of 14 dogs presented with complete ophthalmoparesis/ophthalmoplegia, and 3/14 presented with only internal ophthalmoplegia (Fig. 36.37). Bloodwork was unremarkable in all 14 patients. CSF showed a mild pleocytosis. No infectious etiology could be determined. Magnetic resonance imaging showed enlargement of CN III in 6/14 patients with peripheral mass-effect, although clinical deterioration or involvement of other cranial nerves was not observed for any patient during follow-up ranging between 20 and 41 months. Seven of 11 dogs with total ophthalmoparesis/ophthalmoplegia had improved extraocular signs with resolved strabismus, whereas internal opthalmoparesis/ophthalmoplegia had partially resolved or not resolved in 3/14 and 11/14 patients, respectively. Treatment with corticosteroids does not appear to aid in resolution of clinical signs.



Figure 36.37 Mydriasis secondary to internal ophthalmoplegia, and upper eyelid ptosis and neuromuscular strabismus (dorsolateral) secondary to external ophthalmoparesis of the left eye in a 9.5-year-old male entire Staffordshire Bull Terrier. (*Source*: Tetas Pont et al., 2017.)

Idiopathic Facial Nerve Paralysis

The cause of idiopathic facial nerve paralysis is unknown, although it shares clinical features of Bell's palsy in humans (Smith et al., 2012; Tiemstra & Khatkhate, 2007). Although viruses have been postulated to play a role in idiopathic facial nerve paralysis, none have been proven to be important in the pathogenesis of this disease. Facial nerve paralysis has been found to be idiopathic in 75% of dogs, whereas 25% of cases of facial nerve paralysis are caused by conditions such as otitis media/interna and hypothyroidism (Kern & Erb, 1987). Patients with idiopathic facial nerve paralysis can have concurrent idiopathic peripheral vestibular dysfunction (Jeandel et al., 2016; Motta et al., 2011; Smith et al., 2012). Clinical signs of idiopathic facial nerve paresis/paralysis, depending upon when during the course of the disease the patient is examined, include acute paresis/paralysis of the facial muscles causing a drooping of the lip, reduced or absent menace response, and reduced or absent palpebral reflex (although sensory function is preserved as the trigeminal nerve is not affected). The condition can be unilateral or bilateral in nature, with or without concurrent signs of peripheral vestibular dysfunction (Jeandel et al., 2016; Smith et al., 2012). In some instances, reduced tear production may

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be found, presumably because of involvement of the preganglionic parasympathetic nerve fibers that travel with CN VII. Diagnosis of idiopathic facial nerve paralysis is a diagnosis of exclusion of all potential other causes, for example, hypothyroidism (Jaggy & Oliver, 1994; Jaggy et al., 1994; Kern & Erb, 1987; Vitale & Olby, 2007), peripheral nerve sheath neoplasia (Kern & Erb, 1987), etc. In addition, one should ensure that there is no history of trauma or prolonged anesthesia as both of these can result in facial nerve paralysis. Prognosis is variable with idiopathic facial nerve paralysis with or without concurrent peripheral vestibular dysfunction. Facial function may return for some patients within weeks or months, but it may never return (Kern & Erb, 1987). As mentioned previously, chronic forms of facial nerve paralysis must be differentiated from hemifacial spasm/tetany.

Idiopathic Vestibular Disease

Idiopathic vestibular disease occurs in approximately 40% of canine cases of acute peripheral vestibular disease (Schunk & Averill, 1983). As the name describes, the cause of this condition is unknown. In dogs with polymerase chain reaction (PCR) evidence of canine herpes virus-1 infection involving the vestibular labyrinth or ganglion, there is no evidence of vestibular dysfunction in these animals (Parzefall et al., 2011). Affected animals are 5 years of age and older (Schunk & Averill, 1983). Clinical signs are limited to that seen with peripheral vestibular disease or may occur concurrently with ipsilateral idiopathic facial nerve paralysis (Motta et al., 2011; Smith et al., 2012; Jeandel et al., 2016). Signs of unilateral peripheral vestibular dysfunction may include spontaneous nystagmus in the horizontal or rotary directions, limb ataxia without evidence of postural reaction deficits, and ventrolateral strabismus (Schunk & Averill, 1983; Troxel et al., 2005). Keep in mind, however, that neuroplastic mechanisms may result in the animal compensating for the static vestibular dysfunction (e.g., spontaneous nystagmus is typically the first clinical sign to resolve despite there being active disease) (Darlington & Smith, 2000). As with any idiopathic condition, diagnosis is based upon excluding other causes of acute onset peripheral vestibular dysfunction (e.g., otitis media/interna [Schunk & Averill, 1983]; ototoxicity [Merchant, 1994; Pickrell et al., 1993]; neoplasia [Troxel et al., 2005], hypothyroidism [Higgins et al., 2006; Jaggy & Oliver, 1994; Jaggy et al., 1994], etc.). There is no treatment for this condition. Prognosis for idiopathic vestibular disease is excellent, although recovery may take several weeks and a head tilt may persist (Schunk & Averill, 1983).

Immune-Mediated Retinitis

Immune-mediated retinitis (IMR) is characterized by a sudden onset of complete blindness or night blindness in dogs and has similar features to sudden acquired retinal degeneration syndrome (SARDS) (see later). Dogs with IMR typically present with sudden blindness which is often preceded by months to years of sporadic, temporary bouts of decreased vision (usually night vision). In addition, dogs with IMR may have a history of abnormal pupillary appearance (pupillary dilation in bright light and/or anisocoria with one pupil being dilated). Most dogs with IMR are reportedly healthy; however, some dogs with IMR (20% in one report) also have concurrent health issues including neoplasia and neurological abnormalities. On ophthalmic examination, dogs with IMR appear blind and lack a menace response, although they tend to blink in response to bright light (positive dazzle reflex). Ophthalmoscopic examination of IMR-affected dogs is generally unremarkable; however, a characteristic pale optic disc caused by the presence of vascular attenuation of the optic nerve head may be noted, similar to SARDS-affected patients. When assessing PLRs in IMR-affected dogs using colorimetric PLR testing (blue light versus red light stimulation; please see SARDS later), there is a nearly complete absence of the PLR in response to red light stimulation and a normal PLR when blue light is used. Dogs with IMR have detectable ERG waveforms which can be normal, or reduced, or increased in amplitudes, unlike SARDS-affected patients. The pathogenesis of IMR in dogs remains unknown, although it shares similar symptoms to antibody-mediated retinopathies in humans. Retinal autoantibodies have been documented in two of three serum samples from three dogs with IMR. Treatment for dogs with IMR includes oral doxycycline and steroids typically long-term. Recovery of the PLR in response to red light stimulation is reported to be the most reliable indicator of therapeutic success. Reevaluation of the ERG waveforms for increases in their amplitudes may also be helpful, as progressive, uncontrolled IMR is often linked with a decrease in retinal electrical activity (Grozdanic et al., 2008).

Masticatory Myositis and Extraocular Myositis

Masticatory myositis (masseter, temporalis, pterygoid muscles) and extraocular myositis are two forms of focal inflammatory myopathies (Carpenter et al., 1989; Evans et al., 2004a; Gilmour et al., 1992). Masticatory myositis typically affects young to middle-aged adult dogs and predominantly medium to large breeds (Evans et al., 2004a; Gilmour et al., 1992). Masticatory myositis may occur concurrently with other immune-mediated diseases including myasthenia gravis (Clooten et al., 2003). Signs include spasm of the masticatory muscles and difficulty in opening the mouth, pain on palpation of the muscles, muscle swelling, or muscle atrophy. Muscular atrophy is a more common clinical sign (72% of cases) than muscle swelling (14% of cases) and is likely because of the chronicity of the disease at presentation of most cases (Gilmour et al., 1992). Ocular signs have been documented in 45% of cases and are variable depending on the chronicity of the disease. Ocular manifestations of acute masticatory myositis include exophthalmos and prolapse of the third eyelid caused by swelling of the pterygoid muscle, and possible optic nerve tension/compression causing

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blindness (Evans et al., 2004a; Gilmour et al., 1992; Lewis, 1994; Smith, 1989). Interestingly, unilateral dynamic exophthalmos and lateral strabismus, upon opening the mouth, have been reported in a 5.5-year-old mixed-breed dog (Czerwinski et al., 2015). This patient did not have pain upon opening the mouth or when manually retropulsing the eye (Czerwinski et al., 2015). In cases of chronic masticatory myositis, enophthalmos has been reported (Gilmour et al., 1992). Signs are usually, but not invariably, bilateral.

Clinical signs, ± peripheral eosinophilia, ± elevated levels of serum creatinine kinase, ± abnormal electromyograms (EMGs), ± presence of circulating antibodies for type 2M fibers, and positive muscle immunohistochemistry for antibodies against type 2M fibers are used to provide a diagnosis of masticatory myositis (Evans et al., 2004a). Predominant histopathologic changes identified in affected muscle biopsies include: (1) cellular infiltration with varying degrees of lymphocytes, and/or macrophages, and/or eosinophils; (2) histologic evidence of muscle atrophy, necrosis and fibrosis; (3) presence of fibrosis depending upon the chronicity of the disease; and (4) immune complexes bound to type 2M muscle fibers (Evans et al., 2004a; Shelton et al., 1987). Bacteria containing antigenic similarities to type 2M muscle fibers may initiate the immune-mediated myositis (Shelton et al., 1987). Immunosuppressive doses of systemic corticosteroids (prednisone 1–2 mg/kg PO twice daily) for a minimum of one month before tapering are recommended at any stage of the disease. Prognosis is good for dogs treated appropriately with immunosuppressive dosages of corticosteroids, although some dogs may require life-long therapy with these drugs.

The second form of focal inflammatory myositis is extraocular myositis. Extraocular myositis involves only the extraocular muscles and affects predominantly young large-breed dogs. Bilateral exophthalmos is the predominant clinical sign in the acute form of the disease (Allgoewer et al., 2000; Evans et al., 2004a). Chronic extraocular myositis can result in restrictive strabismus and is caused by chronic fibrosis of the extraocular muscles (see Fig. 37.1.12) (Allgoewer et al., 2000). As opposed to masticatory myositis, circulating antibodies to type 2M muscle fibers are not present (Allgoewer et al., 2000; Evans et al., 2004a). Inflammatory infiltrate of affected muscles include lymphocytes and macrophages, and fibrosis may be present depending on the chronicity of the disease (Evans et al., 2004a). Immunosuppressive corticosteroid therapy is indicated in cases of extraocular myositis (as for masticatory myositis). Adjunctive corrective strabismus surgery may be useful in some cases of chronic extraocular myositis where the disease is in remission (Allgoewer et al., 2000).

Meningoencephalitis of Unknown Etiology

Meningoencephalitis of unknown etiology (MUE) is a term used to group together a variety of seemingly immune-mediated inflammatory diseases involving the CNS in dogs (Coates & Jeffery, 2014; Hoon-Hanks et al., 2018; Talarico & Schatzberg, 2010). The MUE umbrella includes granulomatous meningoencephalitis (GME), necrotizing meningoencephalitis (NME), necrotizing leukoencephalitis (NLE), and eosinophilic meningoencephalitis of unknown etiology (EMUE) (Cardy & Cornelis, 2018; Cooper et al., 2014; Talarico & Schatzberg, 2010). Both NME and NLE can be found predominantly in small breeds and the conditions are both rapidly progressive and fatal despite immunosuppressive therapy (Cooper et al., 2014). EMUE typically affects young large breed dogs and is characterized by an eosinophilic pleocytosis on CSF analysis. EMUE-affected dogs may have a circulating eosinophilia, are negative for infectious/parasitic agents, and these patients respond similarly to immunosuppressive therapy as patients with GME (Cardy & Cornelis, 2018). Visual impairment has been described in patients with NME, NLE, and EMUE. MUEs may share similar pathophysiology, in that they are all seemingly immune-mediated. The following discussion focuses on GME, given that salient clinical differences with NLE, NME, and EMUE, have been described previously.

GME is an idiopathic non-suppurative meningoencephalomyelitis, and seemingly immune-mediated disease, seen in dogs (Braund, 1985; Talarico & Schatzberg, 2010). Histopathologically, GME is characterized by perivascular cuffing with mononuclear cells (Braund, 1985). One study has shown that perivascular cuffs were composed of a heterogeneous population of major histocompatibility complex (MHC) class-II antigen-positive macrophages and mainly CD3 antigen-positive lymphocytes, supporting a hypothesis of T-cell-mediated, delayed type hypersensitivity of an organ-specific autoimmune disease (Kipar et al., 1998). Proposed pathogeneses for GME have included a primary immune-mediated phenomenon, precancerous form of lymphoma, and various infectious etiologies. Studies have failed to show an infectious etiology, although it is possible that infectious diseases may play a role in antigenic stimulation and subsequent MUE development (Barber et al., 2010, 2012; Hoon-Hanks et al., 2018).

The disease is typically seen in young small breeds, although any breed or age of dog may be affected. GME is described as being one of three types, namely: (1) disseminated; (2) focal; or (3) ocular. Any combination or permutation of these forms can occur. In the latter form, GME may involve the optic nerves, thus producing a syndrome of acute blindness, papilledema, retinal and peripapillary hemorrhages, and occasionally, extension into the globe, which in turn produces retinal detachments and retinal infiltrates (Fischer & Wi-Kwand, 1971; Smith et al., 1977). Confinement to the retrobulbar optic nerves may limit ocular lesions to blindness and dilated pupils (Braund, 1985; Garmer et al., 1981; Fischer & Wi-Kwand, 1971; Russo, 1979; Smith et al., 1977; Thomas & Eger, 1981). A retrospective study of optic neuritis in 96 dogs found that the majority of optic neuritis

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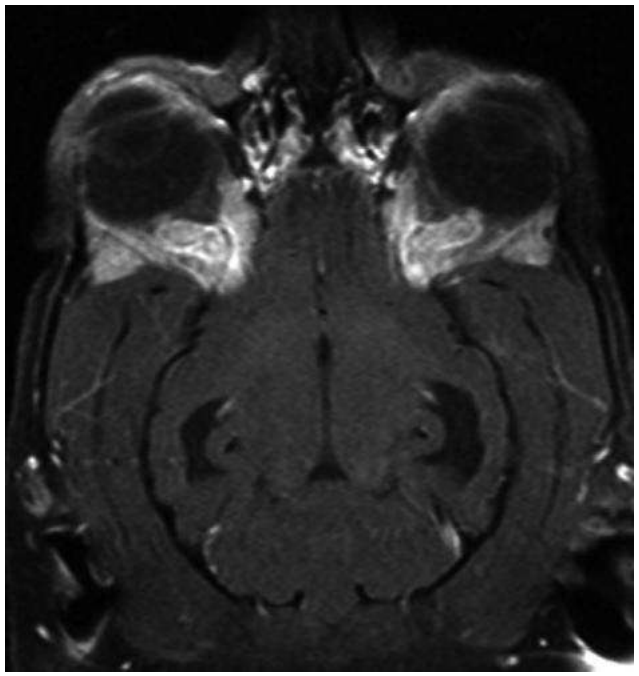


Figure 36.38 Magnetic resonance imaging (contrast T1-weighted) of a 9-year-old, male castrated Maltese with isolated optic neuritis. Marked thickening of both optic nerves with peripheral contrast enhancement is present. (*Source*: Smith et al., 2017.)

in dogs is caused by multifocal GME (35/96 patients) and isolated idiopathic optic neuritis (confirmed and unconfirmed cases) (42/96) (Smith et al., 2018) (Fig. 36.38). Of the confirmed cases of isolated optic neuritis and having had CSF analysis examined (n=17), seven had elevated CSF nucleated cell counts and these patients may have had an ocular form of GME (Smith et al., 2018), although histopathology would be required to confirm a diagnosis.

A definitive antemortem diagnosis of GME is difficult to make, but multifocal CNS dysfunction, lack of infectious agents, increased CSF protein levels, pleocytosis with mononuclear cells, CT and/or MRI findings consistent with inflammation, and a positive response to appropriate immunosuppressive therapy are highly suggestive. Definitive antemortem diagnosis can be made based on the above in concert with brain biopsy (Munana & Luttgen, 1998).

Treatment involves aggressive use of immunosuppressive corticosteroids with or without radiation therapy (Munana & Luttgen 1998) or, more commonly, immunosuppression using a combination of corticosteroids with one or more of cytosine arabinoside (Menaut et al. 2008; Zarfoss et al. 2006;), azathioprine (Wong et al., 2010), leflunomide (Gregory et al. 1998), or cyclosporine-A (Adamo & O'Brien, 2004; Nuhsbaum et al., 2002;) or other immunosuppressive drugs (Coates & Jeffery, 2014). Prognosis for survival varies from weeks to years with appropriate combinatorial immunosuppressive therapy.

Myasthenia Gravis

Myasthenia gravis is a disease affecting the neuromuscular junction (for complete review see Shelton, 2002). Myasthenia gravis is either congenital or acquired. Congenital myasthenia gravis occurs when there is a functional disorder or depletion of nicotinic acetylcholine receptors (AChRs). Congenital myasthenia gravis is reported rarely in dogs (Flagstad et al., 1989; Oda et al., 1984; Palmer & Goodyear, 1978) and will not be considered further here. Acquired myasthenia gravis is the most common form occurring in dogs. The acquired condition develops because of an autoimmune targeting of AChRs which may occur as an autoimmune condition affecting only the AChR (most common: Shelton, 1998), part of another autoimmune condition (e.g., hypothyroidism: Levine et al., 2005; Shelton, 1998), or resulting as part of a paraneoplastic syndrome (e.g., thymoma: Lainesse et al., 1996; Paciello et al., 2003).

Animals with acquired myasthenia gravis can present with either generalized or focal clinical signs. Those animals with generalized myasthenia gravis will have generalized appendicular muscle paresis (weakness) that worsens with prolonged exercise, may have megaesophagus and resultant regurgitation with or without aspiration pneumonia, and spinal and cranial nerve reflexes that weaken with repeated testing. Approximately 43% of dogs with myasthenia gravis will have focalized clinical signs in the absence of appendicular muscle weakness (Shelton et al., 1997). Animals with the focal form of myasthenia gravis may present with regurgitation, and/or dysphagia, and/or change in character of vocalization because of megaesophagus, pharyngeal or laryngeal paresis, respectively (Dewey et al., 1997; Shelton et al., 1990). With respect to the eye, a paretic menace response and/or palpebral reflex may be the predominant clinical sign(s) (Dewey et al., 1997; Clooten et al., 2003; Webb et al., 1997).

A tentative diagnosis of acquired myasthenia gravis is made based on consistent clinical signs combined with immediate short-term improvement in muscular strength (e.g., improved palpebral reflex: Webb et al., 1997) after the administration of the short-acting acetylcholinesterase inhibitor, edrophonium hydrochloride (Tensilon). All presumptive cases of acquired myasthenia gravis should be confirmed by demonstrating the presence of circulating muscular AChR autoantibodies (see the Comparative Neuromuscular Laboratory at http://vetneuromuscular.ucsd.edu/).

The mainstay of therapy for acquired myasthenia gravis is the administration of anticholinesterase drugs. Therapy must be tailored according to the individual's response to therapy (for details pertaining to treatment recommendations see Shelton, 2002). Untoward side-effects of anticholinesterase drug therapy are similar to clinical signs observed in animals with organophosphate exposure including excessive salivation, lacrimation, and gastrointestinal signs

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including nausea and diarrhea. Further, animals may become paretic because of exuberant depolarization and/or desensitization of the postsynaptic (skeletal muscle) membrane. The administration of corticosteroids, or other immunosuppressive medications, concurrently with anticholinesterase drug therapy is warranted when the response to monomodal anticholinesterase therapy is less than ideal. Immunosuppressive therapy may, however, be inappropriate if underlying disease processes such as aspiration pneumonia are evident. Of course, other important aspects of therapy for canine myasthenia gravis include good supportive care (e.g., feeding regimens for dogs with megaesophagus) including appropriate antimicrobial therapy for any secondary complications arising from the disease (e.g., aspiration pneumonia). For a review discussing treatment considerations see Khorzad et al. (2011).

Complete spontaneous remission occurring from 1 to 18 months after the diagnosis of acquired myasthenia gravis is possible and has been seen in 47 of 53 dogs with the disease (Shelton & Lindstrom, 2001). Prognosis for canine myasthenic patients is, however, likely variable depending on the form (focal versus generalized), severity (mild, moderate, or severe fulminating generalized myasthenia gravis), and other underlying disease processes (e.g., neoplasia) (Shelton, 2002).

Neoplasia: Central Nervous System

Intracranial neoplasia, whether primary or secondary, often produces ocular and/or orbital signs. All animals with a suspected space-occupying CNS lesion should undergo ophthalmoscopy to determine whether papilledema, optic neuritis, or optic nerve atrophy is/are present.

The neuro-ophthalmic signs associated with intracranial neoplasia are highly variable and dogs may present with signs as subtle as internal ophthalmoparesis as the predominant clinical sign or with ophthalmic signs associated with abnormalities of multiple cranial nerves and abnormal changes in mentation and/or gait (Cullen et al., 2002; Larocca, 2000; Rossmeisl et al., 2005; Webb et al., 2005). Intracranial neoplasia frequently produces visual deficits and papilledema in association with neurologic signs (Palmer et al., 1974). Because of the great variation in myelination of the canine papilla/optic disc, early papilledema is difficult to detect unless it is asymmetrical or there is a definite rim of peripapillary edema. Intracranial tumors may also produce blindness, which may be acute in nature. Diffuse or multifocal disease may produce blindness by involving multiple sites in the visual pathways and, as a result, produce other neurologic deficits as well (Braund et al., 1977; Palmer et al., 1974). A solitary mass involving the optic chiasm may produce blindness without obvious neurologic signs. Tumors at the base of the brain in the middle cranial or rostral fossa may be varied, but pituitary carcinomas that are nonfunctional, optic nerve gliomas, and meningiomas are likely candidates for optic chiasmal involvement (Davidson et al., 1991; Safaty et al., 1988). Papilledema was not a feature of these lesions, perhaps because of their relatively small size. Clinically, blindness is often acute. In reality, it is progressive, and partial visual deficits are not generally noted by owners. Because blindness is accompanied by afferent pupillary defects with a normal ocular fundus, the syndrome must be differentiated from SARDS using ERG. Early diagnosis and aggressive therapy may result in the return of some vision (Davidson et al., 1991).

Neurogenic Keratoconjunctivitis Sicca

KCS is a progressive inflammation of the cornea and conjunctiva caused by neurogenically derived tear production deficiency. Lesions anywhere along the efferent path, including the parasympathetic nucleus of the facial nerve, the main trunk of the facial nerve, geniculate ganglion, major petrosal nerve, the nerve of the pterygoid canal, the pterygopalatine ganglion, or the postganglionic parasympathetic fibers, will reduce tear production and result in neurogenic KCS.

Lesions to the preganglionic parasympathetic fibers may be caused by otitis (media or interna) or by petrositis (i.e., inflammation of the petrous temporal bone) (Kern & Erb, 1987). In such cases, the reduced tear production may be accompanied by signs of facial paralysis and Horner's syndrome if the adjacent facial nerve motor neurons or sympathetic fibers are involved. Neurogenic KCS may also present without signs of facial paralysis if the major petrosal nerve is damaged distal to the geniculate ganglion of the facial nerve.

Preganglionic parasympathetic denervation can also occur caused by erosive lesions involving the floor of the middle fossa of the skull and affecting the major petrosal nerve. In such cases, the trigeminal nerve may frequently be involved, and the KCS will be accompanied by facial anesthesia and xeromycteria (i.e., dry nasal mucosa).

Lesions involving the pre- and postganglionic parasympathetic fibers, as well as the pterygopalatine ganglion itself, result from diseases affecting the pterygopalatine fossa. Causes include periorbital myositis or cellulitis (frequently caused by maxillary dental disease) or drainage of dental abscesses (Ramsey et al., 1996). Such diseases may be accompanied by periocular anesthesia and xeromycteria. Postganglionic parasympathetic lesions are most commonly caused by orbital trauma (Matheis et al., 2012). As the postganglionic fibers course together with the zygomatic nerve (the first branch of the maxillary division of the trigeminal nerve), periocular anesthesia may also occur. One retrospective study of canine neurogenic KCS has identified that a number of cases may be idiopathic in nature and that some of these idiopathic cases may enter spontaneous remission (Matheis et al., 2012).

Regardless of the cause of neurogenic KCS, patients with primary neurogenic KCS are unlikely to respond to

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immunomodulating drugs such as cyclosporine (Matheis et al., 2012). However, denervation hypersensitivity occurring after postganglionic lesions makes patients with neurogenic KCS responsive to direct-acting parasympathomimetic drugs. Treatment with oral pilocarpine is advocated in these cases (Matheis et al., 2012).

Otitis Media/Interna

As the name implies, otitis media/interna is characterized by inflammation of the middle and inner ears, respectively. Otitis interna represents the most common cause of peripheral vestibular disease in dogs (Schunk & Averill, 1983). The causative agents of otitis media/interna in dogs include primarily bacteria, fungi, and yeast. Otitis media is thought to develop, primarily from extension of a preexisting otitis externa (Webb, 2014). Alternatively, otitis media can result from inoculation via the eustachian tube or via hematogenous spread (Webb, 2011). Neurologic signs of otitis media include aural pain, head shaking, facial nerve paresis/paralysis, Horner's syndrome, and neurogenic keratoconjunctivitis sicca. Signs consistent with peripheral vestibular syndrome exist only if there is otitis interna but not if only otitis media is present alone (Webb, 2011). Diagnosis is based upon aural examination, evidence of conductive hearing loss based upon clinical signs and results of brainstem auditory evoked response (BAER) testing, cross sectional imaging (CT or MRI), and myringotomy with aspiration of middle ear contents (Webb, 2011). Treatment is based upon choosing and implementing an appropriate antimicrobial based upon culture and sensitivity results. Surgical curettage and drainage of the middle ear may be necessary. Prognosis is variable and depends upon the chronicity of the disease and other predisposing factors (Webb, 2011). Importantly, other disease processes that may cause similar clinical signs include neoplasia, nasopharyngeal polyps, and trauma.

Pupillotonia (Adies Pupil)

Presumed pupillotonia has been rarely described in dogs. It is thought that pupillotonia is similar to that observed in humans affected with Holmes–Adie syndrome. The condition in dogs is characterized by a dilated pupil that has a diminished PLR. Affected dogs do not have evidence of other neurologic signs (Gerding et al., 1986; Goldfarb, 1984; Spiess, 1988). A tentative diagnosis is made based upon postganglionic supersensitivity using provocative pharmacologic testing with pilocarpine (see provocative pharmacologic testing in this chapter), recognizing, however, that supersensitivity of the iris to pilocarpine administration may not be different between pre- and postganglionic lesions (Jacobson & Vierkant, 1998). Although people afflicted with Holmes–Adie syndrome also have concurrent decreased or absent segmental spinal reflexes, this has not been shown in dogs. The etiology of pupillotonia in dogs is unknown. It should be mentioned that pupillotonia alone may be the only clinical sign presented by patients with intracranial neoplasia in hospital, and that careful attention to history and complete work-up of cases, including transverse imaging of the skull be performed on any patient presenting with pupillotonia as the primary clinical sign (Webb et al., 2005). Idiopathic pupillotonia requires no treatment and the condition is benign.

Sudden Acquired Retinal Degeneration Syndrome

SARDS is an idiopathic blinding condition consisting of acute blindness in the absence of funduscopic disease (early in disease), and clinical signs suggestive of an underlying metabolic disease. SARDS has been recognized among dogs in the United States for over two decades (Vainisi et al., 1983). Nevertheless, the cause of SARDS is unknown and this, combined with the fact that SARDS is an important cause of blindness in dogs, spawned a "think-tank" to help provide guidance regarding pathogenesis, early diagnosis, and treatment (Komaromy et al., 2016).

Epidemiologic questionnaires have not suggested any common thread for an environmental toxin (Acland et al., 1984). Preliminary investigations into excitotoxins (e.g., glutamate) have found increased levels in the vitreous of affected animals, but the significance of this is unknown (Abrams et al., 1995). Circulating antiretinal antibodies have been found in dogs with SARDS; however, antiretinal antibodies are also found in clinically normal dogs (Bellhorn et al., 1988; Gilmour et al., 2004). Attempts to link SARDS with paraneoplastic processes, as has been shown in human cancer-associated retinopathy, has proven unrewarding (Gilmour et al., 2004). Analysis of tissues from SARDS-affected dogs revealed the presence of immunoglobulin-producing plasma cells in affected retinas which may account for localized intraretinal production of autoantibodies and subsequent development of an antibody-mediated retinopathy (Grozdanic et al., 2008). In addition, strong complement activity has been documented in the retinas of dogs with SARDS which may account for antibody-mediated neuronal damage (Grozdanic et al., 2008).

In one study, 40%–60% of dogs affected with SARDS were reported to have systemic signs and altered clinicopathological test results (van der Woerdt et al., 1991). Animals are characteristically presented with acute blindness and a normal to near-normal ocular fundus (van der Woerdt et al., 1991). Because of the acute onset, most dogs are quite disoriented. In most patients, vision loss occurs over the course of 1–2 weeks, and nyctalopia may be observed (van der Woerdt et al., 1991). The mean age of affliction is 8.5–10 years (Miller et al., 1998; van der Woerdt et al., 1991). The syndrome tends to occur in middle-aged to older ovariohysterectomized females, in both pure and mixed breeds, and with a predisposition for Dachshunds, Pugs, Miniature Schnauzers, and Brittany Spaniels (Acland & Aguirre, 1986; Acland et al., 1984; Auten et al., 2017; Vainisi et al., 1983, 1985; Leis et al.,

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2017; van der Woerdt et al., 1991). A seasonal incidence has been reported as well, with 46% of cases occurring in December and January (Acland et al., 1984). Many affected dogs have polyuria, polydipsia (28%–36% of cases), and polyphagia (39%), as well as a history of weight gain (57%). Systemic hypertension (4 of 10 dogs) and proteinuria (7 of 10 dogs) have also been reported in dogs with SARDS (Carter et al. 2009). Laboratory values are variable, but lymphopenia (30% of cases), lymphopenia with neutrophilia (21%), and abnormal biochemical profiles (68%) may be present. Elevated levels of alkaline phosphatase (30%–40% of cases) and cholesterol (42%) are the most common biochemical changes. Adrenocorticotropic hormone (ACTH) stimulation or a low-dose dexamethasone suppression test may be abnormal (van der Woerdt et al., 1991). Overall, 12%–17% of patients have adrenal profile changes compatible with those of Cushing's disease, but these changes may be adaptations to other diseases as well (Acland et al., 1984; Carter et al., 2003; Mattson et al., 1992; van der Woerdt et al., 1991). These associated alterations in pituitary function have led to the hypothesis that elevations in melanocyte-stimulating hormone (MSH) may accompany an increased ACTH level. Increased MSH may then lead to increased melanin production by the retinal pigment epithelium (RPE), which may impair RPE phagocytosis of photoreceptor outer segments and, consequently, result in retinal degeneration (van der Woerdt et al., 1991). Serum cortisol and sex hormone concentrations have been measured prior to and after ACTH stimulation in 13 dogs with SARDS (Carter et al., 2009). Serum cortisol was elevated in 9 of 13 dogs; elevations in one or more sex hormones were found in 11 of 13 patients with SARDS whereas only one dog had normal ACTH stimulation results (Carter et al., 2009).

On ophthalmic examination, dogs with SARDS appear blind and lack a menace response, although they tend to blink in response to bright light (positive dazzle reflex). The pupils are usually dilated at rest and show sluggish, but present, PLRs (Leis et al., 2017; van der Woerdt et al., 1991). Ophthalmoscopic changes during the acute stages are very minimal, with mild retinal vascular attenuation or variability in retinal vascular caliber and changes in tapetal reflectivity. In the early stages, all dogs with SARDS have a characteristic pale optic disc caused by the presence of vascular attenuation of the optic nerve head (Grozdanic et al., 2008). In patients with SARDS of typically more than 2 months in duration, subtle tapetal hyperreflective spots may be observed, with these hyperreflective spots having been detected in some affected dogs only 7 days after the onset of acute blindness (Grozdanic et al., 2008). After several weeks to months, more advanced retinal vascular attenuation and tapetal hyperreflectivity become apparent. The funduscopic appearance in chronic SARDS is similar to that of inherited retinal degeneration (van der Woerdt et al., 1991). Histopathologic changes have been infrequently reported, but cases of early SARDS have a diffuse loss of photoreceptor outer segments, with more subtle changes in swelling of the dendritic processes and cell bodies in the amacrine, bipolar, and ganglion cells. With chronicity, the entire neuroretina degenerates, and the RPE becomes attenuated and loses its apical processes (Acland et al., 1984; Miller et al., 1998; Vainisi et al., 1985; van der Woerdt et al., 1991).

Optical coherence tomography (OCT) has been used to analyze the structural thickness of retinas of dogs with SARDS. OCT revealed significant retinal thinning even for retinas that appeared relatively normal on funduscopic examination with primary damage of the nerve fiber layer and decreased retinal thickness of the ventral retina early on in this disease and progressing to involve thinning of all retinal layers, including the photoreceptor layer, in the dorsal and ventral quadrants (Grozdanic et al., 2008).

ERG is considered the gold standard for establishing a diagnosis of SARDS. The ERG response is extinguished with SARDS (Auten et al., 2017; Leis et al., 2017; van der Woerdt et al., 1991). A recent study documented the spectral properties of the PLR in eyes of healthy dogs compared with eyes of SARDS-affected dogs (Grozdanic et al., 2007). Dogs that have SARDS have complete pupillary constriction in response to blue light of a narrow wave length (480 nm) and high light intensity (200 kcd/m^2) most likely caused by stimulation of a photosensitive pigment, melanopsin, located in a subpopulation of retinal ganglion cells that can drive PLRs in the absence of photoreceptor activity. When red light of a given wavelength (630 nm) and high light intensity (200 kcd/m^2) was used to evaluate PLRs in SARDS-affected patients, the pupils remained fixed and dilated as this wavelength of red light does not activate the melanopsin pathway but rather activates the photoreceptor-mediated pathway which is absent in dogs with SARDS. A portable, diode-based light source with narrow wavelengths for blue and red light that matches the spectral properties of canine visual pigments is available for colorimetric PLR testing (Melan-100 unit, BioMed Vision Technologies, Inc., Ames, IA, USA) (Grozdanic et al., 2008). A study investigating chromatic PLRs using the Melan-100 unit showed that 75% of eyes with SARDS responded as predicted (miosis with blue light, negative PLR with red light), whereas 12.5% of eyes with SARDS had a weak miotic PLR with red light and miotic response with blue light, and the remaining 12.5% of SARDS eyes had a weak miotic response with blue light and negative PLR with red light (Terakado et al., 2013). As such, an extinguished ERG remains the gold-standard method of confirming SARDS.

SARDS has long been considered an untreatable, irreversible blinding disease of dogs. However, recently, experimental use of intravenous human immunoglobulins (IVIg) has resulted in restoration of limited visual behavior in some SARDS-affected dogs in the early stages of this disease (Grozdanic et al., 2008). Another study examined

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immunosuppressive therapy with mycophenylate mofetil in 10 SARDS patients within 6 weeks of vision loss and found no benefit of 6 weeks of therapy (Young et al., 2018). Most dogs with SARDS still make acceptable house pets provided they adjust well to being blind (Stuckey et al., 2013).

Trigeminal Neuropathy (Trigeminal Neuritis)

Trigeminal neuropathy is an acute to subacute, typically bilateral, idiopathic condition involving inflammation of primarily the mandibular branch of the trigeminal nerve (efferent to muscles of mastication) (Mayhew et al., 2002). Patients with this disease may present with clinical signs of variable degrees of masticatory muscle atrophy and reduced facial sensation, dropped jaw, facial nerve paralysis/paresis, and Horner's syndrome (Mayhew et al., 2002). In some instances, lack of facial sensation may be the predominant clinical sign. As such, some patients with trigeminal neuropathy may have reduced/absent palpebral reflexes, lack of menace response, evidence of enophthalmos caused by atrophy of the pterygoid muscles, corneal anesthesia, and Horner's syndrome (presumably caused by involvement of the postganglionic sympathetic axons as they course alongside the trigeminal ganglion and the ophthalmic branch of the trigeminal nerve). As with other idiopathic conditions, a diagnosis of idiopathic trigeminal neuropathy is made after excluding other possible causes of bilateral trigeminal nerve dysfunction including infectious (e.g., rabies), traumatic, hematopoetic neoplasms (e.g., lymphosarcoma), and idiopathic polyneuritis. Prognosis for this condition is good and the disease is self-limiting with patients recovering anywhere from 0.7 to 9 weeks after onset of symptoms (Mayhew et al., 2002). Treatment is purely supportive and there is no evidence to support the use of corticosteroids (Mayhew et al., 2002).

Vitamin A Deficiency

Vitamin A (retinol), a fat-soluble vitamin, is derived from its precursors (carotenoids) which are found in plants (for review see von Lintig & Vogt, 2004). With regards to the importance of vitamin A in the ocular system, vitamin A (retinol) is stored and transformed into retinal which is translocated between the retinal pigment epithelium and the photoreceptors (Thompson & Gal, 2003). Within the photoreceptors, retinal combines with opsin (a protein) to form the visual pigment rhodopsin (Thompson & Gal, 2003). Vitamin A deficiency has been produced experimentally in young dogs, but it does not appear to be a naturally occurring clinical syndrome (Tvedten & Whitehair, 1977). The earliest sign of such deficiency in young dogs, however, is vestibular disease, but blindness may also be an early manifesting sign (Tvedten & Whitehair, 1977). Papilledema has been noted in some dogs with a deficiency in vitamin A; however, the resultant papilledema could not be correlated with increased CSF pressure (Tvedten & Whitehair, 1977).

Feline: Congenital

Anomalies of the Visual System and Forms of Albinism

Visual system abnormalities associated with forms of albinism have been reported in animals for years (Creel et al., 1982b). A commonly studied model is the Siamese cat, demonstrating a form of partial albinism (i.e., pointed color cats) with retinal hypopigmentation. In particular the pointed-colored Siamese (i.e., possessing darker pigmentation on extremities), coat colors are the result of temperature-dependent genetic alleles in *tyrosinase* (*TYR*) (Lyons et al., 2005). Tyrosinase is the rate-limiting enzyme in melanin production. Aside from these temperature-dependent alleles in *TYR*, Siamese cats can also be born purely albinotic caused by another mutant allele in *TYR* (Imes et al., 2006). As mentioned, pointed-colored Siamese cats lack pigment of the iridal and retinal pigment epithelia (Thibos et al., 1980). The retinal hypopigmentation in these cats is the critical factor resulting in misrouting of many of the projections of the retina to the brain, the nature of the projection error, and the developmental consequences of the relay of the misrouted retinal inputs to the visual cortex (Kaas, 2005; LaVail et al., 1978; Sanderson et al., 1974;). The abnormal retinogeniculate projections in Siamese cats was first described by Guillery in 1969 (Guillery, 1969). Since this study, several reports regarding the visual system of the Siamese cat have been published (Creel, 1971; Guillery & Kaas, 1971; Hubel & Wiesel, 1971; Kalil et al., 1971). Specifically, Siamese cats have reduced ipsilateral retinal projections because many axons originating in the temporal retina which normally project ipsilaterally project contralaterally in Siamese cats. As a consequence, each LGN contains an abnormally greater representation of the ipsilateral visual field (Cooper &



Figure 36.39 Siamese cat with congenital esotropia related to coat color. (*Source*: Reprinted with permission under the Creative Commons Attribution – Share Alike 2.5 generic license. http://commons.wikimedia.org/wiki/File:Siamese_Cat_Cross-Eyed.jpg)

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Blasdel, 1980). Convergent strabismus with or without involuntary horizontal or rotary nystagmus are possible ocular manifestations as a result of this retinogeniculate misdirection (Fig. 36.39) (Blake & Crawford, 1974; Rengstorff, 1976).

Hydrocephalus

Hydrocephalus refers to the active enlargement of the brain ventricular system. However, ventriculomegaly (enlargement of the brain ventricles) is not necessarily synonymous with hydrocephalus (Estey, 2016; Thomas, 2010). The most common cause of congenital hydrocephalus is a primary congenital stenosis or aplasia of the mesencephalic aqueduct associated with fused rostral colliculi (Thomas, 2010). Mesencephalic aqueductal stenosis has been reported in kittens after *in utero* exposure to griseofulvin (Scott et al., 1975), and after transplacental infection with feline panleukopenia virus (Csiza et al., 1971). It has been shown that selection for extreme brachycephaly also selects for clinical and subclinical hydrocephalus in the Persian, and likely, related breeds of cats (Fig. 36.40 and Fig. 36.41) (Schmidt et al., 2017). Congenital hydrocephalus may produce enlargement of the calvarium and failure of closure of the suture lines of the skull. Consequently, affected kittens may have dome-shaped heads and a persistently open fontanelle. Clinical signs of hydrocephalus include behavioral changes, ataxia, compulsive circling, and seizures (Coates & Sullivan, 2001). Ventrolateral strabismus is a common ocular manifestation of congenital hydrocephalus due, in part, to enlargement of the calvarium with subsequent impingement on the orbits from the dorsolateral aspects (Coates & Sullivan, 2001). This consequently pushes the eyes in a ventrolateral direction and produces a "sunset" appearance to the corneas. Congenital hydrocephalus may also cause cranial nerve compromise with subsequent strabismus. Breeders of



Figure 36.40 Comparison of head phenotype of the peke-face (7 years old, male) (**A**, **B**) and the doll-face Persian (6 years old, female) (**C**, **D**). (*Source*: Schmidt et al., 2017.)

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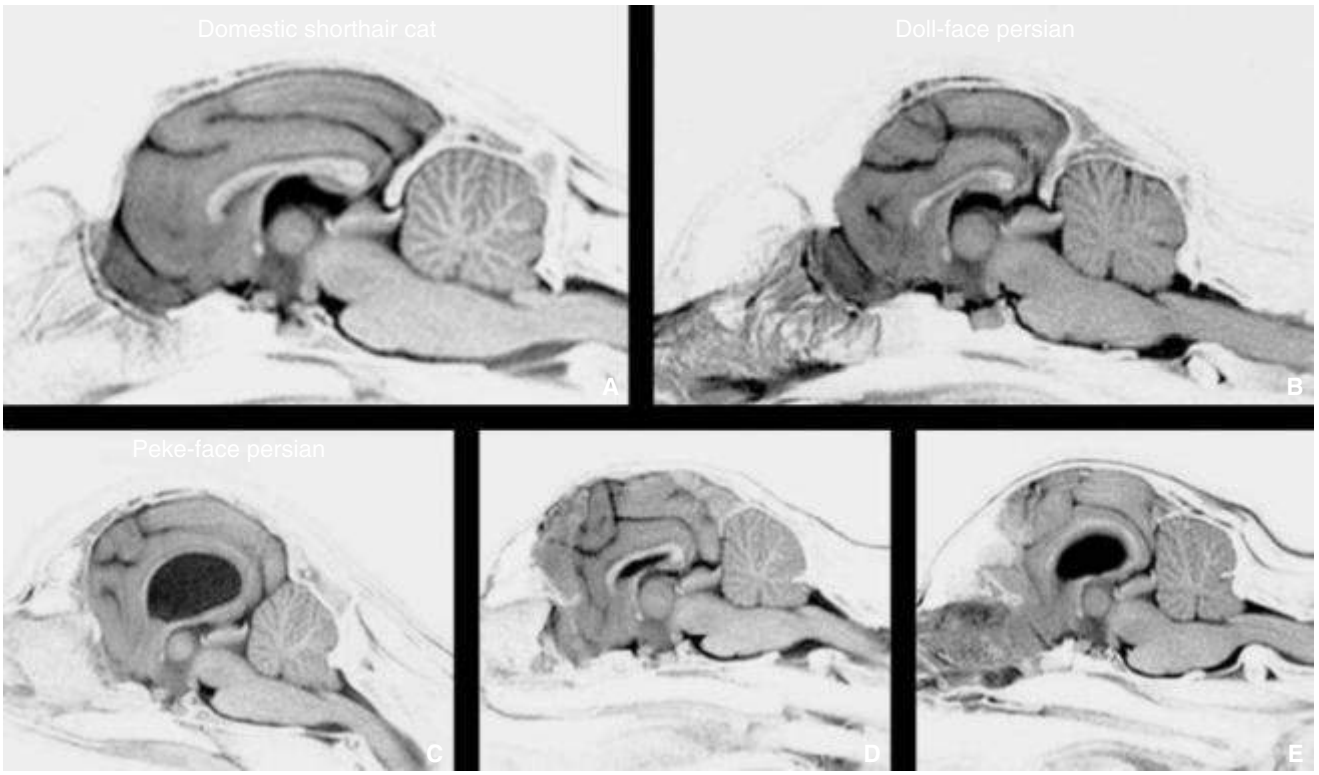


Figure 36.41 Changes in brain morphology. Midsagittal T2-weighted magnetic resonance images of a domestic shorthair cat (**A**: 5 years old, female), a doll-face Persian cat (**B**: 2 years old, female), and peke-face Persian cats (**C**: 5 years old, female; **D**: 2 years old, female; **E**: 2 years old, male). With reduction in the skull length a gradual push back of the conchal bones toward the cranial cavity can be seen. The frontal sinuses are more and more reduced. The frontal lobes are compressed. (*Source*: Schmidt et al., 2017.)

brachycephalic cats should be educated to avoid selecting for extreme brachycephaly phenotype.

Feline: Developmental

Chédiak-Higashi Syndrome

Ch**é**diak-Higashi syndrome (CHS) is an autosomal recessive disorder of cats and other species (Prieur & Collier, 1978, 1981). In cats, CHS is characterized by partial oculocutaneous albinism, increased susceptibility to infections, and bleeding tendencies (Collier et al., 1984). To date, CHS has only been reported in the Persian breed. Ocular manifestations of CHS in cats include photophobia, pale irides, hypopigmentation of the non-tapetal fundus, tapetal degeneration, cataracts ranging from incipient posterior suture-line associated to mature cataracts, and spontaneous nystagmus (Collier et al., 1979, 1985b; Creel et al., 1982a). The ocular hypopigmentation in affected cats is thought to result from fusion of premelanosomes with lysosomes, with resultant destruction of the premelanosomes (Collier et al., 1985a). Melanin granules that do remain in the eyes of cats with CHS are nonuniform in distribution and irregular in shape (Collier et al., 1984). The tapetum develops normally in CHS-affected kittens, but it later rapidly degenerates, so that by 56 days of age, tapetal rods have disappeared and tapetal cells are disorganized (Collier et al., 1985b).

Ophthalmoscopically, the tapetum of affected cats is not visible. Abnormal retinal projections to the LGN (similar to those in the Siamese breed) have also been found in CHS-affected cats, thus accounting for the nystagmus (Creel et al., 1982a). The disease is characterized histologically by giant cytoplasmic granules within lysosomes, melanocytes, and neutrophils. When eyes from older CHS-affected cats were examined histologically and ultrastructurally, lysosomes and residual bodies were found within the RPE (Collier et al., 1986). The residual bodies formed Drusen-like mounds beneath the RPE, and RPE cells had detached and moved into the interphotoreceptor space. A diagnosis of CHS is made based upon identifying enlarged melanin granules histologically within hair shafts of cats combined with clinical signs suggestive of the disease.

Feline: Acquired

Dysautonomia (Key-Gaskell or Dilated Pupil Syndrome)

Feline dysautonomia, which is also known as Key-Gaskell or dilated pupil syndrome, was first reported in England in

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1982 (Key & Gaskell, 1982). The disease, which produces widespread autonomic nervous system dysfunction, has since been reported in many cats throughout Europe (Cave et al., 2003; Rochlitz, 1984; Sharp et al., 1984), but the number of documented cases in the United States remains small, although is endemic in Missouri and Kansas (Kidder et al., 2008). The cause of dysautonomia has not been determined. No evidence of infectious agents has been found, and the lesions are unlike those reported with known toxins (Cave et al., 2003; Sharp et al., 1984; Symonds et al., 1995). It is speculated that an unknown mycotoxin or xenobiotic may contribute to feline dysautonomia given alterations in the amino acid status of cats with dysautonomia (McGorum et al., 2017).

Common systemic signs of feline dysautonomia include general malaise, dehydration, reduced appetite or anorexia, dysphagia, vomiting or regurgitation, xerostoma, bradycardia, urinary bladder distention, and constipation (Cave et al., 2003; Sharp et al., 1984). Ocular signs that have been reported most consistently include dilated unresponsive pupils, decreased tear production, and protruding nictitating membranes (Bromberg & Cabaniss, 1988; Canton et al., 1988; Guilford et al., 1988; Levy et al., 1994; Sharp et al., 1984; Symonds et al., 1995). Vision is unaffected and photophobia is variable.

Pharmacologic testing with ocular autonomic stimulants can aid in establishing the diagnosis of feline dysautonomia. Results of these tests are based on denervation supersensitivity. As such, the dysautonomic eye will respond to dilute concentrations of drugs that will not affect a normal eye. Pilocarpine, which is a direct-acting parasympathomimetic agent, at a concentration of 0.1% will produce constriction of the pupil. Epinephrine, which is a direct-acting sympathomimetic agent, at a concentration of 1:10,000 will induce retraction of a prolapsed third eyelid. Echothiophate iodide, which is an irreversible cholinesterase inhibitor, at a concentration of 0.06% will reportedly cause miosis in a normal cat but have no effect on a dysautonomic pupil (Canton et al., 1988). The same response has been seen with physostigmine, which is a reversible cholinesterase inhibitor, at a concentration of 0.25% (Guilford et al., 1988). The finding of decreased urinary catecholamines can also support the diagnosis of dysautonomia (Levy et al., 1994).

However, a definitive diagnosis of dysautonomia is rarely made antemortem as it involves the histopathologic examination of autonomic ganglia (Cave et al., 2003). Histopathologic examination of affected cats has shown widespread reduction of neurons within both sympathetic and parasympathetic autonomic ganglia, inconsistent neuronal degeneration, and increased numbers of non-neuronal nuclei (Bromberg & Cabaniss, 1988; Canton et al., 1988; Guilford et al., 1988; Levy et al., 1994; McGorum et al., 2017; Sharp et al., 1984; Symonds et al., 1995). Ultrastructural studies of the ganglia and axons have shown degeneration and disorganization (Griffiths et al., 1985). The membrane glycoprotein, synaptophysin, has been shown to be increasingly accumulated in degenerating neurons of both equine and feline dysautonomia cases (Hilbe et al., 2005). The prognosis for cats with dysautonomia must be viewed as being guarded to poor, although some cats have been maintained long-term on supportive therapy (Bromberg & Cabaniss, 1988; Rochlitz, 1984) or have even recovered after a prolonged period (Sharp et al., 1984).

Feline Coronavirus (Feline Infectious Peritonitis)

Infection with feline coronavirus, an RNA virus, may lead to no clinical disease, enteric disease, or feline infectious peritonitis (FIP), which is a disseminated pyogranulomatous vasculitis (Addie & Jarrett, 1992; Addie et al., 1995; Kipar et al., 2005). FIP is caused by a mutated feline coronavirus. At present, the general consensus is that FIP viruses arise by internal mutation of the nonmutant feline enteric virus (Pedersen, 2014b). Mutations occur independently within each cat and there are three different genes (*ORF 3* accessory gene, *S* gene, *7b* accessory gene) associated with the feline enteric coronavirus to FIP virus or biotype conversion (Pedersen, 2014b). FIP replicates within macrophages resulting in the deposition of virus-laden macrophages within the endothelium of small blood vessels (Kipar et al., 2005). Interestingly, the FIP virus has been shown to enter target macrophages/monocytes by first binding to the cell surface and then being internalized by a clathrin- and caveolae-independent and dynamin-dependent endocytosis (Van Hamme et al., 2008). FIP is a fatal arthus-type immune reaction of cats to infection with the virus (Foley et al., 1998). Large multicat indoor environments are known to favor feline enteric coronavirus infection and FIP (Pedersen et al., 2008). Sexually intact cats and purebred cats are more likely to develop FIP (Pesteanu-Somogyi et al., 2006). In a study evaluating the prevalence of FIP in individual breeds reported increased risk of development of disease in Abyssinians, Bengals, Birmans, Himalayans, Ragdolls, and Rexes (Pesteanu-Somogyi et al., 2006). In addition, FIP most commonly occurs in young cats, and it may manifest by an effusive or wet form of the disease, which includes fibrin-rich fluid within the abdominal and peritoneal cavities, or as a noneffusive or dry form of the disease. Ocular and neural lesions are more likely to be present with the noneffusive/dry form (Andrew, 2000; Foley et al., 1998).

The most common ocular manifestation of FIP is bilateral granulomatous anterior uveitis, often with large, mutton-fat keratic precipitates and a fibrinous exudate into the anterior chamber. Chorioretinitis is also frequently observed, and a pyogranulomatous exudate sheathing the retinal vessels may be present as well. Additional findings may include retinal hemorrhages, detachments, and optic neuritis (Campbell & Reed, 1975; Doherty, 1971; Montali & Strandberg, 1972; Slauson & Finn, 1972). FIP has been

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diagnosed in a 7-month-old intact male domestic shorthair cat with unilateral anterior uveitis and pyrexia (Declercq et al., 2008). Interestingly, nonpruritic cutaneous lesions, characterized by slightly raised intradermal papules over the dorsal neck and over both lateral thoracic walls, were recognized at the end stage of the disease in this cat and facilitated a diagnosis of FIP (Declercq et al., 2008).

Histologically, lesions in FIP consist of granulomas comprising mixtures of neutrophils, lymphocytes, plasma cells, and large, spindle-shaped histiocytes and can involve all internal organs (Ziolkowska et al., 2017). Ocular lesions include focal or diffuse granulomatous inflammation of the uvea, retina, and meninges of the optic nerves (Ziolkowska et al., 2017). Fibrinocellular exudates may be present in the ocular chambers (Montali & Strandberg, 1972; Krebiel et al., 1974). Focal retinal detachments can be found histologically and glial fibrillary acidic protein (GFAP) expression is increased in Muller cells; these cells also proliferate in cases of retinal detachment (Ziolkowska et al., 2017). In areas where massive inflammation is present (e.g., uvea), feline coronavirus antigen can be found within macrophages that are most recently derived from blood (Ziolkowska et al., 2017). There is also a predominance of B cells and plasma cells compared with other inflammatory cell types in the eyes of cats with FIP, suggesting that the humoral immune response plays a key role in ocular inflammation in the eyes of cats (Ziolkowska et al., 2017).

In many cases, the definitive diagnosis of FIP, antemortem, is difficult (Addie et al., 2004; Tasker, 2018). Definitive diagnosis requires demonstration of characteristic histopathological changes seen with FIP on biopsy samples, although adjunctive immunohistochemical staining for feline coronavirus proteins and/or amplification of viral RNA via various PCRs (Pedersen, 2014a; Tasker, 2018). Although a definitive diagnosis is often difficult to achieve, gathering sufficient indirect evidence can strongly support a diagnosis of FIP (Pedersen, 2014a). As already mentioned, affected cats are typically young (<2 years old) (Riemer et al., 2016). Affected animals are typically febrile (58% of FIP patients), lethargic (up to 87.4% of FIP patients), and may have a history of weight loss (up to 37.4% of FIP patients) (Riemer et al., 2016). When present, neurologic signs including ataxia, seizures, vestibular signs, and paresis may be present (Riemer et al., 2016). Up to 78% of cats will have ascites (Riemer et al., 2016). Hematologic abnormalities are present in nearly all (99.5%) of affected cats (Riemer et al., 2016). Anemia may or not be present and red blood cell microcytosis is observed in up to 35% of affected cats and this finding is independent of age or the presence of anemia (Riemer et al., 2016). Lymphopenia occurs in nearly 50% of cats with FIP, especially in those with the wet form of the disease (Riemer et al., 2016). A neutrophilia with a left shift may be present (Riemer et al., 2016). As with hematologic evaluation, serum biochemical changes are present in up to 99.5% of cats with FIP. These changes include hyperglobulinemia (reported in up to 89.1% of affected cats) regardless of the wet or dry form of the disease (Riemer et al., 2016). Hyperbilirubminemia in the absence of elevated liver enzyme concentrations or severe anemia is supportive of a diagnosis of FIP (Tasker, 2018). Eight-five percent of cats with FIP have an albumin : globulin ratio of <0.8 and 67.8% had albumin : globulin ratios of <0.6 (Riemer et al., 2016). Additional supportive evidence includes elevations in the acute phase protein, α1-acid glycoprotein (AGP). AGP concentrations of more than 1.5 mg/mL in patients already suspected of having FIP, and concentrations of more than 3 mg/mL are supportive of an FIP diagnosis in patients with no history or clinical findings suggestive of FIP (Paltrinieri et al., 2007). Evaluation of effusion samples, and performing immunocytochemistry and/or RT-PCR for feline coronavirus on effusion samples (wet FIP), CSF (dry FIP), and ocular aqueous fluid (dry FIP) can be helpful when taking into consideration all other clinical and laboratory information, although the sensitivity and specificity of the testing procedure and sample being evaluated must be considered (Doenges et al., 2016; Felten et al., 2017a,b, 2018; Gruendl et al., 2017; Longstaff et al., 2017; Stranieri et al., 2018).

The most important method for reducing feline coronavirus is the elimination of chronic coronavirus shedders (Addie et al., 2004; Foley et al., 1997). Given the prevalence of coronavirus, however, this task is considerably difficult. Treatment of ocular disease is symptomatic and includes use of topical, subconjunctival, or systemic corticosteroids as well as topical atropine. Temporary amelioration of ocular disease may occur, but symptoms will usually rebound in a short period of time. Impressively, however, use of a C3-like protease inhibitor (GC376) has been shown to clear clinical signs, including ocular signs, in cats with naturally occurring FIP (Pedersen et al., 2018).

Specifically, two interesting studies examining novel therapeutants for FIP in cats. In particular, a C3-like protease inhibitor (GC376) has resulted in 6 of 20 cats with naturally occurring FIP, after 12 weeks of twice daily subcutaneous treatment with GC376, to remain disease free for over 1 year after treatment (Pedersen et al., 2018). Another study examined the nucleoside analog, GS-441524, which has been shown to reverse clinical signs of experimentally induced FIP after 2 weeks of twice daily subcutaneous treatment (Murphy et al., 2018). Ten out of 10 cats remained disease free for over 8 months after 2 or 4 weeks of treatment (Murphy et al., 2018). Elimination of FIP from a cattery is only possible by total elimination in endemic FECV infection. For a detailed review of FIP, the reader is referred to (Pedersen, 2014a,b; Tasker, 2018).

Feline Leukemia Virus (FeLV)

Anisocoria or dyscoria may arise because of neurological effects of FeLV on the ciliary ganglia and short ciliary nerves

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of affected cats. Alternatively, dyscoria may result from lymphocytic infiltration of the ciliary body and iris (Nell & Suchy, 1998). In particular, spastic pupil syndrome, involving a static anisocoria during dark adaptation, has been reported in FeLV-positive cats. Anisocoria may have been noted by the patient's owner over time, alternating with periods of normal pupil behavior. Other ophthalmic abnormalities are absent, however, and vision is unaffected. These cats are positive for FeLV but may have no other clinical signs when the anisocoria is noted (Brightman et al., 1977; Scagliotti, 1980). C-type viral particles have been identified in the ciliary ganglia and short ciliary nerves of these cats, however, which is suggestive that the virus has invaded these nerves. The prognosis for long-term survival in these cats is poor.

Fluoroquinolones

Enrofloxacin, a fluoroquinolone antibiotic, has been associated with a rare adverse ophthalmic reaction causing an acute, typically irreversible, retinal degeneration in cats (Gelatt et al., 2001; Giuliano & van der Woerdt, 1999; Grahn et al., 2002; Wiebe & Hamilton, 2002). In addition, this reaction has reportedly been seen with other fluoroquinolones including marbofloxacin and orbifloxacin (Ramirez et al., 2011). Interestingly, enrofloxacin retinal toxicity has not been observed in nondomestic felids (Newkirk et al., 2017).

Affected cats develop signs of partial, temporary, or total blindness. The reported estimated incidence of this adverse reaction is 1 in 122,414 treated cats or 0.0008% (Wiebe & Hamilton, 2002). The association of enrofloxacin, retinal degeneration, and blindness in cats was first described in a retrospective study in which 5 of 26 cats with diffuse retinal degeneration had received oral enrofloxacin (Giuliano & van der Woerdt, 1999). Subsequently, another retrospective study documented the association between enrofloxacin administration and the acute onset of retinal degeneration in 17 cats (Gelatt et al., 2001). All cats were domestic shorthair breed with ages ranging from 3 to 16 years old. All affected cats had variable medical ailments for which enrofloxacin was administered including lymphoma and pancreatitis, otitis, urinary tract disorders, dermatitis, bowel perforation, diarrhea, and upper respiratory infection. The daily enrofloxacin dosages these cats received were highly variable ranging from 4.6 mg/kg PO once daily to 27 mg/kg PO twice daily. Cats in this study generally presented with signs of mydriasis and acute blindness. All cats had generalized retinal degeneration, and vision only returned in a few cases (see Fig. 37.2.25). Five of 17 affected cats underwent electroretinography which revealed no observable responses in any case. Histological assessment of two affected globes showed mainly outer retinal degeneration as evidenced by a diffuse loss of the photoreceptor and outer nuclear layers, and hypertrophy and proliferation of the retinal pigment epithelium. Given the findings in this study, the adverse retinal reaction to enrofloxacin in cats appears to be a rare, idiosyncratic reaction. Adherence to the manufacturer's current recommendation for enrofloxacin dosage in cats of 5 mg/kg PO q 24 hour is advisable. It is, however, unclear as to whether a dosage of 5 mg/kg PO q 24 hour is safe in geriatric cats, especially those with renal or hepatic dysfunction, as safety studies performed by the manufacturer were conducted in young healthy cats (Wiebe & Hamilton, 2002).

Safety studies evaluating the incidence of retinal degeneration with orbifloxacin, another veterinary-labeled fluoroquinolone, revealed a dose- and concentration-dependent adverse ophthalmic reaction, with cats receiving higher doses of the medication developing focal retinal degeneration (Kay-Mugford, 2001). Safety studies conducted on marbofloxacin, another veterinary-approved fluoroquinolone, did not show any ocular lesions after oral administration of up to 20 times the minimum recommended daily dosage. Another study examining pradofloxacin in cats, given at 6 and 10 times the recommended dosages, failed to demonstrate rod or cone dysfunction using electroretinography (Messias et al., 2008). Nonetheless, the manufacturers of marbofloxacin and pradofloxacin indicate that it is a prudent precaution to consider that all fluoroquinolones may have the potential to induce feline ocular lesions and therefore all fluoroquinolones should be used with caution in this species.

Recently, it has been shown that cats have four specific amino acid sequence differences in P-glycoprotein, ABCG2, in comparison with that of other mammals (Ramirez et al., 2011). ABCG2 is a member of the ATP-binding cassette superfamily of proteins and is located in a variety of tissues including the endothelium comprising the blood–retinal barrier. These proteins transport a variety of molecules, including fluoroquinolones, across cell membranes. As such, this protein acts to regulate the concentration of drugs, such as the fluoroquinolones, within the retina. Fluoroquinolones produce reactive oxygen species when exposed to light. When HEK-293 cells are modified to contain (1) no ABCG2, (2) human-specific ABCG2, or (3) feline-specific ABCG2, and are subsequently exposed to ultraviolet light, 50% of cells not containing ABCG2 die when exposed to 1–10 μmol/L of enrofloxacin, 50% of cells with feline specific ABCG2 will die when exposed to 10 μmol/L enrofloxacin, and 50% of cells with human ABCG2 will die when exposed to 50 μmol/L enrofloxacin (Ramirez et al., 2011). These results show that feline-specific ABCG2 is ultimately ineffective at transporting enrofloxacin from within the cells, thus likely explaining the fluoroquinolone-related retinal toxicity described clinically in cats.

Current recommendations to help decrease the risk of retinal degeneration in some cats receiving enrofloxacin include: (1) using split dosing (i.e., 2.5 mg/kg PO q 12 hours) on exact body weight; (2) avoidance of rapid intravenous infusions of the drug and drug interactions; and (3) avoidance

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of UVA light during active treatment may also be beneficial. Owners of a cat receiving parenteral fluoroquinolone therapy should be instructed to monitor their cat for mydriasis and to consult their veterinarian immediately should this sign develop. The pharmacokinetics of parenteral enrofloxacin in neonatal kittens compared with the pharmacokinetics of this medication in young and adult cats have been reported (Seguin et al., 2004). Ophthalmic examinations were not conducted on animals in this study, however.

Griseofulvin Teratotoxicity

Griseofulvin is a fungistatic agent used in cats to treat dermatophytosis. Griseofulvin is teratogenic in the cat. Ocular anomalies reported in affected offspring of cats having received griseofulvin in the first half of gestation include cyclopia, anophthalmia, optic nerve aplasia, and rudimentary optic tracts (Fig. 36.42 and Fig. 36.43) (Scott et al., 1975). Mesencephalic aqueductal stenosis has also been reported in kittens after *in utero* exposure to griseofulvin (Scott et al., 1975). Other widespread malformations also accompany the ocular abnormalities. One adult cat was thought to have retinal degeneration secondary to griseofulvin toxicity (Rottman et al., 1991).

Hypoxia: Cerebral

Hypoxia most commonly occurs during anesthetic episodes, and it may relate to apnea, cardiopulmonary failure, improper intubation, overdose of anesthetic agent, failure of anesthetic equipment, paralysis of the muscles of respiration, use of mouth gags causing occlusion of maxillary artery, and severe systemic hypotension (Barton-Lamb et al., 2013; Gaynor et al., 1999; Jurk et al., 2001; Stiles et al., 2012; Wingfield & Van Pelt, 1992). Neurons are more sensitive to hypoxia than other support tissues, and neuronal tissue affected by severe and prolonged hypoxia ± reperfusion will undergo severe cellular metabolic dysfunction leading to apoptosis and ischemic necrosis (Clarkson et al., 2005; Somjen et al., 1993). Clinical signs of cerebral hypoxia include blindness, stupor or coma, paralysis with decerebrate rigidity, seizures, and deafness. PLRs, however, are generally normal. These signs may be either partially or wholly reversible after a period of days to months. Therapy for systemic and cerebral hypoxia depend upon the etiology. In cases of cardiopulmonary arrest, the reader is referred to the Reassessment Campaign on Veterinary Resuscitation (RECOVER) guidelines (Boller & Fletcher, 2012; Brainard et al., 2012; Cardy & Cornelis, 2018; Fletcher et al., 2012; Hopper et al., 2012; McMichael et al., 2012; Rozanski et al., 2012; Smarick et al., 2012). The RECOVER guidelines have shown to improve outcome (Kawase et al., 2018).



Figure 36.42 Five-week-old Persian kitten with bilateral anophthalmia. Kitten 2 of a litter of four kittens with anophthalmia from the queen, treated with griseofulvin during early pregnancy. (*Source*: Scott et al., Teratology, 1975.)

Ischemic Encephalopathy in Felines

Ischemic encephalopathy occurs when the arterial supply to part of the brain is disrupted. A portion of one side of the cerebrum supplied by the middle cerebral artery is most often involved, thereby resulting in necrosis. The cause is unknown in most cases. However, there is evidence that *Cuterebra* infection may play a role in some cases (Rissi & Howerth, 2013; Williams et al., 1998). In the cat, the condition manifests by a sudden onset of behavior change, seizures, ataxia, and motor deficits (Shell, 1996; Zaki & Nafe, 1980). Visual deficits may accompany other neurologic signs and are usually cortical in origin. Occasionally, the optic chiasm may be involved, thus resulting in dilated unresponsive pupils (de Lahunta, 1977). Anisocoria has been noted as well (Bernstein & Fiske, 1986).

Treatment involves supportive care with improvement in clinical signs typically occurring over days to weeks. Alterations in behavior and seizures may persist, and repeated episodes may occur (de Lahunta, 1977; Quesnel et al., 1997; Williams et al., 1998).

Nictitating Membrane Protrusion

Idiopathic bilateral protrusion of the feline nictitating membranes is a common, poorly understood ophthalmic disorder (see Fig. 37.2.5) (Gruffydd-Jones et al., 1977). Retraction of the nictitating membranes after instillation of topical adrenergic drugs, in affected cats, is suggestive of a loss of sympathetic innervation such as that seen in Horner's syndrome; however, other ophthalmic signs of Horner's syndrome are absent. Cats with this syndrome have normal intraocular structures, and vision is unaffected unless the nictitating membranes protrude to the extent that they cover the pupil.

Affected cats often have concurrent watery diarrhea that precedes nictitating membrane protrusion. Some cats may have diarrhea for weeks. Many cats, however, recover from diarrhea quickly, yet will still have nictitating membrane protrusion. A Tora-like virus has been isolated from the feces of several affected cats in England (Muir et al., 1990). In that study, 17 of 45 cats had nictitating membrane protrusion for more than

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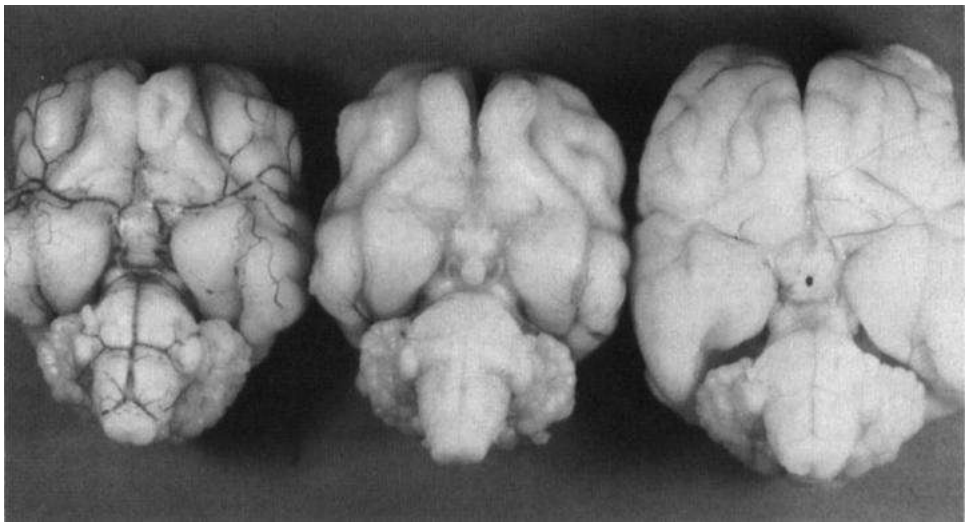


Figure 36.43 Ventral view of brains from 5-week-old Persian kittens described in Figure 36.42. Note the lack of optic nerves and chiasms, and the enlarged brain of kitten 3 (right) caused by hydrocephalus. (*Source*: Scott et al., Teratology, 1975.)

4 weeks, and 16 of 41 cats had diarrhea for more than 4 weeks. In 87% of the cases from multicat households, more than one cat was affected, suggesting an infectious etiology.

The prognosis for this condition is good. The diarrhea and nictitating membrane protrusion are self-limiting, although clinical signs may be long-lasting. Therapy is not indicated, but if the nictitating membrane protrusion is severe, a topical adrenergic agent may be helpful.

Neoplasia: Central Nervous System

Blindness associated with intracranial neoplasia has been reported in cats (Davidson et al., 1991; Duniho et al., 2000; Gordon et al., 1994; Nafe, 1979; Sant'Ana et al., 2002; Troxel et al., 2003). In one study, an acutely blind, 12-year-old cat with afferent pupillary deficits was found to have a pituitary carcinoma that encroached on the optic chiasm (Davidson et al., 1991). In a series of 36 cats with meningiomas, blindness or visual field deficits were found in seven (Nafe, 1979). Six of these seven cats had unilateral visual deficits, whereas the remaining cat was completely blind, with dilated pupils from compression of the optic chiasm by a third-ventricle meningioma. Six cats also had positional nystagmus, and one cat with tentorial herniation had anisocoria, with the smaller pupil being contralateral to the tumor. It is also important to keep in mind that feline patients with internal ophthalmoparesis/ophthalmoplegia with structural intracranial disease (e.g., neoplasia) typically present with other abnormal neurologic signs including changes in mentation/awareness, blindness, altered proprioceptive abilities, among others (Hamzianpour et al., 2017).

Otitis Media/Interna

As the name implies, otitis media/interna is characterized by inflammation of the middle and inner ears, respectively (Webb, 2014). Otitis interna represents a common cause of peripheral vestibular disease in cats (Negrin et al., 2010). The causative agents of otitis media/interna in cats include primarily bacteria, fungi, yeast, and parasites. Otitis media is thought to develop, primarily from extension of a pre-existing otitis externa. Alternatively, otitis media can result from inoculation via the eustachian tube or via hematogenous spread. Otitis interna typically results from extension of otitis media. Neurologic signs of otitis media include aural pain, head shaking, facial nerve paresis/paralysis, Horner's syndrome, and neurogenic keratoconjunctivitis sicca (Kern & Erb, 1987; Kern et al., 1989; Schlicksup et al., 2009; Shanaman et al., 2012). It has been suggested that subclinical otitis media is relatively common, however (Schlicksup et al., 2009; Shanaman et al., 2012). Signs consistent with peripheral vestibular syndrome exist only if there is otitis interna but not when only otitis media is present alone.

Diagnosis is based upon aural examination, evidence of conductive hearing loss based upon clinical signs and results of brainstem auditory evoked response (BAER) testing, cross sectional imaging (CT or MRI), and myringotomy with aspiration of middle ear contents (Webb, 2014).

Treatment is based upon choosing and implementing an appropriate antimicrobial based upon culture and sensitivity results. In some patients, surgical curettage and drainage of the middle ear may be necessary. Prognosis is variable and depends upon the chronicity of the disease and other predisposing factors. Importantly, other disease processes that may cause similar clinical signs include neoplasia, nasopharyngeal polyps, and trauma.

Rabies

Rabies continues to be one of the most feared zoonotic diseases in the world. Nearly 60,000 people are killed by rabies

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each year, many of whom are children in developing countries (World Organisation for Animal Health, 2018). Rabies, a bullet-shaped RNA virus, is a Lyssavirus in the family Rhabdoviridae (Woldehiwet, 2002). Transmission of rabies occurs via a bite by a rabid animal, although infections through aerosols have been documented (Constantine, 1966; Winkler et al., 1973). The virus can infect any warm-blooded animals, with dogs and cats being the main vectors of human infection (Woldehiwet, 2005). Clinically, rabies infection can be divided into three phases: (1) prodromal, (2) furious, and (3) paralytic (Bedford, 1976). In its early stages, rabies in cats can be difficult to diagnose. In one study, the main signs of rabies in cats reported by veterinarians included changes in behavior, gait abnormality, wound or injury within the past 6 months, and an unusual look in the eyes, whereas the most frequently reported signs by owners included aggressiveness, gait abnormality, and, once again, an unusual look in the eyes (Fogelman et al., 1993). Although the unusual expression in the eyes was not further characterized in this study, it may have arisen because of alterations in pupil size (i.e., mydriasis) from rabies-induced neurologic dysfunction. The reader is referred to the World Organisation for Animal Health (2018) for comprehensive information about rabies worldwide.

Thiamine Deficiency

Thiamine deficiency may occur in cats eating large amounts of raw fish, which contains thiaminases, or in cats eating processed commercial foods in which thiamine has been destroyed by heat processing and not replaced adequately (Chang et al., 2017; Markovich et al., 2014; Moon et al., 2013; Pritchard, 2017). Thiamine deficiency has also been reported in cats being fed commercial food containing sulfur dioxide as a food preservative (Malik & Sibraa, 2005; Studdert & Labuc, 1991; Steel, 1997). Further, cats with severe gastrointestinal disease may not absorb sufficient amounts of thiamine. Clinical signs of thiamine deficiency include initial inappetence and occasional vomiting, followed by pupillary dilatation without visual deficits, ataxia, and ventroflexion of the head and neck (Davidson, 1992; Loew et al., 1970; Martin, 1971). A final and irreversible stage of thiamine deficiency is characterized by a progression of clinical signs culminating to a semicomatose state, which is characterized by crying, opisthotonos, and extensor rigidity.

The diagnosis can be made on the basis of dietary history, clinical signs, and measurement of thiamine concentration in food as well as in blood. Normal blood thiamine levels for cats are approximately 32 µg/dL. Before development of a comatose state, cats will respond favorably to parenterally administered vitamin B complex preparations containing 50–75 mg of thiamine per dose every 8 hours. Alimentation should be provided via a nasogastric or gastrotomy tube. Improvement is usually seen within 3 days, although ataxia may be present for 2 weeks. Once the cat is eating, oral vitamin supplementation can be instituted, and the diet should be corrected to include an adequate thiamine intake.

Traumatic Optic Neuropathy

Traumatic optic neuropathy resulting in blindness has been described after enucleation in cats (Donaldson et al., 2014). In particular, cats of varying ages and sex, and having undergone enucleation whereby rostral traction was applied to the eye having undergone enucleation, showed mydriasis (6/6 cats) and vision deficits (4/6 cats) immediately after surgery. Initial ophthalmic examinations revealed multifocal peripapillary retinal lesions with subsequent examinations revealing optic nerve head atrophy (Fig. 36.44). Electroretinography was unremarkable. MRI failed to identify the optic chiasm ipsilateral to the enucleation and also showed evidence of atrophy of the contralateral optic chiasm. Afferent pupillomotor function and vision did not improve over time in any cats.

Equine: Congenital

Congenital Stationary Night Blindness

A condition long thought to be related to the incompletely dominant leopard spotting (LP) allele is congenital stationary night blindness (CSNB) in Appaloosa horses (Joyce & Witzel, 1977; Rebhun et al., 1984; Witzel, 1977; Witzel et al., 1977, 1978). The condition is nonprogressive, affected animals have cautious behavior in dim-light conditions, and may be difficult to train. A dark-adapted ERG lacking a b-wave is diagnostic (Sandmeyer et al. 2007, 2012). Concurrent neuro-ophthalmic signs may include bilateral dorsomedial strabismus (Fig. 36.45) and spontaneous nystagmus.

Congenital stationary night blindness has been reported in a variety of breeds of horses including Appaloosa, Knabstrupper, American Miniature Horses, Thoroughbred, and Paso Fino (Nunnery et al., 2005; Rebhun et al. 1984; Sandmeyer et al., 2007, 2012; Witzel, 1977; Witzel et al., 1977, 1978). CSNB is most commonly documented in breeds with the LP allele (Sandmeyer et al., 2007, 2012). Specifically, it has been shown that of the cases of CSNB occurring in breeds with the LP allele, CSNB is only found in those animals homozygous for LP (i.e., LP/LP) (Sandmeyer et al., 2007, 2012). Animals with LP are characterized along a spectrum of white patterning (very little white patterning to significant white patterning) (Fig. 36.46) (as discussed in Webb & Cullen, 2010). In heterozygous animals (LP/lp), there is typically more "spotting" within the white-patterned regions of the body. Animals homozygous for LP (LP/LP) typically have little to no spotting in the areas of white patterning.

Decreased expression of the calcium ion channel gene, transient receptor potential cation channel member 1

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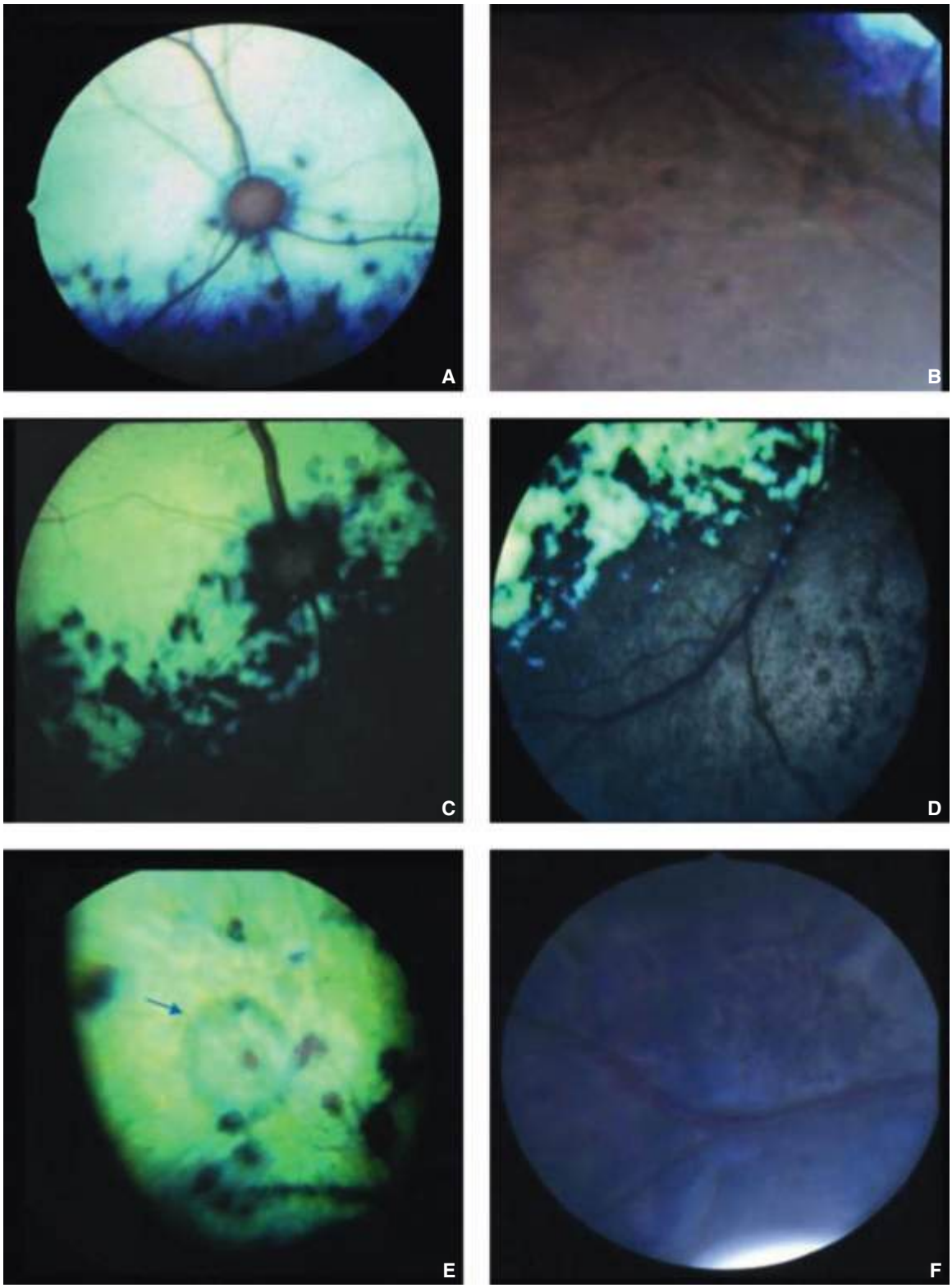


Figure 36.44 **A–D.** Fundus photographs of eyes from cats, 6 weeks postenucleation of the contralateral eye. Multifocal peripapillary hyporeflective areas and bullous changes were identified from 2 to 6 weeks postenucleation. These lesions were transient with active lesions quickly becoming focally hyperpigmented. **E.** The red-orange central region within the focal bullous lesion was a typical feature of early lesions. (*Source*: Donaldson et al., 2014.)

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(*TRPM1*), in the skin and retina has been described in horses homozygous for LP and having CSNB (Bellone et al., 2008). The causative mutation for CSNB and LP has been identified in the *TRPM1* gene (Bellone et al., 2013).

Multiple Congenital Ocular Anomaly Syndrome

Multiple congenital ocular anomaly syndrome (MCOAS) was described in Rocky Mountain Horses in 1999 (Ramsey et al., 1999a). Since this time, MCOAS has been described in crossbred Rocky Mountain Horses, Kentucky Mountain Horses, Mountain Pleasure Horse, Morgans, Belgians, American Miniature Horses, Comtois, and Icelandic Horses (Andersson et al., 2008, 2011a,b; Grahn et al., 2008; Komaromy et al., 2011; Plummer & Ramsey, 2011; Ramsey et al., 1999a; Segard et al., 2013). MCOAS exists in two phenotypes: (1) cyst phenotype and (2) MCOA phenotype.



Figure 36.45 The right eye of a few-spot leopard Appaloosa horse affected by CSNB. The medial aspect of the globe is rotated dorsally. The left eye had a similar appearance. (*Source*: Sandemeyer et al., 2007.)

Animals with the cyst phenotype have cysts arising from the ciliary body, peripheral retina, and/or iris. These patients may also have concomitant retinal dysplasia and/or retinal detachment. Animals with the MCOA phenotype have all of the anomalies seen within the cyst phenotype but also have varying severity and a combination of congenital cataracts, cornea globosa, iris hypoplasia, iridocorneal angle abnormalities, lens subluxation, microphthalmia, and macropalpebral fissures (Ramsey et al., 1999a,b). Neuro-ophthalmic abnormalities consist of miotic pupils and abnormal PLRs with pupils that respond poorly to pharmacologically induced mydriasis (Ramsey et al., 1999a). Affected individuals also have varying degrees of vision loss (Grahn et al., 2008; Ramsey et al., 1999a). Congenital ocular abnormalities observed in Rocky Mountain Horses are, in part, related to coat color (Ramsey et al., 1999a).

Mane and tail colors were found to be associated with the presence of multiple ocular abnormalities. Specifically, 45% of Rocky Mountain Horses with chocolate-colored coats with white manes and tails had multiple ocular abnormalities including megalocornea, congenital miosis, ciliary cysts, and retinal dysplasia (Ramsey et al., 1999a). Meanwhile, only 12%, 6%, and 4% of horses with chocolate-colored coat with flaxen mane and tail, chestnut-colored coat, or some other coat color, respectively, had multiple ocular abnormalities (Ramsey et al., 1999a). Moreover, Rocky Mountain Horses with white manes and tails were more likely to have multiple ocular abnormalities compared with animals with nonwhite manes and tails (Ramsey et al., 1999a). Further investigation into coat-color genetics has revealed that the gene responsible for silver coat color is associated with MCOAS (for review see Bellone, 2017). Genetic mutation of the premelanosome protein gene, *PMEL*, is responsible for silver coat color (dilution of black) (Brunberg et al., 2006). This gene mutation results in dilution of black (eumelanin)

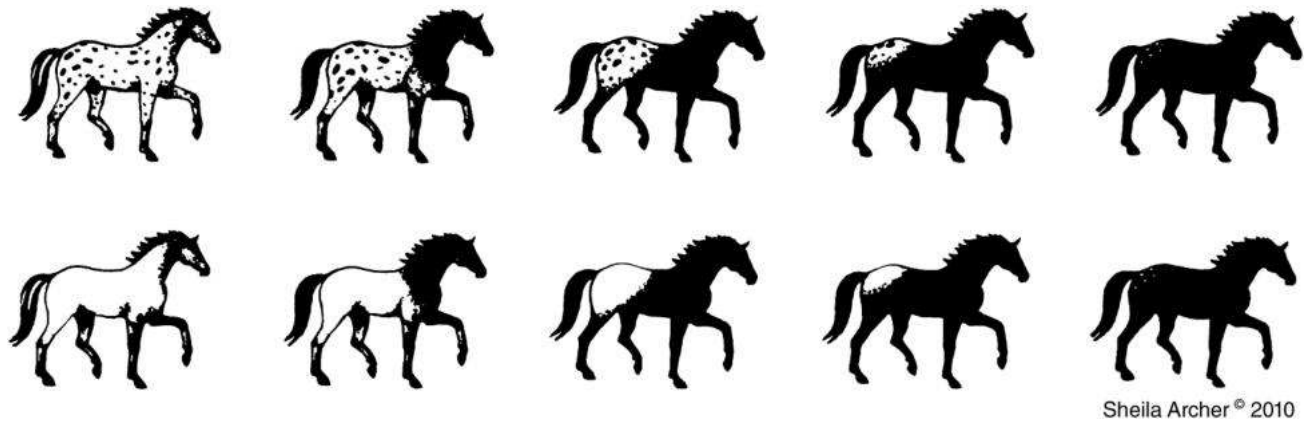


Figure 36.46 White pattern continuum for heterozygote (LP/lp) and homozygote (LP/LP) leopard complex gene. Note that there is a continuum of white pattern in both heterozygote and homozygote horses. Horses homozygous for LP however, have little to no pigmented spotting within the white patterned areas. (*Source*: Reproduced with permission from Sheila Archer). (Webb and Cullen, Can Vet J, 2010)

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but not red/brown (phaeomelanin). As such, chestnut horses may appear normal yet carry *PMEL* (Bellone, 2017). Nonetheless, the severity of ocular lesions appears to be most severe in horses homozygous for mutated *PMEL* (Bellone, 2017).

Equine: Acquired

Borna Disease

Borna disease is caused by a single-stranded, enveloped, RNA virus of the *Flaviviridae* family and is serologically distinct from eastern equine encephalomyelitis, western equine encephalomyelitis, and Venezuelan equine encephalomyelitis (for review see Richt et al., 2000; Rott et al., 2004). The disease is considered endemic in Germany and has been reported in the Netherlands, France, Poland, United States, Iran, and Japan (Rott et al., 2004). Clinical signs are similar to those of the other equine viral encephalitides and include altered PLRs and retinal and/or central blindness. Retinal degeneration has been shown histologically in horses with confirmed Borna disease (Dietzel et al., 2007). Diagnosis of Borna disease is based on consistent clinical signs, serum and CSF antibody titers, and histologic demonstration of pathognomonic Joest–Degen neuronal inclusion bodies in the brain, and the mortality rate varies from 37% to 94% (Rott et al., 2004).

Dysautonomia (Equine Grass Sickness, Mal Seco)

Equine dysautonomia, commonly known as equine grass sickness, has been defined as a "fatal dysautonomia of horses associated with severe neuronal damage, especially in affected autonomic ganglia" (Timoney & Wernery, 2003). The cause of equine dysautonomia remains unknown, although a variety of theories exist. Recently favored hypotheses include: (1) overgrowth of *Clostridium botulinum* type C within the gastrointestinal tract (Hunter et al., 1999; McCarthy et al., 2004); (2) ingestion of some mycotoxin (McGorum & Pirie, 2018); and (3) ingestion of cyanogenic producing plants (McGorum & Kirk, 2001). The highest incidence of equine dysautonomia is in Scotland but has been reported elsewhere in Europe and in South America. In Europe, the disease is most likely to be seen between April and July in young horses kept on pastures (French et al., 2005; Newton et al., 2004).

Clinical signs associated with equine dysautonomia are related to degeneration of autonomic ganglia and the enteric nervous system including pharyngeal and esophageal dysfunction, colic, sweating, tachycardia, and dry nasal mucosa (Milne et al., 2005). The most consistent ocular manifestation of equine dysautonomia is ptosis (Hahn & Mayhew, 2000). Ptosis in equine dysautonomia may result from a primary inability to move the upper eyelid effectively or may occur secondary to abnormal globe position within the orbit (Hahn & Mayhew, 2000). Severe degeneration of neurons in the cranial cervical ganglion (resulting in Horner's syndrome) or abnormally functioning CNs III and/or VII, as indicated by chromatolytic neurons in the nuclei of these nerves, may contribute to the ptosis observed in equine dysautonomia (Hahn & Mayhew, 2000).

Presumptive diagnosis of equine dysautonomia is made based on consistent clinical signs, geographic location of the animal, and time of year. Recently, it has been shown that horses with equine dysautonomia and ptosis have a positive response to ocular administration of topical 0.5% phenylephrine compared with horses not afflicted with equine dysautonomia (Hahn & Mayhew, 2000). Specifically, animals with equine dysautonomia treated with 0.5% phenylephrine will have a wider vertical palpebral fissure opening, as determined by evaluating the angle of the eyelashes relative to the head (opening of the palpebral fissure in the eye treated with phenylephrine subtracted from the opening of the palpebral fissure in the eye not treated with phenylephrine), compared with those animals without equine dysautonomia (Hahn & Mayhew, 2000). Definitive diagnosis of equine dysautonomia is typically made by postmortem examination of affected ganglia and the gastrointestinal system. Therapy is aimed at supportive and intensive nursing care. Prognosis is poor to grave.

Electrocution

Electric shocks and lightning strikes can produce direct ocular sequelae and also cause injury to the CNS (may manifest as blindness, papilledema, cranial nerve palsies) (for review on pathogenesis and human manifestation see Norman et al., 2001). Three horses suspected of being hit by lightning and four horses electrocuted because of a faulty electrical transformer have been reported (Bedenice et al., 2001; Evans et al., 2012; Novales et al., 1998). In some instances, affected animals may die acutely because of peracute heart failure (Bedenice et al., 2001; Evans et al., 2012). Affected animals can become recumbent and exhibit thrashing and/or had exuberant muscle contractions after being struck by lightning or electrocuted. Affected animals may manifest with a variety of neurological signs.

With respect to ocular findings, affected horses have been reported to have ulcerative keratitis (the cause is uncertain but may be secondary to trauma from thrashing on ground), blindness, corneal edema and hydrops, signs of vestibular disease (spontaneous nystagmus), signs of facial nerve paralysis (including ptosis, and absent palpebral reflex and menace response), and absent PLRs (Bedenice et al., 2001). Fundic lesions were not found in one horse after being struck by lightning (Bedenice et al., 2001). In another horse, however, choroidal hemorrhage, retinal detachment, and atrophy were present (Evans et al., 2012). Electric shocks and lightning strikes of a severe nature may produce cataracts that manifest months later.

Although not reported in horses, cataracts are likely to be produced by electrical shocks to the head. The appearance of

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clinical and experimentally induced electric cataracts are quite similar; they consist initially of vacuoles that are present bilaterally in the midperipheral anterior cortical lens (Fraunfelder & Hanna, 1972; Thomas & Hanna, 1974). Ultrastructurally, the vacuoles are extracellular and transient, lasting several weeks. The lens vacuoles are prognostic indicators of later cataract formation. The lens epithelium subsequently proliferates, thereby producing multilayered plaques of lens capsule and lens fibers in the central anterior capsular region. Severe electric shock (e.g., from lightning) may produce both anterior and posterior cortical lenticular opacities (Norman et al., 2001).

Therapy for electrocuted horses is supportive and symptomatic. Horses surviving lightning strike or electrocution may have persistent neurological deficits or return to normal after the incident (Bedenice et al., 2001; Novales et al., 1998).

Equine Protozoal Myeloencephalitis

Equine protozoal myeloencephalitis (EPM) is a multifocal, progressive disease of the CNS caused by infection with *Sarcocystis neurona* or, less commonly, *Neospora hughesi* (for reviews see Dubey et al., 2001, 2004; Furr et al., 2002; Reed et al., 2016; Pusterla & Tobin, 2017). The disease has been reported only in horses born and raised in the Americas including Canada, United States, Brazil, and Panama, with young horses being affected more than older horses and with a breed predilection for Standardbred, Thoroughbred, and Quarter Horses (Dubey, 2004). Infection occurs via ingestion of the organism, although transplacental infection can occur with *Neospora hughesi* (Reed et al., 2016). The parasites can cause inflammation and necrosis throughout the CNS, especially the caudal brainstem and spinal cord. The cerebrum and peripheral nerves may be affected as well. Clinical signs vary depending upon the location of the CNS affected and the chronicity of the disease but may include seizures, ataxia, tetraparesis, focal muscle atrophy, head tilt, facial paralysis, circling, nystagmus, and blindness (with or without pupillary light abnormalities). Horner's syndrome has also been seen in horses with EPM (Mayhew, 1980). Severe temporalis and masseter muscle denervation and atrophy may lead to prominence of the supraorbital fossa, ptosis, and varying degrees of enophthalmos (Mayhew, 1989).

Definitive diagnosis requires demonstrating the causative organism within the CNS (Reed et al., 2016). A working antemortem diagnosis of EPM, in a horse with compatible clinical signs, is made based upon: (1) excluding other diseases; (2) demonstrating intrathecally derived *Sarcocystis neurona* or *Neospora hughesi* antibodies; and (3) demonstration of a positive response to the antiprotozoal medications, Diclazuril or Ponazuril (two medications highly specific in targeting protozoal organisms) (Pusterla & Tobin, 2017). Use of FDA-approved medications is strongly recommended for the treatment of EPM (Pusterla & Tobin, 2017). These FDA-approved medications include: (1) sulfadiazine/pyrimethamine combination (ReBalance, PRN Pharmacal, Pensacola, FL, USA); (2) diclazuril (Protazil, Merck Animal Health, Madison, NJ, USA); and (3) ponazuril sulfone (Marquis, Merial, Lyon, France) (Pusterla & Tobin, 2017). Concurrent administration of systemic anti-inflammatories is recommended because of the significant CNS inflammation, especially within the first week of treating the disease with antiprotozoal medications (Pusterla & Tobin, 2017). Treatment with FDA-approved medications result in clinical improvement and a negative CSF antibody in 57%–62% of patients and approximately 10% of these patients can be expected to relapse 1–3 years after discontinuation of treatment (Pusterla & Tobin, 2017). All three FDA-approved therapies have similar clinical efficacy (Pusterla & Tobin, 2017).

Equine Viral Encephalomyelitis

Viruses of the family *Togaviridae* are transmitted by insects and cause encephalitis in the horse. The most pathogenic of these viruses are called alphaviruses, and these include eastern, western, and Venezuelan equine encephalomyelitis viruses, all of which occur in the Americas (for review see Weaver et al., 1999). All of these viruses are transmitted by biting insects, especially mosquitoes. It is also important to note that these viruses are considered zoonotic. For complete review of various equine encephalitis viruses see Long (2014).

Early clinical signs, regardless of the type of virus, include fever, stuporous state, ataxia, and hyperesthesia. Later signs include aggression, head pressing, blindness, paralyzed tongue and pharynx, nystagmus, strabismus, and pupillary dilatation. Diagnosis of equine viral encephalomyelitis is made based upon time of year (are mosquitoes present?), consistent clinical signs, rising serum antibody titers, and in acute cases, CSF pleocytosis, isolation of the virus from CSF, or demonstration of the virus using RT-PCR (Calisher et al., 1983, 1986; Lambert et al., 2003; Linssen et al., 2000). Treatment is nonspecific and supportive in nature. The mortality rate is high, but horses can recover from viral encephalitis. Most will have residual neurologic signs, although complete recoveries have been reported (Devine & Byrne, 1960). Prevention of equine viral encephalomyelitis is through routine vaccination schedules and by controlling the mosquito population.

Guttural Pouch Disease

The guttural pouch is essentially a diverticulum of the eustachian tube whose function is related to brain cooling (Baptiste et al., 2000). Regardless, there are several nerves located in close proximity to the guttural pouch including the cervical sympathetic trunk, the cranial cervical ganglion, mandibular branch of CN V (trigeminal), CN VII (facial), CN IX (glossopharyngeal), CN X (vagus), CN XI (spinal accessory), and CN XII (hypoglossal) (Manglai et al., 2000). As such, a myriad of clinical signs can emerge when disease

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processes affect the guttural pouch. Clinical signs of guttural pouch disease may include mucopurulent nasal discharge, nonexercise associated epistaxis, and varying signs of dysphagia. Neuro-ophthalmic signs may include signs related to facial nerve paresis/paralysis (i.e., reduced or absent palpebral aspect of the menace response, reduced or absent palpebral reflex, ptosis, Horner's syndrome, and peripheral vestibular syndrome (if the temporal bone is involved). Prognosis and treatment of guttural pouch disease is dependent upon the underlying cause. For discussion of guttural pouch disease and the neurologic manifestations of guttural pouch disease see Borges and Watanabe (2011) and Freeman (2015).

Neoplasia: Central Nervous System

There are few reports of intracranial neoplasms with ophthalmic manifestations in the horse. A pituitary mass in one aged horse resulted in blindness caused by degeneration of the optic nerves, optic chiasm, and optic tracts up to the lateral geniculate bodies (de Lahunta & Cummings, 1967). Another horse with a large intracerebral mass diagnosed as a microglioma had metastasis of the tumor to both eyes, with neoplastic cells being found within the vitreous humor and retina (Finn & Tennant, 1971).

Plants

Numerous plants may be toxic to the horse, and Table 36.14 lists toxic plants along with their systemic and ophthalmic effects. Historically, chronic selenium toxicity has been associated with "blind staggers" in the horse, but horses fed pure selenium compounds fail to develop the blindness, ataxia, or respiratory failure characteristic of blind staggers (Traub-Dargatz & Hamar, 1986). Thus, more recently it has been hypothesized that the toxic effects of alkaloids or other compounds in plants cause blind staggers, and that the condition does not relate directly to the selenium contained within these plants.

Many plants also have teratogenic effects in the horse, especially if they are eaten during the first trimester (Lewis, 1995). Pregnant mares may produce foals with a centrally placed, single eye if they eat *Veratrum eschscholtzii* during early pregnancy, much as ewes will produce such lambs if they eat *Veratrum californicum* on day 14 of gestation (Binns et al., 1962, 1963).

Polyneuritis Equi

Polyneuritis equi is an idiopathic, inflammatory disease of the spinal and cranial nerve roots and peripheral nerves (Mayhew, 2008). The condition is characterized initially by a nonsuppurative neuritis that progresses to a proliferative and granulomatous perineuritis later in the course of the disease (Mayhew, 2008). Polyneuritis equi is thought to be immune-mediated, although it is unknown whether this is a primary or secondary immune-mediated disease (Aleman et al., 2009; Cummings et al., 1979; Kadlubowski & Ingram, 1981; Rousseaux et al., 1984). Affected animals can present with clinical signs of cauda equina involvement predominantly (cauda equine syndrome) or in combination with cranial nerve involvement. Clinical signs referable to unilateral or bilateral involvement of CNs III, V(trigeminal), VII (facial), VIII (vestibulocochlear), IX (glossopharyngeal), X (vagus), XII (hypoglossal), can be seen in severe cases (Aleman, 2011). As with all idiopathic diseases, the diagnosis of polyneuritis equi is a diagnosis of exclusion and is made based upon patient history, clinical signs, demonstration of a mononuclear pleocytosis within the CSF, and failure to identify an infectious or traumatic etiology. Treatment relies upon supportive care; immunosuppressive therapy may slow the progression of the clinical signs (Aleman, 2011). Prognosis is poor (Mayhew, 2008).

Rabies

Rabies, a bullet-shaped RNA virus, is a Lyssavirus in the family Rhabdoviridae (Woldehiwet, 2002). Transmission of rabies occurs via a bite by a rabid animal, although infections through aerosols have been documented (Constantine, 1966; Winkler et al., 1973). Common vector species include bats, foxes, raccoons, and skunks (Woldehiwet, 2002). After an animal has been bitten by an infective rabid animal, virus enters the CNS by migrating up peripheral nerves (for reviews see Begeman, et al., 2018; Lafon, 2005). Consequently, the time from being bitten to showing brain dysfunction is related to the distance of the bite from the head (i.e., the further away the bite from the head, the longer it takes to see signs of brain dysfunction). Once the virus has reached the CNS, a nonsuppurative polioencephalomyelitis and ganglionitis develop and account, in part, for the development of clinical signs (Green et al., 1992b; Hudson et al., 1996). With respect to clinical signs, classical "dumb" and "furious" forms of rabies have been described and are indicative of whether the limbic system is unaffected or affected, respectively.

Clinical signs of equine rabies are highly variable but include behavioral changes, ataxia and paresis of the hind limbs, pharyngeal paralysis, recumbency, and signs of colic (Green et al., 1992b; Hudson et al., 1996). Ocular signs indicative of infection of the central components of the visual and oculomotor systems including blindness, nystagmus, and strabismus may develop (Green et al., 1992b; Hudson et al., 1996). During the clinical course of the disease clinical signs worsen and the animal eventually succumbs to the disease. Antemortem diagnosis can be made by demonstrating antigen, using immunochemical methods, or by detecting the virus using RT-PCR in skin, corneal impressions, or saliva (Woldehiwet, 2005). Definitive diagnosis is made at postmortem by detecting the virus in brain tissue using immunochemical techniques or RT-PCR (Woldehiwet, 2005). Eosinophilic intracytoplasmic inclusion bodies (Negri

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Table 36.14 Toxic plants that may lead to systemic and ophthalmic disease in horses.

Common name	Scientific name	Plant toxin	Systemic signs	Ophthalmic signs
Field bindweed or morning glory	*Convolvulus arvensis*	Tropane alkaloid	Colic	Mydriasis
Jimsonweed	*Datura stramonium, D. metaloides*			
Belladonna	*Atropa belladonna*			
Fiddleneck or tarweed	*Amsinckia* spp.	Pyrrolizidine alkaloid	Hepatic failure, photosensitization, weight loss, neurologic signs, anemia	Cortical blindness
Rattlepod, rattlebox	*Crotolaria* spp.			
Hound's tongue	*Cynoglossum officinale*			
Salvation Jane, Patterson's curse	*Echium* spp.			
Heliotrope, stickseed	*Heliotropium* spp., *Trichodesma* spp.			
Tansy ragwort, stinking willie	*Senecio* spp.			
Lamb's tongue groundsel				
Wooly or threadleaf groundsel				
Ridell's ragwort				
Groundsel				
Broom groundsel				
Butterweed				
Common groundsel				
Horsetail	*Equisetum arvense*	Thiaminase	Weakness, ataxia, diarrhea or constipation, bradycardia, muscle fasciculations	Cortical blindness
Bracken fern	*Pteridium aquilinum*			
Water hemlock	*Cicuta* spp.	Cicutoxin alkaloid	Salivation, teeth grinding, tremors, seizures, respiratory paralysis, sudden death	Mydriasis
Poison hemlock	*Conium maculatum*	Piperidine alkaloid	Salivation, colic, muscle tremors, ataxia, cyanosis, respiratory paralysis, sudden death	Mydriasis
Serviceberry or Saskatoon berry	*Amelanchier alnifolia*	Cyanogenic glycoside	Bright red venous blood, cyanotic membranes, labored breathing, frothing at the mouth, ataxia, seizures, sudden death	Mydriasis
Wild blue flax	*Linum* spp.			
Chokecherry	*Prunus virginiana*			
Elderberry	*Sambucus* spp.			
Johnson grass	*Sorghum halepense*			
Sudan grass, broom, or kafir corn	*Sorghum sudanense*			
Arrow, pod, or goosegrass	*Triglochin* spp.			
Blind grass (Australia)	*Stypandra* spp.	Not defined	Ataxia, weakness	Optic nerve and retinal degeneration

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bodies) may be observed in neurons throughout the CNS, including retinal ganglion cells (Haltia et al., 1989). It is important to note, however, that not all cases of rabies will have Negri bodies present, which is the reason other more specific tests are used. Prevention of rabies is aimed at routine vaccination of susceptible animals.

Temporohyoid Osteoarthropathy

Temporohyoid osteoarthropathy is a condition that involves the bony proliferation of the bones of the temporohyoid joint, namely the stylohyoid and petrous temporal bones (Walker et al., 2002; Yadernuk, 2003). The pathogenesis of temporohyoid osteoarthropathy remains unknown, although it is thought that otitis media or degenerative joint disease of the temporohyoid joint may be important in the pathogenesis of this disease (Walker et al., 2002; Yadernuk, 2003). Temporohyoid osteoarthropathy is commonly associated with facial (CN VII) and vestibulocochlear (CN VIII) nerve dysfunction (Walker et al., 2002; Yadernuk, 2003). Horses with this condition may also exhibit head shaking, hyperesthesia of the ears, and avoidance of bit placement (Yadernuk, 2003). Ocularly, temporohyoid osteoarthropathy commonly manifests secondarily through involvement of the parasympathetic fibers of CN VII (neurogenic keratoconjunctivitis sicca), CN VII (facial nerve paralysis), and the vestibular layrinth and/or vestibulocochlear nerve (signs of peripheral vestibular disease) (Blythe, 1997; Verdegaal et al., 2003; Walker et al., 2002; Yadernuk, 2003). Diagnosis is made based upon consistent clinical signs combined with endoscopic, radiographic, or magnetic resonance or computerized tomographic evidence of asymmetry, inflammation, or osseous proliferation of the temporohyoid joint or stylohyoid bone (Walker et al., 2002). Therapy of temporohyoid osteoarthropathy involves appropriate antimicrobial and/or anti-inflammatory therapy and/or with partial stylohyoid or ceratohyoid ostectomy (Espinosa et al., 2017). Prognosis for this condition, based upon a relatively large retrospective study, is considered good to excellent with surgical intervention and fair with medical therapy, however (Espinosa et al., 2017).

Thiamine Deficiency

Thiamine deficiency occurs in horses primarily because of the ingestion of plants containing the catabolic thiamine enzyme, thiaminase. Plants such as bracken fern (*Pteridium acquilinum*) and horse tails (*Equisetum arvense*) contain thiaminases, and equine thiamine deficiencies have been attributed to chronic ingestion of these particular plants (Carpenter et al., 1950; Evans et al., 1951; Henderson et al., 1952; Roberts et al., 1949). Amprolium, a coccidiostat, has been used to induce thiamine deficiency in horses experimentally (Cymbaluk et al., 1978). Clinical signs of thiamine deficiency in the horse include ataxia, blindness, bradycardia, heart block, muscle fasciculations, weight loss, diarrhea, and hypothermia of the extremities. Diagnosis of thiamine deficiency is made based upon demonstrating exposure to thiaminase-containing plants and demonstrating low serum thiamine or by response to therapy. Therapy includes removal of access to thiaminases and parenteral treatment with thiamine. Clinical signs, including blindness, are reversible if the animal is not in the late stages of deficiency.

Traumatic Optic Neuropathy

Traumatic optic neuropathy in the horse may be caused by blunt head trauma, often caused by the animal flipping over backwards (Blogg & Marc, 1990; Martin et al., 1986; Reppas et al., 1995; van Schaik et al., 1998), causing injury to orbital structures and optic nerve damage. Optic nerve damage is thought to result from shearing and compressive forces applied to the optic nerve at the level of the optic canal. As with any traumatic injury to the CNS, the optic nerve not only sustains primary injury, but also secondary injury (i.e., secondary to primary insult). Such secondary injury is characterized by varying degrees of inflammation, altered permeability to blood vessels, etc. Ultimately, retinal ganglion cell fibers are damaged and varying degrees of optic nerve degeneration occur over weeks and months. Such degeneration is evidenced by optic nerve atrophy and varying degrees of retinal degeneration. Neuro-ophthalmic findings vary from acute to subacute progressive visual field deficits or blindness, variably dilated pupils, reduced or absent PLRs, and inconsistent to absent dazzle reflexes and menace response. Treatment is aimed at reducing edema of the CNS and maintaining oxygenation. Prognosis is typically poor, although improved visual function may develop in animals without basilar skull fractures and with some evidence of vision at the time of injury (Irby, 2011).

Vitamin A Deficiency

Vitamin A (retinol), a fat-soluble vitamin, is derived from its precursors (carotenoids) which are found in plants (for review see Fraser & Bramley, 2004; von Lintig & Vogt, 2004). Vitamin A (retinol) is important in the ocular system; it is stored and transformed into retinal, which is translocated between the retinal pigment epithelium and the photoreceptors (Thompson & Gal, 2003). Within the photoreceptors, retinal combines with opsin (a protein) to form the visual pigment rhodopsin (Thompson & Gal, 2003). Early signs of vitamin A deficiency include: reduced feed intake and growth rate; a dull and brittle, long hair coat; and in foals, an increased incidence of respiratory and diarrheal diseases. A diagnosis of vitamin A deficiency is suspected in horses with excessive tearing and night blindness (Lewis, 1995). An important differential diagnosis for vitamin A deficiency is congenital stationary night blindness in Appaloosa horses (the latter is present from birth, is nonprogressive, and has no clinically evident ocular lesions). Ocular lesions and

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night blindness occur only if vitamin A deficiency is severe and long-standing (Howell et al., 1941). Complete blindness from retinal degeneration eventually occurs if the horse remains on a vitamin A-deficient diet; at that point, the pupils will be dilated and unresponsive to light. In addition, horses with vitamin A deficiency may have hyperkeratinization of the cornea and reduced numbers of conjunctival goblet cells.

Diagnosis of vitamin A deficiency is made based upon documenting low levels of serum retinol and by using the relative dose response test (Greiwe-Crandell et al., 1995). Horses consuming good-quality, green pasture grasses and hay are unlikely to suffer from vitamin A deficiency (Lewis, 1995). Therapy is aimed at providing adequate levels of vitamin A in the diet.

West Nile Virus

West Nile virus (WNV) is single-stranded RNA virus of the family *Flaviviridae* that is maintained in the environment by a bird–mosquito relationship (for review see Garg & Jampol, 2005; Long, 2014; Ostlund et al., 2000). Birds are the reservoir host whereas mosquitoes transmit the virus to a variety of animal species, including birds, horses, cats, dogs, bats, alligators, and humans (Garg & Jampol, 2005; Kulasekera et al., 2001; Nasci et al., 2001; Turell et al., 2002). Horses are similar to humans in that they are considered dead-end hosts (cannot transmit the disease), although transfusion of infected blood products can result in transmission of the disease to the recipient (Pealer et al., 2003). Crows and other members of the *Corvidae* family are highly susceptible to WNV infection and carry a large virus load; they are considered important in the transmission of the disease (Komar et al., 2003). As an aside, it should be noted that WNV infection in birds of prey (Cooper's and Red-Tailed hawks) has been noted to cause a triad of clinical disease including myocarditis, encephalitis, and endophthalmitis similar to the syndromes observed in humans (Garg & Jampol, 2005; Wunschmann et al., 2004).

There does not appear to be any breed or gender predilection for developing the disease (Schuler et al., 2004; Weese et al., 2003). The disease typically affects young adult horses, although any age of horse can have a clinically relevant infection (Schuler et al., 2004; Weese et al., 2003). Clinical signs in horses include ataxia, paresis, generalized muscle fasciculations, pyrexia, hyperesthesia, general malaise, lip droop, bruxism, circling, and animals may be recumbent (Schuler et al., 2004;Weese et al., 2003). Ophthalmic manifestations of WNV infection are that horses may be blind, have facial nerve paralysis, mild keratitis of undetermined cause, and have protrusion of the third eyelid (Autorino et al., 2002; Hyatt & Weese, 2004; Schuler et al., 2004). In humans, however, WNV infection manifests ocularly as chorioretinitis, uveitis, retinal vasculitis, and optic neuritis (Garg & Jampol, 2005). It is possible that horses, too, have similar ocular lesions although complete ophthalmic examinations may not routinely be performed or such lesions have not been reported.

Diagnosis of WNV infection is made based upon determining IgM concentrations in the serum and/or CSF, amplifying WNV DNA using PCR, or isolating the virus (Schuler et al., 2004; Weese et al., 2003). Therapy for WNV infection involves supportive care and administering systemic anti-inflammatory drugs to reduce cerebral edema (Weese et al., 2003). Prognosis is variable. Older horses, horses not vaccinated for WNV, and horses that are recumbent are more likely to succumb to the disease (Schuler et al., 2004; Weese et al., 2003). Specifically, up to approximately 80% of WNV-infected and recumbent horses will succumb to the disease (Schuler et al., 2004). Prevention is aimed at implementing a routine vaccination schedule. The percent mortality for vaccinated (when used according to the manufacturer's instructions) animals that develop clinical signs of the disease is 4%, whereas the mortality of unvaccinated animals has been reported to be 33% (Schuler et al., 2004).

Food Animals: Congenital

Hydrocephalus

Hydrocephalus refers to an increased amount of CSF within the cranial vault. Bovine hydrocephalus is a commonly encountered congenital defect for which concurrent ocular lesions are rarely reported (Greene & Leipold, 1974; Leipold et al., 1971, 1974). In Shorthorn calves, multiple ocular anomalies including microphthalmia, cataracts, retinal detachment, retinal dysplasia, optic nerve, optic chiasm and optic tract hypoplasia, persistent pupillary membranes, and vitreous hemorrhage have been associated with hydrocephalus (Leipold et al., 1971, 1974). The cause has not been determined, but it has been postulated to be genetic (Leipold et al., 1971).

Pendular Nystagmus

Benign pendular nystagmus has been reported in Holstein, Jersey, Ayrshire, and Guernsey breeds of cattle (McConnon et al., 1983; Nurmio et al., 1982; Rebhun, 1979). The condition is characterized by vertical, horizontal, or rotary pendular nystagmus (i.e., spontaneous nystagmus occurring with no clear fast or slow phase). The condition is presumed inherited, although this has not been confirmed.

Food Animals: Developmental

Bilateral Convergent Strabismus with Exophthalmos

Bilateral convergent strabismus with exophthalmos (BCSE) is an inherited disease affecting German Flackvieh, German Holstein, German Brown, and Jersey breeds of cattle (for review see Momke & Distl, 2007). The condition is characterized by a progressive, bilaterally convergent strabismus and

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Figure 36.47 Bilateral convergent strabismus with exophthalmos, stage 4, in a German Brown cow. (*Source*: Reproduced with permission from Momke & Distl, 2007.)

mild to severe exophthalmos (Fig. 36.47). Affected animals can become blind because of severe strabismus. Clinical signs are first noticed as early as 6 months of age, or much more commonly just prior to an animal's first breeding. The disease appears to be inherited in an autosomal dominant fashion in German Brown dairy cattle. There is no treatment or cure for this disease. Single nucleotide polymorphisms for *PLXCN1* (plexin C1) (on bovine chromosome 5 [BTA 5]) and *RDH13* (retinol dehydrogenase 13) (on bovine chromosome 18 [BTA 18]) are significantly associated with BCSE, although the exact causal mutation has yet to be identified (Fink et al., 2012).

Food Animals: Acquired

Bovine Virus Diarrhea

Bovine virus diarrhea (BVD) results from a pestivirus (enveloped single-stranded positive-sense RNA virus) with a worldwide distribution that infects cattle, sheep, goats, and wild ruminants. It is transmitted via inhalation or ingestion of infective secretions or excretions, semen, and transplacentally. Results of one study showed that BVD virus can also be transmitted to susceptible animals if they come into contact with fetal fluids during the birth of persistently infected calves (Lindberg et al., 2004). BVD virus has been implicated with causing abortion, and cerebellar and ocular disease. In cattle, *in utero* infection with BVD virus between 76 and 150 days of gestation may result in congenital defects of the eye and brain. In addition, after experimentally induced BVD infection, persistently infected calves have minor skeletal abnormalities including short limbs, narrow skull with bulging eyes, and/or prognathism (Stokstad & Loken, 2002). CNS lesions include microencephaly, cerebellar hypoplasia, hydranencephaly, and hydrocephalus (Baker, 1987). Ocular lesions of cataracts, retinal degeneration and retinal dysplasia, optic nerve gliosis, optic neuritis, and microphthalmia have also been described with experimentally induced disease (Bistner et al., 1970b; Scott et al., 1973). At ophthalmoscopy, the tapetal coloration is altered, and pigment clumping is visible. Cataracts and optic nerve lesions may not be present in naturally occurring cases of BVD; this may relate to the stage of gestation during which the pregnant dam became infected (Bistner et al., 1970b). Acute histopathologic ocular lesions detected in fetuses taken 17–21 days after inoculation of their dams at 150 days gestation included mild to moderate retinitis causing destruction of the retinal layers, mononuclear cuffing of the inner retinal vessels, proliferation of the retinal pigment epithelium, and choroiditis (Brown et al., 1975).

Ocular lesions of tapetal color alterations, optic nerve atrophy and cataracts, and cerebellar hypoplasia are suggestive of BVD. A diagnosis of BVD, in persistently infected animals, is made based upon using a variety of tests including virus isolation, immunohistochemistry, various antigen-capture ELISAs, and RT-PCR (Khodakaram-Tafti & Farjanikish, 2017). At present, there is no therapy for BVD.

Brain Abscessation

Central blindness has been diagnosed in a 3.5-year-old crossbred steer diagnosed with multiple brain abscesses (Strain et al., 1987). In particular, clinical signs in this steer included depression, head pressing, and circling to the left. Ocular manifestations in this animal included ptosis and absent menace response of the right eye; direct and consensual PLRs were normal in both eyes. Electrodiagnostic testing was performed and revealed essentially normal brainstem auditory evoked potentials and ERGs, whereas visual-evoked potentials (VEPs) were greatly diminished for the right eye and absent for the left eye. On postmortem examination, the brain abscesses were located in the left thalamus, left caudal cerebrum, and right frontal cerebrum (Strain et al. 1987).

Bracken Fern Poisoning (Bright Blindness)

Ingestion of bracken fern (*Pteridium aquilinum*) in chronic, low-level amounts has been suspected of causing the syndrome of bright blindness among sheep and cattle in the United Kingdom (Barnett & Watson, 1968, 1970; Hirono et al., 1993; Watson et al., 1965, 1972). The syndrome manifests as a retinal degeneration with blindness. Retinal lesions are most

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severe centrally and involve degeneration of the rods and cones. Ophthalmoscopic findings include retinal vascular attenuation, tapetal hyperreflectivity, and optic nerve atrophy (see Fig. 37.4.17) (Barnett & Watson, 1968). The active chemical in bracken that causes progressive retinal degeneration following *Pteridium* sp. ingestion is ptaquiloside, a carcinogenic norsequiterpene (Hirono et al., 1993) (for review pertaining to ptaquiloside, see Yamada et al., 2007).

Bullous Empyema

Bullous empyema causing peripheral vestibular syndrome has been described in a pregnant heifer. Clinical signs in this heifer included generalized ataxia, wide-based stance of the hind limbs, abnormal behavior, circling to the left, and left head tilt. In addition, ocular lesions included strabismus to the left and nystagmus with the fast phase to the right (Braun et al., 2004).

Electrocution

Electric shocks and lightning strikes can produce direct ocular sequelae and also cause injury to the CNS (may manifest as blindness, papilledema, cranial nerve palsies) (for review on pathogenesis and human manifestation see Norman et al., 2001). Electric shocks and lightning strikes of a severe nature may produce cataracts that manifest months later. Cataracts are more likely to be produced by electrical shocks to the head. In one report, a herd of Holstein-Friesian cattle experienced a lightning strike while kept on pasture (Boeve et al., 2004). After the lightning strike, 8 of the 18 cattle had an unsteady, swinging gait, 9 calves had visual impairment as evidenced by an absent menace response, and 3 calves showed nystagmus. Four of the 9 blind calves underwent ophthalmic examination which revealed normal PLRs and no morphologic ocular lesions. Histopathologic examination of the brain of affected animals, including one of the blind calves, revealed cerebrocortical necrosis (Boeve et al., 2004).

Helichrysum argyrosphaerum Poisoning

In Africa, sheep and cattle grazing on pastures mainly consisting of *Helichrysum argyrosphaerum* have developed blindness, paresis, and paralysis. Lesions have consisted of bilateral, symmetric edema of the CNS white matter with destruction of myelin, and the optic nerve develops gliosis. The intracanalicular portion of the optic nerve subsequently undergoes fibrosis and atrophy suggestive of compression in the optic canal. Retinal lesions include degeneration and loss of photoreceptor outer segments, mainly in the non-tapetal fundus. The retinal pigment epithelium is hyperplastic and migrates into the neurosensory retina (van der Lugt et al., 1996).

Hypocalcemia (Bovine Parturient Paresis, Milk Fever)

Bovine parturient paresis is a complex metabolic disorder resulting in an acute to peracute flaccid paralysis and/or somnolence of lactating dairy cows which usually occurs at the onset of lactation (Horst et al., 1997). The hypocalcemia arises because of a rapid increase in milk production and subsequent acute depletion of serum ionized calcium. Parturient paresis is divided into three main clinical stages of which stage two hypocalcemia is characterized by depression, anorexia, an inability of the animal to stand, tachycardia, gastrointestinal stasis, and ocular signs of mydriasis with absent or sluggish PLRs (Murray et al., 2008). Recommended treatment for parturient paresis is prompt intravenous therapy with a calcium solution (Murray et al., 2008).

Hypomagnesemia (Grass Tetany)

Hypomagnesemia results from a primary dietary deficiency of magnesium and is a highly fatal condition in ruminants. Clinical signs in lactating cows affected with grass tetany (which occurs mainly in winter and spring when the diet is based on grasses low in magnesium) include anorexia, hyperexcitability, muscle fasciculations, head and neck tremors, followed by poorly coordinated gait and lateral recumbency. In addition, ocular manifestations of grass tetany include nystagmus and a rapid, snapping eyelid retraction. Confinement-housed dairy cows on a controlled feeding program can also develop hypomagnesemia (Donovan et al., 2004). Prevention of hypomagnesemia involves both continuous provision of adequate levels of dietary magnesium and improving absorption of this essential mineral by the ruminal epithelium (Martens & Schweigel, 2000). The reader is referred to current internal medicine textbooks for a detailed discussion on hypomagnesemia in ruminants.

Lead

Lead poisoning is commonly diagnosed in cattle, and, to a lesser extent, sheep and horses. Cattle, especially young calves, are very susceptible to lead poisoning (Neathery & Miller, 1975). The cause of lead poisoning is accidental ingestion of sources of lead compounds (e.g., automobile battery) or of feed containing lead from environmental pollution. Lead poisoning in food animals is of public health significance because of the risk to humans through ingestion of contaminated meat and milk products from affected animals (Rumbeiha et al., 2001). In addition, the half-life of blood lead is variable (ranging from 48 days to 2507 days) and is therefore difficult to predict in accidental cases of lead poisoning in cattle (Rumbeiha et al., 2001). In acute lead poisoning of cattle, clinical signs include staggering, muscle tremors (mainly of the head and neck), clamping of the jaws, frothing at the mouth, in addition to ocular signs such as snapping of the eyelids, rolling of the eyes, and blindness. In the acute syndrome, death usually results during a convulsion as a result of respiratory arrest.

Listeriosis

Listeriosis is caused by a small rod-shaped, Gram-positive bacterium belonging to the genus *Listeria*. The most

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common and important organism causing disease in domesticated animals is *Listeria monocytogenes*. Spoiled or incompletely fermented corn or hay silage is the main source of infection. Small wounds in the lips, oral and nasal mucosae, and the conjunctiva permit entry of the causative agent (Braun et al., 2002). In addition, venereal transmission in ruminants has been described (Wiedmann et al., 1999). For further details regarding the transmission and pathogenesis of listeriosis in food animals, the reader is referred to a current textbook in food animal infectious disease and/or internal medicine.

Listeriosis of the CNS (i.e., meningoencephalitic form) is most likely to be associated with ocular signs in food animal species. The main clinical manifestations of listeriosis include CNS disease with vestibular ataxia and unilateral cranial nerve deficits. Involvement of the brainstem may be associated with facial nerve paralysis and keratoconjunctivitis sicca. Keratitis is the main ocular lesion, although varying degrees of hypopyon and anterior uveitis may also be present. Purulent endophthalmitis may result as well (Saunders & Rubin, 1975). A variety of ocular lesions have been reported in sheep and goats with listeriosis including scleral hyperemia, unilateral keratitis with or without corneal ulceration, bilateral mydriasis, vertical or horizontal nystagmus, ventrolateral or ventromedial strabismus, unilateral or bilateral diminished or absent menace response, lack of palpebral reflex, and diminished or absent PLRs (Braun et al., 2002; Gerros, 1998). In cattle, ocular lesions have been reported to be the most common clinical manifestation of listeriosis, followed by neurologic signs (Erdogan et al., 2001). Recently, listerial ocular infections (conjunctivitis, keratitis, and uveitis) in ruminants have also been related to environmental or host factors, such as direct ocular exposure of susceptible animals to high numbers of the agent (Evans et al., 2004b). In swine, listeriosis usually occurs in newborn pigs, among which oral exposure results in focal necrosis of the parenchymatous organs, lymphoreticular tissue, and a necrotizing vasculitis and septic choroiditis (Busch et al., 1971).

A diagnosis of listeriosis is made based upon consistent clinical signs, and culturing and identifying the organism from body fluids (e.g., CSF) and tissues. Suggested treatments include systemic administration of appropriate antimicrobials (e.g., penicillin or oxytetracycline), supportive therapy, and isolation of affected animals. *L. monocytogenes* can cause serious disease in humans including meningitis and sepsis, and in pregnant women, spontaneous abortion and stillbirth can result (Low & Donachie, 1997).

Locoweed Poisoning

Ingestion of locoweed by cattle, sheep, and horses may produce ocular signs of blindness and a "dull" eye. Histopathologic changes of marked vacuolation of the retinal ganglion and bipolar cells, ciliary epithelial cells, and lacrimal acinar cells have been described in research animals (Van Kampen & James, 1971).

Male Fern Poisoning

Male fern (*Dryopteris filix-mas*) consumption by cattle is associated with lethargy, constipation, and blindness. Acutely blind cattle have dilated pupils and ophthalmoscopic lesions of papilledema, as well as retinal and preretinal hemorrhages. Most animals recover when removed from pastures containing male fern, but some do not. Chronically blind animals develop optic nerve atrophy and vascular attenuation. At histopathology, the retrobulbar optic nerves are twice the normal diameter, myelin sheaths are fragmented and invaded by Gitter cells, and axons are decreased in number. The peripheral nerve, however, is relatively spared. The process appears to be a retrobulbar neuropathy that destroys the myelin sheaths of the nerve (Rosen et al., 1970).

Polioencephalomalacia (Cerebrocortical Necrosis)

Polioencephalomalacia (PEM) is a disorder of the CNS of ruminants that results in necrosis of the cortical gray matter (Gould, 1998; Newsholme & O'Neill, 1985). PEM has a worldwide distribution. There are several causes of PEM including altered thiamine (vitamin B_1) status caused by such factors as excessive ruminal consumption of thiamine by bacterial thiaminases, and ingestion of plants with thiaminolytic activity, among others. However, PEM may also be induced by other neural metabolic disturbances such as water deprivation–sodium ion toxicosis, lead poisoning (see previously), and high sulfur intake (Gould, 1998). Early clinical signs of PEM in affected animals include anorexia, incoordination, muscle tremors, holding the head in an erect position, and appearing blind. As PEM progresses, animals develop blindness, head-pressing, dorsomedial strabismus, miosis, variable nystagmus, excitement, facial twitching, repetitive chewing, and recumbency and opisthotonos (McGuirk, 1987). In addition, a lack of menace responses and reduced palpebral reflexes have been described in PEM-affected cattle (Haydock, 2003). Death usually arises after 3–4 days if the affected animal is not treated.

Electrodiagnostic visual testing (ERG and VEP) has been performed on five ruminants (three lambs, one kid, and one steer) with thiamine-responsive PEM (Strain et al., 1990). The lambs and kid had typical clinical signs of PEM, including blindness. The ERG in these animals was normal but the VEP was abnormal. Follow-up recordings in the kid and one lamb indicated an improvement in VEP recordings subsequent to thiamine treatment and a gradual return of vision. According to the owners, all animals had complete return of vision. The steer did not have signs of blindness, and the ERG and VEP were normal (Strain et al., 1990). The reader is referred to current internal medicine textbooks for a detailed discussion on PEM.

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Porcine Blue Eye Disease (Porcine Rubulavirus; La Piedad Michoacan Virus)

Porcine blue eye disease (PBED) is caused by a rubulavirus of the *Paramyxoviridae* family that infects swine. This disease emerged in 1980 in Central Mexico (Stephano, 1990). PBED is characterized by corneal opacity, encephalomyelitis, respiratory disease and reproductive failure. CNS manifestations (e.g., fatal encephalitis) and corneal opacity are the main signs in piglets 2–21 days old (Ramirez-Herrera et al., 1997, 2001; Stephano & Gay, 1984; Stephan et al., 1998). Older pigs appear more resistant and corneal opacity is a commonly observed feature (Stephan et al., 1998). PBED in pregnant sows has been linked with reproductive failure and infertility. Piglets 2–15 days of age are most susceptible. Affected piglets become prostrate and develop progressive neurologic signs. The affected animals may be blind, with dilated pupils and nystagmus. In addition, PBED-affected pigs may develop conjunctivitis with epiphora, swollen eyelids, and ocular discharge adherent to the eyelids. Piglets older than 30 days of age may have respiratory signs and corneal opacities, or they may strictly have corneal opacities. Up to 30% of affected piglets have either unilateral or bilateral corneal opacities, which tend to resolve spontaneously. Histopathologically, ocular lesions consist of corneal edema and anterior uveitis. The cellular reaction is mononuclear, with some neutrophils and intracytoplasmic inclusions possibly being present in the epithelial cells (Hornedo & Gutierrez, 1986; Stephano, 1990). PBED has also been shown to bind to pig neuronal tissue of the brain stem, hippocampus, olfactory bulb, cerebellum, and frontal, temporal, and parietal lobes of the cerebral cortex in newborn, 60-day-old, and adult pigs (Mendoza-Magana et al., 2001). Clinical signs of encephalitis and corneal edema in piglets, or reproductive failure in adults, is/are suggestive of the diagnosis. The diagnosis is confirmed on the basis of virus isolation and hemagglutination-inhibition tests. At present, there is no specific therapy.

Prion Disease

Scrapie is a neurodegenerative disease of the group of transmissible spongiform encephalopathies (TSEs) affecting sheep and goats. Sheep are regarded as the natural reservoir for scrapie. The incubation period is typically between 2.5 and 3.5 years. According to the prion hypothesis, which explains most of the biological features pertaining to the scrapie agent, scrapie lesions are triggered by the conversion of the cellular prion protein (PrP^{c}) into the abnormal isoform (PrP^{sc}) resulting in its pathological accumulation (Hunter, 1998). Scrapie produces progressive neurological signs, the lesions of which consist mainly of vacuoles within the nervous system, and eventual death. In particular, clinical signs are categorized into three main groups: (1) sensation abnormalities, namely pruritus; (2) changes in mental status including apprehension and occasional aggression, and stupor: and (3) postural and locomotion changes such as low carriage of the head, wide-based or cross-legged stance, pacing (Braun et al., 2004), and ataxia (for a review of scrapie, please refer to Bradley & Verwoerd, 2004).

One study examining the neurophthalmic manifestations of naturally occurring scrapie using 17 affected animals and 6 age-matched control animals has been published (Regnier et al., 2011). In this study there was no evidence of anisocoria, pupil size aberrations, PLR abnormalities, or corneal or palpebral reflex abnormalities. Three affected animals, however, had inconsistent menace responses, although one control animal also had an inconsistent menace response. As such, it is unclear from this study whether sheep with scrapie develop altered vision. Interestingly, however, all scrapie-affected sheep had histopathological changes consistent with retinal degeneration. Future studies would need to examine a larger population of animals to more clearly identify whether visual field deficits exist in sheep affected by scrapie.

Ocular manifestations of scrapie infection of sheep and goats include multifocal, round tapetal lesions that can be as large as the optic disc. Histologically, these lesions are focal retinal detachments resulting from subretinal accumulations of eosinophilic material characterized as lipid (Barnett & Palmer, 1971). These fundic lesions are typical enough to be suggestive of the diagnosis when combined with chronic, progressive neurologic disease. Importantly, however, not all animals with scrapie have retinal changes that can be observed ophthalmoscopically (Regnier et al., 2011).

Electrophysiologically, sheep affected by scrapie have reduced a- and b-wave amplitudes, although waveforms are similar between affected and unaffected animals and there are no differences in implicit times between affected and unaffected animals (Regnier et al., 2011).

There is no effective treatment for scrapie. Animals suspected of having scrapie should be euthanized and their brain should be submitted for laboratory examination.

Pseudorabies (Aujeszky's Disease)

Pseudorabies is caused by Aujeszky's disease virus, a neurotropic alphaherpesvirus, suid herpesvirus-1. Pseudorabies epizootics in swine are noted with drastic climatic changes, and they are characterized by blindness, depression, head pressing, and death. Death or recovery tends to occur by day 3, with blindness occurring as a permanent sequela in recovered animals. Histopathologically, ocular lesions include decreased numbers of retinal ganglion cells, degeneration of retinal ganglion cells, and perivascular cuffing with mononuclear cells and neutrophils in the optic nerve (Howarth & De, 1968). In addition, rapidly progressive punctate corneal ulcers associated with blepharospasm, follicular conjunctivitis, corneal anesthesia, transient blindness, iridal edema,

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miosis, and fever, have been produced after experimental inoculation of traumatized porcine corneas with Aujeszky's disease virus (Schneider & Howarth, 1973). There is no treatment for the disease. Vaccines against Aujeszky's disease virus have been developed (for review see Freuling et al., 2017).

Rabies

Rabies continues to be one of the most feared zoonotic diseases in the world. Rabies, a bullet-shaped RNA virus, is a Lyssavirus in the family *Rhabdoviridae* (Woldehiwet, 2002). Transmission of rabies occurs via a bite by a rabid animal, although infections through aerosols have been documented (Constantine, 1966; Winkler et al., 1972, 1973). The virus can infect any warm-blooded animals, with dogs and cats being the main vectors of human infection (Woldehiwet, 2005). Clinically, rabies infection can be divided into three phases: (1) prodromal, (2) furious, and (3) paralytic (Bedford, 1976). Cattle are most commonly affected among livestock. One study documented that cases of rabies infection reported in the United States in cats, dogs, horses and mules, and sheep and goats decreased 12.5%, 19.7%, 31.8%, and 16.7%, respectively, whereas cases reported in cattle increased 174% (Krebs et al., 2005). Rabies virus is likely the most important cause of bovine encephalitis because of the public health implications (Callan & Van, 2004). The clinical signs of rabies infection in livestock are variable. Clinical manifestations of the prodromal form of rabies in animals include depression, inappetence, pyrexia, significant ataxia, and facial musculature flaccidity, among others. In addition, other signs, including ocular manifestations, may be seen prior to death such as circling, head-pressing, strabismus, nystagmus, and blindness. The reader is referred to current internal medicine textbooks for a detailed discussion on rabies.

Vitamin A Deficiency

Vitamin A deficiency has been studied extensively among cattle, both in spontaneous cases and with experimental induction. In young, growing animals, vitamin A deficiency produces clinical signs when the vitamin A levels fall to less than 20 μg/dL of plasma and less than 2 μg/g of liver (Kohlmier & Burroughs, 1979). A sexual predilection for males has been noted in two clinical reports (Divers et al., 1986; Paulsen et al., 1989). A lag period of 3–12 months may be necessary before the effects of vitamin A deficiency are noted, and these effects depend on age of onset, degree of deficiency, and the amount of liver stores. Animals younger than 6 months of age are more susceptible and more likely to have blindness as a presenting sign because of sphenoid bone overgrowth constricting the optic nerve (Barnett et al., 1970; Blakemore et al., 1957; Booth et al., 1987; Divers et al., 1986; Hayes et al., 1968; Paulsen et al., 1989; Spratling et al., 1965; Van Donkersgoed & Clark, 1988; Wetzel & Moore, 1940). Blindness, with or without convulsions, is the first outward sign noted in most cases among young, growing animals (Barnett et al., 1970; Divers et al., 1986; Kang et al., 2017; Parker et al., 2017; Spratling et al., 1965). Seizures are short and tonic-clonic in nature (Divers et al., 1986). Upon critical examination of animals, night blindness, the first clinical sign noted in experimentally affected animals, may be noted, but it is unlikely to be noted under typical husbandry conditions (Barnett et al., 1970). Blindness is accompanied by fixed, dilated pupils, and on ophthalmoscopy, papilledema will be present (see Fig. 37.4.13 and Fig. 37.4.14). Papilledema occurs well before blindness in both adult- and young-onset deficiencies. Papilledema presumably results from increased CSF pressure, which develops from fibrosis and thickening of the dura mater that, in turn, results in decreased absorption of the CSF by the arachnoid villi. Increased CSF pressure is the first change noted with vitamin A deficiency (Hayes et al., 1968).

Causes of blindness will vary with age of onset for the deficiency. Blindness may result from retinal degeneration at all ages or constriction and ischemic necrosis of the optic nerve at the optic foramen in growing animals. Eventually, optic nerve atrophy develops (see Fig. 37.4.15) (Barnett et al., 1970). Day blindness has not been reversible, but night blindness or papilledema detected before blindness occurs has been responsive to therapy (Spratling et al., 1965). Additional changes in the fundus are papillary and peripapillary hemorrhages as well as disruption of pigment in the non-tapetal region (see Fig. 37.4.16). Retinal degeneration primarily occurs in the non-tapetal region (Barnett et al., 1970; Divers et al., 1986; Paulsen et al., 1989; Van Donkersgoed & Clark, 1988). Tapetal color alterations have not been noted in experimental or in clinical reports until late in the deficiency. Additional ocular lesions that have been attributed to vitamin A deficiency include exophthalmos (origin not understood), epiphora, nystagmus, and corneal ulceration. Although described clinically, corneal lesions have not usually been observed experimentally in calves, but decreased corneal sensitivity has been observed (Barnett et al., 1970). In one study, 25% of calves born to heifers which experienced prolonged hypovitaminosis A during pregnancy had several congenital ocular abnormalities including microphthalmos, ocular dermoids covering the external surfaces of the eyes, and single chambered globes each lacking a uveal tract, lens (i.e., aphakia), and aqueous humor (Mason et al., 2003). Similar congenital malformations have been observed in another report where cataracts and luxated lenses were also observed (Anonymous, 2014). Histopathologic examination of the affected eyes revealed severe retinal dysplasia with retinal rosettes, retinal folds, and a generalized loss of retinal cells. In addition, the optic nerves were more cellular and paler staining than normal (Mason et al., 2003). Concurrent systemic signs will vary

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depending on the source of nutrition, duration of the deficiency, and age of the affected animal. In general, severe vitamin A deficiency will be accompanied by unthriftiness, diarrhea, poor growth, decreased appetite, and pneumonia.

The pathogenesis of the optic nerve lesions associated with vitamin A deficiency in calves has been extensively studied (Blakemore et al., 1957; Hayes et al., 1968; Wetzel & Moore, 1940). In calves made deficient for vitamin A from 35 days onward and examined at 5.5–6 months of age, the optic foramen of the sphenoid bone became deformed into a narrow, horizontal aperture. Normal development of the optic foramen results from new bone growth across the dorsomedial aspect of the optic canal and resorption of bone ventrally, which results in the progressive ventral displacement of the canal. In vitamin A-deficient calves, osteoblastic activity persisted both dorsally and ventrally, thus resulting in the two surfaces growing toward each other and a narrowed, horizontal slit for an optic canal (van der Lugt & Prozesky, 1989). In addition, the dura mater becomes thicker, and the combination produces compression within the canal, thereby compromising the vascular supply for the optic nerve. Optic nerve changes result mainly from ischemic necrosis, but in some instances when vascularity is maintained, the optic nerve pathology is subtle and may result from retinal degeneration. Constriction of the optic canal could not be produced in 2-year-old animals (Hayes et al., 1968), and the retinal histopathology has been reported in both naturally and experimentally deficient calves. Experimentally, degenerative changes were limited to the outer retinal layers and the retinal pigment epithelium, and occurred preferentially in the ventral non-tapetal retina. Clinically, not only outer retinal degeneration but focal areas of full-thickness retinal degeneration and detachments have been reported (Barnett et al., 1970; Booth et al., 1987; Paulsen et al., 1989; Van Donkersgoed & Clark, 1988).

The clinical signs, history, and ophthalmoscopic signs are very suggestive of hypovitaminosis A. If vitamin supplementation has not been instituted, plasma blood levels of less than 20 μg/dL of vitamin A will confirm the diagnosis (Divers et al., 1986; Kohlmier & Burroughs, 1979; Paulsen et al., 1989). Vision will not be restored in calves that are day blind, but animals with vision and papilledema as well as older animals may benefit from parenteral administration of vitamin A at 440 IU/kg (Divers et al., 1986).

Vitamin A deficiency in pregnant sows has, both experimentally and clinically, been responsible for a high incidence of varying degrees of microphthalmos and blindness in piglets. In extreme cases, anophthalmia was present as well. In the clinical setting, the gilts are usually normal, although slow-healing skin wounds may be noted. Milder deficiencies have additional manifestations of hyperkeratotic facial lesions, posterior limb incoordination, inability to fully extend the carpal joint, and a high neonatal mortality rate. In extreme experimental deficiencies of vitamin A, anomalies of cleft palate, accessory ears, and subcutaneous cysts have been produced (Hale, 1935; Maneely, 1951; Watt & Barlow, 1965).

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37.1

Ocular Manifestations of Systemic Disease

Part 1: The Dog

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Ocular examination of animals with systemic disease is an essential diagnostic component of a complete physical examination that can help reduce the list of probable differential diagnoses and can assist in organizing such a differential diagnostic list from most to least likely. In addition, the visual prognosis for the animal with systemic disease may be crucial to owners when deciding how aggressively they wish to pursue diagnostic and therapeutic alternatives. Finally, and often ignored in textbooks, it is important to consider the biolifestyle–social history of the patient with respect to its owner when formulating diagnostic and treatment plans. That is, careful consideration of how the patient "fits-in" with the owner's life, and understanding the expectations and limitations of the owner, will help to determine appropriate diagnostic and treatment plans. For example, recognizing that the patient is a herd animal and is primarily being raised for food may alter diagnostic planning and may warrant a herd examination and postmortem examination of one or more affected individuals in a herd. Meanwhile, patients who are primarily pets, or considered members of the family, may warrant an exhaustive diagnostic plan aimed at treating the individual.

Diseases affecting the vascular and nervous systems are particularly prone to ocular manifestation. Inspection of the uvea and retina, and optic disc of the animal through the transparent cornea and lens permit evaluation of both the peripheral vasculature and central nervous system, respectively. Since the rate of ocular blood flow is very high, there is increased likelihood that the uveal and retinal vasculature will be exposed to, and possibly filter out, hematogenously spread neoplastic cells and/or infectious organisms.

For the purposes of this chapter, ocular manifestations of systemic disease include any disorder not of primary ocular origin that manifests as ocular clinical signs. Systemic diseases have been categorized according to species (dog; cat; horse; food animals), stage of onset (congenital; developmental; or acquired), and have been alphabetically arranged according to the mechanism and/or cause of the systemic disease (cardiovascular; hematologic; idiopathic; immune-mediated; infectious; metabolic; neoplastic – central nervous system versus systemic; nutritional; toxicities). A miscellaneous category has been included for those conditions for which the mechanism underlying the systemic disease is poorly, or not yet, understood.

Several of the diseases discussed in this chapter have a genetic basis for which the genetic mutation is known. As such, we direct your attention to the following websites that can guide you to an appropriate genetic testing laboratory:

PennGen Canine and Feline DNA testing laboratories: https://www.vet.upenn.edu/research/academic-departments/clinical-sciences-advanced-medicine/research-labs-centers/penngen/penngen-tests

Orthopedic Foundation for Animals (OFA) currently available DNA tests: https://www.ofa.org/diseases/dna-tested-diseases/all-dna-tests

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Congenital

Coat Color-Related Diseases/Conditions

Albinism and Partial Albinism

Complete albinism (complete lack of pigmentation) or partial or localized albinism (an absence or reduction in the degree of pigmentation) is associated with not only the phenotypic appearance of an animal's coat and skin color but is also associated with conditions affecting the ear and eye. Albinism or partial albinism may result from the failure of migration of neural crest cells (precursors to melanocytes) and hence result in reduced numbers of melanocytes in a nonpigmented area, or may result because of impaired production of pigment caused by some intrinsic deficiency in melanin production (e.g., tyrosinase deficiency) but where the number of melanocytes in nonpigmented or hypopigmented areas is normal.

Oculocutaneous albinism is a genetic disorder involving abnormal melanin synthesis. There are seven forms of oculocutaneous albinism in humans (OCA 1–7). Of these forms of OCA, mutations in six genes have been described (OCA1, tyrosinase [*TYR*] gene; OCA2 protein [*OCA*] gene; OCA3, tyrosinase-related protein 1 [*TYRP1*] gene; OCA4, solute carrier family 45 member 2 [*SLC45A2*] gene; OCA6, solute carrier family 24 member 5 [*SLC24A5*] gene; and OCA7, leucine rich melanocyte differentiation associated [*LRMDA*] gene) although the genetic basis of OCA-V has yet to be elucidated (Genetics Home Reference, 2018). Oculocutaneous albinism has been described in a variety of breeds of dogs (Caduff et al., 2017; Wijesena & Schmutz, 2015; Winkler et al., 2014). Dogs with oculocutaneous albinism have varying degrees of ocular hypopigmentation and are typically photosensitive. The ocular phenotype in oculocutaneous albinism in the Doberman pinscher breed has been thoroughly described, however (Winkler et al., 2014). Oculocutaneous albinism in the white Doberman Pinscher (WDP) is the result of a partial gene deletion in *solute carrier family 45 member 2* (*SLC45A2*) gene (Winkler et al., 2014). This mutation results in affected dogs having a consistent ocular phenotype of photophobia, hypopigmented adnexal structures, blue irides with a tan periphery, vertically oriented ovoid dyscoria, and hypopigmented pectinate ligaments, retinal pigment epithelium, and choroid (Winkler et al., 2014). Further, WDPs have a higher prevalence of melanocytic neoplasms involving the skin, lips, the eyelid margin, and the iris. The incidence of these neoplasms increases with the age of the animal (Winkler et al., 2014).

Aside from oculocutaneous albinism, dogs with inherited sensorineural deafness and ocular abnormalities have been linked to coat color genes in many breeds of dogs. Hearing loss related to coat color in dogs typically results from cochleosaccular degeneration and can be associated with the absence of pigment within the stria vascularis of the cochlea (Steel & Barkway, 1989). Coat color is often associated, not only with deafness, but also with heterochromia irides, blue irides, and lack of retinal pigment (Strain et al., 1992). Coat color genetics soon becomes complicated when one considers all of the combinations and permutations of coat colours seen in the numerous breeds of dogs that have been developed. Briefly, the S-gene (white spotting gene) determines body pigmentation pattern. The S-gene has been identified more specifically as the *microphthalmia-associated transcription factor* (*MITF*) (Karlsson et al., 2007). There are thought to be four alleles of the S-gene including the dominant S allele, and the recessive s^i (Irish spotting), s^p (piebald), and s^w (extreme-white piebald) alleles (Strain, 2015). Consequently, solid colored animals have at least one copy of the S-allele; coloured bull terriers must have s^is^i, breeds like dalmatians and white bull terriers must have 2 copies of the extreme-white piebald gene (s^ws^w), whereas the whippet and Boston terrier can be s^is^i, s^is^p, or s^is^w (Karlsson et al., 2007; Strain, 2004). Animals homozygous for the recessive S-alleles are predisposed to developing congenital sensorineural deafness. A positive correlation between inherited sensorineural deafness and blue irides has been reported in the dalmatian, English Setter, and English Cocker Spaniel (Strain, 2004). This association has a relevant clinical impact given that approximately 30% of dalmatians in the United States are unilaterally or bilaterally deaf (blue eyes permitted in breed standard) (Strain et al., 1992), whereas the incidence of deafness in dalmatians from Europe is lower (blue eyes not allowed in breed standard) (Wood & Lakhani, 1997). The mode of inheritance of inherited sensorineural deafness associated with white coat colors still remains elusive.

Another gene known as the M- or merle-gene (Clark et al., 2006) has both a dominant (M) and recessive (m) allele and is associated with deafness and ocular abnormalities (see later). In individuals of breeds known to have the dominant merle-gene including collies, Shetland Sheepdogs, Great Danes, and Long-Haired Dachshunds, heterozygote (Mm – merle colored) animals can be predisposed to unilateral or bilateral inner ear defects resulting in deafness (Gwin, 1981; Strain, 2004; Strain et al., 2009). Dogs homozygous for the dominant merle allele (MM – typically have more white than heterozygotes, or may be completely white) are typically deaf, blind with microphthalmic eyes, and may be sterile (Dausch et al., 1978).

The Australian Shepherd has been studied rather extensively, and the mode of inheritance for the ocular lesions in the merle dog has been shown to be a recessive trait with incomplete penetrance (Gelatt et al., 1981). The embryogenesis of the ocular defects stems from a primary abnormality of the retinal pigment epithelium or outer layer of the optic cup (Cook et al., 1991). Ocular lesions described in these dogs include microphthalmia of varying degrees, persistent pupillary membranes, iridal colobomas, dyscoria, corectopia, corneal epithelial dysplasia, scleral staphylomas, goniodysgenesis, cataracts, lenticular colobomas, choroidal

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colobomas, choroidal hypoplasia, retinal dysplasia, retinal detachments, and retinal fibrosis (Gelatt & McGill, 1973; Bertram et al., 1984). Pituitary and adrenal cysts as well as congenital cardiac anomalies may also be observed inconsistently in the Australian Shepherd (Gelatt & McGill, 1973).

Oculodermal Melanocytosis

Oculodermal melanocytosis, also known as Nevus of Ota in human medicine, is a syndrome characterized by typically unilateral (less commonly bilateral) hyperpigmentation of skin of the skull, the oral and nasal mucosa, and in some instances the meninges (Nam et al., 2017; Plateroti et al., 2017; Rutten et al., 2005). Ocularly, a hyperpigmentation of the cornea, conjunctiva, sclera, uvea, retrobulbar fat, and extraocular muscles can be observed, although the eye may not be affected in up to one-third of patients (Nam et al., 2017; Plateroti et al., 2017). The condition is either congenital or acquired and is most commonly observed in people of Asian descent (Nam et al., 2017; Plateroti et al., 2017). The pathogenesis of the condition is unknown, although the hyperpigmentation follows a trigeminal nerve pattern (Plateroti et al., 2017). Patients with Nevus of Ota are at increased risk of developing melanoma, glaucoma, and hearing impairment because of the hyperpigmentation (Alvarez-Cuesta et al., 2002; Nam et al., 2017; Plateroti et al., 2017; Reed & Sugarman, 1974).

A syndrome of unilateral hyperpigmentation of the skin of the skull and with hyperpigmentation of the ipsilateral sclera, conjunctiva, uvea, and tapetal fundus, similar to that described for human patients with Nevus of Ota, has been formally reported in a Rhodesian Ridgeback (Malho et al., 2018). The hyperpigmented eye also was miotic with sluggish pupillary light reflexes (PLRs) compared with the contralateral eye. This patient also had asymmetric brainstem auditory evoked response (BAER) threshold suggestive of mild hearing impairment of the ear ipsilateral to the skin hyperpigmentation (Malho et al., 2018).

In another patient, a 3-year-old Labrador Retriever, similar signs were reported with unilateral, though mild, hyperpigmentation of the hair and with hyperpigmentation of the peripheral cornea, limbus, sclera and conjunctiva, and peripapillary area of the ipsilateral eye (Giannikaki et al., 2019). B-mode ocular ultrasound revealed a thickened optic nerve head, which was later confirmed, histologically, to be melanocytosis (Giannikaki et al., 2019). Nineteen months after the dog was initially presented, the affected eye became nonvisual and a firm scleral mass was identified. The eye was enucleated, and a histopathologic diagnosis of uveal melanosis was made (Giannikaki et al., 2019). The dog was reportedly healthy 46 months after enucleation and the contralateral eye was seemingly visual and comfortable (Giannikaki et al., 2019).

Informally, other dogs, including retrievers and Rhodesian Ridgebacks, with similar unilateral skin/hair pigmentation patterns, have also been documented, although it is unknown if they share other features of Nevus of Ota (Kalahari Rhodesian Ridgebacks, 2018; Westfall, 2011).

Dwarfism (Skeletal Dysplasia–Osteochondrodysplasia)

Osteochondrodysplasias are disorders characterized by abnormalities in growth and development of bone, cartilage, or both. These forms of skeletal dysplasia have been described in several breeds of dogs. In particular, a syndrome of short appendages with a normal axial skeleton (i.e., short-limbed dwarfism) and ocular lesions, so called ocular–skeletal dysplasia, has been recorded as being inherited in the Labrador Retriever and the Samoyed (Aroch et al., 1996; Farnum et al., 1992; Meyers et al., 1983). In particular, in both breeds the complete phenotype, including skeletal and ocular defects, is transmitted as an autosomal recessive trait, whereas ophthalmoscopic findings have indicated a semidominant mode of inheritance in which skeletally normal, heterozygous dogs can have no ophthalmoscopic abnormalities or multiple retinal folds, vitreal membranes, or vitreous degeneration (Goldstein et al., 2010).

The syndrome in the Labrador Retriever was once felt to be recessive for the skeletal lesions and incomplete dominant trait for the ocular lesions (Carrig et al., 1988). The causative locus in ocular–skeletal dysplasia of the Labrador Retriever has been termed *drd1* and it is mapped to canine chromosome 24, and an insertional mutation in exon 1 of the gene *COL9A3* cosegregates with the disease (Goldstein et al., 2010). In this breed, skeletal changes consist of the following: short limbs with the forelimbs being more affected than the hind limbs; prominent elbows and carpi; paws deviated laterally; shortening and bowing of the radius and ulna; hyperextended hind limbs; short and wide tubular bones with thin cortices and flattened and flared metaphyses; delayed development of epiphyses; large and misshapen epiphyses and cuboidal bones; abnormal elbows including un-united anconeal and coronoid processes; and hip dysplasia (Fig. 37.1.1 and Fig. 37.1.2) (Carrig et al., 1977; Carrig et al., 1990). Ocular lesions associated with this syndrome in the Labrador Retriever vary from mild (e.g., retinal folds) to blinding (e.g., retinal detachment), and they typically occur in field-trial lines. In general, those animals manifesting skeletal dysplasia have more severe ocular lesions, but the affected litter may have a spectrum of mild to severe lesions. To date, whether two distinct genetic forms of retinal dysplasia exist in the Labrador retriever (i.e., one linked with skeletal dysplasia and one distinct from this syndrome) remains unresolved (Barnett et al., 1970). Heterozygous animals may, or may not, have retinal lesions. Heterozygous individuals may manifest with focal or geographic retinal dysplasia, which is typically observed as hyperreflective areas having pigment clumping dorsal to the optic disc. Animals with focal retinal lesions may exhibit a loss of central vision as evidenced by failing to mark downed birds or stationary handlers. Milder

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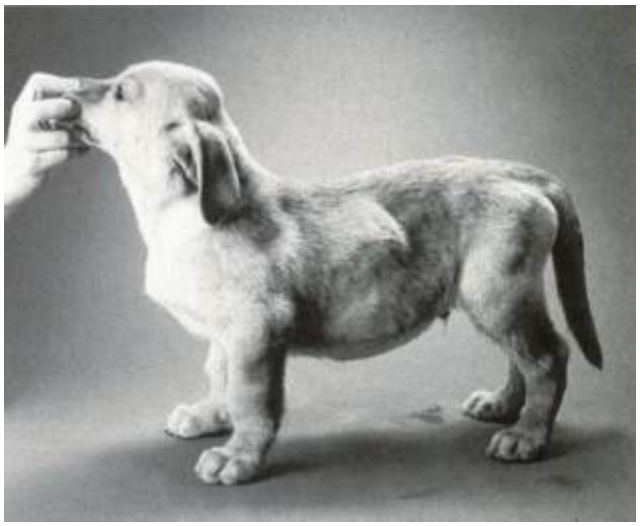


Figure 37.1.1 Short-limbed dwarfism in a Labrador Retriever.



Figure 37.1.2 Clinical presentation associated with oculoskeletal dysplasia, including forelimb varus defects. Inset shows hyphema secondary to retinal detachment. (*Source*: Reprinted with permission from Esson, D.W. (2015) *Clinical Atlas of Canine and Feline Clinical Disease*. Oxford: Wiley-Blackwell.)

degrees of retinal manifestation may have smaller, branching retinal folds and be located in other fundic regions (Nelson & MacMillan, 1983). Animals may be presented as puppies with retinal detachments, or such detachments may occur during the first 2–3 years of life. The emphasis has been placed clinically on the retinal dysplasia. The mechanism of retinal detachment is probably unrelated, however, because many detached retinas have minimal, if any, lesions of dysplasia. Peripheral retinal dialysis occurs and is associated with vitreous traction. Once retinal dialysis occurs, proliferative cellular responses by the ciliary epithelium, retinal pigment epithelium, glial cells, and macrophages produce cellular migration onto the vitreous face, which in turn produces contracting forces that detach the retina (Blair et al., 1985a,b). Homozygous dogs inconsistently exhibit a variety of ocular lesions, including those of axial myopia, superficial corneal opacities, varying degrees of cataract formation, prominent hyaloid artery remnants, tapetal hypoplasia, and alterations in optic nerve color and size.

The Samoyed syndrome of ocular–skeletal dysplasia is an autosomal recessive trait (Goldstein et al., 2010). In particular, the causative locus in ocular–skeletal dysplasia of the Samoyed has been termed *drd2* and it is mapped to canine chromosome 15 and cosegregates with a 1,267 bp deletion mutation in the 5' end of *COL9A2* (Goldstein et al., 2010). Skeletal lesions in the Samoyed consist of the following: short forelimbs; premature closure of ulnar growth plates; bowed radii; varus deformity of elbows; valgus deformity of carpi; and domed forehead (Aroch et al., 1996; Meyers et al., 1983). Ocular lesions in this breed consist of focal cortical cataracts, multifocal retinal dysplasia, retinal detachments, prominent hyaloid remnants, and red tapetal fractures or fissures (Meyers et al., 1983). Retinal detachment usually occurs during the first 6 months of life, and it may occur in retinas with no obvious lesions of dysplasia.

Dogs homozygous for *drd1* or *drd2* typically can be identified by experienced clinicians on physical examination, based upon their skeletal abnormalities (Goldstein et al., 2010). However, dogs heterozygous for *drd1* or *drd2* may or may not have retinal folds/dysplasia (Goldstein et al., 2010). In addition, some Labrador Retrievers diagnosed clinically as affected with short-limbed dwarfism were confirmed normal when tested for the *drd1* mutation indicating that, in this breed, there are likely further, as yet, undetermined genetic mutations to account for retinal folds and/or dwarfism (Goldstein et al., 2010).

Ehlers–Danlos Syndrome

Ehlers–Danlos syndrome, or cutaneous asthenia, has been reported in the dog. It is a congenital, inherited syndrome involving collagen, and it is characterized by fragile and easily torn skin. Some animals also have excessive joint laxity. The mode of inheritance of this syndrome in the dog is autosomal dominant (Barnett & Cottrell, 1987). If the complete syndrome is manifest, ocular lesions may occur. Dogs with the complete syndrome have ocular lesions consisting of lax eyelids, corneal edema, thin sclera, cataracts, bilateral lens

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luxation, and diffuse cortical cataracts (Barnett & Cottrell, 1987; Matthews & Lewis, 1990). In one case, the lenses were subluxated dorsally and were colobomatous ventrally (Barnett & Cottrell, 1987). In another patient, prolapsed gland of the third eyelid and keratoconjunctivitis sicca were present (Rasch, 2017).

A diagnosis of Ehlers–Danlos syndrome is made based upon a clinical syndrome of skin hyperextensibility, clinical signs associated with skin fragility including easily torn skin, and skin histopathology (routine histopathology with Masson-trichome staining and ultrastructural examination) (Paciello et al., 2003a). Determination of skin hyperextensibility can be objectively assessed by calculating the extensibility index (Paciello et al., 2003a; Patterson, 1977). The extensibility index is determined by dividing the vertical height of a skin fold (extending a skin fold over the dorsal lumbar area maximally without eliciting pain) by body length (measured from occipital crest to base of tail), then multiplying by 100. A skin extensibility index greater than 14.5% is considered hyperextensible.

Ehlers–Danlos syndrome is incurable and because of it's hereditary nature owners should be advised to not use affected dogs for breeding. Therapy for affected dogs is directed at preventing skin abrasions and pressure sores.

Hydrocephalus

Hydrocephalus refers to increased amount of cerebrospinal fluid (CSF) within the cranial vault. Hydrocephalus can be categorized by the location of the CSF accumulation (i.e., internal (dilated ventricles) or external (increased subarachnoid space), or may be caused by the loss of brain parenchyma as can be found in geriatric animals (known as hydrocephalus ex vacuo). Hydrocephalus can also be categorized based upon time of development, namely, congenital or acquired. Congenital hydrocephalus is common in some breeds of dogs, with toy and brachycephalic breeds at highest risk for the disease, thereby suggesting a hereditary basis in many of these dogs (Selby, 1979). The most common cause of congenital hydrocephalus is a primary congenital stenosis or aplasia of the mesencephalic aqueduct associated with fused rostral colliculi (Selby, 1979). Hydrocephalus resulting from impediment of CSF outflow from the ventricular system is referred to as obstructive or noncommunicating hydrocephalus. In cases where there is no associated malformation in the mesencephalic aqueduct the cause of congenital hydrocephalus remains unknown. Congenital hydrocephalus may produce enlargement of the calvarium and failure of closure of the suture lines of the skull. Consequently, affected puppies may have a persistently open fontanelle. Clinical signs of hydrocephalus include behavioural changes, ataxia, vision impairment, and seizures. Ventrolateral strabismus is a common ocular manifestation of congenital hydrocephalus due, in part, to enlargement of the calavarium with subsequent impingement on the orbits from the dorsolateral aspects. This consequently pushes the eyes in a ventrolateral direction and produces a "sunset" appearance to the corneas (Fig. 37.1.3). Congenital hydrocephalus also may cause cranial nerve compromise and subsequent ventrolateral strabismus. On relatively rare occasions, hydrocephalus may produce papilledema (Fig. 37.1.4).

Keratoconjunctivitis and Ichthyosiform Dermatosis (KCSID)

A syndrome of congenital keratoconjunctivitis sicca (KCS) and ichthyosiform dermatosis (ID) has been described in the Cavalier King Charles Spaniel (Barnett, 2006; Hartley et al.,



Figure 37.1.3 Congenital hydrocephalus in a toy breed with "sunset eyes." The calvarium is pushing the globes ventrolaterally.

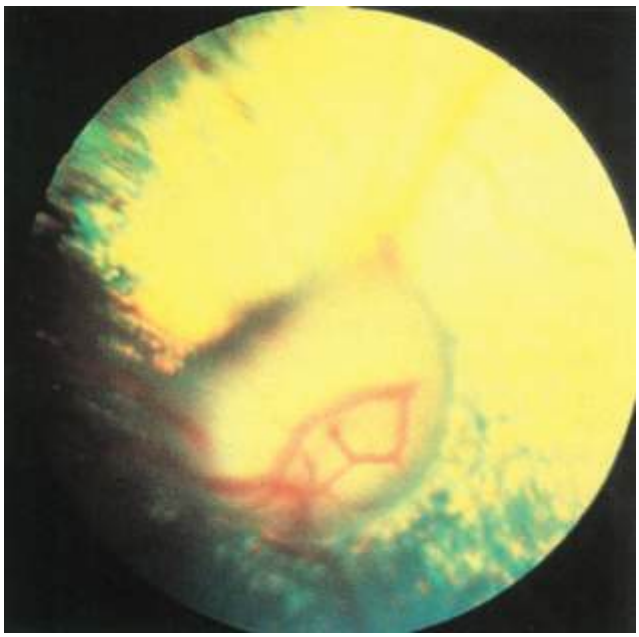


Figure 37.1.4 Marked papilledema in a Chow Chow puppy with hydrocephalus. Note the tilting of the optic disc.

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Figure 37.1.5 **A.** Typical appearance of a curly coat in a 10-week-old Cavalier King Charles Spaniel. **B.** Normal 10-week-old Cavalier King Charles Spaniel. (*Source*: Reprinted with permission from Barnett, K.C. (2006) Congenital keratoconjunctivitis sicca and ichtyyosiform dermatosis in the Cavalier King Charles Spaniel. *Journal Small Animal Practice*, **47**, 524–528.)

2012). This condition is also known as dry eye and curly coat syndrome. Affected animals present with a congenital atypical hair coat characterized by being rough/curly (Fig. 37.1.5) (Barnett, 2006; Hartley et al., 2012). Clinical signs of KCS are present at onset of eyelid opening. Affected animals will go on to develop progressive dermatologic signs including scaling of the skin over the dorsum and involving the flanks, a harsh/curly hair coat with alopecia, and hyperkeratinized footpads (Hartley et al., 2012). Older animals often have signs of intermittent lameness associated with cracked foot pads and/or sloughed nails with exposure of the nail beds (Hartley et al., 2012). Anecdotally, patients with KCSID have concurrent dental disease, although this has not been specifically examined (Forman et al., 2012).

It is unknown why affected animals develop KCS, although histopathologic examination of the lacrimal glands does not reveal inflammation and therefore immune-mediated mechanisms likely do not account for this component of the syndrome (Hartley et al., 2012). Other suggested explanations accounting for KCS in these animals include neurogenic causes, and obstruction through lacrimal ductules (Hartley et al., 2012). Qualitative tear film abnormalities likely exist secondarily to this condition, although qualitatitve tear film abnormalities have yet to be specifically investigated. General treatment for patients with this condition is typically symptomatic, although it has been reported that signs of discomfort caused by the dermatologic component of this syndrome are difficult to manage (Hartley et al., 2012). Treatment of the KCS with immunomodulatory and lacrimostimulant medications has little, if any, affect on tear production (Hartley et al., 2012). Affected animals are prone to developing corneal ulceration and are treated appropriately for corneal ulceration.

KCSID is inherited as an autosomal recessive trait (Forman et al., 2012). The phenotype is caused by a mutation in *FAM83H* (*family with sequence similarity 84, member H*). Different mutations of this gene in humans is associated with autosomal dominant amelogenesis imperfecta type III, a condition associated with dental enamel defects (Wright et al., 2009).

Quadriplegia and Amblyopia

A syndrome of decreased vision with nystagmus, ataxia, and tremors has been described in the Irish Setter. This syndrome is thought to be inherited as a postnatally lethal, autosomal recessive trait (Palmer et al., 1973; Sakai et al., 1994). Most animals, however, are unable to stand at birth, although walking movements are made that propel them in a "seal-like" manner when prone. Vision is difficult to evaluate in a very young animal, but those affected lack fixation responses as well as menace responses and dazzle reflexes. The PLRs are normal. The ocular fundus is normal on fundic examination as well. Electroretinographic findings have not been reported. Central nervous system (CNS) lesions include degeneration and necrosis of the cerebellar cortex, with severe loss of Purkinje cells. Histopathologic findings do not correlate well with clinical neurologic or ocular findings.

Developmental

Inborn Errors of Metabolism

Inborn errors of metabolism (IEM) are diverse genetic diseases involving abnormal cellular metabolism (Vernon, 2015). These diseases are also referred to as inherited metabolic disorders (Sewell et al., 2007). The majority of IEM are caused by a defective cellular enzymatic system resulting in: (1) accumulation of toxic substances upstream from the defective enzyme; (2) reduced substances located downstream from the defective enzyme; or (3) abnormal alternative substrate metabolism (Vernon, 2015).

A wide variety of IEM have been identified and are broadly classified into various categories depending upon the substance

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accumulated, the defective metabolic system, or the organelle responsible for the defective metabolism (Valle et al., 2018). For example, IEMs can be classified as being metabolic disorders involving amino acids (e.g., tyrosinemia), vitamins (e.g., vitamin B_6 IEM), peroxisomes, mitochondria, or lysosomes (i.e., lysosomal storage diseases) (Valle et al., 2018). For the purposes of this section, we focus on only those disorders described in dogs that have significant ocular clinical signs.

Diagnoses of inherited metabolic diseases are made based upon initial suspicion (based upon signalment, history, and clinical examination findings), minimum clinical laboratory database (i.e., complete blood count, serum biochemistry, urinalysis, imaging, +/- CSF analysis), followed by more invasive/specific testing (e.g., tissue biopsy, metabolic disease screening, lysosomal enzyme analysis) (Skelly & Franklin, 2002).

Metabolic disease screening can be done through PennGen at the University of Pennsylvania: https://www.vet.upenn.edu/research/academic-departments/clinical-sciences-advanced-medicine/research-labs-centers/penngen

Specific diagnosis of lysosomal storage disorders can be confirmed by lysosomal enzyme analysis using both affected and age/breed-matched control samples at centres conducting such testing (e.g., Lysosomal Disease Testing Laboratory, Jefferson Medical Center, Philadelphia, PA, https://www.jefferson.edu/university/jmc/departments/neurology/programs/neurogenetics/lysosomal_diseases.html) or via genetic testing for specific canine lysosomal storage diseases for which the genetic basis has been determined. For a relatively complete listing of genetic tests and the laboratories offering testing please see the Orthopedic Foundation for Animals website (https://www.ofa.org/diseases/dna-tested-diseases/all-dna-tests).

Treatments of various IEMs are being attempted with variable success. Current treatments are experimental and are aimed at direct enyzme replacement and/or gene therapy. As such we have included limited discussion regarding therapy of IEMs.

Amino Acid Disorders

Tyrosinemia

Tyrosinemia arises as a result of deficiency in hepatic tyrosine aminotransferase. Tyrosinemia has been described in a young dog presented for dermatologic and ocular problems (Kunkle, 1984). The syndrome was characterized by markedly elevated serum and urine tyrosine levels. Dermatologic lesions consisted of ulcerative lesions of the nasal planum, tongue, footpads, and around the nails. Ocular lesions consisted of small globes (possibly microphthalmos), conjunctivitis with mucopurulent ocular discharge, superficial corneal scarring and vascularization (possibly from a previous ulcer), axial superficial corneal crystals, and cataracts.

Lysosomal Storage Diseases

Many lysosomal storage diseases have been identified in dogs. Like all IEM, lysosomal storage disorders are relatively rare diseases that have received a disproportionate amount of investigation because they represent potential animal models for human diseases. Storage diseases are characterized by an accumulation of metabolic by-products within lysosomes, the cellular organelles which degrade complex macromolecules. The substrates for catabolism within lysosomes include glycoproteins, mucopolysaccharides, oligosaccharides, proteins, and sphingolipids (Jolly & Walkley, 1997; Skelly & Franklin, 2002). Storage diseases result from a deficiency in a specific catabolic enzyme (i.e., acid hydrolases), which allows the enzyme substrate to accumulate in the lysosomes within cells. Consequently, lysosomal storage diseases are subclassified based upon the type of storage product. Important groups include the glycoproteinoses, mucopolysaccharidoses, oligosaccharidoses, proteinoses, and the sphingolipidoses (Jolly & Walkley, 1997; Skelly & Franklin, 2002). Specific lysosomal storage diseases are normally named according to the specific accumulated product. Because this excess material is a normal component, the histopathologic changes result from physical distortion of affected cells rather than from a toxic effect. Most lysosomal storage diseases, with known mode of inheritance, are inherited as an autosomal recessive trait. When homozygous, the syndromes are usually severe, thus resulting in neurologic disease and, eventually, death. The eyes in most patients have histopathologic lesions, but clinical ophthalmic lesions may not be visible (Aguirre et al., 1986; Evans, 1989). Reviews pertaining to lysosomal storage diseases in animals should be consulted for details regarding the clinical signs and diagnosis of lysosomal storage diseases in dogs (see Jolly & Walkley, 1997; Skelly & Franklin, 2002).

Lysosomal storage diseases can be broadly categorized as follows (Greiner-Tollersrud, 2000–2013): (1) defects in glycan degradation; (2) defects in lipid degradation; (3) defects in protein degradation; (4) defects in lysosomal transporters; (5) defects in lysosomal trafficking .

Table 37.1.1 summarizes the various lysosomal storage diseases into these categories (Greiner-Tollersrud, 2000–2013).

Fucosidosis

Fucosidosis is an autosomal recessive glycoproteinosis occurring in the English Springer Spaniel (Healy et al., 1984; Kelly et al., 1983). The disease is produced by a deficiency of the lysosomal enzyme α-L-fucosidase. Some glycolipid and oligosaccharide moieties of glycoproteins contain the sugar, fucose. Deficiency of lysosomal α-L-fucosidase causes the accumulation of these glycolipids and oligosaccharides. The disease is characterized by a progressive decrease in mentation, which begins at approximately 4 months of age. Temperament changes, ataxia, hearing impairment, and ocular signs of diminished vision and nystagmus develop, and death occurs by 4 years of age. Vision impairment usually occurs later, although it may be the presenting complaint.

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Table 37.1.1 Lysosomal storage disorders in humans (modified from (Greiner-Tollersrud 2000–2013)

Chromosomal protein defect localization	Disease
Defects In Glycan Degradation	
Defects in glycoprotein degradation	
α-Sialidase	Sialidosis
Galactosialidosis	Cathepsin A
α-Mannosidase	α-Mannosidosis
β-Mannosidase	β-Mannosidosis
Glycosylasparaginase	Aspartylglucosaminuria
α-Fucosidase	Fucosidosis
α-N-Acetylglucosaminidase	Schindler
Defects in glycolipid degradation	
A. GM1 Ganglioside	
β-Galactosidase	GM1-gangliosidosis/MPS IVB
β-Hexosaminidase α-subunit	GM2-gangliosidosis (Tay-Sachs)
β-Hexosaminidase β-subunit	GM2-gangliosidosis (Sandhoff)
GM2 activator protein	GM2-gangliosidosis
Glucocerebrosidase	Gaucher disease
Saposin C	Gaucher disease
B. Defects in the degradation of sulfatide	
Arylsulfatase A	Metachromatic leukodystrophy
Saposin B	Metachromatic leukodystrophy
Formyl-Glycin generating enzyme	Multiple sulfatase deficiency
β-Galactosylceramidase (Krabbe)	Globoid cell leukodystrophy
C. Defects in degradation of globotriaosylceramide	
α-Galactosidase A	Fabry
Defects in degradation of glycosaminoglycan (mucopolysaccharidoses)	
A. Degradation of heparan sulphate	
Iduronate sulfatase	MPS II (Hunter)
α-Iduronidase	MPS 1 (Hurler, Scheie)
Heparan N-sulfatase	MPS IIIa (Sanfilippo A)
Acetyl-CoA transferase	MPS IIIc (Sanfilippo C)
N-acetyl glucosaminidase	MPS IIIb (Sanfilippo B)
β-glucuronidase	MPS VII (Sly)
N-acetyl glucosamine 6-sulfatase	MPS IIId (Sanfilippo D)
Degradation of other mucopolysaccharides	
N-Acetylgalactosamine 4-sulfatase	MPS VI
Galactose 6-sulfatase	MPS IVA (Morquio A)
Hyaluronidase	MPS IX
Defects in degradation of glycogen	
α-Glucosidase	Pompe
Defects In Lipid Degradation	

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Table 37.1.1 (Continued)

Chromosomal protein defect localization	Disease
Defects In Glycan Degradation	
Defects in glycoprotein degradation	
Defects in degradation of sphingomyelin	
Acid sphingomyelinase	Niemann Pick type A and B
Acid ceramidase	Farber lipogranulomatosis
Defects in degradation of triglycerides and cholesteryl ester	
Acid lipase	Wolman and cholesteryl ester storage disease
Defects in Protein Degradation	
Cathepsin K	Pycnodystostosis
Tripeptidyl peptidase	Ceroide lipofuscinosis 2
Palmitoyl-protein thioesterase	Ceroide lipofuscinosis 1
Defects In Lysosomal Transporters	
Cystinosin (cystin transport)	Cystinosis
Sialin (sialic acid transport)	Salla disease
Defects in Lysosomal Trafficking Proteins	
UDP-N-acetylglucosamine	
Phosphotransferase γ-subunit	Mucolipidosis III (I-cell)
Mucolipin-1(cation channel)	Mucolipidosis IV
LAMP-2	Danon
NPC1	Niemann Pick type C
CLN3	Ceroid lipofuscinosis
CLN 6	Ceroid lipofuscinosis 6
CLN 8	Ceroid lipofuscinosis 8
LYST	Chediak–Higashi
MYOV	Griscelli Type 1
RAB27A	Griscelli Type 2
Melanophilin	Griscelli Type 3
AP3 β-subunit	Hermansky Pudliak 2

MPS, mucopolysaccharidoses.

While retinal ganglion cells are vacuolated from the accumulation of substrate, ophthalmoscopic lesions have not been reported with the visual impairment in the English Springer Spaniel (Healy et al., 1984; Keller & Lamarre, 1992; Kelly et al., 1983). The diagnosis is confirmed on the basis of determining α-L-fucosidase activities in plasma and leukocytes and/or through genetic testing (Skelly et al., 1999). Experimental treatment with intrathecal administration of recombinant α-L-fucosidase has shown decreased oligosaccharide accumulation in the CNS, peripheral lymph nodes and liver, and there is a general reduction in neuropathology, although clinical success of this treatment is unknown (Kondagari et al., 2011; Kondagari et al., 2015).

Galactocerebrosidosis (Globoid Cell Leukodystrophy, Krabbe's Disease, Galactosylceramide Lipidosis)

Galactocerebrosidosis, or globoid cell leukodystrophy or Krabbe's disease, is a member of the inherited sphingolipidoses described in the dog, that results from a deficiency in β-D-galactocerebrosidase (GALC) activity (Skelly & Franklin, 2002). The substrate galactocerebroside (i.e., galactosylceramide), a constituent of myelin, and another metabolite of myelin turnover, psychosine (galactosyl sphingosine), accumulate. Psychosine is highly cytotoxic to oligodendroglia and is thought to be the primary metabolite involved in the pathogenesis of the disease (Miyatake & Suzuki, 1972). Consequent to the build-up of these toxic metabolites, leukodystrophy

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results. Galactocerebrosidosis is pathologically characterized by bilaterally symmetric demyelination of the white matter of the brain, spinal cord, spinal nerve roots, and peripheral nerves and by the accumulation of globoid cells (multinuclear globoid macrophages), predominantly perivascularly. Galactocerebrosidosis is an autosomal recessive trait in West Highland White and Cairn Terriers (Wenger et al., 1999; Capucchio et al., 2008), Australian Kelpies (Fletcher et al., 2010), and Irish Setters (McGraw & Carmichael, 2006). Galactocerebrosidosis in Irish Setters has been characterized by an insertion mutation of 78 base pairs (bp) in the sequence of the GALC cDNA consisting of 16 bp of insertion site duplication and 62 bp of sequence derived from the U4 small nuclear RNA (McGraw & Carmichael, 2006).

Clinical signs of globoid cell leukodystrophy in dogs are generally rapidly progressive (2–6 months) and develop at a young age (2–6 months of age). Cerebellar signs or progressive paraparesis and paraplegia are the predominant clinical manifestations. Visual deficits and blindness may result late in the course of disease, but ophthalmoscopic lesions have not been observed (Aguirre et al., 1986).

Combined intravenous and intracerebroventricular gene therapy has been shown to delay clinical signs, improve longevity, improve biochemical alterations, and attenuate neuropathology (Bradbury et al., 2018). Genetic testing is available for West Highland White and Cairn Terriers (Wenger et al., 1999), and Irish Setters (McGraw & Carmichael, 2006). For testing sites see: Orthopedic Foundation for Animals website (https://www.ofa.org/diseases/dna-tested-diseases/all-dna-tests).

GM1-Gangliosidosis

GM1-gangliosidosis is a member of the sphingolipidoses. A deficiency of lysosomal hydrolase, β-galactosidase, produces an accumulation of GM1-ganglioside in the cerebral cortex and visceral organs. Such deficiencies have been reported in cats, cattle, humans, mice, and sheep. With respect to dogs, GM1-gangliosidosis is an autosomal recessive condition seen in Alaskan Huskies, English Springer Spaniels, Mixed Breed-Beagles, Portugese Water Dogs, and Shiba Inus (Alroy et al., 1992; Muller et al., 2001; Yamato et al., 2003). Abnormal ocular findings in dogs with this disease are limited to: (1) central corneal clouding and has been observed in Shiba Inus and Portugese Water Dogs; (2) vision disturbances seen in Shiba Inus and Portugese water dogs; (3) strabismus has been observed in mixed breed-Beagles and Alaskan Huskies; and (4) nystagmus has been observed in English Springer Spaniels, Portugese Water Dogs, And Alaskan Huskies. For a complete tabular comparison of clinical signs observed between breeds of dogs with GM1-gangliosidosis see Yamato et al. (2003). Affected Shiba Inus develop anterior corneal opacities at approximately 10 months of age which arise from accumulation of neutral carbohydrates in the lysosomes of keratocytes with swelling and dysfunction of keratocytes, and subsequent irregular arrangement of collagen fibrils in the cornea (Nagayasu et al., 2008). Histopathologic lesions of membrane-bound inclusions have been shown throughout the brain, spinal cord, and retinal ganglion cells, but only in cattle and cats have clinical ophthalmoscopic lesions been observed. Those ophthalmoscopic lesions were multifocal, white, small spots that probably resulted from elevations of the internal limiting membrane by swollen ganglion cells. Affected animals typically live 14–15 months of age. Separate genetic mutations have been identified and genetic tests have been developed for Alaskan Huskies (Kreutzer et al., 2005), Portugese Water Dogs (Wang et al., 2000) and Shiba Inus (Chang et al., 2010; Yamato et al., 2004).

GM2-Gangliosidosis

GM2-gangliosidosis is caused by a deficiency of hexosaminidase (for review see Jeyakumar et al., 2002). Hexosaminidase has two subunits, α and β, each coded for by *HEXA* and *HEXB* genes, respectively. There are three types of hexosaminidase – hexosaminidase S (αα dimer), hexosaminidase A (an αβ dimer), and hexosaminidase B (a ββ dimer). In addition, there is a GM2-activator protein coded for by the GM2A gene which is necessary for degrading GM2 ganglioside in concert with hexosaminidase A.

In humans, deficiency in the α subunit, and therefore depletion of hexosaminidase A and S, results in classical GM2-gangliosidosis (Tay-Sachs disease or B-variant). A deficiency in the β subunit, depleting both hexosaminidase A and B, is known as Sandhoff disease or the O-variant. Further, deficiencies in GM2-activator protein results in GM2-activator deficiency, also known as the AB-variant.

Variant forms of GM-2 gangliosidosis have been reported in the German Shorthair Pointer and Japanese Chin (Tay-sachs disease) (Freeman et al., 2013; Sanders et al., 2013; Singer & Cork, 1989), and also in the Golden Retriever, a mixed-breed dog, Shiba Inu, and Toy Poodle (Sandhoff disease) (Kohyama et al., 2015; Kolicheski et al., 2017; Tamura et al., 2010; Wang et al., 2018b; Yamato et al., 2002). Japanese Chins affected by Tay-Sachs disease are at least 15–18 months old at presentation and show progressive cerebellar ataxia, impaired vision, and altered mentation (Sanders et al., 2013). Diffuse brain atrophy is noted on magnetic resonance imaging (MRI) (Freeman et al., 2013; Sanders et al., 2013).

In one Golden Retriever with Sandhoff disease, abnormal neurological signs including vision loss commenced at 11 months of age (Yamato et al., 2002). In another Golden Retriever, progressive neurological abnormalities including blindness, bilaterally weak palpebral reflex, and miosis with absent PLRs bilaterally were noted at 15 months of age (Matsuki et al., 2005). MRI of this dog's brain showed lesions similar to MRI reports in humans affected with Sandoff's disease. In particular, MRI showed bilaterally symmetrical T2 hyperintensity and T1 hypointensity in the nucleus caudatus, and cerebrocortical atrophy, primarily in the temporal lobe (Matsuki et al., 2005).

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Mucopolysaccharidoses

The mucopolysaccharidoses (MPS) are a group of diseases characterized by defective metabolism of mucopolysaccharides (glycosaminoglycans). Five types of MPS have been identified in dogs (MPS I, II, III, VI and VII).

MPS I (Hurler syndrome) has been described in the Plott Hound, and other breeds of dogs, as a deficiency of α-L-iduronidase (Shull et al., 1982). The result of this enzyme deficiency is the tissue accumulation and urinary excretion of dermatan and heparan sulfate (glycosaminoglycans) (Jolly & Walkley, 1997). Affected dogs have stunted growth, excessive joint laxity, multiple degenerative joint disease and cardiac valvular disease, and develop diffuse corneal opacities from the accumulation of substrate in the keratocytes.

MPS II (Hunter syndrome) has been reported in a Labrador Retriever and results from a deficiency in iduronate-2-sulfate sulfatase (Wilkerson et al., 1998). MPS II is unusual, in comparison with the autosomal modes of inheritance of most lysosomal storage diseases, as it is inherited as an X-linked trait. As can be found in MPS I, dermatan and heparan sulfate accumulate in tissues and are excreted in the urine (Wilkerson et al., 1998). One affected dog reported to have MPS II was 3 years of age with a history of progressive incoordination (Wilkerson et al., 1998). The dog was thin yet well-muscled, had labial mucosal thickening, premature graying of hair on the face and the whithers, coarse facial features, hyperextended carpi, and macrodactylia. Neurologically, the animal showed assymetric ataxia, and proprioceptive deficits. With regards to ophthalmic findings, this animal showed positional vertical and rotary nystagmus, multifocal corneal opacities in one of its eyes, and an exaggerated PLR with hippus. This animal had hepatomegaly and generalized osteopenia of its axial skeleton. Light microscopy revealed intracytoplasmic vacuoles of various cell types including the iris pigment epithelium. Definitive diagnosis was made biochemically by comparing iduronate-2-sulfatase activity in fibroblasts from the affected dog and two normal dogs.

MPS III (Sanfilippo syndrome) is a storage disease that develops because of a lack of one of four different enzymes which include heparan sulfate sulfamidase (MPS IIIA), α-N-acetylglucosaminidase (MPS IIIB), acetylCoA:α-glucosaminide-N-acetyl transferase (MPS IIIC), and N-acetylglucosamine 6 sulfatase (MPS IIID). Each of these enzymes acts on heparan sulfate and their deficiency results in cellular accumulation and urinary excretion of heparan sulfate. MPS III has been reported, and the genetic mutation identified, in Wire-Haired Dachshunds (MPS IIIA) (Aronovich et al., 2000), Schipperkes (MPS IIIB) (Ellinwood et al., 2003) and New Zealand Huntaway dogs (Yogalingam et al., 2002); however, no ocular abnormalities have yet been observed in dogs with MPS III. Clinical signs generally develop from 18 months of age and manifest as mainly cerebellar disease. A recent pathologic study of MPS IIIA disease in Huntaway dogs documented histopathological and ultrastructural abnormalities in affected dogs as a means of characterizing them as a model for testing therapeutic methodologies for the analogous disorder in children (Jolly et al., 2007).

MPS VI (Maroteaux–Lamy syndrome), caused by a deficiency of the lysosomal enzyme arylsulfatase-B, has been reported in Chesapeake Bay Retrievers (Haskins et al., 2002), a Great Dane (Wang et al., 2018b), Miniature Schnauzers (Perez et al., 2015), Miniature Pinschers, and Welsh Corgis (Neer et al., 1995). Arylsulfatase-B hydrolyzes dermatan sulfate, therefore lack of this enzyme results in lysosomal accumulation and urinary excretion of dermatan sulfate. Affected animals have skeletal dysmorphia, abnormally small physical stature, and leukocyte inclusions. Corneal opacities can be found with this condition in dogs. Thickening of the sclera and the optic nerve sheath with atrophy of the optic nerve can be found in addition to corneal opacities in humans.

MPS VII (Sly syndrome) resulting from a deficiency of β-D-glucuronidase, has also been described in two puppies (Haskins et al., 1984) and has subsequently been developed as an experimental canine model (Haskins et al., 1984). β-D-glucuronidase deficiency results in impaired catabolism of chondroitin, dermatin, and heparan sulfates (Schuchman et al., 1989). Consequently, these glycosaminoglycans accumulate in tissues and are excreted in the urine (Silverstein et al., 2004). Corneal opacification and systemic lesions are similar to cases of MPS I. Hepatomegaly may be present, and corneal lesions have a diffuse, fine granular appearance with some peripheral edema and focal central cholesterol deposits (Silverstein et al., 2004). Histopathologically, vacuolated cytoplasmic inclusions have been detected in cells of the corneal stroma, retinal pigment epithelium (Silverstein et al., 2004) and retinal degeneration has been reported in one dog affected with MPS VII (Haskins et al., 1984). Enzymatic and DNA-based tests are used to diagnose this condition (Ray et al., 1999; Silverstein et al., 2004). Studies suggest that intravenous gene therapy may be useful for the treatment of this disease (Ponder et al., 2002; Wang et al., 2006).

Neuronal Ceroid Lipofuscinosis

Neuronal ceroid lipofuscinoses (NCLs) are a group of inherited proteinoses characterized by accumulation of proteins in neurons and other tissues, including the retina. These storage products show an autofluorescence similar to ceroid and lipofuscin, lipopigments that accumulate normally with aging.

Ceroid lipofuscinosis has been described in a variety of species including cats, cattle, dogs, goats, humans, mice, and sheep (Jolly & Walkley, 1997). Dogs affected by ceroid lipofuscinosis display a variety of clinical signs including changes in personality, vision loss, loss of learned behaviors, tremors, seizures, cerebellar ataxia, and loss of cognitive and motor function (Katz et al., 2017). Clinical signs can manifest at younger than 6 months of age, as is observed in Dalmatians (Goebel et al., 1988), or may develop into adulthood as can be found in English Setters and Tibetan Terriers. Longevity of

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affected dogs is variable. Affected Tibetan Terriers can live up to 10 years of age whereas other breeds of dogs, including the English Setter, develop acute clinical signs at approximately 1 year of age, and die approximately 1 year later (Koppang, 1988). Diminished vision, most noticeable in dim-light conditions, is tyically the first presenting sign of NCL. Over time, blindness develops in most instances, except for individuals with a late-onset, adult form (e.g., Tibetan Terriers) (Katz et al., 2005). Additional abnormalities also evident with NCL include: confusion, nervousness, unprovoked aggression toward people, inappropriate urination/defecation, difficulty prehending food or water, wide-based stance, ataxia, and hypermetria. Nonambulatory tetraparesis may be observed in later stages of NCL (Evans et al., 2005).

The English Setter and Tibetan Terrier have been studied extensively, but the disease has been observed and described in a whole host of breeds including American bulldogs, American Cocker Spaniel, Alpenländische Dachsbracke, Australian Cattle Dog, Australian Shepherd, Border Collie, Cane Corso, Chihuahua, Chinese Crested, Long and Wire-Haired Dachshunds, Dalmatian, Golden Retriever, Miniature Schnauzer, Mixed Breeds, Polish Owczarek Nizinny, Saluki, Spitz, Standard Poodle, Welsh Corgi, and Yugoslavian Shepherd (for review see Katz et al., 2017). In the English Setter, clinical signs of blindness, seizures, and decreased mentation develop at approximately 12–14 months of age. Although the animals are blind, electroretinogram (ERG) amplitudes are only diminished by 30%–40% (Berson & Watson, 1980). Histopathologically, cellular inclusions of stacked membranes are present in the retinal pigment epithelium, ganglion cells, and other retinal neuronal cells (Neville et al., 1980). Despite these latter findings, ophthalmoscopic lesions have not been noted in the English Setter. In the Polish Owczarek Nizinny breed, fundic lesions may be normal or may consist of grayish plaque-like spots in the central tapetal and in the non-tapetal fundus, areas of tapetal hyperreflectivity, and generalized vascular attenutation in advanced cases (Fig. 37.1.6) (Narfström et al., 2007). In the Miniature Schnauzer, mild tapetal hyperreflectivity, mild retinal vascular attenuation, and optic disc pallor have been noted as early as 2.5 years of age (Smith et al., 1996). Peroxidase activity is decreased in the retina and leukocytes, but the exact enzymatic deficiency has yet to be defined (Armstrong et al., 1978; Siakotos et al., 1978).

In Tibetan Terriers, abnormal behavioural signs develop at approximately 4–6 years of age, whereas abnormal retinal function has been reported as early as 7 weeks of age. A study has shown both light and dark-adapted ERG responses to be reduced in amplitude in 7- to 10-year-old dogs (Katz et al., 2005) whereas another study reported that ERG responses were nearly undetectable in dogs that were 4–6 years of age (Riis et al., 1992). Behaviurally, Tibetan Terriers with NCL have moderate visual impairment in low-light and good vision in bright-light conditions (Katz et al., 2005). Specifically, poor performance in maze testing and following

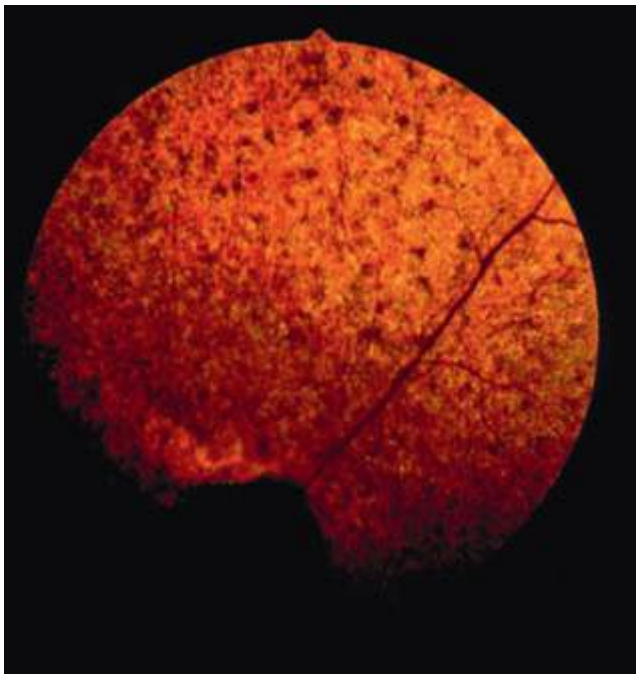


Figure 37.1.6 Fundus photograph of a neuronal ceroid lipofuscinoses-affected Polish Owczarek Nizinny dog at 18 months of age. Note the generalized grayish to brown spots, the hyperreflective areas, and the severely attenuated retinal vessels. (*Source*: Reprinted with permission from Narfström, K., Wrigstad, A., Ekesten, B, et al. (2007) Neuronal ceroid lipofuscinosis: clinical and morphologic findings in nine affected Polish Owczarek Nizinny (PON) dogs. *Veterinary Ophthalmology,* **10**, 111–120.)

falling cotton balls and hand movements has been observed in scotopic conditions (Katz et al., 2005). In dogs ranging between 7 and 10 years of age, ophthalmoscopic examination revealed normal to moderately advanced generalized retinal degeneration. ERG reveals depressed rod cell function in affected dogs. Autofluorescent storage bodies can be observed in Muller cells and neurons within the retina and cerebral and cerebellar cortices. Typical ultrastructural characteristics for NCL are also observed.

Treatment for NCL has been shown to be successful in the Miniature Dachshund variety of the disease. Intracerebroventricular administered enzyme replacement and gene therapy have shown success in significantly delaying disease onset and disease progression (for review see Katz et al., 2017).

Various genetic mutations are constantly being identified for the various forms of NCL. As such, available genetic tests and testing centres are changing. To identify newly identified mutations and current tests that are available it is important frequently scan the most recent publications (e.g., via PubMed: https://www.ncbi.nlm.nih.gov/pubmed) and genetic disease testing databases (e.g., Orthopedic Foundation for Animals website: https://www.ofa.org/diseases/dna-tested-diseases/all-dna-tests).

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Acquired

Cardiovascular Diseases

Cerebrovascular Accidents

Cerebrovascular disease causing neurologic dysfunction is not uncommon in dogs (Boudreau, 2018). Cerebrovascular accidents can either manifest as strokes or transient ischemic attacks (TIAs). Strokes are defined as rapidly occuring focal or generalized cerebral dysfunction lasting longer than 24 hours, or resulting in death, and occur because of vascular disease (Boudreau, 2018). TIAs, however, are characterized by rapid onset focal cerebral dysfunction occurring when no other cause for the clinical signs is found. The character of the dysfunction, during a TIA, implicates a region of the brain served by one vascular supply (Boudreau, 2018).

Cerebrovascular accidents can be the result of cerebral hemorrhage (hemorrhagic stroke) from diseases such as systemic hypertension (primary or secondary), vascular malformations, intracranial neoplasia, coagulopathies, or trauma. Cerebrovascular accidents can also arise from blockage of blood flow to the brain (ischemic stroke) resulting from thrombosis, embolic events, atherosclerosis, vasculitis, or neoplasia. Regardless of the cause of the cerebrovascular accident, ocular manifestations of impaired brain function may manifest and will vary according to the neuroanatomic location of the cerebrovascular accident. Because cerebrovascular accidents are acute, clinical signs are acute. Ophthalmic manifestations of cerebrovascular disease may occur at the time of the cerebrovascular accident or develop shortly thereafter. In addition, considering that cerebrovascular accidents typically affect relatively large areas of the brain, abnormal neuro-ophthalmic findings have not been reported as the sole manifestation of cerebrovascular accidents in dogs. For reviews on cerebrovascular accidents in dogs see Garosi (2010) and Boudreau (2018).

Hypertension

Systemic arterial blood pressure is the product of cardiac output (CO) (CO = heart rate × stroke volume) and total peripheral resistance. Any factor causing persistent elevation in one or more of these determinants of blood pressure can cause systemic hypertension. When hypertension is associated with an underlying causative disease it is called secondary hypertension. Hypertension in veterinary patients is typically secondary hypertension. It should be noted, however, that primary (essential) hypertension has been described, although rarely, in dogs (Bovee et al., 1989; Littman et al., 1988). Primary hypertension is hypertension resulting from unknown reasons. Secondary hypertension is now recognized as being a common complication of renal disease (60%–80% of cases), hyperadrenocorticism (59%–86% of cases), pheochromocytoma (>50% of cases), diabetes mellitus, primary aldosteronism, hypothyroidism, and hyperthyroidism (Dimski, 1988; Howard & Nielsen, 1965; Leblanc et al., 2011; Ortega, 1996).

Previously, the high "normal" range of systolic blood pressure for dogs was reported to be between 160 and 180 mmHg. Renal damage in dogs has been reported to progress with systolic blood pressures in this range, however (Finco, 2004). Consequently, systemic hypertension is defined as a calm animal having repeatable systolic blood pressure measurements greater than 160 mmHg and/or diastolic blood pressure measurements greater than 100 mmHg (Stepien, 2005). It should be noted, however, that results of a large epidemiological study that evaluated blood pressure in clinically normal dogs found that sight hounds had higher blood pressures compared with other breeds (Bodey & Michell, 1996).

Hypertension-induced (hypertensive) retinopathy has been described, not uncommonly, in the dog (Howard & Nielsen, 1965; Gwin et al., 1978; Leblanc et al., 2011; Littman et al., 1988; Sansom & Bodey, 1997; Violette & Ledbetter, 2018). The consequence of experimental ocular vascular hypertensive changes is an initial vascular constriction in the retinal arterioles in response to increased blood pressure; when sustained, it results in occlusion and ischemic necrosis of the vessel walls, with resultant increased vascular permeability. Serous retinal exudates, hemorrhages, and edema also result. Choroidal vascular changes result in subretinal fluid and retinal detachment (Keyes, 1937). Ocular lesions associated with canine hypertension include intracorneal stromal hemorrhage, tortuous retinal vessels, variable-sized retinal and preretinal hemorrhages, papilledema, variable degrees of retinal detachment (Fig. 37.1.7), and tapetal reflectivity changes (Howard & Nielsen, 1965; Gwin et al., 1978; Leblanc et al., 2011; Littman et al., 1988; Sansom & Bodey, 1997; Violette & Ledbetter, 2018). Potential

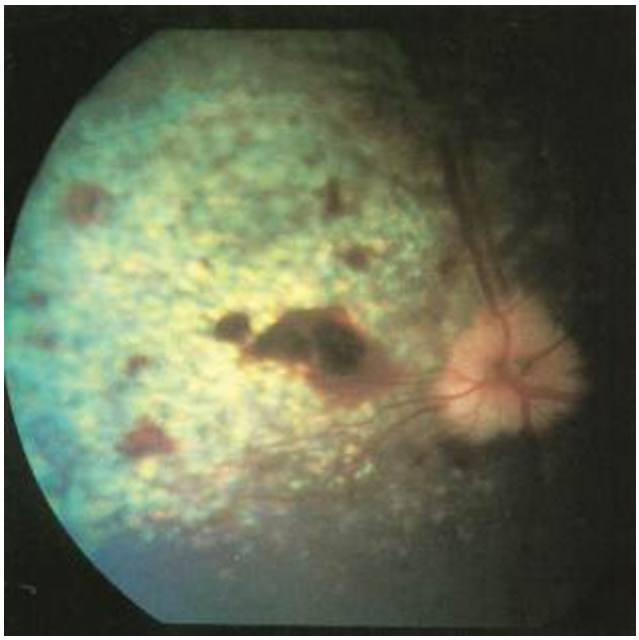


Figure 37.1.7 Multiple retinal hemorrhages and possible papilledema associated with hypertension in a dog.

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complications of systemic hypertension include anterior segment and vitreous hemorrhage, uveitis, and glaucoma, all of which result in variable degrees of vision loss and pain (Keyes, 1937; Paul & Ward, 2003; Rubin, 1975). Hypertension should therefore be ruled out when presented with intracorneal stromal hemorrhage, intraocular hemorrhage, or bullous retinal detachment of unknown origin.

The goals of antihypertensive therapy include lowering blood pressure and slowing the progression of target organ damage caused by chronic hypertension. Successful therapy requires good client compliance with frequent reassessment of the blood pressure. If an underlying cause of the hypertension has been identified, the primary condition should be addressed therapeutically, when possible. However, even if the presumed underlying cause of the hypertension is controlled, antihypertensive therapy is typically required long-term. The number of dogs that are naturally hypertensive is small when compared with the number of cats. As such, there is limited information available regarding effective antihypertensive medications in hypertensive dogs. The current first-line antihypertensive agents of choice in the dog are angiotensin-converting enzyme inhibitors or calcium channel blockers (usually amlodipine).

Hematologic Diseases

Anemia

Anemia is the reduction in red blood cells (RBC) per volume of whole blood. Anemia is classified as regenerative if there has been a normal bone marrow response to erythropoietin (e.g., usually occurs with blood loss or hemolytic disease), or nonregenerative if the normal reticulocyte response is lacking (e.g., may occur with chronic extra-marrow disease which reduces RBC survival time, selective erythropoietin depression, insufficient erythropoietin release, or a combination of these factors) (Rebar et al., 2005a). Severe anemia often manifests systemically as varying palor of mucous membranes, cool mucous membranes, tachycardia, polypnea, weakness, as well as signs specific to the underlying primary condition. Conjunctival palor is even used as an indicator of anemia because of gastrointestinal parasitism in sheep and goats (Kaplan et al., 2004; Sotomaior et al., 2012; Vatta et al., 2001). Ocular manifestations of severe anemia include pale retinal vasculature, varying degrees of retinal hemorrhage, and subtle changes in tapetal reflectivity. Retinal hemorrhages are more likely to be observed, however, and are more dramatic if accompanied by thrombocytopenia (Carraro et al., 2001; Shelah-Goraly et al., 2009). Small intraretinal hemorrhages are typical and may reabsorb quickly with correction of the anemia, but pigmentary disturbances may be a residual retinal alteration. The pathogenesis of the retinal hemorrhage is postulated to be from hypoxia to the vessel walls as a consequence of the anemia (Carraro et al., 2001). Extreme pallor to the retinal vessels may mimic the appearance of generalized/diffuse retinal degeneration/atrophy, with the exception of the marked tapetal hyperreflectivity present in the latter syndrome. In a prospective study evaluating the prevalence and severity of ocular lesions in dogs with anemia and/or thrombocytopenia compared with healthy dogs, both the prevalence and severity of ocular lesions were significantly associated with thrombocytopenia but not with anemia (Shelah-Goraly et al., 2009). In particular, of the 17 dogs with anemia alone, 15/17 had no ocular lesions whereas only 1/17 had focal retinal edema and 1/17 had subconjunctival petechia whereas no dogs with anemia alone had severe ocular lesions. Intracorneal stromal hemorrhage has also been described in a patient with immune-mediated hemolytic anemia (Violette & Ledbetter, 2017).

Hyperlipidemia

Hyperlipidemia refers to an elevation in plasma concentrations of cholesterol and/or triglycerides, and arises because of a disturbance in plasma lipoprotein metabolism (Xenoulis & Steiner, 2015). Lipemia refers to the grossly visible turbid/lactescent appearance of serum or plasma and is because of triglyceride concentrations greater than 2.26–3.39 mmol/L and is not seen with hypercholesterolemia (Xenoulis & Steiner, 2015). Hyperlipidemia represents an abnormal finding in fasted dogs (>12 hours fasting) and, when present, is indicative of either increased production or reduced degradation of lipoproteins (Elliott et al., 2011; Xenoulis & Steiner, 2015). Because triglycerides and cholesterol are transported in the blood by various proteins, the term hyperlipoproteinemia is often used interchangeably with hyperlipidemia (Xenoulis & Steiner, 2015). Postprandial hyperlipidemia is a common cause of hyperlipidemia in the dog. It has been shown that chronic obesity also results in elevations in serum cholesterol and triglycerides (Jeusette et al., 2005). Pathologic elevations in plasma lipids and lipoproteins are classified as primary (i.e., familial or genetic origin) or secondary (i.e., develop as a consequence of an underlying disease) (Crispin, 1993; Rogers et al., 1975; Watson, 1993; Xenoulis & Steiner, 2015). Primary hyperlipidemia/hypercholesterolemia has been described in various breeds including the Beagle, Briard, Collie, Miniature Schnauzer, and Shetland Sheepdog (Jeusette et al., 2004; Manning, 1979; Sato et al., 2000; Watson et al., 1993; Whitney, 1987). Hyperlipidemia can be found in a variety of systemic diseases including hypothyroidism, diabetes mellitus, hyperadrenocorticism, pancreatitis, and renal (e.g., nephrotic syndrome) as well as hepatic (e.g., cholestasis) diseases (Watson, 1993; Xenoulis & Steiner, 2015).

Depending on the quantity and class of elevated lipoprotein, hyperlipidemia may produce ocular lesions. In particular, lipemic aqueous, lipemia retinalis, and lipid keratopathy can occur in dogs with hyperlipidemia.

Visible lipemia in the dog is produced by elevations of triglyceride levels, and it can be detected in the ocular vessels of the conjunctiva and retina (i.e., lipemia retinalis) as pink,

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engorged vessels (Wyman & McKissick, 1973). It is most easily observed in the retinal vessels over the non-tapetal region (Sigler, 1977; Wyman & McKissick, 1973). Hyperlipidemia may also manifest with lipids in the anterior chamber (Crispin, 1993; Kern & Riis, 1980; Nell, 1995). A prerequisite for gaining access to the anterior chamber by the large, lipid-laden molecules is alteration of the blood–aqueous barrier, presumably resulting from preexisting uveitis. It is unclear, however, whether the lipids incite or are the result of uveitis. The syndrome is usually unilateral, which would argue against hyperlipidemia inciting uveitis.

Hyperlipidemia characterized by elevated cholesterol levels may result in corneal lipidosis with varying patterns. A rapid, rather diffuse, and bilateral corneal stromal syndrome has been observed in association with elevated cholesterol levels in hypothyroid dogs. Ocular irritation appears to accompany this syndrome as well, because marked conjunctival hyperemia has been noted (Kern & Riis, 1980). Animals with lipid keratopathy or depositions of superficial plaque-like lesions associated with vascularization often have elevated cholesterol levels. Certain breeds, such as the Shetland Sheepdog and Collie, may be predisposed (Jeusette et al., 2004; Sato et al., 2000). Bilateral lipid arcs near the limbus have been consistently associated with elevated cholesterol and/or triglyceride levels (Crispin, 1993; Linton et al., 1993).

Evidence of ocular lesions consistent with lipemia retinalis and/or aqueous lipids should prompt acquisition of detailed dietary and medical histories, as well as a clinical workup to determine the cause of the hyperlipidemia. Lipid keratopathy can occur from a variety of causes, and all instances do not warrant expensive workups unless they are rapidly progressive, and bilateral in nature, in which case complete systemic workup (e.g., 12–16 hour, fasted, blood samples for complete blood count, serum biochemistry profile, urinalysis, serum triglycerides, cholesterol, ± T4) is advised. Patients with peripheral corneal arcus lesions (limbal-based corneal lipid infiltrates) should have their cholesterol and triglyceride levels determined. All owners of lipid keratopathy patients should be asked about the dietary level of fat their animal is consuming, considering that diet is an important modifier. Treatment and prognosis are variable depending on the underlying cause of the hyperlipidemia. Interestingly, however, corneal lipidosis observed in primary hypercholesterolemia in Collies has been successfully treated by administering short-chain fructo-oligosaccharide supplementation (Jeusette et al., 2004).

Hyperviscosity Syndrome

Hyperviscosity syndrome comprises single or multiple clinicopathologic abnormalities resulting from increased serum viscosity. The severity of hyperviscosity syndrome is linked to the size, shape, type, and concentration of large molecules (e.g., imunoglobulins [Ig]) in the bloodstream. This syndrome can be found with IgA, IgG, or IgM macroglobulinemia (Braund et al., 1978; Center & Smith, 1982; Couto et al., 1984; Giraudel et al., 2002; Hammer & Couto, 1994; Peterson & Meininger, 1997; Ramaiah et al., 2002).

The underlying cause is usually a malignancy, such as lymphoma, chronic lymphocytic leukemia, plasmacytoma, or multiple myeloma, but infectious diseases such as ehrlichiosis may also produce the syndrome (Braund et al., 1978; Center & Smith, 1982; Hammer & Couto, 1994; Harrus et al., 1998; Hendrix et al., 1998; Hoskins et al., 1983; Giraudel et al., 2002; Kirschner et al., 1988; Sansom & Dunn, 1993). The mechanism of producing clinical signs is perhaps multifactorial and is not well understood. Hemorrhage may occur from multiple causes, such as sludging of blood in small vessels, ineffective delivery of oxygen and nutrients to vessel walls, hypertension, coagulation abnormalities as a result of elevated protein levels interfering with clotting factors and platelet function, and thrombocytopenia. The ocular lesions most frequently noted include dilated, tortuous retinal vessels, which may develop kinking or "box carring," or venous dilatation and sacculation; papilledema; retinal hemorrhages; intraretinal cysts; and bullous retinal detachments (Fig. 37.1.8) (Hendrix et al., 1998; Violette & Ledbetter, 2018). Anterior segment complications such as anterior uveitis and glaucoma may develop as well (Center & Smith, 1982; Hendrix et al., 1998; Kirschner et al., 1988; Sansom & Dunn, 1993).

The diagnosis of hyperviscosity syndrome is made on the basis of demonstrating the hyperproteinemia on serum biochemistry profile combined with serum and urine protein electrophoresis and immunoelectrophoresis. A detailed medical workup is necessary to determine the cause of the hyperproteinemia.

Plasmapheresis may be used to treat the hyperviscosity (Lippi et al., 2015; Matus et al., 1983). In addition, appropriate antineoplastic therapy directed at the underlying cause is indicated (Hendrix et al., 1998).

Icterus

Icterus or jaundice is a condition characterized by hyperbilirubinemia and deposition of bile pigments in the skin, sclera, and mucous membranes causing them to appear a shade of yellow. The sclera is the classic location for detection of icterus given its relative lack of pigmentation. The yellow appearance of icterus may be detected in the intraocular structures as well (e.g., blue irides may turn green) (Fig. 37.1.9) and yellow hues may be imparted on the tapetum.

Intravenous Fluid Overload

Ophthalmologists performing consultations for internists may note bullous retinal detachments associated with isotonic fluid administration to patients having varying degrees of renal compromise. This condition begins with multiple, small, subretinal bullae forming in both eyes. The small bullae coalesce to form larger detachments, and eventually, they

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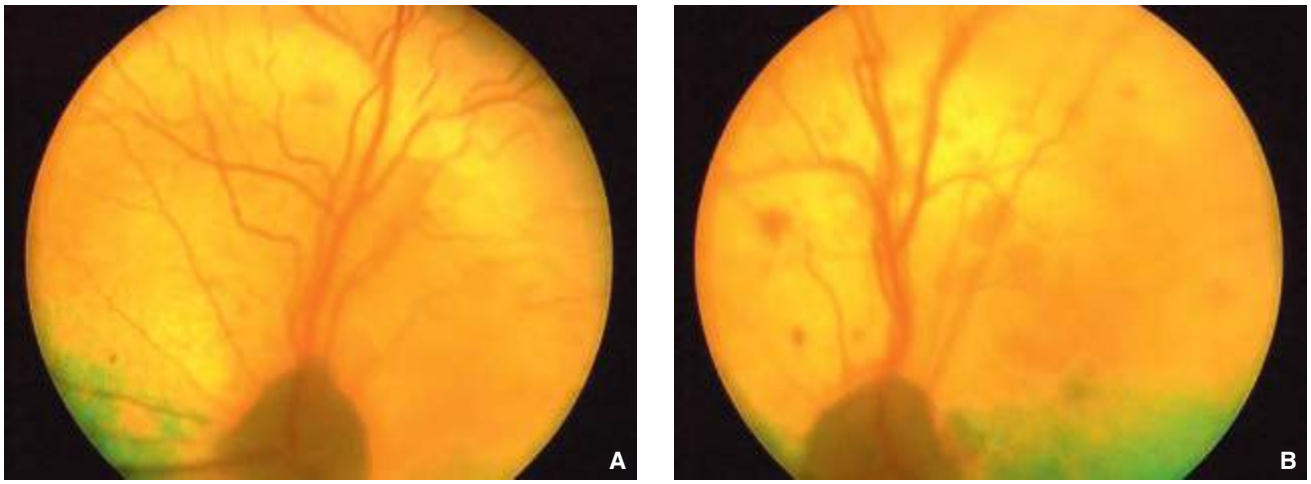


Figure 37.1.8 Fundus photographs of a dog with multiple myeloma. **A.** Left fundus. Note the retinal detachment dorsal to the optic disc and the focal retinal hemorrhage in the medial fundus at the tapetal-nontapetal junction. **B.** Right fundus. Note the multifocal retinal and subretinal hemorrhages and the retinal detachment in the dorsal tapetal region.

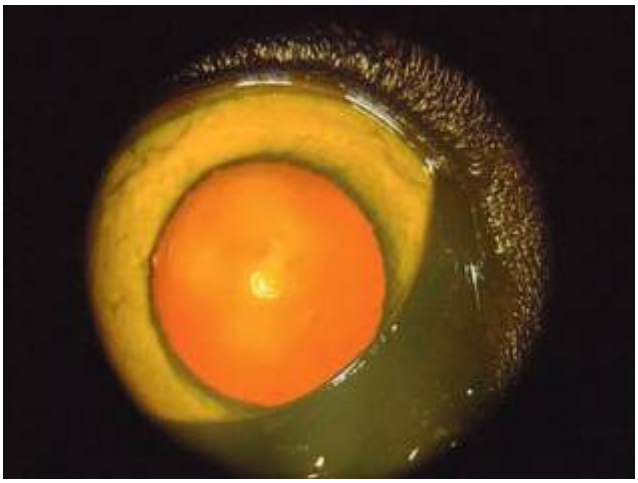


Figure 37.1.9 Yellow-appearing iris in a dog with icterus. The clinically normal appearing iris in this dog was blue.

progress to total retinal detachments associated with a clear subretinal fluid. Retinal hemorrhages are absent, and affected animals have normal blood pressure (Martin, 1999). When observed early in the course of disease, internists are looking for retinal signs of hypertension; when observed late in the course of disease, patients are examined for dilated pupils. Correction of the underlying renal problem or decreasing the fluid intake will cause the fluid to be reabsorbed and the retinas to reattach, even though retinal folds may persist. The exact pathogenesis is unknown, but leakage of solutes into the choroidal extracellular space with drawing of fluid into the interstitium is postulated. A breakdown of the blood–retinal barrier at the retinal pigment epithelium is also necessary for subretinal fluid to accumulate. Impaired renal function is another prerequisite, but affected animals are not usually anuric.

Finding bullous retinal detachments without hemorrhages or exudates in animals receiving intravenous fluids for renal disease is suggestive of the disease. The systemic blood pressure is either normal or low on repeated examinations. Therapy should concentrate on decreasing fluid administration, regaining renal compensation, or both.

Polycythemia

Polycythemia is classified as relative or absolute (primary and secondary forms). Relative polycythemia is an increased packed cell volume with normal RBC mass occurring as a result of a reduction in plasma volume as may arise from external losses of body fluids (e.g., diarrhea, burns).

Absolute polycythemia is an increase in total RBC mass, and it may be classified as either primary or secondary (appropriate and inappropriate). Absolute primary polycythemia (i.e., polycythemia vera) has been described in dogs and is an absolute increase in erythropoiesis without an increase in erythropoietin (for review see Campbell, 1990). The underlying molecular basis of polycythemia vera has yet to be elucidated.

Absolute secondary polycythemia results from altered erythropoietin homeostasis and is described as being appropriate or inappropriate. Absolute secondary appropriate polycythemia occurs as a consequence of persistent hypoxia and can be found in animals with conditions such as congenital cardiac defects causing right-to-left shunting of blood (Moore & Stepien, 2001). Absolute secondary inappropriate polycythemia, however, results from disease processes which lead to inappropriate secretion and elevation of erythropoietin or an erythropoietin-like substance in the absence of systemic hypoxia. Causes of absolute secondary inappropriate polycythemia include diseases which result in the production of erythropoietin or which cause local hypoxia and trigger

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erythropoietin synthesis including malignancies (e.g., cecal leiomyosarcoma [Sato et al., 2002]) and renal disease (e.g., renal neoplasia, amyloidosis, inflammation, infection), respectively (Crow et al., 1995; Snead, 2005; Waters & Prueter, 1988). Polycythemia may manifest as dark, ruddy-colored conjunctival and retinal blood vessels that are dilated and tortuous. In addition, bilateral anterior uveitis with concurrent unilateral chorioretinitis has been described in a dog with polycythemia vera (Gray et al., 2003). Treatment varies according to the cause of the polycythemia. In one case of polycythemia vera, treatment with phlebotomy and oral hydroxyurea resulted in resolution of both systemic and ocular signs (Gray et al., 2003). If left untreated, however, retinal detachment and ocular hemorrhage may occur with persistent polycythemia (Lombard & Twitchell, 1978; Martin et al., 1972b).

Thrombocytopenia and Thrombopathies

Thrombocytopenia results from either decreased platelet production, increased removal, sequestration, or any combination of these (Rebar et al., 2005b). The most common causes of thrombocytopenia include infectious diseases, neoplasia, drug-induced reactions, and immune-mediated disease (Grindem et al., 1991). In particular, the numerous pathogens implicated in causing infectious thrombocytopenia in dogs include arthropod-borne agents (e.g., *Babesia*, *Borrelia*, *Cytauxzoon*, *Dirofilaria* spp., *Ehrlichia* spp., *Leishmania, Rickettsia*), viral agents (e.g., canine distemper virus, herpesvirus, parvovirus, adenovirus), and fungal and bacterial organisms (e.g., *Candida*, *Histoplasma*, *Leptospira* spp.). Thrombocytopenia is also seen in association with: (1) many forms of neoplasia including lymphoma, leukemia, and multiple myeloma; (2) medications which impair platelet production, or cause secondary immune destruction of the platelets (e.g., chloramphenicol, azathioprine, cyclophosphamide, doxorubicin); or (3) it may develop as an idiopathic or primary immune-mediated condition. Immune-mediated thrombocytopenia has been associated with punctate retinal hemorrhages in dogs (Violette & Ledbetter, 2018). In a prospective study evaluating the prevalence and severity of ocular lesions in dogs with anemia and/or thrombocytopenia compared with healthy dogs, both the prevalence and severity of ocular lesions were significantly associated with thrombocytopenia but not with anemia (Shelah-Goraly et al., 2009). In particular, of the 36 dogs with thrombocytopenia alone, 9/36 had mild ocular lesions including conjunctival ($n = 3$), iridal ($n = 1$) or retinal petechiae ($n = 3$), focal retinal edema ($n = 2$), and 6/36 had severe ocular lesions including hyphema ($n = 5$) and retinal hemorrhage ($n = 1$) (Shelah-Goraly et al., 2009).

Thrombopathies are blood coagulation disorders as a result of platelet dysfunction and are either acquired or inherited (Rebar et al., 2005b). Disease processes associated with thrombopathies include anemia, disseminated intravascular coagulation, liver failure, and uremia (Rebar et al., 2005b). Regardless of the origin, both thrombocytopenia and thrombopathies are rather frequent causes of ocular and periocular hemorrhage. The presence of bleeding signs at a given platelet level varies between individuals, but platelet counts are usually fewer than 50,000 cells/μL when ocular petechiae form. Acute loss of platelets is more likely to manifest as hemorrhage at a given level than is a gradual loss of platelets. Petechiae in the ocular fundus are often present without visible petechiae in the skin and other mucous membranes. Therapy is directed at the underlying cause, and if bleeding signs are severe, transfusion of fresh whole blood or platelet-rich plasma is indicated.

Idiopathic Systemic Diseases

Canine Idiopathic Granulomatous Disease

Idiopathic granulomatous disease in the dog is considered to be immune-mediated because of the absence of any demonstrable infectious agent and because favourable responses to immunosuppressive doses of corticosteroids or other immunosuppressive drugs have been reported (Carpenter et al., 1987; Collins et al., 1992; Gionfriddo et al., 2003). Syndromes of sterile granulomatous inflammation are poorly defined and relatively rare. An idiopathic periadnexal multinodular granulomatous dermatitis syndrome has been described that, in one instance, was associated with anterior uveitis (Collins et al., 1992). Multiple sterile granulomas of the eyelids, conjunctiva, and sclera that accompanied dermal granulomas have been described in another case (Collins et al., 1992). Bilateral orbital granulomatous disease that was very responsive to corticosteroids and required therapy indefinitely for remission has been noted (Martin, 1999). Eventually, whereas this animal was off therapy, massive granulomatous disease developed in the chest and abdomen. Necropsy and histopathology did not reveal the cause of the granulomas. A case of idiopathic ocular and nasal granulomatous disease in a dog without dermatologic lesions has been described and may be a different form of the classically described canine idiopathic granulomatous disease (Gionfriddo et al., 2003). In this case, bilateral limbal and intranasal granulomatous masses were observed. These masses were predominantly T-cell rich granulomatous reactions and the dog responded favourably to immunosuppressive doses of oral prednisolone, topical prednisolone acetate, and azathioprine.

Dysautonomia

Canine dysautonomia is an idiopathic disease resulting from a generalized loss of autonomic function. Dogs affected are typically young adults of medium to large physical stature that typically live in rural areas. It is important to note, however, that animals ranging in age from 5 weeks to 15 years of age and of a variety of breeds can be affected (Berghaus et al., 2002; Harkin et al., 2002a). Canine dysautonomia has been reported in Europe (Rochlitz & Bennett, 1983; Presthus &

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Bjerkas, 1987) and the United States (Berghaus et al., 2001; Harkin et al., 2002a; Longshore et al., 1996). The disease is prevalent in dogs living in the midwestern United States, specifically, Kansas and Missouri. Affected dogs present with an acute (days) or subacute (2–3 weeks) history of clinical signs referable to loss of autonomic (sympathetic and parasympathetic) function (Berghaus et al., 2001; Harkin et al., 2002a). Common non-ocular clinical signs include regurgitation, vomiting, diarrhea, anorexia, weight loss, dry mucous membranes, and purulent nasal discharge (Harkin et al., 2002a; Longshore et al., 1996). Dogs may present with limited clinical signs that progress to involve more signs of autonomic failure during the course of the disease. Ocular signs include ocular discharge, protruding third eyelid, mydriasis, and a reduction in Schirmer tear test (STT) values (Harkin et al., 2002a,b; Longshore et al., 1996). Ocular pharmacologic testing with topical 0.05% pilocarpine in dogs with mydriatic pupils, and signalment, history, and clinical signs consistent with dysautonomia provides useful information supporting a diagnosis of dysautonomia. In affected dogs, instillation of 0.05% pilocarpine will cause rapid (<45 minutes) miosis compared with unaffected animals (O'Brien & Johnson, 2002). Severe neuronal degeneration has been reported in a variety of autonomic ganglia including the cranial cervical and ciliary ganglia (Harkin et al., 2002a). In addition, neuronal degeneration of various brainstem nuclei, including the facial, oculomotor and motor nucleus of the trigeminal nerve, has also been reported (Harkin et al., 2002a). At least 85% of dogs affected with dysautonomia succumb to the disease and are euthanized (Harkin et al., 2002a).

Sudden Acquired Retinal Degeneration Syndrome

Sudden acquired retinal degeneration syndrome (SARDS) is an idiopathic blinding condition consisting of acute blindness in the absence of funduscopic disease (early in disease), and clinical signs suggestive of an underlying metabolic disease. SARDS has been recognized among dogs in the United States for over two decades (Vainisi et al., 1983). Nevertheless, the cause of SARDS is unknown and this, combined with the fact that SARDS is an important cause of blindness in dogs, spawned a "think-tank" to help provide guidance regarding pathogenesis, early diagnosis, and treatment (Komaromy et al., 2016).

Epidemiologic questionnaires have not been suggestive of any common thread for an environmental toxin (Acland et al., 1984). Preliminary investigations into excitotoxins (e.g., glutamate) have found increased levels in the vitreous of affected animals, but the significance of this is unknown (Abrams et al., 1995). Circulating antiretinal antibodies have been found in dogs with SARDS; however, antiretinal antibodies are also found in clinically normal dogs (Bellhorn et al., 1988; Gilmour et al., 2004). Attempts to link SARDS with paraneoplastic processes, as has been shown in human cancer-associated retinopathy, has proven unrewarding (Gilmour et al., 2004). Analysis of tissues from SARDS-affected dogs revealed the presence of immunoglobulin-producing plasma cells in affected retinas which may account for localized intraretinal production of autoantibodies and subsequent development of an antibody-mediated retinopathy (Grozdanic et al., 2008). In addition, strong complement activity has been documented in the retinas of dogs with SARDS which may account for antibody-mediated neuronal damage (Grozdanic et al., 2008).

In one study, 40%–60% of dogs affected with SARDS were reported to have have systemic signs and altered clinicopathological test results (van der Woerdt et al., 1991). Animals are characteristically presented with acute blindness and a normal to near-normal ocular fundus (van der Woerdt et al., 1991). Because of the acute onset, most dogs are quite disoriented. In most patients, vision loss occurs over the course of 1–2 weeks, and nyctalopia may be observed (van der Woerdt et al., 1991). The mean age of affliction is 8.5–10 years (Miller et al., 1998; van der Woerdt et al., 1991). The syndrome tends to occur in middle-aged to older ovariohysterectomized females, in both pure and mixed breeds, and with a predisposition for Dachshunds, Pugs, Miniature Schnauzers, and Brittany Spaniels (Acland & Aguirre, 1986; Acland et al., 1984; Auten et al., 2017; Leis et al., 2017; Vainisi et al., 1983, 1985; van der Woerdt et al., 1991). A seasonal incidence has been reported as well, with 46% of cases occurring in December and January (Acland et al., 1984). Many affected dogs have polyuria, polydipsia (28%–36% of cases), and polyphagia (39%), as well as a history of weight gain (57%). Also, systemic hypertension (4 of 10 dogs) and proteinuria (7 of 10 dogs) have been reported in dogs with SARDS (Carter et al., 2009). Laboratory values are variable, but lymphopenia (30% of cases), lymphopenia with neutrophilia (21%), and abnormal biochemical profiles (68%) may be present. Elevated levels of alkaline phosphatase (30%–40% of cases) and cholesterol (42%) are the most common biochemical changes. Adrenocorticotropic hormone (ACTH) stimulation or a low-dose dexamethasone suppression test may be abnormal (van der Woerdt et al., 1991). Overall, 12%–17% of patients have adrenal profile changes compatible with those of Cushing's disease, but these changes may be adaptations to other diseases as well (Acland et al., 1984; Carter et al., 2003; Mattson et al., 1992; van der Woerdt et al., 1991). These associated alterations in pituitary function have led to the hypothesis that elevations in melanocyte-stimulating hormone (MSH) may accompany an increased ACTH level. Increased MSH may then lead to increased melanin production by the retinal pigment epithelium (RPE), which may impair RPE phagocytosis of photoreceptor outer segments and, consequently, result in retinal degeneration (van der Woerdt et al., 1991). Serum cortisol and sex hormone concentrations have been measured prior to and after ACTH stimulation in 13 dogs with SARDS (Carter et al., 2009). Serum cortisol was elevated in 9 of 13 dogs; elevations in one

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or more sex hormones were found in 11 of 13 patients with SARDS whereas only one dog had normal ACTH stimulation results (Carter et al., 2009).

On ophthalmic examination, dogs with SARDS appear blind and lack a menace response, whereas they tend to blink in response to bright light (positive dazzle reflex). The pupils are usually dilated at rest and show sluggish, but present, PLR (Leis et al., 2017; van der Woerdt et al., 1991). Ophthalmoscopic changes during the acute stages are very minimal, with mild retinal vascular attenuation or variability in retinal vascular caliber and changes in tapetal reflectivity. In the early stages, all dogs with SARDS have a characteristic pale optic disc because of the presence of vascular attenuation of the optic nerve head (Grozdanic et al., 2008). In patients with SARDS of typically longer than 2 months duration, subtle tapetal hyperreflective spots may be observed, with these spots detected in some affected dogs only 7 days after the onset of acute blindness (Grozdanic et al., 2008). After several weeks to months, more advanced retinal vascular attenuation and tapetal hyperreflectivity become apparent. The funduscopic appearance in chronic SARDS is similar to that of inherited retinal degeneration (van der Woerdt et al., 1991). Histopathologic changes have been infrequently reported, but cases of early SARDS have a diffuse loss of photoreceptor outer segments, with more subtle changes in swelling of the dendritic processes and cell bodies in the amacrine, bipolar, and ganglion cells. With chronicity, the entire neuroretina degenerates, and the RPE becomes attenuated and loses its apical processes (Acland et al., 1984; Miller et al., 1998; Vainisi et al., 1985; van der Woerdt et al., 1991).

Optical coherence tomography (OCT) has been used to analyze the structural thickness of retinas of dogs with SARDS; OCT revealed significant retinal thinning even for retinas that appeared relatively normal on funduscopic examination with primary damage of the nerve fiber layer and decreased retinal thickness of the ventral retina early on in this disease and progressing to involve thinning of all retinal layers, including the photoreceptor layer, in the dorsal and ventral quadrants (Grozdanic et al., 2008).

ERG is considered the gold standard for establishing a diagnosis of SARDS. The ERG response is extinguished with SARDS (Auten et al., 2017; Leis et al., 2017; van der Woerdt et al., 1991). A recent study documented the spectral properties of the PLR in eyes of healthy dogs compared with eyes of SARDS-affected dogs (Grozdanic et al., 2007). Dogs that have SARDS have complete pupillary constriction in response to blue light of a narrow wave length (480 nm) and high light intensity (200 kcd/m^2) most likely caused by stimulation of a photosensitive pigment, melanopsin, located in a subpopulation of retinal ganglion cells that can drive PLRs in the absence of photoreceptor activity. When red light of a given wavelength (630 nm) and high light intensity (200 kcd/m^2) was used to evaluate PLRs in SARDS-affected patients, the pupils remained fixed and dilated as this wavelength of red light does not activate the melanopsin pathway but rather activates the photoreceptor-mediated pathway which is absent in dogs with SARDS. A portable, diode-based light source with narrow wavelengths for blue and red light that matches the spectral properties of canine visual pigments is available for colorimetric PLR testing (Melan-100 unit, BioMed Vision Technologies, Inc., Ames, IA, USA) (Grozdanic et al., 2008). A study investigating chromatic PLRs using the Melan-100 unit showed that 75% of eyes with SARDS responded as predicted (miosis with blue light, negative PLR with red light), whereas 12.5% of eyes with SARDS had a weak miotic PLR with red light and miotic response with blue light, the remaining 12.5% of SARDS eyes had a weak miotic response with blue light and negative PLR with red light (Terakado et al., 2013). As such, an extinguished electroretinogram remains the gold-standard method of confirming SARDS.

SARDS has long been considered an untreatable, irreversible blinding disease of dogs. However, recently, experimental use of intravenous human immunoglobulins (IVIg) has resulted in restoration of limited visual behaviour in some SARDS-affected dogs in the early stages of this disease (Grozdanic et al., 2008). Another study examined immunosuppressive therapy with mycophenylate mofetil in 10 SARDS patients within 6 weeks of vision loss, and found no benefit of 6 weeks of therapy (Young et al., 2018). Most dogs with SARDS still make acceptable house pets provided they adjust well to being blind (Stuckey et al., 2013).

Immune-Mediated Diseases

Dermatologic Diseases

Immune-mediated and allergic skin diseases often produce a facial dermatitis involving the eyelids and conjunctiva. Immune-mediated skin diseases are divided into two main categories: primary autoimmune diseases, in which the disease results from an attack against self-antigens, and secondary immune-mediated disease, in which the disease results from exogenous material inducing autoimmune disease. Such causes of secondary immune-mediated diseases include bacteria, drugs, and viruses.

The pemphigus complex consists of five autoimmune skin diseases: (1) pemphigus vulgaris, (2) pemphigus vegetans, (3) pemphigus foliaceus, (4) pemphigus erythematosus, and (5) bullous pemphigoid. The pemphigus complex is characterized by autoantibodies directed against intercellular substances. In most cases, facial lesions involve the mucocutaneous regions and are characterized by pustules and vesicles that eventually rupture, thereby leaving erosions and ulcers, crusting, scaling, and hypopigmentation. Discoid lupus erythematosus, a primary autoimmune disease, is also associated with facial dermatitis, consisting of crusts, depigmentation, erosions, and ulcers, which

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predominantly affects the nasal planum and muzzle; oral ulcers are also described with this disease. Systemic lupus erythematosus, a complex syndrome involving autoimmunity with or without the presence of antinuclear antibodies (ANAs), may produce a facial dermatitis and may also be associated with intraocular disease through vasculitis, thrombocytopenia, and severe anemia (Ihrke et al., 1985; Manning et al., 1980; Miller, 1979; Scott, 1981; Scott et al., 1980; Walton et al., 1981).

Allergic dermatitis, urticaria, may arise as a result of flea or food allergies, atopy, drug reactions, or insect bites (Carlotti & Jacobs, 2000; Scott & Miller, 1999; Trepanier, 1999; Zur et al., 2002). Allergic reactions to systemic or topical drugs or drug eruptions often involve the mucocutaneous and cutaneous regions of the head. When caused by a topical drug, the reaction is usually limited to the point of contact, but systemic absorption may produce a generalized reaction. Atopy or clinical allergy to environmental antigens involves the face in approximately 80% of cases, and 50% have conjunctivitis (Martin, 1999). Episodes of conjunctivitis frequently exacerbate with flare-ups of skin lesions (Martin, 1999).

The pattern of skin lesions may be suggestive of the diagnosis, but a specific diagnosis of the immune-mediated disease is made on the basis of patient history, skin biopsy with histopathologic and immunofluorescent testing, and autoantibody tests (e.g., the ANA and lupus erythematosus, preparations for systemic and discoid lupus erythematosus). Intradermal skin tests may find specific antigens to which the atopic patient is sensitive (Zur et al., 2002). For a discussion of appropriate treatments for each of these conditions, the reader should consult current dermatology references.



Figure 37.1.10 Juvenile pyoderma in a young Saint Bernard.

Juvenile Pyoderma/Cellulitis (Puppy Strangles)

Juvenile sterile granulomatous dermatitis (i.e., pyoderma/cellulitis) and lymphadenitis is a syndrome of dogs which usually manifests in animals younger than 8 months of age (Bassett et al., 2005; Hutchings, 2003; Mason & Jones, 1989; Reimann et al., 1989; White et al., 1989). Adult dogs, however, may become affected by this condition (Jeffers et al., 1995; Neuber et al., 2004). One or more puppies in a litter may be involved. Predisposed breeds include the Dachshund, Golden Retriever, Labrador Retriever, Gordon Setter, and Lhasa Apso (Mason & Jones, 1989; Reimann et al., 1989; White et al., 1989). Acute pyoderma affecting mainly the head manifests as pustules which then fistulate and drain, thereby creating a moist, crusty lesion of the pinna, muzzle, and periocular skin (Fig. 37.1.10). Although the lesions appear to be induced by bacteria, they are actually sterile and cannot be transmitted. A bacterial hypersensitivity has been postulated to explain the response to corticosteroids and the explosive course of the disease. During the early stages, a puppy may be presented with only eyelid pustules, but within a few days, the pyoderma may extend to the ears and nose. Regional lymph nodes, particularly the mandibular lymph nodes, become markedly enlarged, and a severe otitis externa is typical as well. Occasionally, puppies will develop a more generalized pyoderma.

Even if the patient is presented with only a blepharitis, the diagnosis should be suspected because of the age of the dog and the bilateral eyelid involvement. Without systemic therapy, the lesions will progress to involve other typical areas. Immunosuppressive doses of systemic corticosteroids, tapered after 3–4 weeks after resolution of the clinical signs, and systemic broad-spectrum antibiotics to treat the secondary bacterial pyoderma, are indicated. Some clinicians prefer treatment with antibiotics for a few days before initiating corticosteroids. Nursing care, consisting of gentle cleansing or soaking of the skin lesions, may also be attempted. With appropriate therapy, prognosis is excellent.

Immune-Mediated Retinitis

Immune-mediated retinitis (IMR) is characterized by a sudden onset of complete blindness or night blindness in dogs and has similar features to SARDS (see previously). Dogs with IMR typically present with sudden blindness which is

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often preceded by months to years of sporadic, temporary bouts of decreased vision usually night vision. In addition, dogs with IMR may have a history of abnormal pupillary appearance (pupillary dilation in bright light and/or anisocoria with one pupil being dilated). Most dogs with IMR are reportedly healthy; however, some dogs with IMR (20% in one report) also have concurrent health issues including neoplasia and neurological abnormalities. On ophthalmic examination, dogs with IMR appear blind and lack a menace response, whereas they tend to blink in response to bright light (positive dazzle reflex). Ophthalmoscopic examination of IMR-affected dogs is generally unremarkable; however, a characteristic pale optic disc caused by the presence of vascular attenuation of the optic nerve head may be noted, similar to SARDS-affected patients. When assessing PLRs in IMR-affected dogs using colorimetric PLR testing (blue light versus red light stimulation; please see SARDS previously), there is a nearly complete absence of the PLR in response to red light stimulation and a normal PLR when blue light is used. Dogs with IMR have detectable ERG waveforms which can be normal, or reduced or increased in amplitudes, unlike SARDS-affected patients. The pathogenesis of IMR in dogs remains unknown, although it shares similar symptoms to antibody-mediated retinopathies in humans. Retinal autoantibodies have been documented in two of three serum samples from three dogs with IMR. Treatment for dogs with IMR includes oral doxycycline and steroids typically long-term. Recovery of the PLR in response to red light stimulation is reported to be the most reliable indicator of therapeutic success. Reevaluation of the ERG waveforms for increases in their amplitudes may also be helpful, as progressive, uncontrolled IMR is often linked with a decrease in retinal electrical activity (Grozdanic et al., 2008).

Keratoconjunctivitis Sicca

KCS is a condition characterized by a decrease in the aqueous tear film beyond that which is compatible with conjunctival and corneal health (Fig. 37.1.11). KCS in the dog has several causes, but one of the most common underlying causes appears to be a multiglandular inflammatory destruction that is most likely immune-mediated. Evidence of immune-mediated glandular inflammation is provided by the presence of circulating autoantibodies (i.e., rheumatoid factor and/or ANA) in a significant number of animals (34% and 40%, respectively), breed specificity, glandular pathology, and the presence of a variety of other diseases in 40% of KCS patients that may have an immune-mediated component. The salivary and thyroid glands are two of the glands that are often involved (in 20% of cases each) concurrently with involvement of the lacrimal glands (Kaswan et al., 1983, 1985 Quimby et al., 1979). Anecdotally, KCS often improves when other systemic problems in the animal improve.

A presumptive diagnosis of suspected immune-mediated KCS is made on the basis of STT results (Hamor et al., 2000),

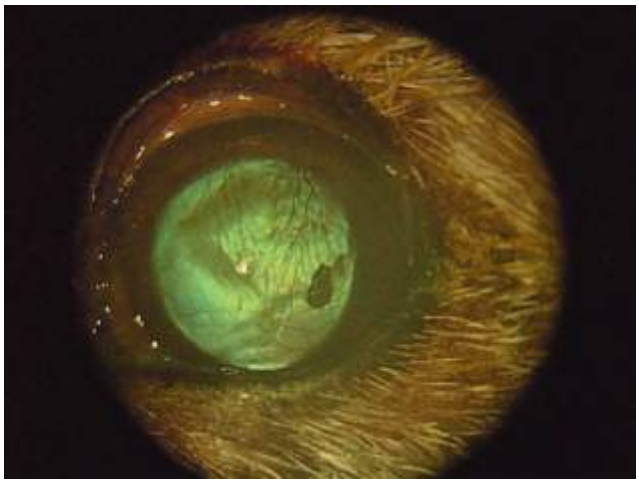


Figure 37.1.11 Left eye of a dog with keratoconjunctivitis sicca. Note the conjunctival hyperemia, mucus overlying the cornea, and diffuse superficial corneal vascularization with associated edema.

breed predisposition, lack of any history of sulfa administration (for review see Trepanier, 1999, 2004) or third-eyelid gland excision, and perhaps, involvement of other systems. Recommended treatment is the use of a topical immunosuppressive agent such as cyclosporine (Salisbury et al., 1990; Sansom et al., 1995; Olivero et al., 1991), tacrolimus (Adkins et al., 2003; Berdoulay et al., 2005), or pimecrolimus (Nell et al., 2005), as needed.

Meningoencephalitis of Unknown Etiology

Meningoencephalitis of unknown etiology (MUE) is a term used to group together a variety of seemingly immune-mediated inflammatory diseases involving the CNS in dogs (Coates & Jeffery, 2014; Hoon-Hanks et al., 2018; Talarico & Schatzberg, 2010). The MUE umbrella includes granulomatous meningoencephalitis (GME), necrotizing meningoencephalitis (NME), necrotizing leukoencephalitis (NLE), and eosinophilic meningoencephalitis of unknown etiology (EMUE) (Cardy & Cornelis, 2018; Cooper et al., 2014; Talarico & Schatzberg, 2010). Both NME and NLE can be found predominantly in small breeds and the conditions are both rapidly progressive and fatal despite immunosuppressive therapy (Cooper et al., 2014). EMUE typically affects young large breed dogs and is characterized by an eosinophilic pleocytosis on CSF analysis. EMUE-affected dogs may have a circulating eosinophilia, are negative for infectious/parasitic agents, and these patients respond similarly to immunosuppressive therapy as patients with GME (Cardy & Cornelis, 2018). Visual impairment has been described in patients with NME, NLE, and EMUE. MUEs may share similar pathophysiology, in that they are all seemingly immune-mediated. The following discussion focuses on GME, given that salient clinical differences with NLE, NME, and EMUE, are described previously.

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GME is an idiopathic nonsuppurative meningoencephalomyelitis, and seemingly immune-mediated disease, seen in dogs (Braund, 1985; Talarico & Schatzberg, 2010). Histopathologically, GME is characterized by perivascular cuffing with mononuclear cells (Braund, 1985). One study has shown that perivascular cuffs were composed of a heterogeneous population of major histocompatibility complex (MHC) class-II antigen-positive macrophages and mainly CD3 antigen-positive lymphocytes, supporting a hypothesis of T-cell-mediated, delayed type hypersensitivity of an organ-specific autoimmune disease (Kipar et al., 1998). Proposed pathogeneses for GME have included a primary immune-mediated phenomenon, precancerous form of lymphoma, and various infectious etiologies. Studies have failed to show an infectious etiology, although it is possible that infectious diseases may play a role in antigenic stimulation and subsequent MUE development (Barber et al., 2010, 2012; Hoon-Hanks et al., 2018).

The disease is typically seen in young small breeds, although any breed or age of dog may be affected. GME is described as being one of three types, namely: (1) disseminated, (2) focal, or (3) ocular. Any combination or permutation of these forms can occur. In the latter form, GME may involve the optic nerves, thus producing a syndrome of acute blindness, papilledema, retinal and peripapillary hemorrhages, and occasionally, extension into the globe, which in turn produces retinal detachments and retinal infiltrates (Fischer & Wi-Kwand, 1971; Smith et al., 1977). Confinement to the retrobulbar optic nerves may limit ocular lesions to blindness and dilated pupils (Braund, 1985; Garmer et al., 1981; Fischer & Wi-Kwand, 1971; Russo, 1979; Smith et al., 1977; Thomas & Eger, 1981). A retrospective study of optic neuritis in 96 dogs found that the majority of optic neuritis in dogs is caused by multifocal GME (35/96 patients) and isolated idiopathic optic neuritis (confirmed and unconfirmed cases) (42/96) (Smith et al., 2017). Of the confirmed cases of isolated optic neuritis and having had CSF analysis examined ($n = 17$), seven had elevated CSF nucleated cell counts and these patients may have had an ocular form of GME (Smith et al., 2017), although histopathology would be required to confirm a diagnosis.

A definitive antemortem diagnosis of GME is difficult to make, but multifocal CNS dysfunction, lack of infectious agents, increased CSF protein levels, pleocytosis with mononuclear cells, computed tomography and/or MRI findings consistent with inflammation, and a positive response to appropriate immunosuppressive therapy are highly suggestive. Definitive antemortem diagnosis can be made based on the above in concert with brain biopsy (Munana & Luttgen, 1998).

Treatment involves aggressive use of immunosuppressive corticosteroids with or without radiation therapy (Munana & Luttgen, 1998) or, more commonly, immunosuppression using a combination of corticosteroids with one or more of cytosine arabinoside (Menaut et al., 2008; Zarfoss et al., 2006), azathioprine (Wong et al., 2010), leflunomide (Gregory et al., 1998), or cyclosporine-A (Adamo & O'Brien, 2004; Nuhsbaum et al., 2002) or other immunosuppressive drugs (Coates & Jeffery, 2014). Prognosis for survival varies from weeks to years with appropriate combinatorial immunosuppressive therapy.

Myasthenia Gravis

Myasthenia gravis is a disease affecting the neuromuscular junction (for complete review see Shelton, 2002). Myasthenia gravis is either congenital or acquired. Congenital myasthenia gravis occurs when there is a functional disorder or depletion of nicotinic acetylcholine receptors (AChRs). Congenital myasthenia gravis is reported rarely in dogs (Flagstad et al., 1989; Oda et al., 1984; Palmer & Goodyear, 1978;) and will not be considered further here. Acquired myasthenia gravis is the most common form of myasthenia gravis occurring in dogs. The acquired condition develops because of an autoimmune targeting of AChRs which may occur as an autoimmune condition affecting only the AChR (most common, see Shelton, 1998), part of another autoimmune condition (e.g., hypothyroidism, see Shelton, 1998; Levine et al., 2005), or resulting as part of a paraneoplastic syndrome (e.g., thymoma, see Lainesse et al., 1996; Paciello et al., 2003b).

Animals with acquired myasthenia gravis can present with either generalized or focal clinical signs. Those animals with generalized myasthenia gravis will have generalized appendicular muscle paresis (weakness) that worsens with prolonged exercise, may have megaesophagus and resultant regurgitation with or without aspiration pneumonia, and spinal and cranial nerve reflexes that weaken with repeated testing. Approximately 43% of dogs with myasthenia gravis will have focalized clinical signs in the absence of appendicular muscle weakness (Shelton et al., 1997). Animals with the focal form of myasthenia gravis may present with regurgitation, and/or dysphagia, and/or change in character of vocalization because of megaesophagus, pharyngeal or laryngeal paresis, respectively (Dewey et al., 1997; Shelton et al., 1990). With respect to the eye, a paretic menace response and/or palpebral reflex may be the predominant clinical sign(s) (Clooten et al., 2003; Dewey et al., 1997; Webb et al., 1997).

A tentative diagnosis of acquired myasthenia gravis is made based on consistent clinical signs combined with immediate short-term improvement in muscular strength (e.g., improved palpebral reflex, see Webb et al., 1997) after the administration of the short-acting acetylcholinesterase inhibitor, edrophonium hydrochloride (Tensilon). All presumptive cases of acquired myasthenia gravis should be confirmed by demonstrating the presence of circulating muscular AChR autoantibodies (see the Comparative Neuromuscular Laboratory at http://vetneuromuscular.ucsd.edu/).

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The mainstay of therapy for acquired myasthenia gravis is the administration of anticholinesterase drugs. Therapy must be tailored according to the individual's response to therapy (for details pertaining to treatment recommendations see Shelton, 2002). Untoward side-effects of anticholinesterase drug therapy are similar to clinical signs observed in animals with organophosphate exposure including excessive salivation, lacrimation, and gastrointestinal signs including nausea and diarrhea. Further, animals may become paretic because of exuberrant depolarization and/or desensitization of the postsynaptic (skeletal muscle) membrane. The administration of corticosteroids, or other immunosuppressive medications, concurrently with anticholinesterase drug therapy is warranted when the response to monomodal anticholinesterase therapy is less than ideal. Immunosuppressive therapy may, however, be inappropriate if underlying disease processes such as aspiration pneumonia are evident. Of course, other important aspects of therapy for canine myasthenia gravis include good supportive care (e.g., feeding regimens for dogs with megaesophagus) including appropriate antimicrobial therapy for any secondary complications arising from the disease (e.g., aspiration pneumonia). For review discussing treatment considerations see Khorzad et al. (2011).

Complete spontaneous remission occurring from 1 to 18 months after the diagnosis of acquired myasthenia gravis is possible and has been seen in 47 of 53 dogs with the disease (Shelton & Lindstrom, 2001). Prognosis for canine myasthenic patients is, however, likely variable depending on the form (focal versus generalized), severity (mild, moderate, or severe fulminating generalized myasthenia gravis), and other underlying disease processes (e.g., neoplasia) (Shelton, 2002).

Myositides

Dermatomyositis

Dermatomyositis is an idiopathic, hereditary condition resulting from a suspected immune-mediated inflammation involving skeletal muscle, skin, and vasculature (Evans et al., 2004). Gene transcript profiling and immunobiology in Shetland Sheepdogs with dermatomyositis documented gene transcripts involved in immune function were differentially regulated in affected skin suggesting dermatomyositis may be immune-mediated (Wahl et al., 2008). For Shetland Sheepdogs and Collies, genetic risk factors have also been identified (Evans et al., 2017). Dogs are typically affected at a young age (<6 months of age). The disease is typically described in Collies and Shetland Sheepdogs (Ferguson et al., 2000; Hargis et al., 1984; Haupt et al., 1985a,b). Other breeds affected include the American Cocker Spaniel, Jack Russell Terrier, Samoyed, and Welsh Corgi (Evans et al., 2004; White et al., 1992). Dermatologic lesions can be found around the face (especially the periocular region), digits, footpads, and tail. Characteristic dermatologic findings include alopecia, vesicles, ulceration, erythema, scaling, and crusting. Clinical signs of myositis occur after the development of the skin lesions and include dysphagia, megaesophagus, generalized weakness, stiff gait, and muscle atrophy (Evans et al., 2004). A diagnosis of dermatomyositis is made based on appropriate history, clinical signs, and demonstration of histopathological findings that are consistent with the disease. Treatment of dermatomyositis is aimed at reducing skin exposure to sun and preventing trauma to the skin. Treatment of dermatomyositis also includes the use of oral vitamin E or fatty acid supplements. Pentoxifylline is also recommended to help improve microvascular blood flow (Rees & Boothe, 2003). Prognosis is variable depending on the severity of the disease. Regardless, the disease is progressive and incurable. It is important to educate breeders about the known genetic risk factors and have breeding animals tested for these. Once the genotype of the breeding stock is known, then appropriate "low-risk" matings can be selected. To find out the laboratories offering genetic testing for dermatomyositis see the Orthopedic Foundation for Animals DNA-testing database: https://www.ofa.org/diseases/dna-tested-diseases/all-dna-tests

Masticatory Myositis and Extraocular Myositis

Masticatory myositis (masseter, temporalis, pterygoid muscles) and extraocular myositis are two forms of focal inflammatory myopathies (Carpenter et al., 1989; Evans et al., 2004; Gilmour et al., 1992). Masticatory myositis typically affects young to middle-aged adult dogs and predominantly medium to large breeds (Evans et al., 2004; Gilmour et al., 1992). Masticatory myositis may occur concurrently with other immune-mediated diseases including myasthenia gravis (Clooten et al., 2003). Signs include spasm of the masticatory muscles and difficulty in opening the mouth, pain on palpation of the muscles, muscle swelling, or muscle atrophy. Muscular atrophy is a more common clinical sign (72% of cases) than muscle swelling (14% of cases) and is likely caused by the chronicity of the disease at presentation of most cases (Gilmour et al., 1992). Ocular signs have been documented in 45% of cases and are variable depending on the chronicity of the disease. Ocular manifestations of acute masticatory myositis include exophthalmos and prolapse of the third eyelid caused by swelling of the pterygoid muscle, and possible optic nerve tension/compression causing blindness (Evans et al., 2004; Gilmour et al., 1992; Lewis, 1994; Smith, 1989). Interestingly, unilateral dynamic exophthalmos and lateral strabismus, upon opening the mouth, has been reported in a 5.5-year-old mixed breed dog (Czerwinski et al., 2015). This patient did not have pain upon opening the mouth or when manually retropulsing the eye (Czerwinski et al., 2015). In cases of chronic masticatory myositis, enophthalmos has been reported (Gilmour et al., 1992). Signs are usually, but not invariably, bilateral.

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Clinical signs (± peripheral eosinophilia, ± elevated levels of serum creatinine kinase, ± abnormal electromyograms, ± presence of circulating antibodies for type 2M fibers, and positive muscle immunohistochemistry for antibodies against type 2M fibers) are used to provide a diagnosis of masticatory myositis (Evans et al., 2004). Predominant histopathologic changes identified in affected muscle biopsies include: (1) cellular infiltration with varying degrees of lymphocytes, and/or macrophages, and/or eosinophils; (2) histologic evidence of muscle atrophy, necrosis and fibrosis; (3) presence of fibrosis depending upon the chronicity of the disease; and (4) immune complexes bound to type 2M muscle fibers (Evans et al., 2004; Shelton et al., 1987). Bacteria containing antigenic similarities to type 2M muscle fibers may initiate the immune-mediated myositis (Shelton et al., 1987). Immunosuppressive doses of systemic corticosteroids (prednisone 1–2 mg/kg PO BID) for a minimum of 1 month before tapering are recommended at any stage of the disease. Prognosis is good for dogs treated appropriately with immunosuppressive dosages of corticosteroids, although some dogs may require life-long therapy with these drugs.

The second form of focal inflammatory myositis is extraocular myositis. Extraocular myositis involves only the extraocular muscles and affects predominantly young large-breed dogs. Bilateral exophthalmos is the predominant clinical sign in the acute form of the disease (Allgoewer et al., 2000; Evans et al., 2004). Chronic extraocular myositis can result in restrictive strabismus and is caused by chronic fibrosis of the extraocular muscles (Fig. 37.1.12) (Allgoewer et al., 2000). As opposed to masticatory myositis, circulating antibodies to type 2M muscle fibers are not present (Allgoewer et al., 2000; Evans et al., 2004). Inflammatory infiltrate of affected muscles include lymphocytes and macrophages and fibrosis may be present depending on the chronicity of the disease (Evans et al., 2004). Immunosuppressive corticosteroid therapy is indicated in cases of extraocular myositis (as for masticatory myositis). Adjunctive corrective strabismus surgery may be useful in some cases of chronic extraocular myositis where the disease is in remission (Allgoewer et al., 2000).

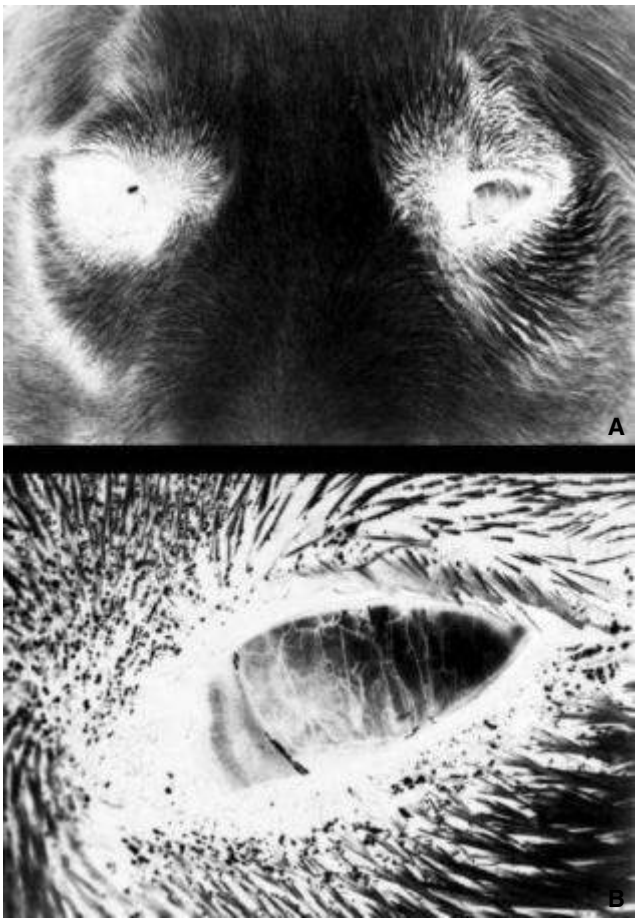


Figure 37.1.12 Extraocular myositis. **A.** Golden Retriever, 1-year-old male, with left ventral strabismus at initial presentation. **B.** Close-up of the left eye, only sclera visible because of severe globe deviation. (*Source*: Reprinted with permission from Allgoewer, I., Blair, M., Basher, T., et al. (2000) Extraocular muscle myositis and restrictive strabismus in 10 dogs. *Veterinary Ophthalmology*, **3**, 21–26.)

Uveodermatologic Syndrome (Vogt–Koyanagi–Harada-like Syndrome)

Vogt–Koyanagi–Harada (VKH) syndrome describes an idiopathic condition in humans characterized by uveitis, poliosis, vitiligo, with or without changes in hearing ability, and meningitis (for review see Herrera & Duchene, 1998; Laus et al., 2004; Morgan, 1989). A similar syndrome is recognized in the dog, except that meningitis is rarely reported (Denerolle et al., 2000), hence the terms uveodermatologic or VKH-like syndrome have been applied. One hypothesis regarding the etiology of the condition is that it results from an immune-mediated destruction of melanocytes (Yamaki et al., 2000). A relatively recent study examining ocular and dermatologic tissue from two dogs with VKH-like syndrome has suggested that skin lesions are the result of a Th1-mediated inflammatory response whereas ocular lesions are the result of a Th2-mediated inflammatory response (Carter et al., 2005). Further, the role of certain dog leukocyte antigen (DLA) class II gene alleles may be important regarding the pathogenesis of VKH-like syndrome in Akitas (Angles et al., 2005).

Originally described in the Akita (Asakura et al., 1977; Carter et al., 2005; Cottrell & Barnett, 1987; Hasegawa, 1985; Massa et al., 2002), several other breeds, including the Australian Shepherd (Kern et al., 1985; Massa et al., 2002; Zarfoss et al., 2018), Beagle (Massa et al., 2002), Brazilian Fila (Laus et al., 2004), Chow Chow (Morgan, 1989), Dachshund (Herrera & Duchene, 1998), Golden and Labrador Retrievers (Kern et al., 1985; Zarfoss et al., 2018), Irish Setter (Bussanich et al., 1982), Old English Sheepdog (Kern et al., 1985), Saint Bernard (Kern et al., 1985; Zarfoss et al., 2018), Samoyed (Bussanich et al., 1982; Zarfoss et al.,

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2018), Shetland Sheepdog (Kern et al., 1985; Campbell et al., 1986), Siberian Husky (Denerolle et al., 2000; Sigle et al., 2006; Zarfoss et al., 2018), Miniature Poodle (Kang et al., 2014), Rat Terrier (Blackwood et al., 2011), and mixed breeds (Zarfoss et al., 2018) have also been diagnosed with this syndrome. Animals are typically affected in young adulthood and ocular lesions usually precede the dermatologic lesions (Zarfoss et al., 2018). Patients are presented for a complaint of sudden blindness or gradual vision loss. Roughly two-thirds of affected dogs are male (Zarfoss et al., 2018). Ocular lesions vary from bilateral anterior uveitis to severe panuveitis. Bullous retinal detachments may occur, and secondary cataracts and glaucoma are common. The iris and retinal pigment epithelium develop progressive depigmentation (Fig. 37.1.13). As the depigmentation progresses, the tapetal fundus becomes hyperreflective, and retinal vascular attenuation as well as optic nerve atrophy may develop. Dermal and hair depigmentation (vitiligo and poliosis, respectively) develop either gradually or rapidly, and they may be ulcerative in nature. The lesions are usually restricted to the face, involving the eyelids, nasal planum, and lips, but the scrotum and footpads are other areas of possible dermal involvement.

At present, there is no specific diagnostic test for uveodermatologic syndrome. The diagnosis is made on the basis of clinical signs and histopathologic examination of skin biopsies (Zarfoss et al., 2018). Routine laboratory tests, including blood work, are typically unremarkable. Skin biopsy specimens have lichenoid dermatitis, histiocytes, and small mononuclear cell as well as giant cell infiltrations. The level of melanin in the epidermis and hair follicles is decreased. Enucleated eyes have a marked panuveal infiltrate of macrophages, plasma cells, and lymphocytes (Lindley et al., 1990).

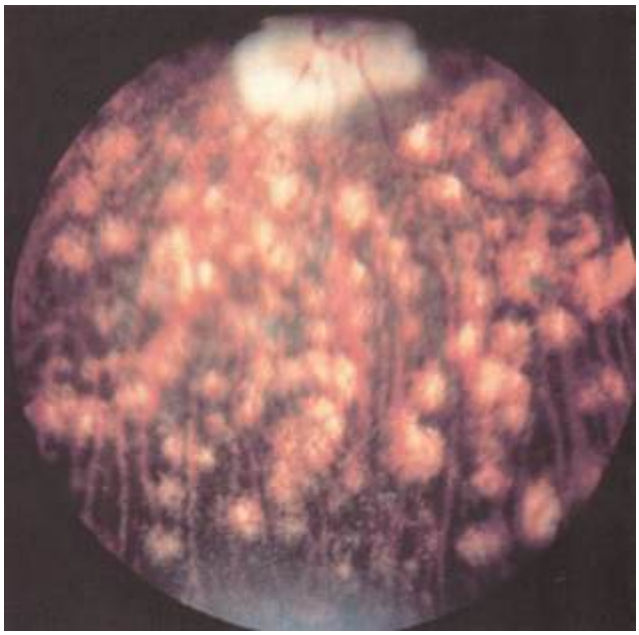


Figure 37.1.13 Multifocal, depigmented lesions in the non-tapetal fundus of a dog with Vogt–Koyanagi–Harada syndrome.

The prognosis, for long-term vision retention and ocular comfort, for dogs affected with uveodermatologic syndrome is guarded, and therapy should be considered to be lifelong. Relapses are frequent if therapy is stopped or tapered. Because of the immunosuppressive therapy, periodic rechecks as well as blood and liver evaluations are necessary. Initial therapy involves immunosuppressive doses of oral prednisone with or without azathioprine or cyclophosphamide. Azathioprine has a lag period of 3–5 weeks before it becomes effective; thus, tapering of corticosteroids should not be attempted before this period (Beale, 1988). Multimodal therapy with various immunosuppressive medications may be helpful in the management of this condition, although evidence for this is lacking. Topical corticosteroids may be used for anterior segment lesions.

Infectious Diseases

Algal Diseases

Protothecosis

Protothecosis is a rare disease in humans and a variety of other animals caused by a colorless, ubiquitous, saprophytic alga of the genus *Prototheca*. *Prototheca* spp. have a wide geographic distribution and are found in soil, water, sewage, and some vegetative matter (Pier et al., 2000). *Prototheca* spp. are thought to be achlorophyllous mutants of green algae. Three species have been recognized, but only *P. wickerhamii* and *P. zophii* are known to be pathogens. *P. zophii* is usually isolated from disseminated cases, whereas *P. wickerhamii* produces a cutaneous syndrome. *Prototheca* spp. appear in tissue as thick-walled, nonbudding, round to ovoid, yeast-like cells (Font & Hook, 1984; Hosaka & Hosaka, 2004; Tyler et al., 1980).

The disease is not considered to be transmissible, and a decrease in cell-mediated immunity may be responsible for the disease itself (Perez et al., 1997; Rakich & Latimer, 1984). Large breeds of dogs are overrepresented, and at least 50% of animals with protothecosis may have ocular involvement (Migaki et al., 1982; Shank et al., 2015). Also, in a review of protothecosis in 17 Australian dogs, females (12/17 cases) and Boxer dogs (7/17 cases) were overrepresented (Stenner et al., 2007). Meanwhile, a study from the USA showed no sex predilection and Labrador Retriever or Labrador Retriever crosses (5/14 cases) and German Shepherds (3/14) accounted for the majority of cases (Shank et al., 2015). A study from North Carolina, USA found that 2 out of 18 cases of infectious uveitis were caused by protothecosis (Massa et al., 2002). Ocular symptoms can be associated with systemic signs (e.g., gastrointestinal disease and weight loss) or may occur as a primary presenting clinical sign (Shank et al., 2015; Stenner et al., 2007). Tissues most commonly affected

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include the eyes, digestive tract, kidney, heart, bone, and brain. Histopathologic lesions may be characterized by minimal inflammation of a mononuclear to pyogranulomatous nature (Migaki et al., 1982). Ocular lesions include a granulomatous, posterior uveitis, or panuveitis that is often bilateral and blinding (Fig. 37.1.14, Fig. 37.1.15, and Fig. 37.1.16) (Shank et al., 2015). Exudative retinal detachments are the usual cause for blindness. Chorioretinal lesions may be either diffuse or focal and need to be differentiated from more common causes of granulomatous uveitis. A definitive diagnosis is usually made on the basis of finding the organism in ocular aspirates, CSF, tissue exudates, excretions (i.e., urine sediment), or biopsy specimens or enucleated eyes (Blogg & Sykes, 1995; Buyukmihci et al., 1975; Carfora et al., 2017; Carlton & Austin, 1973; Cook et al., 1984; Font & Hook, 1984; Lane et al., 2012; Manino et al., 2014; Migaki et al., 1982; Tyler et al., 1980; Pressler et al., 2005; Rizzi et al., 2006; Shank et al., 2015; Stenner et al., 2007; Vince et al., 2014). Because colitis is one of the more common systemic signs, any dog with a history of hemorrhagic diarrhea and ocular lesions should be considered a candidate for protothecosis. The organism can be cultured on Sabouraud's dextrose media and speciated by sugar and alcohol assimilation, electron microscopy, and indirect fluorescent antibodies.

Because of the rarity and sporadic nature of this disease, it is hard to evaluate therapeutic protocols. The most commonly attempted therapy has been amphotericin B, an imidazole antifungal drug, or both. A recent review of systemic protothecosis in 17 Australian dogs revealed combination therapy with amphotericin B and itraconazole was effective in two cases, although one of these dogs should have had treatment for longer duration; ultimately, 16 of 17 dogs died with a median survival time of 4 months (Stenner et al., 2007). Prognosis for dogs with protothecosis is grave for most dogs, although some may survive for years with chronic treatment with antifungal drugs (Shank et al., 2015; Stenner et al., 2007).

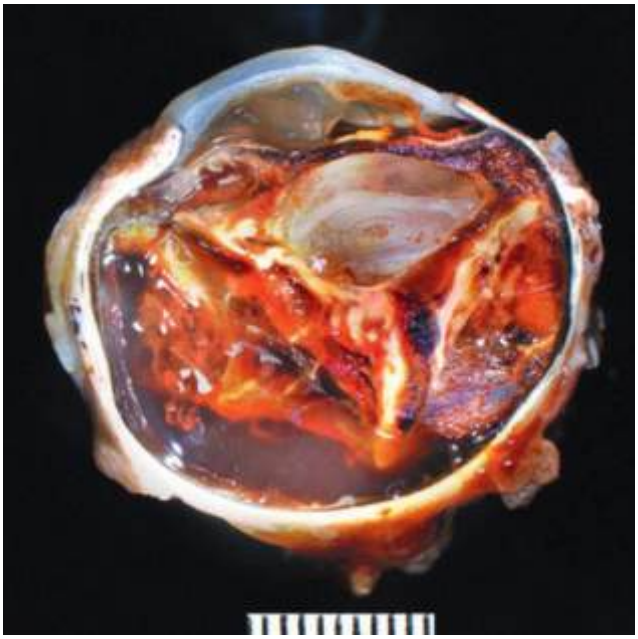


Figure 37.1.14 Gross image of a sectioned globe infected with Prototheca. There is diffuse retinal detachment with associated retinal exudate and hyphema. (*Source*: Reprinted with permission from Shank, A.M., Dubilzieg, R.D., Teixeira, L.B. (2015) Canine ocular protothecosis: a review of 14 cases. *Veterinary Ophthalmology*, **18**, 437–442.)

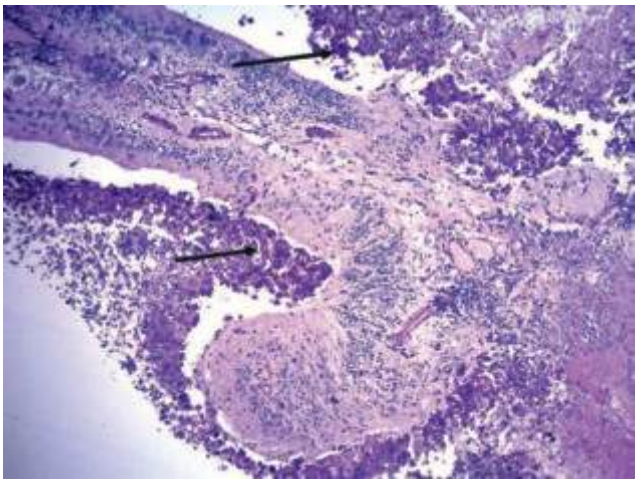


Figure 37.1.15 Periodic acid-Schiff (PAS)-section of detached retinal remnants coated by large numbers of PAS-positive Prototheca organisms within inflammatory exudate (arrows). (*Source*: Reprinted with permission from Shank, A.M., Dubilzieg, R.D., Teixeira, L.B. (2015) Canine ocular protothecosis: a review of 14 cases. *Veterinary Ophthalmology*, **18**, 437–442.)

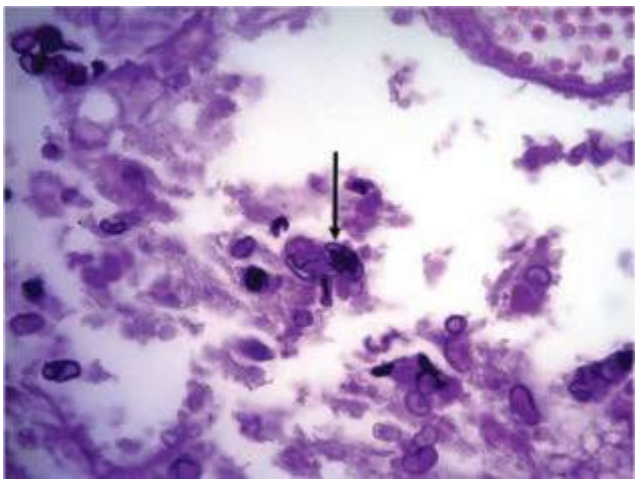


Figure 37.1.16 100-9 oil objective photomicrograph showing internal septations of Prototheca (arrow) (Periodic acid-Schiff). (*Source*: Reprinted with permission from Shank, A.M., Dubilzieg, R.D., Teixeira, L.B. (2015) Canine ocular protothecosis: a review of 14 cases. *Veterinary Ophthalmology*, **18**, 437–442.)

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Bacterial

Any sporadic bacteremia may result in seeding of the uveal tract and create various degrees of inflammation, but only a few bacterial syndromes are relatively consistent regarding involvement of the eye. Sporadically, bacteremia from bacterial infections involving other organ systems (e.g., periodontitis, see Ramsey et al., 1996; pyometra, see Schwink & Barstad, 1986) may result in varying degrees of focal chorioretinal lesions consisting of hemorrhage or exudates (or both), which often go unnoted. Typically, these lesions are associated with the end-arterioles or small vessels in the retina. In small animals, they may develop into a fulminating endophthalmitis, but this appears to be rare (Massa et al., 2002).

Further, bacterial infection of the CNS, causing a meningoencephalitis, can result in ocular signs that are related to the region of the brain involved (e.g., Pritchard et al., 2016). Bacterial meningitis/meningoencephalitis of dogs and cats typically results from local extension or penetration of the CNS by bacterial organisms (Horikawa et al., 2014; Meric, 1988; Seiler et al., 2007) although hematogenous spread sometimes occurs (Pritchard et al., 2016). In large animal species, bacterial meningitis/meningoencephalitis is typically caused by hematogenous spread of bacteria (Dore & Smith, 2017; Fecteau & George, 2004; Stokol et al., 2009; Toth et al., 2012; Viu et al., 2012) although local extension/penetration is possible (Bach et al., 2014; Stokol et al., 2009; Toth et al., 2012).

Bartonellosis

Canine bartonellosis results from infection with the Gram-negative, intracellular bacilli or coccobacilli bacterium, *Bartonella spp*. There are numerous species of *Bartonella*. *Bartonella henselae* (causative agent of cat scratch disease), *B. vinsonii* (*berkhoffi*), *B. clarridgeiae*, and *B. elizbethae* are known or likely to cause naturally occurring disease in dogs (Barnes et al., 2000; Breitschwerdt et al., 1995, 1999, 2004; Michau et al., 2003; Pappalardo et al., 2000) and *B. vinsonii* (*berkhoffii*) appears to be an important species causing clinical disease in dogs (Baneth et al., 1998; Breitschwerdt et al., 2004; Suksawat et al., 2001).

Tick transmission of *Bartonella* spp. is thought to be an important mode of infection in dogs as seroreactivity for *Bartonella* exposure is often found concurrently with other tick-borne infectious agents (Breitschwerdt et al., 1998; Kordick et al., 1999; Mylonakis et al., 2004b).

Clinical presentation is variable (see Breitschwerdt et al. [2004] for complete listing of clinicopathological abnormalities). Nevertheless, canine bartonellosis has been associated with numerous pathological conditions including anterior uveitis, hyphema, retinal detachment caused by systemic hypertension, and choroiditis (Fig. 37.1.17) (Breitschwerdt et al., 2004; Michau et al., 2003), endocarditis (Breitschwerdt et al., 1999), cutaneous vasculitis (Breitschwerdt et al., 2004), granulomatous lymphadenitis (Pappalardo et al., 2000), myocarditis (Breitschwerdt et al., 1995, 1999), and polyarthritis.(Breitschwerdt et al., 2004)



Figure 37.1.17 Bartonellosis in a dog. Fundus photograph demonstrating multifocal, gray, hyporeflective areas in the tapetal fundus. (*Source*: Reprinted with permission from Michau, T.M., Breitschwerdt, E.B., Gilger, B.C., et al. (2003) *Bartonella vinsonii* subspecies *berkhoff* as a possible cause of anterior uveitis and choroiditis in a dog. *Veterinary Ophthalmology*, **6**, 299–304.).

Diagnosis is typically made using serology and polymerase chain reaction (PCR) (Perez et al., 2011). It has been recommended that serology and PCR should be used together to improve the likelihood of diagnosing bartonellosis and other vector-borne diseases (Maggi et al., 2014).

Treatment of canine bartonellosis consists of systemic antimicrobial therapy. Appropriate antimicrobials must be efficacious against *Bartonella* spp. and should achieve high intracellular concentrations (Breitschwerdt et al., 2004). Appropriate antimicrobials include macrolides (e.g., azithromycin), fluoroquinolones (e.g., enrofloxacin), and doxycycline (recommended to be used at high dosages:10 mg/kg q 12 hours for 4–6 weeks) (Breitschwerdt et al., 2004; Kordick et al., 1997; Michau et al., 2003).

Borreliosis (Lyme Disease)

Lyme disease, or borreliosis, is a tickborne spirochetosis produced by *Borrelia burgdorferi*, which comprises several species that affect humans and dogs worldwide. *Borrelia* organisms, like most spirochetes, are small (25 µm long and 0.2 µm in diameter), corkscrew-shaped, motile microaerophilic bacteria of the order Spirochaetales (Fritz & Kjemtrup, 2003). *Borrelia* organisms do not survive free-living in the environment, but rather depend on hosts and are transmitted between vertebrate reservoir hosts and blood-sucking arthropod vectors (Fritz & Kjemtrup, 2003). In particular, *B. burgdorferi* is transmitted primarily by ticks of the *Ixodes* spp., but *Amblyomma americanum* has also been associated with outbreaks (Fritz & Kjemtrup, 2003). The primary reservoirs for *B. burgdorferi* include small rodents and birds (Fritz &

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Kjemtrup, 2003). Tick larvae acquire *B. burgdorferi* when feeding on the mouse and nymph, and adult ticks then transmit the organism to a variety of hosts (Fritz & Kjemtrup, 2003). Successful transmission of the agent relates directly to contact time of the tick on the host, requiring 48–72 hours for a 38%– 92% transmission rate (Appel, 1990; Fritz & Kjemtrup, 2003; Levy et al., 1993). Once inside the host, these organisms rarely spread hematogenously, but rather use their flagella to move through connective tissue (Fritz & Kjemtrup, 2003).

Arthritis and nephritis are the most common manifestations of Lyme borreliosis in dogs (Littman et al., 2018). In the dog, the horse, and humans, however, *B. burgdorferi* may produce ocular lesions. In a retrospective review of 132 seropositive dogs, five had a primary complaint of ocular lesions (Cohen et al., 1990). Ocular lesions were undoubtedly underrepresented, however, because of the study design and the difficulty in making a definitive diagnosis of borreliosis. Documented ocular lesions included conjunctivitis, corneal edema, anterior uveitis, retinal petechia, chorioretinitis, and retinal detachment. In addition to these ocular lesions, dogs with borreliosis may also present with orbital disease (Raya et al., 2010).

Diagnosis is based upon history, compatible clinical signs (usually lameness, joint pain, pyrexia, evidence of proteinuria, and peripheral lymphadenopathy), ruling out other causes of systemic disease in endemic areas, *Borrelia* specific serologic testing, and potentially PCR testing, and based upon response to appropriate antibiotic therapy (Littman et al., 2006).

It is currently recommended that dogs living in endemic regions be screened using C6-based tests (e.g., SNAP4DxPlus [Idexx]) during routine annual examinations (Littman et al., 2018). Should a patient be screened as positive, then follow up to determine if other clinical signs are present, especially proteinuria, is recommended (Littman et al., 2018). It is reasonable to follow up with a quantitative C6 titer prior to and then periodically throughout the course of treatment so as to document evidence of decreased organismal load (Littman et al., 2018). PCR for *B. burgdorferi* can be conducted on skin, synovia, and connective tissue samples (Littman, 2003; Salinas-Melendez et al., 1995).

Vaccination and tick control, both in the environment and on the animal, are important for preventing infection (Fritz & Kjemtrup, 2003; Littman et al., 2005). In particular, Amitraz-impregnated collars may help decrease transmission of *Borrelia spirochetes* in dogs (Elfassy et al., 2001).

Various antimicrobials including tetracyclines, some cephalosporins (e.g., ceftriaxone), and macrolides are useful for treating borreliosis (Littman et al., 2018). Doxycycline is the first-line antimicrobial of choice, although cefovecin (two injections, 14 days apart) has been recommended for dogs that do not tolerate tetracyclines (Littman et al., 2018). It is presently advised that animals with borreliosis be treated for at least 30 days with doxycycline and in cases of chronic borreliosis, experimental evidence indicates that longer-term therapy would be needed (Littman et al., 2018). Topical atropine, and nonsteroidal anti-inflammatory drugs would be indicated for anterior uveal inflammation. For a current consensus statement regarding the diagnosis, treatment, and prevention of Lyme disease in dogs see Littman et al. (2018).

Botulism

Botulism results from the neurotoxin produced by *Clostridium botulinum*. *C. botulinum* is a Gram-positive, spore-forming, saprophytic, anaerobic, rod-shaped bacterium. There are eight subtypes (A – Ca, Cb – G) of *C. botulinum* and they are differentiated from each other based upon the type of neurotoxin they produce. Dogs have been only affected with *C. botulinum* types C and D (Barsanti et al., 1978; Borst et al., 1986; Doutre, 1982, 1983; Fain-Binda et al., 1998; Farrow et al., 1983; Marlow & Smart, 1982; Pommier, 1988; Richmond et al., 1978; Tjalsma, 1990; Wallace & McDowell, 1986).

Clinical signs develop after ingestion of the bacterium in contaminated food including carrion and raw meat (Barsanti et al., 1978; Farrow et al., 1983; Fain-Binda et al., 1998; Marlow & Smart, 1982; Pommier, 1988). After ingestion of contaminated meat, the toxin, botulinal toxin, is absorbed in the gut and prevents the release of acetylcholine at cholinergic synapses. Consequently, clinical signs are suggestive of skeletal muscular weakness and autonomic dysfunction. Signs include symmetrical ascending limb paresis leading to paralysis, depressed or absent tendon reflexes, abnormal motor responses during cranial nerve testing, and excessive salivation. Ocular signs that manifest include mydriasis caused by loss of parasympathetic/sympathetic balance on the iris. Definitive diagnosis is made based on finding the toxin, through use of the neutralization test in mice, in the food, vomitus, feces, or serum. Treatment consists of supportive care and antitoxin administration (to prevent further binding of toxin). Prognosis is variable and is dependent upon the severity of the disease and whether secondary complications (e.g., pneumonia) occur (Barsanti et al., 1978; Marlow & Smart, 1982; Pommier, 1988).

Brucellosis

The etiologic agent of canine brucellosis is *Brucella canis* (for review see Wanke, 2004). *B. canis* is a zoonotic aerobic, Bram-negative coccobacillus. *B. canis* naturally infects dogs by penetrating mucous membranes such as occurs via coitus. Aside from venereal transmission, *Brucella* spp. can be transmitted via fomites such as cages or equipment (Wanke, 2004). Following penetration of mucous membranes, bacteremia ensues. *Brucella* spp. are intracellular bacteria that persist for extended periods in mononuclear phagocytes and produce a prolonged bacteremia (Carmichael, 1976).

B. canis has been isolated from the eye and is recognized as a cause of uveitis or endophthalmitis in both experimental and naturally occurring brucellosis (Gwin et al., 1980a; Gordon et al., 1985; Ledbetter et al., 2009c; Riecke & Rhoades

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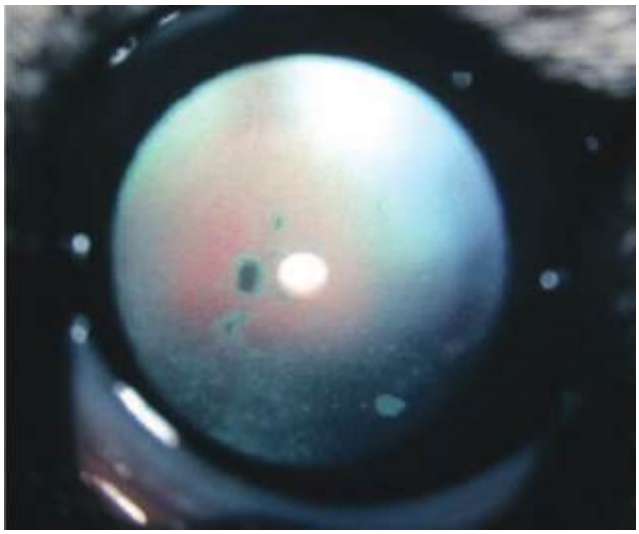


Figure 37.1.18 Right eye of a dog with *Brucella canis* endophthalmitis. Numerous punctate, yellow and white opacities are suspended in the peripheral anterior vitreous. Generalized vitreal haze is present. (*Source*: Reprinted with permission from Ledbetter, E.C., Landry, M.P., Stokio, T., et al. (2009) *Brucella canis* endophthalmitis in 3 dogs: clinical features, diagnosis, and treatment. *Veterinary Ophthalmology*, **12**, 183–191.)

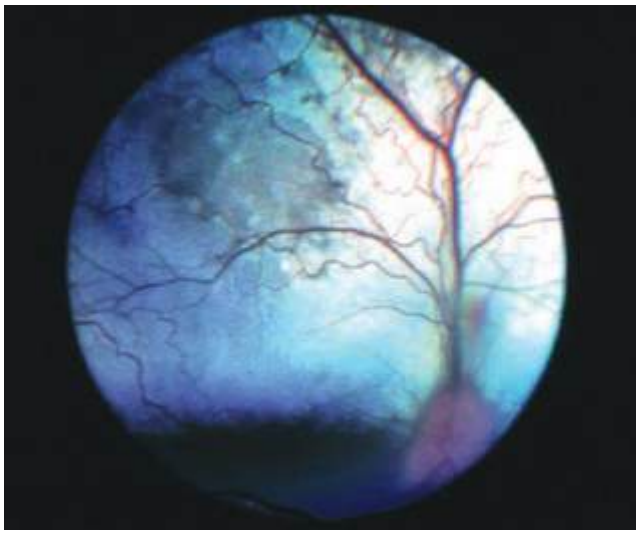


Figure 37.1.19 Fundus photograph of the right eye of a dog with *Brucella canis* endophthalmitis. Irregular zones of hyporeflectivity with indistinct margins are visible in the peripheral tapetal fundus and adjacent to the optic disk. (*Source*: Reprinted with permission from Ledbetter, E.C., Landry, M.P., Stokio, T., et al. (2009) *Brucella canis* endophthalmitis in 3 dogs: clinical features, diagnosis, and treatment. *Veterinary Ophthalmology*, **12**, 183–191.)

1975; Saegusa et al., 1977;Vinayak et al., 2004). Infected dogs are often not systemically ill. Because of the insidious nature of the systemic disease, infected dogs are often presented for ocular disease rather than for systemic signs. A review of records submitted to the Veterinary Medical Data Base at Purdue University revealed that approximately 14% of all brucellosis cases have ocular signs (Vinayak et al., 2004). Some of the more common ocular diagnoses reported included endophthalmic uveitis, chronic uveitis, hyphema, chorioretinitis, and posterior synechia (Fig. 37.1.18 and Fig. 37.1.19) (Vinayak et al., 2004). Ocular inflammation associated with ocular brucellosis is typically chronic and slowly progressive (Vinayak et al., 2004). Brucellosis should be suspected in any dog with a smoldering or recurrent uveitis, and although the syndrome typically occurs in intact animals, neutered animals remain at risk of brucellosis because of the prolonged bacteremia.

Bacteriological isolation of the microorganism is the only means of definitively diagnosing brucellosis (Wanke, 2004). Serological testing for brucellosis is problematic. Nevertheless, serological testing is the most commonly used diagnostic technique for the diagnosis of brucellosis. Many of these antibody tests have not been widely evaluated and may result in false positives and negatives depending upon the stage of the disease (Wanke, 2004). The preferred in-hospital screening procedure is the 2-mercaptoethanol rapid slide agglutination test (ME- RSAT) (D-Tec CB, Synbiotics, San Diego, CA, USA) (Wanke, 2004). False negative results are rare (Wanke, 2004). This test results in a high percentage of false positives so more sensitive tests are used for confirming a diagnosis (Wanke, 2004). A sensitive enzyme-linked immunosorbent assay (ELISA) using cytoplasmic antigens highly specific for canine *Brucella* infection is recommended for confirming a positive diagnosis made by tests such as ME-RSAT (Wanke, 2004). Centesis of the eye for bacterial culture if the inflammation is active should also be considered, as should whole blood cultures. Aqueous titers for *B. canis* are usually equivalent to serum titers (Nicoletti & Chase, 1987). In addition, a PCR test identifying *Brucella* spp. relevant to humans has been developed with potential application in dogs (Nimri, 2003).

Before treatment is recommended, the zoonotic potential and difficulty in clearing the organism from the animal should be carefully explained to the owner. Because *Brucella* can be harboured in reproductive organs, neutering of intact affected animals should be encouraged to decrease any risk of transmission to humans. A variety of systemic antibiotic regimens has been employed, but relapses are common (Vinayak et al., 2004). A treatment regimen of oral tetracycline HCl, 30 mg/kg given twice a day for one month, and intramuscular streptomycin, 20 mg/kg once a day for the first 2 weeks, resulted in an apparent cure rate of 94% (Nicoletti, 1991). Some reports describe the concommitant use of a systemic aminoglycoside (streptomycin), rifamycin (rifampin), fluorquinolone (ciprofloxacin), and tetracycline (doxycycline) classes of antimicrobials, to manage ocular brucellosis successfully (Ledbetter et al., 2009c; Vinayak et al., 2004). The combination of these four classes of

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antimicrobials was chosen because they have been shown to be synergistic in their efficacy against *Brucella* (Mateu-de-Antonio & Martin, 1995). The expense of antibiotics and repeat laboratory testing, risk of human transmission and difficulty in monitoring may result in recommendations to euthanize affected animals by some clinicians. The anterior uveitis is treated with topical corticosteroids and atropine. If the condition is blinding and painful, enucleation is recommended.

Currently, there is no effective vaccine against brucellosis. Furthermore, control of canine brucellosis in a kennel is an arduous task and involves quarantine of the entire kennel, and prompt elimination of infected animals (Wanke, 2004). Because of the complexity of such decision-making and monitoring of both individual animals and populations of dogs in kennels, readers are referred to a current internal medicine or infectious disease reference for further details regarding treatment and prevention of brucellosis.

Leptospirosis

Leptospirosis is a zoonotic disease caused by various species of the Gram-negative, spirochete bacteria belonging to the genus *Leptospira* (Schuller et al., 2015; Sykes et al., 2011). More than 200 serovars have been identified (Levett, 2001). Members of the genus *Leptospira* are motile spirochetal bacteria (Levett, 2001). Predominant serovars responsible for causing clinical disease in dogs include *canicola*, *icterohemorrhagiae*, *grippotyphosa*, *pomona*, and *bratislava* (Birnbaum et al., 1998). It appears, however, that the disease causing serovars, namely *grippotyphosa*, *pomona*, and *bratislava*, are becoming more prevalent (Adin & Cowgill, 2000; Birnbaum et al., 1998; Brown et al., 1996; Ward et al., 2004a). The bacterium is maintained in host-adapted species that act as reservoir hosts and is shed in the urine. Contamination of the environment with the bacterium is thought to be important in the development of outbreaks. It has been shown in one study, for example, that dogs living in periurban areas (increased contact with wildlife) are at higher risk for leptospirosis (Ward et al., 2004b). Direct transmission can occur through contact with infected urine, bites, ingestion of infected material, and contact with contaminated water.

After infection, the organism multiplies and bacteremia ensues. Leptospires sequester in various organs, particularly kidneys, liver, spleen, CNS, and the eyes. Involvement of a particular organ results in expected clinical signs including acute renal or hepatic failure/dysfunction. Nevertheless, in the acute phase of infection, conjunctivitis, scleritis, anterior uveitis or panuveitis, retinal detachment and retinal hemorrhage may present in concert with other systemic signs (Bergstrom et al., 2017; Dziezyc & Stiles, 2000; Thirunavukkarasu et al., 1995; Townsend et al., 2006; Violette & Ledbetter, 2018). Additional reports of naturally occurring leptospirosis have documented nonspecific ocular signs including mucopurulent oculonasal discharge or scleral injection in 42%–45% of cases (Adin & Cowgill, 2000; Birnbaum et al., 1998).

Diagnosis of leptospirosis is dependent on consistent clinical signs and detection of antibodies using the microscopic agglutination test (MAT) or ELISA and/or evidence of the presence of the organism in urine using darkfield microscopy, or by visualizing the organism in histological preparations, directly culturing the organism or by detecting organismal DNA using PCR (Bolin 1996; Goldstein 2010). Overall, the MAT is the preferred diagnostic testing method, but should be used in conjunction with PCR (of urine and blood) in those patients with high postvaccinal titres (Schuller et al., 2015).

Treatment of leptospirosis is directed at: (1) eliminating the bacteremia by initially using penicillins, specifically ampicillin and amoxicillin (Prescott, 1991; Schuller et al., 2015); and (2) eliminating the carrier state by administering tetracyclines, especially doxycycline (Birnbaum et al., 1998; Brown et al., 1996; Kalin et al., 1999; Prescott, 1991; Schuller et al., 2015). Given the zoonotic potential and potential fatal nature of leptospirosis, antibacterial therapy should be commenced as soon as the disease is suspected and the samples have been drawn (if using PCR) to eliminate the bacteremia and the risk of live organisms in the urine that pose a zoonotic risk to humans (Sykes et al., 2011; Schuller et al., 2015). Prognosis for complete recovery is variable depending on the severity of renal injury, pulmonary hemorrhage, hepatopathy, and development of complications such as disseminated intravascular coagulation (Adin & Cowgill, 2000; irnbaum et al., 1998; Schuller et al., 2015; Sykes et al., 2011). Given that leptospirosis is zoonotic, it is important to use necessary precautions when handling infected animals and contaminated material (e.g., urine-soaked blankets).

Tetanus

Tetanus is caused by the neurotoxin produced by the bacterium *Clostridium tetani*. *C. tetani* is a motile, Gram-positive, nonencapsulated, anaerobic, rod-shaped, spore-forming bacterium (for review see Acke et al., 2004; Merrett, 1993). Dogs and cats are naturally resistant when compared with other species such as humans and horses. Clinical signs of tetanus develop when spores of *C. tetani* enter the body through skin wounds or during surgical procedures (Bagley et al., 1994). Spores become vegetative and a toxin, tetanospasmin, retrogradely migrates along axons of motor nerves to the CNS. However, it should be noted that tetanospasmin, the principle neurotoxin, is only one of three toxins produced by the bacterium (Acke et al., 2004). The toxin then prevents inhibitory neurotransmission to motor neurons thereby resulting in the classical signs associated with tetanus. Clinical effects on the autonomic nervous system have also been described (Panciera et al., 1988).

Clinical signs may be localized or generalized. In the localized form, increases in stiffness of specific muscle groups or

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a given limb may be noted. The localized form is described more commonly in cats compared with dogs. In the generalized form, affected dogs will initially have a characteristic smiling/sneering appearance (risus sardonicus) and a stiff gait that may progress to megaesophagus with or without hiatal hernia, and complete rigid paralysis with the appearance of periodic generalized convulsive-type behaviour (Acke et al., 2004). Respiratory compromise may result in death. Ocular signs seen in a tetanic animal include protrusion of the third eyelid and enophthalmus resulting from globe retraction caused by the hypertonicity of the extraocular muscles (Acke et al., 2004).

Diagnosis is made based upon consistent physical examination findings (presence of a wound) and clinical signs. However, culture of the organism from the wound and/or measuring circulating serum antibodies against tetanospasmin may help to confirm the diagnosis. Treatment is aimed at administering tetanus antitoxin and penicillin-G and/or metronidazole to prevent binding of any unbound toxin and to destroy any remaining bacteria, respectively. Tetanus antitoxin therapy should be performed only after intradermal testing with this antitoxin as there is a strong likelihood of anaphylaxis after systemic administration (Acke et al., 2004). Supportive care and wound management are also indicated. Prognosis is variable depending upon the severity of the clinical signs and secondary complications (e.g., aspiration pneumonia).

Mycotic

Acremoniosis

Acremoniosis is a systemic mycotic infection caused by *Acremonium* spp. Acremoniosis has been reported in an adult dog (Simpson et al., 1993). Systemic signs in this dog were similar to those seen in cases of disseminated aspergillosis. Clinical signs include various general malaise, weight loss and anorexia, lymphomegaly, neurological signs (depending on the neuroanatomic focus of the principle pathologic process), and various ocular signs. Ophthalmologic signs include chemosis, corneal edema, anterior uveitis, focal chorioretinitis, and bullous retinal detachments (Simpson et al., 1993).

Diagnosis is made based on detection of the organism on histopathological examination of tissues and by culturing the organism from tissues and urine (Simpson et al., 1993). Postmortem examination of a dog with acremoniosis revealed pyogranulomatous and necrotizing myocarditis, pericarditis, hepatitis, and nephritis (Simpson et al., 1993). Granulomatous lymphadenitis, endometritis, meningoencephalitis, and retinitis have also been noted (Simpson et al., 1993). Treatment is similar to that for systemic aspergillosis, and, as such, supportive therapy combined with systemic itraconazole administration is utilized (Simpson et al., 1993). Because of the relative paucity of cases of acremoniosis, prognosis is difficult to determine.

Aspergillosis

Aspergillosis is caused by the filamentous fungus *Aspergillus* spp. *Aspergillus* spp. are considered ubiquitous in the environment, and animals are infected opportunistically after inhaling *Aspergillus* spores (Gelatt et al., 1991). Infection with *Aspergillus* spp. is either localized or disseminated. Localized aspergillosis involves colonization of the respiratory sinuses and nasal mucosa. Secondary CNS involvement may result from erosion of the cribriform plate. Disseminated infection occurs typically in the immunocompromised patient and involves a whole host of organ systems, although history of respiratory involvement is not typically documented (Lehmann, 1985).

Disseminated aspergillosis occurs frequently in German Shepherd dogs (Day et al., 1986; Gelatt et al., 1991; Kabay et al., 1985; Neer 1988). It is likely that this breed is predisposed because of an inherited impairment in their immune system (Day & Penhale 1988; Day et al., 1985, 1986; Griot-Wenk et al., 1999; Whitbread et al., 1984). In general, the most common clinical signs relate to multiple organ system involvement, and include general malaise, pyrexia, anorexia and weight loss, and bone pain. Other signs are attributed to involvement of the liver, kidneys, CNS, and eyes. Disseminated aspergillosis has been reported to cause panuveitis, lenticular rupture, chorioretinitis, exudative retinal detachments, and endophthalmitis (Bergstrom et al., 2017; Gelatt et al., 1991; Render et al., 1982; Wooff et al., 2018; Watt et al., 1995). Diagnosis is made based on identification and/or culture of urine sediment, serum, synovial fluid, vitreous, lymph node, or intervertebral disc centesis specimens (Gelatt et al., 1991; Render et al., 1982; Watt et al., 1995). Evaluation of antigen-based ELISA for *Aspergillus* galactomannan (a component of *Aspergillus* cell wall) has been valuable in the diagnosis of aspergillosis in dogs (Billen et al., 2009; Cray et al., 2009; Garcia et al., 2001, 2012; Taylor et al., 2015). Treatment is directed at eliminating the organism by administering amphotericin B, itraconazole, or fluconazole intravenously. Long-term therapy with oral azoles may be required. Regardless, the prognosis for recovery from disseminated aspergillosis is poor.

Blastomycosis

Blastomycosis is a systemic mycotic infection caused by the dimorphic fungus, *Blastomyces dermatitidis*. *B. dermatitidis* is a thick-walled yeast that reproduces by budding in infected tissues (i.e., yeast phase), and in nature, is most likely a soil saprophyte which produces infective spores called conidia (i.e., mycelial phase). The tissue budding yeast form is 8–20 µm in size, with a thick, double-contoured wall. *B. dermatitidis* is most commonly found in endemic regions in North America (Castillo et al., 2016) and is also found in Israel, Africa, India, and Central and South America (Castillo et al., 2016). In Canada, blastomycosis is endemic within southern Saskatchewan, Manitoba, Ontario, and Quebec (Davies et al., 2013; Litvinov et al., 2013; Nemeth et al., 2016). Within the United States, blastomycosis is most

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commonly observed along the Mississippi, Missouri, and Ohio River valleys, and the midwestern and southern United States (Castillo et al., 2016; Kerl, 2003).

Young, large breed sporting dogs and hounds living near water are at increased risk of blastomycosis, presumably because of outdoor exposure (Render et al., 1982; Rudmann et al., 1992; Wolf, 1989). The group at highest risk is usually reported to be 2- to 4-year-old intact male dogs, but during an outbreak in Wisconsin, blastomycosis occurred almost exclusively in females (Czuprynski et al., 1988; Legendre et al., 1981; Rudmann et al., 1992). Breeds including Bluetick Coonhounds, Treeing-Walker Coonhounds, Pointers, and Weimaraners have been reported to have the highest risk of *B. dermatitidis* infection (Rudmann et al., 1992).

Blastomycosis is not a contagious or zoonotic disease but has been transmitted to a person through an accidental needle-stick with a syringe and needle used for pulmonary aspirate from a dog with *B. dermatitidis* infection (Ramsey, 1994). Typically, blastomycosis develops after the inhalation of organismal spores. After inhalation of the infective conidia by the host, these infective spores become phagocytized by alveolar macrophages and transform from the mycelial phase to the yeast phase. The common *B. dermatitidis*-infected organs in dogs are the skin, eyes, bones, lymph nodes, subcutaneous tissues, prostate, brain, and testicles (Arceneaux et al., 1998; Bloom et al., 1996; Hendrix et al., 2004; Legendre et al., 1981, 1996).

Clinical signs in dogs with blastomycosis vary significantly because of the multisystemic nature of the disease. Nonspecific signs of anorexia, lethargy, depression, fever, weight loss, and cachexia are common. Pulmonary signs can be found in 43%–88% of dogs affected with blastomycosis, ranging from mild respiratory distress during physical exertion to severe dyspnea at rest (Arceneaux et al., 1998; Legendre et al., 1981). Nearly 60% of dogs with blastomycosis develop lymphadenopathy (Arceneaux et al., 1998), whereas cutaneous lesions are reported in approximately 30% of affected dogs (Arceneaux et al., 1998; Legendre et al., 1981). Ocular involvement has been reported in as many as 48% of dogs with blastomycosis (Bloom et al., 1996). In a study from Indiana, USA, canine patients with panuveitis from multiple causes were examined and 20% of them were because of blastomycosis (Bergstrom et al., 2017). Ocular signs have been reported as the sole indicator of *B. dermatitidis* infection in up to 3% of diagnosed cases (Bloom et al., 1996). Approximately 50% of the ocular lesions caused by *B. dermatitidis* are bilateral (Bloom et al., 1996). For prognostic purposes, the ocular lesions have been divided into anterior segment only (5%–30%), anterior and posterior segment lesions (endophthalmitis, 27%–72%), and posterior segment (22%–43%) (Bloom et al., 1996; Buyukmihci, 1982; Legendre et al., 1981). Buyukmihci and Moore (1987) postulate that the initial lesion is a pyogranulomatous choroiditis arising as a result of hematogenous spread of *B. dermatitidis* to the choroid, thereby producing a pyogranulomatous lesion that may not be initially visible. During this initial phase, the first visible ocular signs are often those of anterior uveal inflammation including conjunctival hyperemia, miosis, synechiae, and flare. Progression of the choroiditis produces an extension into the subretinal space and focal subretinal granulomas, which in turn may progress to exudative retinal detachments (Buyukmihci & Moore, 1987). Severe anterior uveitis, accompanied by secondary glaucoma, is indicative of endophthalmitis even if the posterior segment cannot be visualized. Although anterior segment inflammation may be severe, *B. dermatitidis* is infrequently found in the anterior uvea, and this anterior uveal inflammation has been attributed to a diffusible substance from the posterior segment (Buyukmihci & Moore, 1987). Additional ocular lesions of canine blastomycosis are optic neuritis, retinal and vitreal hemorrhages, and orbital cellulitis (Bloom et al., 1996).

Granulomatous chorioretinitis occurring concurrently with systemic signs such as weight loss, cough, fever, skin lesions, or lameness in an endemic area is suggestive of *B. dermatitidis* infection. Thoracic radiographic assessment is often very useful in the diagnostic evaluation of a dog with suspected blastomycosis. In particular, 70% of canine cases show an interstitial pulmonary pattern on thoracic radiographs including classical nodular (41% of cases), diffuse (24%), or broncho- (5%) interstitial patterns (Walker, 1981). Definitive diagnosis of this disease is made by identification of the *B. dermatitidis* organism via cytology, histopathology, or fungal culture. Blastomycosis is typically easy to diagnose given the large numbers of characteristic yeast found within infected tissues, particularly lesions involving the skin, lymph nodes, and eyes (Arceneaux et al., 1998; Kerl, 2003). The yeast organisms lack a capsule, thereby aiding in differentiation of *B. dermatitidis* from *Cryptococcus*. Examination of tissue aspirates (including ocular centesis) usually shows the causative organism. Specifically, skin lesions yield a diagnostic sample (i.e., *B. dermatitidis* organisms) 85% of the time, vitreal aspirates yield organisms from nearly all affected eyes, whereas lymph node aspirates yield organisms approximately 67% of the time (Arceneaux et al., 1998). If the yeast cannot be seen after repeated tissue imprints or aspirates, or histologically in biopsy specimens, serology and/or identification of *Blastomyces* spp. DNA using PCR should be used (Bialek et al., 2003). An agar-gel immunodiffusion (AGID) test is the most commonly used serologic test for blastomycosis. This test detects antibodies directed against the *B. dermatitidis* organism and has a sensitivity and specificity of approximately 67% and 100%, respectively (Klein et al., 2000). When used in combination, a positive AGID test for the fungal organism and compatible thoracic radiographs are indicative of blastomycosis. It has been found that a radioimmunoassay for anti-WI-1 antibodies is superior to the AGID test. The sensitivity of the radioimmunoassay test is 92% whereas the specificity of this test is 100% (Klein et al., 2000).

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Therapy for systemic mycoses, no matter what etiology, is a financial dilemma. Therapy becomes prohibitively expensive for many owners because most of the affected dogs are large breeds, therapy may be very protracted, and imidazole medications are very costly. Currently, itraconazole is considered the drug of choice for the treatment of blastomycosis (Legendre et al., 1996). Blastomycosis can be clinically cured in approximately up to 80% of appropriately treated dogs (Legendre et al., 1996). However, the degree of pulmonary involvement is the main determinant of successful response to therapy for blastomycosis (Legendre et al., 1996). Relapse occurs in approximately 20% of treated dogs. Recurrence may occur from months to years after the cessation of therapy (Legendre et al., 1996). Relapses should be treated as new *Blastomyces* infections.

Many affected dogs are working hunting dogs, and the visual prognosis is often critical for the owner's decision as to whether or not to attempt treatment. Therapeutic success rates for ocular blastomycosis have been reported to be 42% with oral itraconazole, 5 mg/kg twice a day for 60 days (Brooks et al., 1991), and 40% with a protocol of amphotericin B, 0.5–1.0 mg/kg intravenously every 48 hours for a cumulative dose of 4–6 mg/kg, and ketoconazole, 10–20 mg/kg every 24 hours for 30–90 days (Bloom et al., 1996). The majority of dogs with anterior segment disease (65%) have the affected eye enucleated (Brooks et al., 1991). While eyes of dogs with posterior segment disease have an increased likelihood (76%) of recovering (Brooks et al., 1991). In instances where there is CNS involvement, including the presence of optic neuritis, prognosis is guarded to grave (Brooks et al., 1991; Legendre et al., 1996). The use of fluconazole has been successfully used to treat a dog with CNS involvement, however (Arceneaux et al., 1998). A recent retrospective study evaluating the visual outcome of dogs with ocular blastomycosis showed that the use of systemic corticosteroids in combination with systemic antifungals did not appear to affect survival rate adversely and may have improved the preservation of vision in the majority of affected dogs (Finn et al., 2007). In particular, 14/19 affected eyes (all eyes with mild to moderate lesions and 5/10 severely affected eyes) retained vision at their final reexamination (Finn et al., 2007). Treatment of anterior segment lesions is nonspecific involving the use of topical atropine, and prostaglandin inhibitors (Bloom et al., 1996; Brooks et al., 1991). Carbonic anhydrase inhibitors may be used to treat elevated intraocular pressures, but such eyes are candidates for enucleation given that eyes with secondary glaucoma have been reportedly unresponsive to treatment and had endophthalmitis at histopathologic examination (Bloom et al., 1996). Enucleation is also indicated for blind, painful eyes.

Coccidiodomycosis (Valley Fever; San Joaquin Valley Fever)

Coccidiodomycosis is caused by two species of the dimorphic fungus *Coccidioides* spp. (Fisher et al., 2002). *Coccidioides immitis* inhabits California, especially along the Californian central valley, whereas *C. possadassi* inhabits other regions of the southwestern United States, northern Mexico, and central and South America (Gabe et al., 2017; Grayzel et al., 2017). Clinical manifestation is similar between species of *Coccidioides* spp. (Gabe et al., 2017; Grayzel et al., 2017). *Coccidioides* spp. produce mycelia during seasonal rainfall. As the soil dries, arthrospores develop and become airborne under dry and windy conditions. The major route of *Coccidioides* spp. infection is via inhalation (Wolf, 1989). Cutaneous entry of the organism through a penetrating skin wound is possible but occurs rarely (Wolf, 1989).

Coccidiodomycosis may produce a wide variety of clinical diseases, depending on the immunocompetence of the host, ranging from a mild, subclinical respiratory disease to a severe multisystemic disseminated disease. *Coccidioides* spp. may produce disease in a wide variety of domestic and wild animals as well as in humans. In the lung, the arthrospores transform into their parasitic form, spherules, which gradually enlarge to 200 µm in diameter. These spherules contain endospores that, when released after rupture of the spherule at maturity, form new endosporulating spherules. The incubation period from inhalation to the appearance of respiratory signs is 1–3 weeks in experimental animals (Hugenholtz et al., 1958). If the infection spreads beyond the respiratory system, the disease is considered to be disseminated. Dissemination may occur in up to 42% of dogs with naturally occurring coccidioidomycosis (Johnson et al., 2003). Preferred sites for dissemination are the bones, joints, CNS, pericardium, lymph nodes, skin, and eyes (Angell et al., 1987; Johnson et al., 2003; Millman et al., 1979; Reed, 1956; Shubitz et al., 2001; Simoes et al., 2016). Consequently, clinical signs are variable and include pyrexia, lymphadenomegaly, coughing, neck pain, chronic lameness, swollen joints, back pain, muscle wasting, various neurologic signs, and draining or nondraining skin nodules, and signs of uveitis (Bentley et al., 2015; Johnson et al., 2003; Simoes et al., 2016). There does not appear to be a gender predilection for the development of coccidioidomycosis and dogs with coccidioidomycosis can be of any age or breed/physical stature (Angell et al., 1987; Bentley et al., 2015; Grayzel et al., 2017; Johnson et al., 2003; Simoes et al., 2016).

The exact incidence of ocular lesions in dogs with coccidioidomycosis is unknown. A small study retrospectively evaluating the medical records of 24 dogs with coccidioidomycosis showed only one dog as having uveitis and this dog happened to be coinfected with *Ehrlichia canis* (Johnson et al., 2003). In another study of 35 canine patients, 42% of patients with ocular lesions had no systemic clinical signs, and 80% of the ocular lesions were unilateral (Angell et al., 1987). This study only looked at eyes of dogs that were presented for an ocular complaint, and thus this study has a bias toward the severe end of the clinical spectrum for ocular lesions. Clinical ocular manifestations were most frequent in the

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anterior segment, but they were also difficult to classify because of use of the redundant terms of iritis, uveitis, and chorioretinitis. Ocular signs included keratitis in 49%, anterior uveitis in 43%, and glaucoma in 31% of cases (Angell et al., 1987). Many of these cases may have had posterior segment lesions that were not noted because of difficulty in visualizing the posterior segment. The latter is confirmed at histopathologic examination, which was performed on 54% of eyes, among which the posterior segment was involved in all eyes. The typical histopathologic change in ocular coccidioidomycosis is granulomatous inflammation in the filtration angle, ciliary body, choroid, and retina (Angell et al., 1987). Hemorrhage in the anterior chamber or vitreous is present in all histopathologic ocular specimens (Angell et al., 1987; Cello, 1960; Shively & Whiteman, 1970).

A granulomatous uveitis, either unilateral or bilateral, in a dog from an endemic area with corresponding clinical signs including cough, lethargy, depression, anorexia, weight loss, fever, lameness, and cervical or head pain, is suggestive of coccidioidomycosis. However, it should be noted that nearly half of the patients with ocular lesions do not have overt systemic signs (Angell et al., 1987). Diagnosis of coccidioidomycosis requires the visualization of the organism or determining the presence of antibodies specific for the organism, with consistent travel history and clinical signs (Grayzel et al., 2017). Aspirates of lymph nodes, transtracheal or bronchoalveolar lavage fluid, or vitreous may be useful for identifying the presence of the organism, keeping in mind that false negatives are common. Culturing *Coccidioides* spp. is discouraged because of the highly contagious nature of the mycelial phase. Serologic testing, consisting of precipitin and complement fixation tests, are available if the organism is not found in tissue specimens. Early in the course of coccidioidomycosis (2–5 weeks), a positive precipitin test is indicative of elevated IgM levels. Subsequently, a positive complement fixation test reflects the presence of IgG antibodies to *Coccidioides* spp. The precipitin test becomes negative after 4–5 weeks of infection, thus many affected dogs with ocular lesions will have a negative test result. The complement fixation test remains elevated for months (Johnson et al., 2003).

Treatment of coccidioidomycosis is similar to that for other systemic mycoses (i.e., extended azole therapy or amphotericin B, or these drugs used in combination or in succession) (Wolf, 1989). Response to treatment may also be monitored by evaluating radiographs of the lesions in the thorax and bone (if involved). Relapses are common (Angell et al., 1987).

Cryptococcosis

Cryptococcosis is caused by *Cryptococcus neoformans* or *C. gattii* (previously *C. neoformans* var. *gattii*) (Wolf, 1989). *C. neoformans* is associated with high nitrogen containing environments such as avian feces or soil enriched with avian feces (O'Brien et al., 2004). Hence, birds such as pigeons are considered to be significant vectors of *Cryptococcus* spp. *C. gattii*, however, is associated with eucalyptus and fir trees in Australia and Canada, respectively (O'Brien et al., 2004). More recently, however, *C. gattii* has been found to cause disease in dogs in Europe, South America, and the northwest United States (Headley et al., 2015; Gerontiti et al., 2017; Trivedi et al., 2011). In infected tissue, and often when cultured using standard laboratory conditions, *C. neoformans* is a variably sized yeast-like organism (3.5–7 μm) which typically contains a thick capsule.

Cryptococcosis has been described in a variety of mammals as well as in humans. Importantly, cryptococcosis is not contagious. Rather, inhalation of the yeast-like organism is the likely mode of infection (Wolf, 1989). Dissemination occurs through hematological spread. The predominant signs of cryptococcosis vary with the affected species, immune status of the patient, and perhaps, the strain of organism (Faggi et al., 1993).

Canine cryptococcosis is uncommonly reported in comparison to other systemic mycotic infections such as blastomycosis, and in comparison to feline cryptococcosis (Berthelin et al., 1994a; Bistner et al., 1971; Faggi et al., 1993; Gelatt et al., 1973; Kurtz & Finco, 1970; Malik et al., 1995; O'Brien et al., 2004; Rubin & Craig, 1965; Tiches et al., 1998). As with other systemic mycoses, dogs with medium to large physical stature are typically affected including American Cocker Spaniels, Doberman Pinschers, Great Danes, and Labrador Retrievers. Young adult dogs are generally affected with cryptococcosis. Clinical manifestations of canine cryptococcosis pertain mainly to CNS involvement (Berthelin et al., 1994a; O'Brien et al., 2004), and ocular, upper respiratory, or cutaneous lesions (Malik et al., 1995; O'Brien et al., 2004). Common, nonspecific clinical signs of canine cryptococcosis include anorexia, lethargy, and depression. Fever is not a common clinical finding in dogs with *C. neoformans* infection. Twenty to 40% of dogs with cryptococcosis have ocular and/or periorbital involvement (Malik et al., 1995). The most common ocular lesion of cryptococcosis is granulomatous to pyogranulomatous chorioretinitis with or without exudative retinal detachment. Direct and/or indirect ophthalmoscopic examination may also reveal retinal hemorrhage (Fig. 37.1.20) or chorioretinal scarring. Although less common than posterior segment disease, mild to moderate anterior uveitis may occur as well. The degree of cellular reaction inside the eye varies from a mild chorioretinitis to panophthalmitis. A leptomeningitis of the optic nerves is common and manifests as optic neuritis. *C. albidus* systemic infection has been documented in a Doberman Pinscher with signs of right scleral injection and blindness after surgical removal of masses from the left forelimb and acute mastitis (Labrecque et al., 2005); histopathology revealed granulomatous lesions containing numerous yeast-like cells in the eyes and brain, among other regions (Labrecque et al., 2005).

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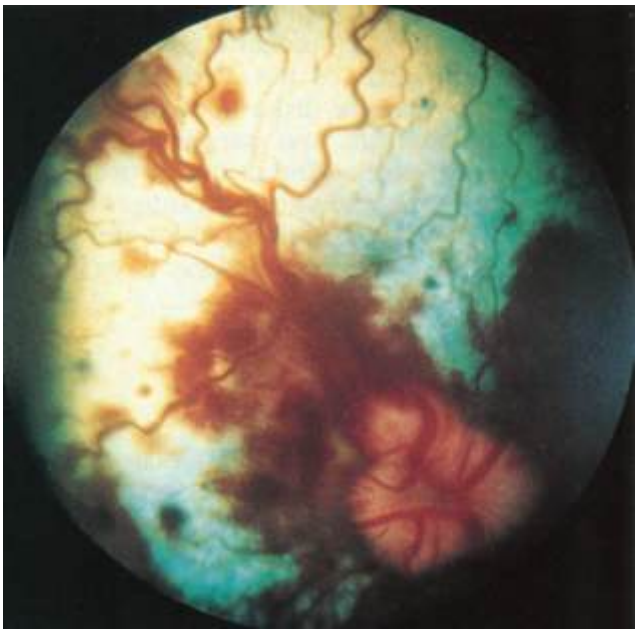


Figure 37.1.20 Labrador Retriever with tetraparesis and *Cryptococcus* in the cerebrospinal fluid. Optic neuritis and multiple retinal hemorrhages are present, and a granuloma adjacent to the disc is obscured by a hemorrhage. Vasculitis is evident, with multiple hemorrhages, perivascular infiltrate around smaller vessels, and marked hyperemia.

Identification of the causative agent permits confirmation of the diagnosis of cryptococcosis. Ocular lesions are suggestive of mycotic chorioretinitis, and vitreous or subretinal fluid centesis, or CSF tap (in CNS-infected cases) will usually reveal the causative organism on cytological assessment (Berthelin et al., 1994b; Render et al., 1982). Histopathological evaluation of infected tissues is also helpful for definitive diagnosis. The thin wall and large capsule of *Cryptococcus* allow ready differentiation from *Blastomyces*. Cryptococcal organisms can also be readily cultured on Sabouraud's agar from infected tissue, CSF, exudate, blood, urine, and joint fluid (Malik et al., 1995). However, positive culture of specimens taken from the nasal cavity may occur in animals without clinical disease (Malik et al., 1997). Alternatively, the latex agglutination test for *C. neoformans* is an antigen test against a cryptococcal capsular antigen (Malik et al., 1996b). This antigen test can be used to make the diagnosis of cryptococcosis using CSF, urine, or serum, as well as to follow the animal's response to therapy. Since most *C. neoformans*-infected animals fail to mount a humoral immune response, antibody titers are not useful diagnostically.

Treatment of cryptococcosis involves subcutaneous, diluted amphotericin B in combination with oral flucytosine (especially helpful for treating CNS-infected cases) or azole therapy (Malik et al., 1995, 1996b,c). Fluconazole is recommended for cases of ocular or CNS cryptococcosus (Berthelin et al., 1994b; Malik et al., 1995). Therapy should be monitored both by clinical improvement and by monitoring *C. neoformans* antigen titers. Therapy should be continued until titers have dropped to 1 : 10 or less (Jacobs et al., 1997). Ideally, treatment should be continued until the titer is negative or for an additional 2 or more months after the clinical signs have resolved (Berthelin et al., 1994b; Jacobs et al., 1997). The prognosis is guarded in most affected dogs because of increased likelihood of CNS involvement.

Dermatophytosis

Dermatophytosis, or cutaneous infections with fungi, are usually caused by *Microsporum canis*, *M. gypseum*, *Trichophyton mentagrophytes*, or some combination of these in dogs (for review see Moriello, 2004). Young animals are more frequently affected by dermatophytosis. Because dermatophytes are a cause of facial dermatitis, they frequently involve the eyelids, typically producing a dry, crusty, periocular alopecia. The condition is diagnosed on the basis of direct microscopic examination of skin scrapings from lesions, Wood's light examination, or more frequently, direct fungal culturing with dermatophyte test medium. Therapy, if necessary, is oral griseofulvin for 4–6 weeks and environmental decontamination. When treating facial dermatophytes with one of a variety of antifungal shampoos, it is important to avoid getting these cleansing agents in the animal's eyes.

Histoplasmosis

Histoplasmosis is caused by a dimorphic fungus, *Histoplasma capsulatum*, which exists in various river bottoms as a mycelial-phase, soil saprophyte. *H. capsulatum* grows best in nitrogen-rich organic matter, such as bat and bird feces (Wolf, 1989). Histoplasmosis in humans has been described worldwide (Bahr et al., 2015). Although quite widespread in North and South America, endemic areas are in the Ohio, Missouri, and Mississippi river valleys (Howard, 1984). The life cycle of *H. capsulatum* is similar to that of *Blastomyces* and *Coccidioides* spp., with a mycelial phase in the soil that produces conidia, which once in the pulmonary system convert to a budding yeast phase (Wolf, 1989). *Histoplasma* organisms can then be disseminated via hematogenous or lymphatic spread.

Histoplasmosis has been observed commonly in dogs and cats (Clinkenbeard et al., 1988; Gwin et al., 1980; Kerl, 2003; Rowley et al., 1954; Sano & Miyaji, 2003). Experimentally, ocular lesions have been identified in 66% of dogs and occurred preferentially in the anterior choroid, iris, ciliary body, and sclera (Salfelder et al., 1965). Young hunting breeds of dogs may have an increased risk (Kerl, 2003). Histoplasmosis typically originates in the lungs and potentially the gastrointestinal tract, then the organism disseminates via monocytes if the exposure is overwhelming or the host is immunocompromised.

Most infections are probably subclinical respiratory infections. Alternatively, clinical signs may be limited to the respiratory system, but if the organism disseminates, the

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digestive tract and reticuloendothelial system become involved. Clinical signs include pyrexia, inappetence and weight loss, general malaise, and coughing (Kerl, 2003). With respect to ocular signs, the choroid appears to be the target. Pyogranulomatous inflammation extending into the subretinal space producing focal or coalescing lesions and retinal detachment has been observed (Gwin et al., 1980; Huss et al., 1994). Optic neuritis and anterior uveitis may also occur. Histoplasmosis-induced granulomatous chorioretinitis is similar in appearance, ophthalmoscopically, to chorioretinal lesions associated with other causes of systemic mycoses (Fig. 37.1.21). Unlike other mycotic infections, *H. capsulatum* organisms are relatively few in number and are small (2–4 μm in diameter), round to oval, intracellular (typically within phagocytic cells of the mononuclear phagocyte system) yeast cells. *H. capsulatum* organisms may, therefore, require enhancement with Gomori methenamine-silver (GMS) staining to visualize them and establish the diagnosis (Render et al., 1982).

Diagnosis of histoplasmosis can be made via histopathology and cytologic identification of the organisms in infected tissue or tissue aspirates/body fluids, respectively. Culture of the organism can be performed by plating biological fluid, including CSF, on Sabouraud's dextrose agar. Serologic diagnosis of histoplasmosis using an AGID test is 80% sensitive and almost 100% specific (Huss et al., 1994). A negative test result does not rule out the disease, however, and a positive test result may only indicate previous exposure in endemic areas. *Histoplasma* spp. antigen testing by enzyme immunoassay (EIA) has been shown, however, to have a sensitivity of 89.47%, negative predictive value of 95.35%, and specificity and positive predictive value of 100% in a study examining the utility of the test by measuring antigen in urine samples from dogs with histopathologically/cytologically confirmed histoplasmosis (Cunningham et al., 2015). Similar to other systemic mycoses, pulmonary forms of histoplasmosis without dissemination have a better prognosis. Dogs with ocular lesions typically do not respond to antifungal therapy. Long-term therapy and a propensity for relapse are characteristic. Readers are referred to current internal medicine or infectious disease textbooks for further details regarding therapy for canine histoplasmosis.

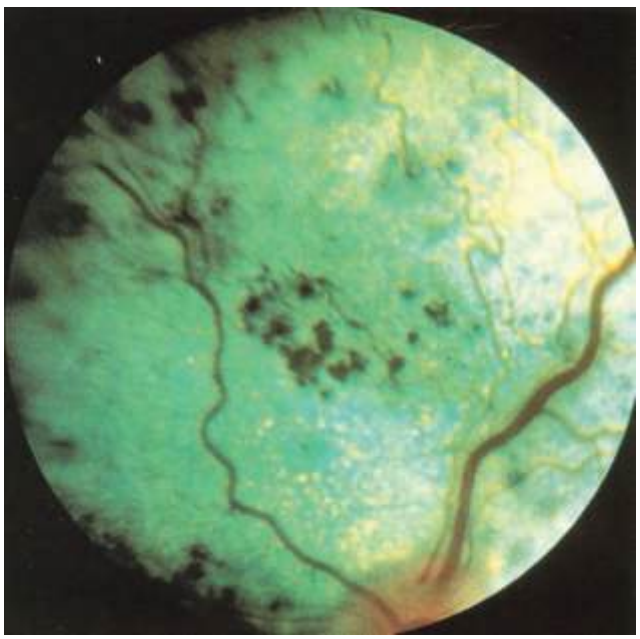


Figure 37.1.21 Active chorioretinal lesions associated with histoplasmosis in a dog. Optic neuritis and neurologic signs also developed in this animal. ((*Source*: Reprinted with permission from Ledbetter, E.C., Landry, M.P., Stokio, T., et al. (2009) *Brucella canis* endophthalmitis in 3 dogs: clinical features, diagnosis, and treatment. *Veterinary Ophthalmology*, **12**, 183–191.)

Parasitic: Dipteric Larvae

Ophthalmomyiasis

Ophthalmomyiasis interna has been observed in the dog and the cat, and refers to either the intraocular (ophthalmomyiasis interna) or external (ophthalmomyiasis externa) migration of fly (*Diptera*) larvae. Animals present with one of three different forms of ophthalmomyiasis. The three forms are named according to location of the larvae and include: (1) ophthalmomyiasis externa, where the larvae are found in the orbital and extraocular tissues; (2) ophthalmomyiasis interna anterior, where the larvae are found in the anterior chamber of the eye; and (3) ophthalmomyiasis interna posterior, where larvae are found in the posterior segment of the eye (Crumley et al., 2011; Harris et al., 2000; Wyman et al., 2005). The point of entry of the fly larvae is unknown but it is postulated that fly larvae cross the conjunctival surfaces. Ophthalmomyiasis may be presented in the acute stages if an anterior uveitis is produced, but more commonly, the syndrome is noted as an incidental finding in the chronic stages. The characteristic ophthalmoscopic lesions are wandering, curvilinear tracts that frequently intersect and are associated with retinal and preretinal hemorrhages in the acute stage. If the larva is observed, it is typically photosensitive, moving away from a strong light (Gwin et al., 1984; Kaswan & Martin, 1984).

Manual removal of externally located organisms with appropriate anti-inflammatory and antimicrobial therapy, along with correcting any extraocular conformational defects have shown positive outcomes (Crumley et al., 2011).

With regard to treatment of ophthalmomyiasis interna, direct visualization of the larvae in either the anterior or the posterior segment of the eye has been reported, but more commonly, the finding is of typical wandering tracts in the ocular fundus. Only acute cases warrant therapy, and topical or systemic corticosteroids are indicated depending on the location of the lesion (or lesions). If the larva is present, laser energy may be attempted to kill the larva, even though it is not pigmented. Physical removal of the larva from the

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anterior chamber has also been performed (Harris et al., 2000). Pars plana vitrectomy has also successfully been used to treat intravitreal ophthalmyiasis (Ollivier et al., 2006). Systemic organophosphates have been used as well to treat ophthalmomyiasis interna, but because the condition spontaneously improves in most instances, the efficacy of this treatment is unknown. Killing the larva may incite more intraocular inflammation, however, and waiting for spontaneous departure of the larva from the eye may be prudent.

Parasitic: Nematodes

Angiostrongylosis (Heartworm of France; French Heartworm)

Angiostrongylosis is caused by the nematode, *Angiostrongylus vasorum*. *A. vasorum* inhabits the pulmonary arteries and right heart of dogs and wild carnivores in parts of Europe, Africa, and Asia (for review see Bolt et al., 1994; Conboy, 2011; Morgan et al., 2005). In addition, cases of *A. vasorum* infection in dogs from Newfoundland and Labrador, a province in Canada, have been described (Conboy, 2004; Bourque et al., 2002). Dogs are infected by eating intermediate hosts such as snails and slugs. Third-stage larvae pass from the gut to the liver, molt to fourth-stage larvae, and then migrate to the heart and the pulmonary arteries. Larvae are coughed, swallowed, and passed in the feces. Migrating larvae may become aberrant and may be found in the eye (Colella et al., 2016; King et al., 2005). Severe granulomatous uveitis and secondary glaucoma have been observed with chronic involvement (King et al., 2005; Perry et al., 1991). *A. vasorum* infection may also manifest in acute cases as a free nematode in the anterior chamber (Colella et al., 2016; King et al., 2005; Perry et al., 1991).

Coughing and right-heart failure are the usual signs of severe *A. vasorum* infestation. A history of exposure to an endemic area should prompt utilization of the Baermann technique or fecal flotation to detect larvae in the feces. False negative results may arise as *A. vasorum* larvae are not shed continuously. Both the worm and the presenting clinical signs need to be differentiated from *Dirofilaria immitis*-induced disease.

Standard therapy for infection with *A. vasorum* is oral levamisole. Treatment with other anthelminthics such as ivermectin, milbemycin, fenbendazole, praziquantel, and moxidectin are reported (Bolt et al., 1994; Bourque et al., 2002; Chapman et al., 2004; Colella et al., 2016; Conboy, 2004).

Dirofilariasis (Canine Heartworm Disease)

Dirofilariasis, canine heartworm infection, caused by *Dirofilaria immitis*, is the most commonly reported intraocular nematode in dogs in North America (Carastro et al., 1992). Heartworm disease is widely distributed. Dirofilariasis is recognized in dogs worldwide. The disease has been reported in the tropics in northern and southern temperate zones, and in the subtropics. Dirofilariasis infects numerous species including dogs, cats, ferrets, sea lions, and humans (Atkins, 2005).

Transmission of *D. immitis* is by mosquitoes. The life cycle of *D. immitis* is complex, thus readers are referred to current internal medicine or infectious disease textbooks for further details. *D. immitis* completes its life cycle within 184–210 days under ideal conditions (Atkins, 2005). The canine host usually develops microfilaremia 6–7 months after infection (Atkins, 2005). Adult heartworms are known to live up to 5 years, whereas microfilaria live up to 30 months in dogs (Atkins, 2005).

Ocular involvement with *D. immitis* is postulated to arise as a result of aberrant migration of fourth-stage larvae from the subconjunctival space into the eye, with subsequent development to immature adults or fifth-stage larvae (Carastro et al., 1992; Dantas-Torres et al., 2009). Approximately half of these infected dogs do not have microfilaremia or are occult. In a retrospective study, the German Shepherd represented 33% of *D. immitis*-infected dogs in a series of 21 dogs (Carastro et al., 1992). All ocular involvement was unilateral. The worm was in the anterior chamber in 20 of the 21 cases, but it may also be found in the vitreous (Carastro et al., 1992). Anterior uveitis was a consistent ocular manifestation, and ocular discomfort was exacerbated by examination of the affected eye with a light, which stimulated parasitic movement (Carastro et al., 1992). With this disease, corneal edema may be severe and may hinder examination of deeper intraocular structures. The uveitis and corneal edema are postulated to be associated with mechanical trauma from the worm, toxic metabolic byproducts from the worm, or an immune reaction to the worm (Beller, 1962; Bellhorn, 1973; Blanchard & Thayer, 1978; Brightman et al., 1977; Carastro et al., 1992; Guterbock et al., 1981; Medcalf & Jordan, 1982; Miller & Cooper, 1987).

The diagnosis of intraocular dirofilariasis is established by finding the worm, usually present in the anterior chamber of dogs in areas endemic for heartworm. Severe corneal edema, however, may preclude visualization of the parasite. Approximately 50% of the affected dogs are occult for microfilaria; thus, occult heartworm testing and thoracic radiography may be needed as well (Carastro et al., 1992).

Therapy has involved removal of the *D. immitis* worm through a limbal incision, and has been successful in 90% of patients so treated. Preoperative treatment with a topical cholinesterase inhibitor may decrease parasite movement, as may avoiding bright surgical lights until required. A retrospective study has shown preservation of vision in 89% of cases, but vision was usually lost when glaucoma was a complication (Carastro et al., 1992). The most commonly reported ocular complication is corneal edema that was persistent in only 4 of 21 cases of intraocular dirofilariasis (Carastro et al., 1992). Corneal edema was more likely to be persistent if the history was chronic (Carastro et al., 1992). Anterior uveitis, in cases of intraocular dirofilariasis, should be treated with topical corticosteroids and atropine.

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Onchocerciasis (Onchocercosis)

Ocular onchocerciasis is caused by the nematode, *Onchocerca* spp. (for review see Sreter & Szell, 2008; Sreter et al., 2002; Zarfoss et al., 2005). *Onchocerca lupi* is the causative species of onchocerciasis in dogs and cats, and is also zoonotic (Labelle et al., 2013; Latrofa et al., 2018; Otranto et al., 2011). The black fly (*Simulium* spp.) has been shown to be the vector for *O. lupi* in California and New Mexico (Hassan et al., 2015; McLean et al., 2017). The vector becomes infected by ingesting microfilaria during feeding on the host. Larval maturation occurs in black flies (Hassan et al., 2015; McLean et al., 2017). Infective stage larvae are then transmitted to the definitive host (dog in this case) via blood feeding of the insect upon the host (McLean et al., 2017; Zarfoss et al., 2005). The parasites then mature, mate, and produce microfilariae that are ingested by the intermediate host, and so on (McLean et al., 2017; Zarfoss et al., 2005). To date, canine ocular onchocerciasis has been reported in dogs from Germany, Greece, Hungary, Portugal, and the southwestern and western United States (Eberhard et al., 2000; Faisca et al., 2010; Gardiner et al., 1993; Hermosilla et al., 2005; Hodzic et al., 2018; Komnenou et al., 2002, 2003, 2016; Labelle et al., 2013; McLean et al., 2017; Orihel et al., 1991; Szell et al., 2001a,b; Zarfoss et al., 2005). Two canine patients have been reported in Canada, but these dogs originated from the southwestern United States (Verocai et al., 2016). Dogs are typically of medium to large physical stature. No age or gender predilection has been reported. The condition may present unilaterally or bilaterally.

Clinically, there are two forms of ocular onchocerciasis, namely acute and chronic ocular onchocerciasis (Sreter et al., 2002). In acute cases, ocular onchocerciasis is characterized by conjunctivitis, chemosis, and periorbital swelling. In some cases, parts of the parasite are observed on the conjunctival surface or other periocular tissues (Sreter et al., 2002). In chronic cases, parasite-containing granulomatous nodules are found in various parts of the eye and periocular tissues (Fig. 37.1.22). Nodules are histopathologically characterized by being highly vascular, containing parasites and are composed of eosinophils, plasma cells, histiocytes, and fibroblasts (Sreter et al., 2002).

Diagnosis is made based on consistent clinical examination findings and, in acute cases, by identifying the presence of worm fragments on the conjunctiva or in periocular tissues. In chronic cases, diagnosis is made by grossly and/or histopathologically identifying *Onchocerca* spp. within the granulomatous nodules or within the periocular tissues. Therapy for ocular onchocerciasis involves, in part, surgical removal of the granulomatous nodules and other tissues containing the worm (Komnenou et al., 2002). *Onchocerca* spp. have endosymbiotic bacteria, *Wolbachia*, which are required for survival of the parasite (Sreter et al., 2002). Consequently, administration of antimicrobials effective against the endosymbiont (tetracyclines) may be useful at eliminating the parasite. Antiparasitic agents such as ivermectin and diethylcarbamazine are not effective against adult worms but are effective against *Dirofilaria* (Sreter et al., 2002). A successful therapeutic regimen resulting in complete destruction of the worm and resolution of clinical signs involves the surgical removal of the parasite containing granulomas followed by immediately administering prednisolone (0.5 mg/kg PO BID) for 9–12 days and doxycycline (5 mg/kg PO BID) for 1 month. One week after surgical debulking, melarsomine (2.5 mg/kg IM SID) is administered for 2 days followed by ivermectin (50 μg/kg SC) 1 month after surgery (Komnenou et al., 2002; Zarfoss et al., 2005). No recurrences have been reported, for up to 1 year, using this therapeutic strategy in dogs from Greece (Komnenou et al., 2002; Zarfoss et al., 2005). Nevertheless, up to 67% of dogs had recurrence in a study from the United States (McLean et al., 2017). It has been suggested that the differences in recurrence rates may be caused by a variety of factors including intrinsic differences between different strains of *O. lupi*, differences in therapy between clinicians, or reinfection of dogs in the study from the United States (McLean et al., 2017).



Figure 37.1.22 Onchocerciasis in a dog. Note the nematodes arising from a 'pseudotumoral mass' at the medial canthus periocular space and presence of a granuloma at the lateral canthus subconjunctival area in the left eye of a British Spaniel. Deep corneal ulcer and corneal edema are also present. (*Source*: Reprinted with permission from Komnenou, A., Eberhard, M., Kaldrymidou, E., et al. (2002) Subconjunctial filariasis caused by Onchocerca spp. in dogs: report of 23 cases in Greece. *Veterinary Ophthalmology*, **5**, 119–126.)

Strongylidiasis (Hookworms)

Strongylidiasis is caused by the aberrant migration of strongyles (order Strongylida) (Gaunt et al., 1982). The most common routes of infection of a common strongyle of dogs, *Ancyclostoma spp*., is through ingestion of larvae or direct penetration of larvae through intact skin (Gaunt et al., 1982).

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Infection may also occur through transplacental migration to the fetus (Gaunt et al., 1982). Aberrant migration is more common after direct penetration of skin compared with after ingestion of the larvae (Gaunt et al., 1982).

A 3-month-old Beagle with ocular strongylidiasis has been described with granulomatous endophthalmitis and secondary glaucoma (Gaunt et al., 1982). The eye was enucleated and submitted for histopatholgy. Histopathologic examination of the affected eye revealed an adult Strongylida worm in the posterior chamber, which was identified as *Ancylostoma caninum,* although *Uncinaria* spp. could not be ruled-out. Successful therapy for this nematode has not been reported.

Toxocariasis (Roundworm Ascarids)

Toxocariasis is caused by the nematode *Toxocara canis* (for review see Despommier, 2003). *T. canis* is an extremely common roundworm or ascarid of the dog, and is thought to be responsible for migrating larvae that may, occasionally, aberrantly migrate to the eye of humans and dogs. Roundworms most often cause disease in young animals. *T. canis* can be transmitted across the placenta and through the milk. Toxocariasis can also occur by ingestion of the eggs from other infected hosts, such as rodents. Infective eggs of *T. canis* have the second-stage larva, which when ingested, normally migrates through the gut wall, enters the portal system to reach the liver, and then passes via the blood to the lungs. In the lungs, they molt to third- and fourth-stage larvae, after which they then migrate up the trachea to be swallowed and mature in the small intestine. *T. canis* larvae also migrate to the uterus to infect the prenatal liver of puppies and then continue their migration to the lungs after birth. Migrating juvenile *T. canis* can cause hepatic, pulmonary, and less commonly, ocular damage.

Both visceral and ocular larval migrans as a result of *T. canis* pose a public health problem. Ocular larval migrans is migration of nematode larvae through the eye. Aberrant migration of *T. canis* to the canine eye has been described as an incidental finding manifesting as small (one-fourth to one-sixth disc diameter), solitary focal granulomas in the posterior segment in four dogs (Rubin & Saunders, 1965). Two dogs had granulomas originating from the choroid that broke into the subretinal space, thus producing focal retinal detachment, and two dogs had granulomas affecting the optic nerve (Rubin & Saunders, 1965).

Although ocular larval migrans is considered to be a rare syndrome, two outbreaks in working herding dogs have been reported (Hughes et al., 1987; Johnson et al., 1989). In rural New Zealand, 39% of 1448 dogs had lesions characterized by multifocal hyperreflective tapetal lesions, with central pigment clumping, focal depigmentation of the non-tapetal fundus, and some mild vitreal clouding that may have been associated with *Toxocara* spp. (Hughes et al., 1987). Approximately half of these animals had bilateral ocular lesions. Ocular examination of young dogs revealed active, hazy, inflammatory changes of the posterior segment that evolved into the characteristic, sharply demarcated lesions. Severely *T. canis*-affected dogs had diffuse tapetal hyperreflectivity and retinal vascular attenuation.

Histopathologic examination of 47 affected eyes with inflammatory lesions revealed three categories of posterior segment lesions: (1) those from dogs 3 years of age or younger with active inflammation of the posterior segment (four dogs in this group had *Toxocara* spp. larvae identified); (2) those with diffuse retinal atrophy and retinitis, with localized retinal necrosis; and (3) those with chronic, low-grade retinitis and variable atrophy, in which the dogs were usually older than 3 years of age (Hughes et al., 1987). Lesions in the young dogs had focal granulomas similar to those in the original description of ocular larval migrans. The second histologic category involved dogs that were blind, most of which were older than 3 years. The retinitis was typically a perivascular plasma cell infiltrate, with peripapillary retinal necrosis. It was postulated that young, severely affected dogs progressed to category-two dogs and, if less severely affected, retained function and appeared as category-three dogs (Hughes et al., 1987). Further study is needed to prove this hypothesis, because larvae were not found in any of the dogs with advanced lesions or in the older animals with lesions. Rural dogs were thought to be at risk either through massive contamination of the environment or through eating raw mutton with migrating larvae (Hughes et al., 1987). A study involving two litters of Border Collies originating from the same pig farm in the United States provided a compelling association between lesions very similar to those observed in New Zealand and ocular larval migrans (Johnson et al., 1989). A case of ocular larval migrans causing orbital cellulitis has also been described in a dog (Laus et al., 2003).

Rural dogs with environmental exposure or those that are fed raw meat, demonstrating asymmetrical retinal atrophy, focal granuloma formation, and occasionally, the observation of an intraocular larva, would be suggestive of possible ocular larval migrans syndrome. Either ophthalmoscopic or histopathologic observation of *T. canis* larvae is the only means of establishing a definitive diagnosis, thus differentiating this syndrome from other causes of chorioretinitis. Differentiation from genetic retinal atrophy would be made on the basis of focal lesions superimposed on diffuse retinal atrophy, age, asymmetric lesions, and histopathologic differences.

Attempts at therapy for *T. canis*-associated ocular larval migrans have not been reported in dogs. However, prevention by adequately cooking the meat fed to dogs, good kennel hygiene, and routine deworming should keep the worm burden down and, thus, minimize the occurrence of this condition.

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Parasitic: Mites

Demodicosis

Canine demodicosis is caused by the parasitic mite *Demodex canis* or less commonly, *Demodex injai* (Bowden et al., 2018). *Demodex* spp. live as commensals in the skin of most mammals, including dogs. Most species of *Demodex*, including the *D. canis* mite, spend their entire life cycle in the hair follicles and sebaceous glands of their host, whereas a few species are found within the epidermis. *Demodex* mites, present in small numbers, are part of the normal skin fauna (for review see Mueller, 2004; Nutting, 1976). It has been shown that *D. canis* mites produce either local or generalized demodicosis via targeting toll-like receptors (Kumari et al., 2018). Generalized demodicosis is either juvenile-onset or adult-onset (Mueller, 2004). Nonetheless, predisposing factors contributing to overgrowth of *Demodex* include poor nutrition, concurrent parasites/infectious disease, allergic dermatoses, short hair coat, nonenrollment into preventive wellness plan, stress, and immunosuppressive drug therapy (Bowden et al., 2018; Plant et al., 2011). Localized demodicosis typically develops in young dogs (3–6 months of age), starting preferentially around the eyes, lips, and forelegs. Skin lesions are typically circumscribed, dry, scaly, and hairless. Most are nonpruritic, but bacterial infection and self-trauma may create moist, erythematous lesions.

Skin scrapings or histopathology are the main methods of establishing a diagnosis, and the mites are typically easy to find (Bowden et al., 2018; Mueller, 2004). All forms of blepharitis should indicate the need for skin scrapings, and demodicosis should be an important differential diagnosis in young dogs with blepharitis.

Dogs with normal immune systems will typically have self-limiting local demodicosis (generally resolves in 6–8 weeks, with or without therapy), but the lesions should be observed for progression to generalization. Local lesions may heal and new skin lesions may develop over a period of several months. Treatment of canine demodicosis involves the use of amitraz dips and/or oral ivermectin or milbemycin administration (Mueller, 2004). Use of avermectin drugs should be limited to animals lacking the mutation for the P-glycoprotein gene (*MDR1*) (see "Ivermectin" in "Systemic Toxicities" section later). For current treatment recommendations and prognoses see Mueller (2012) and Bowden et al. (2018).

Sarcoptic Acariosis (Sarcoptic Mange, Canine Scabies)

Sarcoptic mange is caused by the mite *Sarcoptes scabiei* var. *canis* (Curtis, 2004). Adult mites mate on the surface of the skin and the female mite burrows into the skin, laying eggs as she moves. The eggs hatch and larvae burrow into the surface of the skin, where they mature. Although sarcoptic mites have host species preference, they are able to cause disease in nonpreferred hosts. Consequently, sarcoptes can be tranmitted from dogs to people and vice-versa. Sarcoptes mites can survive off the host at room temperature for up to 6 days. Therefore, the environment in which an affected animal was housed should be cleaned and a period of time should elapse prior to exposing other animals to the environment.

Clinical signs of sarcoptic mange include intense pruritis, alopecia, and reddish papulocrustous eruptions of infected areas. Commonly affected sites include the ventral ears, abdomen, chest, and legs, although in severe cases the entire body, including periocular regions, can be affected.

Presumptive diagnosis is made based on consistent signalment and clinical signs including a positive pinnal-pedal reflex (Mueller et al., 2001). Diagnosis of sarcoptic mange is dependent upon visualizing the mite, eggs, or mite feces via microscopic examination of skin scrapings. It should be noted, however, that skin scrapings are often negative in affected animals (Curtis, 2004). When demonstration of organisms or their feces is not possible, the use of a commercially available ELISA for antisarcoptes antibody is useful (Lower et al., 2001). The sensitivity and specificity of this test are 84% and 90%, respectively (Lower et al., 2001).

Treatment of sarcoptic mange involves the use of amitraz (monoamine oxidase inhibitor), fipronil (GABA-receptor inhibitor), or avermectin drugs (i.e., ivermectin, milbemycin oxime, moxidectin, selamectin). For details of specific therapies see Curtis (2004). Given that sarcoptic mange is highly contagious, and a self-limiting zoonosis, the environment should be thoroughly cleaned and other dogs in contact with the affected animals should be treated even if clinical signs are not present. Provided appropriate therapy of the affected dog, its environment, and other dogs in contact with the animal occurs, prognosis for resolution of this condition is excellent.

Parasitic: Protozoal

Hepatozoonosis

Hepatozoonosis in dogs is a tick-borne disease caused by the protozoans *Hepatozoon canis* and *H. americanum* (Baneth et al., 2000, 2003; Vincent-Johnson et al., 1997). Hepatozoonosis has a worldwide distribution (Baneth et al., 2003). *H. americanum* is transmitted by the gulf coast tick (*Amblyomma maculatum*), whereas *H. canis* is transmitted by the brown dog tick (*Rhipicephalus sanguineus*) (Baneth et al., 2003; Mathew et al., 1998). Unlike most tick-borne diseases where infection results from the bite of an infected tick, infection of a dog with *Hepatozoon* spp. occurs after ingestion of an infected tick (Baneth et al., 2003). After ingestion, sporozoites of *Hepatozoon* spp. infect phagocytic leukocytes, endothelial cells, and the bone marrow. Circulating organisms can further infect various tissues including skeletal muscle and hemolymphatic organs (Baneth et al., 2003; Panciera et al., 1999).

Infection with *H. canis* results in somewhat less severe clinical signs compared with animals infected with

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H. americanum (Baneth & Weigler, 1997; Vincent-Johnson, 2003; Vincent-Johnson et al., 1997). Dogs infected with *H. canis* can be febrile, have signs of general malaise, and may have a leukocytosis.

H. americanum infection manifests as a febrile disease, with generalized emaciation, inappetence, stiff gait, bilateral mucopurulent ocular discharge, and severe generalized hyperesthesia especially along the epaxial musculature (Macintire et al., 2001; Vincent-Johnson, 2003). Most dogs are young adults and there is no gender or breed predisposition to developing the disease (Macintire et al., 2001). Animals infected with *H. americanum* may also have concurrent infection with other tick-borne diseases including *Rickettsia ricketsii*, *Anaplasma platys*, and *Ehrlichia canis* (Macintire et al., 2001). In a series of 22 dogs, chronic, mucopurulent ocular discharge was present in 77% of cases (Macintire et al., 1997). On ocular examination, KCS was present in 36% of cases, retinal scars in 14% of cases, papilledema in one dog, and active uveitis in one dog (Macintire et al., 1997). Additional systemic signs of joint and back pain, paresis and ataxia, and generalized weakness were also common (Macintire et al., 1997). Clinical signs of hepatozoonosis may be intermittent and recurrent.

Chronic fever with loss of condition during the tick season in a dog from an endemic area is suggestive of a tick-borne disease. Neutrophilic leukocytosis, often extreme, with a left shift and a nonregenerative anemia are the most common hematologic findings (Macintire et al., 2001). Biochemistry profiles are typified by an elevated alkaline phosphatase level, hypoglycemia, and hypoalbuminemia (Macintire et al., 2001).

Definitive diagnosis of hepatozoonosis is made upon identifying the organism in circulating leukocytes or muscle biopsy specimens (Macintire et al., 2001). Outside of the United States, gametes are frequently observed in the cytoplasm of peripheral leukocytes and in the bone marrow (Macintire et al., 2001). In one study, the presence of serum antibodies (via ELISA) against *H. americanum* was compared with tissue biopsy results (Mathew et al., 2001). The sensitivity and specificity of using serum antibodies to diagnose hepatozoonosis were 93% and 96%, respectively (Mathew et al., 2001). Another ELISA used for detecting antibodies against *H. canis* has been shown to have a sensitivity and specificity of 86% and 97%, respectively (Gonen et al., 2004). PCR performed on blood is also helpful in reaching a diagnosis of hepatozoonosis in dogs (Baneth, 2011).

There is no therapy to eliminate *H. americanum* or *H. canis* from the body of infected dogs effectively (Baneth, 2011). A retrospective study has shown that a 14-day treatment regimen with trimethoprim-sulfadiazine (15 mg/kg PO q 12 hours), clindamycin (10 mg/kg PO q 8 hours), and pyrimethamine (0.25 mg/kg PO q 24 hours) showed a favourable response for only 6 months (Macintire et al., 2001). In the same study, it was found that administration of a similar 14-day regimen of trimethoprim-sulfadiazine, clindamycin, and pyrimethamine followed by administration of decoquinate (10–20 mg/kg PO q 12 hours) for 3–33 months results in longer-term survival of dogs (Macintire et al., 2001). Other therapies used in the treatment of canine hepatozoonosis include subcutaneous imidocarb diproprionate, 5 mg/kg in two doses at 14-day intervals (drug of choice for *H. canis*), and primaquine phosphate (Macintire et al., 2001). Tick control is important in preventing relapses as well as initial infections.

Leishmaniasis

Leishmania spp. are diphasic protozoal parasites that infect a wide range of vertebrates, including dogs and humans (for reviews see Alvar et al., 2004; Desjeux, 2004; Solano-Gallego et al., 2011). Dogs and other canids are primary reservoirs of *Leishmania* spp., and sandflies *(Phlebotomus* spp. or *Lutzomyia* spp.) are the vectors (Alvar et al., 2004; Travi et al., 2018). *L. infantum* is the species responsible for endemic leishmaniasis in dogs from Greece, Spain, Portugal, Turkey, parts of Africa, Central and South America, and India (Koutinas et al., 1999; Pasa et al., 2005; Pena et al., 2000; Solano-Gallego et al., 2001). Alterations in socioeconomic and possible climate factors have resulted in changes in the distribution in *L. infantum* in Europe (Solano-Gallego et al., 2011). Travel of many dogs to southern Europe or their importation from endemic areas has increased the number of affected dogs in nonendemic countries (Pennisi, 2015). Leishmaniasis caused by *L. donovani* has been reported in the United States and is considered endemic in Oklahoma, Texas, and Ohio (Eddlestone, 2000; Sellon et al., 1993; Swenson et al., 1988). *L. infantum* has been described in the United States and Canada (Duprey et al., 2006).

As previously mentioned, one mode of transmission to vertebrates is via bites from infected sandflies. Further, sandflies are infected by reservoir hosts during feeding. Approximately 90% of infected dogs ultimately develop clinical disease, usually before 5 years of age. The incubation period may be a few months to between 3 and 4 years (Kontos & Koutinas, 1993). Consequently, a thorough travel history needs to be investigated in suspect cases of canine leishmaniasis. Importantly, however, vertical and/or horizontal transmission may be primary modes of transmission of *Leishmania* to dogs where a competent vector does not exist (Boggiatto et al., 2011; Naucke & Lorentz, 2012; Svobodova et al., 2017).

Leishmania spp. cause cutaneous, mucocutaneous, and visceral diseases (Koutinas et al., 1999; Pena et al., 2000). Dogs will typically develop a combination of these forms of leishmaniasis (Pena et al., 2000). The disseminated disease produces emaciation with muscular weakness, chronic renal failure, and chronic, nonpruritic skin lesions. The cutaneous lesions begin on the head, thereby producing a blepharitis characterized by scaliness and loss of hair that begin at the

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Figure 37.1.23 Conjunctivitis in a dog with leishmaniasis. Note the prominent thickening of the ventral bulbar conjunctiva. Cytologic evaluation of the conjunctiva revealed mononuclear inflammatory cells and numerous amastigotes of *Leishmania infantum*. (*Source*: Reprinted with permission from Pena, M.T., Roura, X. & Davidson, M.G. (2000) Ocular and periocular manifestations of leishmaniasis in dogs: 105 cases (1993–1998). *Veterinary Ophthalmology*, **3**, 35–41.)



Figure 37.1.24 Anterior uveitis characterized by the formation of multifocal, gray nodules in the iris stroma. In this case, the uveitis developed after initiation of systemic antiprotozoal therapy. Note also the blepharitis with meibomanitis. (*Source*: Reprinted with permission from Pena, M.T., Roura, X. & Davidson, M.G. (2000) Ocular and periocular manifestations of leishmaniasis in dogs: 105 cases (1993–1998). *Veterinary Ophthalmology*, **3**, 35–41.)

medial canthus (Pena et al., 2000). A vesicular-bullous blepharitis similar to pemphigus complex may also develop, which results in ulcerative/erosive lesions (Pena et al., 2000). Focal granulomatous blepharitis is also a typical eyelid reaction. Most recently, the LeishVet group has developed a staging system that divides canine leishmaniasis into four stages ranging from mild disease to very severe disease aimed at helping the clinician determine appropriate therapeutic and monitoring strategies, as well as assisting with prognostication. The reader is referred to Solano-Gallego et al. (2011) for further details regarding these LeishVet guidelines.

Ocular manifestations of leishmaniasis occur in up to 81% of dogs with the disease (Naranjo et al., 2005). Ocular manifestations of leishmaniasis consist of blepharitis, simple or granulomatous conjunctivitis (Fig. 37.1.23), scleritis, superficial or deep keratitis, anterior uveitis (Fig. 37.1.24), KCS, and secondary glaucoma; signs are typically bilateral (Naranjo et al., 2005; Pena et al., 2000). The anterior vitreous may have an inflammatory reaction, but the posterior choroid and retina are usually spared. The inflammation is mononuclear and the organism can be found in histiocytes (Giles et al., 1975; McConnell et al., 1970; Roze, 1986). *Leishmania* spp. and associated granulomatous inflammatory infiltrates have been recently described in intraocular, extraocular, and adnexal smooth and striated muscles in affected dogs (Fig. 37.1.25) (Naranjo et al., 2010). In another study, ocular tissues noted to be histologically affected, in order of frequency, were conjunctiva and limbus, ciliary body, iris, cornea, sclera and iridocorneal angle, choroid, and the optic nerve sheath with a granulomatous inflammatory infiltrate found in 30% (36/120) of affected globes and

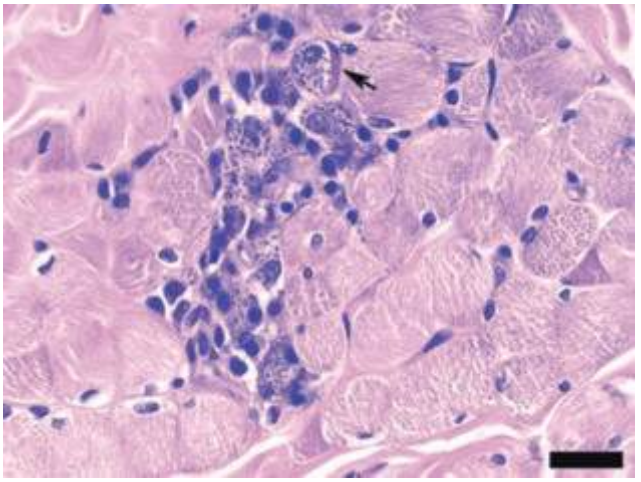


Figure 37.1.25 Orbicularis oculi muscle. Occasionally, *Leishmania* parasites could be seen inside the muscular fiber (arrow). (Bar = 25 µm; Hematoxylin and eosin.) (*Source*: Reprinted with permission from Naranjo, C., Fondevilla, D., Leiva, M., et al. (2010) Detection of Leishmania spp. and associated inflammation in ocular-associated smooth and straited muscles in dogs with patent leishmaniasis. *Veterinary Ophthalmology*, **13**, 139–143.)

immunohistochemical detection of the parasite in 26.6% (32/120) of eyes (Pena et al., 2008).

Clinically, the condition is suspected on the basis of chronic debilitation, facial and pinnal exfoliative dermatitis, and a history of visiting an endemic area. The diagnosis is confirmed on the basis of finding the organisms (i.e., amastigotes), which are round to oval and 2.5–5.0 µm by 1.5–2.0 µm in size, in bone marrow aspirates, lymph node aspirates, or skin impression smears stained with Wright's or Giemsa stains. Other means of identifying the *Leishmania*

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organism include histopathologic or immunoperoxidase evaluation of cutaneous or organ biopsy specimens, PCR performed on anticoagulated blood, or bone marrow or lymph node aspirates, or culture inoculation of hamsters (Ashford et al., 1995; Manna et al., 2004; Solano-Gallego et al., 2001; Vitale et al., 2004). Serologic tests are available that use ELISA and indirect fluorescent antibody testing. Immunoglobulin G titers against *Leishmania* spp. develop 14–28 days after infection and decline 45–80 days after treatment (Ferrer et al., 1995; Solano-Gallego et al., 2001). For a complete review of diagnostic tests and their benefits and limitations see Travi et al. (2018).

It has been shown that *Leishmania* spp. are difficult to eliminate from the body and recurrences are common (Cavaliero et al., 1999; Denerolle & Bourdoiseau, 1999). A variety of drugs has been used for the treatment of leishmaniasis (Noli & Auxilla, 2005). A systematic review regarding the treatment of visceral leishmaniasis recommends the use of meglumine antimoniate (100 mg/kg) daily for at least 3–4 weeks combined with allopurinol (Noli & Auxilla, 2005). One study, however, has shown the successful use of allopurinol combined with sodium stibogluconate for the treatment of canine leishmaniasis with none of the treated animals having relapse up to 24 months after therapy (Pasa et al., 2005). Second-line medications such as miltefosine and paromomycin require further clinical studies regarding their efficacy in dogs. There is no effective vaccine against canine visceral leishmaniasis in the United States, although a secreted parasite antigen-based vaccine has recently been licensed for use in dogs in Brazil (Petersen & Barr, 2009). The prognosis for dogs with leishmaniasis is variable. Relapses are common with leishmaniasis.

Neosporosis

Neosporosis is caused by the coccidian protozoan *Neospora caninum*. The organism is morphologically similar to *Toxoplasma gondii* (for review see Buxton et al., 2002). Canine neosporosis has been reported in many countries worldwide. Dogs are both the definitive and intermediate hosts of this protozoan (McAllister et al., 1998). The sexual cycle of *N. caninum* is completed in the gastrointestinal tract of dogs (definitive host), after ingestion of tissue cysts, and oocytes are shed in feces. Oocysts sporulate in the environment and are then infective. After being ingested in an intermediate host the oocysts release sporozoites in the gut. Sporozoites change into tachyzoites which then spread throughout the body leading to tissue cyst (bradyzoite) formation. Transmission of neosporosis by the transplacental route occurs (Dubey et al., 1990); consequently, reports of canine neosporosis commonly involve neonatal infections. Clinical disease is most often reflective of neuromuscular disease in dogs; however, other clinical signs of polymyositis, myocarditis, hepatitis, and dermatitis may manifest after *Neospora* infection (Barber & Trees, 1996; Barber et al., 1996; Buxton et al., 2002; Ordeix et al., 2002). The most typical sign in puppies congenitally infected with neosporosis is an ascending paralysis with hyperextension of the hindlimbs. Puppies either die or are euthanized because of neurologic signs, but ocular lesions are present in most cases (Dubey et al., 1990). These ocular lesions are mainly a retinitis with extension into the choroid (i.e., retinochoroiditis) (Dubey et al., 1990). A mild anterior uveitis and extraocular myositis may occur as well (Dubey et al., 1990). Further reports are needed for determining the importance and extent of neosporosis on contributing to ocular disease.

Definitive diagnosis is made based upon identifying the organism in CSF, tissue, or feces using routine cytological/histopathological techniques. However, it should be noted that oocyst shedding has not been described in cases of clinically active neosporosis. Given the similar morphologic appearance of *N. caninum* with *T. gondii*, neosporosis may be misdiagnosed as toxoplasmosis at histopathologic examination. However, given that the two organisms are antigenically dissimilar and have unique DNA sequences *N. caninum* can be distinguished from *T. gondii* by using immunohistochemistry and PCR (Lindsay & Dubey, 2000). An indirect fluorescent antibody test can be used for the diagnosis of *Neospora*, although, like all serological tests only indicates exposure to the organism. Clinical signs suggestive of neosporosis combined with positive serology or the presence of antibodies in the CSF, with exclusion of similarly presenting disease such as *T. gondii*, should result in a presumptive diagnosis of neosporosis. Therapy is similar to that for toxoplasmosis. In particular, trimethoprim-sulfadiazine combined with pyrimethamine, sequential treatment with clindamycin, trimethoprim-sulfadiazine, and pyrimethamine, or clindamycin alone have been used to treat neosporosis (Lindsay & Dubey, 2000). The prognosis is grave for dogs with severe neosporosis-induced neurologic disease.

Toxoplasmosis

Toxoplasmosis is caused by the protozoan *Toxoplasma gondii* (for review see Dubey, 2004). *T. gondii*, as with *N. caninum*, has a worldwide distribution. Cats are both definitive and intermediate hosts of *T. gondii*. Because cats are definitive hosts, they are the only species that can shed oocysts. It should be noted, however, that dogs can pass *T. gondii* oocysts in their feces after the ingestion of infected feline feces (Lindsay et al., 1997). Many mammalian species can act as intermediate hosts. In the cat, ingested *T. gondii* bradyzoites (from tissue cysts) undergo a typical coccidian intestinal life cycle, and infected cats excrete oocysts in their feces that, after 1–5 days, sporulate and become infectious sporozoites (Dubey, 2004). The oocysts are resistant to environmental conditions, and they may remain infectious for months to years (Dubey, 2004). Ingestion of the oocysts by a susceptible host results in rapid division of sporozoites in the gut epithelium. The resultant tachyzoites are 4–8 μm by 2–4 μm, and are spread throughout the body via blood and

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lymphatics, and encyst in the brain, skeletal and cardiac muscles, as well as the liver. The encysted forms, termed bradyzoites, survive in tissues for the life of the host. Ingestion of bradyzoites by a new host dissolves the cyst wall and transforms them into tachyzoites, which ultimately encyst again. Transmission of *T. gondii* may occur transplacentally in cats after ingestion of oocysts in contaminated food or water, or from ingestion of tissues containing bradyzoites (Dubey, 1986).

Ocular disease associated with *T. gondii* is more commonly observed in cats than in dogs, and, in the dog, it is usually not associated with systemic manifestations of the disease. In both experimental and natural canine infections with *T. gondii*, the reported ocular lesions (in order of decreasing frequency) were a mononuclear anterior uveitis (35 of 60 dogs), retinitis (27 of 60), choroiditis (18 of 60), extraocular myositis (12 of 60), scleritis (3 of 60), optic neuritis (3 of 60), and keratoconjunctivitis (Piper et al., 1970; Swinger et al., 2009). Keratoconjunctival toxoplasmosis has been identified in dogs receiving topical immunosuppressants (Beckwith-Cohen et al., 2016). Systemic disease in dogs with *T. gondii* is relatively rare, but when it occurs, it is usually associated with other diseases, such as canine distemper virus, or with other systemic, debilitating or immunocompromising states (Dubey, 1985; Dubey et al., 1989; Piper et al., 1970; Webb et al., 2005). *T. gondii* appears to be a very significant cause of ocular lesions in systemically healthy dogs and cats on the basis of correlating lesions with positive serologic results. Because of the ubiquitous presence of *T. gondii*, it should be considered in the differential diagnosis of endogenous anterior uveitis and chorioretinitis regardless of whether systemic signs are present (Bussanich & Rootman, 1985; Dubey, 1985, 1986; Dubey et al., 1989; Piper et al., 1970).

A definitive diagnosis of toxoplasmosis can be made if the organism is detected in tissue. However, bradyzoites or tachyzoites are rarely detected in tissues, effusions, or fluids including aqueous humor and CSF. A diagnosis of toxoplasmosis is usually made on the basis of serologic tests using an ELISA for *T. gondii*-specific immunoglobulin (Ig) M and IgG. Paired serum samples at 2- to 3-week intervals are preferred for determining rising titers or seroconversion from IgM to IgG titers. However, *T. gondii*-specific antibodies can be detected not only in the blood of clinically ill dogs, but also in normal dogs. A positive IgM titer is correlated more with clinical toxoplasmosis than is the IgG titer because IgM antibodies are rarely detected serologically in clinically healthy animals. However, a fourfold or greater increase in IgG titer against *T. gondii* is also suggestive of recent or active toxoplasmosis.

Toxoplasmosis may be a self-limiting disease that does not require therapy, but if systemic signs or active intraocular inflammation is present, systemic therapy is usually advised. Oral clindamycin, 25 mg/kg every 12 hours for 21–30 days, and topical corticosteroids as well as atropine are recommended for ocular surface and anterior uveal inflammation. Clindamycin and oral corticosteroids are recommended for posterior uveal inflammation.

Toxoplasmosis is a significant zoonotic disease (Dubey, 2004). Clinical signs of toxoplasmosis may develop in the fetus of pregnant mothers experiencing a primary *T. gondii* infection. Ocular disease, and other manifestations such as stillbirth, may be noted in infected fetuses. As such, prevention of toxoplasmosis is recommended. Restricting the dog's ability to hunt and the dog's exposure to cat feces will help prevent canine toxoplasmosis. In addition, litter boxes for cats should be changed daily (pregnant woman should avoid this task), and dogs (and humans) should not be fed raw or incompletely cooked meat.

Trypanosomiasis

Trypanosomiasis is caused by the hemoparasitic protozoan of the genus *Trypanosoma*. Transmission of *Trypanosoma* infection is by the tsetse fly; however, dogs may also become infected with the disease by ingesting *Trypanosoma*-infected meat.

Common clinical manfestations of trypanosomiasis in dogs include weakness, anorexia, emaciation, and fever. Ocular signs have been reported in dogs with trypanosomiasis as well. *T. venezuelense* has been reported to produce blepharitis, conjunctivitis, keratitis, and endophthalmitis in a dog (Garcia et al., 1983). The organism was present in the eye as well as the blood of the affected dog (Garcia et al., 1983). *T. brucei* infections in the dog and cat frequently produce corneal opacification, blepharitis, conjunctivitis, and keratitis (Ikede, 1974; Mortelmans & Neetens, 1975; Nwosu & Ikeme, 1992).

The diagnosis of trypanosomiasis is made by identification of the organism on evaluation of blood smears or lymph node aspirates (Bradley et al., 2000; Garcia et al., 1983). Other methods such as indirect fluorescent antibody and ELISA, and PCR may also be used to diagnose the disease (Bradley et al., 2000; Desquesnes & Davila, 2002). In cases of anterior segment ocular disease, aqueous centesis may show the trypanosomes.

Chemotherapy for trypanosomiasis is dependent on the species of *Trypanosoma* causing the infection in the animal (for human reviews see Gaspar et al., 2015; Sra et al., 2004; Sales Junior et al., 2017; Urbina & Docampo, 2003). Drugs used in canine cases include diminizine (infected with *T. Evansii*) (Varshney et al., 2003) and nifurtimox (infected with *T. cruzi*; Chagas disease) (Bradley et al., 2000). Prognosis for animals with trypanosomiasis is considered poor. Infection with *Trypanosoma* is lifelong.

Rickettsial Diseases

Members of the bacterial order Rickettsiales are the cause of numerous conditions in numerous species of vertebrates (for comprehensive review see Allison & Little, 2013; Raoult & Roux, 1997; Parola et al., 2005). All members of the order Rickettsiales are obligate intracellular parasitic bacteria that

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require host cells to replicate (Allison & Little, 2013; McQuiston et al., 2003; Parola et al., 2005). The development of molecular taxonomic methods has resulted in the reclassification of several species of Rickettsia (Dumler et al., 2001). Rickettsial diseases are transmitted via an arthropod, typically fleas or ticks, although some are transmitted via nematodes (flukes) (Allison & Little, 2013; Parola et al., 2005). Two common groups of diseases still considered rickettsial diseases in veterinary medicine include: (1) rickettsioses caused by bacteria of the genus Rickettsia; and (2) ehrlichioses and anaplasmoses caused by bacteria in the family Anaplasmataceae (Parola et al., 2005). Many rickettsial diseases are considered zoonotic (McQuiston et al., 2003). Because of these unique features of bacteria of the order Rickettsiales we consider them here separately from other bacterial diseases that manifest, in part, with ocular disease.

Canine Cyclic Thrombocytopenia

Canine cyclic thrombocytopenia is caused by *Anaplasma platys* (formerly *Ehrlichia platys*), a bacterial organism which strictly replicates in platelets, and is not considered zoonotic (McQuiston et al., 2003; Sainz et al., 1999). A tick vector is the presumed mode of transmission of *A. platys* (Neer et al., 2002). *A. platys* is distributed in the southeastern United States, southern Europe (Greece, Italy, France), and South America (Neer et al., 2002).

A. platys replicates within platelets, resulting in diminished platelet survival and thrombocytopenia. The disease follows a cyclical course. Specifically, platelet counts decline dramatically within a few days of *A. platys* infection, and then rise within a few days, thereby following a cyclical course at 1- to 2-week intervals. *A. platys* has been described as producing uveitis in a dog, but the syndrome was mild and improved rapidly (Glaze & Gaunt, 1986). Diagnosis of *A. platys* depends upon observing the organism within platelets, detecting serum antibodies for the organism or by detecting the presence of organismal DNA via PCR (Allison & Little, 2013; Neer et al., 2002). Treatment is aimed at eliminating the bacteria by using doxycycline as the first drug of choice (Neer et al., 2002). Topical ocular therapy for an underlying uveitis includes use of topical corticosteroids and atropine. Clinical improvement is typically noted within 24–48 hours after commencement of antimicrobial therapy (Neer et al., 2002).

Canine Ehrlichiosis

Canine ehrlichiosis is a tick-borne disease produced by *Ehrlichia canis, E. chaffeensis, E. ewingii, E. equii, Anaplasma platys* (formerly *E. platys*), *A. phagocytophila* (formerly *E. phagocytophila*), and *Neorickettsia risticii* (formerly *E. risticii*) (Dumler et al., 2001; Mylonakis et al., 2004b). As mentioned in the prelude to this section, *Ehrlichia* spp. and *Anaplasma* spp. are small, Gram-negative, pleomorphic, obligate intracellular bacteria (McQuiston et al., 2003; Parola et al., 2005). The distribution of canine ehrlichiosis is related, in part, to the geographical distribution of ticks that act as vectors for these bacteria (Neer et al., 2002). In particular, *E. canis* is transmitted by the brown dog tick, *Rhipicephalus sanguineus*, whereas transmission of *E. chaffeensis* and *E. ewingii* is via the lone star tick, *Amblyomma americanum* (for a list of worldwide geographic distribution of rickettsial diseases and their vectors see Allison & Little, 2013; Neer et al., 2002). Animals may be coinfected with more than one rickettsial agent (Mylonakis et al., 2004a).

Canine ehrlichiosis is divided into an acute disease phase (2–4 weeks), a subclinical phase (months to years), and a chronic disease phase (Mylonakis et al., 2004b). As such, a dog with chronic, subclinical infection may be moved from an endemic to a nonendemic area and develop signs of the disease years after the initial infection (Gould et al., 2000). Acute disease phase clinical signs, including general malaise, anorexia, fever, and ocular and nasal discharge, are typically transient and animals will typically recover spontaneously without treatment. Hematological findings in the acute phase of the disease also include thrombocytopenia, leukopenia, and nonregenerative anemia (Panciera et al., 2001). During the chronic disease phase of ehrlichiosis, common clinical signs include general malaise, bleeding tendencies, anorexia, pale mucous membranes, fever, lymphadenopathy, splenomegaly, and uveitis (Mylonakis et al., 2004b). Hematological features of dogs presenting with the chronic phase of the disease also include nonregenerative anemia, thrombocytopenia, and leukopenia (Mylonakis et al., 2004b).

Ocular signs may be present in all stages, but animals are not usually presented for diagnosis until the chronic stage. Experimental inoculation of *E. canis* in dogs has resulted in the development of chorioretinitis and anterior uveitis in addition to meningitis during the acute phase of the disease (Panciera et al., 2001). Meanwhile, inoculation of *E. ewingii*, *E. chaffeensis*, or *A. phagocytophilum* in dogs did not result in the development of ocular or meningeal pathology (Panciera et al., 2001).

The prevalence of ocular lesions in canine ehrlichiosis has been reported as 10%–37%; when present, such ocular lesions can produce devastating ocular disease that is typically bilateral (Leiva et al., 2005; Swanson & Dubielzig, 1986; Troy et al., 1980). It has also been reported that approximately 18% of the cases of uveitis in North Carolina, USA are the result of some infectious etiology (Massa et al., 2002). Of these infectious causes of uveitis, nearly 40% of them are associated with *E. canis* infection (Massa et al., 2002). The ocular lesions themselves result from either a platelet deficiency or, more commonly, a vasculitis (or both). In a recent retrospective study of dogs with ocular manifestations of canine monocytic ehrlichiosis, uveitis was the most common ocular diagnosis with 58/90 (64.5%), 8/90 (8.9%), and 24/90 (26.6%) of affected dogs having

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anterior, posterior or panuveitis, respectively (Komnenou et al., 2007). Massive orbital and ocular hemorrhages have been observed, but more commonly, a uveitis with hemorrhagic overtones is the basic lesion (Fig. 37.1.26 and Fig. 37.1.27). Retinal vessels may be engorged and have perivascular infiltrates. Retinal hemorrhages are common, and retinal detachments may be observed, either from massive subretinal hemorrhage or from exudates (Fig. 37.1.28 and Fig. 37.1.29) (Leiva et al., 2005). Optic neuritis with engorged retinal vessels and papillary hemorrhages may also occur. In addition, corneal ulceration, necrotic scleritis, low tear production and orbital cellulitis have been reported (Komnenou et al., 2007). Experimentally, discrete perivascular infiltrates have been described during the subacute stage, but such infiltrates have not been described in clinical cases (Ellet et al., 1973). An atypical form of ocular lesion of canine ehrlichiosis involving bilateral, melting scleral lesions associated with uveitis, and resultant subconjunctival uveal prolapse was described (Martin, 1999). Histopathologically, the ocular lesions are typically a mononuclear perivasculitis.

Diagnosis of ehrlichiosis involves the direct visualization of morulae in peripheral blood smears (only been found in 11% of dogs with chronic ehrlichiosis), detection of *E. canis* antibodies, or PCR amplification of *Ehrlichia* spp. DNA (Belanger et al., 2002; Mylonakis et al., 2004b; Neer et al., 2002; Waner et al., 2001; Wen et al., 1997).

The mainstay of therapy for canine ehrlichiosis includes the administration of doxycycline or tetracycline (Neer et al., 2002; Sainz et al., 2000). The short-term prognosis for ehrlichiosis in dogs is typically good during the acute phase or mild chronic phase of the disease; however, long-term prognosis of chronic canine ehrlichiosis is variable to grave (Mylonakis et al., 2004b; Neer et al., 2002). Consensus on treatment of the ocular signs associated with canine ehrlichiosis has not been made. Nevertheless, therapy for ocular lesions associated with canine ehrlichiosis should include topical corticosteroids and atropine for anterior uveitis. In addition, a recommendation for systemic administration of anti-inflammatory dosages of corticosteroids in the presence of posterior segment disease has been made (Stiles, 2000).



Figure 37.1.26 Right eye of a 7-year-old, male mixed-breed dog with monocytic ehrlichiosis. Note the conjunctival hemorrhage, hyphema, and slight miosis. (*Source*: Reprinted with permission from Leiva, M., Naranjo, C. & Pena, M.T. (2005) Ocular signs of canine monocytic ehrlichiosis: a retrospective study in dogs from Barcelona, Spain. *Veterinary Ophthalmology*, **8**, 387–393.)



Figure 37.1.27 Left eye of a 5-year-old, male, mixed-breed dog with monocytic ehrlichiosis. Note the conjunctival hyperemia, rubeosis iridis, and iridal hemorrhages. (*Source*: Reprinted with permission from Leiva, M., Naranjo, C. & Pena, M.T. (2005) Ocular signs of canine monocytic ehrlichiosis: a retrospective study in dogs from Barcelona, Spain. *Veterinary Ophthalmology*, **8**, 387–393.)

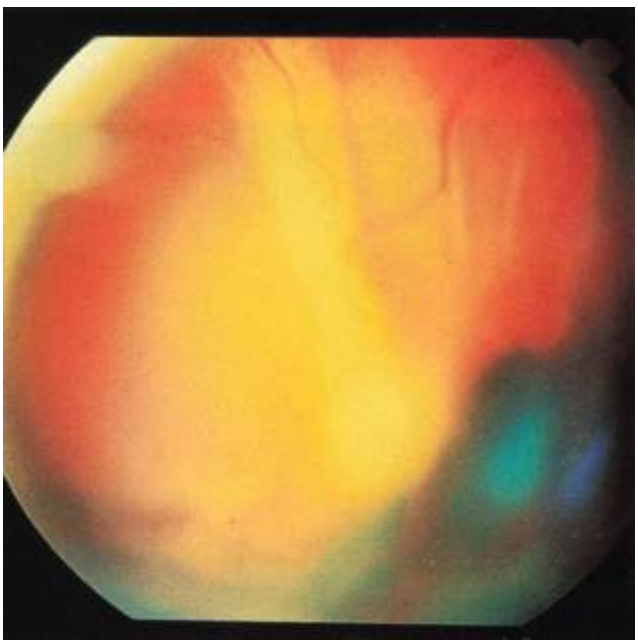


Figure 37.1.28 Bullous retinal detachment in a dog with *Ehrlichia canis* infection. Subretinal fluid is hemorrhagic, and a darker choroidal hemorrhage can be seen under the detachment.

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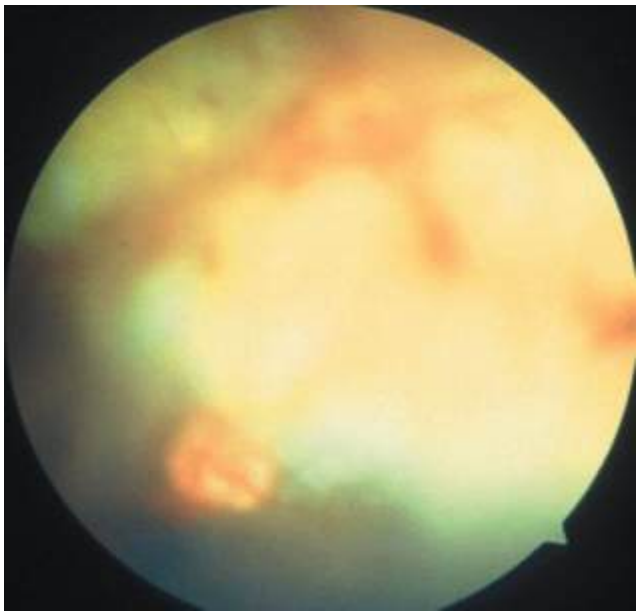


Figure 37.1.29 Left fundus of a 4-year-old, female German Shepherd dog with monocytic ehrlichiosis. Note the exudative retinal detachment and vitreous hemorrhage. (*Source*: Reprinted with permission from Leiva, M., Naranjo, C. & Pena, M.T. (2005) Ocular signs of canine monocytic ehrlichiosis: a retrospective study in dogs from Barcelona, Spain. *Veterinary Ophthalmology*, **8**, 387–393.)

Rocky Mountain Spotted Fever

Rickettsia rickettsii, a small coccobacillary, Gram-negative, obligate intracellular bacterium, is the causative agent of Rocky Mountain spotted fever (RMSF) (for review see Warner & Marsh, 2002) (Parola et al., 2005). Rodents and other small mammals serve as reservoirs for *R. rickettsii* (Warner & Marsh, 2002). *R. rickettsii* is transmitted by ticks; the vector and reservoir ticks are *Dermacentor andersoni* (Rocky Mountain wood tick), *D. variabilis* (American dog tick), *Amblyomma americanum* (Lone star tick), *Amblyomma cajennense* (Cayenne tick), *Rhipicephalus sanguineus* (brown dog tick), and *Haemaphysalis leporispalustris* (rabbit tick) (Warner & Marsh, 2002).

Incubation time varies from 2 to 14 days after infection via a tick bite (Warner & Marsh, 2002). *R. rickettsii* invade small blood vessels and subsequently replicate in endothelial cells, thereby damaging these cells and causing vasculitis and activation of primary and secondary hemostasis systems (Warner & Marsh, 2002). Systemic signs of RMSF include fever within 4–5 days of tick attachment (Warner & Marsh, 2002). Hemorrhages (i.e., petechiae and echymoses) occur commonly and are often seen on mucous membranes including those surrounding the eye (Warner & Marsh, 2002). Common clinicopathologic findings include thrombocytopenia, leukocytosis, hypoalbuminemia, and proteinuria (Mikszewski & Vite, 2005). Ocular and neurologic involvement is common with *R. rickettsia* infection, and clinical findings are consistently caused by vasculitis. Signs of conjunctivitis, chemosis, petechiae of the conjunctiva, iris and retina, hyphema, mild anterior uveitis, retinal edema, and retinal vasculitis are common, occurring in nine of 11 dogs in one series of dogs infected with RMSF (Davidson et al., 1989). In another study, fundic examination revealed chorioretinal lesions and retinal hemorrhage (Mikszewski & Vite, 2005). In experimentally infected dogs, uveitis was noted 14–21 days after onset of the signs of acute infection (Davidson et al., 1990). Fluorescein angiography in these experimentally infected cases revealed increased retinal vascular permeability which developed within 1–2 days after the onset of fever (Davidson et al., 1990). Leakage of vessels peaked during the second week of infection and persisted past the point of clinical and clinicopathologic recovery. The permeable areas involved venules more than arterioles, and smaller vessels were affected more frequently than larger vessels. These areas of retinal vascular leakage developed too early to be associated with immune complexes (Davidson et al., 1990). Other ocular abnormalities that may be noted on ocular examination are found when the CNS is affected. For example, one study found that some dogs with RMSF had abnormal nystagmus (spontaneous or positional nystagmus) and/or loss of menace response (Mikszewski & Vite, 2005).

Diagnosis of RMSF is made based upon consistent history, clinical and hematological findings consistent with RMSF, and identifying *R. rickettsii* through immunofluorescent testing (tissue), presence of circulating antibodies, or by identifying organism DNA using PCR (Allison & Little, 2013; Warner & Marsh, 2002). A fourfold increase in circulating IgG, from acute to convalescent (≥3 weeks apart) measurements, is diagnostic for recent infection (Warner & Marsh, 2002). Similarly, an increase in circulating IgG in acute to convalescent sera is diagnostic for RMSF. Importantly, a single IgG titer is nondefinitive because IgG may remain high for several years after infection (Warner & Marsh, 2002). If the disease is suspected, trial therapy with tetracyclines or chloramphenicol is warranted until test results are available (Warner & Marsh, 2002). Response to therapy is usually rapid and may be used in establishing a presumptive diagnosis (Mikszewski & Vite, 2005; Warner & Marsh, 2002). The inflammatory lesion of the anterior ocular segment should be treated with topical corticosteroids and atropine. The ocular lesions of RMSF usually resolve quickly with therapy. Immunity after infection with *R. rickettsii* is long lasting and provides protection against subsequent reinfection (Warner & Marsh, 2002). Reducing the dog's exposure to ticks and prompt removal of attached ticks are helpful to prevent RMSF (Warner & Marsh, 2002).

Viral

Canine Distemper

Canine distemper virus (CDV) is caused by an enveloped, single-stranded RNA Morbillivirus in the Paramyxoviridae family (for review see Deem et al., 2000). Several lineages or

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genotypes of CDV exist that are variously distributed throughout many continents (Demeter et al., 2007; Martella et al., 2006, 2008). CDV infects a wide variety of families of animals including Canidae (e.g., dogs), Procyonidae (e.g., raccoons), Ursidae (e.g., bears), Mustelidae (e.g., ferrets, skunks), and Hyaenidae (e.g., hyaena). The virus is spread mainly by inhalation of viral particles in aerosolized respiratory or other infected secretions such as urine. Widespread vaccination of dogs has markedly decreased the incidence of typical disease, and partial immunity may produce disease syndromes characterized more by neurologic signs than catarrhal signs of pneumonia and gastroenteritis. Clinical signs of CDV will vary with the strain of virus, immunity, and age of the host.

Acute ocular signs of CDV are usually associated with a bilateral conjunctivitis with serous ocular discharge that progresses to mucopurulent in nature. The palpebral conjunctiva is primarily involved but the cause of this conjunctivitis may be difficult to diagnose if respiratory and gastrointestinal signs are either minimal or subclinical. The cornea has not been described as being a target for the virus unless a lacrimal adenitis or dehydration has resulted in a marked reduction in tear production (i.e., KCS). The CDV may produce an inflammatory reaction in the lacrimal gland characterized by mononuclear and neutrophilic inflammatory infiltration as well as by marked degenerative changes in the glandular tissue (Martin & Kaswan, 1985). A recent study revealed that the histopathological changes in conjunctival samples obtained from dogs with CDV-induced KCS were similar to those with noninfectious KCS (de Almeida et al., 2009). In particular, a predominant lymphoplasmacytic infiltration, and acantholysis and keratinization of the ocular surface were described (de Almeida et al., 2009). Corneal ulceration is often profound with the development of multiple descemetoceles with or without corneal perforations in one or both eyes. KCS usually resolves in 4–8 weeks if the animal recovers from the systemic infection. Another mechanism for corneal involvement is distemper encephalitis producing a fifth cranial nerve palsy (i.e., neurotrophic keratitis).

CDV often produces a multifocal, nongranulomatous chorioretinitis, which is usually an incidental finding. The incidence of chorioretinitis is unknown but probably varies, as do those of the neurologic signs, with the strain of virus and the immunocompetency of the host. In one study, dogs with neurologic forms of CDV had a 41% overall prevalence of chorioretinal lesions; in contrast, 83% of dogs with chronic leukoencephalopathy syndromes had chorioretinal lesions (Thomas et al., 1993). These lesions are typically multifocal, and they are reportedly more frequent in the peripheral to midperipheral non-tapetal fundus (Fischer, 1971). Acute lesions must be differentiated from scars, because the latter will not correlate well with acute systemic signs. Active lesions in the non-tapetal region are white, somewhat fluffy, and have mildly indistinct borders (Fig. 37.1.30). Acute lesions progress to scars that are white, flat, and have sharply demarcated borders. In the tapetal region, the acute lesions are subtle, with loss of tapetal detail, and they may have a mild, overlying haziness. With time, these develop into hyperreflective lesions with sharp borders and varying degrees of pigment clumping. Lesions in both the tapetal and non-tapetal areas are typically circular to oval in shape and often become confluent with adjacent lesions, thus producing a scalloped pattern. Occasionally, chorioretinal lesions are diffuse, blinding, and may mimic the genetic syndrome of progressive retinal atrophy, with diffuse tapetal hyperreflectivity, optic nerve atrophy, and non-tapetal pigment dispersion.

Histopathologic retinal changes are characterized by retinal degeneration with, in some instances, perivascular cuffing. Lesions may be focal or diffuse, characterized by loss of ganglion cells, proliferation and clumping of the retinal pigment epithelium, focal or diffuse atrophy of photoreceptors, disorganization of retinal layers, focal gliosis, choroidal atrophy, and CDV inclusion bodies in glial cells. Acute cases may have retinal edema, vascular congestion, and perivascular cuffing (Jubb et al., 1957). The variations in reported ocular lesions may result from the stage of examination, immunocompetence of the animal, and the multiple mechanisms by which the lesions are produced. In the CNS, lesions of acute infections in young or immunocompromised patients are characterized by neuronal necrosis, with a minimal inflammatory reaction. With immunocompetent hosts or chronicity, the

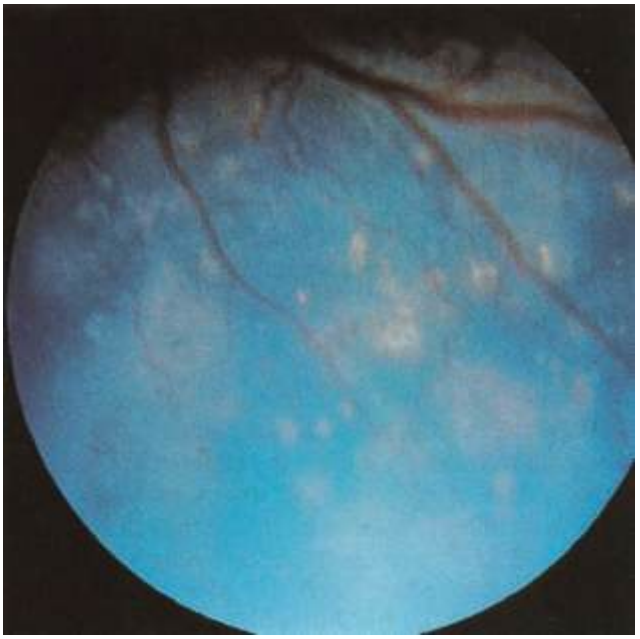


Figure 37.1.30 Distemper-induced, multifocal white lesions deep to the retinal vessels. Most lesions are active, as evidenced by hazy borders, and do not displace the vessels.

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CNS lesions are characterized by mononuclear inflammation and secondary demyelinization (Thomas et al., 1993).

The most dramatic clinical ocular problem associated with CDV is optic neuritis, which is characterized by an acute onset of bilateral blindness and mydriasis. If inflammation extends rostrally to the optic disc/papilla, ophthalmoscopic signs of peripapillary hemorrhages and edema, retinal vascular congestion, and elevation of the papilla are observed (Fig. 37.1.31). If the optic neuritis remains retrobulbar, however, the diagnosis is made on the basis of exclusion (i.e., blind eyes with dilated pupils and normal retinal function as tested by ERG). The optic neuritis syndrome may be isolated, prodromal, or concurrent with other neurologic signs of CDV. Distemper-associated blindness also may occur with inflammation of the optic tracts, lateral geniculate nucleus, optic radiation, or occipital cortex.

Ocular signs are suggestive of, but not definitive for, CDV. Acute lesions of chorioretinitis usually correlate well with concurrent systemic disease, but chorioretinal scars may not. CDV inclusions may be identified in infected monocytes, lymphocytes, neutrophils, or RBCs during evaluation of a stained peripheral blood smear. Alternatively, positive immunofluorescence by detection of viral antigen from conjunctival swabs/scrapings or blood smears, using methods such as fluorescent antibody testing may be helpful in diagnosing CDV early in the course of systemic disease (5–21 days postinoculation), but negative findings are inconclusive (Fairchild et al., 1967). This should not inhibit the examiner from performing immunofluorescent antibody testing, however, because one report on encephalomyelitis found an overall positive rate of 54% (and one as high as 75%) despite the mean duration of neurologic signs being 20 days (Fischer, 1971). Further, CDV has immunohistochemically been identified and diagnosed in skin and footpads from infected dogs (Haines et al., 1999). Reverse-transcriptase polymerase chain reaction (RT-PCR) assays have been shown to be both sensitive and specific for detection of both experimentally induced CDV (Frisk et al., 1999) and naturally occurring CDV (Elia et al., 2015). In particular, CDV RNA has been detected in urine, tonsils, whole blood, and conjunctival swabs from dogs with natural infections with CDV (Elia et al., 2006; Saito et al., 2006). A hemi-nested PCR system with specific probes now permits characterization of major CDV lineages and distinction between certain field- and vaccine-associated CDV strains (Martella et al., 2007). No specific antiviral therapy against CDV is, as yet, commercially available, so treatment is mainly symptomatic. Conjunctivitis and decreased tear production are treated with topical antibiotics and lubricants. Acute optic neuritis is treated with systemic anti-inflammatory dosages of glucocorticoids if other signs of CDV are absent. Vaccination is the key to preventing CDV. The prognosis for dogs with neurologic disease is considered guarded to poor.



Figure 37.1.31 Acute blindness in a dog with distemper associated with papillitis. Note the elevated, hyperemic optic disc. A slight vitreal haze interferes with detail.

Herpesviruses

Canine Herpesvirus Canine herpesvirus is an enveloped, double-stranded DNA virus of the *Alpha-herpesviridae* family and infects all canids. Transmission of the virus can occur *in utero* or during parturition. Puppies make contact with the virus in infectious secretions on passing through the birth canal of an infected bitch or may contract viral infection from contact with other infected puppies. Canine herpesvirus replicates in epithelial cells of the oropharynx and mucosa of the tonsils after oronasal exposure of neonatal puppies. The virus then enters macrophages which spread the infection hematogenously. The virus may remain latent in sensory ganglia and lymphoid tissue (Miyoshi et al., 1999). Litters of stillborn puppies or abortions may occur after transplacental infections. Young puppies (<2–3 weeks of age) most frequently develop clinical signs of canine herpesvirus, whereas infection tends to be confined to the respiratory and genital tracts in older dogs (Hill & Mare, 1974).

For further details on CHV infection, the reader is referred to a review of CHV (Evermann et al., 2011) which documents the clinical features of five forms of CHV-associated infections including the ocular form. Ocular manifestations of CHV infection are dependent on the age and immune competence of the host and may arise during both primary and recurrent infections (Evermann et al., 2011). Canine herpesvirus infection in adults tends to be restricted to ocular surface diseases affecting the cornea, conjunctiva, and eyelids including combinations of blepharitis, conjunctivitis, and keratitis (ulcerative and nonulcerative). In primary

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CHV ocular infections, lesions tend to be bilateral and are not always symmetrical, and most resolve spontaneously without permanent scarring. Naturally acquired recrudescent CHV ocular infections are reported in dogs with immunocompromising systemic diseases and those receiving immunosuppressive medications. In immunocompetent dogs, CHV ocular infection is frequently mild and self-limiting, although it may recur. Canine herpesvirus infection has produced a transient conjunctivitis and vaginitis of 4–5 days duration (Hill & Mare, 1974). The marked follicular reaction in the vagina raised speculation regarding whether it might be responsible for conjunctival syndromes characterized by follicular hyperplasia, but this has been discounted by the lack of transmissibility, inability to culture, and failure to show canine herpesviral antigen from dogs with this syndrome (Jackson & Corstvet, 1975, 1980). Conjunctival petechiae are frequently reported in dogs with CHV and are uncommon with most other causes of canine conjunctivitis, and hence, this lesion should be considered suggestive of CHV (Ledbetter et al., 2009a,b; Malone et al., 2010). Two adult dogs were diagnosed with canine herpesvirus-associated dendritic corneal ulcers (Ledbetter et al., 2005). Dendritic corneal ulcers are strongly indicative of CHV infection in the dog (Ledbetter et al., 2009b). During an outbreak of CHV infection in a colony of 27 young adult laboratory Beagles, conjunctivitis, ulcerative keratitis (ranging from punctate to dendritic to geographic in appearance), and nonulcerative keratitis were detected in 100%, 26% and 19% of affected dogs, respectively (Ledbetter et al., 2009b).

Until recently, canine herpesvirus has been thought of almost exclusively as a disease of the neonate, in which it is usually fatal. Puppies dying of herpesvirus infection have been reported to have bilateral panuveitis with keratitis, synechiae, cataracts, retinal necrosis and disorganization, retinal atrophy and dysplasia, and optic neuritis as well as atrophy. Because of the high fatality rate, the clinical implication of these lesions is unknown.

Diagnosis of canine herpesvirus is by identifying clinical signs suggestive of the disease in young puppies combined with necropsy lesions. Definitive confirmation of canine herpesvirus involves identification of virus, viral antigen, or viral DNA by transmitting electron microscopy, immunohistochemical methods, or PCR of infected tissues, respectively.

Therapy for canine herpesvirus is largely supportive; however, neonatal fatalities are common. Topical ophthalmic antiviral agents such as 0.1% idoxuridine, 1% trifluridine, and cidofovir 0.5% have been used to treat CHV ocular disease. There is no current vaccine for canine herpesvirus in North America, although one is available in various other countries (Eurocan Herpes 205, Merial, Lyon, France). This vaccine is used in CHV-1 seronegative dams to prevent and reduce morbidity and mortality in their offspring in acquired CHV-1 infection postpartum (Ledbetter et al., 2016; Poulet et al., 2001). In an experimental model of CHV-1 ocular disease, however, vaccination was ineffective in preventing ocular reinfection and viral shedding but may have reduced the severity of ocular clinical signs (Ledbetter et al., 2016).

Pseudorabies (Aujeszky's Disease) Pseudorabies is caused by an enveloped, double-stranded DNA virus of the Alphaherpesviridae family (for review see Mettenleiter, 2000; Zhang et al., 2015). This virus is capable of infecting a variety of animals, including the cat, cow, dog, and pig. Pigs are the main reservoirs of pseudorabies. Most infected dogs have a history of ingestion of infected raw pork. After ingestion of the virus, pseudorabies enters peripheral nerve endings in the mucosa and spreads along axons to the brain.

Clinical signs of pseudorabies include pruritis, worsening tachypnea/dyspnea, hypersalivation, hematemesis, tremor, and emesis (Zhang et al., 2015). Variable neurologic disturbances occur including depression, vocalization, ataxia, cervical rigidity, and ptyalism. Once clinical signs of pseudorabies have manifested, death from pseudorabies usually occurs quickly in dogs. In particular, 94% of dogs have been reported to die within 48 hours of the onset of signs of pseudorabies (Monroe, 1989). Ocular manifestations of this disease have been attributed to neurologic lesions, and include blindness, miosis, mydriasis, anisocoria, abnormal PLR, ptosis, facial paralysis, and epiphora (Monroe, 1989).

Presumptive diagnosis of pseudorabies is made based on clinical signs and history of the dog having been exposed to pigs or infected raw pork. The definitive diagnosis of pseudorabies is confirmed based on identification of the virus by *in-situ* hybridization, immunohistochemistry, or PCR of infected brain or tonsil (Cao et al., 2005; Quiroga et al., 1998).

Therapy for canine patients infected with pseudorabies is supportive, but most dogs do not survive the infection. There is no approved vaccine available for dogs against pseudorabies.

Infectious Canine Hepatitis (Canine Adenovirus Type-1)

Canine adenovirus type-1 (CAV-1), a nonenveloped, double-stranded DNA virus in the Adenoviridae family, is the causative agent of infectious canine hepatitis (ICH). ICH produces clinical disease in dogs, foxes, and bears. The virus replicates in regional lymph nodes and tonsils, after which a viremia develops resulting in infection of other tissues. In particular, CAV-1 has a predilection for liver parenchyma, vascular endothelium, and the reticuloendothelial system. The ocular lesions of ICH have mostly become a historical footnote since Rubarth described them in 1947 (Rubarth, 1947). CAV-1 may produce ocular lesions of anterior uveitis and corneal edema (Fig. 37.1.32 and Fig. 37.1.33) and has been estimated to produce ocular lesions in approximately 20% of dogs during the recovery phase of a natural infection (Carmichael, 1965). More troubling was the modified-live strains of CAV-1 used in vaccine production that were also

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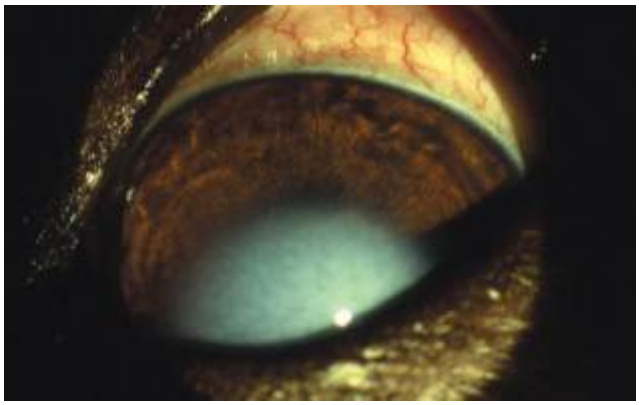


Figure 37.1.32 Transient corneal edema in a dog with CAV-1-induced "blue eye." Note the clearing of the corneal edema from the perilimbal area.

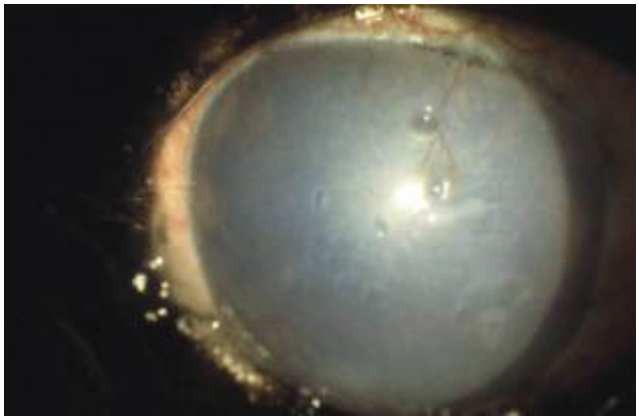


Figure 37.1.33 Severe and permanent corneal edema with early bullous keratopathy in a dog after CAV-1-induced "blue eye." Note the few fine corneal blood vessels from the upper limbus.

capable of producing ocular lesions (Fig. 37.1.34), with an estimated prevalence of 0.4% or less (Curtis & Barnett, 1973b). The universal use of canine adenovirus type-2 (CAV-2) for immunization against ICH, however, has all but eliminated this complication of vaccination.

Ocular lesions of CAV-1 manifest approximately 7–21 days after virus inoculation. Subcutaneous inoculation with CAV-1 produces ocular lesions 2–3 weeks after administration, and intravenous inoculation produces lesions in 7–14 days. This correlates with the observation of ocular lesions developing in the recovery phase of clinical disease. The most apparent ocular lesions are observed after clinical infection, but the virus invades the eye earlier (4–8 days post-inoculation) and may produce a mild, subclinical anterior uveitis (Carmichael, 1965; Carmichael et al., 1975; Curtis & Barnett, 1973b).

The ocular lesions, whether resulting from natural infection or induced by vaccine, are considered to be caused by an immune-complex, arthus, reaction that occurs 10–21 days



Figure 37.1.34 "Blue eye." Mild but extensive corneal edema in a puppy 10–14 days after vaccination with CAV-1. Note the typical mottled appearance of the corneal edema.

after vaccination or in the recovery stage of natural infection. The events suggest that if the virus persists in the anterior segment, it stimulates a local immune response that either restricts growth or, if incomplete, allows for viral persistence. If the response is incomplete, immune complexes form, which, with a balance of antibody and antigen in the presence of complement, stimulate leukocytic, chemotactic, and other inflammatory factors. The resultant neutrophilic and monocytic responses release lysosomal enzymes that, when directed at viral antigen in the corneal endothelium, result in endothelial damage and corneal edema. The histopathologic response is a nongranulomatous anterior uveitis that spares the posterior segment (Carmichael et al., 1975).

The ocular reaction is bilateral in up to approximately 30% of cases. The most visible ocular lesion is corneal stromal edema. Occasionally, however, a dog will have blepharospasm, miosis, hypotony, and aqueous flare 1–2 days before the corneal edema manifests. Corneal edema begins near the limbus, and it may remain focal or progress rapidly to generalized edema. A marked hypotony combined with altered corneal rigidity may result in keratoconus. The conjunctiva and episclera are usually hyperemic, and although the corneal edema may obscure deeper examination, anterior uveitis may manifest, with iris texture changes, plasmoid aqueous, and miosis. Most reactions occur in young animals that have endothelial regenerative capabilities, so the corneal edema is usually transient, taking from a few days to between 2 and 3 weeks to clear. In some instances, the edema is either permanent or may require several months to clear. If the edema persists, eventually scarring and pigmentation develop in the cornea; the Afghan Hound is reported to have an increased risk for persistent corneal edema (Curtis & Barnett, 1981). The anterior uveitis is notable for the lack of residual synechia. Glaucoma, which is the most significant ocular sequela of CAV-1, usually results in blindness, because it is masked during the early stages by the

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preexisting corneal edema and conjunctival hyperemia (Carmichael, 1965; Curtis & Barnett, 1973a,b).

Tentative CAV-1 infection is diagnosed on the basis of the typical ocular lesions combined with a history of recent vaccination or illness (i.e., acute hepatic disease in a dog with poor vaccination) in a puppy or young (<2 years of age) dog. Definitive diagnosis is made based upon immunohistochemistry for CAV-1 and detection of viral DNA using PCR in infected tissue (Caudell et al., 2005; Chouinard et al., 1998).

Therapy of CAV-1 is symptomatic and similar to that for other forms of nonseptic anterior uveitis. Specifically, therapy includes topical corticosteroids, atropine, prostaglandin inhibitors, and perhaps, hypertonic salt solution or ointment in cases of more severe corneal edema.

Papillomavirus

Papillomaviruses are nonenveloped, double-stranded DNA viruses in the family Papillomaviridae (for review see Munday et al., 2017; Nicholls & Stanley, 1999). Two forms of papillomaviruses (oral form and conjunctival form) have been associated with causing papillomas involving the canine eye and adnexa. Papillomaviruses are usually species-specific and antigenically distinct. Oral papillomas, which are usually found in young animals, result from infection with a canine papillomavirus-1 (CPV-1) (previously known as canine oral papillomavirus [COPV]), and the solitary skin lesions of older animals result from infection with cutaneous papillomaviruses (CPV-1, -2, -6, and -7) (Munday et al., 2017). The CPV-1 may, in addition to causing oral papillomas, produce lesions on the eyelids, conjunctiva, and cornea.

Papillomas develop 4–8 weeks after infection with CPV-1, and they usually regress within 4–8 weeks after their development as T-cells migrate into the papilloma from a cell-mediated immunity response (Nicholls & Stanley, 1999). Despite spontaneous regression of most viral papillomas, the ocular forms may not. Ocular viral papillomas have been reported in dogs as old as 9 years of age (Hare & Howard, 1977).

Importantly, however, conjunctival squamous papillomas have been described in older dogs and have not been associated with papillomaviruses (Beckwith-Cohen et al., 2015). Historically, a conjunctival form of papilloma, that is distinct from the large cauliflower lesions of viral papillomas, has been described; it typically manifests as a solitary lesion on the dorsal to lateral bulbar conjunctiva, in proximity to the limbus, and is often pigmented, slightly nodular, and has fronds on the surface, and in these instances, may have represented nonviral conjunctival squamous papillomas (Sansom et al., 1996). Nevertheless, most lesions in older animals are solitary, but multiple lesions may also develop (Bonney et al., 1980b; Hare & Howard, 1977; Sansom et al., 1996). Physical irritation from the lesion may preclude observation and awaiting its spontaneous regression. Excision should involve minimal handling of the papilloma, wide excision (if possible), and perhaps, cryotherapy at the base of the lesion (Bonney et al., 1980a, b; Collier & Collins, 1994; Hare & Howard, 1977). There is no vaccine to prevent canine papillomaviruses.

Tick-Borne Encephalitis Virus

Tick-borne encephalitis virus (TBEV) is a single-stranded, enveloped RNA virus belonging to the genus Flavivirus (for review see Gritsun et al., 2003). TBEV can be found in Europe and Asia. The virus is transmitted to humans and animals via the bite of an infected tick (*Ixodes ricinus* – central Europe; *Ixodes persulcatus* – Ural, Siberia, Far East) (Gritsun et al., 2003). Several cases of TBEV infection have been reported in dogs, most of which are relatively recent and indicate an emerging disease (Gresikova et al., 1972a; Stadtbaumer et al., 2004; Tipold et al., 1993; Weissenbock & Holzmann, 1996; Weissenbock et al., 1998). It has been shown that 16.4% and 24% of dogs have been exposed to the virus in Norway and Austria, respectively (Csango et al., 2004; Leschnik et al., 2002). Clinical signs develop after 5–9 days after infection with the virus (Gresikova et al., 1972b). Dogs infected with TBEV can either: (1) seroconvert without clinical signs; or (2) manifest with peracute (death within 1 week), acute (animals recover, clinical signs improve within 3 weeks), or chronic disease (clinical signs resolve between 1 and 6 months) (Leschnik et al., 2002; Stadtbaumer et al., 2004).

Clinical signs are representative of the neuropathologic changes seen in the CNS and include pyrexia, general malaise, behavioural changes, seizures, tetraparesis, anisocoria, and neck or back pain (Pfeffer & Dobler, 2011). TBEV has been reported as a possible cause of optic neuritis in one dog (Fig. 37.1.35) (Stadtbaumer et al., 2004). Diagnosis of TBEV is made based on measuring acute and convalescent serum and CSF IgG for TBEV using an ELISA or by using immunohistochemistry on CNS tissue at necropsy (Stadtbaumer et al., 2004; Weissenbock et al., 1998). Magnetic resonance techniques can be used to aid in reaching a diagnosis of TBEV (Beckmann et al., 2016; Sievert et al., 2017). Treatment of dogs with TBEV infection is purely supportive as there is no virucidal therapy for the disease. Prognosis is variable depending on the clinical form of the disease.

Metabolic Diseases

Diabetes Mellitus

Diabetes mellitus is the most common disorder of the endocrine pancreas in dogs. Diabetes mellitus is considered a syndrome characterized by either: (1) hyperglycemia resulting from defects in insulin secretion; (2) insulin sensitivity in target tissues; or (3) a combination of (1) and (2) (Gilor et al., 2016). Diabetes mellitus is traditionally described as being either type 1 diabetes mellitus (T1DM)/insulin-dependent diabetes mellitus (IDDM), or type 2 diabetes mellitus (T2DM)/non-insulin-dependent diabetes mellitus (NIDDM)

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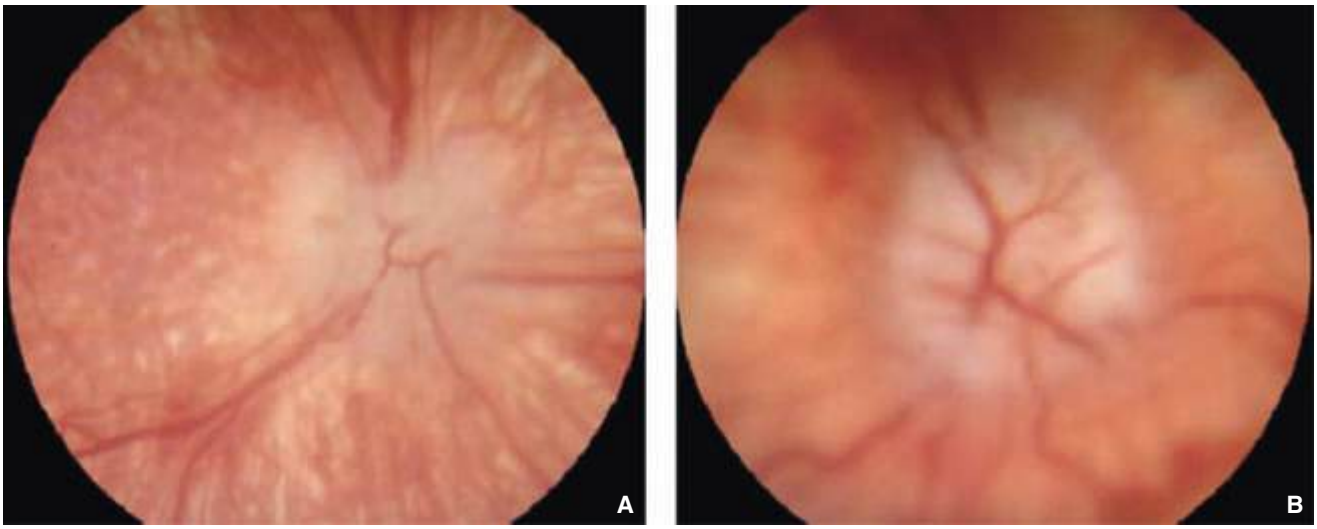


Figure 37.1.35 Tick-borne encephalitis virus in a 3-year-old, spayed female Siberian Husky. Fundus photographs on day 0. **A.** Left eye: the optic disc is swollen with mild peripapillary edema. **B.** Right eye: the optic disc is markedly swollen and elevated. The peripapillary retina is detached. Note some peripapillary hemorrhages. (*Source*: Reprinted with permission from Stadtbaumer, K., Leschnik. M.W. & Nell. B. (2004) Tick-borne encephalitis virus as a possible cause of optic neuritis in a dog. *Veterinary Ophthalmology*, **7**, 271–277.)

(Gilor et al., 2016). A call for a refined classification of diabetes mellitus in dogs, as has been done in humans, is necessary to account for the varying etiopathogeneses of diabetes mellitus and to ensure appropriate treatments are employed (Gilor et al., 2016). As eluded to already, the etiopathogeneses and risk factors of diabetes mellitus in dogs are multifactorial: the reader is referred to the reviews on the topic by Nelson and Reusch (2014) and Gilor et al. (2016).

Ocular manifestations of both experimental and spontaneous diabetes mellitus in the dog have long been used as a model for human diabetic ocular complications (Gepts & Toussaint, 1967). In particular, the galactosemic dog has been used to study diabetic complications because of the accelerated rate of development of vascular complications (Wyman et al., 1988). Ocular manifestations of diabetes mellitus in dogs include cataract formation (Sato et al., 1991), corneal endothelial cell loss (Datiles et al., 1990; Yee et al., 1985), corneal endothelial pleomorphism and polymegathism (Yee et al., 1985), intracorneal stromal hemorrhage (Violette & Ledbetter, 2017), and retinal vascular damage such as microaneurysms (Kador et al., 1990; Landry et al., 2004; Violette & Ledbetter, 2018). In addition, reduced corneal sensitivity (Cullen et al., 2005; Good et al., 2003), and significantly altered keratoconjunctival parameters (Cullen et al., 2005; Williams et al., 2007) have also been reported in diabetic dogs. In particular, diabetic cataractous dogs had: (1) significantly lower STT values and significantly higher corneal touch thresholds than nondiabetic noncataractous dogs; (2) significantly lower mean tear film break up times than nondiabetic cataractous and nondiabetic noncataractous dogs; (3) conjunctival epithelial dysplasia and/or squamous metaplasia in ventral palpebral conjunctival biopsy specimens of 5/7 dogs (Fig. 37.1.36); (4) reductions in goblet cell densities in 4/7 diabetic dogs (Fig. 37.1.36); and (5) elevations in tear glucose concentrations compared with both the noncataractous nondiabetic and cataractous nondiabetic dogs, which did not appear to affect conjunctival microbial isolates (Cullen et al., 2005).

A common ocular manifestation of diabetes mellitus in the dog is cataract formation (Basher & Roberts, 1995; Ling et al., 1977). Diabetic cataract formation varies with the species affected, individual, age of disease onset, duration of the diabetes, and severity of hyperglycemia. The young dog is very susceptible, and the cat resistant, to diabetic cataract formation (Wyman et al., 1988). Cataracts were present at the initial examination of almost 60% of spontaneous canine diabetics, whereas no cataracts were noted in a series of 30 cats (Ling et al., 1977; Schaer, 1977). This percentage of cataracts in the dog increases even after the diagnosis of diabetes is established, because diabetic control is usually erratic. In particular, a study reported that 75% of the canine population diagnosed with diabetes mellitus developed cataracts by approximately 12 months whereas approximately 80% of the affected population formed cataracts by approximately 16 months (Beam et al., 1999).

Research into both ocular and nonocular complications of diabetes now focuses on the role of aldose reductase in the sorbitol or polyol metabolic pathway (Kador et al., 2016). The increase in blood sugar (either glucose or galactose) results in diffusion of increased amounts of sugar into the lens. The principal energy pathway of the lens is anaerobic glycolysis, and the first enzyme in the glycolytic pathway is hexokinase, which is in limited supply. When there is an increased supply of sugar, it becomes shunted to the sorbitol

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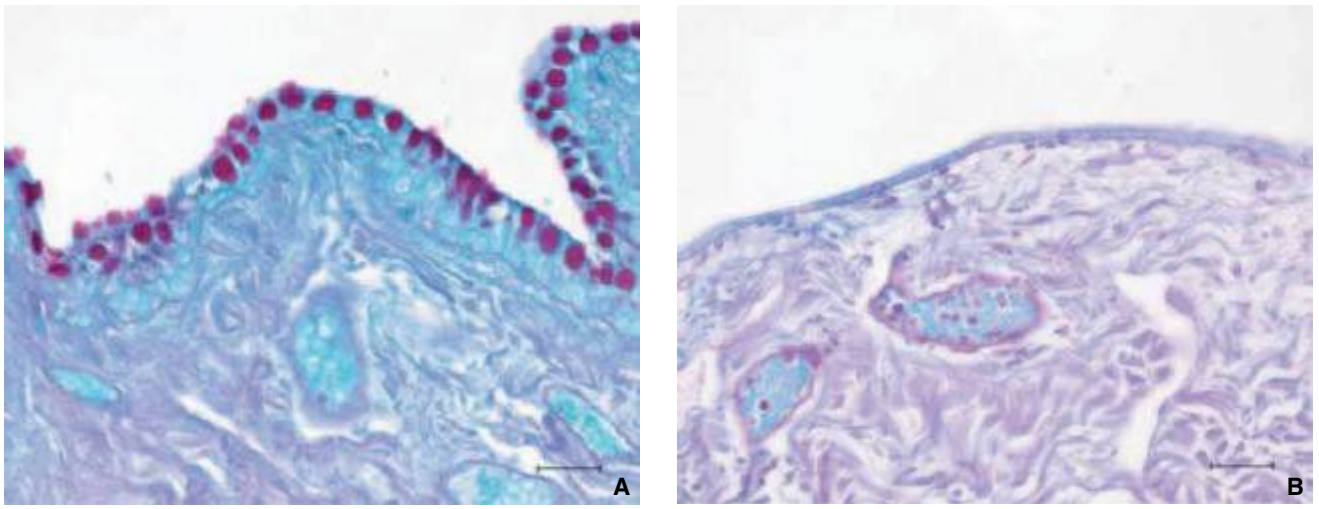


Figure 37.1.36 **A.** Photomicrograph of a section of ventromedial palpebral conjunctiva from a nondiabetic cataractous dog. Note the abundance of periodic acid-Schiff (PAS)-positive goblet cells and normal epithelial architecture. (Bar = 35 µm; PAS.) **B.** Photomicrograph of a section of ventromedial palpebral conjunctiva from a diabetic cataractous dog. Note the epithelial thinning and absence of goblet cells. (Bar = 35 µm; PAS.) (*Source*: Reprinted with permission from Cullen, C.L., Ihle, S.L., Webb, A.A., et al.(2005) Keratoconjunctival effects of diabetes mellitus in dogs. *Veterinary Ophthalmology*, **8**, 215–124.)

pathway, which normally supplies only 5% of the glucose metabolism. Aldose reductase is the first enzyme in this pathway, which forms polyols (i.e., sorbitol with glucose; dulcitol with galactose) that do not diffuse through the cell membranes as well and, thus, accumulate in the lens. This results in an osmotic gradient that draws water into the lens, which in turn results in swelling of lens fibers and opacification of the lens. Sorbitol is slowly metabolized to fructose, which can slowly diffuse across cellular membranes, whereas dulcitol is not further metabolized, thereby resulting in more rapid changes. The speed of the process depends on sugar concentrations and endogenous levels of aldose reductase (Engerman et al., 1982; Wyman et al., 1988). One of the reasons for variations in susceptibility among species, ages, and individuals to diabetic cataracts is the lenticular activity of aldose reductase (Engerman et al., 1982; Kador et al., 2016). Cataractous changes are initially observed as vacuoles in the equatorial cortex that extend into the anterior and posterior cortices (Engerman et al., 1982; Kador et al., 2016). The cortical sutures may be accentuated as well (Fig. 37.1.37). The process progresses to complete cortical opacification of the lens, and the sutures are often either fractured or widened because of water imbibition. Cataracts from a variety of causes may progress rapidly, but diabetes should be considered when a dog is presented with rapidly progressive bilateral cataracts.

The cells of the corneal endothelium in diabetic dogs, when examined with specular microscopy, have more pleomorphism and a wider variation in size (Yee et al., 1985). These changes directly relate to the degree of diabetic control, but the significance of this in the dog has not been documented (Yee et al., 1985).

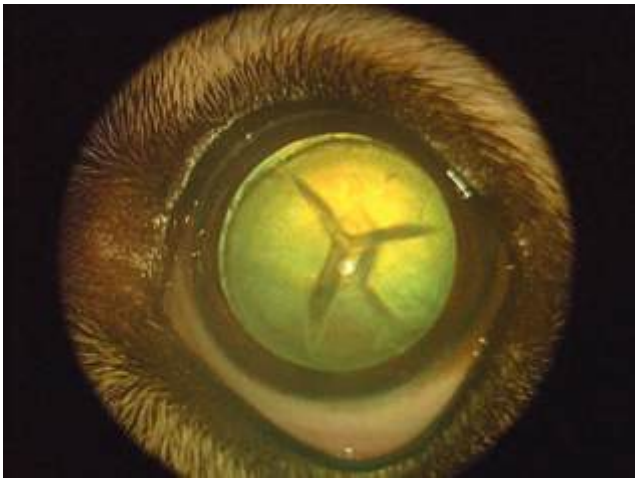


Figure 37.1.37 Immature cortical cataracts in a mixed-breed dog with diabetes mellitus. Note the accentuated anterior and posterior cortical sutures.

Early diabetic retinopathy, which is characterized by microaneurysms, has been shown in both spontaneous and experimental diabetes as well as in the galactosemic canine model. Diabetic retinopathy takes approximately 3–5 years to develop, and almost invariably in this period, cataracts will develop that obscure this change. In the galactosemic model, microaneurysms develop by 27 months. The background retinopathy, or nonproliferative stage, is characterized by the following sequence of events: thickening of the basement membrane of the retinal capillaries, dilation of retinal veins, loss of pericytes, microaneurysms, areas of capillary nonperfusion, retinal hemorrhages, infarction of

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the nerve fiber layer, and edematous residues. The pericytes are thought to support the capillaries, and their loss is thought to be responsible for the dilation and microaneurysm formation (Engerman & Bloodworth, 1965; Wyman et al., 1988). Pericyte loss is linked to aldose reductase activity in these cells, and it can be retarded with use of aldose reductase inhibitors (Kador et al., 1990).

Proliferative diabetic retinopathy, which is devastating to human vision, was difficult to produce experimentally in the diabetic dog (because of the induction time), but it can be produced experimentally in the galactosemic dog by 74–80 months postinduction. Preretinal hemorrhages were noted by 56 months and soft exudates and neovascularization by 60 months. Neovascularization was limited to the disc area. Descriptions of diabetic retinopathy in clinical cases usually have relied on postmortem, flat-mount preparations of the retinal vessels. In a clinical series of diabetic dogs, retinal alterations of venous dilation, tortuosity and sacculation, microaneurysm, retinal hemorrhages (Fig. 37.1.38), color and reflection changes in the tapetum, and exudates were described (Landry et al., 2004; Monti et al., 1976). Evidence of lipid retinopathy may also be present (Fig. 37.1.39) (Halenda & Moore, 1998). Background retinopathy may be suspected at ophthalmoscopy, but fluorescein angiography is necessary for confirmation. Unlike in human diabetics where elevations in aqueous humor levels of vascular endothelial growth factor (VEGF) have been correlated with the severity of diabetic retinopathy, diabetic dogs do not have elevations in aqueous humor levels of VEGF compared with nondiabetic dogs which may explain the low prevalence and severity of diabetic retinopathy in this species (Abrams et al., 2011).

All dogs undergoing evaluation for cataract surgery should have their blood and urinary glucose levels determined. Also, serum fructosamine and/or glycosylated hemoglobin levels help to determine the degree of glycemic control over 2–3 weeks, and 3 months, respectively (Jensen, 1995).

Cataract surgery is the only available therapy for diabetes-induced cataract formation in dogs, although topical medical therapy with the aldose reductase inhibitor, Kinostat™, is on the horizon at the time of writing this chapter (Kador et al., 2016) (as per the manufacturer's website https://therapeuticvision.com/our-products/kinostat/). The success rate of surgical cataract removal in diabetic animals is approximately the same as that for cataract extraction in nondiabetic dogs (Bagley & Lavach, 1994). Lens-induced uveitis is often present and, if possible, should be controlled before performing surgery, but in severe cases this may not be an option. With regards to the keratoconjunctival effects of diabetes mellitus, diabetic dogs may be at risk of devloping ulcerative keratitis after procedures requiring general anesthesia. Afterall, diabetic dogs have: (1) reduced corneal sensation; (2) reduced STT values; (3) accelerated tear film break up times; and (4) altered conjunctival goblet cell numbers and general anesthesia has been shown to alter tear film properties (Cullen et al., 2005). Consequently, the authors recommend that tear supplements be used in diabetic dogs after, and occasionally prior to, procedures requiring anesthesia (such as cataract extraction).

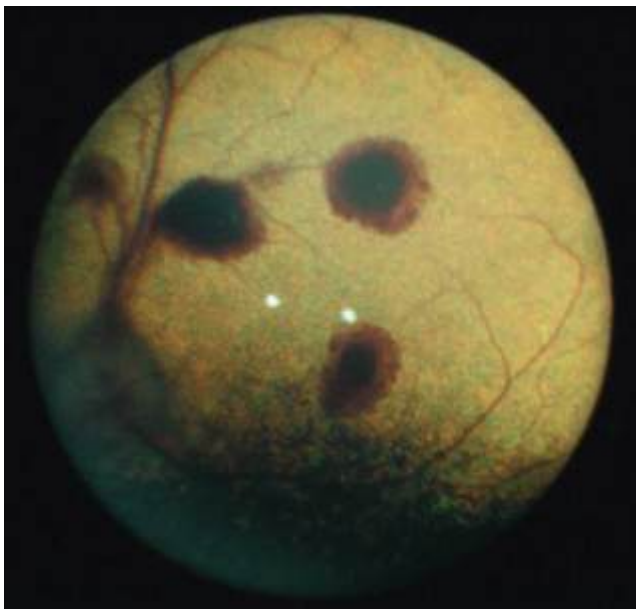


Figure 37.1.38 Representative fundus photograph of a study dog with concurrent diabetes mellitus with punctate retinal hemorrhage. (*Source*: Reprinted with permission from Violette, N.P. & Ledbetter, E.C. (2018) Punctate retinal hemorrhage and its relation to ocular and systemic disease in dogs: 83 cases. *Veterinary Ophthalmology*, **21**, 233–239.)



Figure 37.1.39 Appearance of the fundus of the right eye approximately 5 months after cataract surgery. Axial horizontal white retinal deposits are the predominant finding. Also seen are associated retinal hemorrhages, mild vascular dilation, tortuosity, and mild papilledema. The fundus of the left eye exhibited similar pathology. (*Source*: Reprinted with permission from Halenda, R.M. & Moore, C.P. (1998) Presumed lipid retinopathy in a diabetic dog. *Veterinary Ophthalmology*, **1**, 171–174.)

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Hyperadrenocorticism (Cushing's Syndrome)

Hyperadrenocorticism, or Cushing's syndrome, is a common endocrinopathy in dogs. Hyperadrenocorticism is pathophysiologically divided into three forms: (1) pituitary-dependent hyperadrenocorticism; (2) hyperadrenocorticism from functional adrenocortical tumours; and (3) iatrogenic hyperadrenocorticism. Affected dogs are typically 6 years of age or older. The clinical and laboratory findings associated with canine Cushing's syndrome are mainly attributable to chronic glucocorticoid excess and, to a much lesser degree, overproduction of adrenal androgens.

Hyperadrenocorticism has been associated with ocular lesions of progressive corneal ulceration, nonhealing corneal ulceration, corneal calcification, cataracts, KCS, lipemia retinalis, and lesions associated with systemic hypertension (Lorenz, 1982; Ward et al., 1989; Williams et al., 2007; Violette & Ledbetter, 2017a,b). Hyperlipidemia may produce lipemia retinalis or lipids in the aqueous. An association with KCS has also been observed in a series of cushingoid dogs, in which 11 of 57 cushingoid dogs had KCS (although the STT was not routinely performed) and 18% had corneal ulcers (Lorenz, 1982). The corneal ulcers were typically deep, chronic, and often, the presenting complaint. Tear production and ulcerations often improved with mitotane (o,p'-DDD) therapy and remission of the hyperadrenocorticism. In general, high endogenous corticosteroid levels are thought to aggravate the healing of corneal ulcers rather than to cause ulcers, but spontaneous ulceration has been observed when relapse of the hyperadrenocorticism occurs. The incidence of cataracts may relate more to complications of diabetes mellitus than to elevated levels of corticosteroids.

Any nonhealing corneal stromal ulcer or sterile progressive corneal ulcer should prompt consideration of endogenous predisposing factors, of which elevated corticosteroid levels (either endogenous or exogenous in origin) should be kept in mind. In most instances, clinical signs of Cushing's syndrome will be evident. Readers are advised to consult a current internal medicine textbook for a detailed discussion on the diagnosis of and therapy for hyperadrenocorticism.

Hypothyroidism

Hypothyroidism develops as a result of decreased production of thyroxine (T_4) and triiodothyronine (T_3) by the thyroid gland. Hypothyroidism is a common naturally occurring disease in dogs, with reported prevalence rates of 0.2%–0.8% (Dixon & Mooney, 1996; Milne & Hayes, 1981). The mean age of dogs diagnosed with hypothyroidism is 7 years.

There is a clinical association between hypothyroidism and a variety of ocular lesions, although experimental dogs that were made hypothyroid for 9 months did not develop any ophthalmic lesions. As many as 20% of dogs with hypothyroidism have been reported to have KCS (Peruccio, 1982). The presence of reduced tear production has been described in another study of hypothyroid dogs, although whether these animals go on to develop clinical KCS requires further investigation (Williams et al., 2007). The association between KCS and hypothyroidism has been thought to be one of multiglandular, immune-mediated inflammation. The lack of decreased STT values in experimental hypothyroidism, however, supports an indirect association rather than hypothyroidism per se (Miller & Panciera, 1994). Because hypothyroidism results in vascular disease characterized by atherosclerosis, the association with retinal lesions of hypertension and arteriosclerosis is not surprising, nor is it consistent. Hypertensive retinal changes of retinal hemorrhages and, less frequently, bullous retinal detachments may be observed (Gwin et al., 1978; Liu et al., 1986; Manning, 1979; Miller & Panciera, 1994; Rubin, 1975). The retinal vasculature may provide evidence of arteriosclerosis, with straight, narrow vessels that, when advanced, become irregular and opaque. Hyperlipidemia with hypothyroidism may manifest as lipemia retinalis, corneal lipid degeneration, and lipids in the aqueous humor (Kern & Riis, 1980; Nell, 1995). Corneal lipid deposits with hypothyroidism may take various forms as well, from diffuse and rapidly developing opacities at all levels of the cornea to the characteristic, peripheral arcus lesion adjacent to the limbus (Crispin, 1993). Intracorneal stromal hemorrhage has also been observed in hypothyroid dogs (Violette & Ledbetter, 2017).

In addition to the keratoconjunctival effects, and evidence of hypertension and/or hyperlipidemia, patients with hypothyroidism may also manifest with a variety of neurologic signs. Specifically, hypothyroidism has been associated with the development of various neurological signs including signs of stupor/coma, appendicular lower motor neuron disease (manifesting as generalized weakness), cranial nerve deficits (e.g., facial nerve paresis/paralysis, peripheral and central vestibular disease), laryngeal paresis/paralysis and megaesophagus (Bichsel et al., 1988; Higgins et al., 2006; Jaggy et al., 1994; Rushton et al., 2013; Vitale & Olby, 2007). Of these clinical manifestations, patients most likely will present for ophthalmic assessment based upon demonstration of signs of cranial nerve dysfunction or vestibular disease (e.g., nystagmus, strabismus, facial nerve paresis/paralysis, etc.), although other hypothyroid-associated concurrent clinical signs may be present.

The gold standard for the diagnosis of canine hypothyroidism is made on the basis of comparing resting T_4 levels with those occurring after administration of thyrotrophin-stimulating hormone (Panciera, 1999). Because of the limited availability of thyrotrophin-stimulating homone, however, diagnosis of hypothyroidism is made based upon consistent clinical signs in association with measuring serum levels of total thyroxine, canine thyroid stimulating hormone, and free thyroxine. Readers are advised to consult a current internal medicine textbook for a detailed discussion on the diagnosis of and therapy for canine hypothyroidism.

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Ionic Disturbances

Hypocalcemia

Hypocalcemia in dogs may be caused by several conditions including hypoparathyroidism, postparturient hypocalcemia, acute or chronic renal failure, acute pancreatitis, vitamin D toxicity, severe nutritional secondary hyperparathyroidism (rare in dogs fed diets containing low calcium-to-phosphorus ratios), and intestinal malabsorption syndromes, among others (for review see Dhupa & Proulx, 1998). Neurologic signs of restlessness, muscle fasciculations, and tonic–clonic seizures occur with a total serum calcium level of 6–7 mg/dL or a serum ionized calcium level of less than 2.5 mg/dL (Bruyette & Feldman, 1988). The cause of the hypocalcemia can be determined with renal function tests, radiography, and parathyroid hormone assays.

Hypocalcemia in the dog has been documented, both experimentally and clinically, to be associated with focal punctate to linear opacities in the anterior and posterior cortices of the lens (Jones & Alley, 1985; Kornegay et al., 1980; Lettow et al., 1966). The lenticular opacities may occur at different levels in the cortex, and they may reflect different episodes of hypocalcemia. The degree and duration of hypocalcemia necessary to produce cataracts is unknown, but the appearance of the cataracts is quite suggestive of hypocalcemia.

Treatment of hypocalcemia involves correction of the underlying disease, if possible, and calcium supplementation with vitamin D_2, D_3, or dihydrotachysterol. Additional focal cataracts may manifest for a period after correction of the hypocalcemia, and the existing lenticular opacities will remain.

Neoplasia: Central Nervous System

Intracranial neoplasia, whether primary or secondary, often produces ocular and/or orbital signs. All animals with a suspected space-occupying CNS lesion should undergo ophthalmoscopy to determine whether papilledema, optic neuritis, or optic nerve atrophy is/are present.

The ophthalmic signs associated with intracranial neoplasia are highly variable and dogs may present with signs as subtle as internal ophthalmoparesis as the predominant clinical sign or with ophthalmic signs associated with abnormalities of multiple cranial nerves and abnormal changes in mentation and/or gait (Cullen et al., 2002; Larocca, 2000; Rossmeisl et al., 2005; Webb et al., 2005). Intracranial neoplasia frequently produces visual deficits and papilledema in association with neurologic signs (Palmer et al., 1974). Because of the great variation in myelination of the canine papilla/optic disc, early papilledema is difficult to detect unless it is asymmetrical or there is a definite rim of peripapillary edema. Intracranial tumors may also produce blindness, which may be acute in nature. Diffuse or multifocal disease may produce blindness by involving multiple sites in the visual pathways and, as a result, produce other neurologic deficits as well (Braund et al., 1977; Palmer et al., 1974). A solitary mass involving the optic chiasm may produce blindness without obvious neurologic signs.

Tumors at the base of the brain in the middle cranial or rostral fossa may be varied, but pituitary carcinomas that are nonfunctional, optic nerve gliomas, and meningiomas are likely candidates for optic chiasmal involvement (Davidson et al., 1991; Safaty et al., 1988). Clinically, blindness is often acute. In reality, it is progressive, and partial visual deficits are not generally noted by owners. Because blindness is accompanied by afferent pupillary defects with a normal ocular fundus, the syndrome must be differentiated from SARDS using ERG. Early diagnosis and aggressive therapy may result in the return of some vision (Davidson et al., 1991).

Cavernous Sinus Syndrome

The cavernous sinus is a paired venous sinus anatomically located on the floor of the cranial vault and extending from the orbital fissures to the petro-occipital canals. Cranial nerves III, IV, VI, and the ophthalmic and maxillary branches of V lie in close proximity to the cavernous sinus. Consequently, diseases (including neoplasia) involving the region of the cavernous sinus can result in deficits in any or all of these cranial nerves. The constellation of abnormal clinical signs attributed to dysfunction of cranial nerves III, IV, VI and at least one of the first two branches of cranial nerve V is known as cavernous sinus syndrome (Rossmeisl et al., 2005). Cavernous sinus syndrome can be either unilateral or bilateral (Theisen et al., 1996; Rossmeisl et al., 2005). Clinical signs related to deficits of these cranial nerves may include a fixed and dilated pupil on testing direct and consensual PLR, ptosis, decreased corneal sensation, decreased ability to retract the globe, and complete (i.e., internal and external) ophthalmoplegia. The most common cause of cavernous sinus syndrome in dogs is neoplasia (Rossmeisl et al., 2005). Consequently, prognosis for cavernous sinus syndrome is considered guarded to grave (Rossmeisl et al., 2005).

Neoplasia: Systemic

Lymphosarcoma

Lymphosarcoma is the most common secondary intraocular neoplasia of dogs, and it usually affects both eyes. In most cases, systemic involvement is obvious at the physical examination, but ocular disease may be the presenting complaint. Very rarely, the systemic disease is occult and the ocular lesion is the primary clinical sign. In one large prospective study, 37% of cases of lymphosarcoma had ocular lesions (Krohne et al., 1994). Of these ocular lesions, 49% were anterior uveitis, 9% posterior uveitis, 14% panuveitis, 23% retinal hemorrhages only, and 6% adnexal diseases (Krohne et al., 1994). Most animals with ocular lesions were in the advanced stages of lymphoma (i.e., stage V), and 78% of the cases with leukemia involved ocular disease. This study did not report secondary glaucoma as a presenting feature, although

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previous authors have noted this as being a common complication of intraocular lymphosarcoma (Barron et al., 1963; Cello & Hutcherson, 1962). This may represent the difference between ocular lesions detected after presentation of a case for ocular complaints and those found prospectively by screening patients with lymphosarcoma. Regardless, lymphosarcoma with ocular involvement equates to advanced disease and translates to a shorter survival period for the dog.

A variety of mechanisms may cause retinal hemorrhages, but the cause is often not obvious. Retinal hemorrhages may be associated with inflammation, thrombosis, severe anemia, thrombocytopenia, hypoxia, vasculitis, and interference with clotting factors. The retinal hemorrhages associated with lymphosarcoma may be multifactorial and may not necessarily represent leukemic invasion, but uveitis represents tumor invasion of the eye (Krohne et al., 1994).

A relatively rare syndrome involving rapidly fulminating lymphosarcoma in young dogs, with dramatic orbital and ocular involvement has been observed (Martin, 1999). The orbital involvement produces marked bilateral exophthalmos, chemosis, and exposure keratitis. Rarely, lymphoma will be diagnosed on the basis of a diffusely enlarged third eyelid that has no obvious accompanying systemic lesions.

Lymphadenopathy combined with endogenous bilateral uveitis or hemorrhages should prompt fine needle aspirations of enlarged lymph nodes or other affected organs to confirm the diagnosis of lymphosarcoma cytologically.

For current therapeutic options, the reader should consult appropriate internal medicine textbooks for lymphosarcoma protocols. Lesions affecting the anterior segment of the eye, however, do respond to conventional anterior uveitis therapy using topical corticosteroids. The intraocular pressure should be monitored, and glaucoma should be treated if it develops.

Other: Metastases

Although relatively rare, a variety of carcinomas and sarcomas have been described as metastasizing to the eye and orbit. Bilateral ocular involvement may occur, because most tumors spread via a hematogenous route. The typical site of ocular metastasis is the uveal tract, and, specifically, the ciliary body. The neoplasms may be masked by intraocular hemorrhage, inflammation, and glaucoma; thus, intraocular neoplasia, whether primary or secondary, should be included in the differential diagnosis of undetermined spontaneous intraocular hemorrhage or secondary glaucoma. Ocular metastasis is usually a late occurrence, so the history and/or physical examination of the affected dog will often be indicative of significant systemic disease.

The incidence of ocular metastasis is probably underreported. Systemic and/or neoplastic processes involving the eye include: intravascular lymphoma; hemangiosarcoma (Fig. 37.1.40); malignant melanoma; adenocarcinoma of the pancreas, mammary, salivary, sweat, and thyroid glands; squamous cell carcinoma; transitional carcinoma; mastocytoma; and canine transmissible venereal tumor (Bush et al., 2003; Cullen et al., 2000; Dubielzig, 1990; Habin & Else, 1995; Kilrain et al., 1994; Ladds et al., 1970; Lavach, 1984; Miller et al., 1990; Pereira et al., 2000; Szymanski et al., 1984).

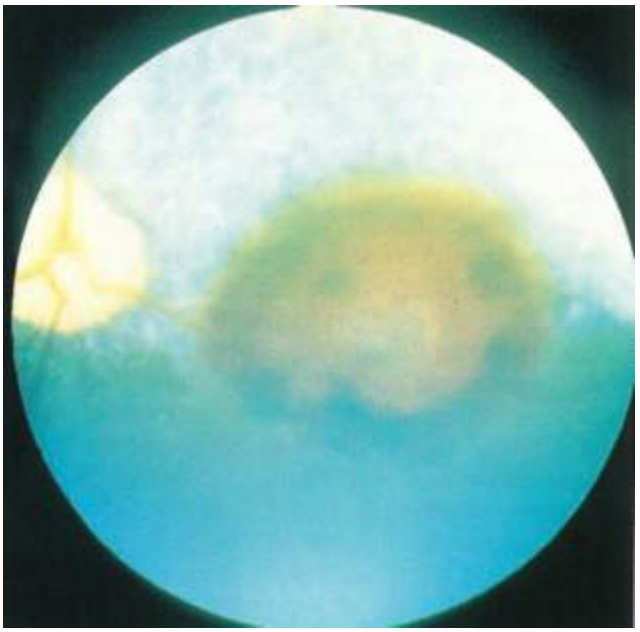


Figure 37.1.40 Metastatic hemangiosarcoma to the eye. This condition was bilateral and appeared as multifocal retinal hemorrhages of various sizes. Thoracic radiographs showed disseminated, small densities suggestive of mycotic pneumonia without hilar lymphadenopathy. The condition was diagnosed on the basis of lung biopsy results.

Nutritional Disorders

Milk Replacer-Induced Disease

Cataract formation has been recognized in puppies and a variety of other species fed commercial or homemade orphan milk formulas. Levels of arginine have been found to be deficient in canine and feline formulas, and supplementation has prevented cataracts in wolf cubs, puppies, and kittens (Remillard et al., 1993; Vainisi et al., 1981). Various attempts to correct commercial milk formulas, however, still result in cataract formation (Glaze & Blanchard, 1983; Martin & Chambreau, 1982; Ranz et al., 2002). Different breeds have been suggested to be more susceptible, but there is no documentation to support this idea. It has been shown that large breeds with rapid growth may need more supplementation with methionine and arginine (Ralston et al., 1990). In order to develop nutrition-related cataracts, milk-replacer diet must be ingested during the first week postpartum, and lenticular changes will be noted by 3 weeks. Lenticular changes begin as vacuolar changes separating the anterior and posterior cortices from the nucleus and

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outlining the sutures. At 5 weeks after milk-replacer supplementation, a lenticular opacity remains as a white, posterior subcapsular opacity. With growth, this opacity occupies the fetal nucleus and appears as a spheroidal or ring-shaped fetal nuclear opacity (Martin & Chambreau, 1982). In exotic or wild animals, lenticular opacities have been more complete, appearing as a diffuse, anterior subcapsular cortical opacity and producing at least a temporary blindness (Vainisi et al., 1981). Because these cataracts rarely produce blindness in the dog, the dilemma lies in differentiating nutritional from inherited congenital cataracts or cataracts caused by other noxious agents. The history of milk replacer supplementation, normal ocular examination in parents of affected dogs, and location of the lenticular opacity usually suggest the nutritional source of the cataract.

Vitamin A Deficiency

Vitamin A (retinol), a fat-soluble vitamin, is derived from its precursors (carotenoids) which are found in plants (for review see von Lintig & Vogt, 2004). With regards to the importance of vitamin A in the ocular system, vitamin A (retinol) is stored and transformed into retinal which is translocated between the retinal pigment epithelium and the photoreceptors (Thompson & Gal, 2003). Within the photoreceptors, retinal combines with opsin (a protein) to form the visual pigment rhodopsin (Thompson & Gal, 2003). Vitamin A deficiency has been produced experimentally in young dogs, but it does not appear to be a naturally occurring clinical syndrome (Tvedten & Whitehair, 1977). The earliest sign of such deficiency in young dogs, however, is vestibular disease, but blindness may also be an early manifesting sign (Tvedten & Whitehair, 1977). Papilledema has been noted in some dogs with a deficiency in vitamin A; however, the resultant papilledema could not be correlated with increased CSF pressure (Tvedten & Whitehair, 1977).

Vitamin E Deficiency

The antioxidant action of vitamin E limits lipid peroxidation and production of free radicals, which are very damaging to cellular constituents. The major sites of oxidant damage are the membranes of subcellular organelles. Phospholipids are a significant structural component of the photoreceptors, and normal shedding and phagocytosis by RPE produces a peroxidized lipoprotein or lipofuscin from the lysosomes in the cell. Lipofuscin is a yellow-brown, autofluorescent pigment.

Ocular consequences of vitamin E deficiency in the dog have been described in both clinical and research animals (Davidson et al., 1998; Hayes et al., 1970; McLellan et al., 2002, 2003; Riis et al., 1981). Systemic lesions consist of muscular and testicular degeneration, reproductive problems, hemolytic anemia, and weak and dying puppies. Ocular lesions in both clinical and research animals occur only with prolonged deficiency, and they consist of cataracts, decreased vision to blindness, and retinal degeneration. The retinal degeneration has been described in detail and is first noted on ophthalmoscopy as a fine stippling in the central deep retina. The mottling increases in intensity, with brown accumulations and night blindness later developing. After 6 months on a vitamin E-deficient diet, the tapetum develops central hyperreflectivity, and retinal vascular attenuation is noted. Eight to 12 months of deficiency results in discrete, yellow-brown, multifocal accumulations in the tapetal fundus, tapetal hyperreflectivity, and attenuated retinal vessels with focal constrictions (Fig. 37.1.41). In one report, the ERG response was extinguished after 3 months of deficiency, although the animals were not blind at this time (Riis et al., 1981).

Histopathologic changes are more severe in the central retina, beginning as RPE hypertrophy with inclusions of lipofuscin. With chronicity, the lipofuscin increases in amount and radiates out from the central retina, and degenerative changes develop preferentially in the rods (although cones also degenerate). With time, the retinal degeneration progresses to involve all layers, and lipofuscin is present in the retina (Riis et al., 1981).

Clinical reports of vitamin E deficiency and retinal pigment epitheliopathy or central retinal degeneration closely parallel those of experimental models (Davidson et al., 1998; McLellan et al., 2002, 2003). The clinical appearance of multifocal, yellowish-brown accumulations in the tapetal retina with modest tapetal hyperreflectivity and vascular attenuation is suggestive of the diagnosis. Further, neurological

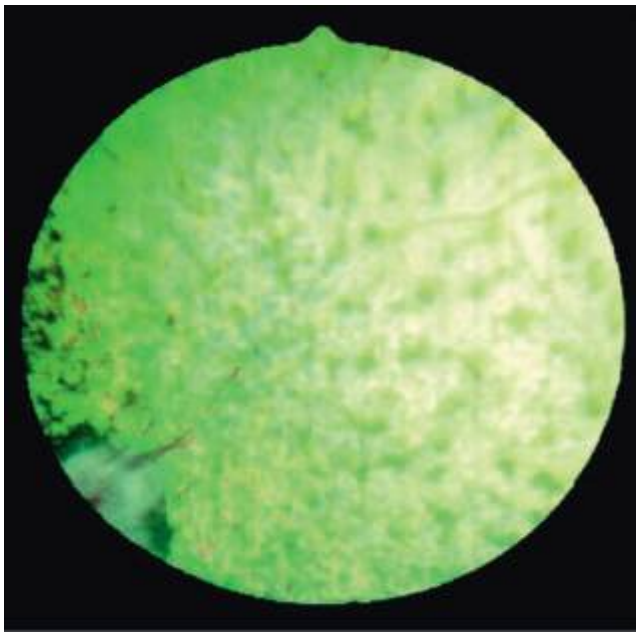


Figure 37.1.41 Funduscopic changes associated with retinal pigment epithelial dystrophy (RPED). Multiple discrete areas representing lipofuscin accumulation are visible. (*Source*: Reprinted with permission from Esson, D.W. (2015) *Clinical Atlas of Canine and Feline Clinical Disease*. Oxford: Wiley-Blackwell.)

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signs including ataxia, generalized paresis, proprioceptive deficits, and abnormal spinal reflexes may be present (McLellan et al., 2003). The condition is thought to be a primary metabolic vitamin E deficiency inherited as an autosomal recessive trait in English Cocker Spaniels (McLellan et al., 2003). Diagnosis is made based upon identifying characteristic clinical signs and identifying low serum concentrations of vitamin E (McLellan et al., 2002). Therapy is directed at supplementation with vitamin E (McLellan et al., 2003).

Zinc Deficiency

Zinc deficiency may result from either reduced intestinal absorption or by consuming a diet deficient in zinc. Zinc deficiency has been implicated in dogs with dermatitis characterized by dry, scaly skin, erythema, alopecia, and change in hair colouration (White et al., 2001). Young, adult Alaskan Malamutes and Siberian Huskies are predisposed to zinc-responsive dermatosis (White et al., 2001). The distribution of cutaneous lesions caused by zinc deficiency involves periocular and perioral regions, mucocutaneous junctions, and pressure points (Fig. 37.1.42) (White et al., 2001). Other ocular manifestations of experimental zinc deficiency in dogs, other than blepharitis, include mucopurulent exudation,and keratitis (Roberston & Burns, 1963). Diagnosis of zinc-responsive dermatosis is made based upon consistent clinical signs, histopathological examination of skin lesions, and response to oral zinc supplementation. Most dogs respond favorably to oral zinc supplementation (White et al., 2001).

Toxicities

Antimicrobials

Ketoconazole

The imidazole drug, ketoconazole, is a widely used antifungal agent. Long-term use of ketoconazole has been found to be associated with the development of bilateral cataracts (Da Costa et al., 1996). Most dogs affected by ketoconazole-induced cataracts are young (<5 years) and have medium to large physical stature. There does not appear to be any gender predisposition. Cataracts develop anywhere from 3.5 to 37 months after initiating ketoconazole therapy. The pathogenesis of ketoconazole-induced cataract formation remains unknown.

Sulfa drugs

Idiosyncratic reactions (non dose-dependent) to sulfonamides result in a variety of medical conditions including



Figure 37.1.42 **A.** Ten-year-old male neutered Siberian Husky with zinc responsive dermatosis. Note unilateral periocular crusts. **B.** Same dog as (**A**), 1 year after initiation of zinc methionine treatment. Resolution of lesions was termed an excellent response. (*Source*: Reprinted with permission from White, S.D., Bourdeau, P., Rosychuk, R.A., et al. (2001) Zinc-responsive dermatosis in dogs: 41 cases and literature review. *Veterinary Dermatology*, **12**, 101–109.)

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polyarthropathy, hepatopathy, blood dyscrasias, skin eruptions, and ocular disease (for review see Trepanier, 2004). One of the most common clinical findings in dogs with idiosyncratic reactions to potentiated sulfonamides is KCS (Trepanier et al., 2003). The lacrimotoxicity is thought to result from the sulfonamides' nitrogen-containing pyridine ring, and the toxicity is not unique to sulfadiazine. The incidence of KCS may be as high as 4%–15% among animals overall, but as many as 63% of animals on the drug may have decreased STT values compared with their baseline, pretreatment levels. The decrease in tear production may occur in a matter of a few days after sulfa therapy is initiated, and although 50% will develop it within 30 days, the average duration has varied from 41 to 91 days of therapy. The resultant KCS may be either unilateral or bilateral (Berger et al., 1995; Diehl & Roberts, 1991; Morgan & Bachrach, 1982; Slatter & Blogg, 1978).

To date, the lacrimotoxicity in dogs has not been related to breed, age, or dose of medication. Improvement in the KCS with cessation of the sulfa therapy and cyclosporine stimulation has been variable. Advanced cases are often resistant to cyclosporine therapy.

Although less frequent, a more life-threatening effect of sulfadiazine is a pancytopenia resulting from bone marrow toxicity. Ophthalmic lesions of intraocular hemorrhages and pale retinal vessels may be associated with the anemia and thrombocytopenia (Fig. 37.1.43).

Sulfadiazine-induced allergy has been documented as a syndrome in the Doberman Pinscher (Giger et al., 1985). Ten to 21 days after the initiation of therapy, an immune-mediated vasculitis produced nonseptic polyarthritis, glomerulonephropathy, polymyositis, skin rash, fever, anemia, and leukopenia. Ocular lesions of mucopurulent conjunctivitis and fundus lesions consisting of multifocal retinitis were found in one dog as well. The fundic lesions may be unilateral, and in this study, they were restricted to the tapetal region. The lesions were one-quarter to one-half the diameter of the optic disc in size, and they were circular lesions of reduced reflectivity. At fluorescein angiography, there was late leakage of fluorescein into the fundic lesions. Spontaneous improvement was noted after cessation of the sulfadiazine therapy (Giger et al., 1985).

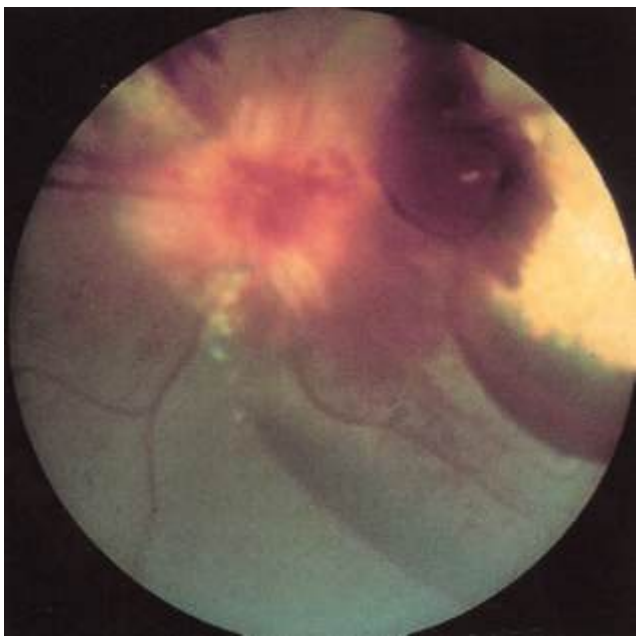


Figure 37.1.43 Fundus of Flat-Coat Retriever that died from complete bone marrow aplasia produced by trimethoprim–sulfadiazine therapy. Note the marked preretinal and nerve fiber hemorrhages.

Drug eruptions have been described with trimethoprim–sulfonamide after 3–12 days of therapy and have varied from generalized pustular dermatitis to erythema multiforme (i.e., Steven–Johnson syndrome) and folliculitis. The Steven–Johnson syndrome may produce a facial dermatitis involving the eyelids and mucocutaneous junctions as well as KCS (McMurdy, 1990; Medleau et al., 1990).

Antiparasitic Drugs

Disophenol

Disophenol (2,6-diiodo-4-nitrophenol) was a popular, injectable anthelmintic for ancylostomiasis during the 1970s. In young neonatal or weanling puppies, either debilitated or overdosed toxic signs might develop, relating to an increased metabolic rate. Experimentally, cataracts could be routinely produced with three times (30 mg/kg) the recommended parenteral dose. The onset of cataracts is within 24–36 hours and is typically a vacuolar lesion beginning at the equator of the lens, then progressing axially, both anteriorly and posteriorly, in the superficial lenticular cortex. In most cases, resolution of the cataracts occurs within 3–7 days (Martin et al., 1972a).

Ivermectin

Ivermectin is an antiparasitic drug that exerts its antiparasitic actions by activating ligand-gated chloride channels in a variety of invertebrates (Cully et al., 1994; Kane et al., 2000). Activation of chloride channels prevents synaptic transmission thereby causing paralysis of the invertebrate parasite (Campbell et al., 1983; Wang & Pong, 1982). Ivermectin concentrations do not typically reach toxic levels within the mammalian CNS when administered at therapeutic antiparasitic dosages. The reason for this is that the mammalian CNS vascular endothelial cell of the blood–brain barrier has a specific ATP-dependent transporter, known as P-glycoprotein, that prevents a variety of molecules (drugs) from entering the CNS. This attribute of the blood–brain barrier prevents the toxic or therapeutic accumulation of a variety of drugs, including ivermectin, within this body compartment (for review on P-glycoprotein see Mealey, 2004; for review on the blood–brain barrier see Webb & Muir, 2000). It should be noted, however, that a variety of tissues will

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express P-glycoprotein (Mealey, 2004). Other drugs that are actively removed by P-glycoprotein include doxorubicin, methylprednisolone, doxycycline, digoxin, and various phenothiazines (Mealey, 2004).

P-glycoprotein is coded for by the multiple drug resistance gene (MDR-1). It is well known that herding dogs, especially Collies, are sensitive to therapeutic dosages of ivermectin (Houston et al., 1987; Paul et al., 1987; Seward, 1983; Tranquilli et al., 1987). A genetic defect in MDR-1 has been found as the cause of ivermectin sensitivity (Mealey et al., 2001). The mutant allele (gene) is thought to have descended from a common ancestor in Great Britain sometime in the nineteenth century (Neff et al., 2004). Breeds having been found to carry the mutant MDR-1 allele include the Australian Shepherd, Miniature Australian Shepherd, Collie, English Shepherd, Longhaired Whippet, McNab, Old English Sheepdog, Shetland Sheepdog, and Silken Windhound (Neff et al., 2004). Animals homozygous for the mutant MDR-1 allele are highly sensitive to ivermectin toxicity (100 μg/kg), heterozygotes may be sensitive to dosages greater than 100 μg/kg, and noncarrier animals are not predisposed to ivermectin toxicity at recommended therapeutic dosages (Mealey, 2004). Assessment of MDR-1 mutations in dogs is possible (Veterinary Clinical Pharmacology Laboratory, College of Veterinary Medicine, Washington State University, http://www.vetmed.wsu.edu/depts-VCPL/) and is advised before administering drugs that are substrates for P-glycoprotein, including ivermectin.

Aside from breeds of dogs hypersensitive to therapeutic dosages of ivermectin, ivermectin toxicosis can occur with gross overdosages of the drug (Hopkins et al., 1990). Ivermectin toxicosis resulting from increased inhibition of neurons within the CNS manifests as impaired level of consciousness (depression to coma), muscle tremors, with or without hyper- or hypothermia, and a variety of abnormal neuro-ophthalmic findings including absent menace response, mydriasis (in normal ambient lighting) with or withour positive PLR, and various types of strabismus. Blindness may occur without marked CNS signs, and this is usually accompanied by mydriasis in normal ambient lighting. Blindness has also been observed with normal PLR and a normal fundus. Ophthalmoscopic findings may include papilledema and retinal edema with folds and low-lying retinal separations (Fig. 37.1.44) (Epstein & Hollingsworth, 2013; Kenny et al., 2008). Residual pigment disruption may be visible in the non-tapetal fundus with recovery. Importantly, however, a normal fundic examination may also be seen in dogs with absent PLR (Pollio et al., 2018). ERG may show extinguished or attenuated a- and b-waveforms (Kenny et al., 2008; Pollio et al., 2018). Vision loss is temporary, with recovery in 2–10 days (Hopkins et al., 1990; Kenny et al., 2008; Ketring, 1990).

Diagnosis of ivermectin toxicosis is based on clinical signs (adverse signs appear within hours of administration or accidental ingestion) and a history of recent administration or ingestion of ivermectin. Therapy for ivermectin toxicosis is aimed at supportive nursing care. Use of intravenous lipid emulsion has been used successfully in dogs with ivermectin toxicosis (Clarke et al., 2011; Epstein & Hollingsworth, 2013; Pollio et al., 2018). Intensive care may be required if clinical signs become severe. Animals typically make full recoveries. However, complete recovery may be prolonged (weeks) and affected dogs may die of severe respiratory/cardiovascular depression in severe cases.

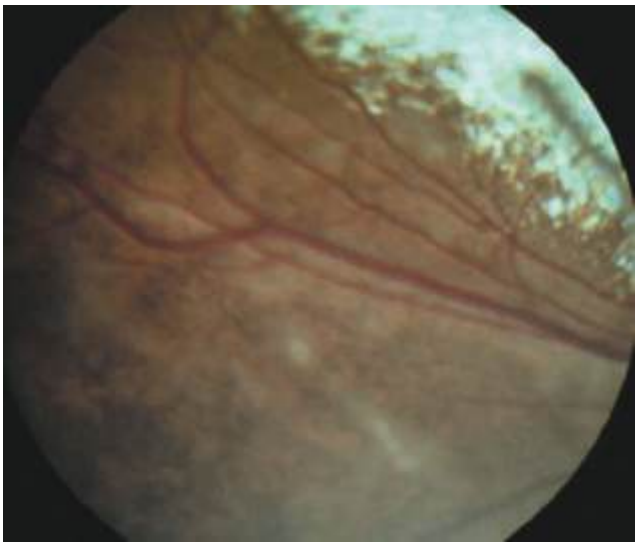


Figure 37.1.44 Retinal examination of dog with ivermectin-induced blindness. The image depicts areas of retinal edema, right eye. (*Source*: Reprinted with permission from Epstein, S.E. & Hollingsworth, S.R. (2013) Ivermectin-induced blindness treated with intravenous lipid therapy in a dog. *Journal Veterinary Emergency and Critical Care*, **23**, 58–62.)

Cardiovascular Drugs

Amiodarone

Amiodarone is a class III antiarrhythmic drug used in dogs with dilated cardiomyopathy and ventricular arrhythmias (Calvert et al., 2000; Jacobs et al., 2000). Adverse reactions to this drug include hepatotoxicosis and blood dyscrasias (Bicer et al., 2002b; Calvert et al., 2000). It has also been shown, experimentally, that corneal opacities may develop after long-term use of amiodarone in dogs (Bicer et al., 2002a). Only one of six dogs treated with amiodarone, however, developed corneal opacities in this study. Considering that these dogs were housed indoors, and that amiodarone-induced corneal opacity development is dependent somewhat on ultraviolet light exposure, the incidence of corneal opacities in dogs receiving amiodarone therapy may increase if dogs have exposure to sunlight.(Bicer et al., 2002a)

Tocainide

Tocainide is an oral, antiarrhythmic agent that has been used in veterinary cardiology. When used in 12 Doberman

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Pinschers with cardiomyopathies at recommended doses for more than 2 months, however, a bilateral, progressive corneal edema developed in three of the animals that was irreversible when well established. When advanced, the edema was severe enough to hinder vision. Early withdrawal of the drug may reverse the edema (Gratzek et al., 1993).

Electricity

Electric shocks and lightning strikes can produce direct ocular sequelae and also cause injury to the CNS (may manifest as blindness, papilledema, cranial nerve palsies) (for review on pathogenesis and human manifestation see Norman et al., 2001). Electric shocks and lightning strikes of a severe nature may produce cataracts that manifest months later. Cataracts are more likely to be produced by electrical shocks to the head. The appearance of clinical and experimentally induced electric cataracts are quite similar, and they consist initially of vacuoles that are present bilaterally in the midperipheral anterior cortical lens (Fraunfelder & Hanna, 1972; Thomas & Hanna, 1974). Ultrastructurally, the vacuoles are extracellular and transient, lasting several weeks. The lens vacuoles are prognostic indicators of later cataract formation. The lens epithelium subsequently proliferates, thereby producing multilayered plaques of lens capsule and lens fibers in the central anterior capsular region. Severe electric shock (e.g., from lightning) may produce both anterior and posterior cortical opacities (Norman et al., 2001). A typical electric cataract has been described in one dog 18 months after chewing on an electric cord (Brightman et al., 1984).

Hypolipidemic Drugs

Hypolipidemic compounds of the hydroxymethylglutaryl–coenzyme A reductase inhibitor group, when administered at high dosages, produce cataracts in the dog. These cataracts typically begin as posterior subcapsular equatorial opacities and, occasionally, anterior equatorial cortical cataracts. In one report, cataracts were noted 9–28 weeks after the initiation of therapy and began around the suture lines (Gerson et al., 1990). Continuation of therapy did result in complete cortical cataracts. Not all animals developed opacities, however. The dose used for cataract induction was 40–60 times the clinical dose, and chronicity of administration of the drug did not increase the incidence of cataracts. Therefore, such cataracts are unlikely to be of clinical importance. The genesis of the cataract was not determined, but it was thought to result from inhibition of cholesterol synthesis in the lens fiber's cellular membrane.

Insect Bites

Insect bites or envenomation from hornets, bees, fire ants, and spiders may occur on the eyelids or cornea of all animals. Acute, severe blepharedema is the usual extent of bites to the eyelids, although bites from insects such as the brown spider or multiple fire ant bites may result in tissue sloughing (Joyce, 1983; Rakich et al., 1993). Acute, focal corneal necrosis with rapid melting of the corneal stroma is not a rare event because of the deposition of proteolytic enzymes. The diagnosis is often presumptive unless multiple bites on the animals are present or insects were observed while biting. Lysis of the corneal stroma may require surgical repair with conjunctival flaps.

Ionizing Radiation

The ocular effects of ionizing radiation are similar no matter the source. Both the ocular effect(s) and the time to develop ocular disease depend on the dose, age of the animal, and the species being studied. In a long-term study of burros, swine, and cattle receiving gamma and mixed neutron-gamma radiation, the swine and burros were resistant to radiation-induced cataracts, but cattle were about as equally susceptible as humans (Brown et al., 1972). The most common source of ionizing radiation-induced ocular lesions is from radiation therapy for neoplasms of the head. All dogs develop a blepharitis at 1 month or less after radiation therapy. In three series involving cobalt-60 radiation therapy and megavoltage therapy for neoplasms of the head, ocular complication rates were between 76% and 84% (Jamieson et al., 1991; Roberts et al., 1987; Theon et al., 1993). Approximately 45%–59% of these complications were sight-threatening or chronic in nature. The mildest sign was a self-limiting conjunctivitis (35% of cases), but more severe and chronic signs of keratoconjunctivitis, KCS, and ulcerative keratitis were more common (64%–78%) and occurred either during or 2–3 months after therapy. Anterior uveal changes such of miosis, hypotony, and flare were relatively uncommon (8%–10%) and occurred within 1 month after therapy. They were also unresponsive to anti-inflammatory drugs. Cataract formation was delayed for 1.0–9.6 months and occurred in 11%–26% of patients. Cataracts were typically in the equatorial and posterior subcapsular regions, but they may be diffuse. Multifocal retinal hemorrhages were delayed from 1 to 6 months and present in 19% of the patients. Optic nerve damage from irradiation was not documented in these three clinical studies, although in one study, four dogs developed blindness 2–6 months after therapy, with no evidence of cataracts or retinal disease. A separate, histopathologic study reported seven dogs that developed optic nerve axonal degeneration 6–24 months after radiation therapy (Ching et al., 1990). Additional late-onset lesions noted at histopathology, but not clinically, included retinal atrophy and tapetal atrophy (Ching et al., 1990).

Histopathologically, several ocular lesions have been identified (Ching et al., 1990). Conjunctivitis is characterized by: epithelial and subepithelial infiltrate of neutrophils, plasma cells, and lymphocytes with vascular congestion; keratitis with mixed inflammatory cells, with or without neovascularization; and corneal epithelial atrophy and thinning. Radiation-induced cataracts are characterized by disorganized lens

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epithelium in the lens bow, posterior migration of nuclei, disorganized lens fibers, bladder cells, and vacuoles. These latter changes occur predominantly at the equator and posterior subcapsular regions. Mononuclear infiltration into the anterior uvea as well as tapetal atrophy and retinal hemorrhages can also be present. Degenerative vasculopathy of retinal and choroidal vessels progresses to replacement of smooth muscle with fibrous tissue. There is also inner retinal degeneration, with decreased numbers and degeneration of ganglion cells, and axonal degeneration in the optic nerve (Ching et al., 1990).

Nonsteroidal Anti-Inflammatory Drugs

Etodolac

Etodolac is a nonsteroidal anti-inflammatory drug that selectively inhibits cyclooxygenase-2 and is used in the management of pain in a variety of conditions, especially osteoarthritis (Jones & Budsberg, 2000). KCS has been reported with its use in dogs (Klauss et al., 2007). The mean age of affected dogs is 10 years and there does not appear to be a breed or gender predisposition (Hampshire et al., 2004). Etodolac-induced KCS is severe and may be irreversible (Klauss et al., 2007; Stiles, 2004), although shorter duration of etodolac administration has been associated with improved outcome (Klauss et al., 2007).

Phenazopyridine

Phenazopyridine has been used as a urinary analgesic, and in the dog, it has a unique lacrimal toxicity. Within 7–10 days after doses of 25 mg/kg in the dog, the STT decreased below 10 mm/min, and signs of KCS developed. Cats, rabbits, and humans do not develop lacrimal toxicity to phenazopyridine. The lacrimal glands develop a grossly visible, brown-black discolouration within 48 hours of drug administration. The product is present only in the lacrimal glands, and the material is found in the secretory granules that fuse into larger degenerative granules with subsequent cellular degeneration. Adjacent acinar cells may have normal secretory granules. Early cessation of therapy may reverse the process (Bryan & Slatter, 1973; Slatter & Davis, 1974; Slatter et al., 1982).

Rodenticides (Anticoagulant Rodenticides)

Anticoagulant rodenticides are a commonly encountered toxin in dogs (Berny et al., 2010; DeClementi & Sobczak, 2012). Anticoagulant rodenticides act by reducing the production of vitamin K-dependent clotting factors II, VII, IX, and X by reducing the conversion of vitamin K_1 from the inactive to active form, and this is done by inhibiting vitamin K_1 reductase in the liver (DeClementi & Sobczak, 2012). Dogs with ocular signs secondary to anticoagulant rodenticide toxicity can present with unilateral or bilateral signs (Griggs et al., 2016). Ocular signs include subconjunctival hemorrhage, blindness, serosanguinous ocular discharge, mild anterior uveitis, and signs attributed to orbital disease (i.e., exophthalmos, periocular swelling, lagophthalmos, increased resistance to manual retropulsion of the globe, protrusion of the third eyelid, signs of orbital pain, ocular hypertension, and exposure keratitis) (Griggs et al., 2016). Subconjunctival hemorrhage likely results from the rostral extension/dissection of orbital hemorrhage (Fig. 37.1.45). Orbital hemorrhage may be confused with other causes of acute orbital disease (e.g., orbital cellulitis). Diagnosis of anticoagulant rodenticide toxicity is made via a history/suspicion of a pet ingesting the rodenticide (either directly or indirectly), compatible clinical signs, evidence of coagulopathy based upon compatible clinical laboratory findings (i.e., a prolonged prothrombin time, normal to prolonged activated partial thromboplastin time, and normal platelet count), and excluding other causes of coagulopathy



Figure 37.1.45 **A.** A 1-year-old male neutered Yorkshire terrier mix at presentation with right-sided subconjunctival hemorrhage, exophthalmia, orbital pain, elevated third eyelid, and a superficial corneal ulcer. **B.** Five days after initial presentation and treatment. All clinical signs were resolved. (*Source*: Reprinted with permission from Griggs, A.N., Albaugh, R.A., Tofflemire, K.L., et al. (2016) Anticoagulent rodenticide toxicity in six dogs presenting with ocular disease. *Veterinary Ophthalmology*, **19**, 73–80.)

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(DeClementi & Sobczak, 2012). Clinical signs resolve with oral administration of vitamin K1, although some patients may require concurrent whole blood or plasma transfusions (DeClementi & Sobczak, 2012; Griggs et al., 2016).

Miscellaneous Diseases

Systemic Histiocytosis

Systemic histiocytosis is a familial disease of Bernese Mountain Dogs and also occurs less frequently in other breeds (Moore, 1984, 2014; Moore & Rosin, 1986; Padgett et al., 1995; Paterson et al., 1995). Overall, systemic histiocytosis is a rare disease (Moore, 2014). Systemic histiocytosis is considered a non-neoplastic, generalized histiocytic proliferative disease that causes prominent skin lesions identical to those reported with cutaneous histiocytosis. However, ocular and nasal mucous membranes, and other organs such as the lungs, bone marrow, and peripheral lymph nodes may also be frequently affected (Moore, 2014). Young to middle-aged dogs (2–8 years of age) are mainly affected by this disease.

Systemic histiocytosis is characterized histologically by multisystemic, perivascular infiltration of large histiocytes, and variable numbers of lymphocytes, neutrophils, and eosinophils (Moore, 1984). Systemic signs vary but include anorexia, depression, weight loss, cutaneous nodules, and nasal infiltration (Moore, 1984; Scherlie et al., 1992). Ulceration of the skin overlying the cutaneous nodules is common. Ocular lesions occurred in three of six affected animals, manifesting as eyelid masses, episcleral masses, exophthalmos, corneal edema, anterior and posterior uveitis, retinal detachment, and glaucoma (Moore, 1984).

Cellular atypia is lacking, and systemic histiocytosis has not been proven to be neoplastic but, rather, has been postulated to be an immunoregulatory disorder involving dermal dendritic cells (Affolter & Moore, 2000; Moore, 2014). Immunohistochemical staining may help to differentiate cutaneous and systemic histiocytosis from histiocytic sarcoma. Specifically, cutaneous and systemic histiocytosis stain positively for Thy-1 (CD90) and CD4 markers for dermal dendritic cells and activated antigen presenting cells, respectively (Affolter & Moore, 2000). Histiocytic sarcoma, however, does not stain for CD4 and inconsistently stains for Thy-1 (Affolter & Moore, 2002; Moore, 2014). Further, the clinical behavior and response of systemic histiocytosis to immunosuppressive therapy with agents that profoundly inhibit T-cell activation have solidified the concept of disorderly immune regulation resulting from defective interaction of dendritic antigen presenting cells and T-cells (Affolter & Moore, 2000).

Systemic histiocytosis is a progressive disease that may wax and wane, especially early in the course of the disease, but typically necessitates continuous immunosuppressive therapy such as corticosteroids. Immunosuppressive doses of systemic cyclosporine A or leflunomide, both potent inhibitors of T-cell activation, are often warranted to treat intractable cases of systemic histiocytosis (Affolter & Moore, 2000). However, in severe cases, lesions may become persistent and fail to respond to therapy.

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37.2

Ocular Manifestations of Systemic Disease

Part 2: The Cat

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Congenital

Coat Color-Related Diseases/Conditions

Chédiak–Higashi Syndrome

Chédiak–Higashi syndrome (CHS) is an autosomal recessive disorder of cats and other species (Prieur & Collier, 1978, 1981). In cats, CHS is characterized by partial oculocutaneous albinism, increased susceptibility to infections, and bleeding tendencies (Collier et al., 1984). To date, CHS has only been reported in the Persian breed. Ocular manifestations of CHS in cats include photophobia, pale irides, hypopigmentation of the non-tapetal fundus, tapetal degeneration, cataracts ranging from incipient posterior suture-line associated to mature cataracts, and spontaneous nystagmus (Creel et al., 1982; Collier et al., 1979, 1985b). The ocular hypopigmentation in affected cats is thought to result from fusion of premelanosomes with lysosomes, with resultant destruction of the premelanosomes (Collier et al., 1985a). Melanin granules that do remain in the eyes of cats with CHS are nonuniform in distribution and irregular in shape (Collier et al., 1984). The tapetum develops normally in CHS-affected kittens, but it later rapidly degenerates, so that by 56 days of age, tapetal rods have disappeared and tapetal cells are disorganized (Collier et al., 1985b). Ophthalmoscopically, the tapetum of affected cats is not visible. Abnormal retinal projections to the lateral geniculate nucleus (similar to those in the Siamese breed) have also been found in CHS-affected cats, thus accounting for the nystagmus (Creel et al., 1982). The disease is characterized histologically by giant cytoplasmic granules within lysosomes, melanocytes, and neutrophils. When eyes from older CHS-affected cats were examined histologically and ultrastructurally, lysosomes and residual bodies were found within the retinal pigment epithelium (RPE) (Collier et al., 1986). The residual bodies formed drusen-like mounds beneath the RPE, and RPE cells had detached and moved into the interphotoreceptor space. A diagnosis of CHS is made based upon identifying enlarged melanin granules histologically within hair shafts of cats combined with clinical signs suggestive of the disease.

Visual System Anomalies and Forms of Albinism

Visual system abnormalities associated with forms of albinism have been reported in animals for years (Creel et al., 1982). A commonly studied model is the Siamese cat, demonstrating a form of partial albinism (i.e., pointed color cats) with retinal hypopigmentation. In particular the pointed-colored Siamese (i.e., possessing darker pigmentation on extremities), coat colors are the result of temperature-dependent genetic alleles in *tyrosinase* (*TYR*) (Lyons et al., 2005). Tyrosinase is the rate-limiting enzyme in melanin production. Aside from these temperature-dependent alleles in *TYR*, Siamese cats can also be born purely albinotic caused by another mutant allele in *TYR* (Imes et al., 2006). As mentioned, pointed-Siamese cats lack pigment of the iridal and retinal pigment epithelia (Thibos et al., 1980). The retinal hypopigmentation in these cats is the critical factor resulting in misrouting of many of the projections of the retina to the brain, the nature of the projection error, and the developmental consequences of the relay of the misrouted retinal inputs to the visual cortex (Kaas, 2005; LaVail et al., 1978; Sanderson et al., 1974). The abnormal retinogeniculate projections in Siamese cats was first described by Guillery in 1969 (Guillery, 1969). Since this study, several reports regarding the visual system of the Siamese cat have been published (Creel, 1971; Guillery & Kaas, 1971; Hubel & Wiesel, 1971; Kalil et al., 1971). Specifically, Siamese cats have reduced ipsilateral retinal projections because many axons originating in the temporal retina which normally project ipsilaterally project contralaterally in Siamese cats. As a consequence, each lateral geniculate nucleus contains an abnormally greater representation of the ipsilateral visual field (Cooper

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& Blasdel, 1980). Convergent strabismus with or without involuntary horizontal or rotary nystagmus are possible ocular manifestations as a result of this retinogeniculate misdirection (Blake & Crawford, 1974; Rengstorff, 1976).

White Coat Color, Blue Irides, and Deafness

Complete albinism (complete lack of pigmentation) or partial or localized albinism (an absence or reduction in the degree of pigmentation) is associated with not only the phenotypic appearance of an animal's coat and skin color but is also associated with conditions affecting the ear and eye (Creel et al., 1983). Albinism or partial albinism may result from the failure of migration of neural crest cells (precursors to melanocytes) and hence result in reduced numbers of melanocytes in a nonpigmented area, or may result because of impaired production of pigment caused by some intrinsic deficiency in melanin production (e.g., tyrosinase deficiency) but where the number of melanocytes in nonpigmented or hypopigmented areas is normal.

Domestic cats with white coat color and blue irides have been reported to have a dominantly inherited deafness characterized by alterations to the membranous labyrinth and bony modiolus (Brown et al., 1971). The syndrome results from an autosomal *dominant white gene*, *W*, that is fully dominant with complete penetrance in producing white fur, with incomplete penetrance of deafness, and is incompletely dominant in producing blue irides (Bergsma & Brown, 1971; Brown et al., 1971). The *dominant white locus* (*W*) has been identified as being the result of retroviral insertions into the *KIT* gene (David et al., 2014). The blue iris is also conditioned by other genes that produce high degrees of white spotting that are allelic to *W* and by other independent genes (Bergsma & Brown, 1971). Importantly, therefore, not all blue-eyed white cats are deaf whereas white cats with nonblue irides may also be deaf (Bamber, 1933). However, in one study, white cats with bilateral blue eyes were more frequently deaf than were heterochromic white cats, which in turn were more frequently deaf than were white cats with bilateral "brown" eyes (Bergsma & Brown, 1971). Different manifestations of cochlear pathology have been described in deaf white cats (Ryugo et al., 2003). The deafness in this colony of cats was not progressive and occurred either unilaterally or bilaterally. However, iris color was not described.

Ehlers–Danlos Syndrome

Ehlers–Danlos syndrome (EDS), or cutaneous asthenia, has been reported in the cat. It is a congenital, inherited connective tissue disorder, and it is characterized by fragile, hyperextensible, and easily torn skin. It has been reported in domestic shorthairs, Himalayan, and Burmese cats, and both autosomal dominant and recessive inheritance patterns have been proposed (Halper, 2014; Holbrook et al., 1980; Sequeira et al., 1999). In contrast to the dominant forms of EDS reported in humans in which excessive joint laxity may be seen in addition to the skin lesions, affected cats only show fragility and hyperextensibility of the skin, thereby suggesting differences in the underlying genetic defect and/or in metabolism of dermal and skeletal collagen in cats compared with humans (Patterson & Minor, 1977). Ocular manifestations of EDS reported in the cat have been linked to excessive laxity of the eyelid skin and include entropion with secondary blepharospasm and keratoconjunctivitis (Patterson & Minor, 1977).

A diagnosis of EDS is made based upon a clinical syndrome of skin hyperextensibility, clinical signs associated with skin fragility including easily torn skin, and skin histopathology (routine histopathology with Masson's trichome staining and ultrastructural examination). Determination of skin hyperextensibility can be objectively assessed by calculating the extensibility index (Patterson & Minor, 1977). The extensibility index is determined by dividing the vertical height of a skin fold (extending a skin fold over the dorsal lumbar area maximally without eliciting pain) by body length (measured from occipital crest to base of tail), then multiply by 100. A skin extensibility index greater than 19% is considered hyperextensible (Freeman et al., 1987).

EDS is incurable and because of its hereditary nature owners should be advised not to use affected cats for breeding. Therapy for affected cats is directed at preventing skin lacerations.

Hydrocephalus

Hydrocephalus refers to the active enlargement of the brain ventricular system. However, ventriculomegaly (enlargement of the brain ventricles) is not necessarily synonymous with hydrocephalus (Estey, 2016; Thomas, 2010). The most common cause of congenital hydrocephalus is a primary congenital stenosis or aplasia of the mesencephalic aqueduct associated with fused rostral colliculi (Thomas, 2010). Mesencephalic aqueductal stenosis has been reported in kittens after *in utero* exposure to griseofulvin (Scott et al., 1975), and after transplacental infection with feline panleukopenia virus (Csiza et al., 1971). It has been shown that selection for extreme brachycephaly also selects for clinical and subclinical hydrocephalus in the Persian, and likely, related breeds of cats (Schmidt et al., 2017). Congenital hydrocephalus may produce enlargement of the calvarium and failure of closure of the suture lines of the skull. Consequently, affected kittens may have dome-shaped heads and a persistently open fontanelle. Clinical signs of hydrocephalus include behavioural changes, ataxia, compulsive circling, and seizures (Coates & Sullivan, 2001). Ventrolateral strabismus is a common ocular manifestation of congenital hydrocephalus due, in part, to enlargement of the calvarium with subsequent impingement on the orbits from the dorsolateral aspects (Coates & Sullivan, 2001). This consequently pushes the eyes in a ventrolateral direction and produces a "sunset" appearance to the corneas.

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Congenital hydrocephalus may also cause cranial nerve compromise with subsequent strabismus. Breeders of brachycephalic cat breeds should be educated to avoid selecting for extreme brachycephaly phenotype.

Myotonia

Myotonia is characterized by muscle spasm and stiffness as the result of continued active contraction of a muscle after cessation of voluntary effort (Gaschen et al., 2004). Myotonia may be a primary disorder or can develop secondary to other disorders such as endocrinopathies and muscular dystrophies. Primary congenital myotonia has been described in the cat (Gandolfi et al., 2014; Hickford et al., 1998; Toll et al., 1998). An autosomal recessive mode of inheritance is suspected for feline congenital myotonia and proven in a feral population of cats from Canada (Gandolfi et al., 2014). In most species, the underlying abnormality of myotonia involves a defect in chloride conductance in the sarcolemma (Vite et al., 1998) as has been shown to be the case for a population of cats in Canada (Gandolfi et al., 2014). The clinical signs associated with myotonia in cats include a stiff awkward gait, generalized muscle hypertrophy, and, when startled, affected kittens may stiffen, fall into lateral recumbency and develop spasms of the facial muscles and eyelids, or may develop excessive bleharospasm upon eliciting the palpebral reflex (Hickford et al., 1998; Gandolfi et al., 2014).

Quadriplegia and Amblyopia

A syndrome of decreased vision with nystagmus, ataxia, and tremors has been described in the Irish Setter, Kerry Blue Terrier, and the cat. This syndrome is inherited as a postnatally lethal, autosomal recessive trait (Palmer et al., 1973; Sakai et al., 1994). Most animals, however, are unable to stand at birth, although walking movements are made that propel them in a "seal-like" manner when prone. Vision is difficult to evaluate in a very young animal, but those affected lack fixation responses as well as menace responses and dazzle reflexes. The pupillary light reflexes are normal. The ocular fundus is normal on fundic examination as well. Electroretinographic (ERG) findings have not been reported. Central nervous system (CNS) lesions include degeneration and necrosis of the cerebellar cortex, with severe loss of Purkinje cells. Histopathologic findings do not correlate well with clinical neurologic or ocular findings (Palmer et al., 1973; Sakai et al., 1994).

Developmental

Lysosomal Storage Diseases

Many lysosomal storage diseases have been identified in cats (Aguirre et al., 1983; Alroy et al., 1991; Blakemore, 1986; Breton et al., 1983; Burditt et al., 1980; Cowell et al., 1976; Cork et al., 1977, 1978; Cummings et al., 1988; Haskins et al., 1979a,b,c, 1980a,b, 1982; Jezyk et al., 1977, 1986; Langweiler et al., 1978; Lowenthal et al., 1990; Mazrier et al., 2003; Murray et al., 1977; Neuwelt et al., 1985; Nowakowski et al., 1988; Sheridan et al., 1994; Stramm et al., 1985, 1986; Vandevelde et al., 1982; Vine et al., 1981). These inborn errors of metabolism are, however, relatively rare diseases that have received a disproportionate amount of investigation, because they represent potential animal models for human syndromes. Storage diseases are characterized by an accumulation of metabolic by-products within lysosomes, the cellular organelles which degrade complex macromolecules. The substrates for catabolism within lysosomes include glycoproteins, mucopolysaccharides, oligosaccharides, proteins, and sphingolipids (Jolly & Walkley, 1997; Skelly & Franklin, 2002). Storage diseases result from a deficiency in a specific catabolic enzyme (i.e., acid hydrolases), thus causing the enzyme substrate to accumulate in the lysosomes within cells. Consequently, lysosomal storage diseases are subclassified based upon the type of storage product. Important groups include the glycoproteinoses, mucopolysaccharidoses, oligosaccharidoses, proteinoses, and the sphingolipidoses (Jolly & Walkley, 1997; Skelly & Franklin, 2002). Specific lysosomal storage diseases are normally named according to the specific accumulated product. Because this excess material is a normal component, the histopathologic changes result from physical distortion of affected cells rather than from a toxic effect. Most lysosomal storage diseases, with known mode of inheritance, are inherited as an autosomal recessive trait. When homozygous, the syndromes are usually severe, thus resulting in neurologic disease and, eventually, death. The eyes in most affected animals have histopathologic lesions, but clinical ophthalmic lesions may not be visible (Aguirre et al., 1986; Evens, 1989). Antemortem diagnosis of a lysosomal storage disease can be confirmed by lysosomal enzyme analysis (e.g., Lysosomal Disease Testing Laboratory, Jefferson Medical Center, Philadelphia, PA, USA: https://www.jefferson.edu/university/jmc/departments/neurology/programs/neurogenetics/lysosomal_diseases.html) or with genetic testing for specific feline lysosomal storage diseases (see PennGen World-Wide DNA tests: https://www.vet.upenn.edu/research/academic-departments/clinical-sciences-advanced-medicine/research-labs-centers/penngen/tests-worldwide).

Alpha-Mannosidosis

Alpha (α)-mannosidosis is a member of the inherited oligosaccharidoses described in Persian, domestic shorthair, and domestic longhair cats, which results from a deficiency in acidic α-mannosidase (Cummings et al., 1988; Maenhout et al., 1988; Raghavan et al., 1988). Specifically, the disease in cats is caused by a four base-pair deletion in the feline α-mannosidase gene (Berg et al., 1997). Systemic manifestations of α-mannosidosis in cats include stunted growth, skeletal deformities, emaciation, hepatomegaly, and neuro-

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logic dysfunction including tremors, ataxia, dysmetria, and progressive weakness (Maenhout et al., 1988). Ocular abnormalities described in affected cats include progressive corneal and lenticular opacification (Alroy et al., 1991) and resting nystagmus (Vite et al., 2005). Visual evoked potentials revealed asymmetry in latency and shape of signal conductions as well (Alroy et al., 1991). Histologic and histochemical ocular findings in eyes of cats with α-mannosidosis revealed cytoplasmic vacuolation of numerous ocular cell types including keratocytes and lens epithelial cells, and positive staining of these cells with Concanavalia ensiformis agglutinin (Con A) and wheat germ agglutinin (WGA). Two phenotypic variants of feline α-mannosidosis have been recognized. Clinical signs of α-mannosidosis in domestic longhair cats were milder and slower to progress than those observed in affected Persian and domestic shorthair cats, and did not include prominent skeletal deformities, hepatomegaly, or ocular lesions reported in the aforementioned breeds (Cummings et al., 1988). Feline α-mannosidosis can thus be categorized into severe acute and milder chronic forms (Type I and Type II α-mannosidosis in humans, respectively) (Cummings et al., 1988). Gene therapy in brains of cats with α-mannosidosis, using multiple intracerebral injections and adeno-associated virus vector, was evaluated experimentally (Vite et al., 2005). Significant improvements in neurological signs and brain myelination were noted in treated cats (Vite et al., 2005).

Globoid Cell Leukodystrophy (Krabbe's Disease)

Globoid cell leukodystrophy, or Krabbe's disease, is a member of the inherited sphingolipidoses described in the cat, that results from a deficiency in galactocerebrosidase (GALC) activity (Salvadori et al., 2005). The substrate galactocerebroside (i.e., galactosylceramide), a constituent of myelin, and another metabolite of myelin turnover, psychosine (galactosyl sphingosine), accumulate. Psychosine is highly cytotoxic to oligodendroglia and is thought to be the primary metabolite involved in the pathogenesis of the disease (Miyatake & Suzuki, 1972). Consequent to the build-up of these toxic metabolites, leukodystrophy results. Globoid cell leukodystrophy is pathologically characterized by bilaterally symmetric demyelination of the white matter of the brain, spinal cord, spinal nerve roots, and peripheral nerves, loss of oligodendrocytes, and by the accumulation, predominantly perivascularly, of globoid cells (multinuclear globoid macrophages) containing nonmetachromatic, nonsudanophilic, periodic acid-Schiff (PAS)-positive material (Suzuki & Suzuki, 2002). The mode of inheritance of globoid cell leukodystrophy in cats has yet to be determined.

Globoid cell leukodystrophy in cats is generally characterized by an early onset, rapidly progressive, and severe disease which has pathological lesions identical to those reported in other domestic animals (Salvadori et al., 2005). Clinical signs are characterized by early posterior dysmetria and ascending incoordination, and generalized tremors, in association with paraplegia and inability to perceive deep pain (Salvadori et al., 2005). Cerebellar signs or progressive paraparesis and paraplegia are the predominant clinical manifestations. Ocular manifestations of this disease in cats include lack of vestibular ocular reflexes, and signs associated with visual deficits including diminished pupillary light reflexes and reduced menace responses (Salvadori et al., 2005). The optic tracts and optic radiation are among the most severely affected regions of the white matter of the brain of cats with globoid cell leukodystrophy (Salvadori et al., 2005), thereby accounting, in part, for the visual deficits. The definitive diagnosis of globoid cell leukodystrophy involves genetic testing to document the mutation in the GALC gene or biochemical assays to show the enzymatic deficiency. Although genetic testing has been developed to diagnose globoid cell leukodystrophy in West Highland White and Cairn terriers (Victoria et al., 1996), this test is not useful in the cat as the feline GALC gene has yet to be cloned (Salvadori et al., 2005).

Gangliosidoses

GM1-Gangliosidosis

GM1-gangliosidosis is caused by a deficiency of lysosomal hydrolase, β-d-galactosidase, which produces an accumulation of GM1-ganglioside in the cerebral cortex and visceral organs. Such deficiencies have been reported in cats, dogs, cattle, and sheep (De Maria et al., 1998). The mode of inheritance of feline GM1-gangliosidosis is autosomal recessive. GM1-gangliosidosis is characterized by mild (3–7 months of age) to severe (>7 months of age) progressive neurological disease and early death (Cox et al., 1998). In particular, clinical manifestations of feline GM1-gangliosidosis include discrete head and/or limb tremors, ataxia with hypermetria, and progressive paraparesis (De Maria et al., 1998) often with blindness and seizures (Cox et al., 1999). GM1-mutant cats have also been shown to have greatly reduced body weight and premature thymic involution (Cox et al., 1998), and electrodiagnostic abnormalities including abnormal brainstem auditory evoked responses and spinal evoked potentials (Steiss et al., 1997). Histopathologic lesions of membrane-bound inclusions are present throughout the brain, spinal cord, and retinal ganglion cells, but only in cats and cattle have clinical ophthalmoscopic lesions been observed. Those ophthalmoscopic lesions were multifocal, white, small spots that probably resulted from elevations of the internal limiting membrane of the retina by swollen ganglion cells. Lesions described outside the CNS of affected cats include empty cytoplasmic vacuoles in specific cells of some visceral organs, including hepatocytes and renal cortical cells, and in peripheral ganglia (De Maria et al., 1998). Cats with GM1-gangliosidoses have also been reported to have a unique, faint corneal opacity associated with intracellular vacuoles (Aguirre et al., 1986). A mutation in exon 14 of the β-galactosidase gene (*GLB1*) has been identified in Korat and

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Siamese cats with GM1-gangliosidosis (Martin et al., 2008). Interestingly, the same mutation has been found in affected non-purebred cats in southeast Asia (Uddin et al., 2013). A genetic test is available for Korat and Siamese cats (https://www.vet.upenn.edu/research/academic-departments/clinical-sciences-advanced-medicine/research-labs-centers/penngen/tests-worldwide).

GM2-Gangliosidosis (Sandhoff Disease)

GM2-gangliosidosis is caused by a deficiency of hexosaminidase. Hexosaminidase has two subunits, α and β, each coded for by *HEXA* and *HEXB* genes, respectively. There are three types of hexosaminidase – hexosaminidase S (an αα dimer), hexosaminidase A (an αβ dimer) and hexosaminidase B (a ββ dimer). In addition, there is a GM2-activator protein coded for by the *GM2A* gene which is necessary for degrading G_{M2} ganglioside in concert with hexosaminidase A. In humans, deficiency in the α subunit, and therefore depletion of hexosaminidase A and S, results in classical GM2-gangliosidosis (Tay-Sachs disease or B-variant). A deficiency in the β subunit, depleting both hexosaminidase A and B, is known as Sandhoff disease or the O-variant. Further, deficiencies in GM2-activator protein results in GM2-activator deficiency, also known as the AB-variant. Feline GM2-gangliosidosis (Sandoff disease or O-variant) has been reported in domestic shorthair (Baker et al., 1979; Cork et al., 1977) and Korat (Muldoon et al., 1994; Neuwelt et al., 1985) and European Burmese (Bradbury et al., 2009) breeds of cats. The mode of inheritance of feline GM2-gangliosidosis is autosomal recessive. The causative mutation of GM2-gangliosidosis in the domestic shorthair cat has been documented as a 25 base-pair inversion at the extreme 3' end of the β-subunit (*HEXB*) coding sequence (Martin et al., 2004). Affected cats show clinical signs of early onset (4–7 weeks of age), progressive neurological dysfunction initially characterized by fine head tremors with or without lacrimation, followed by ataxia, immobility, blindness, and dysphagia, and finally seizures or generalized myoclonus (5 months of age), quadriplegia (6 months of age), and death prior to 8 months of age (Neuwelt et al., 1985). The definitive diagnosis of GM2-gangliosidosis involves biochemical confirmation of the enzyme deficiency. Although GM2-gangliosidosis is mainly a neuronal disease (i.e., gray matter disease), magnetic resonance imaging (MRI) of brains of affected cats can show alterations in myelination of white matter tracts that may arise secondary to the neuronal damage (Kroll et al., 1995). MRI may provide a noninvasive method of monitoring response to treatment once therapeutic strategies are developed for feline GM2-gangliosidosis (Kroll et al., 1995). In Burmese, Korat, and Japanese domestic shorthair cats, the disease is caused by recessive mutations in the hexoaminadase β-subunit (*HEXB)* gene (Bradbury et al., 2009; Kanae et al., 2007; Muldoon et al., 1994). Genetic tests are available for GM2-gangliosidosis in Burmese, Korat, and Japanese domestic shorthair cats (https://www.vet.upenn.edu/research/academic-departments/clinical-sciences-advanced-medicine/research-labs-centers/penngen/tests-worldwide).

Mucolipidosis II (Inclusion-Cell Disease)

Mucolipidosis II, or inclusion cell (I-cell) disease, is caused by deficient activity of the enzyme N-acetylglucosamine-1-phosphotransferase. Unlike other forms of lysosomal storage diseases, mucolipidosis II results from an error in trafficking of enzymes into lysosomes rather than a deficiency of a specific lysosomal hydrolase (Mazrier et al., 2003). As a result, affected lysosomes are secondarily deficient in multiple acid hydrolases (Lightbody et al., 1971, as cited by Mazrier et al., 2003). Clinical signs in affected kittens initially include facial dysmorphism and failure to thrive, with death or euthanasia because of disease progression being reported to occur between the first postnatal day and 216 days of age (mean = 47 days) (Mazrier et al., 2003). Neurologic signs in affected cats included dull, quiet behavior, and progressive hind limb ataxia. Skeletal deformities, such as carpal valgus or varus, were also described. Congenital facial abnormalities in affected cats included thickened eyelids, hypertelorism (widely spaced eyes), depressed nasal bridge, a flat broad face, frontal bossing, and low-set ears (Fig. 37.2.1) (Mazrier et al., 2003). Ocular abnormalities detected in cats affected with mucolipidosis II included, from early to late lesions, absent menace response and diminished pupillary light reflexes, and dilated pupils by 4 months of age. Initially, retinal development appears normal until 2.5 months of age at which time dorsal retinal degeneration developed followed by progressive end-stage

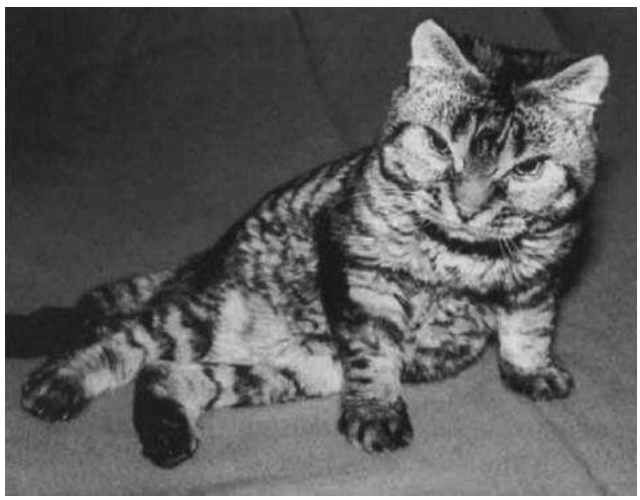


Figure 37.2.1 Cat with mucolipidosis type II in its preferred sitting position. (*Source*: Reprinted with permission from Hubler, M., Haskins, M.E., Arnold, S., et al. (1996) Mucolipidosis type II in a domestic shorthair cat. *Journal Small Animal Practice*, **37**, 435–341.)

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generalized retinal degeneration and blindness by 3.5 months of age (Mazrier et al., 2003).

Mucopolysaccharidosis

The mucopolysaccharidoses (MPS) are a group of diseases characterized by defective metabolism of mucopolysaccharides (glycosaminoglycans). Three types of MPS have been identified in cats (MPS I, VI, and VII) (Fig. 37.2.2). Defects in the degradation of glycosaminoglycans and other proteoglycans result in accumulation of these compounds in many cell types including cells of the most severely affected axial and appendicular skeleton.

MPS I (Hurler syndrome), caused by a deficiency of the lysosomal enzyme α-L-iduronidase, has been reported in domestic shorthair cats (Haskins et al., 1983). The result of this enzyme deficiency is the tissue accumulation and urinary excretion of dermatan and heparan sulfate (Jolly & Walkley, 1997). Affected cats have an abnormal gait caused by bony dysplasia, vertebral fusion and polyarthropathies, stunted growth, joint immobility, cardiac valvular disease, facial deformaties, and develop corneal clouding. Genetic testing is available for MPSI in cats (He et al., 1999) (https://www.vet.upenn.edu/research/academic-departments/clinical-sciences-advanced-medicine/research-labs-centers/penngen/tests-worldwide).

MPS VI (Maroteaux–Lamy syndrome), caused by a deficiency of the lysosomal enzyme arylsulfatase-B (4-sulfatase), has been reported in cats (Crawley et al., 2003; Haskins et al., 1983). MPS VI is one of the more prevalent inherited storage diseases in cats, and occurs commonly in cats with Siamese ancestry (Crawley et al., 2003). Arylsulfatase-B hydrolyzes dermatan sulfate, and therefore lack of this enzyme results in lysosomal accumulation and urinary excretion of dermatan sulfate. Clinical signs in affected cats are similar to those in cats with MPS I including corneal opacities, but also include severe spondylosis and kyphosis, widened intervertebral disc spaces, and severe facial dysmorphism. MPS VI-affected cats also have a high incidence of degenerative joint disease (Crawley et al., 2003). In addition, feline MPS VI results in lysosomal accumulation of dermatan sulfate within connective tissue cells of the cornea, sclera, conjunctiva, uvea, RPE, with corneal clouding being the most debilitating ocular manifestation (Aguirre et al., 1983). The enzyme defect was partially corrected after allogenic bone marrow transplantation in feline MPS VI, thereby resulting in improved clinical signs including clearing of the corneal opacities (Gasper et al., 1984). Recombinant adeno-associated virus-mediated subretinal delivery of feline 4-sulfatase has been shown to correct the histopathologic lesions of RPE cells of feline MPS VI (Ho et al., 2002). Improvements in the clinical signs of feline MPS VI have been reported after enzyme replacement therapy in a feline model of MPS VI (Crawley et al., 1997).

Corneal clouding associated with feline MPS I and VI is felt to be due, in part, to accumulation of substrate in the keratocytes (Mollard et al., 1996). Corneal endothelial cells of MPS I-affected cats were shown to function normally in affected cats, despite these cells having numerous vacuolated lysosomal inclusions or a granular matrix (Mollard et al., 1996). Structural alterations in the corneal stroma, including abnormal spacing, size, and arrangement of collagen fibrils in feline models of MPS I and VI were also reported to account, in part, for the corneal cloudiness observed in affected cats (Alroy et al., 1999). Genetic testing is available for MPS VI (Yogalingam et al., 1996) (https://www.vet.upenn.edu/research/academic-departments/clinical-sciences-advanced-medicine/research-labs-centers/penngen/tests-worldwide).

MPS VII (Sly syndrome) resulting from a deficiency of β-glucuronidase, has also been described in domestic shorthair cats (Gitzelmann et al., 1994; Schultheiss et al., 2000). β-glucuronidase deficiency results in impaired catabolism of chondroitin, dermatin, and heparan sulfates (Schuchman et al., 1989). Consequently, these glycosaminoglycans accumulate in tissues and are excreted in the urine (Silverstein et al., 2004). Clinical signs of feline MPS VII include corneal clouding, facial abnormalities, an awkward gait caused by multiple skeletal deformities, stunted growth, paraparesis, tracheal hypoplasia (Gitzelmann et al., 1994; Schultheiss et al., 2000), and, atypically, generalized seizures which were inducible after cutaneous stimulation over the dorsum of one cat (Gitzelmann et al., 1994). In one such cat, the corneal clouding developed in both eyes by 9 months of age, but had nearly resolved by 21 months of age despite progressive systemic signs and death 2 weeks later (Schultheiss et al., 2000). Genetic mutations in the β-glucuronidase gene (*GUSB*) have been identified (Fyfe et al., 1999; Wang et al., 2015). Genetic testing is available for MPS VII (Fyfe et al., 1999) (https://www.vet.upenn.edu/research/academic-departments/clinical-sciences-advanced-medicine/research-labs-centers/penngen/tests-worldwide).

Sphingomyelin Lipidosis (Niemann–Pick Disease)

In humans, there are six types of Niemann–Pick diseases (NPD; Types A–F), with types A, B, and F demonstrating a deficiency in sphingomyelinase (Summers et al., 1995), whereas a feline model of NPD type C exhibited a defect in cholesterol transport (Brown et al., 1994). Sphingomyelin lipidosis, or NPD, is characterized by sphingomyelin and cholesterol accumulation in tissues. NPD type A has been reported in Siamese and Balinese cats (Baker et al., 1987; Snyder et al., 1982). Clinical manifestations of this disease include head tremors and bobbing, and dysmetria by 3–4 months of age, followed by paresis later in the disease. Cats with NPD type A may also exhibit hepatomegaly (Baker et al., 1987; Snyder et al., 1982). NPD type C has been reported in

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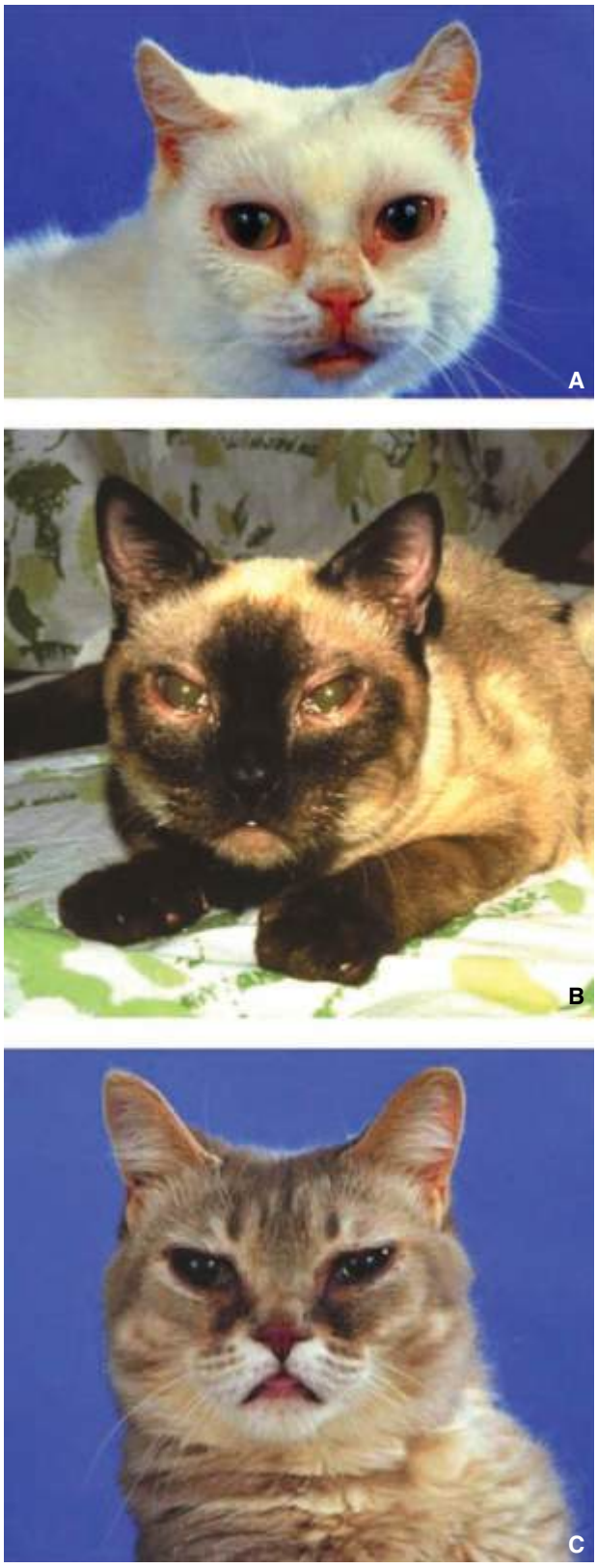


Figure 37.2.2 Three cats with mucopolysaccharidosis (MPS) showing the typical features of this class of disease including small ears, wide-spaced eyes, thick eyelid margins, tear staining caused by occluded nasolacrimal ducts, flattened face with protuberant tongue and corneal clouding. **A.** MPS I (α-L-iduronidase deficiency). **B.** MPSVI (4-sulfatase deficiency). **C.** MPSVII (β-glucuronidase deficiency). (*Source*: Reprinted with permission from Haskins, M.E. (2007) Animal models for mucopolysaccharidosis disorders and their clincial relevance. *Acta Paediatrica,* **96**, 56–62.)

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domestic shorthair cats (Brown et al., 1994; Lowenthal et al., 1990; March et al., 1997; Munana et al., 1994). Clinical signs in NPD type C-affected cats involve progressive neurological dysfunction including intention tremors at 8–12 weeks of age, followed by ataxia, hypermetria, lack of menace response with intact vision, and occasionally, positional nystagmus. In addition, other common manifestations of this disease include hepatosplenomegaly and elevations in serum alkaline phosphatase and alanine aminotransferase. Feline NPD type C is generally fatal by 8–10 months of age (Brown et al., 1994; Lowenthal et al., 1990; March et al., 1997; Munana et al., 1994). Genetic mutations in *NPC1* and *NPC2* genes have been identified (Mauler et al., 2017; Somers et al., 2003; Zampieri et al., 2014). Genetic testing is available for one variant of Niemann–Pick type C1 (Somers et al., 2003) (https://www.vet.upenn.edu/research/academic-departments/clinical-sciences-advanced-medicine/research-labs-centers/penngen/tests-worldwide).

Acquired

Cardiovascular Diseases

Hypertension

Systemic arterial blood pressure (BP) is the product of cardiac output (CO) (CO = heart rate × stroke volume) and total peripheral resistance (TPR) (BP = CO × TPR). Any factor causing persistent elevation in one or more of these three parameters of blood pressure can cause systemic hypertension. When hypertension is associated with an underlying causative disease it is called secondary hypertension. Hypertension in veterinary patients is typically secondary hypertension. It should be noted, however, that primary (essential) hypertension has been described, although less commonly, in cats (Maggio et al., 2000). Primary hypertension is hypertension resulting from unknown reasons. A previous definition of the high "normal" range of systolic blood pressure for cats was between 160 and 200 mmHg. Renal damage in dogs has been reported to progress with systolic blood pressures in this range, however (Brown et al., 2000; Finco, 2004). Consequently, systemic hypertension is defined as a calm animal having repeatable systolic blood pressures measurements higher than 160 mmHg and/or diastolic blood pressure measurements higher than 100 mmHg (Stepien, 2005). Measurement of blood pressure in the cat is most easily accomplished in a clinical setting by indirect measurement using an oscillometric or ultrasonic detection device. Cats aged 11 years of age and older have been noted to have significantly higher systolic, diastolic and mean arterial, and pulse pressures than cats under 11 years of age (Bodey & Sansom,1998). It has been shown that increasing age and elevated systemic blood pressure are, together, associated with the development of retinal lesions in cats (Sandhas et al., 2017). Additionally, a prospective study has shown that 14% of cats older than 8 years of age had ocular signs attributed to systemic hypertension and often prior to any signs attributed to loss of vision (Carter et al., 2014).

Systemic hypertension is a relatively common disease of older cats, and it has most consistently been associated with chronic renal failure and hyperthyroidism (Kobayashi et al., 1990; Littman, 1994; Maggio et al., 2000; Morgan, 1986; Sansom et al., 1994; Stiles et al., 1994). One study reported that 20/103 cats (19.4%) with chronic renal failure were hypertensive (Syme et al., 2002). Other conditions associated with feline hypertension include diabetes mellitus, primary aldosteronism, chronic anemia, and high salt diet (Maggio et al., 2000; van de Sandt et al., 2003).

The ocular manifestations of systemic hypertension can be severe and lead to blindness. The consequence of ocular vascular hypertensive changes is an initial vascular constriction in the retinal arterioles in response to increased blood pressure; when sustained, it results in occlusion and ischemic necrosis of the vessel walls, with resultant increased vascular permeability (Garner, 1982; Garner et al., 1975; Keyes, 1937; Keyes & Goldblatt, 1938). Serous retinal exudates, hemorrhages, and edema also result. Choroidal vascular changes result in subretinal fluid and retinal detachment. Ocular lesions associated with feline hypertension include retinal hemorrhages, retinal detachments, retinal edema, retinoschisis, varying degrees of retinal degeneration, and papilledema (Fig. 37.2.3 and Fig. 37.2.4) (Littman, 1994; Maggio et al., 2000; Morgan, 1986; Sandhas et al., 2017; Sansom et al., 1994; Stiles et al., 1994; Turner et al., 1990). The fundus abnormalities in feline hypertension can be separated into three categories: (1) hypertensive retinopathy which comprises retinal



Figure 37.2.3 Fundus photograph of a geriatric cat with systemic hypertension. Note the multifocal intraretinal and subretinal hemorrhages, and the peripapillary and dorsal tapetal retinal detachments.

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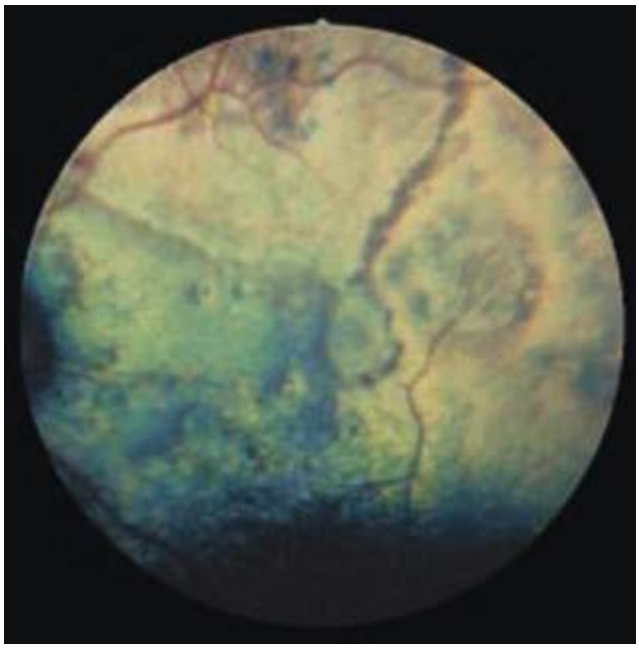


Figure 37.2.4 Eight-year-old male neutered domestic shorthair with hypertensive ocular disease (right eye illustrated, both eyes affected). Mean systolic blood pressure, 183 mmHg. Pigmentary disturbance and retinal degeneration in chronic hypertensive disease presenting initially with bullous serous detachments. (*Source*: Reprinted with permission from Crispin S.M. & Mould, J.R. (2001) Systemic hypertensive disease and the feline fundus. *Veterinary Ophthalmology*, **4**, 131–140.)

edema, "pseudonarrowing" of the retinal arterioles caused by the effects of retinal edema, followed by narrowing and increased totuosity of the retinal arterioles caused by arteriosclerosis, and retinal hemorhages; (2) hypertensive choroidopathy which involves retinal detachments which may be single or multiple, flat, bullous or total detachments, and degenerative RPE lesions; and (3) hypertensive optic neuropathy which includes papilledema, and optic atrophy after end-stage retinal degeneration (Crispin & Mould, 2001). Potential complications of systemic hypertension include anterior segment and vitreous hemorrhage, uveitis, and glaucoma (Littman, 1994; Morgan, 1986; Sansom et al., 1994; Stiles et al., 1994; Turner et al., 1990). Hypertension should therefore be ruled out when presented with intraocular hemorrhage or bullous retinal detachment of unknown origin. Hypertensive cats have been shown to have a greater prevalance of retinal lesions (48%) compared with normotensive cats (3%) (Chetboul et al., 2003). In addition, cats with retinopathies had higher blood pressure (262± 34 mmHg) than hypertensive cats without retinal lesions (221± 34 mmHg) (Chetboul et al., 2003).

The goals of antihypertensive therapy include lowering blood pressure and slowing the progression of target organ damage caused by chronic hypertension. Successful therapy requires good client compliance with frequent reassessment of the blood pressure. If an underlying cause of the hypertension has been identified, the primary condition should be addressed therapeutically, when possible. However, even if the presumed underlying cause of the hypertension is controlled, antihypertensive therapy is typically required long term. Antihypertensive agents used in the cat include β-blockers such as propranolol or atenolol; diuretics such as spironolactone/thiazide, furosemide, and hydrochlorothiazide; and angiotensin-converting enzymes such as captopril (Littman, 1994; Morgan, 1986). Amlodipine, a calcium channel blocker, has been shown to be an effective antihypertensive agent in cats and continues to be a mainstay of therapy for feline hypertension (Elliott et al., 2001; Henik et al., 1997; Komaromy et al., 2004; Maggio et al., 2000; Tissier et al., 2005).

Hypertensive retinopathy in many cats is a slow, insidious process. Vision may be spared if the process is identified and controlled early (Stiles et al., 1994; Young et al., 2019). Even cats with complete retinal detachments, the prognosis for long-term vision is considered good, provided that the systemic hypertension is controlled (Young et al., 2019). Consequently, cats with diseases such as chronic renal failure and hyperthyroidism should be screened for systemic hypertension.

Periarteritis Nodosa

Periarteritis nodosa, an infrequently reported disease in the cat, is characterized by fibrinoid necrosis of the media, adventitia, and endothelium of both small- and medium-sized arteries. Eventually, granulation tissue forms, and vessels become obstructed and nonfunctional. Tissues supplied by these vessels then become ischemic.

Few reports in the literature describe this disease in the cat (Altera & Bonasch, 1966; Campbell et al., 1972; Lewis et al., 1965). Ocular lesions of periarteritis nodosa have included unilateral iritis in one cat (Altera & Bonasch, 1966). Another cat, which was euthanized, had bilateral panuveitis with infiltration of lymphocytes and plasma cells, and hyalin necrosis of the ciliary processes (Campbell et al., 1972). Fibrinous exudates were present in the ocular chambers, and cyclitic membranes spanned the globes. Retinal detachments were also present in both eyes.

In humans, periarteritis nodosa is now accepted to be an immune complex–mediated vasculitis. In some cases, it is associated with viral infections, particularly hepatitis B. Ocular lesions are not uncommon, and treatment often includes immunosuppression with glucocorticoids or azathioprine. In the cat, the diagnosis has usually been made on the basis of necropsy findings.

Hematologic Diseases

Anemia

Anemia is the reduction in red blood cells per volume of whole blood. Anemia is classified as regenerative if there has

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been a normal bone marrow response to erythropoietin (e.g., usually occurs with blood loss or hemolytic disease), or nonregenerative if the normal reticulocyte response is lacking (e.g., may occur with chronic extra-marrow disease which reduces RBC survival time, selective erythropoietin depression, insufficient erythropoietin release, or a combination of these factors) (Rebar et al., 2005). Severe anemia often manifests systemically as pale mucous membranes, cool mucous membranes, tachycardia, polypnea, weakness, as well as signs specific to the underlying primary condition. Ocular manifestations of severe anemia include pale retinal vasculature, varying degrees of retinal hemorrhage, and subtle changes in tapetal reflectivity. Retinal hemorrhages are more likely to be observed, however, and are more dramatic if accompanied by thrombocytopenia (Carraro et al., 2001). Small intraretinal hemorrhages are typical and may reabsorb quickly with correction of the anemia, but pigmentary disturbances may be a residual retinal alteration. In one study of 26 cats with anemia and hemoglobin values of less than 5 g/dL, 20/26 affected cats had retinal hemorrhages (Fischer, 1970). Causes of anemia in these cats included *Mycoplasma haemofelis* (previously *Haemobartonella felis*) infection, thrombocytopenia, autoimmune hemolytic anemia, aplastic anemia, lymphosarcoma, and bleeding duodenal ulcer (Fischer, 1970). In retrospect, some of the cats in this study likely were infected with the feline leukemia virus (FeLV), which was not widely known at that time. Though noted only infrequently in the literature (Brightman et al., 1991), cats with FeLV infections and profound anemia commonly have retinal hemorrhages. Further, ehrlichiosis and anaplasmosis have been suspected as causes of thrombocytopenia and anemia in cats (Breitschwerdt et al., 2002; Peavy et al., 1997; Shaw et al., 2005).

The mechanism of retinal hemorrhage in anemic cats may be multifactorial (Fischer, 1970). Lack of RBCs render vascular endothelial cells hypoxic, thereby increasing vascular fragility. Thrombocytopenia may accompany anemia as well, thus decreasing platelet aggregation in areas of microvascular trauma.

Hyperlipidemia

Hyperlipidemia refers to an elevation in plasma concentrations of cholesterol and/or triglycerides, and arises because of a disturbance in plasma lipoprotein metabolism (Watson, 1993). Hyperlipidemia can occur in cats for several reasons, including postprandial hyperlipidemia, diabetes mellitus, exogenous corticosteroid administration, megestrol acetate administration, nephrotic syndrome, lipoprotein lipase deficiency, idiopathic hyperchylomicronemia, and familial hyperchylomicronemia (Crispin, 1993). Inherited hyperlipidemia in cats arises because of production of an inactive lipoprotein lipase resulting in a fasting chylomicronemia with a slight increase in very-low-density lipoprotein (VLDL) (Jones et al., 1983). If lipemia persists in a fasted blood sample, serum triglyceride and cholesterol levels should be measured. In addition, lipoprotein electrophoresis and ultracentrifugation to determine lipoprotein fractions can be performed.

Lipemia retinalis has been described as an ocular manifestation of hyperlipidemia in cats (Wyman & McKissick, 1973; Crispin, 1993). The term lipemia retinalis describes excess lipid within the retinal vessels, thus giving them a pale appearance. In both cats and dogs, it is the large, triglyceride-rich lipoproteins (e.g., low-density lipoproteins) that produce a visible lipemia (Crispin, 1993). Hyperlipidemia may also manifest with lipids in the anterior chamber. A prerequisite for gaining access to the anterior chamber by the large, lipid-laden molecules is alteration of the blood–aqueous barrier, presumably resulting from preexisting uveitis. It is unclear, however, whether the lipids incite or are the result of uveitis. The syndrome is usually unilateral, which would argue against hyperlipidemia inciting uveitis. Persistent lipemia was induced in kittens with high-dose parenteral methylprednisolone (Wyman & McKissick, 1973), and a primary inherited hyperchylomicronemia has been described (Bauer & Veriander, 1984). The inherited disorder is accompanied by skin masses that, histopathologically, were characteristic of lipogranulomas. Feeding a low-fat diet controls the clinical signs.

Aside from inherited hyperchylomicronemia in cats, a transient hyperlipidemia has also been described in kittens. One report described several unrelated litters of kittens with idiopathic transient hyperlipidemia and anemia as well as lipemia retinalis (Gunn-Moore et al., 1997). Many of these kittens died, but those that survived improved rapidly on a low-fat diet. Similarly, three kittens out of a litter of six were treated successfully with supportive nursing care, low-fat/high protein enteral nutritional support, and ectoparasite control (as many had flea infestation) (Blackstock et al., 2012). It is speculated that a negative energy balance is an important factor in the pathogenesis of noninherited transient hyperlipidemia in kittens (Blackstock et al., 2012).

Finally, another cause of transient hyperlipidemia, causing ocular signs, can be observed after intravenous lipid therapy for toxins (Seitz & Burkitt-Creedon, 2016; Yuh & Keir, 2018). In both instances, it was suspected that corneal lipidosis was present and that the ocular signs resolved within 72 hours to 1 week after intravenous lipid therapy (Seitz & Burkitt-Creedon, 2016; Yuh & Keir, 2018).

Hyperviscosity Syndrome

Hyperviscosity syndrome comprises single or multiple clinicopathologic abnormalities resulting from increased serum viscosity. The severity of hyperviscosity syndrome is linked to the size, shape, type, and concentration of large molecules (e.g., imunoglobulins [Ig]) in the bloodstream. The underlying cause is usually a malignancy, such as lymphoma, chronic lymphocytic leukemia, plasmacytoma, or multiple

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myeloma (Forrester et al., 1992; Hribernik et al., 1982; Kruth & Carter, 1990). Hyperviscosity syndrome in cats has most frequently been associated with multiple myeloma, in which a certain class of immunoglobulin is produced in excess (Forrester et al., 1992; Hribernik et al., 1982; Patel et al., 2005).

Clinical signs are variable, but they often include listlessness, pale mucous membranes, neurologic signs, and lameness. Ocular manifestations are common. Reported ocular lesions in the cat include retinal hemorrhages, dilated and tortuous retinal vessels, retinal detachment, perivascular effusion, papilledema, and retinal degeneration (Hawkins et al., 1986; Hribernik et al., 1982; Forrester et al., 1992; Lane, 1993). The mechanism of producing clinical signs is perhaps multifactorial and is not well understood. Hemorrhage may occur from multiple causes, such as sludging of blood in small vessels, ineffective delivery of oxygen and nutrients to vessel walls, hypertension, coagulation abnormalities as a result of elevated protein levels interfering with clotting factors and platelet function, and thrombocytopenia.

The diagnosis of hyperviscosity syndrome is made on the basis of demonstrating the hyperproteinemia with serum electrophoresis and immunoelectrophoresis, to detect a mono- or polyclonal spike and to categorize the type of gammopathy. A detailed medical workup is necessary to determine the cause of the hyperproteinemia.

Treatment is aimed at defining and treating the underlying disease process, if possible. Reducing serum viscosity by plasmapheresis is sometimes helpful as well.

Hypoxia

Hypoxia most commonly occurs during anesthetic episodes, and it may relate to apnea, cardiopulmonary failure, improper intubation, overdose of anesthetic agent, failure of anesthetic equipment, paralysis of the muscles of respiration, use of mouth gags causing occlusion of maxillary artery, and severe systemic hypotension (Barton-Lamb et al., 2013; Gaynor et al., 1999; Jurk et al., 2001; Stiles et al., 2012; Wingfield & Van Pelt, 1992). Neurons are more sensitive to hypoxia than other support tissues, and neuronal tissue affected by severe and prolonged hypoxia with or without reperfusion will undergo severe cellular metabolic dysfunction leading to apoptosis and ischemic necrosis (Clarkson et al., 2005; Somjen et al., 1993). Clinical signs of cerebral hypoxia include blindness, stupor or coma, paralysis with decerebrate rigidity, seizures, and deafness. Pupillary light reflexes, however, are generally normal. These signs may be either partially or wholly reversible after a period of days to months. Therapy for systemic and cerebral hypoxia depend upon the etiology. In cases of cardiopulmonary arrest, the reader is referred to the Reassessment Campaign on Veterinary Resuscitation (RECOVER) guidelines (Boller & Fletcher, 2012; Brainard et al., 2012; Cardy & Cornelis, 2018; Fletcher et al., 2012; Hopper et al., 2012; McMichael et al., 2012; Rozanski et al., 2012; Smarick et al., 2012). The RECOVER guidelines have shown to improve outcome (Kawase et al., 2018).

Icterus

Icterus or jaundice is characterized by hyperbilirubinemia and deposition of bile pigments in the skin, sclera, and mucous membranes causing them to appear a shade of yellow. Jaundice typically becomes present when serum bilirubin concentrations are greater than five- to 10-fold above "normal" reference range (Sherding, 2000). The sclera is the classic location for detection of icterus given its relative lack of pigmentation. The yellow appearance of icterus may be detected in the intraocular structures as well (e.g., blue irides may turn green). For review of icterus in cats see Sherding (2000).

Polycythemia

Polycythemia is classified as relative or absolute (primary and secondary forms). Relative polycythemia is an increased packed cell volume with normal red blood cell (RBC) mass occurring as a result of a reduction in plasma volume as may arise from external losses of body fluids (e.g., diarrhea, burns).

Absolute polycythemia is an increase in total RBC mass, and it may be classified as either primary or secondary (appropriate and inappropriate). Absolute primary polycythemia (i.e., polycythemia vera) has been described in cats and is an absolute increase in erythropoiesis without an increase in erythropoietin (Evans & Caylor, 1995; Foster & Lothrop, 1988; Nett et al., 2001; Quesnel et al., 1997; Reed et al., 1970). An underlying molecular basis of polycythemia vera has yet to be elucidated.

Absolute secondary polycythemia results from altered erythropoietin homeostasis and is described as being appropriate or inappropriate. Absolute secondary appropriate polycythemia occurs as a consequence of persistent hypoxia, and can be found in animals with conditions such as congenital cardiac defects causing right-to-left shunting of blood (Kirby & Gillick, 1974). Absolute secondary inappropriate polycythemia, however, results from disease processes which lead to inappropriate secretion and elevation of erythropoietin or an erythropoietin-like substance in the absence of systemic hypoxia. Causes of absolute secondary inappropriate polycythemia include diseases which result in the production of erythropoietin or which cause local hypoxia and trigger erythropoietin synthesis including malignancies and renal disease (e.g., renal neoplasia), respectively (Hasler & Giger, 1996; Henry et al., 1999). Polycythemia may manifest as dark, ruddy-colored conjunctival and retinal blood vessels that are dilated and tortuous. In addition, bilateral anterior uveitis with concurrent unilateral chorioretinitis has been described in a dog with polycythemia vera (Gray et al., 2003).

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Treatment varies according to the cause of the polycythemia. If left untreated, however, retinal detachment and ocular hemorrhage may occur with persistent polycythemia.

Thrombocytopenia and Thrombopathies

Thrombocytopenia is an acquired hemostatic defect of cats. Thrombocytopenia in cats results from the following pathophysiolgic mechanisms: decreased platelet production, increased platelet removal, or increased consumption (Ellis et al., 2018). Causes of thrombocytopenia include infectious diseases, neoplasia, drug-induced reactions, and immune-mediated disease. In a retrospective study of 194 thrombocytopenic cats, most common disease processes were infectious, neoplastic, and immune-mediated diseases (Ellis et al., 2018). Numerous pathogens implicated in causing infectious thrombocytopenia in cats include arthropod-borne agents (e.g., *Babesia* [Schoeman et al., 2001], *Cytauxzoon* [Hoover et al., 1994], *Ehrlichia* spp. [Breitschwerdt et al., 2002;Peavy et al., 1997]), viral agents (e.g., feline immunodeficiency virus [Shelton et al., 1990], panleukopenia virus [Peterson et al., 1995]), and fungal and bacterial organisms (e.g., histoplasmosis [Bromel et al., 2005b]). Thrombocytopenia is also seen in association with: (1) many forms of neoplasia including lymphoma, leukemia, and multiple myeloma (Patel et al., 2005; Peterson et al., 1995); (2) medications which impair platelet production, or cause secondary immune destruction of the platelets (e.g., propylthiouracil [Peterson et al., 1984]); or (3) may develop as an idiopathic or primary immune-mediated disease (Garon et al., 1999; Tasker et al., 1999; Wondratschek et al., 2010).

Thrombopathies are blood coagulation disorders resulting from platelet dysfunction. Disease processes associated with thrombopathies include anemia, disseminated intravascular coagulation, liver failure, and uremia. Regardless of the origin, both thrombocytopenia and thrombopathies are rather frequent causes of ocular and periocular hemorrhage. The presence of bleeding signs at a given platelet level vary between individuals, but platelet counts are usually fewer than 50,000 cells/μL when ocular petechiae form. Petechiae in the ocular fundus are often present without visible petechiae in the skin and other mucous membranes. Therapy is directed at the underlying cause, and if bleeding signs are severe, transfusion of fresh whole blood or platelet-rich plasma is indicated.

Idiopathic Systemic Diseases

Dysautonomia (Key–Gaskell or Dilated Pupil Syndrome)

Feline dysautonomia, which is also known as Key–Gaskell or dilated pupil syndrome, was first reported in England in 1982 (Key & Gaskell, 1982). The disease, which produces widespread autonomic nervous system dysfunction, has since been reported in many cats throughout Europe (Cave et al., 2003; Rochlitz, 1984; Sharp et al., 1984), but the number of documented cases in the United States remains small, although is endemic in Missouri and Kansas (Kidder et al., 2008). The cause of dysautonomia has not been determined. No evidence of infectious agents has been found, and the lesions are unlike those reported with known toxins (Cave et al., 2003; Sharp et al., 1984; Symonds et al., 1995). It is speculated that an unknown mycotoxin or xenobiotic may contribute to feline dysautonomia given alterations in the amino acid status of cats with dysautonomia (McGorum et al., 2017).

Common systemic signs of feline dysautonomia include general malaise, dehydration, reduced appetite or anorexia, dysphagia, vomiting or regurgitation, xerostoma, bradycardia, urinary bladder distention, and constipation (Cave et al., 2003; Sharp et al., 1984). Ocular signs that have been reported most consistently include dilated unresponsive pupils, decreased tear production, and protruding nictitating membranes (Bromberg & Cabaniss, 1988; Canton et al., 1988; Guilford et al., 1988; Levy et al., 1994; Sharp et al., 1984; Symonds et al., 1995). Vision is unaffected, and photophobia is variable.

Pharmacologic testing with ocular autonomic stimulants can aid in establishing the diagnosis of feline dysautonomia. Results of these tests are based on denervation supersensitivity. As such, the dysautonomic eye will respond to dilute concentrations of drugs that will not affect a normal eye. Pilocarpine, which is a direct-acting parasympathomimetic agent, at a concentration of 0.1% will produce constriction of the pupil. Epinephrine, which is a direct-acting sympathomimetic agent, at a concentration of 1:10,000 will induce retraction of a prolapsed third eyelid. Ecothiophate iodide, which is an irreversible cholinesterase inhibitor, at a concentration of 0.06% will reportedly cause miosis in a normal cat but have no effect on a dysautonomic pupil (Canton et al., 1988). The same response has been seen with physostigmine, which is a reversible cholinesterase inhibitor, at a concentration of 0.25% (Guilford et al., 1988). The finding of decreased urinary catecholamines can also support the diagnosis of dysautonomia (Levy et al., 1994).

However, a definitive diagnosis of dysautonomia is rarely made antemortem as it involves the histopathologic examination of autonomic ganglia (Cave et al., 2003). Histopathologic examination of affected cats has shown widespread reduction of neurons within both sympathetic and parasympathetic autonomic ganglia, inconsistent neuronal degeneration, and increased numbers of non-neuronal nuclei (Bromberg et al., 1988; Canton et al., 1988; Guilford et al., 1988; Levy et al., 1994; McGorum et al., 2017; Sharp et al., 1984; Symonds et al., 1995). Ultrastructural studies of the ganglia and axons have shown degeneration and disorganization (Griffiths et al., 1985). The membrane glycoprotein, synaptophysin, has been shown to be increasingly accumulated in degenerating neurons of both equine and feline dysautonomia cases (Hilbe et al., 2005). The prognosis for cats with dysautonomia must

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be viewed as being guarded to poor, although some cats have been maintained long term on supportive therapy (Bromberg et al., 1988; Rochlitz, 1984) or have even recovered after a prolonged period (Sharp et al., 1984).

Generalized Osteosclerosis

Generalized osteosclerosis is a rare, poorly understood condition that has been reported in several species. Osteosclerosis involves any abnormal hardening of the bones. In the cat, osteosclerosis is a poorly understood, presumably acquired disorder. Some affected cats are anemic because of FeLV infection (Hoover & Kociba, 1974), whereas others are negative for FeLV (Kramers et al., 1988). Generalized osteosclersosis has been reported in a domestic longhair cat with presenting history involving inspiratory stertor and epiphora of 6 months duration (Hanel et al., 2004). Radiographs and computed tomography of the cat's thorax, right femur and stifle, and skull and pelvis, respectively revealed generalized osteosclerosis, including complete destruction of the nasal turbinates. Nasolacrimal duct obstruction was also detected and was deemed to be the cause of the epiphora.

Ischemic Encephalopathy

Ischemic encephalopathy occurs when the arterial supply to part of the brain is disrupted. A portion of one side of the cerebrum supplied by the middle cerebral artery is most often involved, thereby resulting in necrosis. The cause is unknown in most cases. However, there is evidence that *Cuterebra* infection may play a role in some cases (Rissi & Howerth, 2013; Williams et al., 1998). In the cat, the condition manifests by a sudden onset of behavior change, seizures, ataxia, and motor deficits (Shell, 1996; Zaki & Nafe, 1980). Visual deficits may accompany other neurologic signs and are usually cortical in origin. Occasionally, the optic chiasm may be involved, thus resulting in dilated unresponsive pupils (De Lahunta, 1977). Anisocoria has been noted as well (Bernstein & Fiske, 1986).

Treatment involves supportive care with improvement in clinical signs typically occurring over days to weeks. Alterations in behavior and seizures may persist, and repeated episodes may occur (De Lahunta, 1977; Quesnel et al., 1997; Williams et al., 1998).

Nictitating Membrane Protrusion

Idiopathic bilateral protrusion of the feline nictitating membranes is a common, poorly understood ophthalmic disorder (Fig. 37.2.5) (Gruffydd-Jones et al., 1977). Retraction of the nictitating membranes after instillation of topical adrenergic drugs, in affected cats, is suggestive of a loss of sympathetic innervation such as that seen in Horner's syndrome; however, other ophthalmic signs of Horner's syndrome are absent. Cats with this syndrome have normal intraocular structures, and vision is unaffected unless the nictitating membranes protrude to the extent that they cover the pupil.



Figure 37.2.5 Protrusion of the nictitating membranes in a young cat with diarrhea. (*Source*: Reprinted with permission from Stiles J. (1999) Ocular manifestations of systemic disease: part 2: the cat. In: *Veterinary Ophthalmology* (ed. Gelatt K.N.), 3rd ed., pp. 1448–1473. Philadelphia: Lippincott Williams & Wilkins.)

Affected cats often have concurrent watery diarrhea that precedes nictitating membrane protrusion. Some cats may have diarrhea for weeks. Many cats, however, recover from diarrhea quickly, yet will still have nictitating membrane protrusion. A Tora-like virus has been isolated from the feces of several affected cats in England (Muir et al., 1990). In that study, 17 of 45 cats had nictitating membrane protrusion for more than 4 weeks, and 16 of 41 cats had diarrhea for more than 4 weeks. In 87% of the cases from multicat households, more than one cat was affected, suggesting an infectious etiology.

The prognosis for this condition is good. The diarrhea and nictitating membrane protrusion are self-limiting, although clinical signs may be long-lasting. Therapy is not indicated, but if the nictitating membrane protrusion is severe, a topical adrenergic agent may be helpful.

Immune-Mediated Diseases

Dermatologic Diseases

Several immune-mediated skin diseases may affect the eyelids of cats, usually accompanying other head lesions and with variable lesions on the rest of the body. These include pemphigus foliaceous, pemphigus erythematosus, pemphigus vulgaris, food hypersensitivity, and feline atopy (Carlotti et al., 1990; Chalmers et al., 1994; Preziosi et al., 2003; Scott et al., 1980, 1983. However, pemphigus foliaceous is the most common immune-mediated dermatologic condition affecting the feline eyelid (Sousa, 1995). Biopsy is necessary to establish the diagnosis of pemphigus complex diseases. Food hypersensitivity may be diagnosed on the basis of food elimination trials, whereas atopy may be best diagnosed on the basis of skin testing. Treatment is aimed at the underlying disease process, but it often includes anti-inflammatory therapy, either topically or systemically, as well. For further

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details regarding each of these dermatologic conditions, the reader should consult current dermatology references.

Myasthenia Gravis

Myasthenia gravis is a disease affecting the neuromuscular junction (for complete review see Shelton, 2002). Myasthenia gravis is either congenital or acquired. Congenital myasthenia gravis occurs when there is a functional disorder or depletion of nicotinic acetylcholine receptors (AChRs). Although an uncommon disorder of cats, acquired myasthenia gravis is the most common form of myasthenia gravis occuring in this species. The acquired condition develops because of an autoimmune destruction of AChRs which may occur as an autoimmune condition affecting only the AChR (most common), part of another autoimmune condition (e.g., hypothyroidism), or resulting as part of a paraneoplastic syndrome (e.g., thymoma – 31%–52% of cats with acquired myasthenia gravis [Hague et al., 2015; Shelton et al., 2000]). In cats, naturally occuring hypothyroidism is extremely rare, and has not been associated with feline myasthenia gravis (Shelton et al., 2000). However, myasthenia gravis has been described in cats receiving treatment for hyperthyroidism with methimazole (Hague et al., 2015; Shelton et al., 2000). Abyssinians, including Somalis, are at highest risk for myasthenia gravis, thereby suggesting a hereditary basis for this autoimmune condition (Hague et al., 2015; Shelton et al., 2000).

Animals with acquired myasthenia gravis present with either generalized or focal clinical signs. The two most common clinical manifestations of myasthenia gravis in cats are: (1) generalized weakness with or without megaesophagus/dysphagia (15%–40% and 50%–64%, respectively); (2) generalized weakness associated with a cranial mediastinal mass (25.7%–52% of affected cats); and (3) megaesophagus or dysphagia without generalized weakness (focal form) (10%–21%) (Hague et al., 2015; Shelton et al., 2000). Cats with the focal form of myasthenia gravis may present with dropped jaw, regurgitation and/or dysphagia, and/or change in character of vocalization because of megaesophagus and pharyngeal or laryngeal paresis, respectively (Shelton et al., 2000). With respect to the eye, a diminished or lack of palpebral reflex may be present (Shelton et al., 2000).

Important features regarding acquired myasthenia gravis in cats include the increased frequency with which thymomas are diagnosed in affected cats (up to 52%) compared with dogs (3.4%) (Shelton, 1999; Shelton et al., 2000), and the possibility of methimazole-induced myasthenia gravis in hyperthyroid cats that develop weakness after commencement of this therapy (Hague et al., 2015; Shelton et al., 2000). Diagnosis of acquired myasthenia gravis in cats is based on demonstrating circulating antibodies to the AChRs. Treatment for feline acquired myasthenia gravis includes anticholinesterase and immunosuppressive agents, nutritional and possibly respiratory support, and antibiotics for aspiration pneumonia caused by regurgitation. Surgical removal of thymoma may be performed, although patients may require continued medical therapy for myasthenia gravis (Hague et al., 2015). The reader is referred to current internal medicine textbooks for further details regarding the diagnosis and treatment of myasthenia gravis in cats.

Sjögren's-Like Syndrome

Sjögren's syndrome is a condition in humans, affecting mainly women, characterized by xerophthalmia and xerostomia as a result of lymphocytic infiltration and destruction of exocrine glands (Bell et al., 1999). Sjögren's syndrome is a systemic autoimmune disorder that can affect numerous exocrine glands and internal organs resulting in intermittent fever, salivary gland hypertrophy, pulmonary disease, and dermatologic, gastrenterologic, nephrologic, dental, rheumatologic, gynecologic, and neurologic disorders (Bell et al., 1999). The syndrome may be a primary autoimmune-mediated disease or part of another immune-mediated connective tissue disease. Sjögren's-like syndrome has been reported in a female domestic shorthair cat (Canapp et al., 2001). The presenting clinical signs in this cat included dysphagia and weight loss, mild enlargement of all salivary glands, and ocular signs including blepharospasm and conjunctival hyperemia. Diagnostic testing revealed Schirmer tear test (STT) values of 0 mm/minute for both eyes, and a lack of salivation in response to atropine placed on the cat's tongue (Canapp et al., 2001). Over time, the affected cat also developed corneal ulceration and a corneal sequestrum despite treatment with topical cyclosporine 2% solution and administration of pilocarpine solution (gradually increased from 2% to 6%) on the food with some improvements in tear production and salivation noted (Canapp et al., 2001).

A diagnosis of Sjögren's syndrome in humans requires documenting the presence of xerophthalmia and xerostomia, and requires histologic examination of salivary gland biopsy specimens. In particular, lymphocytic infiltrates in a least four salivary lobules (a grade of 4/4) is required to confirm the diagnosis of Sjögren's syndrome. Laboratory evidence of a systemic autoimmune disease (e.g., positive antinuclear antibody [ANA] test, rheumatoid factor, or anti-Ro or anti-La antibody titers) may also be useful in supporting a diagnosis of this syndrome (Fox et al., 1986). The diagnosis of Sjögren's-like syndrome was made in a cat based on the clinical signs of xerophthalmia and xerostomia, combined with histologic diagnosis of lymphocytic sialoadenitis (Canapp et al., 2001). Fluorescent ANA tests were deemed to be negative at a titer <1 : 40 (Canapp et al., 2001). Treatment of Sjögren's syndrome in humans is primarily symptomatic. The most common treatment is pilocarpine, a direct-acting parasympathomimetic that stimulates tear production and salivation (Bell et al., 1999; Fox et al., 1986). Systemic immunosuppressive therapy is used to treat the most severe complications of Sjögren's syndrome in humans including

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pulmonary manifestations such as obstructive airway disease, bronchiectasis, and interstitial pulmonary disease (Fox et al., 1999). However, the sicca conditions tend not to respond favorably to this form of therapy (Bell et al., 1999).

Infectious Diseases

Bacterial

Any bacteremia may result in seeding of the uveal tract and create various degrees of inflammation, but only a few bacterial syndromes are relatively consistent regarding involvement of the eye. Sporadically, bacteremia arising from bacterial infections involving other organ systems (e.g., periodontitis or endodentic disease [Ramsey et al., 1996] or septic peritonitis [Pumphrey et al., 2011]) may result in varying degrees of focal chorioretinal lesions consisting of hemorrhage or exudates (or both), which often go unnoted. Typically, these lesions are associated with the end-arterioles or small vessels in the retina. In small animals, they may develop into fulminating endophthalmitis, but this appears to be rare (Massa et al., 2002).

Bartonellosis

Bartonella spp. are fastidious, hemotropic, short, pleomorphic, Gram-negative rod-shaped bacteria identified in a wide range of domestic and wild animals (Chomel et al., 2004). *Bartonella* organisms are considered emerging zoonotic agents (Chomel et al., 2004). *Bartonella henselae*, the causative agent for human "cat scratch disease" (CSD), is the prototypic *Bartonella* disease which was originally recognized in humans in 1889. Domestic cats are important reservoir hosts for the following five *Bartonella* spp.: *B. henselae*, *B. clarridgeiae*, *B. elizabethae*, *B. koehlerae*, and *B. Weissii* (Breitschwerdt & Kordick, 2000; Clarridge et al., 1995; Jameson et al., 1995). *Bartonella quintana* DNA has been recovered from dental pulp of a domestic cat thereby suggesting that cats may also be an emerging source of *B. quintana* infection in humans (La et al., 2005). In cats, infection with *B. henselae* is common with up to 81% of cats being seropositive for the bacterium. However, many infected cats do not show clinical signs (Lappin & Black, 1999; Pennisi et al., 2013c). *Bartonella* spp. are typically vector-borne with the vector varying according to the species of *Bartonella* (Chomel et al., 2004). Cat (Rolain et al., 2003) and dog fleas and, less commonly, dog and deer ticks carry the bacteria and act as vectors for transmitting *Bartonella* from cat to cat, and as potential vectors for transmitting the organism from cats to humans (Ketring et al., 2004).

Systemic manifestations of bartonellosis in cats include fever, lymphadenopathy, lethargy, anorexia, CNS disorders, urologic diseases, and endocarditis (Chomel et al., 2003, 2004). Ocular lesions associated with CSD in humans include Parinaud's oculoglandular syndrome as manifested by regional lymphadenopathy and unilateral ocular redness, epiphora, and ulceration of the bulbar conjunctiva (Cunningham & Koehler, 2000). Human manifestations of ocular bartonellosis also may include retinochoroiditis and neuroretinitis (for review see Cunningham & Koehler, 2000). Five percent to 10% of *B. henselae*-infected patients have ocular signs (Cunningham & Koehler, 2000; Wade et al., 2000). Uveitis in cats has been reported to be associated with *Bartonella* (Lappin & Black, 1999; Lappin et al., 2000). Additional ocular diseases associated with *Bartonella* in cats include blepharitis, conjunctivitis, keratitis, and chorioretinitis (Ketring et al., 2004). One cat was reported to develop a transient unilateral focal equatorial cataract and mild perilenticular vitreal degeneration after experimental blood inoculation with *B. henselae* (Kordick et al., 1997). *Bartonella*-infected cats may also show concurrent inflammatory disease including gingivitis, stomatitis, dermatitis, gastroenteritis, and upper respiratory disease that may or may not be linked to *Bartonella* infection (Ketring et al., 2004).

Bartonella spp. are slow growing and extremely difficult to culture. As such, the diagnosis of *Bartonella*-associated ocular diseases in cats is often based on eliminating other causes, positive serology for *Bartonella*, response to therapy, reduction in *Bartonella* antibody titers after therapy, and, in certain cases, lymphocytic–plasmacytic uveitis diagnosed histologically with no other apparent cause (Ketring et al., 2004). Polymerase chain reaction (PCR) can be used on various biological samples including aqueous humor. In particular, *Bartonella*-associated feline uveitis has been reported after positive serology for *Bartonella*, and detection of *Bartonella* antibodies and DNA (i.e., via PCR) in samples of aqueous humor (Lappin & Black, 1999; Lappin et al., 2000). However, the findings of some studies support that it is not possible to correlate clinical signs of ocular and/or systemic disease in cats with positive serology or culture for *Bartonella* spp. when this infectious agent is so widespread in the cat population and is not typically associated with signs of clinical disease. Recently, a study evaluated serum from 113 cats with uveitis, 156 clinically ill cats without uveitis, and 97 healthy cats (Fontenelle et al., 2008a). The healthy group of cats had the highest percentage of serum samples (68 of 97 [70%]) that were ELISA-positive for *Bartonella* spp. IgG antibodies. In addition, a recent study used immunofluorescent antibody tests and blood culture to detect *Bartonella* spp. serum antibody and DNA in 298 ill cats (Sykes et al., 2010). Five of these 298 cats had uveitis and only one such cat was seropositive and culture positive for *Bartonella* spp. A third study compared serum antibodies and PCR DNA amplification from blood and aqueous humor for *Bartonella* spp. and two other infectious agents in 104 cats with uveitis and 19 healthy shelter cats (Powell et al., 2010). Once again, a higher percentage of healthy cats (84%) had positive serum antibody titers than did the group of cats with uveitis (54%). Further, no cats with uveitis had *Bartonella* spp. DNA detected from aqueous humor whereas the aqueous humor from one healthy cat was positive for *Bartonella* spp. DNA.

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Treatment of bartonellosis in cats is challenging. The intermittent bacteremia regarding bartonellosis makes documenting clearance of the organism, even in experimental infections, challenging (Stiles, 2011). Currently, there is no antibiotic regime that has undergone rigorous evaluation for definitively eliminating feline bartonellosis (Greene et al., 1996; Pennisi et al., 2013c). Treatment of bartonellosis in cats involves the use of systemic antibiotics such as azithromycin or doxycycline. There is, however, information to support that azithromycin may have limited efficacy against *Bartonella* and resistance *in vitro* has been documented (Biswas et al., 2010). Current suggestions for treating ill cats with bartonellosis is based on long-term (weeks to a few months) use of either doxycycline, azithromycin, marbofloxacin, or amoxicillin-clavulanate with azithromycin (Breitschwerdt et al., 2010; Pennisi et al., 2013). In one cat with *Bartonella*-associated uveitis, treatment with topical or oral steroids failed to resolve the ocular disease; the uveitis responded to treatment with oral doxycycline (Lappin & Black, 1999). The reader is referred to Pennisi et al. (2013c) for recommendations regarding diagnosis and treatment of bartonellosis in cats.

Chlamydiosis

Chlamydiosis is caused by Gram-negative, obligate intracellular bacteria of the genus *Chlamydia* (for review see Borel et al., 2018; Gunn & Lofstedt, 2016). *Chlamydia felis* is a common pathogen of cats (formerly *Chlamydia psittaci* var. *felis*, although the strain affecting cats was renamed *Chlamydophila felis* and is now currently known as *C. felis*) (Borel et al., 2018). *C. pneumoniae*, a pathogen of humans, has been isolated from the conjunctiva of cats with conjunctivitis, however (Sibitz et al., 2011). The pathogenesis of chlamydiosis in cats remains largely unknown, although *C. felis* appears to have a predilection toward conjunctival epithelial cells (Sykes, 2005). Chlamydiosis is naturally transmitted by direct contact with other infected cats, aerosols, and by fomites (Sykes, 2005, 2014). The incubation period is approximately 3–5 days (Sykes, 2005).

C. felis is endemic in house cats worldwide, mainly causing acute and chronic conjunctivitis (Sykes, 2005). The organism can also infect the respiratory tract causing rhinitis and respiratory problems (Everett, 2000), and it has been isolated from the gastrointestinal (O'Dair et al., 1994) and reproductive (Everett, 2000) tracts of cats. Chlamydiosis has been associated with lameness in experimentally infected cats (TerWee et al., 1998). Two weeks after the development of conjunctivitis, lameness occurred in 10 of 19 infected cats (TerWee et al., 1998).

The acute phase of *C. felis* infection results in conjunctival hyperemia, chemosis, serous ocular discharge, and blepharospasm. Mild nasal discharge and sneezing may also occur in some cats (O'Dair et al., 1994; Sykes, 2005). Conjunctivitis is often unilateral initially, and then progresses to involve the contralateral eye during the next few days. Ocular disease results from host cell lysis that occurs during the release of *Chlamydia* spp. elementary bodies (Wyrick & Richmond, 1989). If untreated, infection with *C. felis* can produce chronic conjunctivitis (O'Dair et al., 1994). Asymptomatic carrier states can exist, and are likely significant in spreading the organism within a population (Storz & Kaltenboeck, 1993). Persistence of the organism in the genital and gastrointestinal systems also may contribute to the spread of chlamydophilosis (Wills et al., 1987).

C. felis infection, unlike chlamydial infections in other species, is rarely associated with keratitis in cats. Concurrent infection with feline herpesvirus-type 1 (FHV-1) should be suspected in *C. felis*-positive cats with keratitis. Other non-*C. felis* chlamydiae, including *Neochlamydia hartmannellae*, were detected in cats with ocular disease (von Bomhard et al., 2003). Further investigations are, however, required to confirm whether or not *N. hartmannellae* is a causative agent of feline conjunctivitis. In addition, *N. hartmannellae* does not appear more likely to cause keratitis than *C. felis* (Sykes, 2005) despite being found within the amoeba *Hartmannella vermiformis* and being a suspected cause of amoebic keratitis in humans (Kinnear, 2003).

Chlamydiosis may be complicated by coinfection with other microorganisms including *Mycoplasma* spp., *Bordetella bronchiseptica* (Shewen et al., 1980a; Sykes, 2005), feline calicivirus (Wills et al., 1988), FHV-1 (von Bomhard et al., 2003), and feline immunodeficiency virus (FIV) (O'Dair et al., 1994). In one study, coinfection with FIV led to a prolonged duration of clinical signs and the development of chronic conjunctivitis (O'Dair et al., 1994). In this same study, clinical signs of conjunctivitis in control cats resolved by day 109 after infection with *Chlamydia* spp., whereas cats with FIV and *Chlamydia* spp. still had conjunctivitis up to day 200. *Chlamydia* spp. were excreted from the conjunctival sac for up to 270 days in FIV-infected cats but for only 70 days in control cats. Both FIV-infected and control cats excreted *Chlamydia* spp. from the gastrointestinal tract for 35 days.

Natural exposure of cats to *C. felis*, as evaluated by serum antibody titers, appears to vary. The prevalence of seropositive cats in England has ranged from 9% among healthy cats (Gunn-Moore et al., 1995) to 69% in those with conjunctivitis (Wills et al., 1988). Another study of cats in England reported a 45% rate of positive antibody titers in a group that included both asymptomatic cats as well as those afflicted with conjunctivitis (Gethings et al., 1987). Reported antibody titers of cats in Japan ranged from no seropositive cats (Yamaguchi et al., 1996) to a 2% seropositive rate (Fukushi et al., 1985) although the presence or absence of conjunctivitis was not reported in these studies. In northern Italy, the prevalence of seropositive cats ranged from 21% and 21.3% of the free-living feral cats and household cats, respectively to 64% of cattery cats (Di Francesco et al., 2004) although the presence of

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clinical signs suggestive of chlamydiosis was not recorded. Studies evaluating the prevalence of *C. felis* in cats using PCR on conjunctival swabs resulted in estimates of 14.3% in Australian cats with upper respiratory tract disease (Sykes et al., 1999a); 17.7% in British cats with ocular signs (McDonald et al., 1998); 20% in Italian cats with conjunctivitis (Rampazzo et al., 2003); and 11.5% in Swiss cats with ocular signs (von Bomhard et al., 2003). The prevalence of *C. felis* in asymptomatic cats is low with estimates of <5% in studies using PCR (Rampazzo et al., 2003; von Bomhard et al., 2003) in comparison with prevalence estimates of non-*C. felis* chlamydial infection in asymptomatic cats of 20% (von Bomhard et al., 2003).

C. felis is considered to be a zoonotic agent. Transmission of this agent from cats to humans has been reported in an HIV-positive man with chronic conjunctivitis (Hartley et al., 2001). *C. felis* has been associated with other diseases in humans including respiratory tract disease, endocarditis, glomerulonephritis, and hepatosplenomegaly (Marrie et al., 2003; Regan et al., 1979). The rate of transmission from cats to humans is, however, probably low, but maintaining hygienic conditions and prompt treatment of infected cats is warranted to help prevent human disease.

Traditionally, the diagnosis of chlamydiosis has been established by using a variety of ELISA antigen kits with varying sensitivities (25%–80%) and specificities (80%–90%) or using cell culture, the "gold standard" for the diagnosis of chlamydial infection (Sykes, 2005). *Chlamydia* spp. can be cultured in many types of mammalian and avian cells (O'Dair et al., 1994; Storz & Kaltenboeck, 1993). However, isolation of the agent in cell culture is technically challenging, expensive, and time consuming (Sykes, 2005). Finding the characteristic inclusion body within the conjunctival epithelial cell cytoplasm on cytologic examination of Giemsa-stained conjunctival smears may be helpful in lending support for a diagnosis of chlamydiosis (Fig. 37.2.6). However, inclusions are typically only detectable during early infection, and in some cases not at all. In particular,

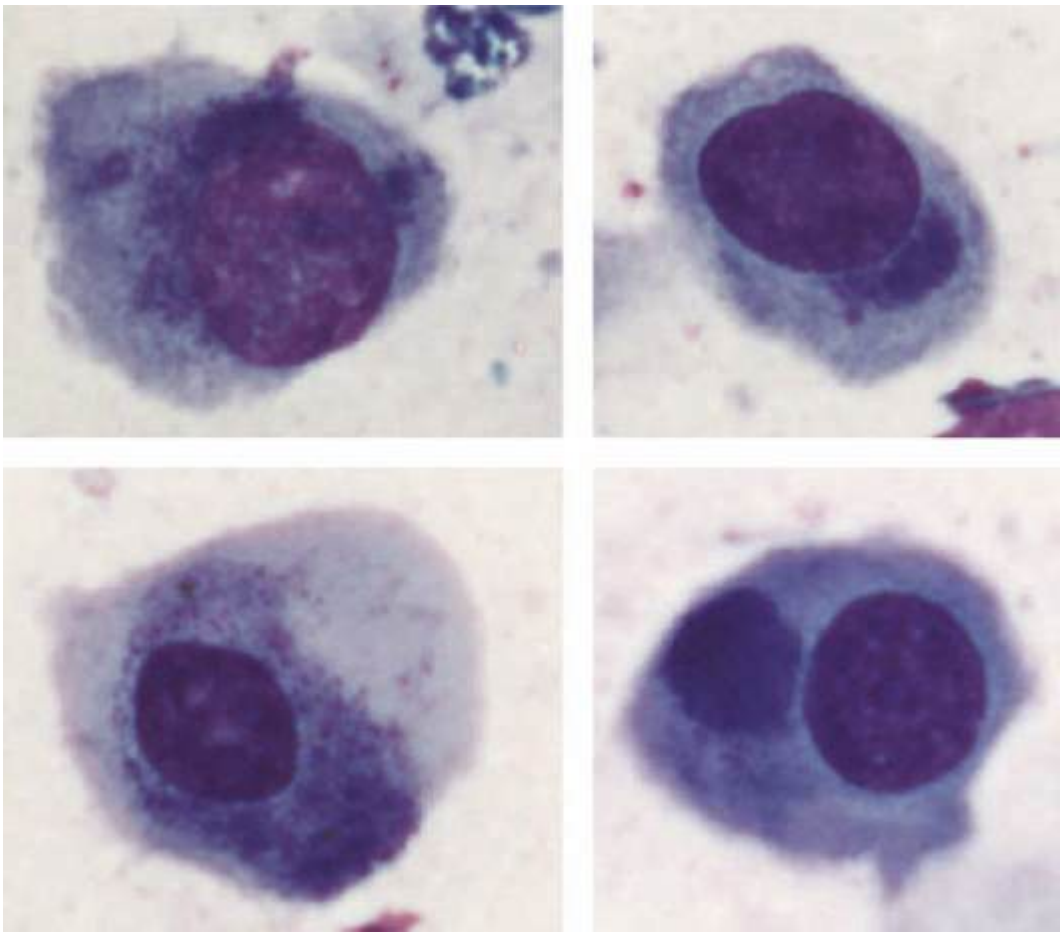


Figure 37.2.6 Epithelial cells with granular dark blue inclusions consistent with chlamydial inclusions, which were often located near the nucleus in cats positive for *Chlamydophila felis* by polymerase chain reaction. Hemacolor, 9100 objective. (*Source*: Reprinted with permission from Hillström, A., Tvedten, H., Källberg, M., et al. (2012) Evaluation of cytologic findings in feline conjunctivitis. *Veterinary Clinical Pathology,* **41**, 283–290.)

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chlamydial inclusion bodies are present in conjunctival cells from the third day after inoculation, and they persist in decreasing numbers for 2 weeks (Storz & Kaltenboeck, 1993). PCR techniques are typically more rapid and sensitive, and less expensive than traditional diagnostic tests such as ELISA and culture (Gruffydd-Jones et al., 2009; Sykes, 2005). Broad-spectrum chlamydial PCR assays, available in certain research laboratories, are used to test for non-*C. felis* chlamydial organisms including *N. hartmannellae* (von Bomhard et al., 2003). A definitive association between feline conjunctivitis and non-*C. felis* agents is necessary prior to routinely screening affected cats for non-*C. felis* chlamydial organisms, however.

Chlamydial organisms are sensitive to tetracyclines, erythromycin (Johnson et al., 1983), rifampin, fluoroquinolones, and azithromycin (Sykes, 2005). Topical administration of tetracycline three to four times daily to both eyes for 1–2 weeks after resolution of conjunctivitis is sufficient in some cats. However, given that chlamydiosis may be systemic, topical therapy alone may be ineffective in certain cats. Oral administration of tetracycline or doxycycline may be necessary to treat refractory infections and may also be necessary to clear the gastrointestinal tract of latent infection (O'Dair et al., 1994). In experimentally infected cats, oral doxycycline alone (5 mg/kg q 12 hour) for 3 weeks effectively eliminated the *C. felis* infection (Sykes et al., 1999b). However, it has been reported that in some cases, 3 weeks of treatment with oral doxycycline (10 mg/kg/day) did not eliminate *C. felis* infection. In fact, at least 4 weeks of therapy with oral doxycycline may be required to ensure elimination of the organism (Dean et al., 2005). Systemic doxycycline has been reported to produce more rapid clinical and microbiological resolution of chlamydiosis than topical chlortetracycline used twice daily (Sparkes et al., 1999). In another study, oxytetracycline, 50 mg twice daily for 60 days, cleared FIV-infected cats of both conjunctival and gastric mucosal infections (O'Dair et al., 1994). In contrast, administration of oral azithromycin (10–15 mg/kg) daily for 3 days and then twice weekly, resulted in rapid resolution of the clinical signs and lack of isolation of *C. felis* early in treatment similar to doxycycline; however, *C. felis* was re-isolated in four of five azithromycin-treated cats from 6 to 14 days into treatment (Owen et al., 2003). Even daily administration of azithromycin to chronically *C. felis*-infected cats failed to clear the infection (Owen et al., 2003). Amoxicillin–clavulanic acid of 4 weeks duration successfully eliminated *C. felis* in experimentally infected cats, with no recurrent infection 6 months after the cessation of therapy (Sturgess et al., 2001).

Both humoral and cell-mediated immunity appear necessary for the resolution of chlamydiosis. As such, kittens that have obtained colostrum from previously exposed queens appear to be protected from chlamydial infection by maternal antibodies until they reach 2–3 months of age. Both modified live and inactivated cell culture vaccines for *C. felis* have been used in the United States and Europe (Gruffydd-Jones et al., 2009; Sykes, 2005). Vaccination with a live chlamydial vaccine provides the best clinical protection (Shewen et al., 1980a; Wills et al., 1987). When challenged by conjunctival and nasal routes, vaccinated cats develop milder ocular and upper respiratory tract signs compared with those in unvaccinated cats. Some vaccinated cats did shed organisms, however, from the eye and respiratory tract, but for a shorter duration than unvaccinated cats. Although vaccination for chlamydia does not prevent infection, it may be beneficial in catteries with endemic chlamydiosis. For current vaccine recommendations see the current AAFP Feline Vaccination Guidelines (www.catvets.com/guidelines/practice-guidelines/feline-vaccination-guidelines).

Mycobacteriosis

Mycobacteria are aerobic, non-spore-forming, non-motile, acid-fast staining bacteria with a world-wide distribution, although the exact species may be geographically limited (e.g., *Mycobacterium bovis*) (Greene & Gunn-Moore, 1998; Gunn-Moore, 2014). Mycobacteria have been associated with causing tuberculosis characterized by internal tubercular granulomas, leprosy characterized cutaneous nodules, or progressive subcutaneous inflammation (Greene & Gunn-Moore, 1998; Gunn-Moore, 2014). The incidence of tuberculous mycobacterial infections in the cat has decreased dramatically since the decline in bovine tuberculosis (*M. bovis*) and pasteurization of milk, although new cases still occur (Gunn-Moore, 2014). Feline mycobacteriosis has been reported to be caused by a variety of organisms including *M.bovis, M. microti*, *M. tuberculosis*, *M. simiae*, *M. genavense*, *M. visibile*, and *M. Avium* (for review on the different organisms responsible see Gunn-Moore, 2014). Route of infection varies depending upon the species of *Mycobacterium* involved, but common routes of infection include ingestion, wound contamination, rodent bites, and direct contact with the organism (Lloret et al., 2013c). Once infected, granulomatous and pyogranulomatous inflammatory responses ensue and clinical signs vary depending upon route of infection, host immune responses, and species of *Mycobacterium* involved (Lloret et al., 2013c).

Ocular involvement varies depending upon the species of *Mycobacterium* involved (Gunn-Moore, 2014). For example, Candidatus "*M. tarwinense*" has a tendency to involve eyes (nictitating membranes, conjunctiva, eyelids) and periocular skin (O'Brien et al., 2017). In a case series of cats with *Mycobacterium* of undetermined species from Great Britain, ocular lesions involved primarily the posterior segment and include retinal hemorrhage, retinal detachment, and granulomatous choroiditis associated with large numbers of tubercle organisms within the eye (Formston, 1994). Unilateral granulomatous chorioretinitis with subretinal hemorrhage, exudation, and retinal detachment has been described in a

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domestic shorthair cat with disseminated *M. simiae*, a nontuberculous mycobacteria (Dietrich et al., 2003). Periocular skin lesions were reported in an FIV-positive cat diagnosed with disseminated *M. genavense* infection; however, these cutaneous lesions were likely caused by numerous mites (*Demodex cati*) which were observed in skin scrapings of the periocular region (Hughes et al., 1999). Interestingly, a conjunctivo-corneal granuloma has been described in a young European shorthair cat (Fig. 37.2.7), and histological examination confirmed a granulomatous lesion with acid-fast bacilli within macrophages (Lamagna et al., 2009). *Mycobacterium* 16S rRNA gene-specific PCR was positive in this case (Lamagna et al., 2009).

A presumptive diagnosis of mycobacterial infection can be made on the basis of identifying acid-fast bacilli from aspiration samples or tissue sections using special stains such as Ziehl–Neelsen or Kinyoun stains (Gunn-Moore, 2014; Jordan et al., 1994; Lloret et al., 2013c). Culture of the organism is required for speciation, but few laboratories are equipped to grow these organisms. PCR techniques are also available for *Mycobacterium* spp. (Lloret et al., 2013c).

Treatment of cats with mycobacterial infections requires long-term combination therapy, and perhaps even life-long therapy. Zoonotic potential should also be considered. Treatment and prognosis varies depending upon the *Mycobacterium* species involved and extent and severity of clinical disease. The reader is directed to current internal medicine textbooks or Lloret et al. (2013c) for more specific recommendations on therapy and prognosis for feline mycobacteriosis



Figure 37.2.7 Two-year-old female European cat with a conjunctivo-corneal mass at presentation. A nodular vascularized mass arising in the dorsal bulbar conjunctiva at the temporal canthus of the left eye and invading the sclera and cornea is apparent. Histological examination confirmed a granulomatous lesion with acid-fast bacilli within macrophages. (*Source*: Reprinted with permission from Lamagna, B., Paciello, O., Ragozzino, M., et al. (2009) Isolated lepromatous conjunctivo-corneal granuloma in a cat from Italy. *Veterinary Ophthalmology*, **12**, 97–101.)

Mycoplasmosis

Mycoplasma spp. are fastidious bacteria that lack cell walls and are found associated with mucous membranes of various mammals (Sykes, 2014). *M. felis*, *M. gatae*, and *M. arginini* have all been isolated from both sick and healthy cats (Tan & Miles, 1974; Tan et al., 1977b). The role of *Mycoplasma* spp. as a cause of conjunctivitis in the cat has been controversial because the organism has been isolated from the eyes of normal cats as well as from those of cats with conjunctivitis (Blackmore et al., 1971; Campbell et al., 1973; Cole et al., 1967; Haesebrouck et al., 1991; Tan et al., 1977a). Experimentally, *M. felis* has caused conjunctivitis among kittens in some studies (Haesebrouck et al., 1991; Tan, 1974) but not in others (Blackmore & Hill, 1973). Experimental infection has not resulted in conjunctivitis in adult cats (Blackmore & Hill, 1973). Importantly, however, *Mycoplasma* spp. have an increased prevalence in cats with conjunctivitis compared with otherwise healthy cats, thereby suggesting that *Mycoplasma* spp. play an important role in conjunctivitis (Haesebrouck et al., 1991; Low et al., 2007).

Most *Mycoplasma* spp. that normally inhabit the upper respiratory tract have been isolated at necropsy from the lungs of cats with pneumonia, but they are not normally present in the lungs of normal cats (Spradbrow et al., 1970; Tan et al., 1977a). *Mycoplasma* spp. inhaled from the upper respiratory tract probably establish infection in a lung that is already compromised by another pathogen. The same view may hold true for the eye, in which another pathogen, such as feline herpesvirus (Schneck, 1972) or *C. felis*, create an environment in which *Mycoplasma* spp. may thrive. Because these organisms have only been shown experimentally to cause conjunctivitis in kittens, an altered or immature immune system may also be a factor in allowing establishment of disease.

The diagnosis of mycoplasmosis can be established on the basis of culturing the organism on special media or finding the characteristic, small coccoid inclusions within the cytoplasm of the epithelial cells (Fig. 37.2.8), or more commonly via PCR (Low et al., 2007). *Mycoplasma* spp. are sensitive to many routinely used antibiotics (e.g., doxycycline, fluoroquinolones, and macrolides).

Tetanus

Tetanus is caused by the neurotoxin produced by the bacterium *Clostridium tetani*. *C. tetani* is a motile, Gram-positive, nonencapsulated, anaerobic, rod-shaped, spore-forming bacterium (for overview see Acke et al., 2004). Dogs and cats are naturally resistant when compared with other species such as humans and horses. Clinical signs of tetanus develop when spores of *C. tetani* enter the body through skin wounds or during surgical procedures (Bagley et al., 1994). Spores become vegetative and a toxin, tetanospasmin, retrogradely migrates along axons of motor nerves to the CNS. However, it should be noted that tetanospasmin, the principle neurotoxin, is only one of three toxins produced by the bacterium (Acke et al.,

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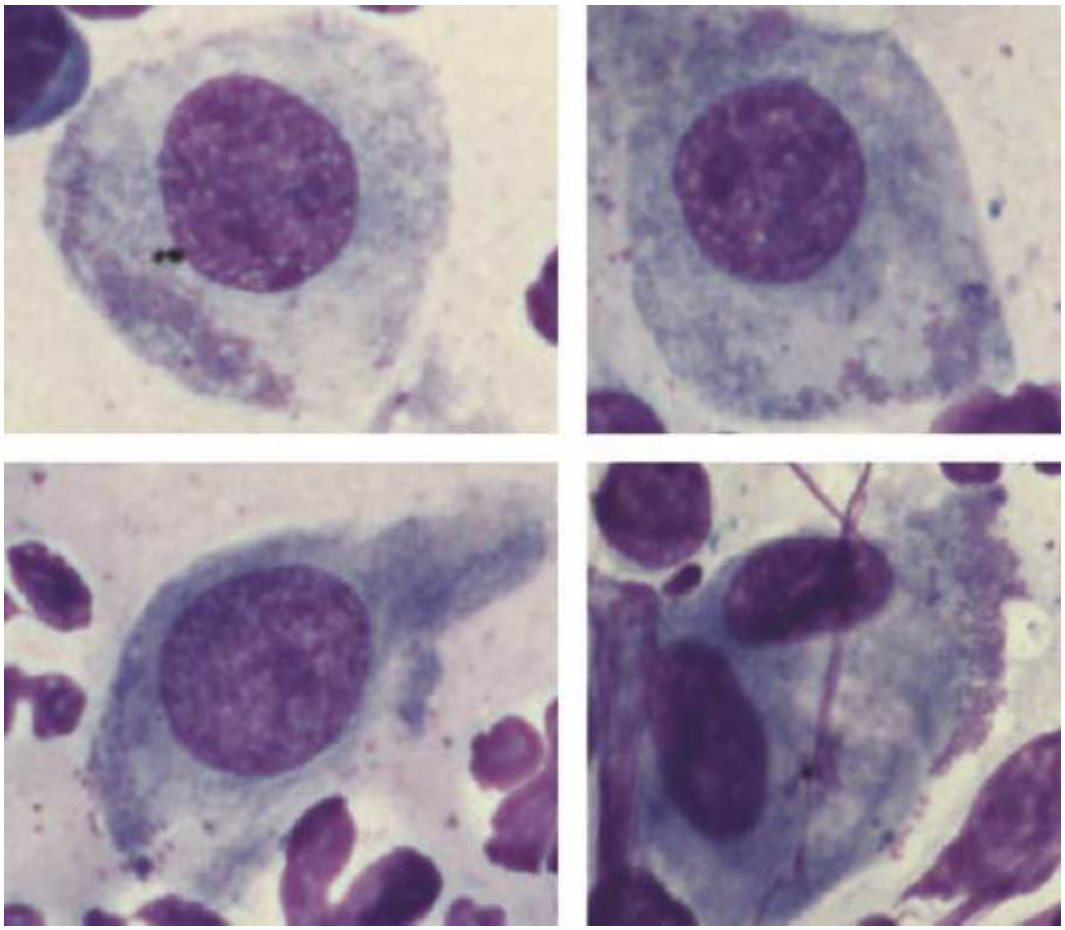


Figure 37.2.8 Epithelial cells with small basophilic coccoid structures consistent with Mycoplasma organisms in a polymerase chain reaction-positive cat. Mycoplasma organisms were paler than chlamydial inclusions and were often near the edge of the epithelial cells. Hemacolor, 9100 objective. (*Source*: Reprinted with permission from Hillström, A., Tvedten, H., Källberg, M., et al. (2012) Evaluation of cytologic findings in feline conjunctivitis. *Veterinary Clinical Pathology,* **41**, 283–290.)

2004). The toxin then prevents inhibitory neurotransmission to motor neurons thereby resulting in the classic signs associated with tetanus. Clinical effects on the autonomic nervous system have also been described (Panciera et al., 1988).

Clinical signs may be localized or generalized. In the localized form increases in stiffness of specific muscle groups or a given limb may be noted (Polizopoulou et al., 2002). The localized form is described more commonly in cats compared with dogs as a result of an inherent inability of the toxin to penetrate and bind to nervous tissue. In the generalized form, affected cats may have a stiff gait, an outstretched or dorsally curled tail, or be recumbent with profound rigidity of the limbs (De Risio & Gelati, 2003). A characteristic smiling/sneering appearance (risus sardonicus) may be seen in affected cats as a result of spasm of the facial muscles causing a drawing back of the lips and a wrinkling of the forehead (Baker et al., 1988). Respiratory compromise may result in death. Ocular signs seen in a tetanic animal include protrusion of the third eyelid and enophthalmus resulting from globe retraction caused by the hypertonicity of the extraocular muscles (Acke et al., 2004).

Diagnosis is made based upon consistent physical examination findings (presence of a wound) and clinical signs. Culture of the organism from the wound and/or measuring circulating serum antibodies against tetanospasmin may help to confirm the diagnosis. Treatment is aimed at administering tetanus antitoxin (usually unnecessary in localized forms of tetanus) and penicillin-G and/or metronidazole to prevent binding of any unbound toxin and to destroy any remaining bacteria, respectively. Tetanus antitoxin therapy should be done only after intradermal testing with this antitoxin as there is a strong likelihood of anaphylaxis after systemic administration (Acke et al., 2004). Symptomatic therapy with muscle relaxants such as diazepam may or may not be helpful in protracted cases. Supportive care and wound management are also indicated. Prognosis is variable depending upon the severity of the clinical signs and secondary complications.

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Mycotic

Aspergillosis

Aspergillosis is caused by the filamentous fungus *Aspergillus* spp. *Aspergillus* spp. are considered ubiquitous in the environment, and animals are infected opportunistically after inhaling *Aspergillus* spores (Barrs et al., 2014; Gelatt et al., 1991). Infection with *Aspergillus* spp. in cats results in either focal (sinonasal aspergillosis [SNA] or sino-orbital aspergillosis [SOA]), or disseminated aspergillosis (for detailed review see Barrs et al., 2014). It is thought that SOA results from an extension of SNA (Barrs et al., 2007, 2014; Kano et al., 2008; Giordano et al., 2010; Kano et al., 2013; McLellan et al., 2006). Secondary CNS involvement may result from erosion of the cribriform plate (Barachetti et al., 2009). Cats typically have historical or active clinical signs referrable to the upper respiratory tract including sneezing, stertor, nasal discharge (serous to mucopurulent), and epistaxis (Barrs et al., 2012). Ocular signs include typical signs associated with other causes of orbital disease including exophthalmos, third eyelid protrusion, deviation of the ipsilateral globe, and exposure keratitis (Fig. 37.2.9) (Barrs et al., 2012). Affected cats may exhibit neurologic signs, including blindness, if extension to the CNS occurs (Barachetti et al., 2009). Fever and ipsilateral lymphadenopathy and oral lesions may be present (Barrs et al., 2012). Importantly, cats with SOA typically have signs of unilateral orbital disease (Barrs et al., 2012), although bilateral signs may be encountered (Barachetti et al., 2009; Barrs et al., 2012).

Diagnosis of feline aspergillosis is based upon use of a combination of clinical techniques, although definitive diagnosis is typically made via identifying the organism via histology or cytology. Culture of the organism or detection using PCR can be helpful. Use of an ELISA for galactomannan, a component of the *Aspergillus* spp. cell wall, can be used, although it has a poor sensitivity (23%) and only moderate specificity (78%). *Aspergillus*-specific detection of antibodies via ELISA has a high sensitivity and specificity, 95.2% and 92% respectively (Barrs et al., 2015). Paired measurement of serum *Aspergillus*-specific IgA and IgG, using ELISA, shows no benefit for diagnosis of feline upper respiratory tract aspergillosis over IgG alone, however (Taylor et al., 2016).

Prognosis is variable depending upon the clinical form of aspergillosis that is present. Cats with SNA appear to have a good prognosis provided therapy is intensive and sufficiently long in duration, and that antifungal susceptibility has been determined for the culture organism, whereas those with SOA and disseminated aspergillosis have a poor prognosis. Prospective clinical evaluation of various antifungals for feline aspergillosis is necessary, because no rigid guidelines can be made regarding specific treaments for feline aspergillosis. Importantly, however, antifungicidal sensitivity of the isolated organism is deemed important (Barrs et al., 2014). The reader is referred to the reviews by Hartmann et al. (2013b) and Barrs et al. (2014) for guidelines regarding therapy of feline aspergillosis.

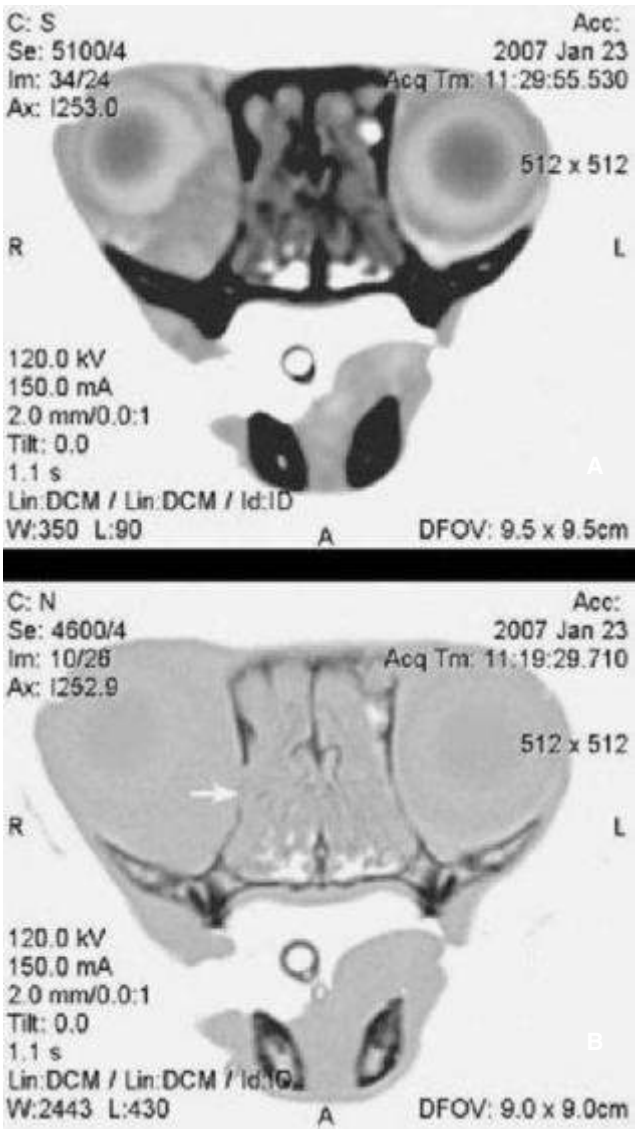


Figure 37.2.9 **A.** Transverse plane, postcontrast, computed tomographic (CT) images, obtained at the level of the orbits. A large soft-tissue mass is visible within the ventromedial right orbit. The mass lesion appears to dorsolaterally displace and indent the globe; an abnormal soft tissue density is also present in both sides of the nasal cavity. **B.** Transverse plane, precontrast CT images obtained at the same level of **A**; hard tissue algorithm showing focal lysis of the right lacrimal bone (arrow). (*Source*: Reprinted with permission from Barachetti, L., Mortellaro, C.M., Di Giancamillo, M., et al. (2009) Bilateral orbital and nasal aspergillosis in a cat. *Veterinary Ophthalmology*, **12**, 176–172.)

Blastomycosis

Blastomycosis is a systemic mycotic infection caused by the dimorphic fungus, *Blastomyces dermatitidis*. *B. dermatitidis* is a thick-walled yeast that reproduces by budding in infected

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tissues (i.e., yeast phase), and in nature is most likely a soil saprophyte which produces infective spores called conidia (i.e., mycelial phase). The tissue budding yeast form is 5–20 µm in size, with a thick, double-contoured wall. *B. dermatitidis* is endemic to various river valleys in the United States, Canada, Europe, Mexico, Latin America, and Africa (Bromel et al., 2005a; McCullough et al., 2000; Seitz et al., 2014).

Blastomycosis is not typically considered a zoonotic disease but has been transmitted to a person through an accidental needle-stick with a syringe and needle used for pulmonary aspirate from a dog with *B. dermatitidis* infection (Ramsey, 1994). Typically, blastomycosis develops after the inhalation of organismal spores. After inhalation of the infective conidia by the host, these infective spores become phagocytized by alveolar macrophages and transform from the mycelial phase to the yeast phase. *B. dermatitidis* has been reported in the cat, although to a much lesser extent than it has been reported in the dog (Breider et al., 1988; Davies & Troy, 1996; Jasmin et al., 1969; Lloret et al., 2013a; McEwen & Hulland, 1984; Meschter & Heiber, 1989; Miller et al., 1990; Nasisse et al., 1985; Sheldon, 1966). In two reports, one from Canada and one from the United States, the frequency of diagnosis of blastomycosis in cats appears significantly less than in dogs (Anderson et al., 2014; Davies et al., 2013;). The distribution of lesions is similar between species, with the lungs, eyes, skin, bone, CNS, and visceral organs being commonly involved. Reported ocular lesions in cats include retinal detachment, pyogranulomatous chorioretinitis, and panophthalmitis (Breider et al., 1988; Miller et al., 1990; Nasisse et al., 1985). The posterior segment of the globe is more commonly affected that the anterior segment (Miller et al., 1990).

A diagnosis of blastomycosis is made based upon cytologic identification of the organism. A positive agar-gel immunodiffusion test is considered to be highly suggestive of disease (Bromel et al., 2005a). PCR and *in situ* hybridization for the organism are becoming important in the clinical diagnosis of blastomycosis (Bromel et al., 2005a).

Few cases in the literature include treatment for blastomycosis in cats. Two cats have been successfully treated, however, one with a combination of amphotericin B and ketoconazole and one with ketoconazole alone (Miller et al., 1990). Three other cats with advanced disease died despite attempted treatment with amphotericin B (Breider et al., 1988; Nasisse et al., 1985). Itraconazole has been used successfully to treat dogs with ocular and systemic blastomycosis (Brooks et al., 1991; Legendre et al., 1996). Itraconazole has also been recommended for treatment of blastomycosis in the cat at the same dose as that used for cryptococcosis (Bromel et al., 2005a).

Candidiasis

Candida albicans is a dimorphic fungus that may cause either localized or generalized disease. Local proliferation of *Candida* spp. within wounds or mucosal surfaces is the first step in the spread of infection, and it generally occurs in immunosuppressed or debilitated cats (Pressler et al., 2003). Panuveitis resulting from candidiasis has been reported in the cat (Gerding et al., 1994; Miller & Albert, 1988). In one case, ophthalmic examination of a diabetic cat revealed corneal ulceration, from which the yeast was observed at cytology (Gerding et al., 1994). This same cat later developed bilateral panuveitis and had disseminated candidiasis at necropsy. A second cat with bilateral panuveitis at presentation was in a generalized debilitated condition, but specific immunosuppression was not documented (Miller & Albert, 1988). Histopathology of the eyes in both cases revealed pyogranulomatous inflammation, and organisms were found within the retina and vitreous humor. The cat with corneal ulcers had large numbers of organisms within the corneal stroma as well.

Coccidioidomycosis

Coccidioidomycosis is caused by two species of the dimorphic fungus *Coccidioides* spp. (Fisher et al., 2002). *C. immitis* inhabits California, especially along Californian Central Valley, whereas *C. possadassi* inhabits other regions of the southwestern United States, northern Mexico, and central and south America (Gabe et al., 2017; Grayzel et al., 2017). Clinical manifestation is similar between species of *Coccidioides* spp. (Gabe et al., 2017; Grayzel et al., 2017). *Coccidioides* spp. produce mycelia during seasonal rainfall. As the soil dries, arthrospores develop and become airborne under dry and windy conditions. The major route of *Coccidiodes* spp. infection is via inhalation (Wolf, 1989). Cutaneous entry of the organism through a penetrating skin wound is possible but occurs rarely (Wolf, 1989).

Coccidioidomycosis has been reported in the cat (Angell et al., 1985; Bentley et al., 2015; Davies & Troy, 1996; Foureman et al., 2005; Greene & Troy, 1995; Simoes et al., 2016). In a retrospective study of 48 cats, 19% had ocular signs that, although not described in detail, included retinal detachments, uveitis, and iritis (Greene & Troy, 1995). One report has described unilateral pyogranulomatous endophthalmitis in a cat with coccidioidomycosis (Angell et al., 1985). This cat did not have detectable systemic disease, and serologic tests for coccidioidomycosis were negative. The cat was clinically normal for a follow-up period of 2 years after enucleation, with no antifungal therapy administered. In a series of three cases of feline ocular cocciodioidomycosis two cats presented for subpalpebral or periorbital periocular swellings (Fig. 37.2.10) with systemic signs including weight loss, lethargy, and unkempt hair coat. One cat presented for bilateral red, swollen eyes and apparent blindness with no systemic signs (Fig. 37.2.11) (Tofflemire & Betbeze, 2010). Clinical ophthalmologic abnormalities were bilateral in each cat and included hyperemic, conjunctival masses, fluid-filled periorbital swellings, granulomatous chorioretinitis, nonrhegmatogenous retinal detachments, and anterior uveitis. The most common systemic signs

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Figure 37.2.10 Left eye of a cat with ocular coccidioidomycosis. Fleshy mass-like protrusions from the upper palpebral and bulbar conjunctiva, enophthalmos, conjunctival hyperemia, and mild aqueous flare are present. Fibrin strands extend from the cornea to cover the anterior lens capsule. (*Source*: Reprinted with permission from Tofflemire, K. & Berbeze, C. (2010) Three cases of feline coccidioimycosis: presentation, clinical features, diagnosis, and treatment. *Veterinary Ophthalmology*, **13**, 166–172.)



Figure 37.2.11 Right eye of a cat with ocular coccidioidomycosis. Fleshy, mass-like protrusions from the upper palpebral and bulbar conjunctiva, enophthalmos, conjunctival hyperemia, severe hypopyon, and deep corneal neovascularization are present. (*Source*: Reprinted with permission from Tofflemire, K. & Berbeze, C. (2010) Three cases of feline coccidioimycosis: presentation, clinical features, diagnosis, and treatment. *Veterinary Ophthalmology*, **13**, 166–172.)

of systemic coccidioidomycosis in cats are subcutaneous skin nodules, respiratory disease, and bone lesions (Greene & Troy, 1995; Simoes et al., 2016).

The most reliable means of diagnosis is identification of the organism from fluid or tissue aspirates. In the above-mentioned retrospective study, 39 of these 48 cats were evaluated with serologic tests (agar-gel immunodiffusion or complement fixating antibody titers), and all were positive at some point in the course of their disease (Greene & Troy, 1995). Forty-four of these cats were treated, 40 with ketoconazole and four with fluconazole and itraconazole. Thirty-two cats became asymptomatic, although relapses were common in cats treated with ketoconazole (Greene & Troy, 1995). In general, fluconazole appears to be most commonly used and most reliable in the treatment of coccidioidomycosis although long-term therapy may be needed in cases of persistent chorioretinal granulomas (Bentley et al., 2015; Simoes et al., 2016; Tofflemire & Betbeze, 2010).

Cryptococcosis

Cryptococcosis is caused by *Cryptococcus neoformans* or *C. gattii* (previously *C. neoformans* var. *gattii*) (Wolf, 1989). *C. neoformans* is associated with high nitrogen containing environments such as avian feces or soil enriched with avian feces (O'Brien et al., 2004). Hence, birds such as pigeons are considered to be significant vectors of *Cryptococcus* spp. *C. gattii*, however, was initially associated with eucalyptus and fir trees in Australia and Canada, respectively (O'Brien et al., 2004). Importantly, however, *C. gattii* has since been identified worldwide (Cogliati, 2013; Herkert et al., 2017; Lester et al., 2011; Lockhart et al., 2016). Cytologically, *Cryptococcus* spp. are approximately 4–15 µm and typically contain a thick capsule (Pennisi et al., 2013b).

Cryptococcosis has been described in a variety of mammals as well as in humans (Pennisi et al., 2013). Importantly, cryptococcosis is not contagious. Rather, inhalation of the yeast-like organism is the likely mode of infection (Pennisi et al., 2013b; Wolf, 1989). Dissemination occurs through hematological spread, and ocular lesions can be experimentally produced by intravenous inoculation of cats with *Cryptococcus* spp. (Blouin & Cello, 1980). The predominant signs of cryptococcosis vary with the species of animal that is affected, immune status of the patient, and perhaps, the strain of organism.

Importantly, there is no difference in the clinical manifestation of feline cryptococcosis caused by *C. neoformans* or *C. gattii* (Pennisi et al., 2013b). The most frequent sites of disease are the nasal passages, skin, and CNS, although systemic cryptococcosis can occur as well (Pennisi et al., 2013b). Chorioretinitis with granulomatous inflammation and retinal detachments (Fig. 37.2.12), anterior uveitis, and exophthalmos have been reported (Dye & Campbell, 1981; Fischer, 1971; Gerds-Grogan & Dayrell-Hart, 1997; Gwin et al., 1977; Rosenthal et al., 1981) and optic neuritis may also occur, particularly if the CNS is involved (Malik et al., 1992). One case of adnexal *Cryptococcus* in a cat without intraocular or systemic lesions has been described (Martin et al., 1996).

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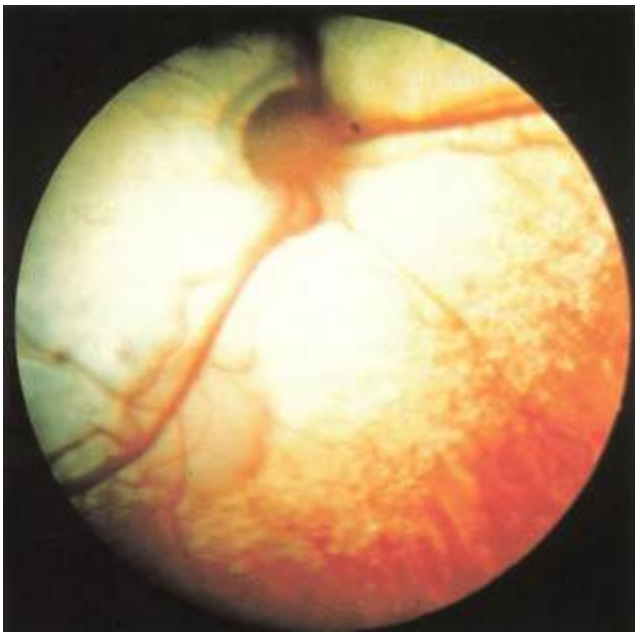


Figure 37.2.12 Chorioretinitis with a circumscribed lesion in a cat with cryptococcosis. (*Source*: Reprinted with permission from Stiles J. (1999) Ocular manifestations of systemic disease: part 2: the cat. In: *Veterinary Ophthalmology* (ed. Gelatt K.N.), 3rd ed., pp. 1448–1473. Philadelphia: Lippincott Williams & Wilkins.)

A diagnosis of cryptococcosis is made on the basis of cytologic identification of the organism aspirated from affected tissue. Antigen can be identified in serum by latex cryptococcal agglutination kits (Medleau et al., 1990), and serum antigen titers can be used to monitor the response to therapy (Jacobs et al., 1997; Medleau et al., 1995). In instances when the antigen test is negative, but cryptococcosis is still suspected, culture and PCR is recommended (Pennisi et al., 2013b).

Cats with cryptococcosis have been successfully treated with a variety of systemic antifungals. In one retrospective study, it was shown that there was no difference in clinical outcome between cats treated with amphotericin B compared with cats treated with monotherapy with itraconazole or fluconazole (O'Brien et al., 2006). Of course, however, many factors play a role in deciding the appropriate treatment for a particular patient, including cost of therapy (e.g., cost of medication and any follow-up testing for drug side-effects, etc.), route of administration required, risk of side-effects, and any preexisting medical comorbidity that a patient may have. Regardless of treatment protocol, it is recommended that treatment continues until the antigen testing is negative or for 2–4 months after resolution of clinical signs (Pennisi et al., 2013b).

Dermatophytosis (Ringworm)

Dermatophytosis, or ringworm, is a cutaneous infection with fungi, and in the cat, it may be caused by one of several species of *Microsporum* or *Trichophyton* (Cafarchia et al., 2004; Frymus et al., 2013; Moriello et al., 2017). The most common species affecting the cat is *M. canis*. Lesions, which are characterized by alopecia with or without scales, most commonly affect the head, pinnae, and paws, but they may also involve the eyelids, typically producing a dry, crusty, periocular alopecia (Fig. 37.2.13). Lesions can become ulcerated as well. Cats are typically young and any breed or gender can be affected, although subcutaneous dermatophyte infections are more commonly reported in Persians (Moriello et al., 2017). Interestingly, immunosuppression is thought to be a predisposing factor in the development of dermatophytosis in cats (Frymus et al., 2013; Moriello et al., 2017), although seropositive FIV or FeLV status in cats, alone, does not increase the risk of developing dermatophytosis (Moriello et al., 2017). Diagnosis of dermatophytosis is based upon the results of multiple complimentary tests including direct microscopic examination of skin scrapings from lesions, Wood's light examination, and direct fungal culturing of the affected hair and scales with dermatophyte test medium (Frymus et al., 2013; Moriello et al., 2017). Treatment includes clipping the hair in the affected region, which is followed by topical (i.e., twice weekly application of lyme sulfur, enilconazole, or miconazole/chlorhexidine shampoos) or systemic (i.e., itraconazole, terbinafine, or griseofulvin) antifungal therapy that continues until two to four negative cultures have been obtained at weekly or biweekly timepoints (for review and consensus statement see Moriello et al., 2017).



Figure 37.2.13 Chronic severe dermatophytosis caused by *M. canis* infection in a Persian cat. (*Source*: Foster, A.P. (2006). Dermatophytosis in cats. *Companion Animal,* **11**, 57–61.)

Histoplasmosis

Histoplasmosis is caused by a dimorphic fungus, *Histoplasma capsulatum*, which exists in various river bottoms as a mycelial-phase, soil saprophyte. *H. capsulatum* grows best in nitrogen-rich organic matter, such as bat and bird feces (Wolf, 1989). Although quite widespread in North and South America,

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endemic areas are in the Ohio, Missouri, and Mississippi river valleys (Bromel & Sykes, 2005b). Cats with histoplasmosis have also been reported in nonendemic regions of North America, Europe, and Japan, however (Fischer et al., 2013; Johnson et al., 2004; Kobayashi et al., 2009; Mavropoulou et al., 2010; Smith et al., 2017). The life cycle of *H. capsulatum* is similar to that of *Blastomyces* and *Coccidioides* spp., with a mycelial phase in the soil that produces conidia, which once in the pulmonary system convert to a budding yeast phase (Wolf, 1989). *Histoplasma* organisms can then be disseminated via hematogenous or lymphatic spread.

Common presenting complaints are nonspecific and include weight loss, anorexia, and weakness (Aulakh et al., 2012; Bromel et al., 2005b; Clinkenbeard et al., 1987; Reinhart et al., 2012). Respiratory signs may be present, but it is important to recognize that disseminated histoplasmosis may present in the absence of respiratory involvement (Aulakh et al., 2012). Common sites of infection in disseminated disease include eye, bone, skin, and visceral organs (Clinkenbeard et al., 1987). Ocular lesions include granulomatous chorioretinitis, subretinal granulomas, anterior uveitis, posterior uveitis, panuveitis, panophthalmitis, retinal detachment, secondary glaucoma, and optic neuritis (Aulakh et al., 2012; Davies & Troy, 1996; Gwin et al., 1980; Hodges et al., 1994; Johnson et al., 2004; Mahaffey et al., 1977; Percy, 1981; Smith et al., 2017).

A diagnosis of histoplasmosis is made based upon cytologic or histologic identification of the fungal organism and/or culture of the organism (Lloret et al., 2013a). Serology is of limited value as these tests have low sensitivity and specificity (Lloret et al., 2013a). Antigen testing for galactomannan has been found useful in feline histoplasmosis when applied to body fluids, especially plasma and urine (Cook et al., 2012; Hanzlicek et al., 2016; Jarchow & Hanzlicek, 2015). Importantly, however, *Histoplasma* antigen testing may not be useful in cats with histoplasmosis with only ocular involvement. Specifically, false negative antigen testing performed on serum, urine, and ocular fluids has been shown in cats with ocular histoplasmosis (Smith et al., 2017).

Itraconazole is considered the treatment of choice for feline histoplasmosis, although amphotericin B and fluconazole can be used in severe cases or in patients with CNS involvement (Lloret et al., 2013a). Readers are referred to current internal medicine or infectious disease textbooks for further details regarding therapy for feline histoplasmosis.

Sporotrichosis

Sporotrichosis is caused by the dimorphic fungus, *Sporothrix schenckii*, which exists in soil rich in decaying organic matter (Lloret et al., 2013b). The organism is endemic worldwide, and grows as a mold at 25–30°C and as a yeast at 37°C (Schubach et al., 2004). Sporotrichosis typically develops from direct cutaneous inoculation of the fungus through contact with soil or plants, or, less commonly, via inhalation of infective conidia (Rippon, 1988). Localized cutaneous and subcutaneous infections with *S. schenckii* occur most frequently, whereas disseminated sporotrichosis occurs rarely.

Despite its worldwide distribution, feline sporotrichosis is reported to occur only sporadically but is an important zoonosis responsible for causing human epidemics in some instances (Davies & Troy, 1996; de Baroni et al., 1998; de Lima Barros et al., 2001; de-Oliveira-Nobre et al., 2001; Gremiao et al., 2015; Schubach et al., 2004, 2005). Cats experimentally infected with *S. schenckii* have been shown to develop both the localized and disseminated forms of the disease (Barbee et al., 1977). In naturally occurring infections, *S. schenckii* primarily affects younger intact male cats (<4 years of age) (da Rocha et al., 2018; Davies & Troy, 1996; Schubach et al., 2004). Clinical signs observed in affected cats ranged from subclinical infection to a self-regressing solitary cutaneous lesion to fatal disseminated forms (Gremiao et al., 2015; Schubach et al., 2004). Cutaneous and subcutaneous lesions included focal crusted areas, subcutaneous nodules that eventually drained purulent material, exudative ulcers, and large regions of necrosis exposing underlying muscle and bone. Sporotrichosis prefentially affects the face, neck, and extremities (Davies & Troy, 1996; Gremiao et al., 2015; Schubach et al., 2004). One study reported cutaneous lesions involving mainly the head and hind limbs in 56.8% and 13.8% of cats, respectively (Schubach et al., 2004). Mucosal lesions, including ulcerated conjunctival granulomas, were observed in 34.9% of cats (Schubach et al., 2004). Systemic signs were present in 57.1% of cats, and included poor body condition, anorexia, vomiting, and most frequently, respiratory signs such as sneezing and dyspnea. Affected cats may also be FIV-positive and/or FeLV-positive, although no differences in presenting clinical signs were noted in FIV-FeLV-positive versus -negative cats (Schubach et al., 2004).

Diagnosis of sporotrichosis involves isolation or demonstration of the causative agent, *S. schenckii* from affected tissues (e.g., nasal or oral swabs, secretions form cutaneous lesions) via mycologic culture, histopathologic examination of a skin biopsy, or via detecting organismal DNA using PCR (Gremiao et al., 2015; Kano et al., 2005; Schubach et al., 2004). The presence or absence of granuloma formation in the cutaneous biopsy specimens has reportedly affected whether or not *S. schenkii* was detected histologically. The fungal organisms were observed in 57.8% of specimens in which granulomatous inflammation was not present, but in only 4.4% of samples which contained granulomas (Schubach et al., 2004).

Cats with sporotrichosis have been successfully treated with itraconazole, combinations of itraconazole and fluconazole or itraconazole and terbinafine, terbinafine, sodium iodide, or ketoconazole (Schubach et al., 2004). In one study, treatment duration ranged from 16 to 80 weeks (median = 36 weeks) (Schubach et al., 2004). Adverse

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treatment effects were seen in 40.5% of cats treated with sodium iodide and 13.7% of cats receiving the other treatment regimens (Schubach et al., 2004). Some patients may develop resistance to itraconazole monotherapy. In these cases it has been shown that combined itraconazole with potassium iodide is useful. Specifically, 24 of 38 cats refractory to itraconazole monotherapy achieved clinical cure with the addition of potassium iodide, although two of these patients had recurrence 3 months after clinical cure (da Rocha et al., 2018). Aside from antifungal therapy, concurrent antibiotic therapy typically is instituted as secondary bacterial infections are common. Readers are referred to current internal medicine or infectious disease textbooks for further details regarding therapy for feline sporotrichosis.

Parasitic: Dipteric Larvae

Ophthalmomyiasis Interna/Externa

Ophthalmomyiasis interna refers to the intraocular migration of fly (*Diptera*) larvae. The syndrome has been observed in the cat and in the dog. The syndrome is quite characteristic, but it is uncommon to determine the type of fly larvae present. The point of entry is unknown but postulated to be across mucous membrane-lined sites such as the conjunctival surfaces, oral cavity, nasal cavity, skin, or other body orifice or wound. The syndrome may be presented in the acute stages if an anterior uveitis is produced, but usually the syndrome is noted as an incidental finding in the chronic stages. The characteristic ophthalmoscopic lesions are wandering, curvilinear tracts that frequently intersect and are associated with retinal and preretinal hemorrhages in the acute stage.

These curvilinear retinal lesions have been reported in the cat (Brooks et al., 1984; Gwin et al., 1984; Kaswan & Martin, 1984), and in one case, a larva was visualized migrating within the retina (Gwin et al., 1984). This cat had bilateral disease, with retinal hemorrhage in one eye and retinal detachment in the other. Only acute cases warrant therapy, and topical or systemic steroids are indicated depending on the location of the lesion (or lesions). If the larva is present, laser energy may be attempted to kill the larva, even though it is not pigmented. Systemic organophosphates have been used as well, but because the condition spontaneously improves in most instances, its efficacy is unknown. Killing the larva may incite more inflammation, however, and waiting for spontaneous departure may be prudent.

Three cases of an intracameral *Cuterebra* spp. larva in cats have also been reported (Johnson et al., 1988; Harris et al., 2000; Stiles & Rankin, 2006). In one case, severe panophthalmitis was present, and even though the larva was surgically removed from the anterior chamber, the eye was blind (Johnson et al., 1988). In another affected cat, the *Cuterebra* larva had directly penetrated the sclera resulting in severe anterior uveitis characterized by a large fibrin clot followed by generalized retinal degeneration and blindness noted 6 weeks after surgical removal of the larva from the anterior chamber (Harris et al., 2000). In the third case, the parasite was surgically removed from the anterior chamber with preservation of vision reported at 6 months postoperatively (Stiles et al., 2006). Ophthalmomyiasis interna in which the *Cuterebra* spp. was found in the vitreous slightly lateral to the optic nerve has been described (Fig. 37.2.14 and Fig. 37.2.15) (Wyman et al., 2005). The larva was shown histologically as were coagulation necrosis and hemorrhage of the optic nerve, retina and choroid, and anterior uveitis. In addition, cerebrospinal cuterebriasis has been reported as a cause of blindness in 6 of 10 affected cats (Williams et al., 1998). Another report involved an adult *Metastrongylidae* spp. nematode within the globe of a cat (Bussanich & Rootman, 1983). This nematode could not be removed surgically, however, and uveitis necessitated enucleation (Bussanich & Rootman, 1983).

Ophthalmomyiasis externa refers to the extraocular migration of fly larvae. Migration of *Cuterebra* spp. larvae in the subcutaneous tissues of the cat is common, and the eyelids or conjunctiva may be affected. In addition, *Cuterebra* have been found within the feline orbit (Harris et al., 2000). Removal of the larva is indicated. Care must be taken not to crush the larva, however, because a severe inflammatory response may occur.

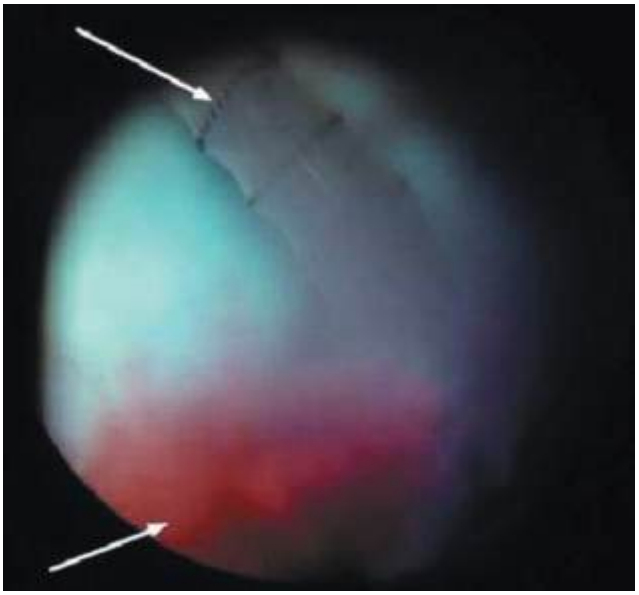


Figure 37.2.14 Cuterebriasis in a cat. Fundus photograph of the organism in the vitreous with vitreal hemorrhage overlying the optic disc. The black cuticular spines can be observed. (*Source*: Reprinted with permission from Wyman, M., Starkey, R., Weisbrode, S., et al. (2005) Ophthalmomyiasis (interna posterior) of the posterior segment and central nervous system myiasis: *Cuterebra spp*. in a cat. *Veterinary Ophthalmology*, **8**, 77–80.)

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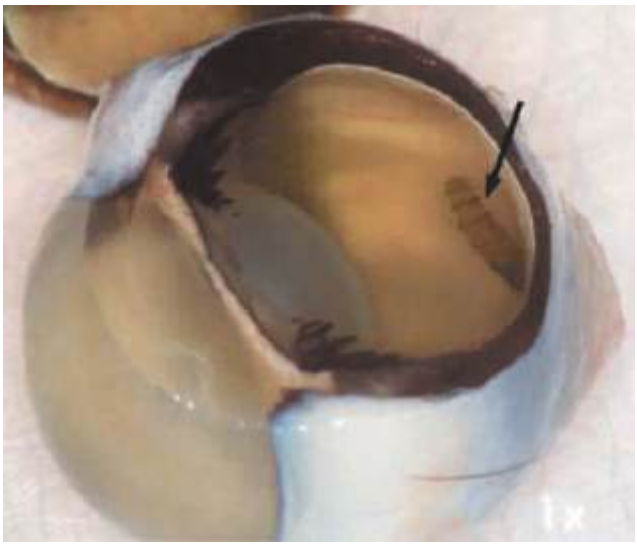


Figure 37.2.15 Gross specimen of the globe in Fig. 37.2.14 demonstrating the *Cuterebra* larva in the vitreous (arrow). (*Source*: Reprinted with permission from Wyman, M., Starkey, R., Weisbrode, S., et al. (2005) Ophthalmomyiasis (interna posterior) of the posterior segment and central nervous system myiasis: *Cuterebra spp.* in a cat. *Veterinary Ophthalmology*, **8**, 77–80.)

Parasitic: Mites

Demodicosis

An uncommon disease, feline demodicosis results from three species of mites: *Demodex cati*, *D. gatoi*, and a third species of *Demodex* that has not yet been named (Ferreira et al., 2015; Silbermayr et al., 2015). Affected animals typically have a concurrent medical condition. Lesions usually affect the eyelids, periocular area, head, and neck. They are variably pruritic, and they are characterized by alopecia, erythema, crusting, and scaling. Demodicosis may be associated with other concurrent cutaneous lesions. A cat with multiple cutaneous xanthomas and concurrent mild demodicosis and dermatophytosis affecting the head and neck has been described (Vogelnest, 2001). The diagnosis of demodicosis is established on the basis of cutaneous scrapings of the lesion(s) and identification of the mite. A thorough review of the literature has identified lime sulfur dips (1.6%–2% every 5–7 days for 4–6 weeks) and amitraz rinses (0.0125%–0.025% twice weekly or every other week for 2–4 weeks) as being the most reliable treatment for the treatment of feline demodicosis (Mueller, 2004). It should be mentioned, however, that favorable response to treatment of feline demodicosis has been seen with subcutaneous administration of doramectin (Johnstone, 2002). The use of ivermectin was not successful in one cat with concurrent infestion with *D. cati* and an unnamed mite species (Lowenstein et al., 2005).

Notoedric Mange

The causative agent of feline scabies is *Notoedres cati*, but cats may also be infected with the mite that causes canine scabies, *Sarcoptes scabiei* var. *canis* (Bornstein et al., 2004; Delucchi & Castro, 2000; Hawkins et al., 1987; Itoh et al., 2004). Importantly, feline mange is zoonotic and owners of affected cats may become infected (Chakrabarti, 1986). Typically, lesions begin around the medial edge of the ear pinna, then progress to involve the upper ear, face, eyelids, and neck. Intense pruritus is characteristic, and the diagnosis is suggested by location of the lesions and intense pruritus. The diagnosis is confirmed on the basis of acetate tape impression with skin squeezing or cutaneous scrapings of the lesion(s), which are examined under low-level light at 10× magnification for the small mite (Milley et al., 2017; Sampaio et al., 2017). Treatment should include clipping of all hair and application of a 3% lime sulfur solution every seventh day until the lesions have resolved. All other cats on the premises must be treated as well. The avermectins are highly effective at treating notoedric mange in cats. Ivermectin has been shown to be effective for use in cats (Oliva & Baldi, 1988; Song, 1992). Ivermectin use in kittens, however, has a low safety margin (Lewis et al., 1994; Muhammad et al., 2004). Doramectin (290 µg/kg SQ) administered as a single dose and selamectin (6–12 mg/kg topically) have also been shown to be effective in the control of notoedric mange in cats (Delucchi & Castro, 2000; Itoh et al., 2004). Selamectin apparently has a wide safety margin and has not been associated with adverse effects in kittens older than 6 weeks of age (Itoh et al., 2004). Additionally, commercially available topical products (fipronil 8.3% w/v, (S)-methoprene 10% w/v, eprinomectin 0.4% w/v, and praziquantel 8.3% w/v [Broadline, Merial, Lyon, France]; and 10% imidacloprid/1% moxidectin [Advocate/Advantage Multi spot-on for cats, Bayer, Whippany, NJ, USA]) have been shown to be effective for notoedric mange in cats (Hellmann et al., 2013; Knaus et al., 2014).

Parasitic: Nematodes

Onchocerciasis (Onchocercosis)

Ocular onchocerciasis is caused by the nematode, *Onchocerca* spp. (for review see Sreter & Szell, 2008; Sreter et al., 2002; Zarfoss et al., 2005). The life cycle of *O. lupi* is not completely understood, but is likely similar to that of other *Onchocerca* spp. (Sreter et al., 2002). Larval maturation is thought to occur in black flies (*Simulium*) or gnats/midges (*Culicoides*), the intermediate hosts (Sreter et al., 2002; Zarfoss et al., 2005). Larvae are then transmitted to the definitive host via blood feeding of the insect (Zarfoss et al., 2005). The parasites then mature, mate, and produce microfilariae that are ingested by the intermediate host, and so on (Zarfoss et al., 2005). Two domestic shorthair cats residing in the southwestern United States were confirmed histologically and by molecular identification to have feline ocular onchocerciasis caused by infection with *O. lupi* (Labelle et al., 2011). The ophthalmic findings reported in one cat included chemosis and conjunctivitis, opacity within the anterior chamber and

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dyscoric pupil with progression to secondary glaucoma and eventual enucleation. Histopathologic assessment of this globe revealed a multinodular, predominantly granulomatous inflammatory infiltrate centered on these parasites affecting the posterior episclera and orbital tissues (Fig. 37.2.16). The second affected cat had persistent conjunctivitis, ipsilateral facial nerve paralysis, facial hypalgesia and corneal ulceration that resulted in subsequent enucleation.

The main histopathologic findings for this eye revealed female parasites in the posterior episclera and orbit surrounded by small numbers of macrophages, lymphocytes, and plasma cells with mild fibrosis. Rare lymphocytes and plasma cells were noted within the iris stroma and ciliary body, and there was evidence of glaucomatous retinal and optic nerve damage. Ocular onchocerciasis should be included in the differential diagnosis list for cats with conjunctivitis and orbital disease. The antiparasitic treatment commenced in the two *O. lupi*-affected cats was epirical, and consisted of two broad spectrum parasiticides, including an avermectin class parasiticide, selamectin, that were selected, in part, based on known safety in cats (Labelle et al., 2011). Further investigation into therapies for onchocerciasis in cats is warranted.

Parasitic: Protozoal

Leishmaniasis

Leishmania spp. are diphasic protozoal parasites that infect a wide range of vertebrates, including dogs, cats, and humans (for reviews see Pennisi & Persichetti, 2018; Pennisi et al., 2013a,2015). Dogs and other canids are primary reservoirs of *Leishmania* spp., and sandflies *(Phlebotomus* spp. or *Lutzomyia* spp.), based upon their ability to feed on cats, are presumed the vectors in cats (Pennisi et al., 2015).

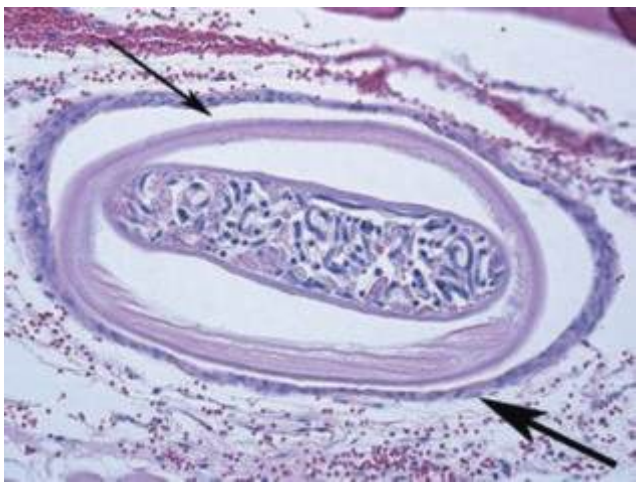


Figure 37.2.16 Histopathologic section of the orbital tissues. (Hematoxylin and eosin. × 200.). A section of the parasite (*Onchocerca lupi*) is bordered by mild fibrosis (bold arrow). The section includes one of the paired uteri that contains numerous microfilariae. Cuticular ridges are visible (arrow). (*Source*: Reprinted with permission from Labelle, A.L., Daniels, J.B., Dix, M., et al. (2011) *Onchocerca lupi* causing ocular disease in two cats. *Veterinary Ophthalmology*, **14**(Suppl. 1), 1005–1110.)

Although vertical and/or horizontal transmission may be primary modes of transmission of *Leishmania* to dogs where a competent vector does not exist (Boggiatto et al., 2011; Naucke & Lorentz, 2012; Svobodova et al., 2017), such modes of transmission have not been shown in cats (Pennisi et al., 2018).

Naturally occurring leishmaniasis has traditionally been uncommonly recognized in cats but has been increasingly reported (Pennisi, 2015; Pennisi & Persichetti, 2018; Pennisi et al., 2013a, 2015). Feline leishmaniasis is caused by a variety of species of *Leishmania* including: *L. amazonensis, L. braziliensis, L. mexicana, L. venezuelensis, L. infantum, L. tropica* and *L. major* (as reviewed by Pennisi & Persichetti, 2018).

As previously mentioned, transmission to vertebrates is via bites from infected sandflies. Further, sandflies are infected by reservoir hosts during feeding. The incubation period may be a few months to between 3 and 4 years (Kontos & Koutinas, 1993). Consequently, a thorough travel history needs to be investigated in suspect cases of feline leishmaniasis.

Leishmania spp. cause cutaneous, mucocutaneous, and visceral diseases (Pena et al., 2000). Dogs will typically develop a combination of these forms of leishmaniasis (Pena et al., 2000). Visceral forms of leishmaniasis are not typically described in cats, although reports of *Leishmania*-induced cutaneous lesions are common. Cutaneous lesions are variable but typically involve an ulcerative dermatitis on the face, pinnae, neck, thorax, and bony protuberances. In addition, generalized alopecia and scaling, and cutaneous nodules on the head and extremities have been reported. Ocular manifestations of leishmaniasis occur in at least 25% of affected dogs (Pena et al., 2000). Ocular manifestations of feline leishmaniasis have been described and include panuveitis, blepharitis, and conjunctivitis (Leiva et al., 2005; Migliazzo et al., 2015; Navarro et al., 2010; Richter et al., 2014; Verneuil, 2013). A case of ocular and visceral leishmaniasis has been reported in a cat (Leiva et al., 2005). This affected cat had bilateral melting ulcerative keratitis, exudative panuveitis and secondary glaucoma, diabetes mellitus, and macrophages with intracytoplasmic *Leishmania* detected cytologically on bone marrow aspirates (Leiva et al., 2005). Leishmaniasis has also been reported in cats with coinfections with FeLV and/or FIV (Grevot et al., 2005; Miro et al., 2014; Pennisi et al., 2004; Poli et al., 2002; Spada et al., 2016; Vides et al., 2011), and in one cat with concurrent pemphigus foliaceus (Rufenacht et al., 2005).

The diagnosis of feline leishmaniasis may be difficult because serology and serum protein electrophoresis patterns are usually less specific than in affected dogs (Merchant

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et al., 1995). A diagnosis is confirmed on the basis of finding the organisms (i.e., amastigotes), which are round to oval and 2.5–5.0 µm by 1.5–2.0 µm in size, in bone marrow aspirates, lymph node aspirates, or skin impression smears stained with Wright's or Giemsa stains. Other means of identifying the *Leishmania* organism include histopathologic or immunoperoxidase evaluation of cutaneous or organ biopsy specimens, PCR performed on anticoagulated blood, or bone marrow or lymph node aspirates, or conjunctival swabs, or culture inoculation of hamsters (Ashford et al., 1995; Benassi et al., 2017; Manna et al., 2004; Oliveira et al., 2015; Solano-Gallego et al., 2001; Vitale et al., 2004). Serologic tests are available that are based upon several techniques including Western blot, ELISA, and immunofluorescent antibody tests (Pennisi & Persichetti, 2018; Persichetti et al., 2017). Importantly, however, a negative result on serology does not necessarily exclude a positive diagnosis of active infection (Pennisi & Persichetti, 2018).

Leishmania spp. are difficult to eliminate from the body and recurrences are common (Cavaliero et al., 1999). A variety of drugs have been used for the treatment of leishmaniasis (Noli & Auxilia, 2005; Pennisi & Persichetti, 2018; Pennisi et al., 2013a, 2015). Due to the limited number of reported cases of feline leishmaniasis, treatment is not clearly defined. Nevertheless, long-term use of allopurinol or meglumine antimoniate are typically used with good clinical response (Pennisi & Persichetti, 2018; Pennisi et al., 2013a). Readers are advised to consult a current internal medicine textbook for further details regarding the treatment of feline leishmaniasis.

Toxoplasmosis

Toxoplasmosis is caused by the obligate intracellular protozoal parasite, *Toxoplasma gondii* (for review see Dubey, 2004). *T. gondii* has a worldwide distribution. Cats are both definitive and intermediate hosts of *T. gondii*. Because cats are definitive hosts, they are the only species that can shed oocysts, which in turn are infective to other species. Cats shed oocysts for approximately one week, beginning 3–5 days after the initial infection, and then are immune to re-shedding oocysts unless they are reinfected. Even when reinfected, however, cats inconsistently re-shed oocysts (Dubey, 1995). Many mammalian species can act as intermediate hosts. In the cat, ingested *T. gondii* bradyzoites (from tissue cysts) undergo a typical coccidian intestinal life cycle, and infected cats excrete oocysts in their feces that, after 1–5 days, sporulate and become infectious sporozoites (Dubey, 2004). The oocysts are resistant to environmental conditions, and they may remain infectious for months to years (Dubey, 2004). Ingestion of the oocysts by a susceptible host results in rapid division of sporozoites in the gut epithelium. The resultant tachyzoites are 4–8 µm by 2–4 µm, and are spread throughout the body via blood and lymphatics, and encyst in the brain, skeletal and cardiac muscles, as well as the liver. The encysted forms, termed bradyzoites, survive in tissues for the life of the host. Ingestion of bradyzoites by a new host dissolves the cyst wall and transforms them into tachyzoites, which ultimately encyst again. Transmission of *T. gondii* to cats may occur from ingesting food or water contaminated with oocysts, from ingesting infected prey, or transplacentally from the queen (Dubey & Carpenter, 1993b; Dubey et al., 1995; Sato et al., 1993).

Ocular disease associated with *T. gondii* is more commonly observed in cats than in dogs, and, in the cat, it is commonly associated with systemic disease including anorexia, fever, hepatitis, myositis, pneumonia, gastrointestinal signs, and neurological signs (Davidson & English, 1998). One case report also describes the first antemortem association of toxoplasmosis with pericardial effusion and infiltrative myocardial disease, presumed to be myocarditis, in a cat (Simpson et al., 2005). Clinical feline toxoplasmosis may also manifest initially as cutaneous nodules (Anfray et al., 2005). *T. gondii* has been implicated as being a major contributor to feline uveitis (Chavkin et al., 1992; Dubey & Carpenter, 1993a; Lappin et al., 1989a, 1992b), yet its role in causing anterior uveitis in an otherwise asymptomatic cat is unclear (Davidson & English, 1998). The uveitis may be anterior, posterior, or both (Fig. 37.2.17 and Fig. 37.2.18). However, chorioretinitis is the most common ocular manifestation (Davidson, 2000; Davidson & English, 1998; Dubey & Carpenter, 1993a). In addition, optic neuritis has also been reported in affected cats (Davidson, 2000; Dubey & Carpenter, 1993a). In a histopathologic study of 100 cats with confirmed toxoplasmosis, 22 had ocular involvement, with the ciliary body being the most severely affected portion of the uvea (Dubey & Carpenter, 1993a). In another study, kittens with congenital or early neonatal toxoplasmosis were reported to develop primary ocular lesions in the absence of clinical illness including chorioretinitis most commonly, with or

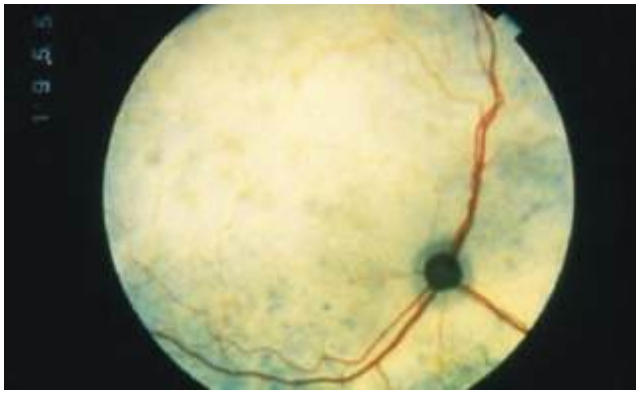


Figure 37.2.17 Fundus photograph of a cat with naturally occurring, histologically confirmed, generalized toxoplasmosis. Multifocal chorioretinitis is present. (*Source*: Reprinted with permission from Davidson, M.G. & English, R.V. (1998) Feline ocular toxoplasmosis. *Veterinary Ophthalmology*, **1**, 71–80.)

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Figure 37.2.18 Acute anterior uveitis with keratic precipitates in a cat with naturally occuring generalized toxoplasmosis. A chorioretinitis was concurrently present. (*Source*: Reprinted with permission from Davidson, M.G. & English, R.V. (1998) Feline ocular toxoplasmosis. *Veterinary Ophthalmology*, **1**, 71–80.)

without concurrent anterior uveitis (Powell et al., 2001). The particular strain of *T. gondii* may also be important in the development of ocular disease (Powell et al., 2001). *T. gondii* DNA has been detected in four of nine corneal sequestra specimens submitted for PCR; the organism was not detected histologically or ultrastructurally in any of the affected keratectomy samples (Cullen et al., 2005). As such, the exact role, if any, of *T. gondii* in the pathogenesis of feline corneal sequestration remains unknown.

Uveitis secondary to toxoplasmosis may result from rapid replication of tachyzoites within ocular tissue (Dubey & Carpenter, 1993a) or from deposition of immune complexes within uveal tissue (Dernouchamps, 1981; Dernouchamps et al., 1977). Intraocular production of antibodies specific for *T. gondii* has been documented (Chavkin et al., 1994; Lappin et al., 1992b, 1995), and the organism has been identified within the uveal tract by histopathology (Dubey & Carpenter, 1993a) and in the aqueous humor by PCR (Burney et al., 1998; Lappin et al., 1996). Uveitis may occur secondarily to recent infection by *T. gondii*. In humans, reactivation of the dormant tissue phase (i.e., bradyzoites) of the organism leads to retinochoroiditis. It is unclear, however, whether uveitis occurs from reactivation in the cat, although it is likely that it does. Stressors that may relate to reactivation include coinfection with agents such FIV (Davidson et al., 1993) or with immunosuppressive doses of corticosteroids (Dubey & Frenkel, 1974). However, a study investigating the factors that trigger development of uveitis in some *T. gondii*-infected cats reported that experimental inoculation with *B. henselae* followed by FHV-1 did not reactivate ocular toxoplasmosis (Powell et al., 2002). In another study, latently infected cats that received weekly injections of methylprednisolone redeveloped serum immunoglobulin (Ig) M titers and circulating antigenemia, but they did not re-shed oocysts or develop clinically apparent disease (Lappin et al., 1991). Correlations have been made between seropositivity for FIV and toxoplasmosis (see the discussion under "Feline Immunodeficiency Virus") (Chavkin et al., 1992; Lappin et al., 1989b, 1992; O'Neil et al., 1991; Witt et al., 1989).

A diagnosis of ocular toxoplasmosis in an otherwise asymptomatic cat is difficult, and histologic demonstration of the parasite is the sole definitive means of confirmation. The diagnosis of toxoplasmosis-related uveitis is, however, generally established on the basis of a positive serum *T. gondii*-antibody titer, although PCR tests to identify *T. gondii* DNA in biologic samples have also been developed (Lappin et al., 1996; Stiles et al., 1996). Laboratory tests that measure both *T. gondii*-specific IgM and IgG are most helpful, because levels of the IgM class of antibody rise and fall over approximately 3–4 months after infection whereas those of the IgG class of antibody may rise more slowly and remain elevated in cats for years after exposure to *T. gondii* (Lappin et al., 1989a). In addition, cats coinfected with FIV and *T. gondii* may develop a positive IgM antibody titer, whereas the IgG antibody titer in these same cats remains negative (Lappin et al., 1992b). *Toxoplasma gondii*-specific IgA has been shown in serum, but these levels rose more slowly than those of IgM or IgG, being detected 34 weeks after experimental infection (Burney et al., 1995). Detection of *T. gondii*-specific antibodies in aqueous humor may aid in establishing an accurate diagnosis (Chavkin et al., 1994; Hill et al., 1995; Lappin et al., 1995, 1992b). The overall seroprevalence of *T. gondii*-specific antibodies (IgM, IgG, or both) in clinically ill cats across the United States was reported to be 31.6% (Vollaire et al., 2005). In particular, the percentage of cats seropositive for *T. gondii* antibodies ranged from 16.1% to 43.5% in the southwestern and northeastern United States, respectively. Another report documented no significant differences in seroprevalence of antibodies to *T. gondii* in stray (50%) versus client-owned (36%) cats, or indoor (26%) versus outdoor (39%) cats (DeFeo et al., 2002). A study compared serum antibodies and PCR DNA amplification from blood and aqueous humor for *T. gondii* in addition to *Bartonella* spp. and FHV-1 in 104 cats with uveitis and 19 healthy shelter cats (Powell et al., 2010). Results supported the addition of the PCR assay to the diagnostic work-up for cats with uveitis to increase the detection of both *T. gondii* and FHV-1, although the diagnostic usefulness of this added information remained unclear.

Current treatment recommendations for cats with toxoplasmosis-induced uveitis include oral clindamycin hydrochloride, 12.5 mg/kg twice daily for 21–30 days, in addition to treatment with a topical corticosteroid, such as 1% prednisolone acetate every 6 hours, and atropine (as needed to maintain mydriasis) (Chavkin et al., 1992; Lappin et al., 1989b). Despite treatment with clindamycin, uveitis in cats with positive *T. gondii* serum antibody titers may be chronic or recurring, and long-term use of topical prednisolone acetate may be needed to control the uveitis.

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Toxoplasmosis is a significant zoonotic disease (Dubey, 2004). Clinical signs of toxoplasmosis may develop in the fetus of pregnant mothers experiencing a primary *T. gondii* infection. Ocular disease, and other manifestations such as stillbirth, may be noted in infected fetuses. As such, prevention of toxoplasmosis is recommended. Restricting the cat's ability to hunt (i.e., maintaining the cat indoors) will help prevent feline toxoplasmosis. In addition, litter boxes for cats should be changed daily (immunocompromised people and pregnant women should avoid this task), and cats (and humans) should not be fed raw or incompletely cooked meat. For review and guidelines on prevention and management see Hartmann et al. (2013a).

Trypanosomiasis

Trypanosoma brucei, which is a parasitic, flagellate protozoa, is the cause of sleeping sickness. It is also highly pathogenic to a number of species. Experimental infection of cats with *T. brucei* leads to marked anterior uveitis and formation of ciliary epithelial cysts containing the organism. Trypanosomes have also been found free within the anterior chamber (Mortelmans & Neetens, 1975).

Prions

Feline Spongiform Encephalopathy

Feline spongiform encephalopathy (FSE) is a transmissible spongiform encephalopathy (TSE) caused by conversion of the cellular prion protein (PrP^{c}) into an insoluble protease-resistant isoform (PrP^{sc}) (Wyatt et al., 1991). This is a fatal neurodegenerative disease that is associated with ingestion of bovine spongiform encephalopathy (BSE)-contaminated food. FSE can be experimentally induced by cervid chronic wasting disease (CWD) protein, thereby raising a concern of natural occurrence of FSE through ingestion of carcasses of cervids affected by CWD (Mathiason et al., 2013). FSE was first documented in 1990 in the UK during the epizootic of BSE. Since 1990 to present, there have been nearly 100 reported cases of FSE, with the majority of cases in Great Britain, one case each from Northern Ireland, Norway, Liechtenstein (Hilbe et al., 2009) and Portugal, and two cases in Switzerland (Hilbe et al., 2009; Imran & Mahmood, 2011; Iulini et al., 2008).

Domestic cats with FSE typically range in age from 4 to 9 years (mean of 6.6 years) (Wyatt et al., 1991). Other felids have also been reported with FSE including the cheetah (Bencsik et al., 2009; Eiden et al., 2010), ocelot, puma (Willoughby et al., 1992), Asian golden cat, lion, tiger (Kirkwood & Cunningham, 1994; Imran & Mahmood, 2011).

The clinical manifestations of FSE involve progressive neurological signs not readily distinguished from those of other, more common feline neurological diseases, and include depression, restlessness, locomotor dysfunction including abnormal or hypermetric gait and ataxia of mainly the hindlimbs, and severe behavioural changes such as fear, uncharacteristic aggressiveness, or timidity. In addition, affected cats often show poor judgement of distance and hyperesthesia to noise and/or touch, and some affected cats stare vacantly, develop tremors, a head tilt or circle. In addition, excessive salivation, polyphagia, polydipsia, and dilated pupils have been reported in some FSE-affected cats (Hilbe et al., 2009; Imran & Mahmood, 2011; Salvadori et al., 2007). FSE is typically fatal after 3–8 weeks of clinical onset of the disease in domestic cats.

The confirming diagnosis of FSE is made only at postmortem by histological, immunohistochemical, or Western blot examination of brain tissue to identify the typical spongiosis and PrP^{sc} deposition. For a review of prion diseases in animals, the reader is referred to Imran & Mahmood (2011) and Aguilar-Calvo et al. (2015).

Viral

Calicivirus

Feline calicivirus (FCV) is a single-stranded RNA virus, and is primarily a respiratory tract pathogen of cats but may cause oral ulcers and polyarthritis (Bennett et al., 1989; Hoover & Kahn, 1975; Ormerod et al., 1979; Pesavento & Murphy, 2014). One study reported that FCV had become a major viral pathogen of the upper respiratory tract of cats in Japan with increased prevalence over FHV-1 (Mochizuki et al., 2000). More virulent forms of FCV are, however, present and cause outbreaks of infection and may result in high mortality rates (Deschamps et al., 2015; Hurley et al., 2004; Pedersen et al., 2000; Reynolds et al., 2009).

Aside from acting as a predominantly respiratory pathogen, calicivirus can be a major contributor to feline conjunctival disease (Fig. 37.2.19). In one experimental study, only 2 of 10 FCV strains tested caused conjunctivitis in cats (Hoover & Kahn, 1975). In another study using only a single strain of FCV, 67% of kittens exposed developed conjunctivitis, which lasted for as long as 2 weeks (Kahn & Gillespie, 1971). A case of FCV and coinfection with feline panleukopenia virus (FPV) was reported in a cat with systemic signs including ocular discharge (Camero et al., 2004). In a study examining 99 cats with upper respiratory tract disease with signs of ocular involvement and being younger than 8 years of age, showed that 11.1% and 19.2% of cats tested positive for calicivirus as a mono-infection or poly-infection, respectively (Gerriets et al., 2012). In the study of 99 cats, those cats with calicivirus infection had moderate serous–mucoid ocular discharge, moderate to severe conjunctivitis, conjunctival epithelial erosions, and oral mucosal ulceration (Gerriets et al., 2012). Of those with calicivirus-only infection, no evidence of keratitis was identified, however (Gerriets et al., 2012).

Cats may be asymptomatic while shedding FCV in ocular and nasal discharges, saliva, and feces (Hurley et al., 2004). In particular, a study in Sweden reported FCV was isolated using virus isolation from 2.6% of clinically healthy cats from breeding catteries (Holst et al., 2005). Interestingly,

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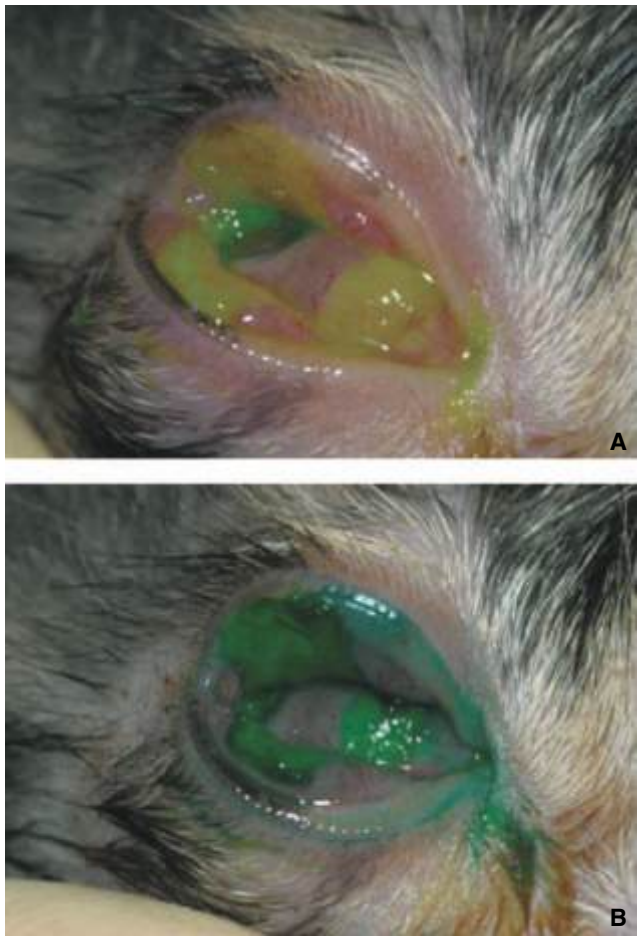


Figure 37.2.19 Appearance of multiple conjunctival erosions stained positive by fluorescein (**A**) and lissamine green (**B**) in a 2-month-old kitten monoinfected with feline calicivirus. (*Source*: Reprinted with permission from Gerriets, W., Joy, N., Huebner-Guthardt, J., et al. (2012) Feline calicivirus: a neglected cause of feline ocular surface infections. *Veterinary Ophthalmology*, **15**, 172–179.)

these cats had all shown signs of respiratory disease or conjunctivitis several years previously. In another study, examining 200 cats suspected as having calicivirus-related clinical signs and 100 healthy cats, 43% of cats with conjunctivitis tested postitive for feline calicivirus, coinfections with other upper respiratory pathogens was common, and 15.3% of healthy cats tested positive for feline calicivirus (Berger et al., 2015). This study underscores the importance of calicivirus in cats with conjunctivitis and also the importance of considering the carrier-state of the animal in reaching a diagnosis.

The diagnosis of FCV can be made by combining clinical history, clinical examination findings, and detecting the presence of virus in affected tissues using laboratory techniques such as virus isolation, immunofluorescence, and various reverse transcriptase-polymerase chain reaction (RT-PCR) assays (Thiry et al., 2009).

Interferons have been investigated as potential therapeutants for cats naturally infected with feline calicivirus (Ballin et al., 2014; Gil et al., 2013; Slack et al., 2013). Subcutaneous administration has been shown to be clinically beneficial in FeLV and/or FIV positive shelter cats that were administered feline interferon omega subcutaneously, although a placebo control group was lacking in this study (Gil et al., 2013). Another study has not shown any clinical difference between non-FeLV/FIV-infected cats treated with feline interferon omega and a placebo-treated group, although interferon treatment may accelerate the reduction in viral FCV load (Ballin et al., 2014). Topical administration of human recombinant interferon alpha-2b or feline recombinant interferon gamma has shown no benefit for treating naturally occurring viral keratoconjunctivitis in cats (Slack et al., 2013).

Given that there is no convincing evidence of effective antiviral therapy for feline calicivirus, treatment is typically supportive. Ocularly, one should consider using an appropriate topical antimicrobial to prevent secondary conjunctival bacterial infections, use of topical antiviral medications where feline herpes virus coinfection is known or suspected, a topical nonsteroidal anti-inflammatory may be beneficial, and use of a tear supplement should be instituted given that tear film stability is likely impaired.

Vaccination with standard inactivated trivalent vaccine including FCV has been correlated with resistance to infection and clinical disease (Lappin et al., 2002; Scott & Geissinger, 1999). Furthermore, a study has reported that most vaccinated cats develop a serologic response to all three viral antigens (FPV/FCV/FHV-1) that surpasses presumed protective levels, lasting up to and beyond 2 years (Mouzin et al., 2004).

Feline Coronavirus (Feline Infectious Peritonitis)

Feline coronavirus infection in cats may lead to no clinical disease, enteric disease, or feline infectious peritonitis (FIP), which is a disseminated pyogranulomatous vasculitis (Addie & Jarrett, 1992; Addie et al., 1995; Kipar et al., 2005). FIP is caused by a mutated feline coronavirus, an RNA virus. At present, the general consensus is that FIP viruses arise by internal mutation of the nonmutant feline enteric virus (Pedersen, 2014b). Mutations occur independently within each cat and there are three different genes (*ORF 3* accessory gene, *S* gene, *7b* accessory gene) associated with the feline enteric coronavirus to FIP virus or biotype conversion (Pedersen, 2014b). FIP replicates within macrophages resulting in the deposition of virus-laden macrophages within the endothelium of small blood vessels (Kipar et al., 2005). Interestingly, the FIP virus has been shown to enter target macrophages/monocytes by first binding to the cell surface and then being internalized by a clathrin- and caveolae-independent and dynamin-dependent endocytosis (Van Hamme et al., 2008). FIP is a fatal arthus-type immune reaction of cats to infection with the virus (Foley et al., 1998).

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Large multicat indoor environments are known to favor feline enteric coronavirus infection and FIP (Pedersen et al., 2008). Sexually intact cats and purebred cats are more likely to develop FIP (Pesteanu-Somogyi et al., 2006). A study evaluating the prevalence of FIP in individual breeds reported increased risk of development of disease in Abyssinians, Bengals, Birmans, Himalayans, Ragdolls, and Rexes (Pesteanu-Somogyi et al., 2006). In addition, FIP most commonly occurs in young cats, and it may manifest as an effusive or wet form of the disease, which includes fibrin-rich fluid within the abdominal and peritoneal cavities, or as a noneffusive or dry form of the disease. Ocular and neural lesions are more likely to be present with the noneffusive/dry form (Andrew, 2000; Foley et al., 1998).

The most common ocular manifestation of FIP is bilateral granulomatous anterior uveitis, often with large, mutton-fat keratic precipitates and a fibrinous exudate into the anterior chamber. Chorioretinitis is also frequently observed, and a pyogranulomatous exudate sheathing the retinal vessels may be present as well. Additional findings may include retinal hemorrhages, detachments, and optic neuritis (Campbell & Reed, 1975; Doherty, 1971; Montali & Strandberg, 1972; Slauson & Finn, 1972). FIP has been diagnosed in a 7-month-old intact male domestic shorthair cat with unilateral anterior uveitis and pyrexia (Declercq et al., 2008). Interestingly, nonpruritic cutaneous lesions, characterized by slightly raised intradermal papules over the dorsal neck and over both lateral thoracic walls, were recognized at the end stage of the disease in this cat and facilitated a diagnosis of FIP (Declercq et al., 2008).

Histologically, lesions in FIP consist of granulomas comprising mixtures of neutrophils, lymphocytes, plasma cells, and large, spindle-shaped histiocytes and can involve all internal organs (Ziolkowska et al., 2017). Ocular lesions include focal or diffuse granulomatous inflammation of the uvea, retina, and meninges of the optic nerves (Ziolkowska et al., 2017). Fibrinocellular exudates may be present in the ocular chambers (Krebiel et al., 1974; Montali & Strandberg, 1972). Focal retinal detachments can be found histologically and glial fibrillary acidic protein (GFAP) expression is increased in Muller cells. These cells also proliferate in cases of retinal detachment (Ziolkowska et al., 2017). In areas where massive inflammation is present (e.g., uvea), feline coronavirus antigen can be found within macrophages that are most recently derived from blood (Ziolkowska et al., 2017). There is also a predominance of B cells and plasma cells compared with other inflammatory cell types in the eyes of cats with FIP, suggesting that the humoral immune response plays a key role in ocular inflammation in the eyes of these cats (Ziolkowska et al., 2017).

In many cases, the definitive diagnosis of FIP, antemortem, is difficult (Addie et al., 2004; Tasker, 2018). Definitive diagnosis requires demonstration of characteristic histopathological changes seen on biopsy samples, although adjunctive immunohistochemical staining for feline coronavirus proteins and/or amplification of viral RNA via various PCRs (Pedersen, 2014a; Tasker, 2018). Although a definitive diagnosis is often difficult to achieve, gathering sufficient indirect evidence can strongly support a diagnosis of FIP (Pedersen, 2014a). As already mentioned, affected cats are typically young (<2 years old) (Riemer et al., 2016). Affected animals are typically febrile (58% of FIP patients), lethargic (up to 87.4% of FIP patients), and may have a history of weight loss (up to 37.4% of FIP patients) (Riemer et al., 2016). When present, neurologic signs including ataxia, seizures, vestibular signs, and paresis may be present (Riemer et al., 2016). Up to 78% of cats will have ascites (Riemer et al., 2016). Hematologic abnormalities are present in nearly all (99.5%) of affected cats (Riemer et al., 2016). Anemia may or not be present and red blood cell microcytosis is observed in up to 35% of affected cats and this finding is independent of age or the presence of anemia (Riemer et al., 2016). Lymphopenia occurs in nearly 50% of cats with FIP, especially in those with the wet form of the disease (Riemer et al., 2016). A neutrophilia with a left shift may be present (Riemer et al., 2016). As with hematologic evaluation, serum biochemical changes are present in up to 99.5% of cats with FIP. These changes include hyperglobulinemia (reported in up to 89.1% of affected cats) regardless of the wet or dry form of the disease (Riemer et al., 2016). Hyperbilirubinemia in the absence of elevated liver enzyme concentrations or severe anemia is supportive of a diagnosis of FIP (Tasker, 2018). Eighty-five percent of cats with FIP have an albumin:globulin ratio of less than 0.8 and 67.8% had an albumin:globulin ratio of less than 0.6 (Riemer et al., 2016). Additional supportive evidence includes elevations in the acute phase protein, α1-acid glycoprotein (AGP). AGP concentrations higher than 1.5 mg/mL in patients already having a strong suspicion of having FIP, and concentrations of higher than 3 mg/mL are supportive of an FIP diagnosis in patients not having a history or clinical findings suggestive of FIP (Paltrinieri et al., 2007). Evaluation of effusion samples, and performing immunocytochemistry and/or RT-PCR, for feline coronavirus, on effusion samples (wet FIP), cerebrospinal fluid (dry FIP), and ocular aqueous fluid (dry FIP) can be helpful when taking into consideration all other clinical and laboratory information. However, the sensitivity and specificity of the testing procedure and sample being evaluated should be considered (Doenges et al., 2016; Felten et al., 2017a,b, 2018; Gruendl et al., 2017; Longstaff et al., 2017; Stranieri et al., 2018).

The most important method for reducing feline coronavirus is the elimination of chronic coronavirus shedders (Addie et al., 2004; Foley et al., 1997). Given the prevalence of coronavirus, however, this task is considerably difficult. Treatment of ocular disease is symptomatic and includes use of topical, subconjunctival, or systemic corticosteroids as well as topical atropine. Temporary amelioration of ocular

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disease may occur, but symptoms will usually rebound in a short period of time. Impressively, however, use of a C3-like protease inhibitor (GC376) has been shown to clear clinical signs, including ocular signs, in cats with naturally occurring FIP (Pedersen et al., 2018).

There is no cure at present for FIP, although there are two interesting studies examining novel therapeutants for FIP in cats. In particular, a C3-like protease inhibitor (GC376) has resulted in 6 of 20 cats with naturally occurring FIP, after 12 weeks of twice daily subcutaneous treatment with GC376, remaining disease free for over 1 year after treatment (Pedersen et al., 2018). Another study has examined the nucleoside analog, GS-441524, which has been shown to reverse clinical signs of experimentally induced FIP after 2 weeks of twice daily subcutaneous treatment (Murphy et al., 2018). Ten out of 10 cats remained disease free for over 8 months after 2 or 4 weeks of treatment (Murphy et al., 2018). Elimination of FIP from a cattery is only possible by total elimination of endemic feline enteric coronavirus infection. For a detailed review of FIP, the reader is referred to Pedersen (2014a,b) and Tasker (2018).

Feline Herpesvirus-Type 1

FHV-1, a double-stranded DNA virus and a member of the alphaherpesvirus subfamily, is highly species-specific. Infection with FHV-1 is common, and the virus is widespread among cat populations. Studies have estimated that over 90% of cats are seropositive to the virus (Maggs et al., 1999b) with as much as 80% of infected cats remaining latently infected on a life-long basis, and with approximately 45% of these latently infected cats shedding virus throughout life (Gaskell & Povey, 1977; Townsend et al., 2004). The virus is spread from cat to cat either by direct contact, fomites, or by aerosolization of virus. FHV-1 infects the epithelial surfaces of the respiratory tract and conjunctiva and, to a lesser degree, the corneal epithelium, thereby causing necrosis of these tissues as the virus replicates and invades the adjacent cells (Hoover et al., 1970; Nasisse et al., 1989b). The virus then ascends by axons of sensory neurons to the trigeminal ganglion to establish life-long latency (Maggs, 2005). Cats may therefore develop chronic or recurrent ocular disease associated with FHV-1. Though cats can be reinfected with FHV-1 despite previous infection or vaccination, recurrent ocular disease is most likely to be associated with recrudescence of latent virus (Bistner et al., 1971; Bodle, 1976).

FHV-1 produces disease via at least two mechanisms (Maggs, 2005). The first mechanism involves cytolytic infection during active viral replication. Cell rupture can occur during primary FHV-1 infection or after viral reactivation from latency. FHV-1 infection can also induce disease via a second mechanism, immune-mediated inflammation. Primary FHV-1 disease in kittens generally produces upper respiratory and ocular diseases, and is characterized by malaise, fever, inappetence, sneezing or coughing, and nasal as well as ocular discharge. Polymorphonuclear cell infiltrate is marked and results in purulent ocular and nasal discharge, even if secondary bacterial infection is not present. Primary respiratory tract and conjunctival FHV-1 infection usually lasts for 10–14 days and resolves spontaneously, but the course can be variable (Stiles, 2000). Clinical ophthalmic manifestations of FHV-1 cytolytic infection are numerous and include conjunctivitis characterized by hyperemia, blepharospasm, chemosis, and ocular discharge. Conjunctivitis, whether unilateral or bilateral, is probably the most common FHV-1-related ocular disorder in adult cats without active respiratory disease, although some of these cats will have concurrent sneezing or other mild signs of respiratory tract infection. Keratoconjunctivitis sicca (KCS) has been reported in cats with FHV-1-related conjunctivitis as well (Andrew, 2001; Stiles, 1995). FHV-1 is the sole documented viral cause of keratitis in cats (Andrew, 2001). Corneal ulcers, whether dendritic or geographic, are thus a common manifestation of cytolytically induced FHV-1 ocular disease usually accompanied by conjunctivitis. If both the cornea and conjunctiva are ulcerated because of the cytolytic effects of FHV-1, corneal stroma and conjunctival substantia propria become exposed thereby facilitating adhesion formation between these tissues (i.e., symblepharon). Neonatal ophthalmia may be caused by FHV-1, either from maternal transmission to the kitten or infection shortly after birth (Andrew, 2001; Bistner et al., 1971). Raised, plaque-like lesions on the eyelids of a cheetah cub with FHV-1 have also been reported (Junge et al., 1991).

Clinical disease caused by the immunopathological mechanism of FHV-1 is an uncommon response to the viral infection (Maggs, 2005). Stromal keratitis results from immune-mediated response to viral antigen and is probably the most serious ocular manifestation of FHV-1. Subconjunctival dexamethasone predisposed experimentally infected cats to develop stromal keratitis (Nasisse et al., 1989b). Stromal keratitis is often secondary to chronic ulceration and is characterized by deep corneal vascularization, edema, and cellular infiltrates. Stromal keratitis may be a source of chronic pain, and it can lead to significant corneal scarring as well (Nasisse et al., 1995).

Corneal sequestration is a common disorder in the cat, particularly in the Persian, Burmese, and Himalayan breeds (Fig. 37.2.20) (Featherstone & Sansom, 2004; Graham et al., 2017). The cause in many cats remains undetermined, but sequestra may occur after chronic corneal ulcers or keratitis caused by infection with FHV-1 (Morgan, 1994; Startup, 1988). The condition is characterized by an area of corneal degeneration with a brown-to-black discoloration. The lesions vary from pinpoint sequestra to those occupying more than half the cornea. Vascularization may be intense or absent, and ocular pain ranges from none to marked. Corneal sequestration has been noted to occur after topical corticosteroid use in cats experimentally infected with

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Figure 37.2.20 Photomontage of corneal sequestra of several different cats. Note the varying degrees of corneal vascularization and the variable appearance of the sequestra, yet many corneal sequestra are central or paracentral in their location.

FHV-1 (Nasisse et al., 1989b) as well as in naturally infected cats. In a study that analyzed 28 keratectomy specimens from Persian and Himalayan cats with corneal sequestra by PCR for the presence of FHV-1 DNA, five samples were positive (Stiles et al., 1997a). In another study, four of nine corneal sequestra keratectomy specimens were positive for the presence of FHV-1 DNA using PCR, and one of these four corneal sequestra was also positive for *T. gondii* DNA (Cullen et al., 2005b). In another study, three conjunctival swabs from 2 of 11 cats with sequestra were positive for FHV-1 using PCR (Grahn et al., 2005). In addition, a retrospective study detected FHV-1 DNA, via PCR, in 5.9% (1/17) of corneas from clinically normal cats, 55.1% (86/156) of corneal sequestra, and 76.3% (45/59) of scraping specimens from cats with proliferative (eosinophilic) keratitis (Nasisse et al., 1998). Like stromal keratitis, corneal sequestration can be

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one of the most serious and potentially blinding sequela of FHV-1 infection. The necrotic cornea can be surgically removed by keratectomy, and placement of a conjunctival graft after keratectomy may help to prevent recurrence (Blogg et al., 1989; Morgan, 1994). However, one retrospective study reported no significant difference in rate of recurrence between globes receiving a graft procedure ($n = 5$) and eyes that did not ($n = 11$) (Featherstone & Sansom, 2004). In a study investigating surgical keratectomy of the sequestrum with corneoconjunctival transposition, favorable results were found with this procedure, with only 9/109 (8%) affected eyes having recurrence of corneal sequestration (Graham et al., 2017).

Establishing an accurate diagnosis of FHV-1-related ocular disease in adult cats without respiratory tract disease has been problematic. Diagnostic tests such as the virus isolation (VI) and fluorescent antibody (FA) tests, both of which are widely available, are relatively insensitive in cats with chronic or recurrent ocular disease (Nasisse et al., 1993; Stiles et al., 1997b). In addition, serum antibody titers are only potentially useful in unvaccinated cats, and even then, such titers may not rise in a predictable manner (Nasisse, 1990). PCR techniques are more sensitive and have become the most commonly used diagnostic test. In a study of 50 cats with either acute or chronic conjunctivitis, 54% were positive for FHV-1 DNA by PCR (Stiles et al., 1997a). In another study, however, only 19% of 91 cats with chronic conjunctivitis could be positively identified as being infected with FHV-1 when evaluated by VI and FA (Nasisse et al., 1993). When the techniques of nested PCR, VI, and FA were compared in three groups of cats (conjunctivitis only, respiratory tract disease and conjunctivitis, or clinically normal), PCR was found to be much more sensitive than VI or FA in cats with conjunctivitis only and in cats with respiratory tract disease and conjunctivitis (Stiles et al., 1997b). An RT-PCR assay has been used to detect FHV-1 latency-associated transcripts (Townsend et al., 2004). Results of this study revealed that a high percentage of cats that did not have clinical signs of ocular disease had detectable FHV-1 DNA via PCR in their corneas and trigeminal ganglia. RNA was isolated from the samples that tested positive for FHV-1 and were tested via RT-PCR. Of the samples where RNA could be collected, 4/16 trigeminal ganglia, but no corneal samples, tested positive for latency-associated transcripts. Nevertheless, this assay may serve to improve our current understanding of the pathobiology of FHV-1 (Townsend et al., 2004).

Several studies have been published which have evaluated ocular samples from clinically healthy or diseased feline eyes for the presence of FHV-1 using PCR. In particular, conjunctival swabs for FHV-1 PCR screening, among other agents, were collected from eyes of young healthy cats (Cullen et al., 2005a) and cats with conjunctivitis (Lim & Cullen, 2005) after tear film break-up time (TFBUT) and STT evaluations. In the young healthy cats, 5 of 18 cases were FHV-1-positive in the blood, and 3 conjunctival samples from 3 eyes of these 5 cats were FHV-1-positive (Cullen et al., 2005a). However, TFBUT and STT values obtained from these clinically healthy cats were not correlated with the blood or conjunctival PCR findings (Cullen et al., 2005a). Blood samples from 9 of 14 cats with conjunctivitis tested positive for FHV-1 (Lim & Cullen, 2005). Mean TFBUTs (±SD) from these cats were significantly lower (mean TFBUT = 6.8 [±3.1] seconds) than mean TFBUTs for affected cats from which no such DNA was isolated from the blood (mean TFBUT = 11.4 [±5.5] seconds) (Lim & Cullen, 2005). Another study reported FHV-1 also induced qualitative tear film abnormalities in experimentally infected cats, as measured by TFBUT and goblet cell density (Lim et al., 2009). In another study, a significant association was found between viral presence and epithelial keratitis, but no significant association was noted between viral presence and conjunctivitis (Volopich et al., 2005). Specifically, FHV-1 DNA was detected in 3 of 7 cats with conjunctivitis, and 5 of 6 cats with epithelial keratitis, 3 of 11 cats with stromal keratitis, and 3 of 12 cats with corneal sequestration. In a Spanish study, FHV-1 was associated with upper respiratory tract disease, but not gingivostomatitis. In particular, FHV-1 DNA was found in 28.3% of cats with upper respiratory tract disease ($n = 127$), 24.2% of cats with conjunctivitis ($n = 149$), and 15.6% of cats with gingivostomatitis ($n = 154$),whereas FHV-1 was found in 6.1%, of cats in the control group ($n = 98$) (Fernandez et al., 2017). Another study concluded that using the presence of FHV-1 DNA alone for the diagnosis of FHV-1-associated conjunctivitis is not suitable because their results showed FHV-1 DNA in 33% of cats with conjunctivitis and 20% of control cats in northern Italy (Rampazzo et al., 2003). FHV-1 has also been shown to infect feline intraocular tissues and may be associated with uveitis in some cats (Maggs et al., 1999a). In particular, 22 of 44 cats with idiopathic uveitis and 11 of 29 cats with toxoplasma-associated uveitis had evidence of intraocular FHV-1 antibody production, whereas 12 cats had FHV-1 DNA detected in the aqueous humor, of which 11 had uveitis. For a review regarding ocular manifestation of FHV-1 including its diagnosis and treatment options, the reader is referred to Gould (2011).

Treatment of recurrent FHV-1 ocular disease may, or may not, be required. Many cats with transient conjunctivitis recover spontaneously and need no therapy. The combined results of two *in vitro* studies (Maggs & Clarke, 2004; Nasisse et al., 1989a) have shown FHV-1 to be susceptible to the following antiviral agents, which are listed in order of decreasing effect:

1) trifluridine
2) idoxuridine ≈ ganciclovir
3) cidofovir ≈ penciclovir
4) vidarabine

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5) bromovinyldeoxyuridine
6) acyclovir ≈ foscarnet.

An additional *in vitro* study further showed the efficacy of cidofovir against FHV-1 infection of a primary culture of feline corneal epithelial cells (Sandmeyer et al., 2005). However, cidofovir also had cytostatic effects on cultured cells at concentrations of 0.05 mg/mL. In another *in vitro* study, (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl) adenine (HPMPA) was found to have the greatest antiviral activity against FHV-1, acyclovir was least active, and penciclovir and bromovinyldeoxyuridine had intermediate activity (Williams et al., 2004).

Certain medications above (e.g., topical trifluridine, idoxuridine, and vidarabine) have been widely tested and used in cats with FHV-1 infection whereas the clinical efficacy and safety of others remain unknown. For review of antiviral drugs used against FHV-1, the reader is directed to the review by Thomasy and Maggs (2016).

Nevertheless, an oral antiviral medication effective against FHV-1 that is commonly used in patients suffering from FHV-1 clinical symptoms is famciclovir. Famciclovir is a prodrug of penciclovir (Thomasy et al., 2016). Famciclovir requires di-deacetylation to BRL42359 in the blood, liver, or small intestine. BRL24359 is then oxidized to penciclovir by aldehyde oxidase in the liver (Thomasy et al., 2016). Neither BRL24359 nor famciclovir have any antiviral activity (Thomasy et al., 2016). Although cats have significantly less hepatic aldehyde oxidase activity compared with humans, accumulation of BRL24359 has seemingly minimal toxicity to cats when dosages used to attain therapeutic concentrations of penciclovir are achieved (Thomasy et al., 2016). Based upon a detailed pharmacokinetic study of famciclovir and BRL42359 in plasma and tears and another study examining the clinical utility of famciclovir for clinical cases at varying dosages, it is recommended that 90 mg/kg of famciclovir be given by mouth twice daily to cats requiring therapy for FHV-1 related clinical signs (Sebbag et al., 2016; Thomasy et al., 2016).

Treatment of cats with viral corneal ulcers should include debridement to reduce the number of viral particles (Missotten, 1994) and an ophthalmic antiviral medication, both to hasten healing and to prevent development of keratitis or sequestration. Importantly, however, grid keratotomies should not be performed as clinical signs may be exacerbated and formation of corneal sequestration may be encouraged (La Croix et al., 2001). Topical antiviral agents can be used in cats with chronic conjunctivitis as well, although the results in these cases are variable. Many cats are irritated by various topical antiviral agents and many of these drugs require dosing frequencies that are not tolerated by many cats. Cidofovir, a cytosine analog, however, is well tolerated and only requires twice daily administration. Cats with experimentally induced FHV-1 showed reduced viral shedding and reduced clinical disease after topical application of a 0.5% ophthalmic solution of cidofovir (Fontenelle et al., 2008b). Cidofovir is not commercially available and must be compounded, although refrigerated or frozen storage in normal saline does not affect the drug efficacy for up to 6 months (Stiles et al., 2010). Given that topical cidofovir has been associated with nasolacrimal stenosis in humans, it is recommended that cats be monitored for similar complications (Thomasy & Maggs, 2016).

Treatment for KCS in cats with FHV-1 conjunctivitis can include topical 0.2% cyclosporine ointment in addition to antiviral therapy. In rabbits experimentally infected with herpes simplex virus, intramuscular administration of cyclosporine resulted in more severe and persistent stromal disease and both greater incidence and recovery of virus from the cornea (Meyers-Elliott et al., 1987a,b). Another study reported that concomitant topical use of cyclosporine and ganciclovir decreased the severity of herpetic stromal keratitis in rabbits (Naito et al., 1991), and use of topical cyclosporine and trifluridine also resulted in reduced stromal keratitis in a rabbit model (Boisjoly et al., 1984). In one study it has also been shown that feline herpesvirus-related clinical signs recur after oral cyclosporine or systemically administered corticosteroids in some cats previously infected by feline herpesvirus, although the clinical symptoms were mild and self-limiting in most cats (Lappin & Roycroft, 2015). If an anti-inflammatory is required to treat FHV-1-related ocular disease, however, corticosteroids should be avoided and instead topical nonsteroidal anti-inflammatories should be considered and used judiciously.

Recombinant interferon has been used in cats with herpesvirus-related ocular disease, although studies to document its effectiveness have been limited. In one report, natural oral human interferon at a dose of 5 and 25 IU reduced the severity of clinical signs in experimentally infected cats when given on days 1 and 2 of infection (Nasisse et al., 1996). In addition, synergistic antiviral activity of recombinant and natural human interferon and acyclovir on FHV-1 replication has been shown *in vitro* (Weiss 1989), although the effectiveness of this combination has not been reported in cats.

Interferons are a group of cytokines with immunological and antiviral properties and are important in host–virus homeostasis *in vivo* (Fensterl et al., 2015). Interferons have been investigated for use in naturally occurring feline herpesviral-related illness in cats (Ballin et al., 2014; Fenimore et al., 2016; Fiorito et al., 2016; Gil et al., 2013; Slack et al., 2013). One case report of a 14-year-old Abyssinian with facial FHV-induced dermatologic lesions was successfully treated with a combination of intradermal perilesional injections and subcutaneous injections, remote from the lesion, of recombinant feline interferon omega (Gutzwiller et al., 2007).

Two studies, neither with placebo groups, evaluated clinical response to interferon administration in shelter cats with

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upper respiratory tract disease (Fenimore et al., 2016; Gil et al., 2013). In one study, FeLV- and/or FIV-positive cats treated with recombinant feline interferon omega, administered subcutaneously, showed reduced FHV-1 excretion (Gil et al., 2013). Improvement in oral ulceration and gingivostomatitis was the most obviously improved clinical sign, although this is most likely caused by this interferon's effect on feline calicivirus and not FHV-1. However, even this is difficult to know with certainty given the lack of a placebo-controlled group. In the other nonplacebo-controlled study, FeLV/FIV-negative shelter cats with upper respiratory tract disease were clinically evaluated before and after subcutaneous administration of recombinant human interferon alpha 2b (Fenimore et al., 2016). This study showed clinical improvement in 8/13 cats, although a placebo-controlled group was not available for comparison.

Of the three placebo-controlled studies evaluating interferons, one evaluating topical human recombinant interferon alpha-2b or topical feline recombinant interferon did not improve clinical signs or virus shedding compared with placebo-treated cats (Slack et al., 2013). Another study evaluating recombinant feline interferon-omega, administered via combined subcutaneous/topical/oral routes, did not show improvement in clinical signs in cats with naturally occurring upper respiratory tract disease, although a reduction in feline calicivirus load may have been accelerated (Ballin et al., 2014). The third placebo-controlled study evaluated combination therapy with orally administered sequential kinetic activated (SKA) human interleukin-12 plus human interferon gamma FHV-1-positive cats with clinical signs consistent with FHV-1 (Fiorito et al., 2016). In this study, significant improvement of clinical signs was shown for treated cats compared with placebo (Fiorito et al., 2016). Twelve of 15 cats in the treatment group became PCR-negative for FHV-1, whereas 0/10 cats in the placebo-treated group became negative for FHV-1 (Fiorito et al., 2016). Altogether, results of studies investigating interferons for treatment of FHV-1 do not support the use of interferons alone but may show usefulness when combined with other cytokines. At present, given the paucity of studies demonstrating positive effects and low sample sizes, a definitive recommendation of using interferons for use in FHV-1-related ocular disease cannot be made.

Another treatment that has received considerable attention for treating FHV-1 is oral administration of the amino acid L-lysine. The rationale for use of lysine in the treatment of FHV-1 stems from L-lysine being a competitive inhibitor of arginine. Arginine is an essential amino acid for FHV-1 replication. Treatment with oral lysine has been of some benefit among humans in accelerating recovery from herpes simplex infection and in suppressing recurrence (Griffith et al., 1978). An *in vitro* study has shown lysine to be effective at reducing FHV-1 synthesis, in conjunction with low arginine levels, by antagonizing the availability of arginine, an essential amino acid used for viral synthesis (Maggs et al., 2000). Another *in vitro* study, however, examined numerous concentrations of lysine and arginine combinations and found that various L-lysine concentrations did not inhibit *in vitro* replication of FHV-1 at L-arginine concentrations sufficient to maintain cell growth in culture (Cave et al., 2014). Clinical studies reveal that oral lysine is safe (Fascetti et al., 2004), and reduces both the severity of conjunctivitis in cats with primary FHV-1 infection (Stiles et al., 2002) and the ocular viral shedding rate in FHV-1 latently-infected cats (Maggs et al., 2003). One study evaluated the effect of dietary lysine supplementation fed to 261 adult cats housed in an animal shelter for 4 weeks (Drazenovich et al., 2009); this study revealed that cats fed the lysine-supplemented diet (5.7% dietary lysine compared with controls fed 1.7% dietary lysine) had increased severity of FHV-1 disease and increased detection of FHV-1 DNA at given time periods throughout the study (Drazenovich et al., 2009). A meta-analysis was published based upon reviewing relevant literature pertaining to lysine supplementation on FHV-1 (Bol & Bunnik, 2015). The authors of this meta-analysis concluded that there was no evidence supporting the use of L-lysine in improving FHV-1 related clinical disease and that L-lysine is hypothetically determinental to the health of cats given the absolute dietary requirement of arginine by cats (Bol & Bunnik, 2015). Despite the lack of evidence regarding lysine and its effectiveness in cats with FHV-1, there are no current studies evaluating its effectiveness in client-owned cats with recurrent FHV-1 related disease. Further, there is anecdotal information that some cats may benefit from lysine supplementation more than others (Stiles, 2014). Current recommendations for lysine administration in cats, if chosen as a therapeutant, are 500 mg PO (adult cats) or 250 mg PO (kittens) twice daily with food (Stiles, 2014).

Feline Immunodeficiency Virus

FIV is a lentivirus. The transmission of FIV is most likely via bites between animals (Pedersen et al., 1989). However, FIV has been detected in semen from acutely and chronically infected male cats, indicating that FIV may also potentially be transmitted to queens via infected semen (Jordan et al., 1995, 1999). Earlier in the course of disease, FIV infection results in progressive loss of $CD4^+$ T-helper cells, followed by depletion of $CD8^+$ T-cells in the advanced stages of the disease (English et al., 1994). FIV was first reported in 1987 (Pedersen et al., 1987) and has subsequently been related to a number of diseases in the cat, including ocular manifestations. The virus causes ocular lesions via (1) direct damage of ocular tissues, (2) inciting secondary immune phenomena, and/or (3) by promoting opportunistic ocular infections (English et al., 1994). In one experimental study, three of 20 cats developed anterior uveitis and conjunctivitis after infection with FIV (Callanan et al., 1992). In a study of nine cats with naturally occurring FIV infection, all cats had ocular

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disease, with anterior uveitis being the most frequent clinical diagnosis (English et al., 1990). In addition, pars planitis was seen in four of these nine cats, being evidenced by anterior vitreal, white infiltrates presumed to be inflammatory cells. In a retrospective study of cats with lens luxations, FIV infection was diagnosed in tested cases more often than any other infectious disease (Olivero et al., 1991). FIV is associated with the development of lymphosarcoma which can manifest ocularly or periocularly (Beczkowski et al., 2015; Beatty et al., 1998a,b; Gabor et al., 2001; Hutson et al., 1991; Magden et al., 2013). FIV has not, however, been detected in any of 36 formalin-fixed, uveal melanomas, suggesting FIV does not appear to play a role in naturally occurring feline uveal melanomas (Stiles et al., 1999).

Correlations have been made between FIV and seropositivity for toxoplasmosis. Positive serum antibody titers for toxoplasmosis have been found more frequently in FIV-positive cats than in FIV-negative cats (O'Neil et al., 1991; Witt et al., 1989). In a study of 54 clinically ill cats seropositive for antibody to FIV, 19 had ocular disease, and 76% of these 19 were also positive for *T. gondii*-specific serum antibodies. Anterior uveitis and chorioretinitis were the most common ocular findings (O'Neil et al., 1991). Of cats coinfected with both FIV and *T. gondii*, 43% had positive *T. gondii*-specific IgM serum antibody titers without a positive *T. gondii*-specific IgG titer, thus emphasizing the need for a laboratory test that includes both classes of antibody.

The diagnosis of FIV infection has depended upon the use of positive antibody results in ELISA, Western blot, or immunofluorescent antibody tests (Levy et al., 2004). This has made it difficult to assess reliably the FIV infection status of cats using current serological tests because the antibodies produced in response to vaccination against FIV are indistinguishable from those used to diagnose FIV infection (Levy et al., 2004). Interestingly, however, three different point-of-care FIV antibody test kits have been examined (Westman et al., 2015, 2016, 2017a). Results have shown that two of the three test kits could differentiate FIV infection status regardless of vaccination status of the cat, and provided vaccination was not administered in the 6 months prior to testing (Westman et al., 2015, 2017a). It was further determined that test results were achieved with high sensitivity and specificity on saliva samples (Westman et al., 2016). RT-PCR has been shown to be useful in identifying FIV infection status independent of history of FIV vaccination (Westman et al., 2017a).

Treatment of uveitis in cats with both FIV and toxoplasmosis should be the same as that for toxoplasmosis. Cats with uveitis associated only with FIV, however, should be treated with a topical corticosteroid, such as prednisolone acetate 1%, and atropine 1% (as the uveitis dictates). Some cats may also benefit from oral prednisolone, and long-term use of topical prednisolone acetate may be needed to control the anterior uveitis. Response of pars planitis to oral and topical prednisolone, however, is often poor. Of course, however, if a cat is coinfected with FHV-1, use of oral and/or topical corticosteroids should be avoided and instead a topical nonsteroidal anti-inflammatory drug should be considered.

Feline Leukemia Virus

FeLV is a retrovirus that replicates in many epithelial tissues. Transmission of FeLV is primarily through saliva. FeLV infection eventually results in malignant transformation or cytopathic depletion of specific lymphocytic/hematopoietic cell lines (Onions et al., 1982; Rojko et al., 1979). Infection with FeLV appears to cause little in the way of ocular disease, with primarily the exception of its role in lymphosarcoma (Brightman et al., 1991). The uveal tract is a common site for metastasis of neoplastic lymphocytes, probably via hematogenous spread. Cats with ocular lymphosarcoma may present initially with signs of mild uveitis, including miosis, aqueous flare, and keratic precipitates, or subtle iridal masses. As the disease progresses, the iris becomes greatly thickened and distorted with the infiltration of tumor cells (Fig. 37.2.21 and Fig. 37.2.22), and glaucoma is a common sequela as tumor cells infiltrate the iridocorneal angle (Corcoran et al., 1995). In association with neoplastic invasion of the anterior uvea, iris motility becomes restricted (Willis, 2000). Aqueous centesis may be helpful in establishing the diagnosis, because neoplastic lymphocytes exfoliate into the aqueous humor.

Anisocoria or dyscoria may also arise because of neurological effects of FeLV on the ciliary ganglia and short ciliary nerves of affected cats. In particular, spastic pupil syndrome, involving a static anisocoria during dark adaptation, has

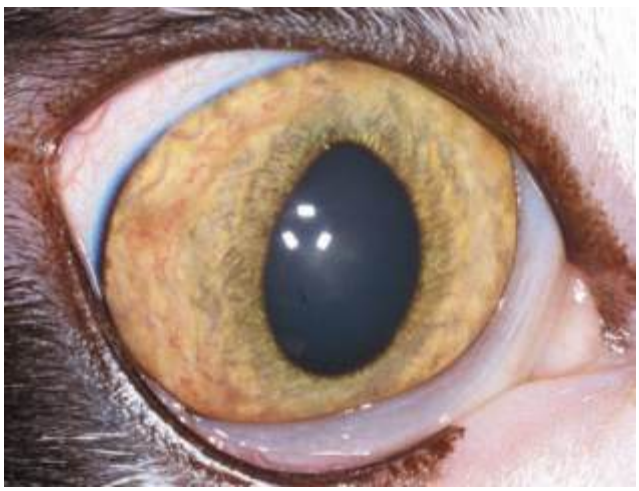


Figure 37.2.21 Early intraocular lymphosarcoma (FrVL) presented as anterior uveitis. Note the raised infiltrate of cells and neovascularization in the lateral iris. (*Source*: Reprinted with permission from Gelatt, K.N. & Plummer, C.E (2017) *Color Atlas of Veterinary Ophthalmology*, 2nd ed., p. 260. Oxford: Wiley-Blackwell.)

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Figure 37.2.22 Twelve-year-old male neutered domestic shorthair cat with histologically confirmed feline lymphoma.

been reported in FeLV-positive cats. Anisocoria may have been noted by the patient's owner over time, alternating with periods of normal pupil behavior. Other ophthalmic abnormalities are absent, however, and vision is unaffected. These cats are positive for FeLV but may have no other clinical signs when the anisocoria is noted (Brightman et al., 1977; Scagliotti, 1980). C-type viral particles have been identified in the ciliary ganglia and short ciliary nerves of these cats, however, which is suggestive that the leukemia virus has invaded these nerves. The prognosis for long-term survival in these cats is poor.

In one experimental study, kittens were infected with FeLV either systemically *in utero* or intraocularly on the day after birth (Albert et al., 1977). The most consistent ocular abnormalities with both routes of infection were retinal dysplasia and diffuse uveitis. One kitten developed an intraocular neoplasm of probable retinal origin. FeLV may also induce anemia which could result in secondary retinal hemorrhages (Brightman et al., 1991; Fischer, 1970).

Other studies have investigated the role of FeLV/feline sarcoma virus (FeSV) in the tumorigenesis of feline uveal melanomas and ocular sarcomas (Cullen et al., 1998, 2002; Stiles et al., 1999). Two studies reported a lack of detection of FeLV/FeSV in either intraocular tumor type based on negative immunohistochemical staining for FeLV gp 70 and negative PCR results of formalin-fixed, paraffin-embedded tissue samples (Cullen et al., 1998, 2002). Another report, using nested PCR, detected FeLV/FeSV in 3 of 36 formalin-fixed, uveal melanomas, suggesting a possible link between FeLV/FeSV and certain naturally occurring feline uveal melanomas (Stiles et al., 1999). FeLV antigens and proviral DNA have also been detected in normal corneal tissues from FeLV-infected cats, suggesting the importance of screening potential feline corneal donors for FeLV (Herring et al., 2001).

Diagnosis of FeLV is based upon detecting antigen from serum (Westman et al., 2017b). A large study examining the utility of three commonly used point-of-care antigen tests showed all of the tests had low sensitivities (≤63%), although specificities were reasonably high (≥95%). As such recommendations from this study include: (1) follow-up testing using RT-PCR for all cats testing positive with these point-of-care tests, and (2) follow-up testing with real-time testing for cats that test negative with these point-of-care tests yet are exposed to FeLV positive cats (Westman et al., 2017b).

Feline Panleukopenia Virus

Feline panleukopenia virus (FPV) is a parvovirus. Transmission of FPV occurs most commonly by direct contact with infected cats or their excretions (e.g., feces, urine, saliva, and vomitus). Fleas may also transmit FPV from infected to susceptible cats. The virus may also be spread by contact with fomites, such as food bowls, litter pans, bedding, and cages. Clinical signs vary depending upon the age and immune status of the kitten (Stuetzer & Hartmann, 2014). The most common clinical signs include anorexia, pyrexia, and lethargy/depression (Stuetzer & Hartmann, 2014). Some kittens may develop vomiting or diarrhea and may succumb to the disease because of dehydration and septicemia (Stuetzer & Hartmann, 2014). Kittens infected with FPV during gestation or shortly after birth develop cerebellar hypoplasia and retinal dysplasia (Csiza et al., 1971; Kilham et al., 1967, 1971; Percy et al., 1975; Schatzberg et al., 2003). Mesencephalic aqueductal stenosis has been reported in kittens after transplacental infection with FPV (Csiza et al., 1971). The cerebellar disease becomes apparent at approximately 3–4 weeks of age (i.e., when the kittens begin walking). Hypermetria and ataxia are apparent as well. Retinal dysplasia, which is characterized by thinning of neural tissue, loss of normal architecture, and rosette formation, has also been reported in a naturally infected kitten (Percy et al., 1975).

Presumed infection by FPV is made based upon clinical signs and the presence of leukopenia. Point-of-care fecal parvovirus antigen tests have a sufficient sensitivity and specificity to act as good screening tests, although false positive results can occur if testing is performed within 3 weeks of vaccination with modified live vaccine (Neuerer et al., 2008). PCR testing can be performed on blood, feces, or infected tissues and it is recommended to be performed in FPV-infected cats without diarrhea or to confirm point-of-care antigen testing (Stuetzer & Hartmann, 2014).

Feline Sarcoma Virus

FeSV is a naturally occurring, replication-defective, acute, transforming FeLV that has incorporated one of several

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cellular oncogenes (Cullen et al., 1998). These viruses can be transmitted either horizontally or vertically, and they can cause spontaneous tumors in the cat (Essex, 1975; Shelton et al., 1990). In experimental models, injection of the virus into the feline anterior chamber has resulted in formation of malignant uveal melanomas (Albert et al., 1981; Shadduck et al., 1981). In structure, these melanoma cells have been spindle-shaped and epithelioid, much like naturally occurring feline uveal melanomas (Albert et al., 1981; Niederkorn et al., 1981; Shadduck et al., 1981). In one study, enucleation of eyes with melanomas induced by FeSV resulted in a high percentage of cats developing secondary tumors (Niederkorn et al., 1982). This finding was interpreted to result from local transformation of virus shed from the intraocular neoplasm, not from metastases. In cats that developed uveal melanomas, production of antibodies against feline oncornavirus-associated cell membrane antigen was much higher in cats with nonprogressive lesions than in those with progressive melanomas (Niederkorn et al., 1981). Subcutaneous injection of FeSV leads to fulminant anterior uveitis in the cat (Lubin et al., 1983), and limbal fibrosarcomas have also been produced at the site of such injection (Shadduck et al., 1981). The role of FeSV in naturally occurring feline uveitis is unknown. Studies have, however, investigated the role of FeLV/FeSV in the tumorigenesis of naturally occurring feline uveal melanomas and ocular sarcomas (Cullen et al., 1998, 2002; Stiles et al., 1999). Two studies reported a lack of detection of FeLV/FeSV in either intraocular tumor type based on negative immunohistochemical staining for FeLV gp 70 and negative PCR results of formalin-fixed, paraffin-embedded tissue samples (Cullen et al., 1998, 2002). Another report, using nested PCR, detected FeLV/FeSV in 3 of 36 formalin-fixed, uveal melanomas, suggesting a possible link between FeLV/FeSV and certain naturally occurring feline uveal melanomas (Stiles et al., 1999).

Rabies

Rabies continues to be one of the most feared zoonotic diseases in the world. Nearly 60,000 people are killed by rabies each year, many of whom are children in developing countries (World Organisation for Animal Health, 2018). Rabies, a bullet-shaped RNA virus, is a Lyssavirus in the family Rhabdoviridae (Woldehiwet, 2002). Transmission of rabies occurs via a bite by a rabid animal, although infections through aerosols have been documented (Constantine, 1966; Winkler et al., 1973). The virus can infect any warm-blooded animals, with dogs and cats being the main vectors of human infection (Woldehiwet, 2005). Clinically, rabies infection can be divided into three phases: (1) prodromal, (2) furious, and (3) paralytic phases (Bedford, 1976). In its early stages, rabies in cats can be difficult to diagnose. In one study, the main signs of rabies in cats reported by veterinarians included changes in behavior, gait abnormality, wound or injury within the past 6 months, and an unusual look in the eyes, whereas the most frequently reported signs by owners included aggressiveness, gait abnormality, and, once again, an unusual look in the eyes (Fogelman et al., 1993). Although the unusual expression in the eyes was not further characterized in this study, it may have arisen because of alterations in pupil size (i.e., mydriasis) from rabies-induced neurologic dysfunction. The reader is referred to the World Organisation for Animal Health for comprehensive information about rabies worldwide (World Organisation for Animal Health, 2018).

Metabolic Diseases

Diabetes Mellitus

Diabetes mellitus is considered a syndrome characterized by: (1) hyperglycemia resulting from defects in insulin secretion, (2) insulin sensitivity in target tissues, or (3) a combination of (1) and (2) (Gilor et al., 2016). Diabetes mellitus is traditionally described as being either type-1 diabetes mellitus (T1DM)/insulin-dependent diabetes mellitus (IDDM), or type-2 diabetes mellitus (T2DM)/noninsulin-dependent diabetes mellitus (NIDDM) (Gilor et al., 2016). A call for a refined classification of diabetes mellitus in dogs and cats, as has been done in humans, is necessary to account for the varying etiopathogeneses of diabetes mellitus and to ensure appropriate treatments are employed (Gilor et al., 2016). Nevertheless, cats with diabetes mellitus are typically affected by a form of diabetes that shares similarities to type-2 diabetes mellitus in humans where there is pancreatic β-cell dysfunction with insulin resistance (Sparkes et al., 2015).

Diabetes mellitus is a common endocrine disorder of cats. It is estimated that feline diabetes mellitus occurs at a prevalence of between 1:100 and 1:500 in family practices (Sparkes et al., 2015). In a large epidemiologic study from the United Kingdom, a 5-year period prevalence, reviewing over 190,000 cats presenting to family practices, was 0.58% (O'Neill et al., 2016). Breeds predisposed to developing diabetes mellitus include Tonkinese, Burmese, and Abyssinian (Ohlund et al., 2015; O'Neill et al., 2016). Obesity, increasing age, physical inactivity and prior treatment with progestigens or glucocorticoids are considered important risk factors for developing diabetes mellitus in cats (O'Neill et al., 2016; Sparkes et al., 2015). The most common form of feline diabetes mellitus is T2DM, although many cats are insulin dependent upon initial diagnosis (Rand et al., 2005). Results of a recent study suggest that up to nearly two-thirds of cats with diabetes mellitus may have T2DM (Bennett et al., 2005). The cause of diabetes mellitus in cats is multifactorial.

The most common ocular manifestation of diabetes mellitus in the dog is cataract formation (Basher & Roberts, 1995; Ling et al., 1977). Diabetic cataract formation varies with the species affected, individual, age of disease onset, duration of the diabetes, and severity of hyperglycemia. The young dog is very susceptible, and the cat resistant, to

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diabetic cataract formation (Wyman et al., 1988). Cataracts were present at the initial examination of almost 60% of spontaneous canine diabetics, whereas no cataracts were noted in a series of 30 cats (Ling et al., 1977; Schaer, 1977). In a retrospective study of 268 patients with feline cataracts, only 0.4% of these patients were suspected as having diabetes mellitus-related cataracts (Guyonnet et al., 2019). Aldose reductase plays a role in the formation of cataracts when glucose levels are elevated in diabetes mellitus (Kador et al., 2016). One of the reasons for variations in susceptibility among species, ages, and individuals to diabetic cataracts is the lenticular activity of aldose reductase (Engerman et al., 1982). Older cats are not susceptible to diabetic cataracts because the level of intralenticular aldose reductase is low in comparison with that of dogs (Richter et al., 2002). Younger cats (<4 years of age) do, however, have elevated levels of aldose reductase in their lenses (Richter et al., 2002), but because diabetes mellitus is rarely reported in younger cats, feline diabetic cataracts are uncommon (Guyonnet et al., 2019; Thoresen et al., 2002). One case of diabetes mellitus and related secondary bilateral nuclear and cortical cataracts has been reported in a kitten (Thoresen et al., 2002). One study evaluated 2000 normal cats, 50 cats with diabetes, and 100 cats with a history of dehydrational crises to determine the presence of cataract (Williams & Heath, 2006). The age at which the prevalence of cataract was 50% (C(50)) for diabetic cats was 5.6 ± 1.9 years which was significantly different than the C(50) for the normal cats (C(50) = 12.7 ± 3.4 years). In addition, the C(50) for cats with a history of dehydrational crises was 9.9 ± 2.5 years. The prevalence of cataract was therefore noted to be increased in the cats with diabetes (Fig. 37.2.23) and the cats with dehydrational crises as compared with normal cats. This study also identified cataracts in almost all (48/50) of the cats examined with diabetes mellitus (Williams & Heath, 2006). This is in contrast to two studies examining

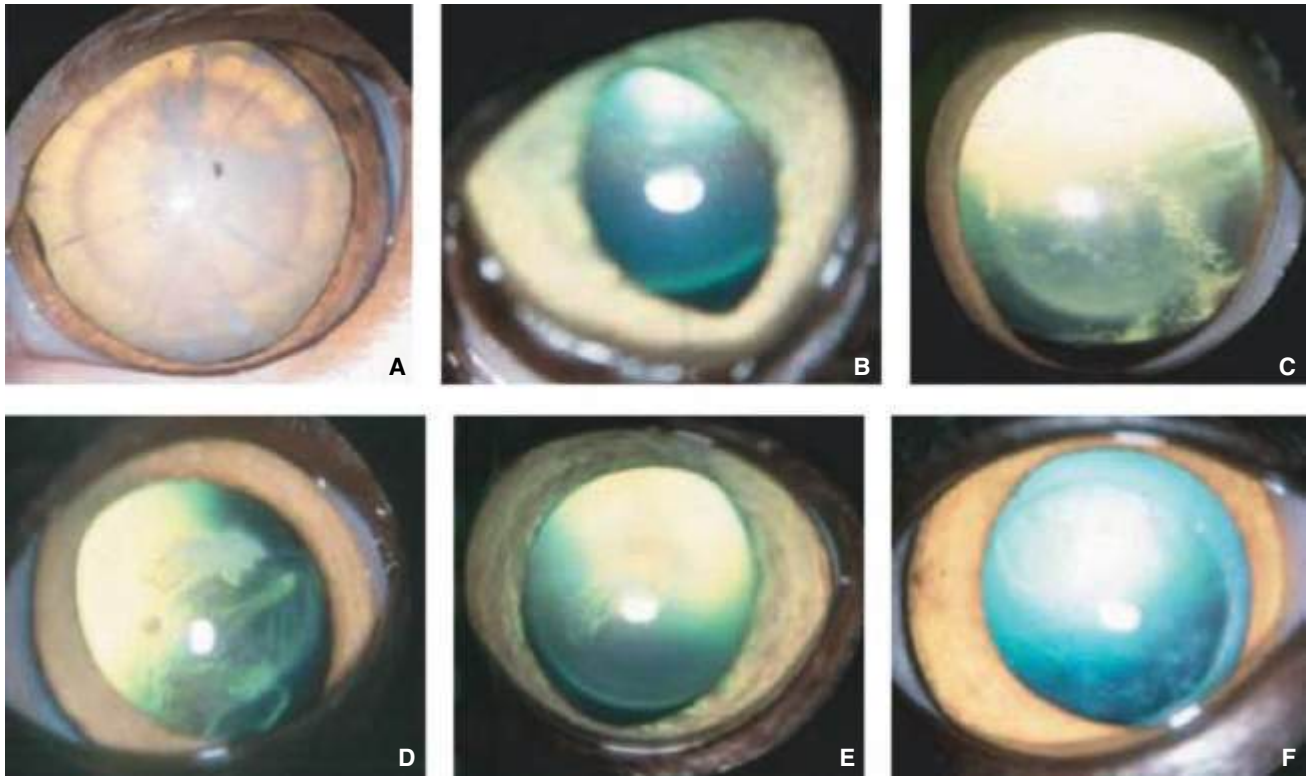


Figure 37.2.23 Cataracts in diabetic cats. **A.** Eighteen-year-old male neutered domestic shorthaired cat, diabetic for 3 years with pronounced nuclear and posterior cortical opacities after pharmacological mydriasis – dense focal paracentral opacity is corneal. **B.** Fifteen-year-old female spayed domestic shorthaired cat, diabetic for 2 years with nuclear sclerosis and posterior cortical opacities. **C.** Twelve-year-old female spayed domestic shorthaired cat, diabetic and acromegalic for 6 months with pronounced anterior and posterior opacities and nuclear sclerosis. **D.** Eleven-year-old, male neutered domestic shorthaired cat, diabetic for 18 months with posterior subcapsular focal opacity, posterior cortical dot opacities, perinuclear plaque opacity and early nuclear sclerosis. **E.** Thirteen-year-old female spayed domestic shorthaired cat, diabetic for 2 years with posterior subcapsular plaque and nuclear sclerosis. **F.** Fourteen-year-old female spayed domestic shorthaired cat, diabetic for 6 months with early nuclear sclerosis and posterior cortical hazy opacities. (*Source*: Reprinted with permission from Williams, D.L. & Heath, M.F. (2006) Prevalence of feline cataracts: results of a cross-sectional study of 2000 normal animals, 50 cats with diabetes and one hundred cats following dehydrational crises. *Veterinary Ophthalmology*, **5**, 1–9.)

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feline cataracts where cats are rarely noted to have diabetes mellitus-related cataracts (Guyonnet et al., 2019; Salgado et al., 2000). It is unclear why the discrepancy exists between the reported incidence of cataracts in diabetic cats. Regardless of the incidence of cataracts, however, the size, location, and severity of the cataracts observed in cats seems to be different than that of dogs with diabetic cataracts (Williams & Heath, 2006).

Diabetic retinopathy and cataracts have been described in a cat after experimental pancreatectomy (Hatchell et al., 1995). In this cat, nonbleeding microaneurysms and scattered punctate intraretinal hemorrhages were identified, and leakage of fluoroscein from microaneurysms and possible neovascularization extending from the retinal surface were detected with fluoroscein angiography (Hatchell et al., 1995). Diabetic retinopathy has been described in two cats which developed diabetes mellitus after long-term treatment with megestrol acetate for dermatologic disease (Herrtage et al., 1985). Both cats had bilateral retinal hemorrhage and retinal detachment, and in one cat, microaneurysms were seen (Herrtage et al., 1985). Cessation of the drug resulted in resolution of the retinal hemorrhages, but the cats were blind because of retinal detachment, retinal degeneration, or cataract. The role that systemic hypertension may have played was not addressed. Systolic blood pressure was measured in 14 diabetic cats. None of these cats had evidence of hypertensive retinopathy and systolic blood pressures were all <180 mmHg suggesting that hypertension does not occur or rarely occurs in cats with diabetes mellitus (Sennello et al., 2003). Nonetheless, two cats with diabetes mellitus and systemic hypertension, with no other cause of systemic hypertension have been described (Carter et al., 2014; Maggio et al., 2000); therefore, systemic hypertension may play a role in diabetic cats with retinopathy.

Hyperthyroidism

Hyperthyroidism is a common endocrine disease of the cat. Feline hyperthyroidism usually develops as a result of functional adenomatous hyperplasia, or less commonly adenoma, of one or both thyroid lobules. Hyperthyroidism causes systemic hypertension in cats (Kobayashi et al., 1990), which in turn, causes hypertensive retinopathy (see "Hypertension" section) (Carter et al., 2014; Maggio et al., 2000; van der Woerdt & Peterson, 2000). In one study, only 1 of 13 hyperthyroid cats had ocular disease as evidenced by retinal arterial tortuosity and focal retinal degeneration (Stiles et al., 1994). Retinal hemorrhages and retinal detachment have also been reported in hyperthyroid cats secondary to systemic hypertension (Littman, 1994; Sansom et al., 1994). One retrospective study reported active retinal lesions in five eyes of only 3 of 100 hyperthyroid cats (van der Woerdt et al., 2000). Another study described hyphema in 1 of 25 hyperthyroid cats, but complete ophthalmic examinations were not performed in these cases (Bucknell, 2000). In addition, neither of these two particular studies evaluated systemic blood pressure in the affected cats (Bucknell, 2000; van der Woerdt et al., 2000). The reader is referred to current internal medicine textbooks regarding the diagnosis and treatment of feline hyperthyroidism.

Ionic Disturbances

Hypocalcemia

Hypocalcemia in cats may be caused by several conditions including hypoparathyroidism, postparturient hypocalcemia, acute or chronic renal failure, acute pancreatitis, vitamin D toxicity, severe nutritional secondary hyperparathyroidism, and after surgical thyroidectomy, among others (for review see Dhupa & Proulx, 1998; Holowaychuk, 2013). Neurologic signs of restlessness, muscle fasciculations, and tonic-clonic seizures occur with a total serum calcium level of 6–7 mg/dL or a serum ionized calcium level of less than 2.5 mg/dL. The cause of the hypocalcemia can be determined using a combination of renal function tests, radiography, and parathyroid hormone assays.

Hypocalcemia in the cat has been documented clinically to be associated with focal punctate to linear opacities in the anterior and posterior cortices of the lens (Bassett, 1998; Peterson et al., 1991; Stiles, 1991). The lenticular opacities may occur at different levels in the cortex and they may reflect different episodes of hypocalcemia. The degree and duration of hypocalcemia necessary to produce cataracts is unknown, but the characteristic appearance of the cataracts is quite suggestive of hypocalcemia.

Treatment of hypocalcemia involves correction of the underlying disease, if possible, and calcium supplementation with vitamin D_2, vitamin D_3, or dihydrotachysterol. Additional focal cataracts may manifest for a period after correction of the hypocalcemia, and the existing lenticular opacities will remain.

Neoplasia: Central Nervous System

Blindness associated with intracranial neoplasia has been reported in cats (Davidson et al., 1991a; Duniho et al., 2000; Gordon et al., 1994; Nafe, 1979; Sant'Ana et al., 2002; Troxel et al., 2003). In one study, an acutely blind, 12-year-old cat with afferent pupillary deficits was found to have a pituitary carcinoma that encroached on the optic chiasm (Davidson et al., 1991a). In a series of 36 cats with meningiomas, blindness or visual field deficits were found in seven (Nafe, 1979). Six of these seven cats had unilateral visual deficits, whereas the remaining cat was completely blind, with dilated pupils from compression of the optic chiasm by a third-ventricle meningioma. Six cats also had positional nystagmus, and one cat with tentorial herniation had anisocoria, with the smaller pupil being contralateral to the tumor. It is also important to keep in mind that cranial nerve disturbances will also be apparent with some cases of feline intracranial neoplasia.

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Neoplasia: Systemic

Lymphosarcoma

A common systemic neoplasm of cats with ocular involvement is lymphosarcoma (Carlton, 1976; Corcoran et al., 1995; Davidson et al., 1991b; Meincke, 1966; Peiffer & Wilcock, 1991). In a retrospective study of 49 cats with lymphosarcoma confirmed at histopathology, ocular manifestations of disease preceded systemic disease in most cases (Corcoran et al., 1995). The uveal tract was involved in all eyes, and nodular iris lesions were the most common manifestation, being present in 35 of 50 eyes. Seventeen of these cats were tested for FeLV, and seven were positive. Survival ranged from 0 days to 31 months, with a mean survival of 14 months. Aggressive treatment of cats with ocular lymphosarcoma using topical corticosteroids, such as 1% prednisolone acetate, as well as using systemic therapy with corticosteriods or other chemotherapeutic protocols is indicated.

Other: Metastases

Adenocarcinomas have been reported to metastasize to the feline eye, with the site of origin being the lung (Gionfriddo et al., 1990), mammary tissue (West et al., 1979), uterus (Bellhorn, 1972; O'Rourke & Geib, 1970), and disseminated adenocarcinoma of undetermined origin (Murphy et al., 1989a). Four cases of feline angioinvasive pulmonary carcinoma have been reported to metastasize to the posterior segment of the eye (Cassotis et al., 1999). One case of renal transitional cell carcinoma has been reported to metastasize to the eye causing bilateral retinal detachments (Grader et al., 2016). A case of a soft-tissue fibrosarcoma with widespread metastasis including the eye has been reported as well (Fulton et al., 1991). One retrospective study reported 55 cases of extraskeletal osteosarcoma, four of which were orbital (Heldmann et al., 2000). Forty-five of the 55 cases (80%) were also detected in subcutaneous sites, 54% of which were consistent with sites used for vaccination. Squamous cell carcinoma has also been reported to invade intraocular structures, either by direct extension from the head (Hayden, 1976; Murphy et al., 1989b) or via hematogenous spread (Cook et al., 1984; Hamilton et al., 1984) from a more distant site. Plasmacytomas may also invade the orbit and globe. One report described a plasma cell tumor of the orbit in a cat that had originated from the masticatory muscle (Ward et al., 1997). Another study reported an extramedullary plasmacytoma in the iris and ipsilateral mandibular lymph node. However, no other evidence of disseminated disease was noted in this cat (Michau et al., 2003). In addition, ocular manifestations of multiple myeloma in cats are reported and include intraocular hemorrhage (two of nine cats) (Hanna, 2005), and ocular lesions associated with associated hyperviscosity syndrome such as retinal hemorrhages, dilated and tortuous retinal vessels, retinal detachment, perivascular effusion, papilledema, and retinal degeneration (Forrester et al., 1992; Hawkins et al., 1986; Hribernik et al., 1982; Lane, 1993) (see "Hyperviscosity Syndrome" section).

Nutritional Disorders

Milk Replacer-Induced Disease

Cataracts have been reported in growing kittens fed a commercial milk-replacer diet (Remillard et al., 1993). The low serum arginine concentration in these kittens was thought to relate to the diet and, possibly, to the cataract formation. A study of growing kittens documented cataract development in kittens fed diets containing fewer than 3.0 g of histidine per kilogram of body weight (Quam et al., 1987).

Taurine Deficiency

Feline central retinal degeneration (FCRD) was first described by Bellhorn and colleagues in 1970 and 1974 (Bellhorn & Fischer, 1970; Bellhorn et al., 1974). The lesion was characterized as a focus of outer retinal layer degeneration in the area centralis. A few years later, taurine-deficiency retinopathy was described, with early lesions being identical to those described with FCRD (Aguirre, 1978; Berson et al., 1976; Hayes et al., 1975a; Knopf et al., 1978; Schmidt et al., 1976a,b; Walser-Reinhardt et al., 2010). During the ensuing years, controversy existed regarding whether these were the same or two different syndromes. In the mid-1980s, taurine deficiency was determined to be a cause of dilated cardiomyopathy in the cat (Pion et al., 1987). Subsequently, cat food companies increased the levels of taurine in commercial, processed cat foods. Cases of FCRD reported to The Veterinary Medical Databases have since declined, dropping off precipitously in 1990 (Riis, 1992), thus adding further support that FCRD and taurine-deficiency retinopathy are the same syndrome.

Typical lesions of taurine deficiency begin with a granular appearance, which progresses to a hyperreflective focus in the area centralis. A nasal focus of degeneration may develop next, extending to a horizontal streak on both sides of the optic disc (Fig. 37.2.24). Further degeneration also occurs, eventually encompassing the entire retina, but there is no predictable time frame for lesion progression.

Taurine, which is a sulfur-containing amino acid, is an essential nutrient in the cat, which lacks the enzyme cysteine sulfinic acid decarboxylase needed to synthesize taurine (Knopf et al., 1978; Lombardini, 1991). Taurine is not a component of proteins, but it is dissolved in the cytosolic fluids of cells (Jacobsen & Smith, 1968). It is generally associated with excitable tissues, with the highest concentrations being found in the retina, heart, CNS, and skeletal muscle (Pion et al., 1990).

Taurine is essential for photoreceptor survival, and it is highly concentrated in the inner and outer segments. Possible functions of taurine in the retina include protection of the photoreceptors from light and chemical damage,

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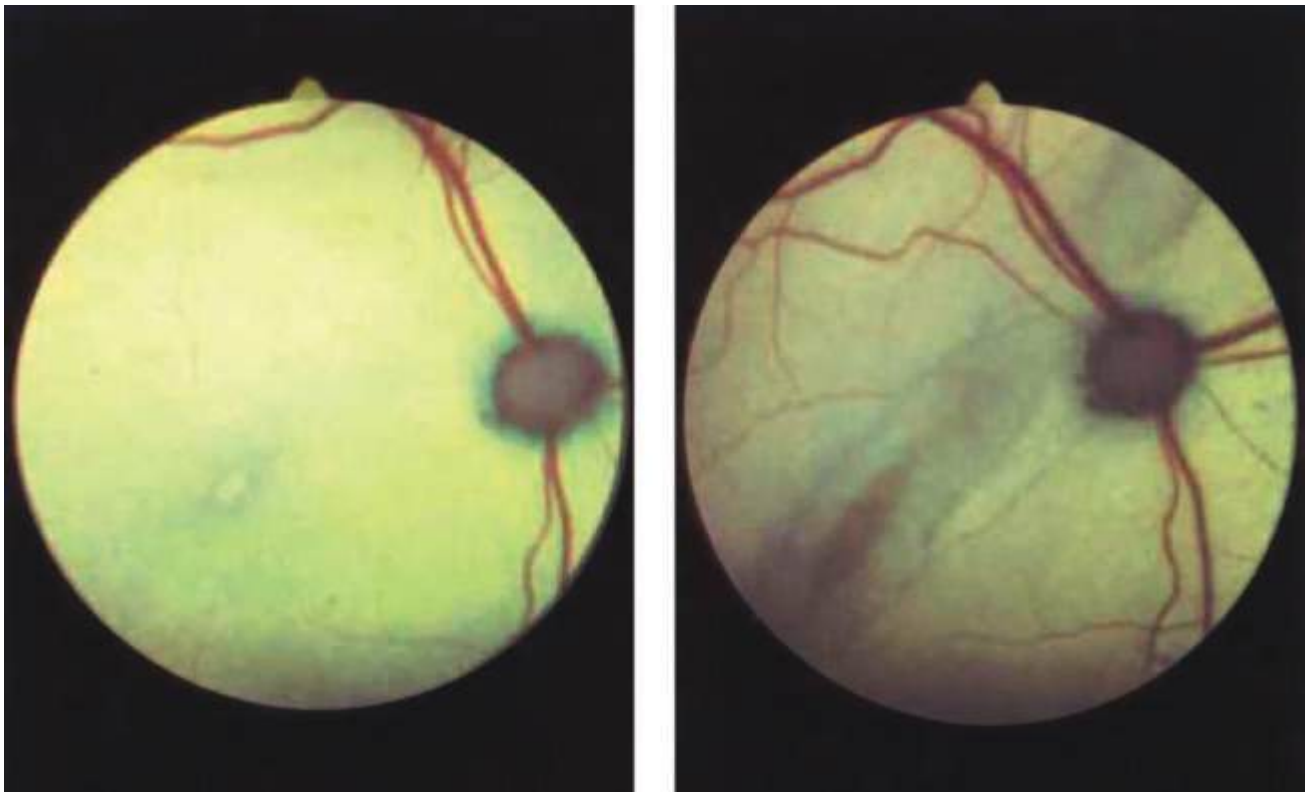


Figure 37.2.24 Early taurine deficiency retinopathy in a cat. In the *area centralis* there is a small, oval, hyperreflective lesion with a darker border (left). The same eye 8 months later. The original lesion has enlarged considerably, forming a horizontal dark band immediately above the optic disc (right). (*Source*: Reprinted with permission from Curtis, R. (1988) Retinal diseases in the dog and cat: an overview and review. *Journal of Small Animal Practice,* **29**, 397–415.)

regulation of calcium ion transport, and regulation of signal transduction (Lombardini, 1991; Militante & Lombardini, 2002, 2003a,b, 2004). Ultrastructural studies of the taurine-deficient feline retina show initial disorganization and vesiculation of rod and cone outer segment lamellar discs in the area centralis (Hayes et al., 1975b. Subsequent loss of outer segments and photoreceptor nuclei occurs in the area centralis as well as in the midperipheral retina. Electroretinographic findings are of progressive loss of rod and cone amplitudes and a delay in the temporal aspects of the cone response. The early receptor potential is preserved, however, even when the a and b waves are substantially reduced (Berson et al., 1981; Hayes et al., 1975b). In cats with minimal to moderate degeneration, supplementation with taurine returned both rod structure and rod function to normal, whereas some abnormalities of cone structure and cone function remained.

A cause for the geographic distribution of the lesion in taurine-deficiency retinopathy has not been definitively elucidated. Early work suggested the lesions followed cone cell distribution (Bellhorn et al., 1974). There is evidence that cones are preferentially damaged in the area centralis during the early stage of disease (Hayes et al., 1975b), but there is no evidence for a band of cone cell density in the horizontal streak, where lesions are seen during a later stage (Leon et al., 1995). Areas containing the highest retinal concentrations of the visual pigment rhodopsin in the cat have a similar distribution to the areas that preferentially degenerate (Jacobson et al., 1987). Rhodopsin has been documented to diminish following this pattern in taurine-deficient cats, and this has been suggested to cause the characteristic geographic lesion. This theory, which involves preferential light damage to areas of high rhodopsin concentration, was not supported in one study, however, in which unilateral tarsorrhaphy of taurine-deficient cats still resulted in characteristic lesions (Leon et al., 1995).

Cats with *area centralis* lesions have demonstrable deficits in visual acuity (Blake & Bellhorn, 1978), but in a normal home environment, these cats usually do not have discernible problems. The finding of an *area centralis* lesion does not indicate current taurine deficiency, because the lesions will remain for the life of the cat. Measurement of plasma taurine levels is the best way to determine a deficient animal. Plasma levels of 20 nmol/mL are critically low; to be safe, cats with values of less than 40 nmol/mL should be switched to a different diet, one that is known to support higher plasma taurine levels (Pion & Kittleson, 1990). Because commercial cat foods today contain much more taurine than

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they used to, active cases of taurine deficiency are likely to occur in cats fed inappropriate diets or in those with intestinal diseases that alter proper nutrient absorption. A recent study documented that the dietary requirement for taurine in cats is dependent on dietary protein concentration and quality (Backus et al., 1998). Increasing the dietary protein concentration increases the need for taurine, as does a reduction in protein quality.

Thiamine Deficiency

Thiamine deficiency may occur in cats eating large amounts of raw fish, which contains thiaminases, or in cats eating processed commercial foods in which thiamine has been destroyed by heat processing and not replaced adequately (Chang et al., 2017; Markovich et al., 2014; Moon et al., 2013; Pritchard, 2017). Thiamine deficiency has also been reported in cats being fed commercial food containing sulfur dioxide as a food preservative (Malik & Sibraa, 2005; Steel, 1997; Studdert & Labuc, 1991). Further, cats with severe gastrointestinal disease may not absorb sufficient amounts of thiamine. Clinical signs of thiamine deficiency include initial inappetence and occasional vomiting, followed by pupillary dilatation without visual deficits, ataxia, and ventroflexion of the head and neck (Davidson, 1992; Loew et al., 1970; Martin, 1971). A final and irreversible stage of thiamine deficiency is characterized by a progression of clinical signs culminating in a semicomatose state, which is characterized by crying, opisthotonos, and extensor rigidity.

The diagnosis can be made on the basis of dietary history, clinical signs, and measurement of thiamine concentration in food as well as in blood. Normal blood thiamine levels for cats are approximately 32 μg/dL. Before development of a comatose state, cats will respond favorably to parenterally administered vitamin B complex preparations containing 50–75 mg of thiamine per dose every 8 hours. Alimentation should be provided via a nasogastric or gastrotomy tube. Improvement is usually seen within 3 days, although ataxia may be present for 2 weeks. Once the cat is eating, oral vitamin supplementation can be instituted, and the diet should be corrected to include an adequate thiamine intake.

Systemic Toxicities

Antimicrobials

Fluoroquinolones

Enrofloxacin, a fluoroquinolone antibiotic, has been associated with a rare adverse ophthalmic reaction causing an acute, typically irreversible, retinal degeneration in cats (Gelatt et al., 2001; Grahn et al., 2002; Giuliano & van der Woerdt, 1999; Wiebe & Hamilton, 2002). In addition, this reaction has reportedly been seen with other fluoroquinolones including marbofloxacin and orbifloxacin (Ramirez et al., 2011). Interestingly, enrofloxacin retinal toxicity has not been observed in nondomestic felids (Newkirk et al., 2017).

Affected cats develop signs of partial, temporary, or total blindness. The reported estimated incidence of this adverse reaction is 1 in 122,414 treated cats or 0.0008% (Wiebe & Hamilton, 2002). The association of enrofloxacin, retinal degeneration, and blindness in cats was first described in a retrospective study in which 5 of 26 cats with diffuse retinal degeneration had received oral enrofloxacin (Giuliano & van der Woerdt, 1999). Subsequently, another retrospective study documented the association between enrofloxacin administration and the acute onset of retinal degeneration in 17 cats (Gelatt et al., 2001). All cats were domestic shorthair breed with ages ranging from 3 to 16 years old. All affected cats had variable medical ailments for which enrofloxacin was administered including lymphoma and pancreatitis, otitis, urinary tract disorders, dermatitis, bowel perforation, diarrhea, and upper respiratory infection. The daily enrofloxacin dosages these cats received were highly variable ranging from 4.6 mg/kg PO once daily to 27 mg/kg PO twice daily. Cats in this study generally presented with signs of mydriasis and acute blindness. All cats had generalized retinal degeneration, and vision only returned in a few cases (Fig. 37.2.25). Five of 17 affected cats underwent electroretinography which revealed no observable responses in any case. Histological assessment of two affected globes showed mainly outer retinal degeneration as evidenced by a diffuse loss of the photoreceptor and outer nuclear layers, and hypertrophy and proliferation of the RPE. Given the findings in this study, the adverse retinal reaction to enrofloxacin in cats appears to be a rare, idiosyncratic reaction. Adherence to the manufacturer's current recommendation for enrofloxacin dosage in cats of 5 mg/kg PO q 24 hours is advisable. It is, however, unclear as to whether a dosage of 5 mg/kg PO q 24 hours is safe in geriatric cats, especially those with renal or hepatic dysfunction, as safety studies performed by the manufacturer were conducted in young healthy cats (Wiebe & Hamilton, 2002).

Safety studies evaluating the incidence of retinal degeneration with orbifloxacin, another veterinary-labeled fluoroquinolone, revealed a dose- and concentration-dependent adverse ophthalmic reaction, with cats receiving higher doses of the medication developing focal retinal degeneration (Kay-Mugford et al., 2001). Safety studies conducted on marbofloxacin, another veterinary-approved fluoroquinolone, did not demonstrate any ocular lesions after oral administration of up to 20 times the minimum recommended daily dosage. Another study examining pradofloxacin in cats, given at 6 and 10 times the recommended dosages, failed to demonstrate rod or cone dysfunction using electroretinography (Messias et al., 2008). Nonetheless, the manufacturer of marbofloxacin indicates that it is a prudent precaution to consider that all fluoroquinolones may have

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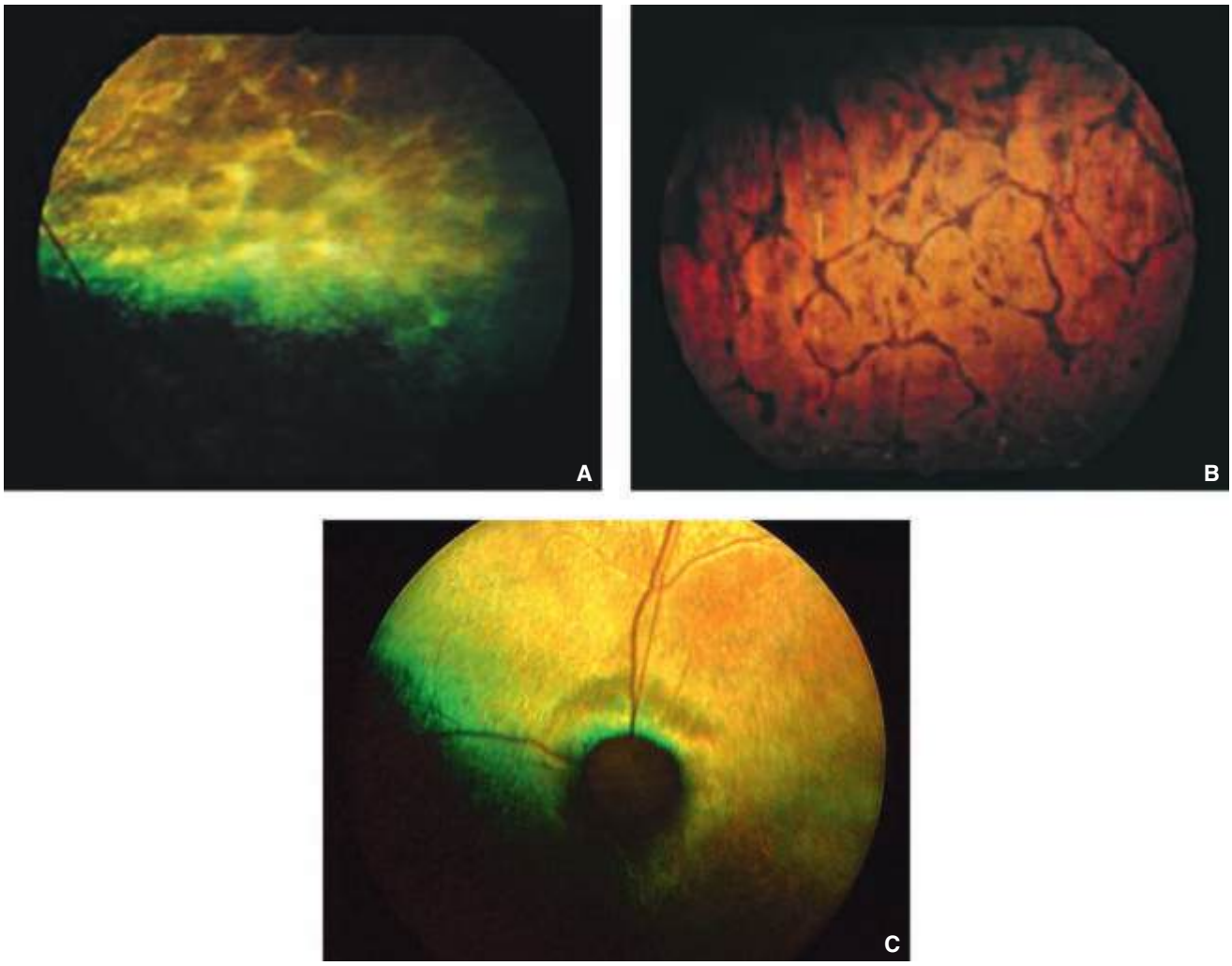


Figure 37.2.25 Acute retinal degeneration in a 15-year old male castrated cat after 196 days of enrofloxacin administration. **A.** Tapetal changes characterized by loss of retinal vessels, focal increased tapetal reflectivity, and large gold- to rust-colored foci scattered throughout the tapetal fundus. **B.** Pigment loss and clumping within the non-tapetal fundus. (*Source*: Reprinted with permission from Gelatt, K.N., et al. (2001) Enrofloxacin-associated retinal degeneration in cats. *Veterinary Ophthalmology*, **4**, 99–106.) **C.** Fundus photograph from a mature domestic shorthair cat after 5 days of enrofloxacin therapy. Note the tapetal granularity, focal tapetal hyperreflectivity, and moderate generalized retinal vessel attenuation.

the potential to induce feline ocular lesions. Therefore, all fluoroquinolones should be used with caution in this species (Wiebe & Hamilton, 2002).

It has been shown that cats have four specific amino acid sequence differences in P-glycoprotein, ABCG2, in comparison with that of other mammals (Ramirez et al., 2011). ABCG2 is a member of the ATP-binding cassette superfamily of proteins and is located in a variety of tissues including the endothelium comprising the blood–retinal barrier. These proteins transport a variety of molecules, including fluoroquinolones, across cell membranes. As such, this protein acts to regulate the concentration of drugs, such as the fluoroquinolones, within the retina. Fluorquinolones produce reactive oxygen species when exposed to light. When HEK-293 cells are modified to contain (1) no ABCG2, (2) human-specific ABCG2, or (3) feline-specific ABCG2, and are subsequently exposed to ultraviolet light, 50% of cells not containing ABCG2 die when exposed to 1–10 μmol/L of enrofloxacin, 50% of cells with feline specific ABCG2 will die when exposed to 10 μmol/L of enrofloxacin, and 50% of cells with human ABCG2 will die when exposed to 50 μmol/L of enrofloxacin (Ramirez et al., 2011). These results show that feline-specific ABCG2 is ultimately ineffective at transporting enrofloxacin from within the cells, thus likely explaining the fluoroquinolone-related retinal toxicity described clinically in cats.

Current recommendations to help decrease the risk of retinal degeneration in some cats receiving enrofloxacin

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include: (1) using split dosing (i.e., 2.5 mg/kg PO q 12 hours) on exact body weight; (2) avoidance of rapid intravenous infusions of the drug and drug interactions; and (3) avoidance of UVA light during active treatment may also be beneficial. Owners of cats receiving parenteral fluoroquinolone therapy should be instructed to monitor their cat for mydriasis and to consult their veterinarian immediately should this sign develop. The pharmacokinetics of parenteral enrofloxacin in neonatal kittens compared with the pharmacokinetics of this medication in young and adult cats have been reported (Seguin et al., 2004). Ophthalmic examinations were not conducted on animals in this study, however.

Griseofulvin

Griseofulvin is a fungistatic agent used in cats to treat dermatophytosis. Griseofulvin is teratogenic in the cat. Ocular anomalies reported in affected offspring of cats having received griseofulvin in the first half of gestation include cyclopia, anophthalmia, optic nerve aplasia, and rudimentary optic tracts (Scott et al., 1975). Mesencephalic aqueductal stenosis has also been reported in kittens after *in utero* exposure to griseofulvin (Scott et al., 1975). Other widespread malformations also accompany the ocular abnormalities. One adult cat was thought to have retinal degeneration secondary to griseofulvin toxicity (Rottman et al., 1991).

Ivermectin

Ivermectin is a broad-spectrum anthelmintic that has been used in cats for the treatment of ear mites and notoedric mange. Ivermectin toxicosis has been observed in kittens and adult cats (Houston, 1985; Jourdan et al., 2015; Kidwell et al., 2014; Lewis et al., 1994; Mealey & Burke, 2015; Meekins et al., 2015; Muhammad et al., 2004; Pritchard, 2010; Rowley, 1988; Tudbury & Lorenzoni, 1987). Signs of toxicosis typically become apparent within 1–12 hours of administration of the ivermectin and include altered behaviour, lethargy, weakness, ataxia, recumbency, coma, and death (Lewis et al., 1994). Cats with *ABCB1* (*MDR1*) gene mutation have been shown to be sensitive to ivermectin, and related drugs, as can be found in dogs with mutations in this gene (Mealey & Burke, 2015).

Ocular manifestations of feline ivermectin toxicosis include apparent blindness, and alterations in pupil size including mydriasis and miosis (Houston, 1985; Lewis et al., 1994; Rowley, 1988; Tudbury & Lorenzoni, 1987). Fundic examinations are normal, although b-wave amplitudes on electroretinography are reduced (Meekins et al., 2015). Treatment of cats with intravenous lipid therapy and supportive care, or supportive care alone, has been shown to be successful in cats with ivermectin toxicosis (Jourdan et al., 2015; Kidwell et al., 2014; Pritchard, 2010).

Ethylene Glycol

Ethylene glycol intoxication is a common cause of poisoning in small animals, including cats. The lethal dose of 95% ethylene glycol in cats is 1.4 mL/kg. A single report in the literature describes a cat with acute renal failure secondary to ethylene glycol intoxication (Barclay & Riis, 1979). This cat developed bilateral retinal detachments and edema, which was thought (but not confirmed) to be secondary to oxalate crystals within the retina. Systemic blood pressure was not evaluated in this cat, and hypertension may have contributed to the retinal disease.

Ionizing Radiation

The ocular effects of ionizing radiation are similar no matter the source (see "Ionizing Radiation" in "Part 1: The Dog"). Both the ocular effect(s) and the time to develop ocular disease depend on the dose, age of the animal, and the species being studied. The most common source of ionizing radiation-induced ocular lesions is from radiation therapy for neoplasms of the head. Three of 16 cats undergoing irradiation for nasal or paranasal neoplasia developed chronic ocular conditions (Theon et al., 1994).

Megestrol Acetate

Megestrol acetate is a synthetic derivative of progesterone. It is generally used, systemically, in the treatment of dermatologic disorders and as a contraceptive, and has been used to treat proliferative (eosinophilic) keratoconjunctivitis in cats (Bedford & Cotchin, 1983; Romagnoli, 2015; Spiess et al., 1991). A topical ophthalmic formulation has been used successfully to treat cats with eosinophilic keratitis (Stiles & Coster, 2016). Nevertheless, two cats treated long-term with systemic megestrol acetate for dermatologic disease developed diabetes mellitus and diabetic retinopathy (Herrtage et al., 1985). Both cats had bilateral retinal hemorrhage and retinal detachment, and in one cat, microaneurysms were seen. Cessation of the drug resulted in resolution of the retinal hemorrhages, but the cats were blind because of retinal detachment, retinal degeneration, or cataract. The role that systemic hypertension may have played was not addressed.

Tissue Plasminogen Activator

Tissue plasminogen activator (tPA) is a thrombolytic enzyme available for clinical use in facilitating clot dissolution. In veterinary ophthalmology, intracameral injection of tPA is most common. However, a recent experimental study reported a dose-dependent retinal toxicity in feline eyes having received intravitreal injections of commercial tPA (Hrach et al., 2000). Specifically, eyes receiving doses of tPA greater than 50 µg/0.1 mL had fundus pigmentary changes. Electroretinography revealed diminished mean B-wave amplitudes in eyes of cats receiving at least 50 µg of tPA. Histologic findings in affected globes involved regions of photoreceptor loss with necrosis and proliferation of the RPE.

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Miscellaneous Diseases

Dental Disease

Varying degrees of focal chorioretinal lesions consisting of hemorrhage or exudates (or both) have been reported from bacterial infections involving organ systems including periodontitis or endodontic disease (Ramsey et al., 1996). Recently, chronic ocular discharge in the form of epiphora and mucopurulent discharge of the left eye has been described in a 10-year-old cat with severe periodontal disease and a fractured upper left canine tooth (Fig. 37.2.26) (Anthony et al., 2010). Dental radiographs revealed findings consistent with a tooth root abscess at the apex of the upper left canine tooth. Dacryocystorhinography revealed narrowing of the nasolacrimal duct above the root of the fractured upper left canine tooth. Following removal of the fractured canine tooth, the ocular discharge resolved. The suspected tooth root abscess reportedly resulted in extralumenal compression of the nasolacrimal duct.



Figure 37.2.26 Domestic shorthair cat with left nasolacrimal duct obstruction. Note left sided ocular discharge. (*Source*: Reprinted with permission from Anthony, J.M., Sandmeyer, L.S. & Laycock, A.R. (2010) Nasolacrimal obstruction caused by root abscess of the upper canine in a cat. *Veterinary Ophthalmology*, **13**, 106–109.)

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37.3

Ocular Manifestations of Systemic Disease

Part 3: The Horse

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Congenital

Coat Color-Related Diseases/Conditions

Complete albinism (complete lack of pigmentation) or partial or localized albinism (an absence or reduction in the degree of pigmentation) is associated with not only the phenotypic appearance of an animal's coat and skin color but is also associated with conditions affecting the eye and other organ systems. Albinism or partial albinism may result from the failure of migration of neural crest cells (precursors to melanocytes) and hence result in reduced numbers of melanocytes in a nonpigmented area, or may result because of impaired production of pigment caused by some intrinsic deficiency in melanin production (e.g., tyrosinase deficiency) but where the number of melanocytes in nonpigmented or hypopigmented areas is normal. In any case, albinism or partial albinism may manifest ocularly as something as benign as pale blue irides and/or subalbinotic fundi or be associated with generalized systemic disease such as lethal white foal syndrome.

Congenital Stationary Night Blindness

A condition long thought to be related to the incompletely dominant leopard spotting (LP) allele is congenital stationary night blindness (CSNB) in Appaloosa horses (Joyce & Witzel, 1977; Rebhun et al., 1984; Witzel, 1977; Witzel et al., 1977, 1978). The condition is nonprogressive, and affected animals that have cautious behavior in dim light conditions may be difficult to train. A dark-adapted electroretinogram lacking a b-wave is diagnostic (Sandmeyer et al., 2007, 2012). Concurrent neuro-ophthalmic signs may include bilateral dorsomedial strabismus (Fig. 37.3.1) and spontaneous nystagmus.

CSNB has been reported in a number of breeds of horses including Appaloosa, Knabstrupper, American Miniature Horses, Thoroughbred, and Paso Fino (Nunnery et al., 2005; Rebhun et al., 1984; Sandmeyer et al., 2007, 2012; Witzel, 1977; Witzel et al., 1977, 1978). However, CSNB is most commonly documented in breeds with the LP allele (Sandmeyer et al., 2007, 2012). Specifically, it has been shown that of the cases of CSNB occurring in breeds with the LP allele, CSNB is only found in those animals homozygous for LP (i.e., LP/LP) (Sandmeyer et al., 2007, 2012). Animals with LP are characterized along a spectrum of white patterning (very little white patterning to significant white patterning) (Fig. 37.3.2) (as discussed in Webb & Cullen, 2010). In heterozygous animals (LP/lp), there is typically more "spotting" within the white-patterned regions of the body. Animals homozygous for LP (LP/LP) typically have little to no spotting in the areas of white patterning.

Decreased expression of the calcium ion channel gene, transient receptor potential cation channel member 1 (*TRPM1),* in the skin and retina has been described in horses homozygote for LP and having CSNB (Bellone et al., 2008). The causative mutation for CSNB and LP has been identified in the *TRPM1* gene (Bellone et al., 2013).

Lethal White Foal Syndrome (Lethal White Overo Syndrome)

In horses, coat color is often associated with iris color and heterochromia irides. For example, it is not uncommon to see Paint horses with one blue eye and one darkly pigmented eye or with two blue eyes. A condition known as lethal white foal syndrome (an equine model of Hirschsprung disease in humans) can be found in white, typically blue-eyed foals with typically two overo-colored parents (McCabe et al., 1990; Trommershausen-Smith, 1977; Vonderfecht et al., 1983). In this instance, these foals are born with two copies (homozygous) of a mutated endothelin-B receptor gene (Metallinos et al., 1998; Santschi et al., 1998; Yang et al., 1998). Endothelin-3, a ligand for the endothelin-B receptor, is a signaling molecule important in the maturation and

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Figure 37.3.1 Right eye of a few-spot leopard horse affected by congenital stationary night blindness. The medial aspect of the globe is rotated dorsally. The left eye had a similar appearance. (*Source*: Reprinted with permission from Sandmeyer, L.S., Breaux, C.B., Archer, S., et al. (2007) Clinical and electroretinographic characteristics of congenital stationary night blindness in the Appaloosa and the association with the leopard complex. *Veterinary* Ophthalmology, **10**, 368–375.)

migration of neural crest cells (McCallion & Chakravarti, 2001). Neural crest cells are precursors to melanocytes and neurons in the peripheral nervous (including enteric) systems. In addition, migration of neural crest cells also migrate to the inner ear and are important in maintenance of normal hearing ability. Consequently, foals afflicted with lethal white foal syndrome are not only white with blue eyes but also have aganglionic colon resulting in gastrointestinal motility dysfunction and may also be deaf (Aleman et al., 2014; Magdesian et al., 2009; McCabe et al., 1990; Trommershausen-Smith, 1977; Vonderfecht et al., 1983).

Lethal white foal syndrome is inherited as an autosomal recessive trait and therefore both parents of affected foals are carriers of the affected gene. Specifically, coat colors associated with heterozygotes for the endothelin receptor-B mutation include frame overo, highly white calico overo, and frame blend overo (Santschi et al., 2001). Heterozygous animals with tobiano, sabino, minimally white calico overo, splashed white overo, nonframe overo, and breeding-stock solid coat colors may also exist, however (Santschi et al., 2001). Importantly, however, not all white foals of Paint horse breeding with blue eyes will be homozygous for the endothelin-B receptor gene mutation, and consequently will not have lethal white foal syndrome. A genetic test has been developed to screen for carrier animals or to test white blue-eyed foals and thereby reduce the prevalence of this condition in the American Paint horse population and prevent the premature euthanasia of white, blue-eyed foals (Metallinos et al., 1998; Santschi et al., 1998, 2001). Genetic testing for lethal white foal syndrome is commercially available at Veterinary Genetics Laboratory, University of California at Davis (http://www.vgl.ucdavis.edu/).

Multiple Congenital Ocular Anomaly Syndrome

Multiple congenital ocular anomaly syndrome (MCOAS) was described in Rocky Mountain Horses in 1999 (Ramsey et al., 1999a). Since this time, MCOAS has been described in crossbred Rocky Mountain Horses, Kentucky Mountain Horses, Mountain Pleasure Horse, Morgans, Belgians, American Miniature Horses, Comtois, and Icelandic Horses (Andersson et al., 2008; Andersson et al., 2011a, b; Grahn et al., 2008; Komaromy et al., 2011; Plummer & Ramsey, 2011; Ramsey et al., 1999a; Segard et al., 2013). MCOAS exists in two phenotypes: (1) cyst phenotype, and (2) MCOA phenotype. Animals with the cyst phenotype have cysts arising from the ciliary body, peripheral retina, and/or iris. These patients may also have concomitant retinal dysplasia and/or retinal detachment. Animals with the MCOA phenotype have all of the anomalies seen within the cyst phenotype but also have varying severity and combination of congenital cataracts, cornea globosa, iris hypoplasia, iridocoreneal angle abnormalities, lens subluxation, microphthalmia, and macropalpebral

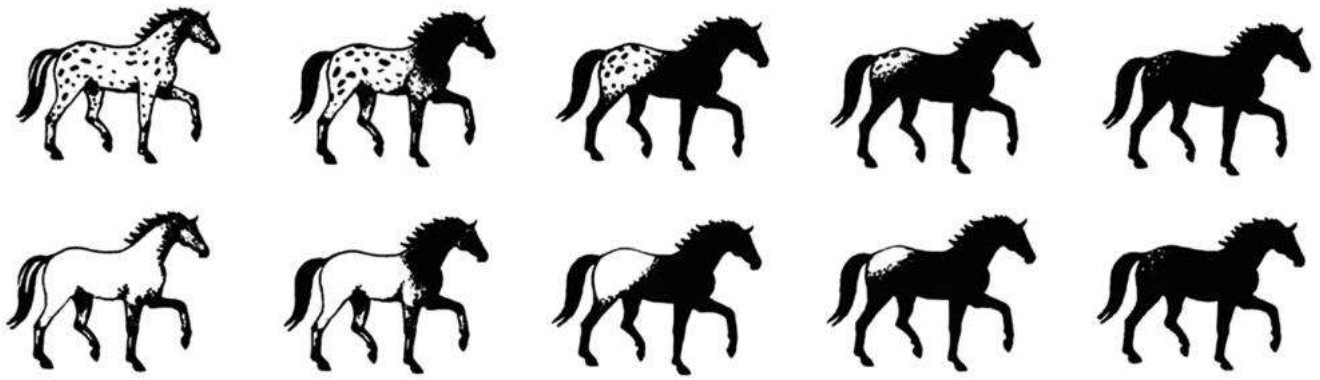


Figure 37.3.2 White pattern continuum for heterozygote (LP/lp) and homozygote (LP/LP) leopard complex gene. There is a continuum of white pattern in horses heterozygous and homozygous for LP. Horses homozygous for lp, however, have little to no pigmented spotting within the white patterned areas. (*Source*: Courtesy of Sheila Archer.)

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fissures (Ramsey et al., 1999a, b). Neuro-ophthalmic abnormalities consist of miotic pupils, abnormal pupillary light reflexes, with pupils that respond poorly to pharmacologically induced mydriasis (Ramsey et al., 1999a). Affected individuals also have varying degrees of vision loss (Grahn et al., 2008; Ramsey et al., 1999a). Congenital ocular abnormalities observed in Rocky Mountain Horses is, in part, related to coat color (Ramsey et al., 1999a).

Mane and tail color was found to be associated with the presence of multiple ocular abnormalities. Specifically, 45% of Rocky Mountain Horses with chocolate-colored coats with white manes and tails (Fig. 37.3.3) had multiple ocular abnormalities including megalocornea (Fig. 37.3.4), congenital miosis (Fig. 37.3.5), ciliary cysts (Fig. 37.3.6), and retinal dysplasia (Fig. 37.3.7) (Ramsey et al., 1999a). Meanwhile, only 12%, 6%, and 4% of horses with chocolate-colored coat with flaxen mane and tail (Fig. 37.3.8), chestnut-colored coat, or some other coat color, respectively, had multiple ocular abnormalities (Ramsey et al., 1999a). Moreover, Rocky Mountain Horses with white manes and tails were more likely to have multiple ocular abnormalities compared with animals with nonwhite manes and tails (Ramsey et al., 1999a). Further investigation into coat-color genetics has revealed that the gene responsible for silver coat color is associated with MCOAS (for review see Bellone, 2017). Genetic mutation of the premelanosome protein gene, *PMEL*, is responsible for silver coat color (dilution of black) (Brunberg et al., 2006). This gene mutation results in dilution of black (eumelanin) but not red/brown (phaeomelanin). As such, chestnut horses may appear normal yet carry *PMEL* (Bellone, 2017). Nonetheless, the severity of ocular lesions appears to be most severe in horses homozygous for mutated *PMEL* (Bellone, 2017).



Figure 37.3.3 Rocky Mountain Horse with a chocolate coat color and a white mane and tail. Ophthalmic lesions appear to be more common in this breed of horse with this coat coloration. (*Source*: Courtesy of David Ramsey.)

Griseofulvin Teratogenicity

Griseofulvin is a commonly used antifungal agent used especially for dermatomycosis (Schutte et al., 1997). Griseofulvin can readily cross placental membranes and has been associated with microphthalmia, brachygnathia superior (shortened maxilla), and palatocheiloschisis (cleft lip and palate) in a foal born to a dam that was administered griseofulvin at 48 days of gestation (Schutte & van den Ingh, 1997). The foal was born without complication but was euthanized because of malformations that rendered the foal blind and unable to nourish itself. Aside from the forementioned abnormalities,

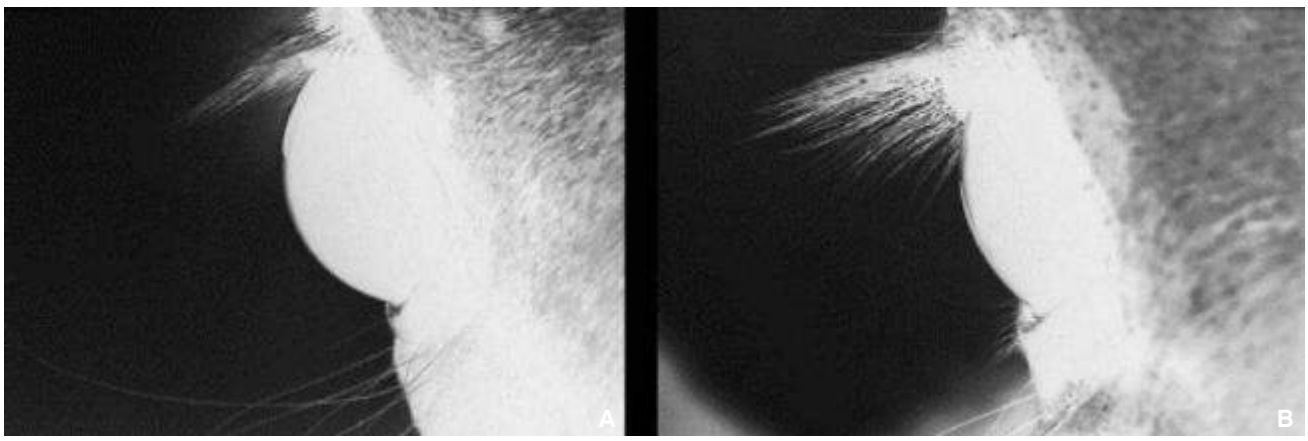


Figure 37.3.4 Profile photographs of the right cornea of two age- and gender-matched Rocky Mountain Horses. **A.** Megalocornea is characterized by a grossly observable, excessively large corneal optical diameter with a short radius of curvature, and a notably globular contour of the cornea with atypical and excessive protrusion. **B.** Normal cornea from an age- and gender-matched Rocky Mountain Horse. (*Source*: Reprinted with permission from Ramsey, D.T., Ewart, S.L., Render, J.A., et al. (1999) Congenital ocular abnormalities of Rocky Mountain Horses. *Veterinary Ophthalmology*, **2**, 47–59.)

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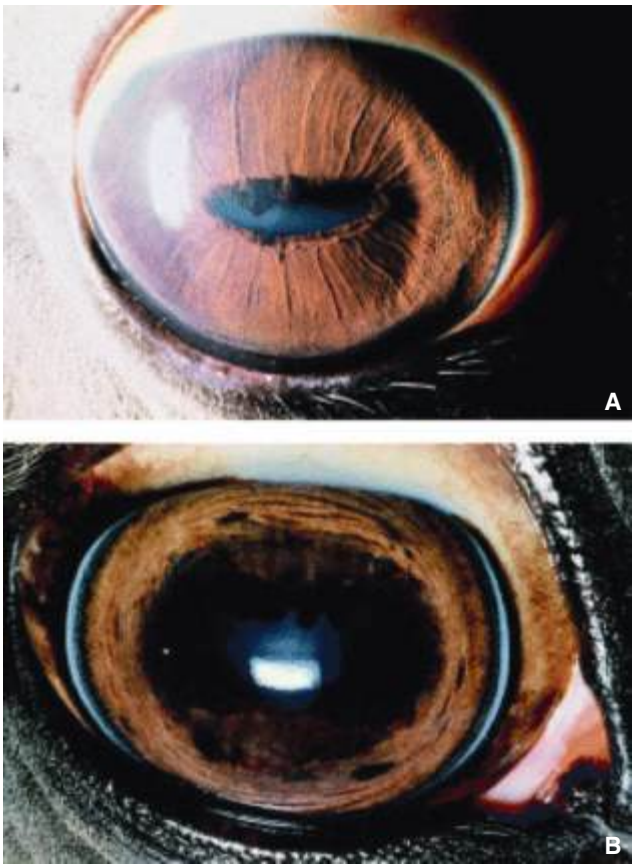


Figure 37.3.5 **A.** Eye of a Rocky Mountain Horse with congenital miosis and megalocornea. Abnormalities include a miotic pupil, stromal hypoplasia with a flattened, circumferentially oriented granula iridica at the pupillary ruff, visible sphincter pupillae muscle, and an absence of a discernable collarette. Radially oriented deep stromal strands of iris tissue extend from the papillary ruff toward the ciliary zone of the iris. **B**. Normal iris of an age- and gender-matched Rocky Mountain Horse. (*Source*: Reprinted with permission from Ramsey, D.T., Ewart, S.L, Render, J.A., et al. (1999) Congenital ocular abnormalities of Rocky Mountain Horses. *Veterinary Ophthalmology*, **2**, 47–59.)

there was a notable absence of third eyelids. The use of griseofulvin in pregnant animals should not be advised.

Hereditary Equine Regional Dermal Asthenia (Cutaneous Asthenia, Dermatosparaxis, Ehlers–Danlos Syndrome, Hyperelastosis Cutis)

Hereditary equine regional dermal asthenia (HERDA) has been reported most commonly in purebred and partbred Quarter Horses, although it has been reported sporadically in other breeds (Brounts et al., 2001; Gunson et al., 1984; Mochal et al., 2010; Solomons, 1984; Witzig et al., 1984; White et al., 2004). In Quarter Horses, HERDA is a congenital disorder of collagen that is characterized by fragile and easily torn skin with slow-healing wounds (Tryon et al., 2005; White et al., 2004).

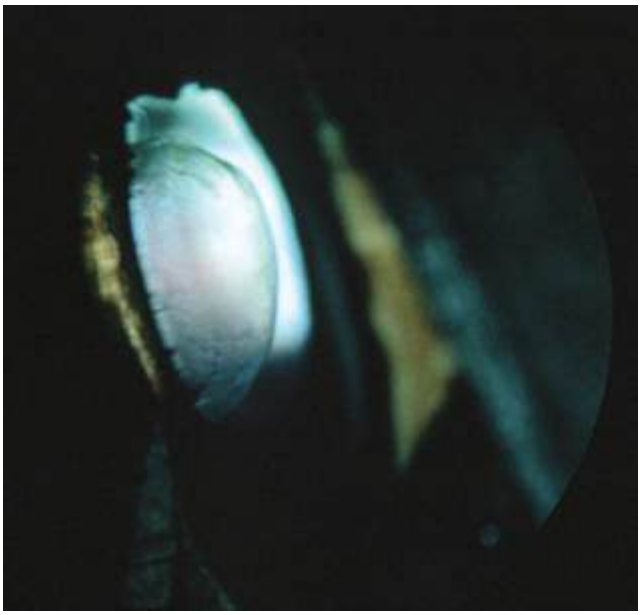


Figure 37.3.6 Right eye of a Rocky Mountain Horse. Note the large, translucent cystic structure arising from the ciliary body. (*Source*: Courtesy of David Ramsey.)

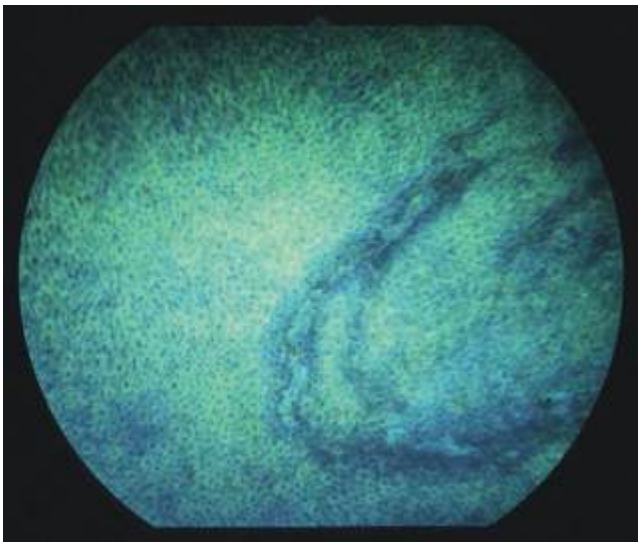


Figure 37.3.7 Fundus photograph of the left eye of a Rocky Mountain Horse. Note the multiple, darkly pigmented curvilinear streaks of retinal pigment epithelium in the peripheral tapetal fundus. (*Source*: Courtesy of David Ramsey.)

There is no gender predilection and HERDA is inherited as an autosomal recessive disorder in Quarter Horses (Tryon et al., 2005). Horses with HERDA have a regional distribution of friable and hyperelastic skin (White et al., 2004). Specifically, seroma or hemotoma formation, open wounds or sloughing skin, hyperextensible skin that does not return to regular position after skin tent, and scars may be seen along the dorsum, gluteal region, neck, and lateral thorax and/or abdomen.

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Figure 37.3.8 A Rocky Mountain Horse with chocolate coat color and flaxen mane and tail. Rocky Mountain Horses with this particular coloration appear to be less likely to have multiple congenital ocular lesions. (*Source*: Courtesy of David Ramsey.)

With respect to the eye, horses with HERDA have thinner corneas, larger corneal diameters and curvatures, are prone to developing corneal ulceration, and have disorganized corneal collagen fibrils compared with horses not affected by HERDA (Badial et al., 2015; Mochal et al., 2010). Considering that animals with HERDA only manifest the condition regionally and do not have excessive joint laxity or evidence of internal organ collagen dysfunction, HERDA is not considered to be synonymous with Ehlers–Danlos syndrome described in humans (White et al., 2004).

A diagnosis of HERDA is made based upon a clinical syndrome of regional skin hyperextensibility, clinical signs associated with skin fragility including easily torn skin, and skin histopathology and ultrastructural examination (White et al., 2004). The use of Masson–Trichome staining, although useful in the diagnosis of Ehlers–Danlos syndrome, does not appear to be reliable in the diagnosis of HERDA (White et al., 2004). A mutation in cyclophilin B (*PPIB*) as a novel, causal candidate gene for HERDA has been described, and verified as segregating with carriers and affected horses (Tryon et al., 2007). Screening of control Quarter Horses in the United States indicated a 3.5% carrier frequency (Tryon et al., 2007), whereas the carrier frequency in Quarter Horses in Brazil and France is 5.8% and 1.6%, respectively (Badial et al., 2014; White & Bourdeau, 2011).

HERDA is incurable and because of its hereditary nature, owners should be advised to not use affected horses for breeding. Therapy for affected horses is directed at preventing skin abrasions and pressure sores (e.g., sores from tack).

Severe Combined Immunodeficiency

Severe combined immunodeficiency is a condition that manifests as lymphopenia (both combined B and T lymphocyte deficiency) and lack of lymphocytes in lymph nodes and the spleen, subsequent lack of immunoglobulin synthesis, and thymic hypoplasia (for review of the condition see Crisman, 2008; Perryman, 2004). The condition is inherited as an autosomal recessive trait in purebred and part-bred Arabian foals (Perryman & Torbeck, 1980) with as many as 25% of Arabian horses being carriers (Bernoco & Bailey, 1998; Poppie & McGuire, 1977; Studdert, 1978). The condition has been reported in a Caspian foal that is not related to the mutation described for Arabians, however (Larson et al., 2011). The prevalence is estimated to be 2.3% in foals of Arabian descent. Affected foals may survive a few months provided they have developed passive immunity from ingesting the dam's colostrum. Clinical signs include general malaise, serous to mucupurulent nasal and/or ocular discharge, coughing, diarrhea, and are nonresponsive to antimicrobial therapy. Affected foals may have uveitis secondary to sepsis or other disseminated opportunistic pathogens. Diagnosis is made based on measuring serum immunoglobulin levels and detecting a persistent lymphopenia. Prognosis is grave. The cause of death is usually adenoviral pneumonia, other secondary infections, or both. Considering that the condition is inherited, carrier animals should be identified and removed from the breeding population.

Developmental

Immunoglobulin-M Deficiency

Deficiency of immunoglobulin (Ig) M is common in all breeds of horse, especially Arabians and Quarter Horses (for review see Crisman et al., 2008; Perryman, 2000). It may occur as a primary genetic disorder or as a result of immunosuppression (Crisman, 1988; Perryman et al., 1977). Most commonly, foals will present at 4–8 months of age with respiratory tract infection or enteritis. As opposed to severe combined immunodeficiency, foals with IgM deficiency will have a normal blood lymphocyte count (both B- and T- cells) but will have reduced or absent serum IgM concentrations. Affected foals may have uveitis resulting from this inherited immunodeficiency.

Acquired

Dystocia

Although not a systemic disease, dystocia is related, in part, to the physical stature of the foal. A study examining the prevalence of retinal hemorrhages in Thoroughbred foals found that approximately 16% of foals had either unilateral or bilateral retinal hemorrhages occurring in the tapetal fundus or at the optic disc (Munroe, 2000). Thoroughbred foals

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weighing more than 51 kg are more likely to have retinal hemorrhage than foals weighing less than 51 kg (Munroe, 2000). Further, it has been shown that prolonged second-stage parturition, related to size of the foal, is associated with retinal hemorrhage in Thoroughbred foals. Various factors contributing to increased intracranial and intravenous pressures (presumably the pathophysiological phenomena responsible for congenital retinal hemorrhage) likely include the force of maternal contraction, the length of the second stage of labor, disparity between fetal and maternal size, excessive traction during assisted delivery, and the size of the foals cranium and/or chest (Munroe, 2000). Alternatively, ischemia (a seemingly important factor in neonatal maladjustment syndrome) may play an important role in the pathogenesis of neonatal retinal hemorrhage (Munroe, 2000). In one study, it was found that some foals with neonatal maladjustment syndrome had various ocular abnormalities including uveitis, corneal ulcers, and retinal hemorrhage (Labelle et al., 2011). Nevertheless, foals that acquire retinal hemorrhage caused by dystocia are otherwise clinically healthy and retinal hemorrhages resolve within 10 days (Munroe, 2000).

Hematologic Diseases

Anemia

Anemia is the reduction in red blood cells per volume of whole blood. Anemia is classified as regenerative if there has been a normal bone marrow response to erythropoietin (e.g., usually occurs with blood loss or hemolytic disease), or non-regenerative if the normal reticulocyte response is lacking (e.g., may occur with chronic extra-marrow disease which reduces red blood cell survival time, selective erythropoietin depression, insufficient erythropoietin release, or a combination of these factors) (Rebar et al., 2005). Severe anemia often manifests systemically as varying palor of mucous membranes, cool mucous membranes, tachycardia, polypnea, weakness, as well as signs specific to the underlying primary condition. Conjunctival palor is even used as an indicator of anemia caused by gastrointestinal parasitism in sheep and goats (Kaplan et al., 2004; Vatta et al., 2001).

Icterus (Jaundice)

Icterus or jaundice is a condition characterized by hyperbilirubinemia and deposition of bile pigments in the skin, sclera, and mucous membranes causing them to appear a shade of yellow. The causes of icterus in the horse are numerous and include any condition where hyperbilirubinemia results. The conjunctiva or sclera is the classic location for detection of icterus given its relative lack of pigmentation. The yellow appearance of icterus may be detected in the intraocular structures as well (e.g., blue irides may turn green, and yellow hues may be imparted on the tapetum).

Neonatal Isoerythrolysis (Alloimmune Hemolytic Anemia of Foals, Isoimmune Hemolytic Anemia of Foals)

Neonatal isoerythrolysis is an acquired immune-mediated phenomenon observed in foals (Bailey, 1982; MacLeay, 2001; Traub-Dargatz et al., 1995). This condition is considered the most common cause of icterus in neonatal foals (Boyle et al., 2005). The condition results from the ingestion of colostrum-containing antibodies directed at the antigenically distinct foal's red blood cells (inherited from sire) (Boyle et al., 2005). The dam typically develops these antibodies after exposure to the specific red blood cell antigen during a previous pregnancy or blood transfusion or via transplacental exposure of fetal red blood cell antigen during pregnancy. Affected foals develop clinical signs including general malaise, tachypnea, tachycardia, mucous membrane palor, and icterus (Boyle et al., 2005). Affected foals are typically younger than 1 week of age (Boyle et al., 2005). Ocular signs include conjunctival palor and jaundice, and hemorrhages affecting the conjunctiva and sclera (Lavach, 1992). Hyphema may also result (Lavach, 1992).

Diagnosis of neonatal isoerythrolysis is made based upon consistent clinical signs and hemolytic crossmatch between the dam's serum or colostrum with the foal's red blood cells (Becht et al., 1983). Treatment is aimed at providing supportive care and transfusing compatible blood (Boyle et al., 2005). Prognosis for recovery with appropriate medical care is considered good. The owner should be made aware of the pathogenesis of the condition and instructed to not repeat the same breeding. Also, the dam should not be bred to stallions with the same incriminating red blood cell antigen.

Idiopathic Systemic Diseases

Dysautonomia (Equine Grass Sickness, Mal Seco)

Equine dysautonomia, commonly known as equine grass sickness, has been defined as "fatal dysautonomia of horses associated with severe neuronal damage, especially in affected autonomic ganglia" (Timoney & Wernery, 2003). The cause of equine dysautonomia remains unknown, although a variety of theories exist. Recently favoured hypotheses include: (1) overgrowth of *Clostridium botulinum* type C within the gastrointestinal tract (Hunter et al., 1999; McCarthy et al., 2004); (2) ingestion of some mycotoxin (McGorum et al., 2018); and (3) ingestion of cyanogenic producing plants (McGorum & Kirk, 2001). The highest incidence of equine dysautonomia is in Scotland but has been reported elsewhere in Europe and in South America. In Europe, the disease is most likely to be seen between April and July in young horses kept on pastures (French et al., 2005; Newton et al., 2004).

Clinical signs associated with equine dysautonomia are related to degeneration of autonomic ganglia and the enteric

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nervous system including pharyngeal and esophageal dysfunction, colic, sweating, tachycardia, and dry nasal mucosa (Milne et al., 2005). The most consistent ocular manifestation of equine dysautonomia is ptosis (Hahn & Mayhew, 2000). Ptosis in equine dysautonomia may result from a primary inability to move the upper eyelid effectively or may occur secondary to abnormal globe position within the orbit (Hahn & Mayhew, 2000). Severe degeneration of neurons in the cranial cervical ganglion (resulting in Horner's syndrome) or abnormally functioning cranial nerves III and/or VII, as indicated by chromatolytic neurons in the nuclei of these nerves, may contribute to the ptosis observed in equine dysautonomia (Hahn & Mayhew, 2000).

Presumptive diagnosis of equine dysautonomia is made based on consistent clinical signs, geographic location of the animal, and time of year. Recently, it has been shown that horses with equine dysautonomia and ptosis have a positive response to ocular administration of topical 0.5% phenylephrine compared with horses not afflicted with equine dysautonomia (Hahn & Mayhew, 2000). Specifically, animals with equine dysautonomia treated with 0.5% phenylephrine will have a wider vertical palpebral fissure opening, as determined by evaluating the angle of the eyelashes relative to the head (opening of palpebral fissure in eye treated with phenylephrine subtracted from the opening of palpebral fissure in eye not treated with phenylephrine), compared with those animals without equine dysautonomia (Hahn & Mayhew, 2000). Definitive diagnosis of equine dysautonomia is typically made by postmortem examination of affected ganglia and gastrointestinal system. Therapy is aimed at supportive and intensive nursing care. Prognosis is poor to grave.

Vitamin E Deficient Retinopathy

Vitamin E is a potent antioxidant and plays an important role in neuromuscular function, stabilizing plasma membranes, and preventing outer retinal oxidative damage (for review see Finno et al., 2012, 2017). Vitamin E deficient retinopathy has been identified and described in neurologic/neuromuscular diseases where vitamin E deficiency plays an important role, namely, equine motor neuron disease (EMND) (Fig. 37.3.9) and neuroaxonal dystrophy/equine degenerative myeloencephalopathy (NAD/EDM) (Fig. 37.3.10) (Finno et al., 2017; Riis et al., 1999). Another vitamin E deficiency-related disease in horses is vitamin E deficient myopathy, although retinal lesions have not been described in patients affected by this condition (Bedford et al., 2013; Finno et al., 2012).

Equine motor neuron disease is a disease characterized by spinal and brainstem motor neuron loss and degeneration (Divers et al., 1997). Equine motor neuron disease can be observed in horses of any age or gender, although it is most common in middle-aged to older horses of Thoroughbred or Quarter Horse ancestry (Mohammed et al., 1993, 1994). Clinical signs are typically attributed to muscular weakness (paresis) and lower motor neuron disease. Affected animals will often have a short-strided gait and will have muscular fasciculations that worsen after exercise. These animals will also frequently shift their body weight between limbs when standing in one position and have evidence of varying degrees of generalized muscle atrophy and weight loss. In more severe cases, horses are unable to stand. With regards to ophthalmic signs, horses with equine motor neuron disease may have fundic changes characterized by a honeycomb pattern of yellow/brown pigment within the tapetal fundus similar to that seen in dogs with vitamin E deficiency (Riis et al., 1999; Verhulst et al., 2001). This yellow/brown pigment has been identified as accumulation of ceroid/lipofuscin. In some instances, pupillary light reflexes may be abnormal (Verhulst et al., 2001).

The exact etiopathogenesis of EMND is unknown. Nonetheless, vitamin E deficiency is thought to be important in the pathogenesis of the disease. Horses are at risk for developing EMND if they are fed a diet low in vitamin E and they are not being supplemented with vitamin E. Importantly, however, EMND has been reported in horses with low vitamin E status despite some affected horses having been fed diets sufficient in vitamin E (McGorum et al., 2006). Further,

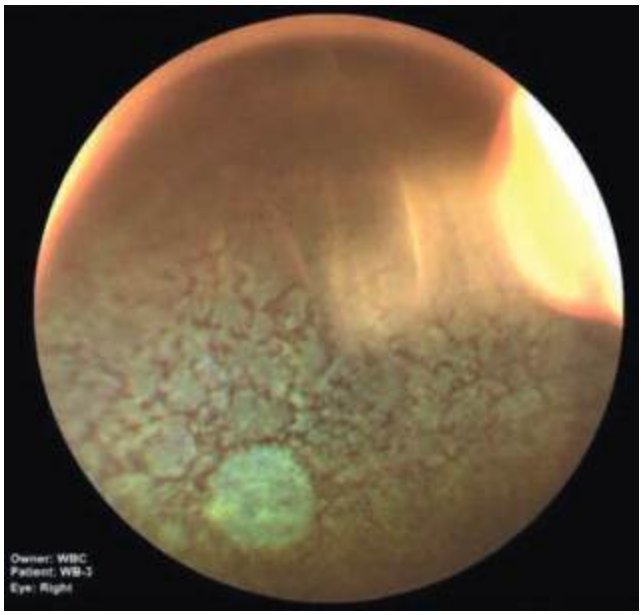


Figure 37.3.9 Tapetal fundus from the right eye of a Warmblood horse diagnosed with clinical equine motor neuron disease. Note the distinct reticulated arrangement of pigment through the tapetal zone. (*Source*: Reprinted with permission from Finno, C.J., Kaese, H.J, Miller, A.D., et al. (2017) Pigment retinopathy in warmblood horses with equine degenerative myeloencephalopathy and equine motor neuron disease. *Veterinary Ophthalmology*, **20**, 204–209.)

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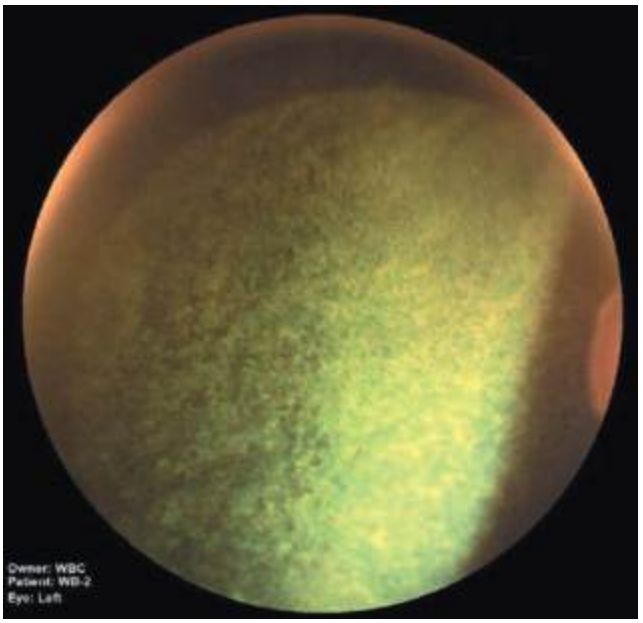


Figure 37.3.10 Tapetal–non-tapetal junction from the left eye of a Warmblood horse diagnosed with postmortem confirmed concurrent equine degenerative myeloencephalopathy and equine motor neuron disease. Note the pigment bars along the entire tapetal–non-tapetal junction with pigment clumping in the tapetal fundus. (*Source*: Reprinted with permission from Finno, C.J., Kaese, H.J., Miller, A.D., et al. (2017) Pigment retinopathy in warmblood horses with equine degenerative myeloencephalopathy and equine motor neuron disease. *Veterinary Ophthalmology*, **20**, 204–209.)

a 16-year-old Standardbred stallion with normal vitamin E concentrations but high tissue concentration of iron was found to be affected by EMND (Syrja, 2006). Additionally, in an experimental study examining EMND in horses fed a diet deficient in vitamin E for 30 months, only 50% of the horses developed clinical signs of EMND despite being vitamin E deficient (Divers et al., 2006). In another study, 15 Andalusian horses between 1 and 3 years of age with EMND, being fed poor quality feed and with vitamin E deficiency, were found to have eosinophilic enteritis and large ciliated protozoa (found in 5/5 horses undergoing postmortem examination) (Diez de Castro et al., 2016). The authors of this study suggested that impaired vitamin E absorption may play a role in EMND in young horses (Diez de Castro et al., 2016). Altogether, individual susceptibilty to EMND appears variable and may be caused by genetic and other factors that affect the absorption and/or metabolization of vitamin E. Diagnosis of equine motor neuron disease is made based on consistent clinical findings, reduced serum vitamin E concentration, and electromyography and muscular peripheral nerve histopathology (Kyles et al., 2001; Palencia et al., 2005; Polack et al., 2000; Rua-Domenech et al., 1997). Vitamin E supplementation can be helpful in slowing or stopping the progress of the clinical signs. Approximately 40% of patients with EMND will respond to treatment, although complete return to performance/working is variable and may be dangerous for the rider/handler (Divers, 2001). Another 40% may have clinical signs stabilize but be permanently disfigured, and 20% will continue to decline despite appropriate therapy (Divers, 2001).

Another disease where vitamin E is considered important, and where vitamin E deficient retinopathy has been documented, is neuroaxonal dystrophy (NAD)/equine degenerative myeloencephalopathy (EDM). Clinically, patients with these conditions are indistiguishable from each other and it is thought that NAD and EDM have similar etiopathogeneses (Finno et al., 2012). NAD and EDM are differentiated from one another based upon distribution of dystrophic neurons/axons, spheroids, and vacuolation, and histopathologic signs of NAD and EDM can be observed in the same horse (Finno et al., 2012). NAD/EDM can occur in any breed or sex, although affected animals are typically 6–12 months of age but can be up to 3 years old (Finno et al., 2012). It is thought that NAD/EDM has a heritable component although a genetic cause has yet to be identified (Finno et al., 2013, 2014). Transcriptome profiling has led to discovering an increased expression of liver X receptor target genes (Finno et al., 2016). Nonetheless, genetically susceptible foals fed a vitamin E deficient diet within the first year of life developed NAD (Finno et al., 2015). Patients with NAD/EDM show signs of symmetric ataxia that is most pronounced in the hindlimbs (Finno et al., 2012). Affected animals have wide-based stance when standing and have proprioceptive loss (Finno et al., 2012). Aside from abnormal neurologic findings, a pigment retinopathy found in other species with vitamin E deficient retinal pigment dystrophy may be found. In one study, 4 of 10 horses with NAD/EDM had mild to moderate pigment dystrophy and 3 of 3 of these horses that had serum vitamin E concentrations measured were deficient in vitamin E (Finno et al., 2017). As opposed to EMND, serum vitamin E concentrations may be normal or below normal in horses with NAD/EDM (Finno et al., 2012). As such, a clinical diagnosis of NAD/EDM is made based upon signalment, clinical signs, and excluding other possible causes of neurologic symptoms. Definitive diagnosis is made based upon typical histopathologic changes within the brainstem and spinal cord (Finno et al., 2012). There is no treatment for NAD/EDM specifically; supplementation with vitamin E does not improve neurologic status (Finno et al., 2012). Affected horses are considered unfit for performance/work (Finno et al., 2012).

Immune-Mediated Diseases

Dermatologic Diseases

The pemphigus group of dermatoses are immune-mediated diseases characterized by vesiculobullous skin lesions. Pemphigus foliaceus is a rare immune-mediated skin disease

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occurring in a variety of species including the horse (for case series and review of the literature see Vandenabeele et al., 2004). Although rare, pemphigus foliaceus is the most common autoimmune skin disease occurring in the horse (Vandenabeele et al., 2004). There are no breed or sex predilections for developing pemphigus foliaceus in horses (Vandenabeele et al., 2004). Lesions are typically observed on the head (including palpebrae), limbs, and ventrum and they are characterized initially by vesicles, erosions, epidermal collarettes, scaling, and crusting (Fig. 37.3.11). Pruritus and pain are variable (Vandenabeele et al., 2004). Affected animals may show signs of general malaise, weight loss, poor appetite, and pyrexia.

Diagnosis of pemphigus foliaceus is made based upon characteristic clinical and dermatohistopathological findings. Direct immunofluorescence testing reveals diffuse intercellular deposition of immunoglobulin and, occasionally, complement within the epidermis (George & White,1984; Scott, 1987). Therapy requires immunosuppression, usually with high doses of oral glucocorticoids possibly combined with chrysotherapy (therapy with gold compounds) or azathioprine (Vandenabeele et al., 2004). Chrysotherapy has been successful in horses with pemphigus (Power et al., 1982; Vandenabeele et al., 2004), but use of high-dose glucocorticoids in such horses carries the risk of inducing laminitis (George & White, 1984; Vandenabeele et al., 2004).

Another member of the pemphigoid dermatoses is bullous pemphigoid, a disease rarely reported in the horse (George & White, 1984; Manning, 1981). As the name implies, the disease is a vesiculobullous, ulcerative disorder caused by separation at the dermoepidermal junction, and it may affect mucocutaneous junctions, the oral cavity, and skin (Olivry et al., 2000). The presence of pain and pruritus is variable; however, animals afflicted with bullous pemphigoid may have general malaise, be febrile and/or anorexic. Diagnosis is made based upon consistent clinical signs and characteristic dermatohistopathologic findings. Therapy is the same as that for pemphigus foliaceus, although response to therapy has not been successful.

Other immune-mediated diseases, such as systemic lupus erythematosus, discoid lupus erythematosus, erythema multiforme, and cutaneous vasculitis, occur infrequently in the horse, but these diseases may also affect the face and eyelids (Scott, 1988). Cutaneous vasculitis, in addition to skin lesions, may be manifested by hemorrhages in mucous membranes, including the conjunctiva.

Urticaria, or hives, refers to the sudden onset of transient focal erythema, edema, and pruritus (Rufenacht et al., 2005). Urticaria may develop caused by type I (most common), II, or III hypersensitivity reactions or may be complement-mediated (Byars, 1984; Rufenacht et al., 2005). Consequently, urticaria may be associated with anaphylaxis. Eyelid edema and chemosis frequently accompany generalized wheal (focal swellings of skin and mucous membranes) formation. Factors contributing to urticaria are numerous, but a variety of allergens and/or drug-related causes including penicillin, phenylbutazone, aspirin, and tetracyclines have been implicated. Diagnosis of urticaria is made based upon consistent clinical signs (Fig. 37.3.12), intradermal skin testing, elimination trials, and consistent dermatohistopathological findings (Jose-Cunilleras et al., 2001; Rufenacht et al., 2005). Treatment consists of eliminating the offending drug or environmental condition, if possible. Corticosteroids to control the acute condition are helpful as are antihistamines (Rees, 2001; Rufenacht et al., 2005).



Figure 37.3.11 Five-year-old crossbred mare with generalized crusting caused by pemphigus foliaceus. (*Source*: Reprinted with permission from Vandenabeele, S.I., White, S.D., Affolter, V.K., et al. (2004) Pemphigus foliaceus in the horse: a retrospective study of 20 cases. *Veterinary Dermatology*, **15**, 381–388.)



Figure 37.3.12 Right hind quarters of a horse with clinical signs consistent with urticaria. (*Source*: Courtesy of R. Holyoak.)

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Infectious Diseases

Bacterial

Borreliosis (Lyme Disease)

Lyme disease is a tick-borne disease caused by *Borrelia burgdorferi* sensu lato, a spirochete bacteria (Littman et al., 2005). Borreliosis is transmitted to vertebrates by *Ixodes* spp. ticks in North America (Divers et al., 2018). Typically, ticks must remain attached for more than 24 hours in order to transmit the spirochaete (Piesman et al., 1987). Horses in endemic areas show serologic evidence of exposure to *B. burgdorferi*, but most are clinically unaffected (Bernard et al., 1990; Divers et al., 2018; Magnarelli & Anderson, 1989; Marcus et al., 1985). Clinical signs reported in association with equine Lyme disease include arthritis and lameness, encephalitis, limb edema, dermatitis, abortion, and foal mortality (Madigan, 1993b; Parker & White, 1992). Neuroborreliosis, uveitis, and cutaneous pseudolymphoma are the best documented clinical manifestations (Divers et al., 2018). *B. burgdorferi* spirochetes have been found using silver stain and immunofluorescent antibody within the eye of a pony with arthritis and panuveitis (Burgess et al., 1986). Bilateral uveitis has also been described in two adult horses (Priest et al., 2012). Spirochaetal organisms were identified in smears of vitreous from the eyes (one horse antemortem, one horse postmortem) (Priest et al., 2012). Polymerase chain reaction (PCR) for *B. burgdorferi* using aqueous and vitreous was negative in one horse, and was negative in one eye and positive in the other eye of another horse (Priest et al., 2012). Antibodies to *B. burgdorferi* were, however, detected in ocular fluids from both horses. Histopathology of multiple tissues, including the eyes of both of these patients failed to identify bacteria with either modified Steiner silver staining or immunohistochemical staining (Priest et al., 2012). As such, a combination of cytologic assessment, antibody, and/or PCR testing of ocular fluids has been recommended in patients where the clinical suspicion for Lyme uveitis is high (Priest et al., 2012). Given the difficulty in achieving a diagnosis of Lyme uveitis, the prevalence of Lyme uveitis is likely underreported.

Diagnosis of Lyme disease is made based upon consistent clinical signs, positive serologic tests (e.g., immunofluorescent antibody, ELISA, or Western blot), and positive response to therapy (Divers et al., 2018; Madigan, 1993b; Parker & White, 1992). Detection of *B. burgdorferi* DNA using PCR for *B. burgdorferi* on skin, synovia, and connective tissue samples may be useful in diagnosing borreliosis (Littman, 2003; Salinas-Melendez et al., 1995).

A consensus statement pertaining to Lyme disease in horses recommends that oral and parenterally administered tetracycline antibiotics and a select number of parenterally administered β-lactam antibiotics be used for the treatment of horses with confirmed Lyme disease (Divers et al., 2018).

Treatment of borreliosis-related uveitis is nonspecific, but might include systemic nonsteroidal anti-inflammatory drugs, topical corticosteroids and/or nonsteroidal anti-inflammatory drugs, and atropine. Of course, treatment with systemic antibiotics, as recommended above, is likely important.

Botulism (Forage Poisoning)

Botulism results from the neurotoxin, botulinum, produced by *Clostridium botulinum*. *C. botulinum* is a Gram-positive, spore-forming, saprophytic, anaerobic, rod-shaped bacterium. There are eight distinct subtypes (A, B, Ca, Cb, D, E, F, G) of *C. botulinum* and they are differentiated from each other based upon the type of neurotoxin they produce (Wilkins & Palmer, 2003a). Aside from causing botulism, there is growing evidence incriminating *C. botulinum* as an important etiology of equine dysautonomia (see "Dysautonomia (Equine Grass Sickness)"). Horses are most commonly affected by types B and C (Haagsma et al., 1990; Kelly et al., 1984; Kinde et al., 1991; MacKay & Berkhoff, 1982; Mitten et al., 1994; Ricketts et al., 1984; Swerczek, 1980; Wichtel & Whitlock, 1991; Wilkins & Palmer, 2003a). The mechanism of action of the neurotoxin is via blocking presynaptic acetylcholine release (Kao et al., 1976). The toxin or organism may be ingested in contaminated forage or commercial feed or may gain entry through wounds (Haagsma et al., 1990; Kelly et al., 1984; Kinde et al., 1991; MacKay & Berkhoff, 1982; Mitten et al., 1994; Ricketts et al., 1984; Swerczek, 1980; Wichtel & Whitlock, 1991; Wilkins & Palmer, 2003a). Clinical signs develop within 1 to 7 days and are variable depending on the stage and/or severity of the disease. Nevertheless, clinical signs in adult horses include weakness, dysphagia, drooling and inability to retract the tongue, ptosis, mydriasis (with slow pupillary light reflexes), dyspnea, and generalized paresis/paralysis resulting in recumbency (Johnson et al., 2015; Ricketts et al., 1984). In foals affected by botulism (shaker foals), foals are initially alert but progression occurs from a stiff gait with muscle trembling to complete recumbency. Foals may have sluggish pupillary light reflexes, ptosis, and other lower motor neuron signs (MacKay & Berkhoff, 1982; Swerczek, 1980; Wilkins & Palmer, 2003a). In adult horses with botulism, 17 of 90 horses developed corneal ulceration likely secondary to facial paralysis and recumbency (Johnson et al., 2015).

The diagnosis of botulism may be difficult to establish. Identification of the toxin in serum, gastrointestinal contents, or food is definitive. The mouse bioassay has been shown to be useful in that positive results are highly suggestive of the disease, whereas negative results do not exclude the diagnosis of botulism (i.e., positive predictive value = 100% for foals, 89% for adults; negative predictive value = 51% for foals, 67% for adults) (Johnson et al., 2016). Culture of *C. botulinum* from feedstuffs is usually difficult. Testing feces or gastrointestinal contents with a quantitative real-

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time PCR assay for the neurotoxin gene of *C. botulinum* type B has shown to have a 95% and 96% sensitivity and specificity, respectively (Johnson et al., 2012).

Therapy involves supportive nursing care, administration of antitoxin, and appropriate antimicrobials including metronidazole. Antimicrobials associated with neuromuscular dysfunction (e.g., aminoglycosides) should be avoided. Some horses will recover from botulism, and although mortality in foals has been thought to be traditionally high, a study has shown that more than 96% of foals younger than 6 months of age will survive with appropriate intensive care (Wilkins & Palmer, 2003a). In another study of adult horses hospitalized with botulism, a survival rate of 48% was described (Johnson et al., 2015).

Leptospirosis

Leptospirosis is caused by systemic infection by spirochetal bacteria of the genus *Leptospira* (Levett, 2001). More than 200 serovars have been identified (Levett, 2001). Of these serovars, those most commonly isolated in horses include *Leptospira autumnalis*, *L. bratislava*, *L. icterohaemorrhagiae*, and *L. pomona* (for review see Bernard, 1993). The bacterium is commonly excreted in the urine of infected animals, but any bodily secretion may contain the bacteria during the acute stage of the disease (Bernard, 1993). The organism may survive in warm and moist conditions for several weeks. Horses typically become infected by ingesting water or feed previously contaminated by a carrier host's urine (e.g., wildlife, cattle). The organism may enter the vascular system via conjunctival, nasopharyngeal, oral, esophageal, small intestinal, and genital mucous membranes (Hanson, 1982; Thiermann, 1984). Exposure of open wounds to the bacterium may also be an important route of infection in some instances. Horses with leptospirosis may have clinical signs attributed to acute renal failure, abortion, and hepatitis in foals (Divers et al., 1992; Frazer, 1999; Hathaway et al., 1981; Hodgin et al., 1989; Twigg et al., 1971; van den Ingh et al., 1989). Leptospirosis is also highly incriminated in equine recurrent uveitis (ERU) (for review see Chapter 29). Specifically, anterior uveitis and peripapillary chorioretinitis may be seen in association with leptospirosis (Williams et al., 1971), and corneal opacities as well as binding of leptospiral antibodies to the cornea have also been reported among experimentally infected horses (Parma et al., 1985, 1987). For a general review of leptospirosis in horses see Divers et al. (2019).

L. interrogans serovar *pomona* has been the strain most frequently associated with uveitis in the horse, although the serovars *icterohaemorrhagiae*, *grippotyphosa*, *canicola*, and *hardjo* have also been reported (Davidson et al., 1987; Sillerud et al., 1987). In both experimental and naturally occurring infections, ocular lesions develop 12–24 months after the primary infection (Roberts, 1958; Roberts et al., 1952; Williams et al., 1971).

Diagnosis of leptospirosis is made by identifying the organism in the urine using dark-field microscopy, demonstrating the presence of circulating anti-*Leptospira* antibodies using the microscopic agglutination test or ELISA, and culturing the organism from urine or blood. The finding of specific leptospiral antibody titers in the aqueous humor that are higher than those in the serum or detecting DNA of leptospiral organisms in the aqueous humor, however, support a diagnosis of leptospirosis as a cause of ERU (Davidson et al., 1987; Faber et al., 2000; Halliwell et al., 1985). In one study, however, only 1 horse of 52 with ERU and 1 horse of 17 with non-ERU inflammation had definitive intraocular production of antibodies against *Leptospira* organisms (Gilger et al., 2008). Most recently, *Leptospira* spp. were reported to be the trigger of ERU, a most likely autoimmune disease, in the majority of European cases (Spiess, 2010).

Therapy for equine leptospirosis includes appropriate antimicrobial therapy using penicillins or tetracyclines. Fencing off streams, ponds, and marshes as well as controlling access of wildlife to farm structures are means by which the spread of disease can be controlled and contained (Hanson, 1982). A variety of therapies and prevention strategies have been attempted and studied for leptospirosis-related ERU (Gilger, 2010; Lowe, 2010; Spiess, 2010) (see Chapter 29 for review).

Rhodococcus equi

Rhodococcus equi is a soil-dwelling, Gram-positive, catalase-positive, aerobic, coccoid bacteria. This bacterium is well known, worldwide, to cause pneumonia in foals (for review see Prescott, 1991). Adult horses are typically spared from *R. equi* infection. Immunocompromised foals (e.g., foals having failure of passive transfer and severe combined immunodeficiency), however, are susceptible to infection with *R. equi* infection. Foals will typically present with pyrexia, nasal discharge, and other signs of respiratory tract infection. In addition to respiratory illness, foals may have clinical signs related to gastrointestinal, orthopedic, or ocular disease. The bacteria has been cultured from the eye of a foal and the resultant uveitis resulted in blindness (Blogg et al., 1983). Foals with *R. equi* infection may develop uveitis, panophthalmitis, or keratouveitis (Giguere & Prescott, 1997; Huber et al., 2018; Reuss et al., 2009, Tarancon et al., 2019). However, a study reported the prevalence of ocular signs in foals with *R. equi* infection was low with 16 of 150 (11%) of foals with *R. equi* pneumonia reported to have uveitis (Reuss et al., 2009). Although, in another study of foals that had complete ophthalmic examinations and had *R. equi*, 12/39 (30.8%) had bilateral uveitis (Tarancon et al., 2019). Experimentally, 14/25 foals infected intratracheally with *R. equi* developed uveitis and the organism could be cultured from 11/14 foals' aqueous humor samples (Huber et al., 2018).

Diagnosis of *R. equi* infection is made based upon positive culture or PCR of the organism from fluid obtained from

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transtracheal wash or bronchoalveolar lavage, although as previously mentioned, the organism may be cultured antemortem via aqueous centesis. Treatment of *R. equi* infection typically involves supportive nursing care, supplemental oxygen, and antimicrobial therapy using erythromycin, clarithromycin, or azithromycin combined with rifampin (Davis et al., 2002; Giguere et al., 2004; Jacks et al., 2001, 2003). A retrospective study found that clarithromycin–rifampin therapy was superior to erythromycin–rifampin or azithromycin–rifampin for the treatment of *R. equi*-associated pneumonia in foals (Giguere et al., 2004). Importantly, however, resistance to macrolides and rifampin is being increasingly identified (Giguere et al., 2017). Given that many foals that have subclinical and small pulmonary lesions spontaneously recover without therapy, and that therapy does not hasten clinical recovery, one should use antimicrobials in these patients judiciously (Giguere, 2017). Ocular therapy, when indicated, should include frequent topical administration of corticosteroids (e.g., prednisolone acetate or dexamethasone) and judicious use of atropine. Prognosis for foals with *R. equi* infection is variable depending upon the severity of the disease and the duration of illness prior to commencing therapy.

Salmonellosis (Paratyphoid)

Salmonellosis is caused by Gram-negative motile rod-shaped bacteria of the genus *Salmonella*. Salmonellosis frequently occurs in the horse, and it is a commonly diagnosed infectious cause of diarrhea among adult horses. *Salmonella* spp. are frequently present in the environment, and disease occurs mainly among stressed animals or in those with altered host defenses (Spier, 1993). Diarrhea results from malabsorption secondary to gut epithelial cell destruction and host inflammatory response to bacterial endotoxin.

Ocular manifestations of salmonellosis may include iridocyclitis and hypopyon, and such manifestations are most likely to be seen in bacteremic animals. The organism has been cultured from the anterior chamber of affected horses (Whitley & Gelatt, 1981). The diagnosis of salmonellosis is established on the basis of positive cultures from fecal samples, blood, or tissues (Hyatt & Weese, 2004). The reader is referred to a recent internal medicine textbook for discussion of treatment, control, and prevention strategies used for salmonellosis. Nevertheless, treatment of salmonellosis-related uveitis should be aimed at controlling intraocular inflammation, preventing synechiae formation, and reducing ocular pain by administering topical corticosteroids and atropine.

Sepsis

Sepsis is defined as the presence of pathogenic microorganisms or their toxins in the blood or other tissues (Blood & Studdert, 1990). With respect to bacterial sepsis, specifically bacteremia, a variety of bacteria cause clinical disease in foals and adult horses, and include *Rhodococcus equi*, *Streptococcus equi* subspp., *Leptospira* spp., *Mycobacteria avium*, *Salmonella* spp., and *Clostridium* spp. to name a few (for special mention, see specific bacteria mentioned in this chapter). Particular etiologies of bacteremia are, in part, dependent on the age and concurrent disease status of the animal. Clinically, animals with bacteremia will present with a variety of clinical signs depending on the organ system(s) affected. With respect to ocular conditions, a variety of manifestations of bacteremia may occur either during the active stages of bacteremia or after the bacteremia has been treated or subsided (e.g., leptospiral-associated ERU). Often, ocular signs will accompany clinical signs resulting from the involvement of other organs. Uveitis, keratitis, chorioretinitis, optic neuritis, or endophthalmitis may manifest secondarily to systemic bacterial disease or disease disseminating from a primary infectious nidus. Foals with uveitis are more likely to have sepsis than those that are not septic (Labelle et al., 2011). It has also been documented that foals with sepsis and uveitis are less likely to survive compared with foals with sepsis without uveitis (Labelle et al., 2011). Ocular signs may present unilaterally or bilaterally. For example, unilateral uveitis, optic neuritis, and concomitant meningoencephalitis have been reported as secondary complications of bacterial endocarditis in adult horses (Hatfield et al., 1987; Kaplan & Moore, 1996).

Definitive diagnosis of bacteremia is made by identifying the causative organism in the blood and/or multiple organs (e.g., transtracheal wash samples from the lungs, joint fluid samples, aqueous and/or vitreous from clinically affected eyes) using current bacterial culture methods. Antimicrobial susceptibility should be performed on isolated organisms and appropriate systemic therapy implemented. Topical use of anti-inflammatory drugs and atropine should be instituted for general management of uveitis. Further symptomatic management and appropriate nursing and supportive care should be implemented. Prognosis is variable depending on the cause of the bacteremia and whether management of concurrent clinical disease is possible (e.g., Arabian foals with severe combined immunodeficiency versus adult case of equine strangles).

Streptococcus equi ***(Strangles, Distemper)***

Streptococcus equi var. *equi* is a Gram-positive coccoid bacterium. *S. equi* var. *equi* infection is a reportable disease in many countries (Boyle et al., 2018). Infection occurs via direct contact from infected horses' nasal secretions or from coming in contact with fomites including feed and water troughs, housing, etc. *S. equi var equi* colonizes within the pharyngeal and nasal mucosae and then drains into regional lymph nodes and in some instances can result in bacteremia (for review see Boyle et al., 2018; Timoney, 1993, 2004; Sweeney et al., 2005;). *S. equi* var. *equi* infection is relatively

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common and is often observed as an outbreak on a farm or in a stable. Clinical signs of *S. equi* var. *equi* infection include pyrexia, general malaise, anorexia, serous (initial) and purulent (later) nasal discharge, pharyngitis manifesting as an inability to swallow, and pharyngeal, submaxillary, and parotid lymphadenitis that may become abscessed. In some instances, clinical signs related to multiple organ involvement (bastard strangles) may occur. Ocular abnormalities associated with strangles include initially serous and later mucopurulent ocular discharge (Knight et al., 1975; Yelle, 1987), panophthalmitis (Barratt-Boyes et al., 1991), and chorioretinitis (Roberts, 1971). In some cases, blindness may occur because of the development of brain abscessation (Audigie et al., 2004; De Lahunta & Cummings, 1967; Spoormakers et al., 2003).

Diagnosis of *S. equi* var. *equi* infection is made based on characteristic clinical signs and positive culture of *S. equi* from abscesses. Therapy for *S. equi* var. *equi* infection is controversial and the reader is referred to recent internal medicine textbooks and a recent concensus statement made by the American College of Veterinary Internal Medicine (Boyle et al., 2018).

Tetanus

Tetanus is caused by the neurotoxin produced by the bacterium, *Clostridium tetani*. *C. tetani* is a motile, Gram-positive, nonencapsulated, anaerobic, rod-shaped, spore-forming bacterium. The organism is prevalent in soil worldwide, and spores typically enter the body through an open wound. Incubation times vary from 10 days to 1 month. Spores become vegetative and a toxin, tetanospasmin, retrogradely migrates along axons of motor nerves to the central nervous system (CNS). However, it should be noted that tetanospamin, the principle neurotoxin, is only one of three toxins produced by the bacterium (Acke et al., 2004). The toxin then prevents inhibitory neurotransmission to motor neurons thereby resulting in the classical signs associated with tetanus.

Clinical signs include initial stiffness progressing to generalized spasticity. Infected horses generally have a sawhorse stance, retraction of the ears and lips, elevation of the tail, and rapid retraction of the globe, thereby resulting in prolapse of the third eyelids. In one study of 20 horses, hyperesthesia and third eyelid prolapse were the most common signs (Green et al., 1994). Death can occur from respiratory and cardiac failure.

Therapy for tetanus consists of providing muscle relaxation, providing an appropriate substrate footing and bedding, eliminating infection by treatment with penicillin, neutralizing unbound toxin by administering tetanus antitoxin, maintaining hydration and nutritional status, and immunization with tetanus toxoid to stimulate an immune response. Prognosis is poor to grave. Prevention is attained by vaccinating animals with tetanus toxoid.

Mycotic

Aspergillosis

Aspergillosis is caused by the filamentous fungus *Aspergillus* spp. *Aspergillus* spp. are considered ubiquitous in the environment, and animals are infected opportunistically after inhaling *Aspergillus* spores (Gelatt et al., 1991). Infection with *Aspergillus* spp. is either localized or disseminated. Localized aspergillosis involves colonization of the respiratory sinuses, guttural pouch, and nasal mucosa. Secondary CNS involvement may result from erosion of the cribriform plate. Disseminated aspergillosis occurs typically in the immunocompromised patient and involves a whole host of organ systems, although history of respiratory involvement is not typically documented (Lehmann, 1985; Shoham & Levitz, 2005).

Clinical manifestations of *Aspergillus* infection include mycotic rhinitis (Korenek et al., 1994), mycotic pneumonia (Blue et al., 1987; Hattel et al., 1991; Slocombe & Slauson, 1988; Sweeney & Habecker, 1999), otitis media (Newton & Knottenbelt, 1999), and guttural pouch mycosis (Johnson et al., 1973; Hatziolos et al., 1975; Lepage et al., 2004; Ludwig et al., 2005; Rawlinson & Jones, 1978). *Aspergillus* spp. are also isolated from the cases of equine keratomycosis (Brooks et al., 1998; Gaarder et al., 1998; Grahn et al., 1993; Kern et al., 1983; Peiffer, 1979). Horner's syndrome and optic neuritis may result secondarily from guttural pouch mycosis (Cook, 1968; Hardy et al., 1990; Hatziolos et al., 1975).

Cryptococcosis

Cryptococcosis is caused by *Cryptococcus neoformans* or *C. gattii* (previously *C. neoformans* var. *gattii*) (Duncan et al., 2011; Kinne et al., 2017; McGill et al., 2009; Riley et al., 1992; Secombe et al., 2017; Wolf, 1989). *C. neoformans* is associated with high nitrogen-containing environments such as avian feces or soil enriched with avian feces (O'Brien et al., 2004). Hence, birds such as pigeons are considered to be significant vectors of *Cryptococcus* spp. *C. gattii*, however, is associated with eucalyptus and fir trees in Australia and Canada, respectively (O'Brien et al., 2004). Importantly, however, *C. gattii* has since been identified worldwide (Cogliati, 2013; Duncan et al., 2011; Herkert et al., 2017; Kinne et al., 2017; Lester et al., 2011; Lockhart et al., 2016; McGill et al., 2009; Secombe et al., 2017). Cytologically, *Cryptococcus* spp. are approximately 4–15 μm and typically contain a thick capsule (Pennisi et al., 2013).

Cryptococcus neoformans is less commonly reported in the horse compared with the dog or the cat. *C. gattii* is a more common cause of equine cryptococcal pneumonia in Australia compared with *C. neoformans* (Secombe et al., 2017). Clinically, *C. neoformans* has been reported to cause abdominal abscessation, abortion, infection of the upper and lower respiratory tract, and meningitis (Barclay & De Lahunta,1979; Begg et al., 2004; Blanchard & Filkins, 1992; Boulton & Williamson, 1984; Cho et al., 1986; Dickson & Meyer, 1970;

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Freeman et al., 1990; Pearson et al., 1983; Riley et al., 1992; Ryan & Wyand, 1981; Petrites-Murphy et al., 1996; Scott et al., 1974; Steckel et al., 1982). The incidence of cryptococcosis appears to be somewhat higher in western Australia than that in other regions of the world (Dickson & Meyer, 1970; Riley et al., 1992). Ocular lesions have not been reported in most cases of equine cryptococcosis. Nonetheless, *Cryptococcus* has been reported as causing chorioretinal lesions and frontal sinusitis with a mass within the retrobulbar space of a horse causing exophthalmos and periorbital distention (Scott et al., 1974). In addition, *Cryptococcus* has been described in a horse with with meningitis and optic neuritis (Hart et al., 2008).

Diagnosis of equine cryptococcosis is based upon identifying the organism histologically, cytopathologically, or via culture of infected tissue. Determining the presence of cryptococcal antigen via agglutination on serum and/or cerebrospinal fluid can also be diagnostic (Secombe et al., 2017). Prognosis is considered guarded in cases of equine cryptococcosis (Riley et al., 1992), although some animals may survive with appropriate medical therapy including treatment with an appropriate antifungal drug such as amphotericin-B or fluconazole (Begg et al., 2004; Hart et al., 2008; Secombe et al., 2017).

Dermatophytosis (Ringworm)

Dermatophytosis is a mycotic skin infection, and in the horse it may be caused by *Microsporum equinum, M. canis*, *M. gallinae*, *M. gypseum*, *Trichophyton equinum*, *Arthroderma vanbreuseghemii*, *T. verrucosum*, *T. soudanense*, *T. bullosum*, and *T. quinkeanum* (Carter, 1966; Carter et al., 1970; Chollet et al., 2015; Connole, 1973; Georg et al., 1957; Kane et al., 1982; Kaplan et al., 1957; Lyskova et al., 2015; Maurice et al., 2016). A higher incidence of dermatophytosis can be found in hot, humid climates. Lesions are characterized by alopecia, with or without crusts, and often with a brownish color, and they may affect any part of the body, including the head and eyelids. Pruritus and pain vary from none to intense.

Diagnosis of dermatophytosis is made based upon positively culturing the fungus. Histopathologic examination of skin biopsy specimens may also identify dermatophytes. Dermatophytosis in the horse is generally self-limiting, and may not require treatment. Topical therapy with 2% lime sulfur, 3% captan, or 0.5% sodium hypochlorite, however, may hasten resolution of skin lesions.

Histoplasmosis (Epizootic Lymphangitis)

Histoplasmosis is caused by the fungal organism *Histoplasma capsulatum*. Histoplasmosis is not uncommonly reported in the horse. Pulmonary infections, placentitis with abortion, and disseminated disease have been reported (al Ani, 1999; Ameni & Siyoum, 2002; Cornick, 1990; Johnston et al., 1995; Rezabek et al., 1993;s).

Epizootic lymphangitis is a chronic and contagious disease caused by *H. farciminosum* (for review see al Ani, 1999). This disease is endemic in West, North, and East Africa as well as the Middle East, India, and the Far East. Epizootic lymphangitis is transmitted between horses via insects (biting flies) feeding on open wounds or some other transmission of infected secretions into traumatized skin or conjunctiva. Soil does not appear to be a source of the organism, and infection does not occur in normal, undamaged tissue. Outbreaks have occurred in which large numbers of horses were housed together. In most areas of the world, this is a reportable disease.

Clinical signs include skin nodules that eventually erupt into draining lesions located along the subcutaneous lymphatics. Ocular lesions begin as serous and then purulent ocular discharge, with blepharitis. Later, papules on the conjunctival surfaces develop and ulcerate, thus leading to a thick, purulent ocular discharge. Diffuse swelling of the eyelids occurs, and lesions may erupt on the epidermal palpebral surface. Horses may not be able to open their eyes, and the nasolacrimal duct may become occluded (Singh, 1956). Palpebral granulomas have been seen (Singh, 1963), and keratitis may occur secondary to the conjunctival disease (Al-Ani & Al-Delaimi, 1986).

Diagnosis of epizootic lymphangitis is made based upon identifying the organism cytologically or via culture (Selim et al., 1985). Fluorescent antibody and ELISA tests have been described (Gabal et al., 1983, 1985). Frequently, no treatment is allowed and affected horses are euthanized. Mildly affected horses may recover, however, and are reportedly immune to reinfection. Antifungal agents such as amphotericin-B are considered useful for treating epizootic lymphangitis (al Ani, 1999). Prognosis for horses with epizootic lymphangitis is variable but may cause mortality. Vaccination of horses living in endemic areas is recommended (al Ani, 1999).

Parasitic: Lice and Mites

Demodicosis

Demodex equi and *D. caballi* have both been reported as causing dermatologic disease in horses, although not with the frequency of demodicosis in some other species (Bennison, 1943; Besch & Griffiths, 1956). *Demodex* spp. live as commensals in the skin of most mammals, including horses. Most species of *Demodex*, including *D. equi* and *D. caballi,* spend their entire life cycle in the hair follicles and sebaceous glands of their host, whereas a few species are found within the epidermis. *Demodex* mites, present in small numbers, are part of the normal skin fauna (for review see Mueller, 2004; Nutting, 1976). Consequently, pathologic sequela of these mites probably relates in some way to immunocompromise. Lesions are characterized by alopecia and scaling, and the development of small nodules and pustules, especially over the face, neck, shoulders, and forelimbs. *D. caballi* tends to inhabit the eyelids and the muzzle, whereas *D. equi* affects the entire body. The diagnosis is established on the basis of identifying the mite in deep skin scrapings obtained after firmly squeezing the affected areas.

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Therapy for equine demodicosis includes the administration of systemic ivermectin.

Pediculosis

Pediculosis, or louse infestation, occurs in horses particularly during the winter months, when the hair coat is long and crowded barn conditions may favor spread of the condition. Important species contributing to disease in horses include *Haematopinus asini* (sucking louse) and *Werneckiella equi* (previously *Damalinia equi*) (biting louse) (Larsen et al., 2005). The primary clinical sign seen in cases of pediculosis includes an intense pruritus accompanied by an excoriated and dull or scaly coat, including the hair on the face and periocular regions. Diagnosis of pediculosis is made based upon consistent clinical signs and demonstrating louse eggs that are attached to the hair coat (Larsen et al., 2005; Mencke et al., 2004, 2005). Treatment should be two applications of water-based insecticides at 2-week intervals (Fadok, 1984) or, for *W. equi* infestations, spot-on formulation of imidacloprid has been shown to be highly efficacious (Mencke et al., 2004, 2005).

Sarcoptic Mange

Sarcoptic mange, which is a highly contagious disease caused by *Sarcoptes scabei*, is uncommon in the horse, but it does occur (Scott, 1988). Scabies lesions are characterized by crusty alopecic areas, which are sometimes excoriated, and intense pruritus. In the horse, lesions generally begin on the head, including the eyelids, and then spread caudally. The diagnosis is established on the basis of identifying the mite in skin scrapings. Affected horses may be treated with spray or dip applications of 0.5% malathion, 0.03% lindane, 0.06% coumaphos, 0.5% methoxychlor, or 2% lime sulfur. At least two treatments at 14-day intervals should be administered, with care being taken not to allow these agents to contact the eye. Use of systemic ivermectin may also be effective.

Trombiculiasis (Chiggers)

Trombiculiasis refers to an infestation with the larvae of mites of the family *Trombiculidae* (chiggers). Chiggers (harvest mites) are most commonly found on horses housed on open pasture or that have been ridden in the woods. Mites are commonly found on the face and cause papules that become crusted. Pruritus is variable. Diagnosis is made based upon consistent history and clinical findings. Early in the course of the disease, chiggers are found as small, orange dots in the center of the papules. The disease is self-limiting, although one application of 2%–5% lime sulfur may be helpful (Fadok, 1984).

Parasitic: Nematodes

Dirofilariasis

Dirofilariasis is rarely reported in the horse. With respect to the eye, there is one report of successful surgical removal of a nematode from the anterior chamber of a horse; the parasite was identified as an adult *Dirofilaria immitis* (Fig. 37.3.13) (Moore et al., 1983).

Habronemiasis (Habronemiosis, Summer Sores)

Habronemiasis is a parasitic disease caused by the aberrant migration by larvae of the nematodes *Habronema muscae*, *H. majus*, and *Draschia megastoma* (Moore et al., 1983; Pusterla et al., 2003). Habronemiasis can be found in tropical and temperate climates worldwide. These nematodes normally are found within the stomach of horses. Flies, including *Musca domestica* (house fly) and *Stomoxys calcitrans* (stable fly), are used as the intermediate host (Pusterla et al., 2003). Larvae are passed in the feces and are consumed by maggots of the intermediate host. When the adult fly emerges, the third-stage larvae (L3) within the fly are infective, and horses become infected by ingesting the fly or the L3 larvae that have been deposited near the mouth of the horse. *Habronema* or *Draschia* larvae may be deposited on wounds or near the eye, and larval migration through these tissues results in a granulomatous inflammatory response. Habronemiasis is commonly seen in young and middle-aged adult horses, although any age may be affected (Pusterla et al., 2003). There is no gender predilection for developing habronemiasis (Pusterla et al., 2003). Pale-colored horses (e.g., gray, palomino) appear more likely to be affected and this may be caused by flies being attracted to lighter rather than dark colors (Pusterla et al., 2003). Lesions are typically concurrent with the fly season and may regress with cold weather only to resume when the weather becomes warm again (Pusterla et al., 2003). Lesions may affect the conjunctiva or the periocular area, and the papules have a raised, irregular, yellow (i.e., "sulphur granules") appearance (Fig. 37.3.14) (Gasthuys et al., 2004; Glaze, 1983; Pusterla

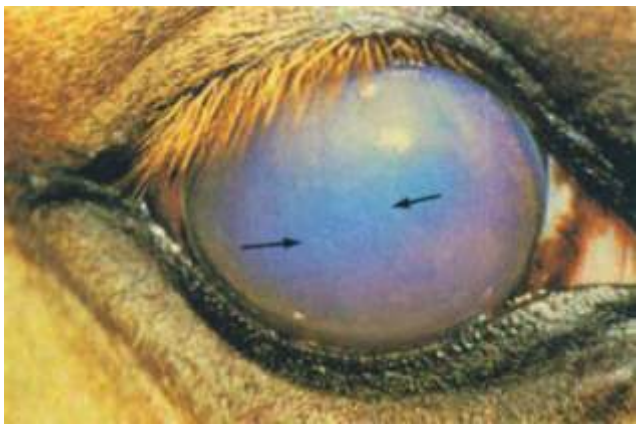


Figure 37.3.13 Adult *Dirofilaria immitus* (arrowed) in the anterior chamber of the right eye of a six-year-old American Quarter Horse. Note the marked anterior uveitis as evidenced by extensive corneal edema and intense miosis. (*Source*: Reprinted with permission from Moore, C.P., Sarazan, R.D., Whitley, R.D., et al. (1983) Equine ocular parasites: a review. *Equine Veterinary Journal* (Suppl. 2), 76–85.)

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Figure 37.3.14 Ulcerative granuloma of the medial canthus of the right eye of a horse with ocular habronemiasis. Raised nonhealing lesions, such as the one illustrated, are often pruritic and self trauma is common. (*Source*: Reprinted with permission from Moore, C.P., Sarazan, R.D., Whitley, R.D., et al. (1983) Equine ocular parasites: a review. *Equine Veterinary Journal* (Suppl. 2), 76–85.)

et al., 2003; Rebhun et al., 1981). Affected tissue tends to bleed easily, and pruritus and self-trauma may be evident.

Diagnosis of cutaneous habronemiasis is made based upon consistent clinical signs and histopathologically consistent features observed in biopsy specimens. Specifically, granulomatous inflammatory infiltrate with eosinophils and mast cells can be found, along with collagenolysis (Rebhun et al., 1981). Larvae may not be identified histopathologically. In fact, nematode larvae are only present in 44%–50% of biopsy specimens (Pusterla et al., 2003). As such, concurrent use of PCR may be employed to arrive at a definitive diagnosis (Traversa et al., 2007; Verhaar et al., 2018). Therapy is aimed at destroying the nematodal larvae by administering systemic, and in some instances subconjunctival and/or nasolacrimal, doses of avermectins (Gasthuys et al., 2004; Herd & Donham, 1981; Pusterla et al., 2003; Verhaar et al., 2018). Surgical debulking large nodules may be necessary (Verhaar et al., 2018). Further, topical, subconjunctival, and/or systemic anti-inflammatory drugs may be used to control inflammatory responses to dead and dying larvae (Gasthuys et al., 2004; Pusterla et al., 2003; Verhaar et al., 2018). Control of the fly population by removal of horse manure and implementing appropriate fly control measures is useful in reducing habronemiasis in the horse population.

Halicephalobus gingivalis

Halicephalobus gingivalis is a free-living nematode that resides in organic material, including manure, that may act as a facultative parasite in both horses and people. Specifically, *H. gingivalis* can cause severe pathology of a variety of systems including the CNS, musculoskeletal system, respiratory system, renal system, and the eyes. Clinical signs will vary with the system being affected. With respect to ocular lesions, clinical signs may include blindness, chorioretinitis, optic neuritis, and uveitis (Kinde et al., 2000; Majzoub et al., 2000; Rames et al., 1995). Considering that ocular *H. gingivalis* is uncommonly reported, and that it has been associated with concurrent encephalopathy, it is difficult to determine an appropriate therapy or prognosis, although *H. gingivalis* CNS and systemic infection is grave (Pearce et al., 2001).

Onchocerciasis (Onchocercosis)

Onchocerciasis is a parasitic disease that affects a variety of species including horses. In horses, onchocerciasis causing clinically relevant ocular signs is caused by *Onchocerca cervicalis*. *Onchocerca* larvae are transmitted to animals by infected gnats/midges or black flies (*Culicoides* or *Simulium* spp., respectively). Following infection, larvae migrate to the nuchal ligament where they develop into adult worms. The adult worms persist and produce microfilaria that migrate to various subcutaneous sites where the intermediate host (midges/gnats and blackflies) can become infected and then infect another host (Cello, 1971; Lloyd & Soulsby, 1978; Schmidt et al., 1982b). It is the migrating microfilariae, not the adult worms, that cause disease in the horse.

The prevalence of *O. cervicalis* microfilariae among horses in the United States appears to be have been high, but is now markedly reduced because of the widespread use of ivermectin. On the basis of skin biopsy findings, prevalence rates of approximately 50%–77% have been reported in horses from the western, midwestern, and southeastern United States (Cummings & James,1985; Rabalais et al., 1974; Stannard & Cello, 1975); prevalence rates of as high as 76% in the Gulf Coast area and 82% in Louisiana have also been reported (Klei et al., 1984). The prevalence in the United Kingdom appears to be less than that in the United States, with reports of positive skin biopsy specimens between 2.3% to 24% (Attenburrow et al., 1983; Mellor, 1973). The prevalence of ocular microfilariae has been reported to be 18% in 292 horses from the eastern, southeastern, and midwestern United States (Moran & James, 1987), 11% in 368 eyes of horses from the midwestern United States (Schmidt et al., 1982a), and 49% in 121 horses from the eastern United States (Lloyd & Soulsby, 1978). The most common sites of ocular microfilariae are the conjunctiva and eyelids, followed by cornea/sclera and the intraocular structures or aqueous humor.

As alluded to already, ocular manifestations of onchocerciasis include anterior and posterior uveitis, peripapillary chorioretinitis, keratitis, keratoconjunctivitis, and lateral conjunctival vitiligo (Attenburrow et al., 1983; Cello, 1971; Hammond et al., 1983; Munger, 1983; Schmidt et al., 1982a). Diagnosis of onchocerciasis is made based upon microscopically identifying the nematode in biopsy specimens of affected tissues including conjunctiva or skin.

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Treatment of onchocerciasis has been most effective with systemically administered ivermectin (0.2 mg/kg) or moxidectin (0.4 mg/kg) (Herd & Donham, 1983; Mancebo et al., 1997). It is important to note, however, that there is no efficacious therapy for destroying the adult nuchal ligament-residing nematodes. Further, concurrent treatment of ocular signs should be implemented to control ocular inflammatory responses because dead and dying microfilaria may exacerbate ocular disease. Systemic nonsteroidal anti-inflammatory agents as well as topical or subconjunctival corticosteroids should be used.

Parelaphostrongylosis

Parelaphostrongylus spp. are metastrongyloid nematodes; there are three species of *Parelaphostrongylus* all of which are extrapulmonary parasites of definitive ungulate hosts including cervids and bovids. Among these three parasites, *P. tenuis* (meningeal worm) is relatively large with males ranging from 31 to 62 mm in length, and equipped anatomically with spicules that typically exceed 200 µm in length, and a gubernaculum of >100 µm in length (Reinstein et al., 2010). *P. tenuis* is considered to be a common neurotropic parasite in white-tailed deer, the definitive host, in parts of the United States, including eastern to central North America. Noncervid domestic livestock, including llamas, goats, sheep, and cattle, are also susceptible. In white-tailed deer, the larvae of this parasite migrate cranially through the grey matter of the spinal cord and into the brain where they mature into adult parasites. Adult meningeal worms reside in the meninges of white-tailed deer and rarely cause clinical signs of disease. For details regarding the life cycle of this parasite the reader is referred to Pugh et al. (1995). Successful surgical extraction of *P. tenuis* from the anterior chamber of a horse has been reported (Reinstein et al., 2010).

Setariasis

Setaria spp. are nematodes of the superfamily *Filarioidea* and consequently, are transmitted to their hosts by blood-feeding insects. Like *Dirofilaria* spp., *Setaria* spp. can be found within circulating blood by examining blood smears. *S. digitata* and *S. equina* are the species known to migrate to the equine eye. Intraocular *Setaria* spp. have been reported in the horse and donkey (Jemelka, 1976; Marzok et al., 2009; Shin et al., 2017; Schwartz, 1927; Tamilmahan, 2013). Successful surgical removal of *S. digitata* from the anterior chamber has been reported in equids (Jemelka, 1976; Marzok et al., 2009; Tamilmahan, 2013). A recent study reported successful treatment of equine ocular setariasis with ivermectin (Muhammad & Saqib, 2007).

Parasitic: Protozoal

Equine Protozoal Myeloencephalitis

Equine protozoal myeloencephalitis (EPM) is a multifocal, progressive disease of the CNS caused by infection with *Sarcocystis neurona* or, less commonly, *Neospora hughesi* (for reviews see Dubey, 2004a; Dubey et al., 2001; Furr et al., 2002; Pusterla et al., 2017; Reed et al., 2016). The disease has been reported only in horses born and raised in the Americas including Canada, United States, Brazil, and Panama, with young horses being affected more than older horses and a breed predilection for Standardbred, Thoroughbred, and Quarter Horses (Dubey, 2004a). Infection occurs via ingestion of the organism, although transplacental infection can occur with *Neospora hughesi* (Reed et al., 2016). The parasites can cause inflammation and necrosis throughout the CNS, especially the caudal brainstem and spinal cord. The cerebrum and peripheral nerves may be affected as well. Clinical signs vary depending upon the location of the CNS affected and the chronicity of the disease but may include seizures, ataxia, tetraparesis, focal muscle atrophy, head tilt, facial paralysis, circling, nystagmus, and blindness (with or without pupillary light abnormalities). Horner's syndrome has also been seen in horses with EPM (Mayhew, 1980). Severe temporalis and masseter muscle denervation and atrophy may lead to prominence of the supraorbital fossa, ptosis, and varying degrees of enophthalmos (Mayhew, 1989).

Definitive diagnosis requires demonstrating the causative organism within the CNS (Reed et al., 2016). A working antemortem diagnosis of EPM, in a horse with compatible clinical signs, is made based upon: (1) excluding other diseases; (2) demonstrating intrathecally derived *Sarcocystis neurona* or *Neospora hughesi* antibodies; and (3) demonstration of a positive response to the antiprotozoal medications, diclazuril or ponazuril (two medications highly specific in targeting protozoal organisms) (Pusterla et al., 2017). Use of Food and Drug Administration (FDA)-approved medications is strongly recommended for the treatment of EPM (Pusterla et al., 2017). These FDA-approved medications include: (1) sulfadiazine/pyrimethamine combination (ReBalance, PRN Pharmacal, Pensacola, FL, USA); (2) diclazuril (Protazil, Merck Animal Health, Madison, NJ, USA); and (3) ponazuril sulfone (Marquis, Merial, Lyon, France) (Pusterla et al., 2017). Concurrent administration of systemic anti-inflammatories is recommended because of the significant CNS inflammation, especially within the first week of treating the disease with antiprotozoal medications (Pusterla et al., 2017). Treatment with FDA-approved medications result in clinical improvement and a negative cerebrospinal fluid antibody in 57%–62% of patients. Approximately 10% of these patients can be expected to relapse 1–3 years after discontinuation of treatment (Pusterla et al., 2017). All three FDA-approved therapies have similar clinical efficacy (Pusterla et al., 2017).

Piroplasmosis (Equine Babesiosis, Biliary Fever)

Piroplasmosis is caused by the tickborne, intraerythrocytic, protozoal parasites of the order Piroplasmida, and include *Theileria equi* and *Babesia caballi* (for review see Bruning,

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1996; De Waal & Van Heerden, 2004; Wise et al., 2014). The disease occurs in tropical and subtropical climates. Tick vectors for equine babesiosis belong to a variety of genera including *Dermacentor*, *Hyalomma*, *Amblyomma*, *Boophilus*, *Anocentor*, and *Rhipicephalus* (Battsetseg et al., 2002a,b; De Waal, 1990; De Waal & Potgieter, 1987; Potgieter et al., 1992; Teglas et al., 2005; Ueti et al., 2005). The incubation period is from 5 to 28 days, and clinical signs include pyrexia, hemolytic anemia, thrombocytopenia, peripheral edema, petechiation of mucous membrances, jaundice, hemoglobinuria, and death.

Ophthalmic signs include swelling of the eyelids as well as icterus of the conjunctiva and sclera. The color of the conjunctiva varies from yellow to dark brown, often with petechial and ecchymotic hemorrhages over the third eyelid and other conjunctiva (Sippel et al., 1962). Red-colored, serous ocular discharge has also been noted in some horses, and distention of the supraorbital fossa may be seen.

Diagnosis of equine babesiosis is made based upon identifying the organism within erythrocytes on a blood smear. Other more sophisticated, and in some instances, more reliable diagnostic tests include ELISA, Western blot, immunofluorescent and complement fixation antibody tests, and detecting DNA of the infectious agent using PCR (Alhassan et al., 2005; Bose & Daemen, 1992; Bose & Peymann, 1994; Holman et al., 1993; Kappmeyer et al., 1999; Posnett et al., 1991; Rampersad et al., 2003; Weiland, 1986). Consensus regarding appropriate therapeutic regimes for the treatment of equine babesiosis has not been reached (for current therapeutic strategies see Bruning, 1996; De Waal & Van Heerden, 2004; Wise et al., 2014). A variety of drugs including diminazene diaceturate, amicarbalide diisethionate, and imidocarb diproprionate are effective against both *B. caballi* and *B. equi* (De Waal & Van Heerden, 2004).

Toxoplasmosis

Toxoplasmosis is caused by the protozoan *Toxoplasma gondii* (for review see Dubey, 2004b). *T. gondii*, similar to *N. caninum*, has a worldwide distribution. Cats are both definitive and intermediate hosts of *T. gondii*. Because cats are definitive hosts, they are the only species that can shed oocysts. It should be noted, however, that dogs can pass *T. gondii* oocysts in their feces after the ingestion of infected feline feces (Lindsay et al., 1997). Many mammalian species can act as intermediate hosts. In the cat, ingested *T. gondii* bradyzoites (from tissue cysts) undergo a typical coccidian intestinal life cycle, and infected cats excrete oocysts in their feces that, after 1–5 days, sporulate and become infectious sporozoites (Dubey, 2004b). The oocysts are resistant to environmental conditions, and they may remain infectious for months to years (Dubey, 2004b). Ingestion of the oocysts by a susceptible host results in rapid division of sporozoites in the gut epithelium. The resultant tachyzoites are 4–8 μm by 2–4 μm, and are spread throughout the body via blood and lymphatics, and encyst in the brain, skeletal and cardiac muscles, as well as the liver. The encysted forms, termed bradyzoites, survive in tissues for the life of the host. Ingestion of bradyzoites by a new host dissolves the cyst wall and transforms them into tachyzoites, which ultimately encyst again. The reported prevalence of serum antibodies, indicating exposure to *T. gondii*, among horses ranges from 1% in Sweden (Uggla et al., 1990), 12% in India (Chhabra et al., 1985), 17% –37% in Nigeria (Aganga et al., 1983; Osiyemi et al., 1985), to <1%–34% in North America (Dubey et al., 1999; Eugster & Joyce, 1976; Riemann et al., 1975). *T. gondii* has been identified in horse meat destined for human consumption (Klun et al., 2017; Pastiu et al., 2015; Pena et al., 2018; Shaapan et al., 2007).

Uveitis has been reported in association with positive *T. gondii* serum antibody titers and the organism itself has been identified by PCR in the retina, choroid, and sclera of a pony without apparent ocular disease (McDonald & Cleary, 1970; Turner & Savva, 1991). In one study of 130 horses with uveitis in Germany, a correlation could not be made with serum antibody titers for *T. gondii*, but a correlation could be made with titers to *Leptospira* spp. (Alexander & Keller, 1990).

Horses experimentally infected via the oral route with *T. gondii* oocysts did not develop clinical disease, but they did develop low-level serum antibody titers, as determined on the basis of a modified agglutination test (Dubey & Desmonts, 1987). Persistence of the encysted form of *T. gondii* in muscles and other tissues, including the eye of one horse, was shown even months after inoculation (Dubey, 1985). Because the organism has been isolated from the equine eye, toxoplasmosis is a likely etiology in some instances of uveitis. Its role in ERU, if any, remains undefined.

Parasitic: Tapeworms

Echinococcus granulosus (Hydatid Disease)

Equine hydatid disease is caused by infection with the tapeworm *Echinococcus granulosus* subspecies *equinus*. Hydatid disease is relatively common in the horse, but reports of ocular hydatid disease are uncommon (Barnett et al., 1988; Capatina et al., 1969; Summerhays & Mantell, 1995). Domestic and wild canids are the definitive hosts of *E. granulosus* subspecies *equinus*, whereas horses and mules are this species' intermediate hosts. With respect to ocular disease, hydatid cysts have been reported in the equine orbit and these animals present with signs of orbital disease (Barnett et al., 1988; Capatina et al., 1969; Summerhays & Mantell, 1995). Ultrasonography may aid in the presumptive diagnosis of hydatid disease in the horse (Summerhays & Mantell, 1995). Treatment is aimed at enucleation and surgical excision of the hydatid cyst in the case of blind eyes (Barnett et al., 1988). Alternatively, vision has been maintained in a horse by aspirating the cyst contents and concurrently administering systemic albendazole (10 mg/kg for

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7 days, then 7 days of no treatment, repeat this cycle of therapy 6 times) (Summerhays & Mantell, 1995). Diagnosis of retrobulbar hydatid disease is established on the basis of a positive histopathologic examination of excised tissue (Barnett et al., 1988). It should be mentioned, however, that diagnosis may be confirmed via microscopically identifying portions of the worm within fluid aspirated from the cyst (Summerhays & Mantell, 1995)

Rickettsial Diseases

Members of the bacterial order Rickettsiales are the cause of numerous conditions in numerous species of vertebrates (for comprehensive review see Parola et al., 2005; Raoult & Roux, 1997). All members of the order Rickettsiales are obligate intracellular parasitic bacteria that require host cells to replicate (Parola et al., 2005; McQuiston et al., 2003). The development of molecular taxonomic methods has resulted in the reclassification of several species of *Rickettsia* (Dumler et al., 2001). Rickettsial diseases are transmitted via an arthropod, typically fleas or ticks (Parola et al., 2005). Two common groups of diseases still considered rickettsial diseases in veterinary medicine include: (1) rickettsioses caused by bacteria of the genus *Rickettsia*; and (2) ehrlichioses and anaplasmoses caused by bacteria in the family Anaplasmataceae (Parola et al., 2005). Many rickettsial diseases are considered zoonotic (McQuiston et al., 2003). Because of these unique features of bacteria of the order Rickettsiales, we consider them here separately from other bacterial diseases that manifest, in part, with ocular disease.

Equine Granulocytic Anaplasmosis (Equine Granulocytic Ehrlichiosis, Ehrlichiosis)

Equine granulocytic anaplasmosis is caused by the rickettsial organism *Anaplasma phagocytophila* (previously *Ehrlichia equi*) (Dumler et al., 2001). As mentioned above, equine granulocytic anaplasmosis is transmitted to horses via ticks, specifically ticks of the genus *Ixodes* (Reubel et al., 1998; Richter et al., 1996). Clinically, horses have general malaise, and are pyrexic, anorexic, and icteric (can be observed periocularly). Limb edema, mucosal petechiation (including conjunctiva), and ataxia are also observed. Animals are also thrombocytopenic and leukopenic. Ocular manifestations of equine granulocytic anaplasmosis include ocular icterus, petechial hemorrhages, and uveitis (Ziemer et al., 1987).

Diagnosis of equine granulocytic anaplasmosis is made based upon consistent clinical findings, identifying the organism within the cytoplasm of granulocytic leukocytes (neutrophils and eosinophils), detecting DNA within the blood of affected animals, and demonstrating circulating anti-*Anaplasma* antibodies (Magnarelli et al., 1999). Therapy is aimed at eliminating the organism by administering tetracyclines. Prognosis is good in uncomplicated cases of equine granulocytic anaplasmosis (Madigan, 1993a).

Viral

Adenovirus

Adenoviral infection is primarily a problem in immunodeficient Arabian foals (McChesney et al., 1974). Affected animals develop fever, pneumonia, and leukopenia (McChesney et al., 1973, 1974). Clinical signs include a thick, yellow discharge from the eyes and nares that adheres to the eyelids, muzzle, and forelegs, as well as dyspnea, cough, and diarrhea. Necrosis of the epithelial surfaces occurs, including the conjunctiva and epithelium of the lacrimal glands. Microscopic lesions in the uvea have been seen, as has panuveitis. The conjunctiva may contain intranuclear inclusion bodies as well (McChesney et al., 1973). The diagnosis is established on the basis of virus isolation results, serum antibody titers, and viral inclusions in exfoliated epithelial cells. Therapy is supportive in nature, although demonstrated benefit from blood or serum with a high antibody titer has been reported. The mortality rate is high among foals with marked leukopenia.

African Horse Sickness

African horse sickness (AHS), an infectious but not contagious disease, is caused by a virus named African horse sickness virus and this virus belongs to the family Reoviridae, genus *Orbivirus* (for review see Carpenter et al., 2017; House, 1993; Mellor & Hamblin, 2004). There are nine serotypes which are transmitted by *Culicoides* sp. (biting midges) and, possibly, mosquitoes. AHS typically affects equidae in sub-Saharan Africa, but it has also been reported in the Middle East, Spain, and Portugal. There are four syndromes associated with AHS:

1) the peracute or pulmonary form;
2) the subacute, edematous, or cardiac form;
3) the acute or mixed form; and
4) the horse sickness fever form.

In the peracute or pulmonary form, the clinical signs are fever followed by vascular congestion of the conjunctiva and mucous membranes, sweating, and cough. The mortality rate with this form of AHS is very high; death often occurs in 1–3 days.

The subacute or cardiac form has the early clinical signs of fever and vascular congestion of the conjunctiva and mucous membranes. Subcutaneous edema (from localized damage by the virus) develops in multifocal areas, including the eyelids and the supraorbital fossa, which may bulge (Maurer, 1961). Bulging of the supraorbital fossa is considered to be pathognomonic for the cardiac form. Petechial hemorrhages of the conjunctiva and ventral tongue may occur as well. The mortality rate is approximately 50%, with death occurring between 4 and 8 days after the onset of signs.

The acute or mixed form is the most common form of AHS, and it has the clinical signs of both the pulmonary and the cardiac forms. The mortality rate ranges from 50% to 95% with death occurring from 3 to 6 days after the onset of fever.

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The horse sickness fever form is the mildest form of AHS, and it may even go undetected. Clinical signs include low-grade fever, conjunctival vascular congestion, mild depression, and anorexia. Affected animals make a full recovery. The diagnosis of AHS is established on the basis of virus isolation, demonstration of the organism using molecular probes or reverse transcriptase-polymerase chain reaction (RT-PCR), and antibody test results (Zientara et al., 1998). The disease is reportable in the United States and Canada. Treatment is supportive and symptomatic in nature.

Borna Disease

Borna disease is caused by a single-stranded, enveloped, RNA virus of the *Flaviviridae* family and is serologically distinct from eastern equine encephalomyelitis, western equine encephalomyelitis and Venezualan equine encephalomyelitis (for review see Richt et al., 2000; Rott et al., 2004). The disease is considered endemic in Germany and has been reported in the Netherlands, France, Poland, United States, Iran, and Japan (Rott et al., 2004). Clinical signs are similar to those of the other equine viral encephalitides and include altered pupillary light reflexes and retinal and/or central blindness. Retinal degeneration has been shown histologically in horses with confirmed Borna disease (Dietzel et al., 2007). Diagnosis of borna disease is based on consistent clinical signs, serum and cerebrospinal fluid antibody titers, and histologic demonstration of pathognomonic Joest–Degen neuronal inclusion bodies in the brain. The mortality rate varies from 37% to 94% (Rott et al., 2004).

Equine Herpesvirus

There are five equine herpesviruses and they are logically named equine herpesvirus (EHV) -1, -2, -3, -4, and -5. Only EHV-1, -2, and -5 have been shown to manifest ocularly. EHV-1 is a common etiologic agent of rhinopneumonitis, abortion, and neurological disease (for review see Patel & Heldens, 2005). With respect to ocular disease EHV-1 has been shown to have the potential to produce chorioretinitis (Slater et al., 1992). These chorioretinal lesions typically develop after acute clinical signs (mild upper respiratory tract signs) have disappeared (Slater et al., 1992).

EHV-2 has been associated with upper respiratory tract infections and ocular disease in the horse (Borchers et al., 1997, 1998; Collinson et al., 1994; Kershaw et al., 2001; Matthews et al., 1983; Miller et al., 1990). With respect to ocular disease, EHV-2 results in keratoconjunctivitis that is characterized clinically by excessive tearing, mucopurulent ocular discharge, chemosis, conjunctival hyperemia, linear and punctate keratopathy, corneal irregularity, and corneal edema as well as vascularization. Fluorescein staining is often negative, although pinpoint areas of dye uptake may be seen. In one report, EHV-2 and -5 were implicated in an outbreak of keratoconjunctivitis in a group of Icelandic horses (Rushton et al., 2016). Isolation of EHV-2 or demonstration of DNA from EHV-2 and/or -5 from the cornea and conjunctiva of affected horses combined with a favorable response to treatment with topical antiviral medication confirms EHV-2 and -5 as an ocular pathogen in the horse (Collinson et al., 1994; Kershaw et al., 2001; Miller et al., 1990; Rushton et al., 2016).

Equine Infectious Anemia

Equine infectious anemia (EIA) is caused by equine infectious anemia virus, a retrovirus transmitted via biting flies and mosquitos (for review see Cook & Issel, 2004; Issel et al., 2014; Sellon, 1993). EIA is observed in various equids worldwide. The virus causes cyclical immune-mediated anemia, thrombocytopenia, fever, general malaise, and ventral edema. If infected with a highly virulent strain, horses may die during the initial manifestation of disease. Recurring bouts of disease may taper off over time and infected horses will remain as asymptomatic carriers. Ocular lesions are few, although intraocular and conjunctival hemorrhages may occur in association with thrombocytopenia. The diagnosis is established on the basis of a positive Coggins test (i.e., agar-gel immunodiffusion test) or competitive enzyme-linked immunosorbent assay (ELISA), or immunoblot assays. There is no treatment for EIA. Horses positive for EIA are usually not allowed to cross international boundaries and have restricted movement within a country. Because of the persistent infection in animals recovering from this virus, humane euthanasia is often advocated. It is important to remember that instruments in contact with infected animals must be properly sanitized in order to prevent the spread of the disease.

Equine Viral Arteritis

Equine viral arteritis is a contagious equine disease caused by a togavirus known as equine viral arteritis virus, an RNA virus (for review see Del Piero, 2000; Timoney et al., 1993a). Equine viral arteritis virus is transmitted via inhalation of the virus and through sexual contact. The virus causes a panvasculitis, with necrotizing arteritis of the small arteries of muscles commonly being seen (Del Piero, 2000). Outbreaks and serologic evidence of the virus have been reported from many countries around the world. Clinical signs include fever, depression, coughing, nasal and ocular discharge (Fig. 37.3.15 and Fig. 37.3.16), and abortion. Periorbital and peripheral edema, conjunctivitis, corneal opacity, and photophobia have also been described (Jones, 1969; Timoney et al., 1993b; Traub-Dargatz et al., 1985). Diagnosis of equine viral arteritis is made based upon consistent clinical signs, detecting a rising serum titer and/or isolation of the virus and/or detecting the organism using RT-PCR (Del Piero, 2000). Treatment is aimed at supportive care, and most adult horses make a full recovery although stallions may become chronic carriers of the virus (Del Piero, 2000).

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Figure 37.3.15 Left eye of a horse with equine viral arteritis. Note the serous ocular discharge from the medial canthus. (*Source*: Courtesy of R. Holyoak.)



Figure 37.3.16 Left eye of a horse with equine viral arteritis. Note the marked conjunctival hyperemia and mild chemosis consistent with conjunctivitis. (*Source*: Courtesy of R. Holyoak.)

Equine Viral Encephalitis

Viruses of the family Togaviridae (RNA viruses) are insect-transmitted and cause encephalitis in the horse. The most pathogenic of these viruses are called alphaviruses, and these include eastern, western, and Venezuelan equine encephalitis (EEE, WEE, and VEE, respectively) viruses, all of which occur in the Americas (for review see Weaver et al., 1999). All of these viruses are transmitted by biting insects, especially mosquitos. Also important to note, these viruses are considered zoonotic. For complete review of various equine encephalitis viruses see Long (2014).

Early clinical signs, regardless of the type of virus, include fever, stuporous state, ataxia, and hyperesthesia. Later signs include aggression, head pressing, blindness, paralyzed tongue and pharynx, nystagmus, strabismus, and pupillary dilatation. Diagnosis of equine viral encephalitis is made based upon time of year (are mosquitos present?), consistent clinical signs, rising serum antibody titers, and in acute cases, cerebrospinal fluid pleocytosis, isolation of the virus from cerebrospinal fluid or demonstration of the virus using RT-PCR (Calisher et al., 1983, 1986; Lambert et al., 2003; Linssen et al., 2000). Treatment is nonspecific and supportive in nature. The mortality rate is high, but horses can recover from viral encephalitis. Most will have residual neurologic signs, although complete recoveries have been reported (Devine & Byrne, 1960). Prevention of equine viral encephalitis is through routine vaccination schedules and by controlling the mosquito population.

Influenza

Equine influenza is caused by infection with orthomyxoviruses of the influenza A type (for review see van Maanen & Cullinane, 2002; Wilson, 1993). Influenza is highly contagious, and it is transmitted through aerosolized virus. Clinical signs include sudden onset of a harsh, dry, and nonproductive cough, fever, lethargy, and anorexia. Ocular signs include conjunctival hyperemia and excessive tearing. Treatment is symptomatic, with rest in a clean, well-ventilated area being important. Horses generally recover in 3–4 weeks.

Rabies

Rabies is caused by rabies virus, an enveloped RNA rhabdovirus (for review see Woldehiwet, 2002). Rabies virus is purely a neurotropic virus and the source of the infection is another infected animal. Rabies virus is transmitted through inoculating infected saliva by biting a "naïve" animal. Interestingly, however, infection may occur via inhalation or ingestion of the virus (Gibbons, 2002). Common vector species include bats, foxes, racoons, and skunks (Woldehiwet, 2002). After an animal has been bitten by an infective rabid animal, virus enters the CNS by migrating up peripheral nerves by binding to rabies virus receptors at the neuromuscular junction (for review see Lafon, 2005). Consequently, the time from being bitten to showing brain dysfunction is related to the distance of the bite from the head (i.e., the further away the bite from the head, the longer it takes to see signs of brain dysfunction). Once the virus has reached the CNS, a nonsuppurative polioencephalomyelitis and ganglionitis develop and account, in part, for the development of clinical signs (Green et al., 1992; Hudson et al., 1996). With

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respect to clinical signs, classical "dumb" and "furious" forms of rabies have been described and are indicative of whether the limbic system is unaffected or affected, respectively.

Clinical signs of equine rabies are highly variable but include behavioral changes, ataxia and paresis of the hind limbs, pharyngeal paralysis, recumbency, and signs of colic (Green et al., 1992; Hudson et al., 1996). Ocular signs indicative of infection of the central components of the visual and oculomotor systems including blindness, nystagmus, and strabismus may develop (Green et al., 1992; Hudson et al., 1996). During the clinical course of the disease clinical signs worsen and the animal eventually succumbs to the disease. Antemortem diagnosis can be made by demonstrating antigen, using immunochemical methods or by detecting the virus using RT-PCR, in skin, corneal impressions, or saliva (Woldehiwet, 2005). Definitive diagnosis is made at postmortem by detecting the virus in brain tissue using immunochemical techniques or RT-PCR (Woldehiwet, 2005). Eosinophilic intracytoplasmic inclusion bodies (Negri bodies) may be observed in neurons throughout the CNS, including retinal ganglion cells (Haltia et al., 1989). It is important to note, however, that not all cases of rabies will have Negri bodies present and is the reason that other more specific tests are used. Prevention of rabies is aimed at routine vaccinating of susceptible animals.

West Nile Virus

West Nile virus (WNV) is single-stranded RNA virus of the family Flaviviridae that is maintained in the environment by a bird–mosquito relationship (for review see Garg & Jampol, 2005; Long, 2014; Ostlund et al., 2000). Birds are the reservoir host whereas mosquitos transmit the virus to a variety of animal species, including birds, horses, cats, dogs, bats, alligators, and humans (Garg & Jampol, 2005; Kulasekera et al., 2001; Nasci et al., 2001; Turell et al., 2002). Horses are similar to humans in that they are considered dead-end hosts (cannot transmit the disease), although transfusion of infected blood products can result in transmission of the disease to the recipient (Pealer et al., 2003). Crows and other members of the Corvidae family are highly susceptible to WNV infection and carry a large virus load, and are considered important in the transmission of the disease (Komar et al., 2003). As an aside, it should be noted that WNV infection in birds of prey (Cooper's and Red-Tailed Hawks) has been noted to cause a triad of clinical disease including myocarditis, encephalitis, and endophthalmitis similar to the syndromes observed in humans (Garg & Jampol, 2005; Wunschmann et al., 2004).

There does not appear to be any breed or gender predilection for developing the disease (Schuler et al., 2004; Weese et al., 2003). The disease typically affects young adult horses, although any age of horse can have a clinically relevant infection (Schuler et al., 2004; Weese et al., 2003). Clinical signs in horses include ataxia, paresis, generalized muscle fasciculations, pyrexia, hyperesthesia, general malaise, lip droop, bruxism, circling, and animals may be recumbent (Schuler et al., 2004; Weese et al., 2003). With regards to ophthalmic manifestations of WNV infection, horses may be blind, have facial nerve paralysis, mild keratitis of undetermined cause, and have protrusion of the third eyelid (Autorino et al., 2002; Hyatt & Weese, 2004; Schuler et al., 2004). In humans, however, WNV infection manifests ocularly as chorioretinitis, uveitis, retinal vasculitis, and optic neuritis (Garg & Jampol, 2005). It is possible that horses, too, have similar ocular lesions although complete ophthalmic examinations may not routinely be performed or such lesions have not been reported.

Diagnosis of WNV infection is made based upon determining IgM concentrations in the serum and/or cerebrospinal fluid, amplifying WNV DNA using PCR, or isolating the virus (Schuler et al., 2004; Weese et al., 2003). Therapy for WNV infection involves supportive care and by administering systemic anti-inflammatory drugs to reduce cerebral edema (Weese et al., 2003). Prognosis is variable. Older horses, horses not vaccinated for WNV, and horses that are recumbent are more likely to succumb to the disease (Schuler et al., 2004; Weese et al., 2003). Specifically, up to approximately 80% of WNV-infected and recumbent horses will succumb to the disease (Schuler et al., 2004). Prevention is aimed at implementing a routine vaccination schedule. In addition, the percent mortality for animals that develop clinical signs of the disease, yet are vaccinated (when used according to the manufacturers instructions) is 4%, whereas the mortality of unvaccinated animals has been reported to be 33% (Schuler et al., 2004).

Metabolic Diseases

Hypothyroidism

Hypothyroidism develops as a result of decreased production of thyroxine (T_4) and triiodothyronine (T_3) by the thyroid gland. Hypothyroidism is an uncommon condition in adult horses and the prevalence of this endocrinopathy is unknown (Breuhaus, 2011; Messer & Johnson, 2007). Clinical signs in horses with naturally occurring hypothyroidism are reportedly more subtle and vague than those in experimentally thyroidectomized horses which include lethargy, low exercise tolerance, and poor quality of the haircoat (Breuhaus, 2011; Messer & Johnson, 2007). A recent case report documented bilateral keratoconjunctivitis sicca and dry nares attributable to parasympathetic nerve dysfunction, headshaking syndrome with paresthesia and dysesthesia of the face attributable to sensory trigeminal nerve disorder, and hypothyroidism in a 6-year-old German Warmblood gelding (Schwarz et al., 2008). The two nerve dysfunctions were considered peripheral neuropathies that were most likely caused by the hypothyroidism. Readers are advised to

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consult a current large animal internal medicine textbook for a detailed discussion on the diagnosis of and therapy for equine hypothyroidism.

Pituitary Pars Intermedia Dysfunction (Equine Cushing's Disease)

Pituitary pars intermedia dysfunction (PPID) is a condition seen in geriatric equids (for review see Schott, 2002). It has been shown that hyperplasia of the pars intermedia likely results from loss of inhibition by neuronal degeneration of dopaminergic neurons (McFarlane et al., 2005). Because dopamine normally is inhibitory to melanotropes of the pituitary pars intermedia, and this inhibitory input is lost in horses with pars intermedia dysfunction, elevations in corticotropin, α-melanocyte stimulating hormone (α-MSH), endorphin, and corticotropin-like intermediate lobe peptide can be found in the serum of affected horses (Orth et al., 1982). Approximately 0.001%–0.5% of horses, of any age, are estimated to be affected by PPID (Brosnahan & Paradis, 2003; van der Kolk et al., 1993). The prevalence of PPID is estimated to be at least 10% of the geriatric equine cases seen in one referral institution, however (Brosnahan & Paradis, 2003).

Clinical signs of PPID in equids include generalized muscle wasting, hirsutism, hyperhidrosis, impaired wound healing, laminitis, and polyuria/polydypsia. With respect to ocular manifestations of equine PPID, bulging to the supraorbital fat pad may occur (caused by presumed disease-related fat redistribution) and blindness (with or without concurrent neurological signs) may also develop in cases of optic nerve compression caused by the hyperplastic pars intermedia of the pituitary (Brosnahan & Paradis, 2003; Donaldson et al., 2002). It has been shown that horses with PPID have reduced corneal sensitivity compared with age-matched non-PPID and young horses without PPID (Miller et al., 2013). Additionally, tear cortisol concentrations have been found to be elevated in horses and ponies with PPID (Hart et al., 2016). Altogether, reduced corneal sensitivity and increased tear cortisol concentrations may contribute to corneal ulceration and impaired corneal healing in horses/ponies with PPID. Interestingly, horses with corneal degeneration are less likely to have PPID compared with horses having calcific band keratopathy (Berryhill et al., 2017). As such, it may be important to evaluate horses with calcific band keratopathy for PPID. Further, although not definitively proven, it is suspected that senile retinopathy may be related to PPID in horses and ponies (Chandler et al., 2003). Clinically, senile equine retinopathy manifests as an accumulation of linear or geographic depigmented areas combined with heavily pigmented regions in the non-tapetal fundus with the tapetal fundus only rarely involved (Cutler, 2002). Senile retinopathy is characterized histologically by a loss of retinal pigment epithelium, loss of rods and cones, and a cystic degeneration of the inner layers of the peripheral retina (Barnett, 1972).

Diagnosis of PPID is made based upon consistent historical and clinical findings combined with positive results of a dexamethasone suppression test or by demonstrating elevated serum adrenocorticotropin hormone (ACTH). It should be noted, however, that laboratory diagnosis of PPID may be hindered by season (Donaldson et al., 2005). Treatment of equine PPID involves medically managing the disease by administering dopamine agonists, such as pergolide, or serotonin antagonists such as cyproheptadine (Schott, 2002). Further, it is important to implement appropriate husbandry and feeding regimes in addition to managing complications that may arise secondarily to PPID. Given the nature of the disease, therapy is needed for the duration of the animal's life. Secondary complications, including susceptibility to various infections, are more likely in some horses with PPID.

Neoplasia: Central Nervous System

There are few reports of intracranial neoplasms with ophthalmic manifestations in the horse. A pituitary mass in one aged horse resulted in blindness caused by degeneration of the optic nerves, optic chiasm, and optic tracts up to the lateral geniculate bodies (De Lahunta & Cummings, 1967). Another horse with a large intracerebral mass diagnosed as a microglioma had metastasis of the tumor to both eyes, with neoplastic cells being found within the vitreous humor and retina (Finn & Tennant, 1971).

Neoplasia: Systemic

Lymphosarcoma

Lymphosarcoma is the most common systemic neoplastic disease affecting the equine eye, but the disease in the horse occurs much less frequently than in the dog or the cat. Reported ocular manifestations of equine lymphosarcoma include eyelid swelling, third eyelid masses, uveitis (Fig. 37.3.17), chemosis and conjunctivitis, corneoscleral masses, and orbital lymphosarcoma (Blodi & Ramsey, 1967; Glaze et al., 1990; Germann et al., 2008; Lavach & Severin,1977; Murphy et al., 1989; Rebhun & Bertone, 1984; Rebhun & Del Piero, 1998).

Nutritional Disorders

Thiamine Deficiency

Thiamine deficiency occurs in horses primarily because of the ingestion of plants containing the catabolic thiamine enzyme, thiaminase. Plants such as bracken fern (*Pteridium acquilinum*) and horse tails (*Equisetum arvense*) contain thiaminases, and equine thiamine deficiencies have been attributed to chronic ingestion of these particular plants (Carpenter et al., 1950; Evans et al., 1951; Henderson et al., 1952; Roberts et al., 1949). Amprolium, a coccidiostat, has

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Figure 37.3.17 Left eye of a 6-year-old Thoroughbred gelding with uveitis caused by T-cell lymphoma. Note the conjunctival injection, iridal swelling, miotic pupil, and blood and fibrin in the ventral aspect of the anterior chamber. (*Source*: Reprinted with permission from Germann, S.E., Richter, M., Schwarzwald, C.C., et al. (2008) Ocular and multicentric lymphoma in a young racehorse. *Veterinary Ophthalmology*, **11**, 51–56.)

been used to induce thiamine deficiency in horses experimentally (Cymbaluk et al., 1978). Clinical signs of thiamine deficiency in the horse include ataxia, blindness, bradycardia, heart block, muscle fasciculations, weight loss, diarrhea, and hypothermia of the extremities. Diagnosis of thiamine deficiency is made based upon demonstrating exposure to thiaminase-containing plants and demonstrating low serum thiamine or by response to therapy. Therapy includes removal of access to thiaminases and parenteral treatment with thiamine. Clinical signs, including blindness, are reversible if the animal is not in the late stages of deficiency.

Vitamin A Deficiency

Vitamin A (retinol), a fat-soluble vitamin, is derived from its precursors (carotenoids) which are found in plants (for review see Fraser & Bramley, 2004; von Lintig & Vogt, 2004). Vitamin A (retinol) is important in the ocular system; it is stored and transformed into retinal which is translocated between the retinal pigment epithelium and the photoreceptors (Thompson & Gal, 2003). Within the photoreceptors, retinal combines with opsin (a protein) to form the visual pigment rhodopsin (Thompson & Gal, 2003). Early signs of vitamin A deficiency include: reduced feed intake and growth rate; a dull and brittle, long haircoat; and in foals, an increased incidence of respiratory and diarrheal diseases. A diagnosis of vitamin A deficiency is suspected in horses with excessive tearing and night blindness (Lewis, 1995). An important differential diagnosis for vitamin A deficiency is CSNB in Appaloosa horses (the latter is present from birth, is nonprogressive, and has no clinically evident ocular lesions). Ocular lesions and night blindness occur only if vitamin A deficiency is severe and long-standing (Howell et al., 1941). Complete blindness from retinal degeneration eventually occurs if the horse remains on a vitamin A-deficient diet; at that point, the pupils will be dilated and unresponsive to light. In addition, horses with vitamin A deficiency may have hyperkeratinization of the cornea and reduced numbers of conjunctival goblet cells.

Diagnosis of vitamin A deficiency is made based upon documenting low levels of serum retinol and by using the relative dose response test (Greiwe-Crandell et al., 1995). Horses consuming good-quality green pasture grasses and hay are unlikely to suffer from vitamin A deficiency (Lewis, 1995). Therapy is aimed at providing adequate levels of vitamin A in the diet.

Toxicities

Electrocution

Electric shocks and lightning strikes can produce direct ocular sequelae and also cause injury to the CNS (may manifest as blindness, papilledema, cranial nerve palsies) (for review on pathogenesis and human manifestation see Norman et al., 2001). Three horses suspected of being hit by lightning and four horses electrocuted because of a faulty electrical transfomer have been reported (Bedenice et al., 2001; Evans et al., 2012; Novales et al., 1998). In some instances, affected animals may die acutely because of peracute heart failure (Bedenice et al., 2001; Evans et al., 2012). Affected animals can become recumbent and exhibit thrashing and/or had exuberant muscle contractions after being struck by lightning or electrocuted. Affected animals may manifest with a variety of neurological signs.

With respect to ocular findings, affected horses have been reported to have ulcerative keratitis (unsure as to cause, i.e., may be secondary to trauma from thrashing on ground), blindness, corneal edema and hydrops, signs of vestibular disease (spontaneous nystagmus), signs of facial nerve paralysis (including ptosis, and absent palpebral reflex and menace response), and absent pupillary light reflexes (Bedenice et al., 2001). Fundic lesions were not found in one horse after being struck by lightning (Bedenice et al., 2001). In another horse, however, choroidal hemorrhage and retinal detachment and atrophy were present (Evans et al., 2012). Electric shocks and lightning strikes of a severe nature may produce cataracts that manifest months later.

Although not reported in horses, cataracts are likely to be produced by electrical shocks to the head. The appearance of clinical and experimentally induced electric cataracts are quite similar, and they consist initially of vacuoles that are present bilaterally in the midperipheral anterior cortical lens (Fraunfelder & Hanna, 1972; Thomas & Hanna, 1974). Ultrastructurally, the vacuoles are extracellular and transient, lasting several weeks. The lens vacuoles are prognostic

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indicators of later cataract formation. The lens epithelium subsequently proliferates, thereby producing multilayered plaques of lens capsule and lens fibers in the central anterior capsular region. Severe electric shock (e.g., from lightning) may produce both anterior and posterior cortical lenticular opacities (Norman et al., 2001).

Therapy for electrocuted horses is supportive and symptomatic. Horses surviving lightning strike or electrocution may have persistent neurological deficits or return to normal after the incident (Bedenice et al., 2001; Novales et al., 1998).

Fungal

Fumonisin Toxicity (Blind Staggers, Moldy Corn Disease, Equine Leukoencephalomalacia)

Equine leukoencephalomalacia (EL) is a disease caused by the ingestion of a toxin (fumonisins, namely fumonisins B1 and B2), produced by *Fusarium* spp. (for review see (Riet-Correa et al., 2013). In particular, *Fusarium verticillioides* (previously *F. moniliforme* and still referenced in literature as *F. moniliforme*; Seifert, 2003), *F. proliferatum*, and *F. subglutinans* are known to produce fumonisins in feed stuffs (Meireles et al., 1994). The disease has been reported worldwide, and it results in liquefaction necrosis of the white matter of one or both cerebral hemispheres (Wilson et al., 1985). Clinical signs appear suddenly and may affect a group of horses if all are fed from the same food source. Signs include depression, sialorrhea, ataxia, recumbency, central blindness (with or without abnormal pupillary light reflexes), head pressing, circling, seizures, colic, or frantic running behavior (Shanks et al., 1995; Naranjo et al., 1996; Vendruscolo et al., 2016).

Diagnosis is made antemortem based upon identifying clinical signs consistent with EL and by identifying a chronic exposure of the affected horse to infected feed. Hepatic encephalopathy is clinically indistinguishable from EL. Field corn has been most commonly implicated in this disease, but other feed sources may also be sources of *Fusarium* spp. (Vendruscolo et al., 2016; Wilson et al., 1985). Culture of *Fusarium* spp. and isolation of fumonisin toxins should be performed if the feed source is available (Naranjo et al., 1996; Wilkins et al., 1994). Aside from supportive therapy, there is no treatment for EL. Prognosis for horses affected with EL is commonly grave (Naranjo et al., 1996; Vendruscolo et al., 2016; Wilkins et al., 1994).

Plants

Numerous plants may be toxic to the horse (see Table 36.14 which lists toxic plants along with their systemic and ophthalmic effects). Historically, chronic selenium toxicity has been associated with "blind staggers" in the horse, but horses fed pure selenium compounds fail to develop the blindness, ataxia, or respiratory failure characteristic of blind staggers (Traub-Dargatz & Hamar, 1986). Thus, it has more recently been hypothesized that the toxic effects of alkaloids or other compounds in plants cause blind staggers, and that the condition does not relate directly to the selenium contained within these plants.

Many plants also have teratogenic effects in the horse, especially if they are eaten during the first trimester (Lewis, 1995). Pregnant mares may produce foals with a centrally placed, single eye if they eat *Veratrum eschscholtzii* during early pregnancy, much as ewes will produce such lambs if they eat *Veratrum californicum* on day 14 of gestation (Binns et al., 1962, 1963).

Miscellaneous Diseases

Hyperkalemic Periodic Paralysis

Hyperkalemic periodic paralysis (HyPP) is a condition resulting from an abnormality of a skeletal muscle sodium channel alpha-subunit and is inherited as an autosomal dominant condition (Naylor et al., 1992; Spier et al., 1993). It has been shown that descendants of the Quarter Horse stallion named "Impressive" are affected by this condition (Naylor, 1994). Consequently, HyPP should be considered in Quarter Horse-crosses and breeds of horses with Quarter Horse lineage (e.g., American Paint horses and Appaloosas) with consistent clinical signs. As previously mentioned, HyPP is the result of a genetic mutation in a gene coding for a particular skeletal muscle sodium channel subunit (Cannon et al., 1995; Hanna et al., 1996; Rudolph et al., 1992a,b). A result of this sodium channel defect in skeletal muscle membrane potential is predominantly a failure of sodium channel inactivation (Cannon et al., 1995; Hanna et al., 1996; Rudolph et al., 1992b). In conditions where the serum potassium concentration is elevated (e.g., high intensity exercise, renal failure), the membrane potential rises, threshold for an action potential is met, in HyPP-affected horses sodium channels fail to inactivate, and persistent depolarization of the skeletal muscle membrane occurs. The clinical consequence of persistent sodium channel inactivation is intermittent episodes of muscular fasciculation and weakness that often result in recumbency. During attacks, serum potassium levels are often, although not always, elevated (Naylor, 1994; Spier et al., 1990, 1993; Stewart et al., 1993).

Ocular manifestations of HyPP include third eyelid protrusion secondary to retraction of the globe. Definitive diagnosis of HyPP is made based upon demonstrating the genetic mutation (see the following genetic testing laboratories: Veterinary Genetics Laboratory, University of California at Davis, http://www.vgl.ucdavis.edu/; Animal Genetics Incorporated, https://www.animalgenetics.us/Equine/Genetic_Disease/HYPP.asp; Healthgene Corporation, http://www.healthgene.com/veterinary-testing/genetic-dna-testing/large-animals/). Acute therapy for severe episodes is aimed at facilitating intracellular movement of potassium by administering intravenous calcium gluconate, glucose,

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or bicarbonate during attacks resulting in rapid recovery (Meyer et al., 1999; Naylor, 1997). Management practices involve reducing dietary potassium intake (avoiding potassium-rich alfalfa-based feed), enhancing renal excretion of potassium (e.g., acetazolamide administration), and avoiding metabolic states associated with elevated potassium (e.g., exercise). Owners of affected animals should be educated about the inheritance of this condition and should be discouraged from using the animal for breeding.

Temporohyoid Osteoarthropathy

Temporohyoid osteoarthropathy is a condition that involves the bony proliferation of the bones of the temporohyoid joint, namely the stylohyoid and petrous temporal bones (Walker et al., 2002; Yadernuk, 2003). The pathogenesis of temporohyoid osteoarthropathy remains unknown, although it is thought that otitis media or degenerative joint disease of the temporohyoid joint may be important in the pathogenesis of this disease (Walker et al., 2002; Yadernuk, 2003). Temporohyoid osteoarthropathy is commonly associated with facial (cranial nerve VII) and vestibulocochlear (cranial nerve VIII) nerve dysfunction (Walker et al., 2002; Yadernuk, 2003). Horses with this condition may also exhibit head shaking, hyperesthesia of the ears, and avoidance of bit placement (Yadernuk, 2003). Ocularly, temporohyoid osteoarthropathy commonly manifests secondarily through involvement of the parasympathetic fibers of cranial nerve VII (neurogenic keratoconjunctivitis sicca), cranial nerve VII (facial nerve paralysis), and the vestibular layrinth and/or vestibulocochlear nerve (signs of peripheral vestibular disease) (Blythe, 1997; Verdegaal et al., 2003; Walker et al., 2002; Yadernuk, 2003). Diagnosis is made based upon consistent clinical signs combined with endoscopic, radiographic, or magnetic resonance or computerized tomographic evidence of asymmetry, inflammation, or osseous proliferation of the temporohyoid joint or stylohyoid bone (Walker et al., 2002). Therapy of temporohyoid osteoarthropathy involves appropriate antimicrobial and/or anti-inflammatory therapy and/or with partial stylohyoid or ceratohyoid ostectomy (Espinosa et al., 2017). Prognosis for this condition, based upon a relatively large retrospective study, is considered good to excellent with surgical intervention and fair with medical therapy (Espinosa et al., 2017).

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37.4

Ocular Manifestations of Systemic Disease

Part 4: Food Animals

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Congenital

Coat Color-Related Diseases/Conditions

Complete or Incomplete Albinism

Complete albinism (complete lack of pigmentation) or incomplete or partial albinism (an absence or reduction in the degree of pigmentation) is associated with not only the phenotypic appearance of an animal's coat and skin color but is also associated with conditions affecting the eye. Albinism or incomplete albinism may result from the failure of migration of neural crest cells (precursors to melanocytes) and hence result in reduced numbers of melanocytes in a nonpigmented area, or may result because of impaired production of pigment because of some intrinsic deficiency in melanin production (e.g., tyrosinase deficiency) but where the number of melanocytes in nonpigmented or hypopigmented areas is normal.

Complete albinism is rare in domesticated food-producing animals. In sheep, albinism has been reported in Icelandic and Suffolk sheep (Adalsteinsson, 1977; Rowett & Fleet, 1993). In cattle, albinism and incomplete albinism have been reported in several breeds including Brown Swiss/Braunvieh in Europe (Winzenreid & Lauvergne, 1970), a Guernsey (Leipold et al., 1968), Shorthorns (Greene et al., 1973), and Herefords (Leipold & Huston, 1966,1968b, 1969) in the United States, and Murboden in Austria (Schlegler, 1959). Inheritance of complete albinism in these breeds appears to be recessive. Clinical and ophthalmoscopic manifestations of complete albinism in cattle include white coat, photophobia, blepharospasm, nystagmus, and nonpigmented irides and ciliary processes (Greene et al., 1973). In contrast, forms of dominant incomplete albinism have been reported in cattle in which the coat color of these animals is white with occasional pigmented spots over the body (Gelatt et al., 1969; Huston et al., 1968; Leipold & Huston, 1966, 1968a, 1969). The irides of cattle with incomplete albinism vary from white to blue to grey with occasional brown sectors. In addition, tapetal hypoplasia and optic disc colobomas are commonly noted. The fundi of both complete and incomplete albino cattle have yellow tapeta lucida and nonpigmented tapeta nigra with large choroidal blood vessels distributed normally throughout this non-tapetal region (Greene et al., 1973).

Genetic mutations have been identified as a cause of albinism in some breeds of cattle. In the Brown Swiss/Braunvieh, a mutation in *TYR* (tyrosinase gene) and also likely in *SCL45A2* (*MATP* – membrane-associated transporter protein or *AIM1* – antigen isolated from immunoselected melanoma 1) have been identified (Rothammer et al., 2017; Schmutz et al., 2004). In Fleckvieh cattle with Tietz syndrome, animals have a dominant white coat colour with pink skin, subalbinotic fundi, and blue irides and deafness. Tietz syndrome in these cattle is the result of a mutation in *MITF* (microphthalmia-associated transcription factor) (Philipp et al., 2011). Interestingly, although not associated with complete albinism in Holstein Friesian cattle, bilateral iridal hypopigmentation has been associated with a locus on bovine chromosome 8 (BTA8) (Hollmann et al., 2017). With respect to sheep, although a genetic mutation has not been identified, it has been shown, *in vitro*, that albinism in Suffolk sheep likely results from defective tyrosinase protein (Rowett & Fleet, 1993).

Chédiak–Higashi Syndrome

Chédiak–Higashi syndrome (CHS) is an autosomal recessive disorder described in cattle, cats, mink, and mice (Ogawa et al., 1997; Prieur & Collier, 1978, 1981; Yamakuchi et al., 2000). Animals have a partial oculocutaneous albinism, an increased susceptibility to infection, a tendency for prolonged bleeding, and enlarged cytoplasmic granules in most, but not all, granule-containing cells. Ocular manifestations of CHS include photophobia, light or pale irides, pale tapetal fundus,

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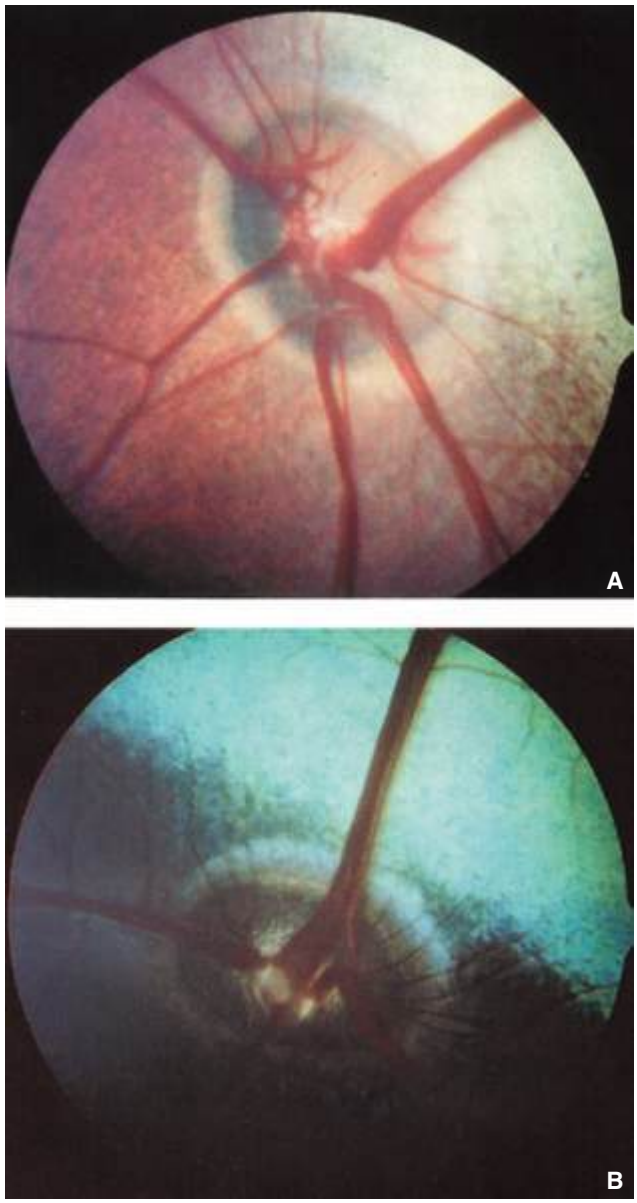


Figure 37.4.1 Ocular fundus of a Chediak–Higashi-affected (**A**) and a normal (**B**) calf. **A.** Pale yellow-green, less brilliant tapetum and relative lack of pigment in the disk and non-tapetal zone. The choroidal vessels are seen easily in this area. **B.** Brilliant tapetum and heavily pigmented disk and non-tapetal zone.

and fundic hypopigmentation (Fig. 37.4.1). In affected cattle, the corpora nigra are also absent (Collier et al., 1979).

Ehlers–Danlos Syndrome (Dermatosparaxis, Hyperelastosis Cutis, Cutaneous Asthenia)

Ehlers–Danlos syndrome is a group of connective tissue disorders. In 2017, 13 types of Ehlers–Danlos syndrome were categorized in humans. Many of these syndromes have overlapping features. Alterations in connective tissues can result in clinical manifestations affecting the skin, bones, joints, vasculature, eye, etc. (for recent classification sytem in humans see Bowen et al., 2017; Brady et al., 2017). Ehlers–Danlos syndrome has been reported in crossbred and Dorper sheep breeds and in Drakensberger, Charolais, Hereford, Holstein, Simmental, Belgian Blue, Limousin, and mixed-breed cattle (Carty et al., 2016; Colige et al., 1999; Holm et al., 2008; Joller et al., 2017; Monteagudo et al., 2015; Steffen, 1993; Zhou et al., 2012).

Clinical signs can manifest a few weeks to several months after birth (Holm et al., 2008). Affected animals are clinically characterized by fragile and easily torn hyperelastic skin. Some animals have fragile vasculature and joint capsules. The mode of inheritance of this syndrome in both sheep and cattle is autosomal recessive.

In the Belgian Blue, and in a flock of mixed breed sheep and in Dorper sheep, mutations involving *ADAMTS2* (ADAM metallopeptidase with thrombospondin type 1 motif, 2 gene) have been identified (Colige et al., 1999; Joller et al., 2017; Monteagudo et al., 2015; Zhou et al., 2012). A variant form of Ehlers–Danlos syndrome has been reported in a Holstein calf consisting of a genetic defect of the core protein of dermatan sulfate proteoglycan which caused the functional abnormality in cutaneous tissues (Tajima et al., 1999).

A diagnosis of Ehlers–Danlos syndrome is made based upon a clinical syndrome of skin hyperextensibility, clinical signs associated with skin fragility including easily torn skin, and skin histopathology (routine histopathology with Masson's trichome staining and ultrastructural examination) (Paciello et al., 2003).

Ehlers–Danlos syndrome is incurable and because of its hereditary nature owners should be advised to not use affected animals for breeding.

Facial Dysplasia Syndrome

A syndrome of facial dysplasia has been described in Holstein cattle (Agerholm et al., 2017). The trait is lethal. Affected calves have severe facial dysplasia and complete prolapse of the ocular globes and bilateral cataracts are present. Additionally, arthrogryposis, microcephaly, and brain malformations including hydrocephalus are present. The syndrome is caused by a dominantly inherited mutation involving *FGFR2* (fibroblast growth factor receptor 2 gene) (Agerholm et al., 2017).

Hydrocephalus

Hydrocephalus refers to the active enlargement of the brain ventricular system. Ventriculomegaly (enlargement of the brain ventricles) is not necessarily synonymous with hydrocephalus (Estey, 2016; Thomas, 2010). Bovine hydrocephalus is a commonly encountered congenital defect for which concurrent ocular lesions are rarely reported (Greene & Leipold,

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1974; Leipold et al., 1971, 1974). In Shorthorn calves, multiple ocular anomalies including microphthalmia, cataracts, retinal detachment, retinal dysplasia, optic nerve, optic chiasm and optic tract hypoplasia, persistent pupillary membranes, and vitreous hemorrhage have been associated with hydrocephalus (Leipold et al., 1971, 1974). The cause has not been determined, but it has been postulated to be genetic (Leipold et al., 1971). Presumed heritable hydrocephalus has been reported in purebred Duroc and crossbred swine (Blunn, 1938; Gilman, 1956; Smith & Stevenson, 1973).

Marfan Syndrome

Marfan syndrome is a condition characterized in cattle, and humans, by joint/tendon laxity, spinal curvature, long thin limbs, aortic dilatation and mitral valve malformation, myopia, microspherophakia, and lens luxation (Fig. 37.4.2) (Besser et al., 1990; Pessier & Potter, 1996; Potter & Besser, 1994; Singleton et al., 2005). Affected animals may sucumb to the disease in early adulthood because of rupture of major cardiovascular structures (e.g., aorta). Like human Marfan syndrome, a genetic defect in the gene encoding fibrillin-1

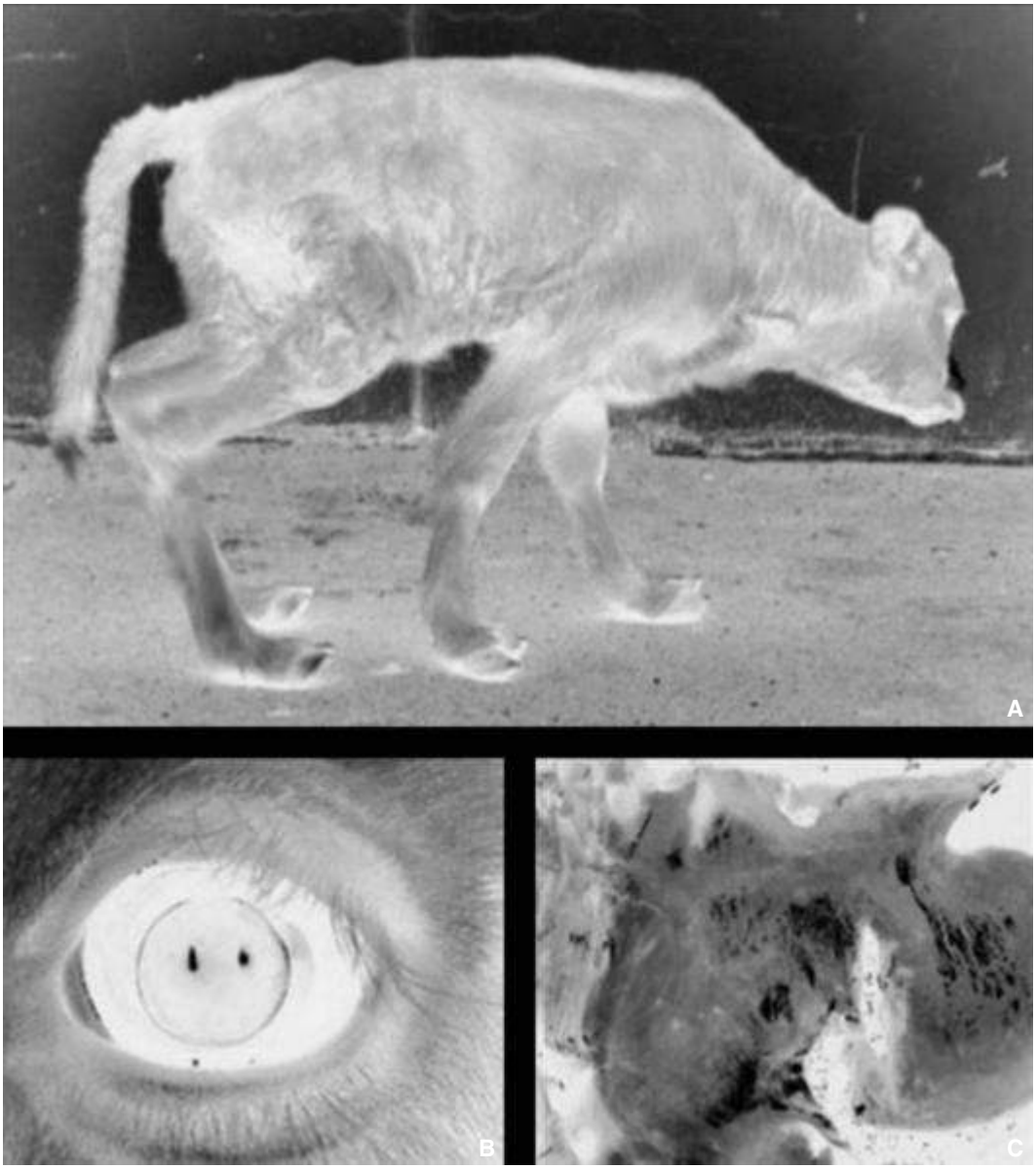


Figure 37.4.2 Bovine Marfan syndrome includes skeletal, cardiovascular, and ocular defects. **A.** Affected calves had unusually long legs and did not stand directly on their hooves, indicating the presence of skeletal defects and joint hypermobility. **B.** Eye lenses were abnormally small and round with some displacement. **C.** Calves died in the first few years of life because of ruptured aortas. (*Source*: Reprinted with permission from Singleton, A.C., Mitchell, A.L., Byers, P.H., et al. (2005) Bovine model of Marfan syndrome results from an amino acid change (c.3598G4A, p. E1200K) in a calcium-binding epidermal growth factor-like domain of fibrillin-1. *Human Mutation*, **25**, 348–352.)

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(i.e., *FBN1*), a protein important in extracellular microfibrils, has been shown (Hirano et al., 2012; Singleton et al., 2005).

Multiple Ocular Defect Syndrome

Multiple ocular defect syndrome (MODS) is inherited in an autosomal recessive fashion. This syndrome has been reported in Japanese black cattle and is characterized by lenticular hypoplasia and/or dysplasia, retinal dysplasia and detachment, persistence of the hyaloid artery, persistence of the primary vitreous, and microphthalmia (Uchida et al., 2006). A genetic mutation in *WFDC1* (WAP Four-Disulfide Core domain 1 gene) has been identified as the cause of MODS (Abbasi et al., 2009).

Developmental

Lysosomal Storage Diseases

Lysosomal storage diseases have been identified in cattle and sheep, and occasionally in goats. These inborn errors of metabolism are, however, relatively rare diseases that have received a disproportionate amount of investigation, because they represent potential animal models for human syndromes. Storage diseases are characterized by an accumulation of metabolic by-products within lysosomes, the cellular organelles which degrade complex macromolecules. The substrates for catabolism within lysosomes include glycoproteins, mucopolysaccharides, oligosaccharides, proteins, and sphingolipids (Jolly & Walkley, 1997; Skelly & Franklin, 2002). Storage diseases result from a deficiency in a specific catabolic enzyme (i.e., acid hydrolases), which allows the enzyme substrate to accumulate in the lysosomes within cells. Consequently, lysosomal storage diseases are subclassified based upon the type of storage product. Important groups include the glycoproteinoses, mucopolysaccharidoses, oligosaccharidoses, proteinoses, and the sphingolipidoses (Jolly & Walkley, 1997; Skelly & Franklin, 2002). Specific lysosomal storage diseases are normally named according to the specific accumulated product. Because this excess material is a normal component, the histopathologic changes result from physical distortion of affected cells rather than from a toxic effect. Most lysosomal storage diseases, with known mode of inheritance, are inherited as an autosomal recessive trait. When homozygous, the syndromes are usually severe, thus resulting in neurologic disease and, eventually, death. The eyes in most patients have histopathologic lesions, but clinical ophthalmic lesions may not be visible (Aguirre et al., 1986; Evans, 1989).

Ceroid Lipofuscinosis

Ceroid lipofuscinoses (CL) are a group of inherited proteinoses characterized by accumulation of proteins in neurons and other tissues, including the retina. These storage products show an autofluorescence similar to ceroid and lipofuscin, lipopigments that accumulate normally with aging.

Neuronal ceroid lipofuscinosis (NCL) has been described in cattle, sheep and goats, as well as cats, dogs, humans, and mice (Harper et al., 1988; Jolly, 1995; Jolly & Walkley, 1997). This condition is inherited as an autosomal recessive trait (Prieur et al., 1990). NCL is classified on the basis of age at onset. Clinical signs include a slowly progressive ataxia and animals will eventually succumb to the disease. Blindness develops in most instances, except with the late-onset adult form.

The sheep model has been studied most extensively (Jolly et al., 1994; Kappang, 1970; Perentos et al., 2015; Sisk et al., 1990; Smith, 1996). Hampshire sheep present with blindness and, in advanced cases, manifest with slight retinal vascular attenuation (Jolly & Palmer, 1995). In one report, Devon cattle in Australia with lipofuscinosis manifested visual and neurologic signs by 14 months of age, and they had ophthalmoscopic signs of altered tapetal reflectivity, optic disc pallor, and depigmentation of the non-tapetal region (Smith & Harper, 1987). Autofluorescing lysosomal storage products accumulate in neural tissue including the retinal photoreceptors (Armstrong & Jolly, 1986). Peroxidase activity is decreased in the retina and leukocytes, but the exact enzymatic deficiency has not yet been defined (Armstrong et al., 1978; Jolly & Palmer, 1995; Siakotos et al., 1978).

Galactocerebrosidosis (Globoid Cell Leukodystrophy, Krabbe's Disease, Galactosylceramide Lipidosis)

Galactocerebrosidosis, or globoid cell leukodystrophy or Krabbe's disease, is a member of the inherited sphingolipidoses described in dogs, cats, and sheep that results from a deficiency in β-D-galactocerebrosidase (GALC) (also known as galactosylceramidase) activity (Pritchard et al., 1980; Skelly & Franklin, 2002). The substrate galactocerebroside (i.e., galactosylceramide), a constituent of myelin, and another metabolite of myelin turnover, psychosine (galactosyl sphingosine), accumulate. Psychosine is highly cytotoxic to oligodendroglia and is thought to be the primary metabolite involved in the pathogenesis of the disease (Miyatake & Suzuki, 1972). Consequent to the build-up of these toxic metabolites, leukodystrophy results. A progressive, diffuse neurologic syndrome develops at a young age, and death occurs within a few months. Visual deficits and blindness may result late in the disease, but ophthalmoscopic lesions have not been observed (Aguirre et al., 1986). Globoid cell leukodystrophy is pathologically characterized by bilaterally symmetric demyelination of the white matter of the brain, spinal cord, spinal nerve roots, and peripheral nerves and by the accumulation of globoid cells (multinuclear globoid macrophages), predominantly perivascularly.

Generalized Glycogenosis (Pompe's Disease)

Generalized glycogenosis (glycogen storage disease type II; Pompe's disease) is caused by a deficiency of acidic 1,4

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α-glucosidase (AAG) and has an autosomal recessive mode of inheritance (Reichmann et al., 1993). The disease has been described in humans, dogs, quail, sheep, and Shorthorn, Brahman, Droughtmaster, or other Brahman-type cattle in Australia. The disease occurs just prior to or after weaning at approximately 6 months of age in Brahman cattle. Affected cattle usually live less than 12 months (Reichmann et al., 1993). The earliest presenting clinical signs typically include failure to thrive and muscular weakness. As the disease progresses, the calves develop a wide-based stance, concave arch of the neck, and apparent enophthalmos. Histopathologic lesions in affected calves included diffuse swelling and cytoplasmic vacuolation of neurons in the brain and spinal cord, and marked vacuolation in skeletal muscle fibres (Reichmann et al., 1993). In this same study, 2 of 96 affected Brahman or Brahman-type calves displayed apparent congenital blindness. The eyes of one such affected blind calf were examined histologically and had mild vacuolation of the retinal ganglion cells and glial cells in the optic nerves, similar to histopathologic lesions noted in two older affected calves with vision (Reichmann et al., 1993). Given these results, it remains unclear as to whether or not the blindness in these calves was directly related to generalized glycogenosis.

Mutations in AAG have been identified in Brahman, Shorthorn, and Droughtmaster cattle. In particular, Pompe's disease can be named according to the exon where the mutation occurs. In Brahman and Droughtmaster cattle a frameshift mutation in exon 7 of AAG (Pompe's E7) (Dennis et al., 2002; Lyons et al., 2017) has been identified, whereas another mutation occuring at exon 13 (Pompe's E13) (Dennis et al., 2002) has been reported in Brahman cattle, and a mutation in exon 18 has been identified in Shorthorn cattle (Pompe's E18) (Dennis & Healy, 2001).

GM1-Gangliosidosis

GM1-gangliosidosis is a member of the sphingolipidoses. A deficiency of lysosomal hydrolase, β-galactosidase, produces an accumulation of GM1-ganglioside in the cerebral cortex and visceral organs. Such deficiencies have been reported in cats, cattle, dogs, humans, mice, and sheep. With respect to food animals, the condition has been reported to occur in Friesian cattle and sheep (Donnelly & Sheahan, 1981; Donnelly et al., 1973; Murnane et al., 1989a,b, 1991; Sheahan et al., 1978). Histopathologic lesions of membrane-bound inclusions have been shown throughout the brain, spinal cord, and retinal ganglion cells, but only in cattle have clinical ophthalmoscopic lesions been observed consisting of multifocal tiny white spots. These ophthalmoscopic lesions resulted from elevations of the internal limiting membrane by swollen retinal ganglion cells (Sheahan et al., 1978). Wallerian degeneration has also been reported in the optic nerves of affected calves (Sheahan et al., 1978). Affected animals typically live up to approximately 15 months of age.

GM2-Gangliosidosis (Tay-Sachs Disease, Sandhoff Disease, O-Variant, B-Variant, AB-Variant)

GM2-gangliosidosis is caused by a deficiency of hexosaminidase (for review see Jeyakumar et al., 2002). Hexosaminidase has two subunits, α and β, each coded for by *HEXA* and *HEXB* genes, respectively. There are three types of hexosaminidase: hexosaminidase S (αα dimer), hexosaminidase A (an αβ dimer), and hexosaminidase B (a ββ dimer). In addition, there is a GM2-activator protein coded for by the *GM2A* gene which is necessary for degrading GM2 ganglioside in concert with hexosaminidase A. In humans, deficiency in the α subunit, and therefore depletion of hexosaminidase A and S, results in classic GM2-gangliosidosis (Tay-Sachs disease or B-variant). A deficiency in the β subunit, depleting both hexosaminidase A and B, is known as Sandhoff disease or the O-variant. Tay-Sachs disease has been reported in Jacob sheep (Porter et al., 2011; Torres et al., 2010; Wessels et al., 2014). Affected lambs present between 6 and 8 months of age with signs of general failure to thrive, ataxia, proprioceptive losses, involuntary twitching, and star-gazing behaviour (Wessels et al., 2014). Microscopically, neurons throughout the brain and spinal cord have marked neuronal perikaryonal swelling with pale amphophilic granular material or microvacuolar change and associated with eccentric nuclear and Nissl substance displacement (Wessels et al., 2014). Similar findings are found within retinal ganglion cells and neurons within the spinal and trigeminal ganglia (Wessels et al., 2014). Clinical ophthalmic examination of these sheep has not been described to date.

Further, deficiencies in GM2-activator protein results in GM2-activator deficiency, also known as the AB-variant. GM2-gangliosidosis has been reported in Yorkshire pigs (Kosanke et al., 1978; Read & Bridges, 1968). Clinical signs in affected pigs include ataxia after 3 months of age, reduced growth, and gray–white spots within the retina.

Mannosidosis

Mannosidosis, a member of the inherited oligosaccharidoses, is a recessively inherited deficiency of mannosidase resulting in the excessive storage of mannose-rich glycoproteins, glycopeptides, and oligosaccharides. Deficiencies of alpha (α) and beta (β) forms of mannosidase have been described. Alpha-mannosidosis has been described in Angus, Murray Grey, and Galloway cattle, and Nubian goats (Borland et al., 1984; Embury & Jerrett, 1985; Healy & Cole, 1976; Hocking et al., 1972; Jolly, 1978). Beta-mannosidosis has been reported in Saler cattle and Nubian goats (Abbitt et al., 1991; Bryan et al., 1993; Jolly et al., 1990; Jones et al., 1983; Render et al., 1989, 1992).

Alpha-mannosidosis has been studied extensively in Aberdeen Angus, Galloway, and Murray Grey cattle (Aguirre et al., 1986; Jolly, 1978). Affected calves are stunted, and they develop a progressive ataxia as well as intention tremors of the head and body. Death occurs within a year.

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Clinical ocular lesions have not, however, been reported (Aguirre et al., 1986).

Kid goats with β-mannosidosis have neurologic impairment, facial deformities, carpal contraction, hyperextension of pasterns, and muscle atrophy (Hartley & Blakemore, 1973). Ocular manifestations of this disorder include small palpebral fissures, ptosis, miosis, prolapsed third eyelids, and apparent enophthalmos. The eyelids may be thickened and immobile, and a ventrolateral strabismus may be present. Vision appears to remain intact. On ophthalmoscopy, however, the vitreous is hazy, and the optic disc has decreased myelination. Histopathologically, most cells in the eye are distended with intracytoplasmic vacuoles (Jones et al., 1983; Render et al., 1989).

In Saler calves with β-mannosidosis, calves typically succumb to the disease or are euthanized within 24 hours of birth (Abbitt et al., 1991; Bryan et al., 1993; Jolly et al., 1990; Render et al., 1992). Nevertheless, affected calves have a dome-shaped skull, mild prognathism, and vertically narrowed palpebral fissures, although the globes are normal-sized compared with age-matched unaffected calves. In bovine β-mannosidosis, the positioning, size, and shape of the pinnae, the external auditory meatus, and the tympanic bullae are also abnormal (Render et al., 1992). Affected calves also have other distinctive characteristics including an inability to stand at birth, head tremors, nystagmus, and opisthotonos (Render et al., 1992). Aside from nystagmus and narrowed palpebral fissures, clinical ophthalmic examination of affected calves is unremarkable. Histopathologically, similar to affected goats, most ocular cells are distended with intracytoplasmic vacuoles (Jones et al., 1983; Render et al., 1989), except cattle with β-mannosidosis also have vacuolation of both the inner and outer ciliary epithelial cells (Render et al., 1992). Optic nerve hypomyelination is also reported in calves with β-mannosidosis (Patterson et al., 1991).

Acquired

Hematologic Diseases

Anemia

Anemia is the reduction in red blood cells (RBC) per volume of whole blood. Anemia is classified as regenerative if there has been a normal bone marrow response to erythropoietin (e.g., usually occurs with blood loss or hemolytic disease), or nonregenerative if the normal reticulocyte response is lacking (e.g., may occur with chronic extra-marrow disease which reduces RBC survival time, selective erythropoietin depression, insufficient erythropoietin release, or a combination of these factors) (Rebar et al., 2005a). Severe anemia often manifests systemically as varying palor of mucous membranes, cool mucous membranes, tachycardia, polypnea, weakness, as well as signs specific to the underlying primary condition. Conjunctival pallor is even used as an indicator of anemia caused by gastrointestinal parasitism in sheep and goats (Kaplan et al., 2004; Vatta et al., 2001). Ocular manifestations of severe anemia include pale retinal vasculature, varying degrees of retinal hemorrhage, and subtle changes in tapetal reflectivity. Retinal hemorrhages are more likely to be observed, however, and are more dramatic if accompanied by thrombocytopenia (Carraro et al., 2001). Small intraretinal hemorrhages are typical and may reabsorb quickly with correction of the anemia, but pigmentary disturbances may be a residual retinal alteration. The pathogenesis of the retinal hemorrhage is postulated to be from hypoxia to the vessel walls as a consequence of the anemia (Carraro et al., 2001). Extreme pallor to the retinal vessels may mimic the appearance of generalized/diffuse retinal degeneration/atrophy, with the exception of the marked tapetal hyperreflectivity present in the latter syndrome.

Icterus

Icterus or jaundice is a condition characterized by hyperbilirubinemia and deposition of bile pigments in the skin, sclera, and mucous membranes causing them to appear a shade of yellow. The sclera is the classic location for detection of icterus given its relative lack of pigmentation. The yellow appearance of icterus may be detected in the intraocular structures as well (e.g., blue irides may turn green and yellow hues may be imparted on the tapetum).

Polycythemia

Polycythemia is classified as relative or absolute (primary and secondary forms). Relative polycythemia is an increased packed cell volume (PCV) with normal RBC mass occurring as a result of a reduction in plasma volume as may arise from external losses of body fluids (e.g., diarrhea, burns).

Absolute polycythemia is an increase in total RBC mass, and it may be classified as either primary or secondary (appropriate and inappropriate). Absolute primary polycythemia (i.e., polycythemia vera) is an absolute increase in erythropoiesis without an increase in erythropoietin, and appears to be rare in food animals (Fowler et al., 1954).

Absolute secondary polycythemia results from altered erythropoietin homeostasis and is described as being appropriate or inappropriate. Absolute secondary appropriate polycythemia occurs as a consequence of persistent hypoxia, and can be found in animals with conditions such as congenital cardiac defects causing right-to-left shunting of blood (Cote & Ettinger, 2001; Lombard et al., 1989; Moore & Stepien, 2001), and certain forms of chronic pulmonary disease. In large animals, congenital cardiac defects causing right-to-left shunts, such as tetralogy of Fallot and ventricular septal defect, are common causes of absolute secondary appropriate polycythemia (Bayly et al., 1982; Martin et al., 1972). Absolute secondary inappropriate polycythemia, however, results from disease processes which lead to inappropriate secretion and elevation of erythropoietin or an erythropoietin-like

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substance in the absence of systemic hypoxia. Causes of absolute secondary inappropriate polycythemia include diseases which result in the production of erythropoietin or which cause local hypoxia and trigger erythropoietin synthesis including renal (e.g., renal neoplasia, cystic disease, and hydronephrosis), hepatic, or endocrine disease, especially that caused by neoplasia (e.g., hepatocellular carcinoma and interstitial nephritis) (Beech et al., 1967). The most prominent ocular manifestations of polycythemia reported in animals include engorged and tortuous, dark, ruddy colored conjunctival and retinal blood vessels. In addition, varying degrees of papilledema, retinal hemorrhage, and occlusion of the retinal veins caused by increased blood viscosity may occur. A heifer with absolute secondary appropriate polycythemia resulting from congenital cardiac disease developed hyphema and vitreous hemorrhage later in the course of the disease (Martin et al., 1972). Treatment varies according to the cause of the polycythemia. In one case of secondary appropriate polycythemia, in a calf, treatment with two phlebotomies, performed 3 days apart, resulted in short-term relief followed by recurrent systemic signs, miosis and hyphema, and euthanasia 2 months later (Martin et al., 1972). If left untreated, however, retinal detachment and ocular hemorrhage may occur with persistent polycythemia (Lombard & Twitchell, 1978; Martin et al., 1972).

Thrombocytopenia and Thrombopathies

Thrombocytopenia results from either decreased platelet production, increased removal, sequestration, or any combination of these (Rebar et al., 2005b). The most common causes of thrombocytopenia in food animals include infectious diseases, immune-mediated disease, and drug-related or toxin-related causes. In particular, the numerous pathogens implicated in causing infectious thrombocytopenia in food animals include bovine viral diarrhea virus (Hamers et al., 2000), *Theileria annulata* (Omer et al., 2002; Singh et al., 2001), *Babesia bovis* (Yeruham et al., 2003), and classic swine fever (Bautista et al., 2002; Gomez-Villamandos et al., 2003). Thrombocytopenia is also seen: (1) as an idiopathic (Hoyt et al., 2000; Yasuda et al., 2002) or primary immune-mediated thrombocytopenia; or (2) caused by medications which impair platelet production, or cause secondary immune destruction of the platelets.

Thrombopathies are blood coagulation disorders as a result of platelet dysfunction and are either acquired or inherited (Rebar et al., 2005b). Disease processes associated with thrombopathies may include anemia, disseminated intravascular coagulation, liver failure, and uremia (Irmak & Turgut, 2005; Rebar et al., 2005b). Inherited thrombopathies can be found in cattle affected with Chediak–Higashi syndrome or may be inherited as a primary disorder in Simmental and Japanese Black cattle (Akuzawa et al., 1991; Mapletoft et al., 2000; Searcy et al., 1990). Regardless of the origin, both thrombocytopenia and thrombopathies are rather frequent causes of ocular and periocular hemorrhage. A case of idiopathic thrombocytopenia, diagnosed in a Japanese Black cow, resulted in sudden severe subconjunctival hemorrhage and hemorrhage under the mucous membranes of the vagina (Yasuda et al., 2002). The presence of bleeding signs at a given platelet level vary between individuals, but platelet counts are usually less than 50,000 cells/μL when ocular petechiae form. Acute loss of platelets is more likely to manifest as hemorrhage at a given level than is a gradual loss of platelets (Breitschwerdt, 1988). Therapy is directed at the underlying cause, and if bleeding signs are severe, transfusion of fresh whole blood or platelet-rich plasma is indicated.

Idiopathic Diseases

Idiopathic Bovine Uveitis (Bovine-Specific Ophthalmia)

An idiopathic uveitis affecting cattle has been described (Davidson et al., 1992; Marolt, 1968). As the name of this condition implies, the cause of this condition remains elusive. Clinical signs of idiopathic bovine uveitis are compatible with uveitis and, in addition, chorioretinal edema and hemorrhage may be noted. Therapy for this condition is aimed at ameliorating intraocular inflammation. Prognosis is unknown given the paucity of clinical reporting of this disease.

Immune-Mediated Diseases

Allergic Conjunctivitis

Allergic conjunctivitis has been reported in food animals (Fledderus et al., 1988; Krahwinkel et al., 1988; Wiseman et al., 1982). Allergic conjunctivitis is mediated by immunoglobulin-E (IgE) and subsequent activation of histamine receptors by mast cell degranulation (Rosenwasser et al., 2005). Exuberant lacrimation, ocular pruritis, and hyperemic and edematous conjunctiva are common clinical signs of allergic conjunctivitis. Allergic conjunctivitis has been described in a herd of cattle with familial allergic rhinitis (Krahwinkel et al., 1988), and in veal calves being fattened with cow's milk or milk replacer (Fledderus et al., 1988). The veal calves fattened with milk replacer showed signs of increased severity of diarrhea, hyperemia of the conjunctiva and nose, and skin hypersensitivity compatible with food allergy (Fledderus et al., 1988). Allergic conjunctivitis is typically diagnosed in food animals after excluding all other causes of conjunctivitis. Treatment is aimed at identifying and removing the inciting allergen.

Infectious Diseases

For excellent comprehensive reviews see Coetzer and Oberem (2018).

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Bacterial

Botulism

Botulism is an intoxication resulting from the neurotoxin produced by *Clostridium botulinum*. *C. botulinum* is a Gram-positive, spore-forming, saprophytic, anaerobic, rod-shaped bacterium. There are eight subtypes (types A, B, C-alpha and C-beta, D, E, F, G) of *C. botulinum* and each is differentiated from the other based upon the type of neurotoxin they produce. Cattle, sheep, goats, and horses are considered to be quite susceptible to botulism compared with dogs, cats, and swine. Livestock are predominantly affected by *C. botulinum* type C or D, and less commonly type A or B (Kriek & Odendaal, 2004).

Clinical signs in livestock typically develop after ingestion of food, water, and soil contaminated by decomposed organic materials (e.g., carrion and putrid bones) containing neurotoxins produced by the bacterium (Driehuis et al., 2018; Kriek & Odendaal, 2004). In addition, nutritionally deprived animals may directly ingest infected carrion. After ingestion, the botulinum toxin is absorbed in the gut and subsequently prevents the release of acetylcholine at cholinergic synapses. Consequently, clinical signs are suggestive of skeletal muscular weakness and autonomic dysfunction, regardless of the food animal species affected.

Clinical signs vary depending on the type and quantity of toxin ingested. General clinical signs include symmetrical ascending limb paresis leading to flaccid paralysis, depressed or absent tendon reflexes, abnormal motor responses during cranial nerve testing, excessive salivation, regurgitation of feed and water, and depressed ruminal movements. Sensory perception and reflexes associated with the eye persist for a significant period of time after the onset of skeletal muscular paralysis (Kriek & Odendaal, 2004). Ocular signs that may manifest include mydriasis caused by loss of parasympathetic/sympathetic balance on the iris, and diminished pupillary light reflexes. Definitive diagnosis is made based on finding the toxin through use of the neutralization test in mice, in the food, vomitus, feces, or serum. Treatment consists of supportive care and the administration of hyperimmune serum specific to the toxin type involved (to prevent further binding of toxin). Prognosis is variable and is dependent upon the severity of the disease and whether secondary complications (e.g., pneumonia, compartmental syndrome) occur. In cases of herd outbreaks, it is important to identify the source of food, water, and/or soil contamination.

Chlamydiosis

Chlamydiosis is caused by Gram-negative, obligate intracellular bacteria of the genus *Chlamydia* (for review see Borel et al., 2018; Gunn & Lofstedt, 2016). Several strains of bacteria in the family *Chlamydiaceae* cause disease in food animals. Chlamydial diseases in ruminants and swine are mainly caused by the species *Chlamydia pecorum*, *C. abortus*, and *C. suis*. However, *C. pecorum* is the main chlamydial pathogen responsible for disease in domestic ruminants.

The intestine is the natural habitat of this organism, and transmission is via fecal contamination, aerosol, and contact with infected secretions. It has been suggested that if contact is by aerosol, pneumonia and keratoconjunctivitis are the clinical manifestations (Idtse, 1984). Factors influencing the clinical signs that manifest include the strain of chlamydiae (each strain has a predilection for different tissues and, hence, causes different disease[s]), age of animal, route of infection, and perhaps, the means of transmission. *C. pecorum* may produce a wide range of diseases in cattle, sheep, and swine including encephalomyelitis, enteritis, polyarthritis, metritis, pneumonia, and conjunctivitis (Andersen, 2004; Longbottom, 2004; Walker et al., 2015). Outbreaks of this particular disease are typically sporadic and usually affect young animals. In swine, *C. suis* strains have also been isolated from the conjunctiva, and intestinal and respiratory tracts in association with conjunctivitis, enteritis, and pneumonia. In severe cases of conjunctivitis, lymphofollicular hyperplasia of the palpebral conjunctiva is common. However, *C. suis* strains have also been isolated from the conjunctiva of clinically healthy pigs (Rogers et al., 1993).

Chlamydiosis among lambs and kids may produce both ocular signs and polyarthritis (Hopkins et al., 1973). Up to 85% of affected lambs may develop polyarthritis as evidenced by a stiff gait or lameness. Lambs may be febrile, gaunt, and spend most of their time lying down. The infection may reach epidemic proportion in flocks as a result of being transmitted by close contact. The ocular signs are bilateral in 80% of cases. Conjunctival lesions include conjunctivitis, petechial hemorrhages, epiphora and mucopurulent exudation, and conjunctival lymphoid follicular proliferation that become confluent, thereby producing folds. The cornea may become involved in advanced cases with peripheral edema and neovascularization (preferentially of the dorsal region) (Fig. 37.4.3). Rarely, the entire cornea may become opacified, and corneal ulceration may develop. In uncomplicated cases, the condition is self-limiting, with resolution occurring within 2–3 weeks (Hopkins et al., 1973).

A definitive diagnosis of chlamydiosis is made based upon the isolation or demonstration of the organism from infected tissues, combined with the presence of consistent clinical and/or pathological findings. Chlamydial agents may be indicated by conjunctival cytology, which may be positive for chlamydial inclusions in 35% of cases, and culture of *Chlamydia* spp. which may be positive in 42% of cases. Isolation of the agent by cell culture is the method of choice; however, *C. pecorum* strains grow better in embryonated chicken eggs (Andersen, 2004). In addition, complement fixation tests and enzyme-linked immunosorbant assay (ELISA) kits are available for the detection of chlamydiae, but the sensitivity and specificity of these tests should be considered. Polymerase chain reaction (PCR) techniques for the detection of various species of chlamydia are also available (Everett et al., 1999; Kaltenboeck et al., 1992; Walker et al., 2015).

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Figure 37.4.3 Chlamydial conjunctivitis in a young goat. Conjunctival inclusion bodies were present on conjunctival scrapings, and the condition responded well to treatment with topical tetracycline. Note the peripheral keratitis. (*Source*: Reprinted with permission from Martin, C.L. (1999) Ocular manifestations of systemic disease. Part 4: Food animals. In: *Veterinary Ophthalmology* (ed. Gelatt, K.N.), 3rd ed., pp. 1492–1504. Philadelphia: Lippincott Williams & Wilkins.)

Differentiation of chlamydial agents from *Mycoplasma* spp. may be achieved on the basis of culture results, fewer inflammatory cells at conjunctival cytology with *Mycoplasma* spp., lack of follicle formation with *Mycoplasma* spp., and tendency toward bilateral ocular involvement with *Chlamydia* spp.

Chlamydial organisms are ubiquitous in the livestock population. Hence, vaccination (available for ovine abortion strain [*C. abortus*] only) and antibiotic therapy are the main methods of control (Andersen, 2004). Treatment usually includes topical or systemic tetracycline therapy, although recurrence of clinical signs or chronic persistent infections can occur (Walker et al., 2015).

Histophilus somnus (Thromboembolic Meningoencephalitis, Histophilosis Sleeper Calves)

Histophilosis is caused by infection with a pleomorphic, Gram-negative bacterium, *Histophilus somnus* of the family Pasteurellaceae (Angen, 2016). *H. somnus* produces a peracute to chronic septicemia of yearling cattle, usually in feedlots, although pastured animals have also experienced outbreaks. Most infections occur during the early winter months, and mortality rates may be as high as 95%. The infection produces a vasculitis with thrombosis.

Clinical signs reflect the body system that is affected. *H. somnus* can cause mastitis, meningoencephalitis, myocarditis, otitis, orchitis, metritis, pneumonia, polysynovitis, and vulvitis (for review see Harris & Janzen, 1989; O'Toole & Sondgeroth, 2016). Peracute cases are found either dead or with neurologic signs. Calves may appear to have closed to semiclosed eyelids, hence the colloquial name "sleeper calves" (O'Toole & Sondgeroth, 2016). Cranial nerve deficits are often present. Blindness may also be present, as may strabismus and nystagmus. Blindness may result from ocular disease or be central in origin caused by multifocal hemorrhage and necrosis within the brain (MacDonald et al., 1973; Panciera et al., 1969; Stephens et al., 1981). Ocular lesions of conjunctivitis, and, less commonly, corneal opacities and anterior uveitis may occur, but the most characteristic lesions are in the fundus. Ocular fundus lesions characteristic of thromboembolic meningoencephalitis (TEME) are varying degrees of retinal hemorrhages and focal exudates, so called "cotton spots", associated with end-arterioles (Fig. 37.4.4). Focal retinal detachments may be associated with the exudates as well, and modest papilledema is often present. Histopathologically, thrombosis of the retinal vessels, focal retinal necrosis, focal neutrophilic exudates in the retina, focal detachments, cytoid bodies in the nerve fiber layer, degeneration and neutrophilic inflammation of the vitreous, and an optic neuritis are typical lesions. The cellular reaction is mainly neutrophilic, but mononuclear

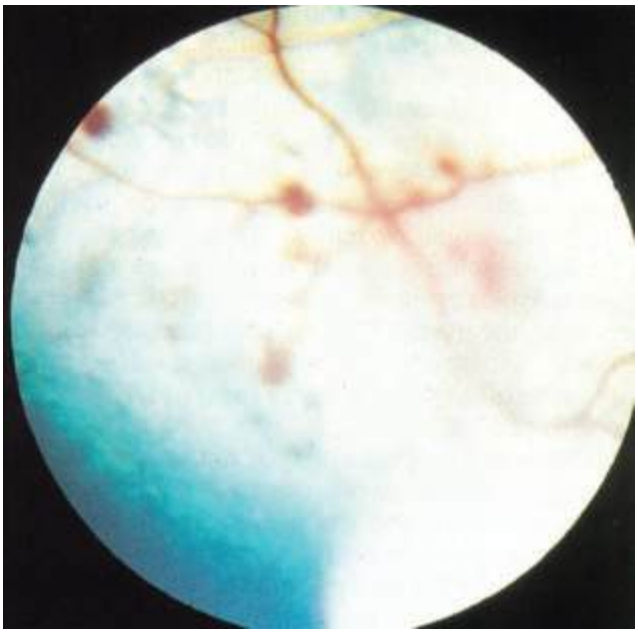


Figure 37.4.4 Recumbent heifer with thromboembolic meningoencephalitis-related retinal lesions. Multiple intraretinal hemorrhages were associated with the small retinal vessels, subretinal exudate, and a bullous retinal detachment. (*Source*: Reprinted with permission from Martin, C.L. (1999) Ocular manifestations of systemic disease. Part 4: Food animals. In: *Veterinary Ophthalmology* (ed. Gelatt, K.N.), 3rd ed., pp. 1492–1504. Philadelphia: Lippincott Williams & Wilkins.)

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perivascular reactions in the retina and choroid are also present. In the later stages of the disease, fibrous chorioretinal adhesions are also seen (Little & Sorensen, 1969; Dukes, 1971).

Peracute to acute deaths with neurologic signs as well as retinal hemorrhages and exudates in feedlot cattle are highly suggestive of the diagnosis. Demonstration of elevated circulating serum antibodies for *H. somnus* can be helpful in the diagnosis of TEME (Stephens et al., 1981). Lesions of fibrinopurulent meningitis and multifocal hemorrhagic necrosis of the brain at necropsy are "pathognomonic." PCR detection of *H. somnus* has been reported (Christensen et al., 2003).

Early treatment before the animal is recumbent using appropriate antimicrobials may prevent death. Vaccination is available.

Listeriosis (Silage Eye)

Listeriosis is caused by a small rod-shaped, Gram-positive bacterium belonging to the genus *Listeria* (Morin, 2004). The most common and important organism causing disease in domesticated animals is *Listeria monocytogenes*. Spoiled or inappropriately fermented corn or hay silage is the main source of infection (Driehuis et al., 2018). Small wounds in the lips, oral and nasal mucosae, and the conjunctiva permit entry of the causative agent (Braun et al., 2002). In addition, venereal transmission in ruminants has been described (Wiedmann et al., 1999). For further details regarding the transmission and pathogenesis of listeriosis in food animals, the reader is referred to a current textbook in food animal infectious disease and/or internal medicine.

Listeriosis of the central nervous system (CNS) (i.e., meningoencephalitic form) is most likely to be associated with ocular signs in food animal species. The main clinical manifestations of listeriosis include CNS disease with vestibular ataxia and unilateral cranial nerve deficits (Morin, 2004). Involvement of the brainstem may be associated with facial nerve paralysis and keratoconjunctivitis sicca. Keratitis is the main ocular lesion, although varying degrees of hypopyon and anterior uveitis may also be present. Purulent endophthalmitis may also result (Saunders & Rubin, 1975). A variety of ocular lesions have been reported in sheep and goats with listeriosis including scleral hyperemia, unilateral keratitis with or without corneal ulceration, bilateral mydriasis, vertical or horizontal nystagmus, ventrolateral or ventromedial strabismus, unilateral or bilateral diminished or absent menace response, lack of palpebral reflex, and diminished or absent pupillary light reflexes (Braun et al., 2002; Gerros, 1998). In cattle, ocular lesions have been reported to be the most common clinical manifestation of listeriosis, followed by neurologic signs (Erdogan, 2010; Erdogan et al., 2001). Listerial ocular infections (conjunctivitis, keratitis, and uveitis) in ruminants have also been related to environmental or host factors, such as direct ocular exposure of susceptible animals to high numbers of the agent (Evans et al., 2004). In swine, listeriosis usually occurs in newborn pigs, among which oral exposure results in focal necrosis of the parenchymatous organs, lymphoreticular tissue, and a necrotizing vasculitis and septic choroiditis (Busch et al., 1971).

A diagnosis of listeriosis is made based upon consistent clinical signs, and culturing and identifying the organism from body fluids (e.g., cerebrospinal fluid) and tissues (Morin, 2004). Definitive diagnosis is typically made postmortem (Morin, 2004). Treatment is effective only when instituted early (Morin, 2004). Suggested treatments include systemic administration of appropriate anitmicrobials (e.g., penicillin or oxytetracycline), supportive therapy, and isolation of affected animals (*L. monocytogenes* is shed in the feces) (Morin, 2004). *L. monocytogenes* can cause serious disease in people including meningitis and sepsis, and, in pregnant women, spontaneous abortion and stillbirth can result (Low & Donachie, 1997).

Mycobacterium bovis (Bovine Tuberculosis)

Bovine tuberculosis, caused by *Mycobacterium bovis*, is a zoonotic disease which affects cattle worldwide. *M. bovis* also infects other animals, both domesticated and wild, thereby complicating attempts to control or eradicate the disease in cattle. The wildlife species acting to maintain the bacterium in the environment vary depending upon the geographic location (e.g., white-tailed deer in Michigan, USA, brushtail possum in New Zealand, wild boar in central Europe, badgers in the UK, bison and elk in Canada) (Coleman & Cooke, 2001; Fitzgerald & Kaneene, 2013; Palmer & Whipple, 2006; Shury et al., 2015; Smith et al., 2012). Furthermore, bovine tuberculosis most commonly presents as apparently healthy cattle showing an immunologic response to tuberculin rather than animals with clinical disease (Collins, 2005). Ocular tuberculosis has rarely been observed as part of systemic disease in cattle and swine; however, the ocular syndrome has been observed most frequently in cattle. As with most systemic infections, tuberculosis initially involves the choroid, eventually to cause subretinal exudation and retinal detachment. Ocular tuberculosis may also progress to involve the anterior uvea, thus resulting in an endophthalmitis. Ocular lesions are granulomatous, and hence, similar to systemic tubercles for the species (Saunders & Rubin, 1975).

Often, affected small companion animals are in farm settings and drinking unpasteurized milk. History as well as vitreous centesis with cytology and culture would establish a definitive diagnosis. Bovine tuberculosis is a reportable disease in many developed countries and large-scale eradication programs have been implemented and are effective in many countries although maintenance species make complete eradication challenging (for review see Collins, 2005; Cousins, 2001; Fitzgerald & Kaneene, 2013).

Mycoplasmosis (Infectious Keratoconjunctivitis)

Mycoplasmosis occuring in sheep and goats, and other small ruminants (wild and domesticated), is caused by members

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of the genus *Mycoplasma* including *M. conjunctivae*, *M. mycoides*, *M. agalactiae*, and *M. Arginini* (al-Aubaidi et al., 1973; Arbuckle & Bonson, 1980; Baas et al., 1977; Bar-Moshe & Rapapport, 1981; Coetzer & Oberam, 2018; Fernandez-Aguilar et al., 2017a,b; Gelormini et al., 2017; Jones, 1983; McCauley et al., 1971; Rodriguez et al., 1995; Trotter et al., 1977; Whitley & Albert, 1984). The disease may be seen in individual animals or may be seen as an epidemic. Mycoplasmosis in sheep and goats has been reported to cause keratoconjunctivitis as a sole manifestation of infection or in association with various other systemic abnormalities including respiratory disease, arthritis, and mastitis. Mycoplasmosis has also been reported to cause an anterior uveitis, choroiditis, and hyalitis.

In cattle, multiple *Mycoplasma* spp. have been reported to cause systemic disease including pneumonia, arthritis, mastitis, meningitis, infertility, and subcutaneous abscesses (Coetzer & Oberem, 2018). *M. bovis* and *M. bovoculi* may also cause keratoconjunctivitis in affected cattle (Kirby & Nicholas, 1996; Levisohn et al., 2004).

Diagnosis of mycoplasmosis is made based upon consistent clinical signs, identifying the organism cytologically from conjunctival swabs, positively culturing the organism from conjunctival swabs and/or body fluids (e.g., synovial fluid), or identifying organismal DNA from affected animals (Bashiruddin et al., 2005; Thomas et al., 2004). Treatment is aimed at appropriate topical and/or systemic antimicrobial therapy (e.g., tetracyclines) (Rosenbusch et al., 2005).

Neonatal Septicemias

Neonatal septicemias in calves, piglets, kids, and lambs may arise from umbilical infections or ingestion of bacteria. Neonatal septicemias may be associated with polyarthritis, meningitis and/or diarrheal signs, and may sporadically involve the eye. A variety of organisms may be associated with these syndromes, including *Streptococcus* sp., *Escherichia coli*, *Cornybacterium pyogenes*, *Salmonella* sp., *Actinobacillus* sp., *Klebsiella* sp., and *Pasteurella* sp. The usual ocular signs relate to the anterior segment, such as episcleral and conjunctival injection, fibrin clots in the anterior chamber, hypopyon or hyphema, and miosis (Fig. 37.4.5). Posterior segment lesions may be observed if the anterior segment is spared, and they are typical embolic lesions of multifocal hemorrhages, exudates, and focal retinal detachments. Many anterior segment lesions resolve with treatment, but the end result may be a fulminating endophthalmitis.

Tetanus

Tetanus is caused by the neurotoxin produced by the bacterium, *Clostridium tetani*. *C. tetani* is a motile, Gram-positive, nonencapsulated, anaerobic, rod-shaped, spore-forming bacterium. The organism is prevalent in soil worldwide, and spores typically enter the body through an open wound (Herd & Riches, 1964; O'Connor et al., 1993; Ramsay, 1973; Robinson, 1968). In some cattle, exuberant gastrointestinal growth of *C. tetani* may also be associated with causing the disease (Ellison, 1992; Ramsay, 1973; Wallis, 1963). Incubation times vary from 10 days to 1 month. Spores become vegetative and a toxin, tetanospasmin, retrogradely migrates along axons of motor nerves to the CNS. However, it should be noted that tetanospasmin, the principal neurotoxin, is only one of three toxins produced by the bacterium (Acke et al., 2004). The toxin then prevents inhibitory neurotransmission to motor neurons thereby resulting in the classic signs associated with tetanus.



Figure 37.4.5 Left eye of a septicemic goat with uveitis. Note the intracameral fibrin and corneal edema. (*Source*: Courtesy of Ralph Hamor.)

Clinical signs include initial stiffness progressing to generalized spasticity and paralysis. Infected animals generally have a sawhorse stance, retraction of the ears and lips, elevation of the tail, and rapid retraction of the globe, thereby resulting in prolapse of the third eyelids (McGuirk, 1983; Rebhun, 1972). Ruminants with tetanus may develop bloat (McGuirk, 1983). Death can occur from respiratory and cardiac failure.

Therapy for tetanus consists of providing muscle relaxation, providing an appropriate substrate for footing and bedding, eliminating infection by treatment with penicillin, neutralizing unbound toxin by administering tetanus antitoxin, maintaining hydration and nutritional status, and immunization with tetanus toxoid to stimulate an immune response (McGuirk, 1983). Prognosis is poor to grave (Ansari & Matros, 1982). Prevention is attained by proper hygiene and disinfection of surgical instruments during surgical procedures such as castration. Vaccinating animals with tetanus toxoid is successful, although cost effectiveness likely precludes vaccinating entire flocks of sheep or herds of cattle (Maru et al., 1986).

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Mycotic

Dermatophytosis

Dermatophytosis, or clinically relevant cutaneous infections with fungi, are usually caused by the following dermatophytes: *Trichophyton verrucosum* (bovids, goats, and sheep), *T. ovis* (sheep), *Microsporum nanum* (pigs), *M. canis* (pigs), and *T. metagrophytes* (pigs) (for review see Coetzer & Oberem, 2018; Picard & Vismer, 2004). Importantly, dermatophytosis is contagious and zoonotic. The severity and extent of experimentally induced dermatophytosis in calves caused by *T. verrucosum* has been shown to be directly dependent on the degree of cutaneous damage at the site of mycotic inoculation (Oborilova & Rybnikar, 2005). In cattle, goats, and sheep, facial involvement is common and may manifest as dry, crusty, periocular alopecic and nonpruritic lesions. Lesions may be localized or generalized and involve the periocular skin. The disease is typically self-limiting and animals are immune to reinfection.

Diagnosis of dermatophytosis is made based upon consistent clinical signs typically affecting more than one animal in a group, microscopically identifying the organism on skin scrapings, and positively culturing the organism from skin scrapings on an appropriate culture medium (causing a "positive" color change in the culture media). Therapy is typically not implemented in food animals because of the expense incurred by treating a group of animals. In valuable individuals, however, appropriate antifungal drugs (e.g., griseofulvin) are administered and animals can be bathed in appropriate antifungal shampoos. Careful disinfection of affected animals' housing is necessary to prevent spread of the disease and a commercially available vaccine is effective and available for use in cattle (Gudding & Lund, 1995; Gudding & Naess, 1986).

Disseminated Rhizopus

Rhizopus is an opportunistic fungus. Although rare, systemic infections with opportunistic fungi, such as *Rhizopus*, occur most commonly in immunocompromised animals. In adult cattle, systemic mycoses typically arise because of pulmonary or alimentary invasion (Dion et al., 1987). In calves, systemic mycotic infection is rare, and is thought to arise because of hematogenous spread to the fetus from placental infection of the dam (Cordes et al., 1967). A calf with disseminated *Rhizopus* infection has been described with bilateral ocular lesions including endophthalmitis and intumescent immature cataracts (Vasconcelos & Grahn, 1995). Histopathologic ocular abnormalities included vasculitis, suppurative keratitis, anterior uveitis and chorioretinitis, and extensive subcapsular cataracts. Hyphae, most numerous adjacent to blood vessels, and numerous neutrophils were noted in all ocular regions (Vasconcelos & Grahn, 1995).

Parasitic: Flagellates

Trypanosomiasis

African trypanosomes cause sleeping sickness in humans and trypanosomiasis in livestock. Sleeping sickness is caused by *Trypanosoma brucei*, an extracellular eukaryotic flagellate parasite. Livestock trypanosoniasis is caused by closely related *Trypanosoma* spp., and mainly affects animals in sub-Saharan Africa where the tsetse fly vector is common, but also occurs in Asia and South America (Berriman et al., 2005). Experimental *T. brucei* infection in sheep has produced an initial bilateral epiphora, photophobia, and mucous exudation; ocular lesions were more likely to develop the longer the animals survived. Late in the course of disease, hypopyon may develop, which spontaneously improves and then relapses. The cornea may remain clear or develop a mild keratitis. Eyelid edema develops late in the course of disease and is part of extensive subcutaneous edema (Ikede, 1974). Histopathologic examination reveals trypanosomes in the fibrin of the anterior chamber and iris as well as the ciliary body. The anterior uvea is edematous, with a mononuclear inflammatory infiltrate. The retina and choroid have perivascular mononuclear cuffing, and optic neuritis is common. Extraocular muscles often have intense mononuclear inflammation, with trypanosomes being visible. Brain and eye involvement in goats with *T. brucei* and *T. vivax* infections are thought to act as niduses of infection, from which relapses may originate after chemotherapy or spontaneous improvement (Whitelaw et al., 1988). Aqueous centesis may show the trypanosomes, and suramin, pentamidine, and berenil have been advocated for therapy.

Parasitic: Metazoans

Cysticercosis

Cysticercosis is a zoonotic disease caused by the larval form of *Taenia solium* (pork tapeworm). Swine are the natural intermediate host of *T. solium*. Previously, humans were thought to be the sole definitive hosts and tapeworm carriers, and hence the source of infective eggs through which oral–fecal transmission causing cysticercosis would arise in humans and pigs. However, an alternative pig-to-pig route of transmission consisting of second-hand transmission of *T. solium* eggs has been reported (Gonzalez et al., 2005). In humans, these metacestodes invade the brain (neurocysticercosis) and are responsible for many cases of adult-onset epilepsy in the developing world (Gonzalez et al., 2005). The larval stage of *T. solium* may also invade the eye and orbit of various species. Among 39 abattoir swine diagnosed with cysticercosis, 17 had orbital cysts, and 2 had ocular cysts (Cardenas et al., 1984). The parasite stimulates a fibrous sheath, which is formed by the host, that initially does not have inflammatory cells. Macrophages accumulate around the cyst, however, with a halo of lymphocytes and plasma cells that, eventually, surround the parasite (Cardenas et al., 1984). In particular, the active inflammatory response against the metacestode of *T. solium* in swine includes the participation, in sequence, of CD4+, CD8+, and IgM+ lymphocytes (Perez-Torres et al., 2002). Current strategies aimed at controlling/treating cysticercosis in pigs includes systemic administration of oxfendazole (Paranthic, MCI Santé

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Animale, Mohammedia, Morocco) and vaccination using the TSOL18 vaccine (commercially available as Cysvax, Indian Immunologicals Ltd, Hyderabad, India) (Okello & Thomas, 2017).

Setariasis

Adult *Setaria digitata* are found free within the abdominal cavity of many ungulates including cattle and sheep (Shin et al., 2002). The larvae of *Setaria* spp. can migrate into the CNS of animals such as sheep and goats and cause serious disease (Innes & Shoho, 1953). Typically, the adult worms of *Setaria* spp. within the abdominal cavity of cattle are mainly harmless. Heterotropic parasitism of cattle with *Setaria* spp., although rare, has been reported in the cavity of a cystic corpus luteum (Nair et al., 1993) and the eye (Shin et al., 2002). In particular, two cattle in Korea each had a single opaque, blind eye with the presence of motile white worms in the aqueous humor, which were later identified as *S. digitata* in one such case.

Parasitic: Mites

Demodicosis

Demodex spp. live as commensals in the skin of most mammals. In cattle, demodicosis is caused by a burrowing mite, *Demodex bovis*, that lives in the hair follicles. The clinical signs associated with *D. bovis* typically include tiny to egg-sized nodules, containing mites in a purulent material, with generalized distribution over the forelimbs and withers (Nutting, 1976). Demodecosis may also affect the eyelids. Interestingly, it has been found that *D. bovis* is prevalent in skin lesions of cattle with demodicosis, whereas *D. ghanensis* has been found in meibomian glands of cattle with demodicosis (Abu-Samra & Shuaib, 2014). In one study, 72.7% of 300 cattle with demodicosis had diffuse body skin lesions with concurrent meibomianitis, whereas 27.3% had diffuse skin lesions but no ocular involvment (Abu-Samra & Shuaib, 2014). Diffuse, firm swellings of the eyelids has been reported (Gearhart et al., 1981). Skin lesions typically consist of a combination of papules, nodules, pustules, and crusts (Abu-Samra & Shuaib, 2014). For generalized demodicosis, treatment with systemic antibiotics, ivermectin, and amitraz baths has been shown to be successful (Reddy & Sivajothi, 2016).

Parasitic: Protozoal

Besnoitiosis

Besnoitiosis, elephant skin disease, is a relatively common disease of cattle caused by the protozoan parasite *Besnoitia besnoiti* (Jacquiet et al., 2010). Besnoitiosis in goats is caused by *Besnoitia caprae* and is endemic in Kenya, Nigeria, and Iran (Oryan et al., 2014). In cattle, the disease has been identified in Africa, Asia, throughout Europe and most recently in the United Kingdom (Alvarez-Garcia et al., 2013; Ryan et al., 2016). Transmission to cattle is thought to occur via mechanical transmission via blood feeding arthropods (e.g., *Tabanus* spp. [horse fly] and *Stomoxys* spp.) and possibly direct mucosal contact via nasal secretions and oral contact (e.g., licking) (Ryan et al., 2016). The infection may be clinically inapparent, or, in its severe form, it manifests as two sequential stages: (1) the acute stage characterized by fever and anasarca, and orchitis in bulls; and (2) the chronic stage as evidenced by scleroderma, alopecia, and hyperkeratosis (Fig. 37.4.6, Fig. 37.4.7, Fig. 37.4.8 and Fig. 37.4.9). Fever is the initial clinical sign followed, a few days later, by hyperemia of the muzzle, periorbital skin and scrotum in pale-skinned animals (for reviews and clinical descriptions see Dubey et al., 2013; Oryan et al., 2014; Rostaher et al., 2010; Ryan et al., 2016).

Leishmaniasis

Leishmania spp. are diphasic protozoal parasites that infect a wide range of vertebrates, mainly dogs and humans. Dogs are primary reservoirs of *Leishmania* spp., and sandflies (*Phlebotomus* spp. or *Lutzomyia* spp.) are the vectors. Leishmania is rarely reported in ruminant livestock (Dubey et al., 1998; Lobsiger et al., 2010; Mutinga et al., 1989; van der Lugt et al., 1992; Williams et al., 1991). The cutaneous form of leishmaniosis has been described in sheep from South Africa (van der Lugt et al., 1992). Clinical signs included severe swelling and diffuse cutaneous thickening and crusty exudate of one pinna, and small cutaneous crusts around the external nares, upper lip, muzzle, lateral aspects of the face, as well as the eyes. Alopecia, hyperpigmentation, hyperkeratosis, and crust formation have also been described in affected sheep and involving the periocular skin, and the skin along the dorsum of the nose and both ears. In one cow, pruritic, ulcerative, exudative, and eosinophilic lesions were described and involving the skin of the muzzle, udder, base of the ear, and carpi (Lobsiger et al., 2010).



Figure 37.4.6 Pinhead-sized papules (arrow) in the scleral conjunctiva of a bull with besnoitiosis. (*Source*: Reprinted with permission from Rostaher, A., Mueller, R.S., Majzoub, M., et al. (2010) Bovine besnoitiosis in Germany. *Veterinary Dermatology*, **21**, 329–334.)

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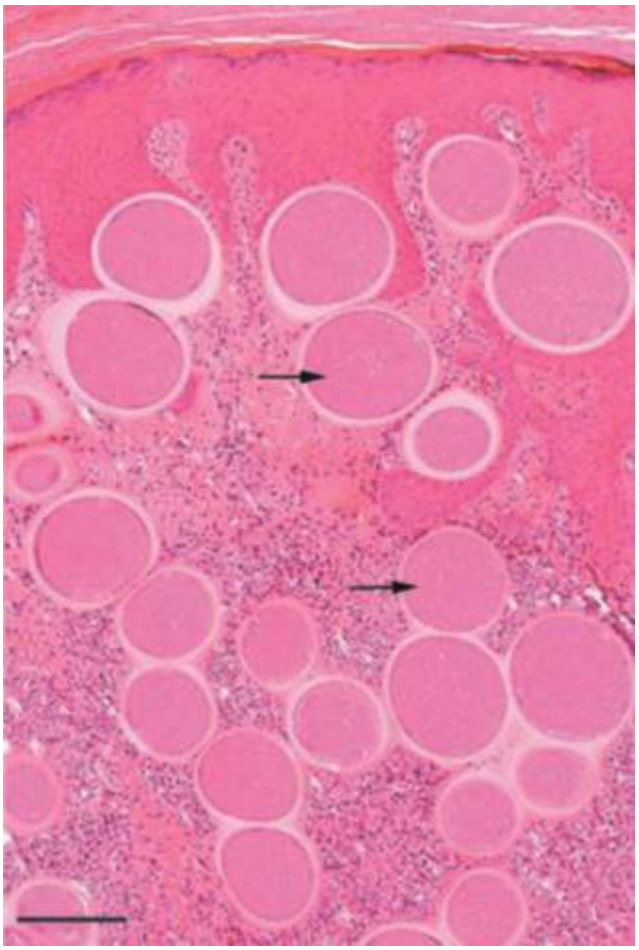


Figure 37.4.7 Photomicrograph: non-haired skin of a cow. Characteristic cysts of *Besnoitia* spp. (arrows) in the dermis. (Hematoxylin and eosin. Bar = 200 m.) (*Source*: Reprinted with permission from Rostaher, A., Mueller, R.S., Majzoub, M., et al. (2010) Bovine besnoitiosis in Germany. *Veterinary Dermatology*, **21**, 329–334.)

Neosporosis

Neospora caninum is a protozoal parasite, having structural and biological similarities to *Toxoplasma gondii*, that can infect livestock. Neosporosis can be transmitted vertically and horizontally. In naturally infected cattle, sheep, and goats, *N. caninum* can be transmitted transplacentally. In adult cows, abortion is the sole observable clinical sign (Dubey, 1999). However, *N. caninum*-infected calves may be born underweight with neurological signs including inability to rise, ataxia, and loss of conscious proprioception. Ocular manifestations of neosporosis in affected calves, such as exophthalmia or an asymmetrical appearance of the eyes, may also be observed (Barr et al., 1993; Dubey, 2003; Dubey et al., 1990).

Sarcocystosis

Sarcocystosis is caused by tissue cyst-forming coccidia, *Sarcocystis* spp. Cattle are intermediate hosts. Sarcocystosis has been reported in the ocular musculature of cattle in India infected with *Sarcocystis cruzi*, with a prevalence of 71.5% (Juyal et al., 1982). The affected ocular musculature contained a heavy concentration of cysts, and appeared to be the preferred site for the development of sarcocystosis in this species, second only to cardiac musculature. Sarcocysts have also been reported in the ocular muscles of sheep experimentally infected with *S. ovicanis* sporocysts from dogs (Leek & Fayer, 1978).



Figure 37.4.8 Multiple greyish-white foci similar in appearance to unrefined granulated sugar can be seen on the scleral conjunctiva of a female goat naturally infected with *Besnoitia caprae*. (*Source*: Reprinted with permission from Oryan, A., Silver, I.A. & Sadoughifar, R. (2014) Caprine besnoitiosis: an emerging threat and its relationship to some other infections of ungulates by Besnoitia species. *Research in Veterinary Science*, **97**, 1–7.)



Figure 37.4.9 Lateral aspect of head of a naturally infected goat showing alopecia. (*Source*: Reprinted with permission from Oryan, A., Silver, I.A. & Sadoughifar, R. (2014) Caprine besnoitiosis: an emerging threat and its relationship to some other infections of ungulates by Besnoitia species. *Research in Veterinary Science*, **97**, 1–7.)

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Prions

Scrapie

Scrapie is a neurodegenerative disease of the group of transmissible spongiform encephalopathies (TSEs) affecting sheep and goats. Sheep are regarded as the natural reservoir for scrapie. The incubation period is typically between 2.5 to 3.5 years. According to the prion hypothesis, which explains most of the biological features pertaining to the scrapie agent, scrapie lesions are triggered by the conversion of the cellular prion protein (PrP^{c}) into the abnormal isoform (PrP^{sc}) resulting in its pathological accumulation (Hunter, 1998). Scrapie produces progressive neurological signs, the lesions of which consist mainly of vacuoles within the nervous system, and eventual death. In particular, clinical signs are categorized into three main groups including: (1) sensation abnormalities, namely pruritis; (2) changes in mental status including apprehension and occasional aggression, and stupor; and (3) postural and locomotion changes such as low carriage of the head, wide-based or cross-legged stance, pacing (Braun et al., 2004a), and ataxia (for a review of scrapie, please refer to Bradley & Verwoerd, 2004). Ocular manifestations of scrapie infection of sheep and goats include multifocal, round tapetal lesions that can be as large as the optic disc (Fig. 37.4.10). Histologically, these lesions are focal retinal detachments resulting from subretinal accumulations of eosinophilc material characterized as lipid (Barnett & Palmer, 1971). These fundic lesions are typical enough to be suggestive of the diagnosis when combined with chronic, progressive neurologic disease. There is no effective treatment for scrapie. Animals suspected of having scrapie should be euthanized, and their brain should be submitted for laboratory examination.

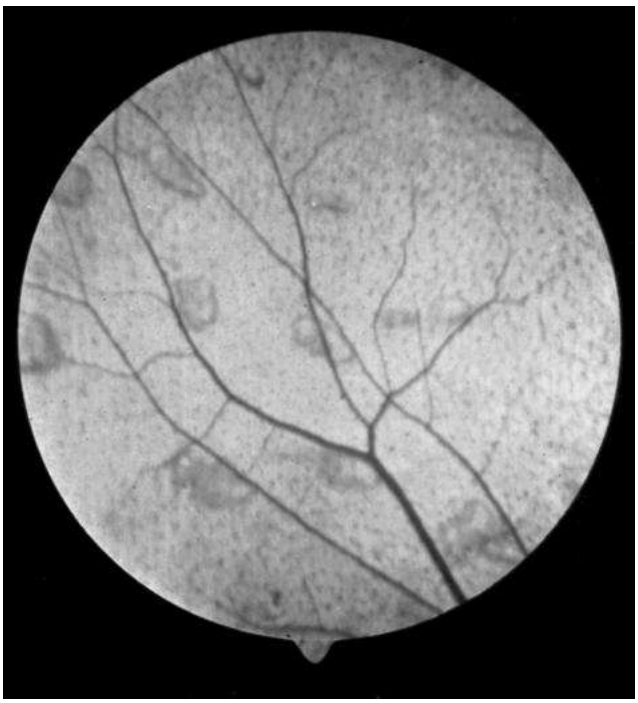


Figure 37.4.10 Retinal photograph from scrapie-affected sheep showing raised blister-like areas scattered in the tapetum lucidum. (*Source*: Reprinted with permission from Barnett, K.C. & Palmer, A.C. (1971) Retinopathy in sheep affected with natural scrapie. *Research in Veterinary Science*, **12**, 383–385.)

Viral

African Swine Fever

African swine fever (ASF), caused by ASF virus, a DNA virus, is the only member of the Asfarviridae family (Ninth Report of the International Committee on Taxonomy of Viruses, 2012). ASF is endemic in sub-Saharan Africa, parts of Russia, Eastern and Central Europe, Sardinia, Transcaucasia, and has most recently been reported in China (Brown & Bevins, 2018; Franzoni et al., 2018; Sanchez-Cordon et al., 2018; Wang et al., 2018). There are several disease forms of ASF ranging from a highly lethal hemorrhagic disease of domestic swine to subclinical infections (Mebus, 1988). Ocular lesions have been reported in affected pigs, including conjunctival hemorrhages, and serous to mucupurulent conjunctival and nasal discharges in the early and latter stages of ASF, respectively. In addition, blindness in phthisical globes with keratitis has also been reported in ASF-infected pigs (Vestre, 1984). A diagnosis of ASF is made based upon detection of the infectious virus, viral antigens, and specific antibodies, and by using PCR assays for the detection of genomic DNA (King et al., 2003).

Bluetongue

Bluetongue is caused by an arbovirus. The virus is transmitted by *Culicoides* gnats and causes disease in ruminants. Clinical signs of bluetongue in cattle include fever and vasculitis, and severe conjunctivitis accompanied by mucosal lesions, laminitis, and edema of the lips. In sheep, attenuated, modified live vaccine strains of bluetongue virus may produce deformed lambs, brain deformities, and ocular lesions when injected during the eighth to eleventh week of pregnancy. The ocular lesions from such injections are primarily a choroiditis and retinitis centered around retinal vessels, with retinal necrosis and retinal dysplasia. Similar lesions have not been reported with natural infections (Silverstein et al., 1971). Reverse-transcription PCR (RT-PCR) and competitive ELISA techniques are commonly used to detect virus in reaching a diagnosis. For review see Rojas et al. (2019).

Bovine Herpesvirus-Type 4

Bovine herpesvirus-type 4 (BHV-4), a gammaherpesvirus, is another widespread herpesviral pathogen of cattle. The clinical significance of BHV-4 on bovine health is considered minimally significant, although disease symptoms may be compounded when present with other infectious disease (Chastant-Maillard, 2015). BHV-4 is predominantly thought of as being important in reproductive health (Chastant-Maillard, 2015). Clinical signs associated with BHV-4 infection, however,

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include conjunctivitis, pneumonia, metritis, enteritis, cutaneous lesions, ulcerative mammilitis, and tumors of the rumen and urinary bladder (Goyal & Naeem, 1992). BHV-4 has also been isolated from conjunctival swabs in cases of naturally occurring BHV-4 keratoconjunctivitis (Bartha et al., 1966). One study detected BHV-4 DNA, using a nested PCR assay, in the conjunctiva and cornea of experimentally infected calves at 62 days postinfection, indicating persistence of BHV-4 infection in these tissues (Egyed & Bartha, 1998).

Bovine Leukosis

Bovine leukemia virus (BLV) is an oncogenic retrovirus with worldwide distribution. In adult cattle, lymphosarcoma is commonly caused by BLV. Cattle sometimes experience a syndrome of orbital involvement with lymphosarcoma that results in a progressive, bilateral, or unilateral exophthalmos. For more information regarding this syndrome, the reader is referred to "Lymphosarcoma" later in this chapter.

Bovine Virus Diarrhea

Bovine virus diarrhea (BVD) results from a pestivirus with a worldwide distribution that infects cattle, sheep, goats, and wild ruminants. It is transmitted via inhalation or ingestion of infective secretions or excretions, semen, and transplacentally. BVD virus has been shown to be transmitted to susceptible animals if they come into contact with fetal fluids during the birth of persistently infected calves (Lindberg et al., 2004). BVD virus has been implicated with causing abortion, and cerebellar and ocular disease. In cattle, *in utero* infection with BVD virus between 76 and 150 days of gestation may result in congenital defects of the eye and brain. In addition, after experimentally induced BVD infection, persistently infected calves have minor skeletal abnormalities including short limbs, narrow skull with bulging eyes and/or prognathism (Stokstad & Loken, 2002). CNS lesions include microencephaly, cerebellar hypoplasia, hydranencephaly, and hydrocephalus (Baker, 1987). Ocular lesions of cataracts, retinal degeneration and retinal dysplasia, optic nerve gliosis, optic neuritis, and microphthalmia have also been described with experimentally induced disease (Bistner et al., 1970; Scott et al., 1973). At ophthalmoscopy, the tapetal coloration is altered, and pigment clumping is visible. Cataracts and optic nerve lesions may not be present in naturally occurring cases of BVD; this may relate to the stage of gestation during which the pregnant dam became infected (Bistner et al., 1970). Acute histopathologic ocular lesions detected in fetuses taken 17–21 days after inoculation of their dams at 150 days gestation included mild to moderate retinitis causing destruction of the retinal layers, mononuclear cuffing of the inner retinal vessels, proliferation of the retinal pigment epithelium, and choroiditis (Brown et al., 1975).

The reader is referred to current internal medicine textbooks and online resources from diagnostic laboratories with regard to the diagnosis, control, and prevention of BVD.

Hog Cholera

Hog cholera is a highly contagious viral disease of swine caused by hog cholera virus (HCV), a member of the genus *Pestivirus*. The organism has a close antigenic relationship with bovine viral diarrhea virus and border disease virus. The pig is the only natural reservoir of HCV. Blood, tissues, secretions and excretions from an infected animal contain HCV. Transmission typically occurs by the oral route, although infection can occur through the conjunctiva, mucous membranes, a skin abrasion, insemination, and percutaneous blood transfer (e.g., common needle). Transplacental infection with viral strains of low virulence often results in persistently infected piglets, which constitute a major cause of virus dissemination to noninfected farms.

Hog cholera occurs in several forms including acute, subacute, chronic, or persistent. In the acute form, the disease is characterized by high fever, depression, multiple superficial and internal hemorrhages, and high morbidity and mortality. In the chronic form, the signs of depression, anorexia, and fever are less severe than in the acute form, and recovery is occasionally seen in mature animals. In the acute form of hog cholera, conjunctivitis is frequent and is manifested by copious ocular discharge, periocular crusting, and the eyelids may adhere together as a result of the exudate. Histopathologic ocular lesions of mononuclear inflammation of the retina and uvea may develop with hog cholera if the animal survives for 1 week or more. In addition, iridociliary congestion, edema, and, less frequently, hemorrhage may develop (Vestre, 1984). Anterior uveitis, focal choroiditis, retinitis with perivascular cuffing and gliosis, and optic neuritis may also occur with time (Saunders et al., 1958).

For details regarding the diagnosis, and control and prevention of hog cholera, the reader should consult a current large animal internal medicine or infectious disease textbook.

Infectious Bovine Rhinotracheitis

Infectious bovine rhinotracheitis (IBR), caused by bovine herpesvirus-type 1 (BHV-1), a member of the alphaherpesvirus family, is an important pathogen of cattle. Infection with BHV-1 typically arises ocularly or via the nasal cavity. After acute infection, the primary site for BHV-1 latency is within sensory neurons in the trigeminal ganglia (Lovato et al., 2003). Sporadically, reactivation of the virus from latency occurs, causing viral shedding and transmission to susceptible cattle. The persistence and reactivation of BHV-1 has also been reported within the germinal centers of pharyngeal tonsil of latently infected calves (Winkler et al., 2000). Depending on the strain of virus involved, IBR can cause various forms of disease including conjunctivitis/keratitis, severe respiratory infection, abortion, vulvovaginitis, balanoposthitis, and systemic infection in neonatal calves (Wyler et al., 1989). BHV-1 is also one of several agents linked with "shipping fever" or bovine respiratory complex (Tikoo et al., 1995). Outbreaks usually consist of a predominant form. The

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ocular form may be the only sign or it may be associated with respiratory signs. The ocular lesions of IBR are either unilateral or bilateral and may be confined to the conjunctiva. Conjunctivitis is thus the most common ocular manifestation of IBR, and may be characterized by raised, red to white plaques of lymphocyte follicles in chemotic bulbar and palpebral conjunctivae (Abinati & Plumer, 1961; Rebhun et al., 1978). The ocular discharge is initially serous, after which it progresses to become mucopurulent. A nonulcerative keratitis of varying degrees may develop in some animals. The keratitis is characterized by peripheral edema and deep neovascularization that spreads centrally. In severe cases, the cornea becomes completely opaque from the edema and leukocytic infiltration, thereby producing blindness. Anterior uveitis, which is evidenced by miotic pupils and thickened iris, may accompany the keratitis. The course of the conjunctivitis is approximately 2 weeks, but as with other herpesvirus infections, latent carrier states develop, and such animals may become symptomatic with stress. One study showed that a latency-related protein promotes ocular viral shedding during acute IBR infection in calves (Inman et al., 2001). In addition, anti-apoptotic properties of the latency-related gene were thought to play an important role during the establishment of BHV-1 latency (Lovato et al., 2003). IBR may also produce ocular lesions of conjunctivitis and keratitis with respiratory disease in goats (Mohanty et al., 1972). The diagnosis of IBR is established on the basis of viral isolation and fluorescent antibody testing of conjunctival scrapings. PCR techniques are also being used. Specific antiviral therapy is usually not given as cattle typically recover spontaneously from the conjunctival form of the disease. Genistein, an inhibitor of tyrosine kinase activity found in soya products, resulted in inhibition of BHV-1 replication *in vitro* (Akula et al., 2002). Vaccines are available to prevent and control the disease in susceptible animals.

Maedi-Visna

Maedi-visna is a systemic disease of sheep caused by a lentivirus, maedi-visna virus (MVV). Transmission of MVV is generally by pulmonary aerosols, semen, or colostrum. MVV mainly affects the lungs, CNS, and other tissues including joints and the mammary glands. MVV proviral DNA has been detected, via nested PCR, in the third eyelid of sheep naturally infected with maedi-visna (Capucchio et al., 2003). In particular, maedi-visna viral DNA has been detected *in situ* within macrophages, and glandular, ductal, and surface epithelia in the third eyelid of affected sheep. In this same study, a moderate to severe lymphoproliferative inflammation was also noted in the third eyelids of all MVV-infected sheep (Capucchio et al., 2003).

Malignant Catarrhal Fever

Malignant catarrhal fever (MCF), caused by ovine herpesvirus-2 or alcelaphine herpesvirus-1, is an often fatal and communicable disease in cattle. The disease may affect other cloven-hoofed animals including some wild ruminants and occasionally domestic pigs as well. It may produce either sporadic disease affecting one or more animals in a herd or epizootics involving large numbers of animals. It typically produces an acute syndrome of pansystemic vasculopathy that results in death from 1 to 10 days after the onset of clinical signs.

Four to five variations in clinical signs have been described. The most prominent clinical manifestations of MCF are pyrexia, profuse nasal and/or ocular secretions, hyperventilation, and death (Brenner et al., 2002). The "head-and-eye" form of MCF is the classic manifestation, and when this is observed, the diagnosis can be established on the basis of clinical signs (Pierson et al., 1973, 1978). Ocular lesions associated with this form of MCF include corneal edema, exophthalmos, bilateral blindness, photophobia, nystagmus, and severe lacrimation (Brenner et al., 2002). Corneal edema is the most obvious ocular lesion and develops within 36 hours of the onset of disease (Fig. 37.4.11). The edema may vary from mild, peripheral edema to dense, diffuse edema. Epithelial erosion is common and may occur from either subepithelial bullae or degenerative changes in the epithelium. If the cornea is clear, an anterior uveitis is evident by fibrin, cells, and flare in the anterior chamber as well as by miosis and iris texture changes (Fig. 37.4.12) (Whiteley et al., 1985). Histopathologically, a panophthalmitis is present, with lesions being characterized by marked lymphocytic vasculitis, and this characteristic proliferation results in lymphocytes and lymphoblasts within the lesions. Lymphocytic ciliary neuritis and optic meningitis were detected, although less commonly (Whiteley et al., 1985). In addition, corneal endothelial degeneration secondary to endotheliitis has been described (O'Toole et al., 1997). The pathogenesis of the lesions is speculated to be immune-mediated.

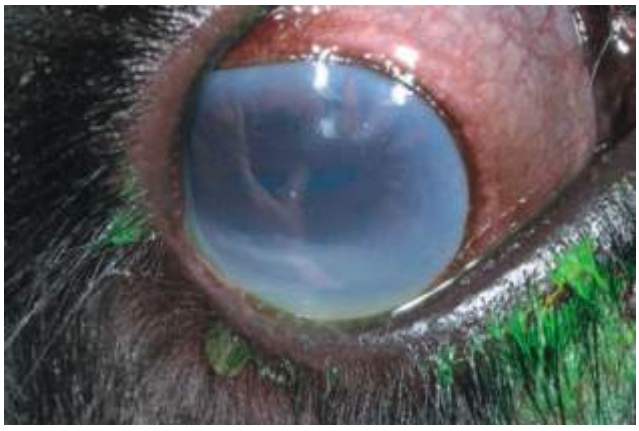


Figure 37.4.11 Malignant catarrhal fever in a cow. Note the conjunctival and scleral injection, marked limbal-based corneal edema, and signs of uveitis including miotic pupil. (*Source*: Courtesy of Ralph Hamor.)

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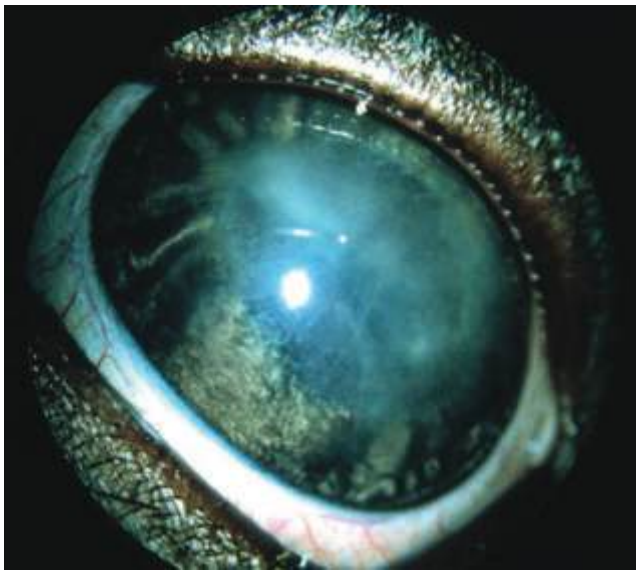


Figure 37.4.12 Malignant catarrhal fever in a cow. Note the extremely miotic pupil, iris texture changes, and intracameral fibrin. (*Source*: Courtesy of Ralph Hamor.)

The clinical signs are diagnostic if classic, but other clinical variations must be diagnosed on the basis of the classic lymphocytic vasculitis in histopathologic specimens. At present, there is no therapy and no vaccine available to protect animals.

Paramyxovirus (Blue Eye Disease)

Pig paramyxovirus of blue eye disease (PPBED), porcine rubulavirus, is a member of the Paramyxoviridae family that infects swine. This disease emerged in 1980 in Central Mexico (Kirkland et al., 2019). PPBED is characterized by corneal opacity, CNS disorders, and reproductive failure. CNS manifestations (e.g., fatal encephalitis) and corneal opacity are the main signs in piglets 2–21 days old (Ramirez-Herrera et al., 1997, 2001; Stephano & Gay, 1984; Stephano et al., 1988). Older pigs appear more resistant and corneal opacity is a commonly observed feature (Stephano et al., 1988). PPBED in pregnant sows has been linked with reproductive failure and infertility. Piglets 2–15 days of age are most susceptible. Affected piglets become prostrate and develop progressive neurologic signs. The affected animals may be blind, with dilated pupils and nystagmus. In addition, PPBED-affected pigs may develop conjunctivitis with epiphora, swollen eyelids, and ocular discharge adherent to the eyelids. Piglets older than 30 days of age may have respiratory signs and corneal opacities, or they may strictly have corneal opacities. Up to 30% of affected piglets have either unilateral or bilateral corneal opacities, which tend to resolve spontaneously. Histopathologically, ocular lesions consist of corneal edema and anterior uveitis. The cellular reaction is mononuclear, with some neutrophils and intracytoplasmic inclusions possibly being present in the epithelial cells (Stephano, 1990). PPBED has also been shown to bind to pig neuronal tissue of the brain stem, hippocampus, olfactory bulb, cerebellum, and frontal, temporal, and parietal lobes of the cerebral cortex in newborn, 60-day-old, and adult pigs (Mendoza-Magana et al., 2001). Clinical signs of encephalitis and corneal edema in piglets, or reproductive failure in adults, is/are suggestive of the diagnosis. The diagnosis is confirmed on the basis of virus isolation and hemagglutination-inhibition tests. At present, there is no specific therapy. For a thorough review of this disease see Kirkland et al. (2019).

Pseudorabies (Aujeszky's Disease)

Pseudorabies is caused by Aujeszky's disease virus, a neurotropic alphaherpesvirus. Pseudorabies epizootics in swine are noted with drastic climatic changes, and they are characterized by blindness, depression, head pressing, and death. Death or recovery tends to occur by day 3, with blindness occurring as a permanent sequela in recovered animals. Histopathologically, ocular lesions include decreased numbers of retinal ganglion cells, degeneration of retinal ganglion cells, and perivascular cuffing with mononuclear cells and neutrophils in the optic nerve (Howarth & De, 1968). In addition, rapidly progressive punctate corneal ulcers associated with blepharospasm, follicular conjunctivitis, corneal anesthesia, transient blindness, iridal edema, miosis, and fever, have been produced after experimental inoculation of traumatized porcine corneas with Aujeszky's disease virus (Schneider & Howarth, 1973). There is no treatment for the disease. Vaccines against Aujeszky's disease virus have been developed (Pastoret & Jones, 2004).

Rabies

Rabies continues to be one of the most feared zoonotic diseases in the world. Rabies, a bullet-shaped RNA virus, is a *Lyssavirus* in the family Rhabdoviridae (Woldehiwet, 2002). Transmission of rabies occurs via a bite by a rabid animal, although infections through aerosols have been documented (Constantine, 1966; Winkler et al., 1972, 1973). The virus can infect any warm-blooded animals, with dogs and cats being the main vectors of human infection (Woldehiwet, 2005). Clinically, rabies infection can be divided into 3 phases: (1) prodromal, (2) furious, and (3) paralytic phases (Bedford, 1976). Cattle are most commonly affected among livestock. Rabies virus is likely the most important cause of bovine encephalitis because of the public health implications (Callan & Van, 2004). The clinical signs of rabies infection in livestock are variable. Clinical manifestations of the prodromal form of rabies in animals include depression, inappetance, pyrexia, significant ataxia, and facial musculature flaccidity, among others. In addition, other signs, including ocular manifestations, may be seen prior to death such as circling, head pressing, strabismus, nystagmus, and blindness. The reader is referred to current internal medicine textbooks for a detailed discussion on rabies.

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Metabolic Diseases

Ionic Disturbances

Hypocalcemia (Bovine Parturient Paresis, Milk Fever)

Bovine parturient paresis is a complex metabolic disorder resulting in an acute to peracute flaccid paralysis and/or somnolence of lactating dairy cows which usually occurs at the onset of lactation (Horst et al., 1997). The hypocalcemia arises because of a rapid increase in milk production and subsequent acute depletion of serum ionized calcium. Parturient paresis is divided into three main clinical stages of which stage two hypocalcemia is characterized by depression, anorexia, an inability of the animal to stand, tachycardia, gastrointestinal stasis, and ocular signs of mydriasis with absent or sluggish pupillary light reflexes. Recommended treatment for parturient paresis is prompt intravenous therapy with a calcium solution.

Hypomagnesemia (Grass Tetany)

Hypomagnesemia results from a primary dietary deficiency of magnesium. Hypomagnesemia is a highly fatal condition of ruminants. Clinical signs in lactating cows affected with grass tetany (i.e., occurs mainly in winter and spring when grasses which are low in magnesium comprise the diet) include anorexia, hyperexcitability, muscle fasciculations, head and neck tremors, followed by poorly coordinated gait and lateral recumbency. In addition, ocular manifestations of grass tetany include nystagmus and a rapid, snapping eyelid retraction. Confinement-housed dairy cows on a controlled feeding program can also develop hypomagnesemia (Donovan et al., 2004). Prevention of hypomagnesemia involves both continuous provision of adequate levels of dietary magnesium and improving absorption of this essential mineral by the ruminal epithelium (Martens & Schweigel, 2000). The reader is referred to current internal medicine textbooks for a detailed discussion on hypomagnesemia in ruminants.

Neoplasia: Systemic

Lymphosarcoma

Bovine lymphosarcoma occurs as a sporadic or an adult form. The adult, or enzootic, form is the most common neoplastic disease of cattle, usually affecting cattle older than 4 years of age. However, cattle as young as 2 years of age may also be affected. Adult lymphosarcoma is typically associated with BLV infection. The disease is very rare in cattle uninfected with BLV (Burridge et al., 1982). Cattle sometimes experience a syndrome of orbital involvement with lymphosarcoma that results in a progressive, bilateral or unilateral exophthalmos. The resultant exposure keratitis may be severe, but intraocular involvement is rare. Systemic involvement of the peripheral or the visceral lymph nodes is usually present (Rebhun, 1982). A case of bilateral conjunctival involvement without obvious orbital involvement has also been observed. The clinical appearance in this case mimicked that of chemosis; however, the conjunctiva contained solid cellular infiltration rather than edema (Joyce, 1973).

A general physical examination will usually find lymphadenopathy or other organ involvement and, thus, fine-needle aspiration biopsy of the affected tissues is warranted. A complete blood count demonstrating lymphocytosis and a positive BLV agar-gel immunodiffusion test or ELISA are also supportive of the diagnosis (Rebhun, 1982).

Other: Metastases

A strain of miniature Sinclair swine has a high incidence (54%) of congenital cutaneous melanomas. As the animals mature, further tumor development occurs, until approximately 85% of the animals have melanomas. The tumors may metastasize, but most animals have spontaneous regression of both primary and secondary tumors, which is accompanied by depigmentation (80%). Depigmentation occurs not only at the tumor site but in other melanin-containing structures, such as skin, hair, and eyes. Although intraocular melanomas have not been described, the depigmentation of the uveal tract results in an inflammatory cascade that often produces blindness. Ocular depigmentation is usually detectable by 4–5 weeks of age. This is accompanied by an invasion of macrophages into the eye and mononuclear cells into the ciliary body. The macrophages accumulate pigment and cluster around veins. The pigment epithelium of the iris, ciliary body, and the pigment in the choroid are destroyed, but the retinal pigment epithelium is spared. Approximately 50% of the animals with uveal depigmentation have photoreceptor degeneration. Calcification of the cornea or band keratopathy eventually develops in approximately 9% of the animals that develop severe depigmentation. Severity of the ocular changes correlates with the tumor burden and speed of tumor regression (Feeney-Burns et al., 1988).

Nutritional Disorders

Polioencephalomalacia (Cerebrocortical Necrosis)

Polioencephalomalacia (PEM) is a disorder of the CNS of ruminants that results in necrosis of the cortical gray matter (Gould, 1998; Newsholme & O'Neill, 1985). PEM has a worldwide distribution. There are several causes of PEM including altered thiamine (vitamin B_1) status caused by such factors as excessive ruminal consumption of thiamine by bacterial thiaminases, and ingestion of plants with thiaminolytic activity, among others. However, PEM may also be induced by other neural metabolic disturbances such as water deprivation–sodium ion toxicosis, lead poisoning (see "Lead" later in this chapter), and high sulfur intake (Gould, 1998). Early clinical signs of PEM in affected animals include anorexia, incoordination, muscle tremors, holding the head in an erect position, and appearing blind. As PEM progresses,

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animals develop blindness, head pressing, dorsomedial strabismus, miosis, variable nystagmus, excitement, facial twitching, repetitive chewing, and recumbency and opisthotonos (McGuirk, 1987). In addition, a lack of menace responses and reduced palpebral reflexes have been described in PEM-affected cattle (Haydock, 2003). Death usually arises after 3–4 days if the affected animal is not treated.

Electrodiagnostic visual testing (electroretinogram [ERG] and visual-evoked potential [VEP]) has been performed on five ruminants (three lambs, one kid, and one steer) with thiamine-responsive PEM (Strain et al., 1990). The lambs and kid had typical clinical signs of PEM, including blindness. The ERG in these animals was normal but the VEP was abnormal. Follow-up recordings in the kid and one lamb indicated an improvement in VEP recordings subsequent to thiamine treatment and a gradual return of vision. According to the owners, all animals had complete return of vision. The steer did not have signs of blindness, and the ERG and VEP were normal (Strain et al., 1990). The reader is referred to current internal medicine textbooks for a detailed discussion on PEM.

Vitamin A Deficiency

Vitamin A deficiency has been studied extensively among cattle, both in spontaneous cases and with experimental induction. In young, growing animals, vitamin A deficiency produces clinical signs when the vitamin A levels fall to less than 20 g/dL of plasma and less than 2 g/g of liver (Kohlmier & Burroughs, 1979). A sexual predilection for males has been noted in two clinical reports (Divers et al., 1986; Paulsen et al., 1989). A lag period of 3–12 months may be necessary before the effects of vitamin A deficiency are noted, and these effects depend on age of onset, degree of deficiency, and the amount of liver stores. Animals younger than 6 months of age are more susceptible and more likely to have blindness as a presenting sign because of sphenoid bone overgrowth constricting the optic nerve (Barnett et al., 1970; Blakemore et al., 1957; Booth et al., 1987; Diver et al., 1986; Hayes et al., 1968; Paulsen et al., 1989; Spratling et al., 1965; Van Donkersgoed & Clark, 1988; Wetzel & Moore, 1940). Blindness, with or without convulsions, is the first outward sign noted in most cases among young, growing animals (Barnett et al., 1970; Divers et al., 1986; Spratling et al., 1965). Seizures are short and tonoclonic (Divers et al., 1986). On critical examination of animals, night blindness, the first clinical sign noted in experimentally affected animals, may be noted, but it is unlikely to be noted under typical husbandry conditions (Barnett et al., 1970). Blindness is accompanied by fixed, dilated pupils, and on ophthalmoscopy, papilledema will be present (Fig. 37.4.13 and Fig. 37.4.14). Papilledema occurs well before blindness in both adult- and young-onset deficiencies. Papilledema presumably results from increased cerebrospinal fluid (CSF) pressure, which develops from fibrosis and thickening of the dura mater that, in turn, results in decreased absorption of the CSF by the arachnoid villi. Increased CSF pressure is the first change noted with vitamin A deficiency (Hayes et al., 1968).

Causes of blindness will vary with age of onset for the deficiency. Blindness may result from retinal degeneration at all

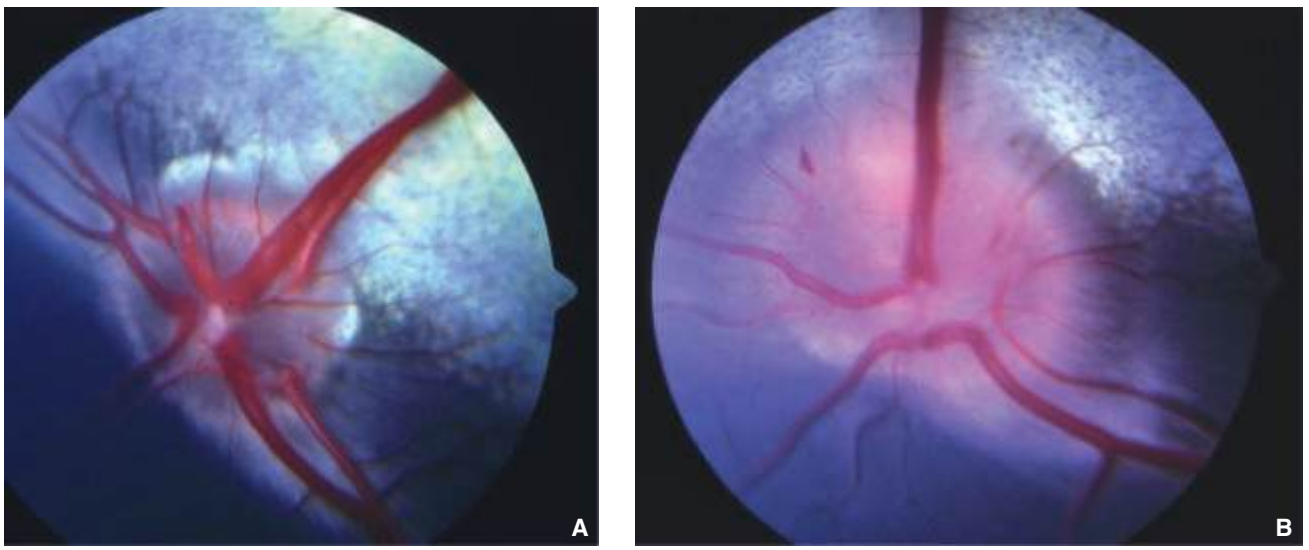


Figure 37.4.13 **A.** Normal fundus appearance of a Friesian calf. Note the presence of the conus vestigialis, the obvious difference between arteries and veins, and the color and clear outline of the optic disc. **B.** Papilledema caused by vitamin A deficiency in a calf of comparable age and breed. Note the size of the disc, the indistinct and raised border, and the small flame shaped hemorrhage at 11 o'clock. (*Source*: Courtesy of Keith C. Barnett.)

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Figure 37.4.14 Marked papilledema in a steer that was blind and experiencing periodic seizures because of vitamin A deficiency. (*Source*: Reprinted with permission from Martin, C.L. (1999) Ocular manifestations of systemic disease. Part 4: Food animals. In: *Veterinary Ophthalmology* (ed. Gelatt, K.N.), 3rd ed., pp. 1492–1504. Philadelphia: Lippincott Williams & Wilkins.)

ages or constriction and ischemic necrosis of the optic nerve at the optic foramen in growing animals. Eventually, optic nerve atrophy develops (Fig. 37.4.15) (Barnett et al., 1970). Day blindness has not been reversible, but night blindness or papilledema detected before blindness occurs has been responsive to therapy (Spratling et al., 1965). Additional changes in the fundus are papillary and peripapillary hemorrhages as well as disruption of pigment in the non-tapetal region (Fig. 37.4.16). Retinal degeneration primarily occurs in the non-tapetal region (Barnett et al., 1970; Booth et al., 1987; Divers et al., 1986; Paulsen et al., 1989; Van Donkersgoed & Clark, 1988). Tapetal color alterations have not been noted in experimental or in clinical reports until late in the deficiency. Additional ocular lesions that have been attributed to vitamin A deficiency include exophthalmos, epiphora, nystagmus, and corneal ulceration. Although described clinically, corneal lesions have not usually been observed experimentally in calves, but decreased corneal sensitivity has been observed (Barnett et al., 1970). In one study, 25% of calves born to heifers which experienced prolonged hypovitaminosis A during pregnancy had several congenital ocular abnormalities including microphthalmos, ocular dermoids covering the external surfaces of the eyes, and single chambered globes each lacking a uveal tract, lens (i.e., aphakia), and aqueous humor (Mason et al., 2003). Histopathologic examination of the affected eyes revealed severe retinal dysplasia with retinal rosettes, retinal folds,

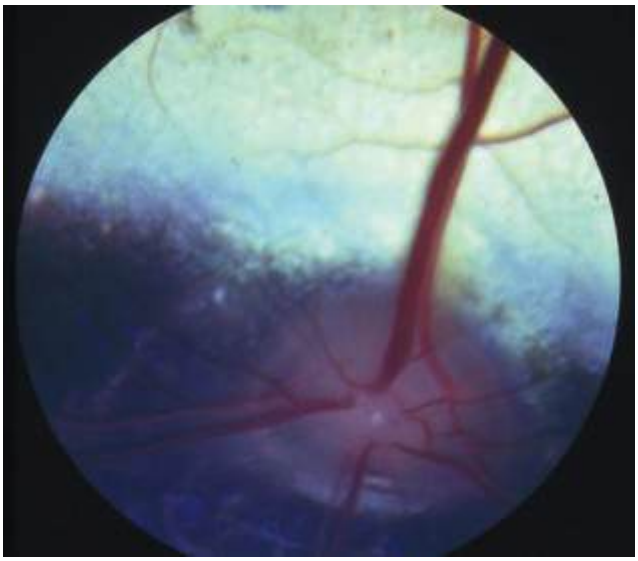


Figure 37.4.15 Optic and early retinal atrophy after papilledema in a vitamin A-deficient calf. (*Source*: Courtesy of Keith C. Barnett.)

and a generalized loss of retinal cells. In addition, the optic nerves were more cellular and paler staining than normal (Mason et al., 2003). Concurrent systemic signs will vary depending on the source of nutrition, duration of the deficiency, and age of the affected animal. In general, severe vitamin A deficiency will be accompanied by ill-thrift, diarrhea, poor growth, decreased appetite, and pneumonia.

The pathogenesis of the optic nerve lesions associated with vitamin A deficiency in calves has been extensively studied (Blakemore et al., 1957; Hayes et al., 1968; Wetzel & Moore, 1940). In calves made deficient for vitamin A from 35 days onward and examined at 5.5–6 months of age, the optic foramen of the sphenoid bone became deformed into a narrow, horizontal aperture. Normal development of the optic foramen results from new bone growth across the dorsomedial aspect of the optic canal and resorption of bone ventrally, which results in the progressive ventral displacement of the canal. In vitamin A-deficient calves, osteoblastic activity persisted both dorsally and ventrally, thus resulting in the two surfaces growing toward each other and a narrowed, horizontal slit for an optic canal (van der Lugt & Prozesky, 1989). In addition, the dura mater becomes thicker, and the combination produces compression within the canal, thereby compromising the vascular supply for the optic nerve. Optic nerve changes result mainly from ischemic necrosis, but in some instances when vascularity is maintained, the optic nerve pathology is subtle and may result from retinal degeneration. Constriction of the optic canal could not be produced in 2-year-old animals (Hayes et al., 1968), and the retinal histopathology has been reported in both naturally and experimentally deficient calves. Experimentally, degenerative changes were limited to the outer retinal layers and the retinal pigment epithelium and

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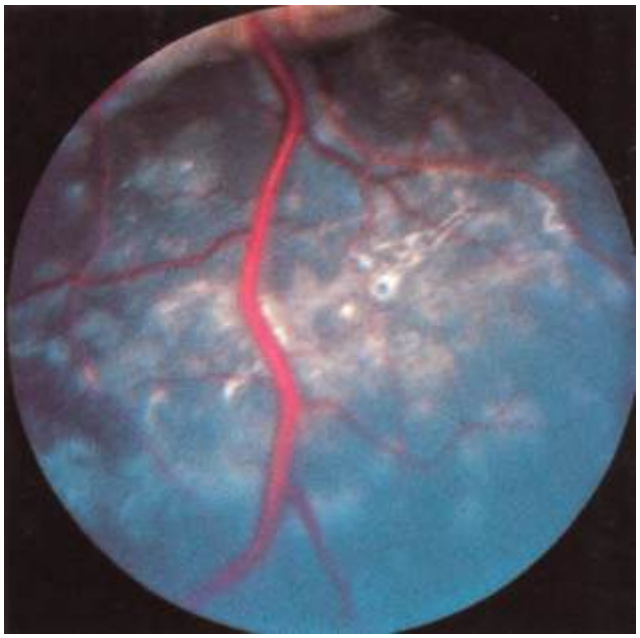


Figure 37.4.16 Retinopathy from vitamin A deficiency characterized by disruption of the retinal pigment epithelium. (*Source*: Reprinted with permission from Martin, C.L. (1999) Ocular manifestations of systemic disease. Part 4: Food animals. In: *Veterinary Ophthalmology* (ed. Gelatt, K.N.), 3rd ed., pp. 1492–1504. Philadelphia: Lippincott Williams & Wilkins.)

occurred preferentially in the ventral non-tapetal retina. Clinically, not only outer retinal degeneration but focal areas of full-thickness retinal degeneration and detachments have been reported (Barnett et al., 1970; Booth et al., 1987; Paulsen et al., 1989; Van Donkersgoed & Clark, 1988).

The clinical signs, history, and ophthalmoscopic signs are very suggestive of hypovitaminosis A. If vitamin supplementation has not been instituted, plasma blood levels of less than 20 g/dL of vitamin A will confirm the diagnosis (Divers et al., 1986; Kohlmier & Burroughs, 1979; Paulsen et al., 1989). Vision will not be restored in calves that are day blind, but animals with vision and papilledema as well as older animals may benefit from parenteral administration of vitamin A at 440 IU/kg (Divers et al., 1986).

Vitamin A deficiency in pregnant sows has, both experimentally and clinically, been responsible for a high incidence of varying degrees of microphthalmos and blindness in piglets. In extreme cases, anophthalmia was also present. In the clinical setting, the gilts are usually normal, although slow-healing skin wounds may be noted. Milder deficiencies have additional manifestations of hyperkeratotic facial lesions, posterior limb incoordination, inability to fully extend the carpal joint, and a high neonatal morality rate. In extreme experimental deficiencies of vitamin A, anomalies of cleft palate, accessory ears, and subcutaneous cysts have been produced (Hale, 1935; Maneely, 1951; Watt & Barlow, 1965).

Systemic Toxicities

Antimicrobials

Hygromycin B

Hygromycin B is an aminoglycoside antibiotic that has been used in the swine industry as a feed additive to control gastrointestinal helminths. The mixture is fed at 13.2 g per 1000 kg of feed for 8 weeks on, and then 8 weeks off, the mixture. Cataracts developed experimentally after 10–11 months on continuous feed with elevated levels of hygromycin B and after 14 months at the recommended level. The cataracts begin as axial, posterior subcapsular opacities and then progress to complete cortical cataracts. The opacities are often asymmetric as well. In the field, cataracts developed only in sows, but this predilection may result from their increased feed consumption, with farrowing and culling of the boars at an earlier age (Sanford & Dukes, 1978; Sanford et al., 1978).

Arsanilic Acid

Arsanilic acid has been used in swine both as a growth stimulant and as a therapy for swine dysentery. Arsanilic acid poisoning has occurred from its long-term administration, errors in feed formulation, or when water has been restricted. Clinical signs of blindness and pupillary dilation occur with toxicity, and additional signs of ataxia, torticollis, and paralysis may also develop. Optic disc atrophy is noted ophthalmoscopically in affected swine. The ERG in affected animals is normal, whereas the visual evoked response is nonrecordable. Histopathologic examination of eyes of these pigs reveals optic nerve degeneration and atrophy (Witzel et al., 1976).

Electricity

Electric shocks and lightning strikes can produce direct ocular sequelae and also cause injury to the CNS (may manifest as blindness, papilledema, cranial nerve palsies) (for review on pathogenesis and human manifestation see Norman et al., 2001). Electric shocks and lightning strikes of a severe nature may produce cataracts that manifest months later. Cataracts are more likely to be produced by electrical shocks to the head. In one study, a herd of Holstein-Friesian cattle experienced lightning strike while kept on pasture (Boeve et al., 2004). After the lightning strike, 8 of the 18 cattle had an unsteady, swinging gait, 9 calves had visual impairment as evidenced by an absent menace response, and 3 calves showed nystagmus. Four of the nine blind calves underwent ophthalmic examination which revealed normal pupillary light reflexes and no morphologic ocular lesions. Histopathologic examination of the brain of affected animals, including one of the blind calves, revealed cerebrocortical necrosis (Boeve et al., 2004).

Insect Bites

Insect bites, or envenomation, from hornets, bees, fire ants, and spiders may occur on the eyelids or cornea of all animals.

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Acute, severe blepharedema is the usual extent of bites to the eyelids, although bites from insects such as the brown spider or multiple fire ant bites may result in tissue sloughing (Joyce, 1983; Rakich et al., 1993). Acute, focal corneal necrosis with rapid melting of the corneal stroma is not a rare event because of the deposition of proteolytic enzymes. The diagnosis is often presumptive unless multiple bites are present on the animal or insects were observed while biting. Lysis of the corneal stroma may require surgical repair with conjunctival flaps.

Insecticides

Organophosphorus Compounds and Carbamates

Organophosphorus (OP) and carbamate insecticides are used commonly to control pests of crops and animals. These compounds are toxic and livestock poisoning has occurred from mistaken addition of unused insecticide to feeds and animal access to materials which have been improperly disposed. The toxicologic effects of OP and carbamate insecticides arise because of the inactivation of cholinesterase (ChE) resulting in an increase in acetylcholine (ACh) in tissues. The accumulation of ACh results in uninhibited impulse transmission of the parasympathetic nervous system and of the postganglionic cholinergic nerves of the sympathetic nervous system. The toxic effects of these compounds therefore mimic the muscarinic and nicotinic responses of ACh administration. There is typically increased sensitivity of young animals to this toxicity. Clinical signs of OP or carbamate insecticide poisoning include muscarinic signs of salivation, excessive lacrimation, frequent urination, and diarrhea. In addition, signs pertaining to the nicotinic effects of these insecticides include muscle tremors followed by weakness and paralysis. Miosis with subsequent vision impairment may be observed as well. A diagnosis of OP or carbamate insecticide poisoning is made based on demonstrating clinical signs and history that are consistent with this toxicity. In addition, detection of the chemical compound in stomach or rumen contents and tissues, and demonstration of the adverse biological effect, ChE inhibition, also help confirm the diagnosis (Meerdink, 1989).

Ionizing Radiation

The ocular effects of ionizing radiation are similar regardless of the source. Both the ocular effect(s) and the time to develop ocular disease depend on the dose, age of the animal, and the species being studied. In a long-term study of burros, swine, and cattle receiving gamma and mixed neutron-gamma radiation, both the swine and the burros were resistant to radiation-induced cataracts, but the cattle were about as equally susceptible as humans (Brown et al., 1972). The most common source of ionizing radiation-induced ocular lesions is radiation therapy for neoplasms of the head.

Lead

Lead poisoning is commonly diagnosed in cattle, and, to a lesser extent, sheep and horses. Cattle, especially young calves, are very susceptible to lead poisoning (Neathery & Miller, 1975). The cause of lead poisoning is accidental ingestion of sources of lead compounds (e.g., automobile battery) or of feed containing lead from environmental pollution. Lead poisoning in food animals is of public health significance because of the risk to humans through ingestion of contaminated meat and milk products from affected animals (Rumbeiha et al., 2001). In addition, the half-life of blood lead is variable (ranging from 48 days to 2507 days) and, hence, difficult to predict in accidental cases of lead poisoning in cattle (Rumbeiha et al., 2001). In acute lead poisoning of cattle, clinical signs include staggering, muscle tremors (mainly of the head and neck), clamping of the jaws, frothing at the mouth, in addition to ocular signs such as snapping of the eyelids, rolling of the eyes, and blindness. In the acute syndrome, death usually results during a convulsion as a result of respiratory arrest.

Phenothiazine

Cattle on a low plane of nutrition may develop a photochemical reaction within 24 hours after being dosed with phenothiazine as a dewormer. After subsequent exposure to sunlight, diffuse corneal edema results, which is typically in the lower two-thirds of the cornea. Corneal ulceration may develop secondary to the edema, and recovery may occur in 1 week (if the animal is restricted indoors) or be prolonged for 2–3 months (if the animal is kept out on pasture). Uveitis is not present, nor is there any reaction in the eyelids or skin. Susceptibility to the photodynamic reaction varies between species because of the variable conversion of phenothiazine in the gut to phenothiazine sulfoxide, which is absorbed by the portal system. If phenothiazine sulfoxide is incompletely metabolized in the liver, it reaches the systemic circulation and the aqueous humor, where it then acts as a photoreactive agent. A similar syndrome has also been described in pigs (Bistner et al., 1980; Clare et al., 1947). However, affected pigs may also develop eyelid edema (Swales et al., 1942).

Plants

Food animals are subject to the adverse effects from poisonous plants, which are not infrequently encountered in their environment. The clinical effects of some of these plants primarily involve the visual system.

Bracken Fern Poisoning (Bright Blindness)

Ingestion of bracken fern (*Pteridium aquilinum*) in chronic, low-level amounts has been suspected of causing the syndrome of bright blindness among sheep and cattle in England and Wales. The syndrome manifests as a retinal degeneration with blindness. Retinal lesions are most severe centrally and involve degeneration of the rods and cones.

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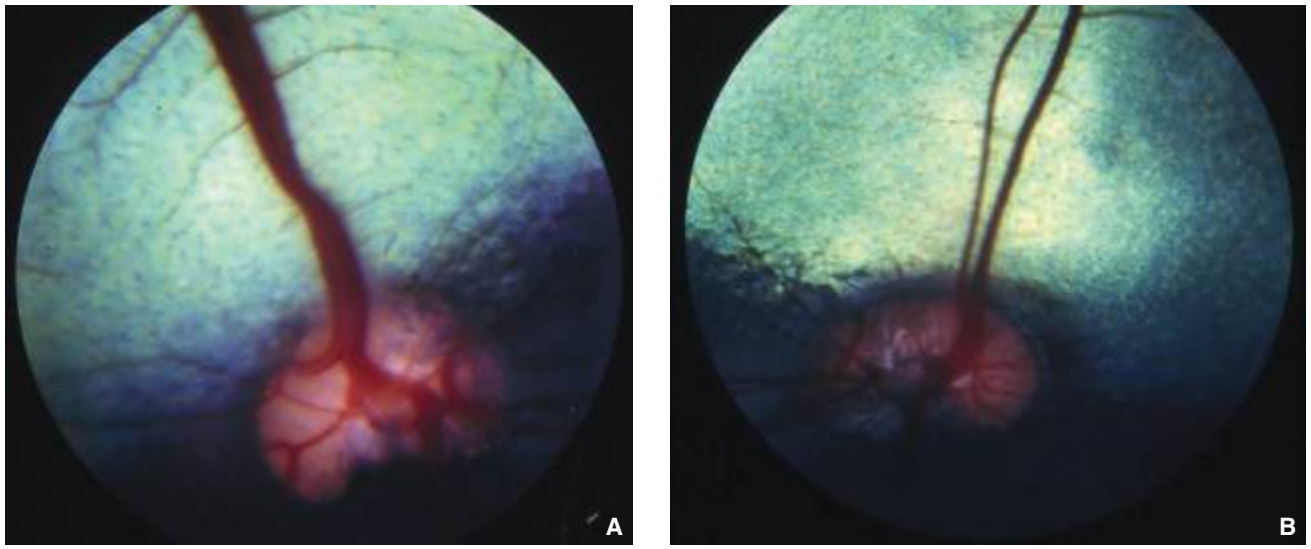


Figure 37.4.17 **A.** Normal fundus appearance of a hill breed of sheep. **B.** Bracken, retinopathy ("bright blindness") in a hill breed of sheep. Note narrowed retinal blood vessels and tapetal hyperreflectivity. (*Source*: Courtesy of Keith C. Barnett.)

Ophthalmoscopic findings include retinal vascular attenuation, tapetal hyperreflectivity, and optic nerve atrophy (Fig. 37.4.17) (Barnett & Watson, 1968).

Helichrysum argyrosphaerum Poisoning

In Africa, sheep and cattle grazing on pastures mainly consisting of *Helichrysum argyrosphaerum* have developed blindness, paresis, and paralysis. Lesions have been bilateral, symmetric edema of the white matter with destruction of myelin, and the optic nerve has developed gliosis. The intracanalicular portion of the optic nerve later undergoes fibrosis and atrophy suggestive of compression in the optic canal. Retinal lesions include degeneration and loss of photoreceptor outer segments, mainly in the non-tapetal fundus. The retinal pigment epithelium was hyperplastic and migrated into the neurosensory retina (van der Lugt et al., 1996).

Locoweed Poisoning

Ingestion of locoweed by cattle, sheep, and horses may produce ocular signs of blindness and a "dull" eye. Histopathologic changes of marked vacuolation of the retinal ganglion and bipolar cells, ciliary epithelial cells, and lacrimal acinar cells have been described in research animals (James & Van Kampen, 1971; Van Kampen & James, 1970, 1971).

Male Fern Poisoning

Male fern (*Dryopteris filix-mas*) consumption by cattle is associated with lethargy, constipation, and blindness. Acutely blind cattle have dilated pupils and ophthalmoscopic lesions of papilledema, as well as retinal and preretinal hemorrhages. Most animals recover when removed from pastures containing male fern, but some do not. Chronically blind animals develop optic nerve atrophy and vascular attenuation. At histopathology, the retrobulbar optic nerves are twice the normal diameter, myelin sheaths are fragmented and invaded by Gitter cells, and axons are decreased in number. The peripheral nerve, however, is relatively spared. The process appears to be a retrobulbar neuropathy that destroys the myelin sheaths of the nerve (Rosen et al., 1970).

Veratrum Poisoning in Sheep

Cyclopia in lambs may be produced by ingestion of *Veratrum californicum* or skunk cabbage in pregnant ewes on day 14 of gestation (Binns et al., 1965). Exposure to *Veratrum* after day 14 increases the fetal death rate, but the embryos are normal. The teratogenic dose is less than the toxic dose to the ewes. The steroid alkaloids primarily responsible for the teratogenic effects of *Veratrum* are cyclopamine and jervine. These teratogens were found mainly in the green leaves, stems, and especially the roots. The toxicity of *Veratrum* may vary widely, both from year to year and from pasture to pasture. The teratogenic effect is limited mainly to the head, with distortion of the bones of the upper jaw and cranium, fusion of the cerebrum, hydrocephalus, cyclopia, and anophthalmia. Usually, a protrusion from above the eye on the midline is also present. Anomalies may be present in one twin even though the other is normal. The incidence of anomalies may be as high as 25% (Binns et al., 1963). An ELISA has been developed to detect and measure cyclopamine and jervine (Lee et al., 2003).

Rodenticides

In all species, coumarin poisoning may manifest with ocular or orbital hemorrhages. The source of coumarin may be rodenticides or sweet-clover poisoning in cattle, sheep, pigs, and horses. When hemorrhages are either limited or predominantly located in the eye and orbit, the diagnosis may

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be less obvious. Unless the orbital hemorrhage is visible by dissecting anteriorly to the subconjunctival space, orbital hemorrhage may be confused with other causes of acute space-occupying lesions, such as orbital cellulitis (Heider & Hart, 1993; Griggs et al., 2016).

Miscellaneous Diseases

Brain Abscess

Central blindness has been diagnosed in a 3.5-year-old crossbred steer diagnosed with multiple brain abscesses (Strain et al., 1987). In particular, clinical signs in this steer included depression, head pressing, and circling to the left. Ocular manifestations in this animal included ptosis and absent menace response of the right eye; direct and consensual pupillary light reflexes were normal in both eyes. Electrodiagnostic testing was performed and revealed essentially normal brainstem auditory evoked potentials and ERGs, whereas VEPs were greatly diminished for the right eye and absent for the left eye. On postmortem examination, the brain abscesses were located in the left thalamus, left caudal cerebrum, and right frontal cerebrum (Strain et al., 1987).

Bullous Empyema

Bullous empyema (left-sided) causing peripheral vestibular syndrome has been described in a pregnant heifer. Clinical signs in this heifer included generalized ataxia, wide-based stance of the hind limbs, abnormal behaviour, circling to the left, and left head tilt. In addition, ocular lesions included strabismus to the left, and nystagmus with the fast phase to the right (Braun et al., 2004b).

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